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The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals

153. Occupational chemical exposures and cardiovascular disease

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Preface

The main task of the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG) is to produce criteria documents to be used by the regulatory authorities as the scientific basis for setting occupational exposure limits for chemical substances. For each document, NEG appoints one or several authors. An evaluation is made of all relevant published, peer-reviewed original literature found. Whereas NEG adopts the document by consensus procedures, thereby granting the quality and conclusions, the authors are responsible for the factual content of the document.

The evaluation of the literature and the drafting of this document on *Occupational chemical exposures and cardiovascular disease* were done by Dr Bengt Sjögren, Dr Carolina Bigert and Prof. Per Gustavsson at the Institute of Environmental Medicine, Karolinska Institutet, Sweden.

The draft versions were discussed within NEG and the final version was adopted at the NEG meeting on 9 May 2019. Editorial work and technical editing were performed by the NEG secretariat. The following experts participated in the elaboration of the document:

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All criteria documents produced by NEG may be downloaded from *www.nordicexpertgroup.org*.

Gunnar Johanson, Chairman of NEG

Contents

Abbreviations and acronyms

ACGIH	American Conference of Governmental Industrial Hygienists
AHA	American Heart Association
AHR	aryl hydrocarbon receptor
ApoE	apolipoprotein E
ARDS	acute respiratory distress syndrome
BaP	benzo(a)pyrene
BMI	body mass index
CeVD	cerebrovascular disease
CFC	chlorofluorocarbons
CHD	coronary heart disease
CI	confidence interval
CNS	central nervous system
CNT	carbon nanotube
CO	carbon monoxide
COHb	carboxyhaemoglobin
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
CTPV	coal-tar pitch volatiles
CVD	cardiovascular disease
CYP	cytochrome P450
DEP	diesel exhaust particles
DHA	docosahexaenoic acid
DMF	*N,N*-dimethylformamide
DPA	docosapentaenoic acid
EC	elemental carbon
ECG	electrocardiogram
ED_{50}	effective dose for 50% of the exposed group
EFSA	European Food Safety Authority
EPA	Environmental Protection Agency
EU	European Union or endotoxin unit
FEV_1	forced expiratory volume in the first second
FICZ	6-formylindolo[3,2-*b*]carbazole
HCFC	hydrochlorofluorocarbons
HDL	high-density lipoprotein
HFC	hydrofluorocarbons
HR	hazard ratio
HRV	heart rate variability
ICAM-1	intercellular adhesion molecule 1
ICD	International Classification of Diseases
IHD	ischaemic heart disease
IL	interleukin
IQR	interquartile range

JEM	job-exposure matrix
LDL(R)	low-density lipoprotein (receptor)
LOAEC	lowest observed adverse effect concentration (at inhalation)
LOAEL	lowest observed adverse effect level
MI	myocardial infarction
MMMF	man-made mineral fibres
MMVF	man-made vitreous fibres
MONICA	Monitoring Trends and Determinants in Cardiovascular Disease
mppcf	million particles per cubic foot
MRI	magnetic resonance imaging
MSM	marginal structural models
MWCNT	multi-walled carbon nanotube
NEG	Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals
NHANES	National Health and Nutrition Examination Survey
NTP	National Toxicology Program
OEL	occupational exposure limit
OR	odds ratio
PAH	polycyclic aromatic hydrocarbons
PBS	phosphate-buffered saline
PCB	polychlorinated biphenyl
PFAS	per- and polyfluoroalkyl substances
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulphonic acid
PIVUS	Prospective Investigation of the Vasculature in Uppsala Seniors
PM_x	particulate matter with maximal aerodynamic diameter of x μm
PMR	proportionate mortality ratio
PVC	polyvinyl chloride
RR	relative risk, risk ratio, rate ratio
SAA	serum amyloid A
SCOEL	Scientific Committee on Occupational Exposure Limits
SIR	standardised incidence ratio
SMR	standardised mortality ratio
SRR	standardised relative risk
STEL	short-term exposure limit
STEMI	ST-elevation myocardial infarction
SWCNT	single-walled carbon nanotube
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
TCE	trichloroethylene
TWA	time-weighted average
UK	United Kingdom
US	United States
WHO	World Health Organization

1. Introduction

This document reviews occupational chemical exposures in relation to cardiovascular disease (CVD). The scientific data used for the evaluations are primarily epidemiological studies, supplemented with experimental human and animal data. Some chemical air pollutants are widely distributed and with exposure including the general population. When appropriate, such exposures have been included in this presentation. Occupational air pollutant exposures are often mixtures of many different chemicals, e.g. welding fumes and farming dust, which complicates exposure-effect analyses. Even individuals with their main occupational exposure restricted to one chemical (e.g. tetrachloroethylene in dry cleaning) may have a complex lifetime history of occupational exposures.

CVD includes several diseases, the main categories being heart and cerebrovascular diseases (CeVD), respectively.

The main group of the former is ischaemic heart disease (IHD) or myocardial ischaemia which is characterised by reduced blood flow (ischaemia) to the heart muscle. The most common cause of this condition is atherosclerosis in the coronary arteries and consequently IHD is often called coronary heart disease (CHD). The most common vascular disease is high blood pressure (hypertension).

The main CeVD is stroke, which signifies the abrupt impairment of brain function caused by a variety of changes involving one or several cerebral blood vessels. Approximately 85% of all strokes are caused by diminished blood flow (ischaemic stroke) and the remaining 15% comprise haemorrhage in the brain tissue and the surrounding subarachnoid space (1056).

Some reviews have been presented regarding occupational chemical exposures and CVD. In 1989, Kristensen presented well-documented relationships between exposures to carbon disulphide and nitroglycerine/nitroglycol, respectively, and CVD. Causal relationships between lead and second-hand smoke (passive smoking) and CVD were considered less likely at the time (518). Attributable fractions for the occupational burden of deaths in Finland and Sweden due to circulatory disease and IHD have been estimated for some chemical and non-chemical agents (473, 719).

Fang and coworkers reviewed studies on occupational particulate exposures and found a possible association with IHD (279). In another review, exposure to some metals (e.g. arsenic and lead) was found to be associated with CVD (881). In 2013, Jakobsson and Gustavsson evaluated the evidence of relationships between occupational exposures and stroke. They found limited evidence for a relationship between exposure to carbon disulphide and stroke and insufficient evidence for relationships between dynamite and combustion products and stroke (451).

In 2017, the Swedish Agency for Health Technology Assessment and Assessment of Social Services presented a review on chemical exposures and CVD. The review included occupational epidemiological studies but excluded environmental epidemiological, and experimental human and animal studies. The conclusion was that there is evidence that workplace exposure to crystalline silica dust, engine

exhaust and welding fumes is associated with IHD. An association with IHD was also seen for workplace exposure to arsenic, asbestos, benzo(a)pyrene (BaP), lead, dynamite, carbon disulphide, carbon monoxide, metalworking fluids and tobacco smoke. Associations were also found between IHD and work with electrolytic production of aluminium and exposure to compounds which are banned in many countries, such as asbestos and phenoxy acids containing dioxins. There was further evidence that workplace exposure to crystalline silica dust and asbestos, respectively, is associated with pulmonary heart disease (*cor pulmonale)* and that workplace exposure to lead, carbon disulphide, phenoxy acids containing dioxin, as well as working in an environment where aluminium is being electrolytically produced, is associated with stroke (835).

Some of the agents included in the present review have recently been evaluated by the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG), in documentations covering also cardiovascular effects, e.g. carbon nanotubes (395), diesel engine exhaust (941) and carbon monoxide (918).

2. Definitions

In 1899, Jacques Bertillon presented a report at the meeting of the International Statistical Institute at Christiania. The report contained the progress of the Bertillon Classification of Causes of Death and included a recommendation from the American Public Health for decennial revisions. This was the start of the generally accepted International Classification of Diseases (ICD). Diagnoses have changed and developed during the years and the coding of diseases in effect at present is ICD-10 (1014). Chapter IX in the 10th revision (ICD-10) comprises diseases of the circulatory system (ICD-code I00–I99).

By the authors of the present document, cardiovascular disease (CVD) comprises heart and vascular diseases and covers the diseases listed in Table 1. Consequently, CVD is equivalent to diseases of the circulatory system. In the conclusions for each chemical agent, the term CVD is generally used, but more specific diagnoses are given when appropriate, e.g. IHD (ICD-10, I20–I25), CeVD (ICD-10, I60–I69), pulmonary heart disease including *cor pulmonale* (ICD-10, I27.9), and cardiomyopathy (ICD-10, I42).

In the description of individual epidemiological studies, the diagnoses used in the publications were kept, e.g. sometimes CVD comprised fewer diagnoses and excluded CeVD (242, 867). No attempt was made to translate previous ICD-codes to current ICD-10 codes.

The concept coronary heart disease (CHD) appears in the literature. According to ICD-8 or -9 (codes 410–414), CHD is equal to IHD. According to ICD-7 (code 420), CHD means arteriosclerotic heart disease (1014). Arteriosclerosis literally means “hardening of the arteries” and refers to a group of processes which have in common thickening and loss of elasticity of arterial walls. At least two morphological variants are included in the term: *atherosclerosis and arteriolosclerosis.*

Atherosclerosis is an extremely common arterial disease characterised by the deposition of elevated focal, fatty-fibrous plaques, known as atheromas, within the intima and inner media of the walls of arteries. Arteriolosclerosis is characterised by proliferative fibromuscular or endothelial thickening of the walls of small arteries and arterioles (780). Although atherosclerosis is a specific type of arteriosclerosis, the terms are sometimes used interchangeably in the literature.

Table 1. Diseases of the circulatory system falling under the category cardiovascular disease (CVD) according to the definition in the present document. ICD-10 codes are according to WHO (1014).

ICD-10 code	Diagnosis
I10–I15	Hypertensive diseases
I20–I25	Ischaemic heart diseases
I20	Angina pectoris
I21	Acute myocardial infarction
I25	Chronic ischaemic heart disease (atherosclerotic heart disease)
I26–I28	Pulmonary heart disease and diseases of pulmonary circulation
I26	Pulmonary embolism
127.2	Secondary pulmonary hypertension
I27.9	Pulmonary heart disease, unspecified (chronic *cor pulmonale*) [a]
I30–I52	Other forms of heart disease
I30–I31	Pericarditis
I33	Endocarditis
I40–I41	Myocarditis
I42	Cardiomyopathy
I46	Cardiac arrest
I48	Atrial fibrillation and flutter
I49	Other cardiac arrhythmias
I50	Heart failure
I60–I69	Cerebrovascular diseases
I60	Subarachnoid haemorrhage
I61	Intracerebral haemorrhage
I63	Cerebral infarction
I70–I79	Diseases of arteries, arterioles and capillaries
I70	Atherosclerosis
I71	Aortic aneurysm and dissection
I80–I89	Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified
I80	Phlebitis and thrombophlebitis
I95–I99	Other and unspecified disorders of the circulatory system
I95	Hypotension

[a] For a description of *cor pulmonale*, see Section 4.4.

ICD-10: The 10th revision of the International Classification of Diseases, WHO: World Health Organization.

3. Occurrence

CVD is the number one cause of death in the developed as well as in the developing world. In 2010, there were 52.8 million deaths globally of which CVD contributed to 15.6 million, i.e. 30%. The most common CVD was IHD (7.0 million) and CeVD (5.9 million). The annual CVD mortality has increased dramatically from 11.9 million in 1990 to 15.6 million in 2010 (578) and is expected to reach 23.6 million by 2030 (17). However, the age-standardised death rates from CVD decreased from 298 to 235 per 100 000 persons in the period 1990–2010, thus the increase in total CVD mortality is driven by population growth and ageing (578).

The World Health Organization (WHO) has launched the project Monitoring Trends and Determinants in Cardiovascular Disease (MONICA), which during the mid-1980s until the mid-1990s revealed substantial differences in coronary event rates [myocardial infarction (MI) and coronary deaths] across countries. Thus, the coronary event rate (per 100 000) in men varied 10-fold, being highest in Finland (835 in North Karelia) and lowest in China (81 in Beijing). Among women, an 8-fold variation was observed with the highest coronary event rate observed in Scotland (265 in Glasgow), and the lowest rates of 35 in Spain and China (321).

During the same period (mid-1980s to mid-1990s) the average coronary event rates decreased by 23% among women and by 25% among men and the mortality of CHD decreased even more; 34% among women and 42% among men. The greatest decline in coronary event rates in men occurred in north European populations (Finland and Northern Sweden). Populations experiencing notable increases in coronary event rates were predominantly from Asia and the central and eastern parts of Europe, although the general pattern of increases and decreases appeared to be less consistent in women (321).

Reliable and comparable occupational disease statistics based on compensated cases are not available at the global level. This lack has been compensated for by calculations of the population attributable fractions for work-related illnesses found in different studies. These attributable fractions are commonly used to measure the fraction of illnesses and deaths that are related to work. The International Labour Organization (ILO) has used the attributable fraction 12.4% (14.4% for males and 6.7% for females) to estimate the global burden of work-related diseases regarding the circulatory system (936).

In 2001, Nurminen and Karjalainen estimated the attributable fraction for the occupational burden of deaths due to circulatory disease to 12%, with shift work, work strain and second-hand smoke as the most important agents (719). In 2013, Järvholm and coworkers estimated the attributable fraction for work-related IHD from motor exhaust to 3.5% and that from other combustion products to 4.4% among Swedish males (473).

4. Mechanisms for development of cardiovascular disease

The main hypothesis for the association between inhalation of air pollutants and development of CVD is that of a general inflammatory process. Other hypothetical pathways include disturbances of the autonomic nervous system and systemic uptake of particles from the lungs to the cardiovascular system (126).

The potential health risk from inhalation of chemical agents depends on mass concentration as well as particle or droplet size. The conventional particle fractions of total airborne particles are the inhalable, thoracic and respiratory fractions. The inhalable fraction consists of all particles inhaled through the mouth and nose. The thoracic fraction consists of particles reaching beyond the larynx. The respirable particle fraction reaches the alveolar region (1027). In the European Standard EN 481:1993 defining sampling conventions for particle size fractions (target specifications for sampling instruments), it is stated that the collection efficiency should be 50% of particles with aerodynamic diameters of 100, 10 and 4 μm for the inhalable, thoracic and respirable fractions, respectively (265). Other frequently used and generally accepted particle-size selective criteria for aerosol sampling are $PM_{2.5}$ and PM_{10} (particulate matter with maximal aerodynamic diameter of 2.5 and 10 μm, respectively). $PM_{2.5}$ is not related to particle-size deposition within the respiratory tract, but rather to the source-related properties from atmospheric combustion processes. The thoracic and the PM_{10} criteria represent basically the same fraction, but the thoracic fraction allows for sampling up to 25 μm, whereas the PM_{10} collection efficiency has a cut off around 15 μm (1027). Particles may also be divided in coarse (2.5–10 μm), fine ($\leq$ 2.5 μm) and ultrafine ($\leq$ 0.1 μm) (126).

Mouse models have been useful for studying development and progression of atherosclerotic lesions. Current mouse models are based on genetic modifications of lipoprotein metabolism. Low-density lipoprotein receptor-deficient mice (LDLR-/-) and apolipoprotein E-deficient (atherosclerosis prone) mice (ApoE-/-) are the most widely used (380). Overexpression of serum amyloid A (SAA) increases plaque progression in the arteries, and inhibition of SAA synthesis lowers plaque progression, in mouse models of CVD (958).

4.1 Inflammation originating from the airways

Already in the 1840s, the inflammatory nature of atherosclerosis was described by the Austrian pathologist Carl von Rokitansky and by Rudolf Virchow. Virchow considered atherosclerosis to be a primary inflammatory disease while Rokitansky viewed atherosclerotic inflammation as secondary to other disease processes (318, 613). The “response to injury hypothesis” was summarised by Ross in 1993 (802). This theory postulated an alteration of the endothelium and smooth muscle of the artery wall, due to e.g. mechanical injury, toxins and oxygen radicals, as the initiating event leading to endothelial dysfunction. During the last two decades

more data have linked inflammation to the occurrence of atherosclerosis and thrombosis (261, 563, 778, 803).

In the mid-1990s, the observed association between environmental as well as occupational air pollutants and IHD was proposed to occur via a low-grade inflammation (850, 878).

Several markers of inflammation such as interleukin-6 (IL-6), fibrinogen and leukocyte cell count are established markers for an increased risk of IHD (209-211, 288).

Acute respiratory tract infections were associated with increases of inflammatory markers and a raised risk of MI the following 10 days (629). Influenza was followed by increased risk of MI within 7 days (523). Likewise, short-term (days) elevations of urban particulate air pollution are associated with an increased daily CVD mortality. It is assumed that endothelial cell activation and blood coagulation are engaged in the rapid response leading to thrombosis in the coronary arteries (126).

Long-term exposure to airborne particles is capable of augmenting the development and progression of atherosclerosis (126). Thus, long-term inflammatory responses after exposure to particles may have similarities with several chronic inflammatory diseases which are associated with an increased risk of IHD. Examples of such diseases are chronic bronchitis (371, 465), periodontitis (108), systemic lupus erythematosus (373), rheumatoid arthritis (792) and psoriasis (516). Reduced forced expiratory volume in the first second (FEV_1) may be an expression of inflammatory lung disease, and is associated with CVD mortality (872). Certain occupational exposures have been associated with some of the diseases mentioned above. For example, exposure to dusts, gases and fumes has been related to an increased incidence of chronic bronchitis (925) and silica exposure has been associated with the development of rheumatoid arthritis (919).

Cigarette smoke is an example of an air pollutant containing both particles and gases. Smoking and second-hand smoke are established risk factors for CHD. It has also been suggested that the risk of CHD from smoking is higher in women than in men (433). Smoking and second-hand smoke are also major causative factors for stroke (743).

When rats were exposed by inhalation to titanium dioxide particles of equal gravimetrical dose (mg/m^3) but different sizes, ultrafine particles (20 nm) induced more inflammation in the lungs than larger particles (250 nm) (721). For a given particle mass concentration, a 100-fold decrease in diameter (e.g. from 2 to 0.02 μm) corresponds to a million-fold increase in particle count and a 100-fold increase in total surface area (239). Some characteristics of the ultrafine particles, such as high particle number and large surface area, suggest that they may pose a particularly high cardiovascular risk after inhalation (126, 814).

Volunteers exposed to zinc oxide or swine dust reacted with a stronger inflammatory response after the first exposure than after repeated exposures (290, 731). These reactions indicate an adaptation process and may be one explanation of the increased CVD mortality on Mondays (1032).

In 2010, the American Heart Association (AHA) reviewed the literature and presented a statement regarding particulate matter air pollution and CVD. They summarised the epidemiological evidence of the cardiovascular effects of $PM_{2.5}$ (traffic-related and combustion-related air pollution exposure at ambient levels); there was strong overall epidemiological evidence for an association between both short-term exposure (days) and long-term exposure (months to years) and IHD. AHA also evaluated the biological pathways leading to effects on the cardiovascular system. There was strong overall mechanistic evidence of a relation between a systemic proinflammatory response and CVD in humans as well as in animals (126). In more recent reviews, the weight of evidence further suggests that acute exposure to $PM_{2.5}$ induces a shift in the haemostatic balance towards a prothrombotic or pro-coagulative state (781) and also a causal link between pulmonary acute phase response, induced by inhalation of nanoparticles, and CVD (814).

4.2 Systemic uptake of inhalable particles

Inhaled particles may be translocated from the lungs to the blood and further to other organs in the body. When volunteers inhaled radioactive 35-nm carbon particles for 6 minutes, 1% of the initially deposited activity was detected in blood 80 minutes after exposure (1017). Inhalation of slightly bigger carbon particles (84 nm) resulted in a lower translocation to blood (0.3%) (500).

Several animal studies showed small but significant increases in systemic levels of engineered nanomaterials after inhalation exposure, suggesting that these materials are absorbed to a low but measurable degree via the respiratory route. The systemic uptake of gold nanomaterials is less than 1% of the inhaled dose in animal experiments. Small engineered nanomaterials tend to be taken up to a greater extent than large nanomaterials. The uptake of molecules from soluble or degradable engineered nanomaterials, e.g. silver and zinc oxide, can be much higher (457, 488).

Inhaled asbestos fibres entrapped in the lungs may become coated by proteins and form ferrugineous bodies which in general consist of a fibrous core coated by protein and haemosiderin, a result from oxidation of ferritin (333). These coated fibres have a unique appearance under the microscope and are usually called asbestos bodies. Electron microscopic studies have shown that only a tiny proportion of the asbestos fibres present in the lungs of asbestos workers become coated. Asbestos bodies have been detected in many organs including the heart (53), which indicates translocation of fibres from the lungs.

A case of epicardial anthracosis in a coal miner emphasises extrapulmonary dissemination of inorganic carbon particles (23).

Generally, particles in the heart and blood vessels may disturb function in these organs, but the relationship with CVD is unclear.

4.3 Disturbances of the autonomic nervous system

The heart rate is regulated by the autonomic nervous system. Stimulation of the sympathetic system will increase the heart rate while parasympathetic stimulation

will decrease it. Heart rate variability (HRV) is a measure of the cyclic variations of beat-to-beat intervals that reflects cardiac autonomic function. Decreased HRV is associated with increased occurrence of cardiac events (972) and increased risk of mortality (219, 950).

In 2010, AHA stated that there was moderate overall mechanistic evidence of a relation between disturbed balance in the autonomic nervous system and cardiovascular effects in humans (126). In addition, reduced HRV indices (indicating dysregulation of the autonomic nervous system) were associated with increased levels of an inflammatory marker (C-reactive protein, CRP) (368). It has also been shown that air pollution in cities can increase the incidence of ventricular tachyarrhythmias among patients with implantable cardioverter defibrillators (491).

4.4 Other mechanisms

Inhaled *carbon monoxide* (CO) forms a complex with haemoglobin in the erythrocytes. The complex, carboxyhaemoglobin (COHb), will decrease the available oxygen to the heart muscle and exposure to CO may consequently increase the risk for ischaemia (918).

Asphyxiants such as cyanide (122), hydrogen sulphide (666) and phosphine (1) inhibit mitochondrial cytochrome oxidase. Cardiac arrhythmias are associated with these intoxications.

Exposure to *nitroglycerine and other organic nitrates* is associated with cardiovascular symptoms which develop in three stages. The first stage is characterised by vasodilation. The second stage that develops after days to months includes compensatory responses of vasoconstriction. The third stage relates to withdrawal of exposure. During a period of 3–4 days vasoconstriction may overcome vasodilation and this imbalance may cause coronary insufficiency or acute MI (534).

It is well-known from animal and clinical studies that *halogenated volatile anaesthetic hydrocarbons* can sensitise the heart to the arrhythmogenic action of various catecholamines (e.g. adrenaline) (124, 424, 459). Several additional halocarbons show evidence of cardiac sensitisation to catecholamines in animal studies (408, 812).

Pulmonary arterial hypertension results from diseases affecting the structure and function of the lungs like pneumoconiosis (e.g. silicosis and asbestosis) and extrinsic allergic alveolitis. Chronic obstructive pulmonary disease (COPD) is the leading cause of this disease. Pulmonary arterial hypertension may lead to right ventricular enlargement and to heart failure, a condition often called *cor pulmonale* (1002, 1003).

Dyslipoproteinaemia is a well-known risk factor for CVD and an association between *carbon disulphide* exposure and dyslipoproteinaemia has been suggested (447, 588).

When blood DNA methylation of *nitric oxide synthase 3* (*NOS3*) and *endothelin-1* (*EDN1*) was studied in a group of steel workers exposed to different levels

of *metal-rich air particles*, a relationship between blood hypomethylation of these inflammatory genes and increased blood coagulation was found (940).

The aryl hydrocarbon receptor (AHR) pathway is believed to play an important role in the development of the cardiovascular system. *Ahr* gene-deficient mice develop cardiac hypertrophy, abnormal vascular structure in multiple organs and altered blood pressure depending on their host environment (1052). There are two different potent activators of *AHR* signalling which exhibit strong negative influence on the cardiovascular system: *polycyclic aromatic hydrocarbons (PAH)*, such as benzo(*a*)pyrene (BaP) and *halogenated aromatic hydrocarbons*, such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). AHR is an orphan receptor which earlier was thought primarily to function in mediating xenobiotic metabolism through transcriptional activation of drug-metabolising enzymes, since the most highly induced genes encode the cytochrome P450 (CYP1) enzymes. Today, some high-affinity physiological activators of *AHR* have been suggested (227) and it is established that the receptor participates in xenobiotic-independent functions and is a key transcription factor controlling cell physiology and organ homeostasis (682). In particular, one natural compound, the tryptophan-derived 6-formylindolo[3,2-*b*]carbazole (FICZ), has attracted a lot of interest with regard to the physiological role of AHR. FICZ binds AHR with the highest affinity of all natural and xenobiotic ligands described and is also a perfect substrate for the induced CYP1 enzymes (772, 1026). Therefore, this molecule causes transient *AHR* signalling of importance for normal physiology and disease prevention (452, 771). Activation of *AHR* can be an underlying mechanism of atherosclerosis mediated by certain environmental contaminants. This was suggested in mouse models where atherogenic effects of e.g. dioxin-like polychlorinated biphenyls (PCBs) and BaP were stronger in mice with an intact AHR system (400, 487).

Hydrogen fluoride easily penetrates the skin. An exposure area of the human skin of 2.5–3% is enough for the fluoride ions to reach the circulation, disturb the electrolytic balance and cause development of hypocalcaemia, hypomagnesaemia and heart arrhythmias (1038), which may be fatal (947).

5. Measures of risk and interpretation of epidemiological studies

The most common study designs in occupational epidemiology are cohort and case-control studies. Both give estimates of measures of risk associated with the exposure, often expressed as relative risk (RR), i.e. the ratio of the disease rate among the exposed to the disease rate among the unexposed. Occupational cohort studies using the disease rate in the general population as a proxy for the disease rate among unexposed, report risk as a standardised mortality ratio (SMR). Studies based on cohort-internal comparisons of risk are often analysed by Cox regression, with relative risk expressed as a hazard ratio (HR). In case-control studies, the frequency of exposure is studied among cases of a specific disease (cases) and within a sample of the study base (controls). The information obtained is used to

estimate the odds ratio (OR), which in a well-designed study is an unbiased estimate of the relative risk. Sometimes there is information on exposure for dead persons only, e.g. in studies based on occupational titles on death certificates. In such cases, it is possible to compare the distribution of causes of death among those with a certain exposure (e.g. those in a certain occupation) to the distribution among those in an unexposed control population. A relative over-representation of a certain cause of death among the exposed may be interpreted as an effect of the exposure, and it is possible to calculate the proportional mortality ratio (PMR). There are several weaknesses associated with this method, the most obvious is that an apparent excess of a certain diagnosis may as well be caused by an under-representation of the diagnoses used for comparison (804).

In order to study the health effects of one specific chemical substance, a group of workers exposed to this agent is ideally compared with an identical group of workers without the exposure. The two groups should be similar regarding all other possible exposures and determinants associated with the health effects of interest, or the comparison may be biased. There are many determinants and risk factors associated with IHD. In reality, the incidence of IHD among occupationally exposed groups is often compared with national rates of the disease based on hospital registers or mortality. Such comparisons are likely to underestimate the true risks as the general population includes sick and disabled people unable to work. This underestimation is known as the healthy worker effect (61, 625).

Lower socioeconomic classes have an increased risk of IHD compared to higher social classes (797). Suadicani and coworkers found an increased risk of IHD [RR 1.44, 95% confidence interval (CI) 1.06–1.95] among lower social classes compared to higher classes after adjusting for age. After further adjustment for smoking, alcohol, physical activity, systolic and diastolic blood pressure, hyper-tension, body mass index (BMI), cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, serum selenium levels and retirement status, the RR decreased to 1.38 (95% CI 1.0–1.9). After further adjusting for two significant occupational exposures (soldering fumes and organic solvents), the RR decreased to 1.24 (95% CI 0.87–1.76). Thus, exposure to particles and irritant gases might be one factor explaining the difference between social classes and consequently socioeconomic adjustments may mask possible associations between chemical exposures and IHD as chemical exposures are common in lower social classes but rare in higher social classes (923).

In order to avoid comparisons with the general population or non-comparable socioeconomic classes, the occupationally exposed social class can be compared with the same social class without the specific occupational exposure (886, 1015). Another method to avoid bias is to perform internal comparisons by dividing the cohort of workers in different exposure categories thereby creating a possibility to study exposure-response relationships. Exposure categorisation can be based on duration or constructed as cumulative exposure. Cumulative exposure is an integration of air concentration of a chemical and duration of exposure. An exposure category as duration can bias an exposure-response relationship by the

healthy worker survivor effect. This effect describes a continuing selection process where workers who remain employed tend to be healthier than those who leave employment. The healthy worker survivor effect generally attenuates an adverse effect of exposure (49). In order to control for this effect, marginal structural models have been applied e.g. in an investigation of United States (US) aluminium workers (702) and g-estimation among autoworkers exposed to metalworking fluids (168). The healthy worker survivor effect can be reduced by excluding subjects who have been exposed prior to the first time period of follow-up (37).

Epidemiological studies of occupational chemical exposures and CVD may be confounded (disturbed) by other non-chemical occupational exposures. Recently the Swedish Agency for Health Technology Assessment and Assessment of Social Services evaluated contributions of the work environment from non-chemical occupational exposures to IHD. There was moderately strong evidence for a relationship between job strain and small decision latitude on one hand and IHD incidence on the other hand. Limited evidence was found for a relationship between IHD and iso-strain, pressing work, effort-reward imbalance, low support, lack of justice, lack of skill discretion, insecure employment, night work, long working week and noise (834, 953).

Independent epidemiological studies of the same chemical exposure may lead to seemingly contradictory results. Combined analysis of data from multiple studies is a way to resolve such ambiguities. There are two types of such analyses; a combination of summary statistics from individual studies (meta-analysis) and a combined analysis of the raw data from the individual studies (pooled analysis).

6. Criteria for evaluation of evidence

In general, evaluations of human health risks from chemical exposures are based on animal and human experimental studies, as well as mechanistic and epidemiological studies. Animal studies have a huge impact in the evaluation of chemical carcinogens, but so far only to a limited extent in the investigation of chemical exposures and CVD. There are animal models to study the development of atherosclerosis, see Chapter 4.

The data base for each chemical agent in this document was evaluated according to criteria regarding strength of evidence of an association between air pollutant exposure and occurrence of CVD (Table 2). These criteria are mainly based on those presented by the Swedish Council on Health Technology Assessment (833). Bias and confounding in epidemiological studies are discussed in Chapter 5.

The evaluations of chemical risks in this document are mostly based on epidemiological studies. Sometimes evaluations are supported by animal or human experimental studies, and also by investigations of markers of disease and inflammation. Human experimental studies may provide the key data in the evaluation.

Table 2. Criteria for evaluation of human experimental and epidemiological evidence for an association between chemical exposures and CVD (as used in this document).

Evaluation	Criteria
Strong evidence	Several high-quality human experimental or epidemiological studies including exposure-response data consistently support an association. Chance, bias and confounding can be excluded with high confidence.
Moderately strong evidence	Several human experimental or epidemiological studies support an association. Chance, bias and confounding can be reasonably excluded.
Limited evidence	Some epidemiological studies support an association. Chance, bias and confounding cannot be excluded.
Insufficient evidence	Studies are lacking or few epidemiological studies with similar quality show contradictory results. Chance, bias and confounding cannot be excluded.

7. Combustion-generated air pollutants

7.1 General background

Combustion of organic materials such as wood, coal, coke, oil, diesel and petrol fuel generates a large number of air pollutants, particles and chemical substances such as PAH. Inhalation is the major exposure route for these agents, but also skin exposure may be of great importance.

This chapter focuses on occupations and exposure circumstances involving exposure to high and moderate levels of combustion-generated air pollutants, and where important potential confounders are not present. The chapter is mainly organised according to occupational activities. Studies from the metal industry, foundry work and smelting are delimited to electrolytic aluminium smelting only, due to the very high levels of PAH present in this environment. Foundry work was excluded because of the presence of both noise and silica in the work environment, both being suspected risk factors for CVD.

Epidemiological studies are generally unable to distinguish if health effects from combustion products are related to the particles as such, to PAH or to both since they typically occur together in the work environment. Animal studies may provide additional evidence for mechanism of action and evidence of causal associations. The studies reviewed in this chapter sometimes used gravimetric exposure measures of the particle phase (e.g. $PM_{2.5}$), and sometimes PAH or BaP as indicator of exposure, although this approach does not imply that the health effects observed are related specifically to the chosen exposure indicator. A summary of estimated lowest observed adverse effect concentrations (LOAECs) for the different combustion-generated air pollutants is presented in Table 3 (Section 7.14).

BaP is often used as an indicator of total airborne PAH exposure. Exposures to BaP and dust (particulate air pollution) in various industries and occupations involving exposure to PAH were reviewed by Armstrong *et al.* in 2004 (45). The review included 39 cohort studies of coke oven and gas production workers,

aluminium smelter, carbon anode plant, asphalt, tar distillation, thermoelectric power plant and carbon black workers, as well as chimney sweeps. Dust levels were classified in four categories: low (< 1 mg/m^3), moderate (1–5 mg/m^3), high (5–10 mg/m^3) and very high (10–25 mg/m^3). Very high dust levels were found for Söderberg potroom workers during electrolytic aluminium smelting and for chimney sweeps, high levels were found for coke oven top workers, aluminium smelter workers (except Söderberg potroom workers) and carbon anode plant workers. Moderate dust levels were present among coke oven side workers, coal gas retort, asphalt and tar distillation workers, and low levels among coal gasification by-product workers and thermoelectric power plant workers. Levels of BaP were very high among coke oven top workers (average 20 µg/m^3) and Söderberg potroom workers during electrolytic aluminium production (15 µg/m^3). Intermediate levels of BaP were found e.g. among carbon plant workers in the aluminium industry (2 µg/m^3), carbon anode plant workers (1 µg/m^3) and among chimney sweeps (1 µg/m^3). The lowest levels were found among thermoelectric power plant and carbon black workers (0.05 µg/m^3) (45).

7.2 Electrolytic aluminium smelting

7.2.1 General

Bauxite is the main raw material for aluminium production (517). Metallic aluminium is produced from bauxite in two stages. First, alumina (Al_2O_3) is extracted from bauxite by a chemical process (Bayer process). In the second step, alumina is reduced to aluminium by an electrolytic process (Hall-Héroult process). There are two main types of electrolytic processes used in the potrooms. The Söderberg type furnace consists of an anode in paste form, which is continuously supplied to the pots as it is consumed. In the second type of process, the prebake, the anode is previously manufactured and replaced periodically after consumption. The electrolytic smelting is associated with occupational exposure to a wide array of chemical pollutants such as aluminium oxide, fluorides, carbon monoxide, sulphur dioxide and PAH (954). The Söderberg process is usually associated with high exposure to PAH (45).

Epidemiological studies and risk estimates are presented in Appendix, Table A1. Exposure to aluminium *per se* is presented in Section 9.1.

7.2.2 Occupational epidemiological studies

Björ *et al.* studied 2 264 male production workers at a Swedish primary aluminium smelter employed 1942–1987 and followed for mortality 1952–2004. Expected numbers of deaths were derived from national and local mortality rates. The overall SMR for MI was low, and there was no statistically significant trend with duration of employment. The SMR for CeVD was close to 1 and there was no positive trend with duration of employment (99).

The mortality in a cohort of 1 085 male workers at a Norwegian primary aluminium smelter using prebaked electrodes was reported by Rønneberg (813). The cohort [later included in a study by Romundstad *et al*. (794)] comprised

workers employed 1922–1975 and was followed for mortality 1962–1991. The SMRs for IHD and CeVD were not elevated, neither among the short-term (< 3 years) nor among the long-term (> 3 years) employed. However, the number of deaths from peripheral arteriosclerotic disease was elevated in both groups, with statistical significance in the latter. A subgroup analysis among those employed > 3 years subdivided by the time window of exposure as well as cumulative exposure showed a significantly elevated RR for all atherosclerotic diseases among those with a high cumulative exposure to coal-tar pitch volatiles (CTPV) more than 40 years ago (813).

Romundstad *et al*. studied 10 587 male workers at six Norwegian primary aluminium smelters [including the one earlier reported by Rønneberg (813)]. The cohort was followed 1962–1996. SMRs for IHD and CeVD were not elevated. There was no exposure-response relationships in terms of cumulative exposure to PAH or fluorides and the risk of circulatory disease (794).

A cohort of 6 455 male aluminium smelter workers from 11 plants in France was followed 1950–1976. The mortality from circulatory disease was not significantly elevated. Analysis of SMRs in relation to length of employment and type of process – Söderberg or prebake process – showed no evidence of an exposure-response relationship (685).

Moulin *et al*. reported the mortality in a cohort of 2 133 male aluminium smelter workers in France [earlier included in the study by Mur *et al.* (685)]. Follow-up was updated to encompass the period 1968–1994. The SMRs for circulatory diseases and IHD were not elevated and there was a statistically significant deficit of deaths from CeVD (674).

The mortality in a cohort of 2 103 male workers in a US aluminium plant in state Washington was reported by Milham. The cohort was followed up to 1976. There was a statistically significant deficit of deaths from circulatory diseases both among workers classified as exposed and among those classified as unexposed. An analysis by duration of employment gave no firm evidence of an exposure-response relationship, but analysis by latency showed a statistically significant elevated SMR for circulatory diseases after more than 25 years since first hire (642).

A cohort of 21 829 workers from 11 aluminium reduction plants (smelters) in the US was followed up to 1977. There was a statistically significant deficit of deaths from CVD both among whites and non-whites. Subgroup analyses, not presented in detail, showed a statistically significant excess of deaths from “all other heart disease” among white workers in plants using the Söderberg process (789). The category “all other heart disease” was not defined but is likely not to include arteriosclerotic heart disease. It was not mentioned if the plant earlier investigated by Milham (642) was included in this study.

Costello *et al*. performed a cohort study of 11 966 aluminium workers from eight plants in the US including both smelter workers and other occupational categories. Diagnoses 1998–2009 were obtained from health insurance claims, and smoking habits (not complete) were obtained from occupational health clinic records. The study was designed to investigate if recent exposure to particulate matter increased

the risk of IHD, using a job exposure matrix (JEM). Of five exposure classes, the risk of IHD was higher in classes 2–5 (representing > 0.05 to > 1.15 mg/m^3 of $PM_{2.5}$) than in the lowest class (≤ 0.05 mg/m^3 of $PM_{2.5}$), but there was no evidence of an exposure-response trend over classes 2–5. No relationship between cumulative exposure and IHD was found (199).

The cohort study reported by Costello *et al*. (199) was extended and further analysed by Neophytou *et al*. Time of follow-up was extended to 2012 and Cox marginal structural models (MSM) were applied to adjust for the healthy worker survivor effect, using an index of cardiovascular risk factors as a measure of health status that may affect future exposure. Exposure at 0.260–1.469 mg/m^3 of $PM_{2.5}$ in smelter workers was associated with a statistically significantly increased risk of IHD (MSM-model, HR 2.00, 95% CI 1.16–3.45), but no further increase in risk was seen at higher exposure. Adjustment for the healthy worker survivor effect by Cox MSM-analysis indicated a stronger effect of the exposure than did regular Cox regression (702). A later analysis of the same cohort indicated that the risk of IHD was better predicted by $PM_{2.5}$ than by total particle matter (703).

A case-control study investigated sick leave or death from IHD in a cohort of 6 000 Canadian primary aluminium smelter workers. The study identified 306 cases and 575 matched referents. The risk of IHD associated with work in various parts of the plant was estimated by conditional logistic regression, adjusted for smoking habits. Work in the reduction plant was associated with a statistically significantly increased risk of IHD (OR 1.72, 95% CI 1.09–2.97) especially among workers using prebaked electrodes or Söderberg electrodes. No exposure-response relationship for duration of work in the reduction plant was found (954).

Friesen *et al*. reported the findings of a cohort study of 6 423 male and 603 female Canadian aluminium smelter workers. The plant, located in Kitimat in British Columbia used vertical stud Söderberg electrodes. Mortality from IHD was followed 1954–1999. Both external and internal comparisons of mortality were performed. Information on tobacco smoking was available for 88% of the cohort. Acute and chronic exposure to CTPV and BaP was estimated by a JEM. Men with the highest cumulative exposure to BaP (≥ 66.7 µg/m^3 BaP-years, calculated with a 5-year lag) had a statistically significantly higher risk of death from IHD than those unexposed to BaP, adjusted for smoking habits. The exposure-response trend was of borderline statistical significance (P = 0.053). No association was seen with current exposure (312). According to a method used by the US Environmental Protection Agency (EPA), the average exposure in an open-ended upper exposure class can be estimated to 5/3 of the lower boundary of the upper class (982). Thus, the average cumulative exposure can be estimated to 66.7 × 5/3 = 111 µg/m^3 BaP-years.

Gibbs *et al*. reported the mortality in male aluminium smelter workers from three plants in Quebec, Canada. All workers on the payroll 1 January 1950 or 1951 were included. Mortality was followed 1950–1999 and expected numbers of deaths were derived from the Quebec population. The study was focused on cancer but reported deaths from IHD and CeVD as well. BaP exposure measurements were structured

in a JEM, which was used to calculate cumulative exposure. The SMR for IHD was not increased in any of the three cohorts, whereas the mortality from CeVD was increased in all cohorts, and statistically significant in the combined cohort (SMR 1.14, 95% CI 1.01–1.27). An exposure-response analysis using seven classes of cumulative exposure showed that the risk of death from CeVD was significantly increased among men with the highest cumulative exposure to BaP (> 320 $\mu g/m^3$-years) (SMR 2.79, 95% CI 1.34–5.13). The trend was not statistically significant (P = 0.16) (337). The mortality among those workers in the three cohorts that were hired after 1 January 1951 (with presumably lower exposure) was reported by Gibbs and Sevigny (339). No statistically significant excess of IHD or CeVD was found in any of the cohorts or in the combined cohort. An exposure-response analysis relating SMR for CeVD to cumulative exposure to BaP showed no statistically increased risks and P for trend was > 0.2 (339).

Mortality was investigated among 4 396 male workers from two prebake aluminium smelters in Victoria, Australia. One of the factories started production in 1962 and the other in 1986. The cohort included workers employed for more than 3 months 1983–2002 and was followed to 2002. Expected numbers of deaths were derived from the Australian population. Observed numbers of deaths from CVD and CeVD were below or close to the expected and there was no significantly increased risk of CVD among production or maintenance workers. The risks did not increase with duration of work. The authors pointed out that the cohort was relatively young with a limited time of follow-up (867).

Friesen *et al*. further investigated mortality and cancer incidence in the cohort reported by Sim and coworkers (867). The cohort was limited to 4 316 men with full occupational histories. Mortality was investigated in relation to exposure to BaP, the benzene-soluble fraction, fluoride and inhalable dust. Exposure to BaP and the benzene-soluble fraction were used as index for exposure to CTPV. A large set of in-company measurements were used to develop a JEM, which was linked to the work histories of the subjects in the cohort. Ever exposure to CTPV or inhalable dust was not associated with a significantly increased mortality from CVD or CeVD. Contrasting high/medium to low/unexposed revealed no evidence of exposure-response relationships in the risk for CeVD, neither for CTPV nor for fluorides (310).

7.2.3 Markers of effect

Smelter workers at Söderberg pots exposed to high levels of air pollutants had slightly (non-significantly) higher levels of fibrinogen than those working with prebaked electrodes and exposed to lower levels of air pollutants (885).

7.2.4 Conclusion

There were around ten cohorts and one case-control study regarding mortality from CVD among electrolytic aluminium smelter workers. Findings were mixed. Three studies of high-exposed workers are especially informative since they used JEMs to estimate personal exposure. A large US study of eight plants showed an increased

risk of IHD (199, 702) and a Canadian study from British Columbia showed a smoking-adjusted increased risk of IHD in the highest class of cumulative exposure to BaP (312). A study from Quebec, Canada, showed an increased risk of CeVD but no excess of IHD (337).

Of the remaining studies, a Canadian case-control study showed a smoking-adjusted increased risk of IHD among workers involved in the Söderberg and prebake processes (954), three studies showed weak indications of an increased risk of circulatory diseases and five studies showed negative or inconclusive results.

One of the studies above showed that cumulative exposure to 111 $\mu g/m^3$ BaP-years was statistically significantly associated with an elevated risk of death from IHD (312). A cumulative exposure of 111 $\mu g/m^3$ BaP-years corresponds to an average exposure level of 2.78 $\mu g/m^3$ of BaP over a 40-year working life. $PM_{2.5}$ exposures of 0.26–1.47 mg/m^3 in US electrolytic aluminium smelter workers (estimated average exposure at class midpoint: 0.86 mg/m^3) were associated with a statistically significantly increased risk of IHD, but no further increase in risk was seen with higher exposure (702).

Risk estimates of CeVD were presented in seven studies of which only one showed an increased risk in the group with the highest cumulative exposure of BaP but with no significant trend (337).

There is *moderately strong evidence* for an association between exposure in electrolytic aluminium smelting and IHD.

7.3 Coke production

7.3.1 Occupational epidemiological studies

Bye *et al*. studied the mortality among 888 male Norwegian coke plant workers 1962–1992. A JEM was developed to classify the exposure to PAH and a number of other exposure factors. SMRs for IHD and CeVD were not significantly elevated versus the general male population of Norway. There was no evidence of exposure-response relationships in terms of cumulative exposure to PAH ($P > 0.3$). Group-level data on tobacco smoking indicated that the cohort members smoked less than the general population (135).

The mortality from CVD was lower than expected among 610 male coke oven workers in the United Kingdom (UK) followed to 1965. Death rates for England and Wales were used as reference. No analysis of exposure-response relationships was performed (213).

Hurley *et al*. reported the mortality in two British companies with 2 753 (Cohort I) and 3 885 (Cohort II) coke workers, respectively. Expected numbers were based on national death rates for Scotland, England and Wales. The death rates for IHD and CeVD were lower than in the reference population. A subgroup of oven workers, with higher exposure, showed a risk for IHD that was close to significantly elevated (SMR 1.11, $P = 0.06$). There was no relationship between duration of oven

work and risk. The proportion of smokers in the cohort was reported to be similar to that of manual workers in Britain in general (429).

Mortality was investigated in a cohort of 5 639 male Dutch coke plant workers employed 1945–1968 and followed until 1984. The mortality from circulatory diseases was not elevated, neither among the coke oven workers nor among by-product workers. National Dutch death rates were used to derive expected numbers of deaths. Exposure-response relationships were not investigated (926).

Chau *et al*. studied the mortality among 536 male French coke plant workers followed 1963–1987. There was a statistically significant excess of deaths from CVD in the cohort compared to the general male French population. However, a subdivision of the cohort with regard to proximity to the coke ovens showed no indication of higher risk among those working at the ovens than among the non-exposed or those working near the ovens (152).

The death rate from circulatory diseases among 538 male Italian coke plant workers followed from 1960–1990 was lower than in both the general Italian and local Tuscan populations (308). Exposure-response relationships were not investigated.

Lloyd *et al*. reported the mortality in 3 530 male coke plant workers in a large cohort of US steel workers followed 1953–1961. Overall, SMRs for heart disease and vascular damage to the central nervous system (CNS) were not significantly elevated among the coke plant workers compared to steel workers in general. No excess of deaths from heart disease was noted among the oven top-side workers, a group that showed a high risk to develop lung cancer from the oven gases, rich in PAH (572).

Epidemiological studies and risk estimates are presented in Appendix, Table A2.

7.3.2 Conclusion

Seven studies of coke plant workers were identified. A cohort of French workers showed a statistically significantly elevated risk of CVD, with no indication of an association between a crude dose measure (proximity to the ovens) and risk (152). In a study from the UK, there was an elevated risk of death from IHD of borderline statistical significance (P = 0.06) for the high-exposed oven workers (429). A study of US coke plant workers showed a very high risk of lung cancer among the oven workers but no excess of CVD, neither in total nor among the oven workers (572). Four other studies, of which one investigated exposure-response relationships, showed no evidence of an increased risk of CVD among coke production workers.

There is *insufficient evidence* for an association between exposure in coke production and CVD.

7.4 Coal gasification

7.4.1 Occupational epidemiological studies

Gustavsson and coworkers studied 295 male gas production workers in Stockholm, Sweden, employed 1965–1972 and followed 1966–1986. The mortality from both

IHD and CeVD was higher in the cohort than in the general population in the Stockholm County. The mortality from circulatory diseases was significantly elevated among those employed for more than 30 years as well as in the entire cohort after a long follow-up time (> 40 years). BaP was measured by area sampling on top of the ovens in 1964, showing an arithmetic average of 4.3 $\mu g/m^3$ of BaP (range 0.007–33 $\mu g/m^3$). Group level data on tobacco smoking habits did not indicate excess tobacco smoking in the cohort compared to the general male population (365).

Doll *et al*. studied two cohorts of in all over 16 000 male gas production workers in the UK, which were followed from 1953 (Cohort I) and 1957 (Cohort II) to 1965. The analysis was focused on lung cancer mortality. The death rates from arteriosclerotic and degenerative heart disease in Cohort I were lower than among men in England and Wales in general, both among high- and low-exposed subcohorts. In Cohort II, the death rates from arteriosclerotic and degenerative heart disease were higher in a high-exposed subcohort than in the general male population, but no testing of statistical significance was reported. The death rates from arteriosclerotic and degenerative heart disease in intermittently or low-exposed workers in Cohort II were similar to or lower than in the general population. No adjustment for tobacco smoking habits was made (236, 238).

Blot *et al*. reported the mortality up to 1997 among more than 50 000 male workers employed between 1971 and 1986 in a Californian gas and electricity production company. SMRs from heart disease and CeVD in the entire cohort were lower than in the reference population. In a subcohort of 513 generator gas workers, the SMR for heart diseases was lower than among the referents while the SMR for CeVD was close to 1 (111).

Epidemiological studies and risk estimates are presented in Appendix, Table A3.

7.4.2 Conclusion

Three studies of coal gasification workers were located. A cohort of male coal gas production workers in Stockholm, Sweden, showed an elevated risk of both IHD and CeVD compared to occupationally active men in the Stockholm County. The risk of circulatory diseases was statistically significantly elevated among those employed for more than 30 years (365). A large cohort of British coal gas production workers showed higher death rates from arteriosclerotic and degenerative heart disease in a high-exposed subcohort than in other gas workers and the general population, but no testing of statistical significance was reported (236, 238). A small cohort of coal gas production workers in the US showed no excess of heart disease or CeVD compared to the general population. Exposure-response relationships were not investigated (111).

There is *limited evidence* for an association between exposure in coal gasification and CVD.

7.5 Graphite electrode production

7.5.1 Occupational epidemiological studies

Gustavsson *et al*. studied a cohort of workers at a graphite electrode manufacturing company in Härnösand, Sweden. The cohort comprised 807 men and 94 women, employed between 1968 (when the production commenced) and 1988, and was followed for mortality 1969–1989. Expected numbers of deaths were derived from local (county) death rates. The numbers of deaths from IHD and CeVD were very small and close to the expected. The authors pointed out that the cohort was small, and time of follow-up limited (360).

The mortality in a cohort of 1 115 male workers at a French carbon electrode manufacturing company was reported by Moulin *et al*. Workers in employment 1957–1984 were included and expected deaths were derived from national statistics. There was a statistically significant deficit of deaths from circulatory diseases. Exposure to BaP was likely to be comparatively low, 15–740 ng/m^3 in 1983–1984 (677).

A cohort of 1 291 male workers employed 1950–1989 in a graphite electrode manufacturing company in Brescia, Italy, was followed for mortality 1950–1997. The number of deaths from circulatory diseases was lower than expected and there was no evidence of exposure-response relationships in terms of duration or association with time since first employment (635).

Donato *et al*. reported the mortality in a cohort of 1 006 male workers employed 1945–1971 in a graphite electrode manufacturing plant in Brescia, Italy. The cohort was followed 1955–1996. The number of deaths from circulatory diseases was lower than expected. Exposure-response relationships were not investigated. About half of the workforce was considered to be substantially exposed to PAH (240).

Teta *et al*. studied the mortality 1974–1983 among 2 219 white male workers employed in carbon electrode and special products operations for more than 10 years as part of a corporate wide mortality surveillance system in the US. Expected numbers were derived from national white male statistics. The SMRs were low for both circulatory diseases in general and for CeVD. In a cohort-internal analysis, the risk of death from circulatory diseases correlated positively and significantly with years of prior employment ($P = 0.02$), although this correlation was mainly caused by a low risk among those employed 10–19 years. The RR among those employed > 30 years was 1.1. A subdivision of the cohort in supervisory/office employees, crafts and operation/labourers (with assumed highest exposure) gave no evidence of higher risk in the highest exposed group (949).

A cohort of 332 male workers employed 1951–1974 in a Japanese graphite electrode manufacturing plant was followed for mortality 1951–1988. There were few deaths from CVD or CeVD, neither deviated significantly from the expected number derived from national Japanese statistics (671).

Epidemiological studies and risk estimates are presented in Appendix, Table A4.

7.5.2 Conclusion

There were six studies of graphite electrode manufacturing workers. None of the studies showed any excess of circulatory diseases in comparison with the general population, but several of them were small with low numbers of expected deaths. A large study from the US showed a statistically significant positive trend in the risk of circulatory diseases with prior years of employment. This was caused by an unusually low risk in the group with lowest number of years of employment, and the relation to occupational exposure was uncertain (949).

There is *insufficient evidence* for an association between exposure in graphite electrode production and CVD.

7.6 Chimney sweeping

7.6.1 Occupational epidemiological studies

A cohort of male Swedish chimney sweeps employed 1918–2006 was followed for mortality 1952–2006. Expected numbers were calculated from national statistics. There was a statistically significant excess of deaths from IHD (SMR 1.20, 95% CI 1.10–1.32), while the number of deaths from CeVD was lower than expected. A subcohort of chimney sweeps first employed after 1950 also showed a statistically significant excess of deaths from IHD. An analysis by duration of employment and time since first exposure showed no positive association with IHD or CeVD (453).

The same cohort of 4 436 men as above was followed by Gustavsson *et al*. for incident cases (both lethal and non-lethal) of MI 1991–2005, identified from a national register of in-patients diagnosed with MI. Expected numbers were based on similarly identified cases in skilled manual workers in the service sector in Sweden. There was a statistically significant excess of MI among the chimney sweeps, but the risk did not correlate with duration of employment (362).

Hansen *et al*. reported the mortality from IHD among 713 male Danish chimney sweeps identified from the Danish national 1970 census and followed 1970–1975. There were only 12 deaths from IHD, but this was statistically significantly more than expected, based on the reference population of Danish men identified from the same census (381).

Epidemiological studies and risk estimates are presented in Appendix, Table A5.

7.6.2 Conclusion

There were two cohorts of chimney sweeps, both showing an excess of IHD (362, 381, 453).

There is *limited evidence* for an association between chimney sweeping and IHD.

7.7 Asphalt paving

7.7.1 Occupational epidemiological studies

Burstyn *et al.* reported the mortality from IHD and CVD in a multicentre study of 12 367 male asphalt workers from Denmark, Finland, France, Germany, Israel, the Netherlands and Norway. The cohort included workers engaged in asphalt paving 1913–1999 from 217 companies. The earliest follow-up started in 1953 and the latest ended in 2000. Cohort-internal analyses of risk were performed. Exposure to BaP was quantitatively assessed from a model based on historical measurements of personal exposure, production characteristics and work organisation, and was organised in a JEM. Exposure to coal-tar bitumen was assessed semi-quantitatively and was a strong predictor of exposure to BaP. The risk of death (RR) from CVD increased with increasing average exposure to BaP and significantly so at average exposure levels of 68–105 ng BaP/m^3 versus the reference category of 0–68 ng/m^3 (P for trend < 0.001). In the highest exposure group (> 273 ng/m^3), the risk of death from CVD and IHD was increased, with RRs (95% CIs) being 1.58 (1.16–2.15) and 1.64 (1.13–2.38), respectively. There was also a positive trend in risk for both diagnoses with cumulative exposure, but weaker and not statistically significant. No individual data on tobacco smoking were available, but a sensitivity analysis indicated that it is not likely that the observed exposure-response associations were caused by confounding from tobacco smoking habits (134).

Further details are presented in Appendix, Table A6.

7.7.2 Conclusion

The only retrieved publication of asphalt pavers was a well-conducted multicentre study. The investigation showed an excess of CVD that correlated clearly with average exposure levels of BaP. There was an excess of CVD at exposures of 68–105 ng BaP/m^3 or higher (134).

There is *limited evidence* for an association between asphalt paving and CVD.

7.8 Tar distillation work, roofing and creosote work

7.8.1 Occupational epidemiological studies

A cohort of 255 male British tar distillation workers at four plants was followed for mortality 1967–1983. Expected numbers of deaths were derived from national statistics for England and Wales. The numbers of deaths from circulatory diseases in general, IHD, CeVD and diseases in arteries and veins were not statistically significantly elevated. An analysis of SMR in relation to time since joining the plant showed no evidence of an exposure-response relationship (595).

Swaen *et al*. studied 907 tar distillery workers and 866 roofers in the Netherlands. The cohort comprised male workers employed 1947–1980 and was followed for mortality 1947–1988. Expected numbers were calculated from Dutch national statistics. The mortality from circulatory diseases was below the expected in the tar

workers and equal to the expected in the roofers. Exposure-response relationships were not investigated (927).

A cohort of 5 939 US male roofers and waterproofers who were members of the trade union in 1960 was followed for mortality 1960–1971 and expected numbers were derived from national statistics. The numbers of deaths from heart disease and cerebrovascular lesions were below the expected and the risk showed no positive trend with years since joining the union (378).

Wong *et al*. studied 2 179 male and female workers at 11 US wood-treating plants using creosote. The cohort included workers employed 1979–1999 and was followed for mortality 1979–2001. The numbers of deaths from all heart diseases, IHD, endocardial disease, other heart disease and CeVD were all close to the expected and no statistically significant elevations were found. Increased duration of employment was not related to increased mortality for any of the diagnoses (1034).

Epidemiological studies and risk estimates are presented in Appendix, Table A7.

7.8.2 Conclusion

The few studies located, representing varying occupations and exposure circumstances, did not indicate any excess of CVD.

There is *insufficient evidence* for an association between tar distillation work, roofing or creosote work and CVD.

7.9 Diesel engine exhaust

7.9.1 General

Diesel engine exhaust is a complex mixture of gases and particulates produced during combustion of diesel fuels. The main components of the gas phase are nitrogen, carbon dioxide, water vapour, nitrogen oxides (NO_x) and carbon monoxide. These gases comprise over 99% of the mass of the whole diesel exhaust. Diesel exhaust particles (DEP) contain elemental carbon (EC), organic compounds, sulphates, nitrates, and trace amounts of metals and other elements. PAH and their oxygen and nitrogen derivatives comprise up to 1% of the particulate mass of untreated diesel exhaust. The composition of the exhaust varies, depending on the type, age and operational condition of the engine and on the exhaust after-treatment system. In comparison with pre-2005 diesel engines, exhaust from new technology diesel engines is characterised by a significant reduction of particle mass and EC, and an increased proportion of NO_2 of the total NO_x. EC comprises 30–90% of the particulate mass of pre-2000 diesel engine exhaust, with a typical proportion of 75% for heavy-duty diesel engines. By contrast, the average EC percentage of the particle mass emitted by heavy-duty diesel engines fulfilling the 2007 US emission standards was 13% (941). Nearly all of the mass emitted by diesel engines is in the fine particle range (< 2.5 μm) (495). Concentrations expressed as DEP in the

experimental studies below are therefore considered numerically equal to concentrations expressed as $PM_{2.5}$.

Some previous studies estimated the occupationally attributable mortality due to MI in Sweden (473) and IHD in Finland (719). Both studies included exposure to motor exhaust as a work-related risk factor for IHD and the attributable fraction was estimated to 3.5% for MI for Sweden (men and women combined) and 1.0% for men in Finland (based on disease risk from one US study).

7.9.2 Animal studies

DEP (0.5 mg) instilled intratracheally in rats induced an inflammatory response in the lungs, which reduced the time to thrombotic occlusion through increased platelet activation (935).

In atherosclerotic ApoE-/- mice, an increase in aortic lipid peroxides and macrophage accumulation was observed in atherosclerotic plaques after exposure to diesel engine exhaust at 300 µg DEP/m^3 or higher for 7 weeks (6 hours/day, 7 days/week). No significant effects were observed at 109 µg DEP/m^3 (142). In atherosclerotic ApoE-/- mice, oropharyngeal aspiration of DEP (35 µg of a standard reference material, SRM-2975, twice weekly for 4 weeks) induced pulmonary inflammation, increased atherosclerotic lesion size, produced more lesions per vessel and generated more buried fibrous connective tissue compared with controls (648).

Saa3 mRNA levels were increased in the lung tissue of mice exposed to DEP by inhalation (20 000 µg DEP/m^3, 4 days, 1.5 hours/day) (815).

A single intratracheal instillation of DEP (18, 54 or 162 µg) induced a strong neutrophil influx 1 and 3 days, but not 28 days post-exposure in mice. *Saa3* mRNA levels were increased at all time-point after the 162-µg dose (524).

As mentioned, new technology diesel engine exhaust contains drastically reduced DEP concentrations. In an inhalation experiment using diesel engine exhaust generated from a 2007-compliant diesel engine, male and female Wistar Han rats were exposed to air (control) or low, mid or high levels of diesel exhaust (0.1, 0.8 or 4.2 ppm nitrogen dioxide) for 16 hours/day, 5 days/week for 2 years. Evidence of exposure-induced effects was limited. Elevated plasma levels of soluble intercellular adhesion molecule 1 (ICAM-1) and IL-6 along with decreased plasma concentrations of total and non-HDL cholesterol were observed in females only (189).

7.9.3 Human experimental studies

Exposure of 6 healthy volunteers to diesel engine exhaust containing 300 µg DEP/m^3 for 2 hours gave a reduction of baseline brachial artery diameter of borderline statistical significance. No reductions were observed at exposures of 100 and 214 µg DEP/m^3 (965). In a double-blind crossover study, exposure of volunteers (10 healthy and 17 with metabolic syndrome) to diesel engine exhaust containing 200 µg DEP/m^3 for 2 hours elicited a decrease in brachial artery diameter with a smaller effect at 100 µg/m^3. There was an increase of endothelin-1 at 200 µg/m^3 but

not at 100 µg/m^3 (736). A transient increase in arterial stiffness was detected among 12 healthy volunteers after 1 hour of exposure to 330 µg DEP/m^3 (585).

Exposure to diesel engine exhaust containing 300 µg DEP/m^3 for 1 hour was associated with exercise-induced ST-segment depression in electrocardiogram (ECG) among 20 men with stable coronary artery disease (650).

7.9.4 Occupational epidemiological studies

Exposure to diesel exhaust among Swedish construction workers was associated with an increased mortality (SMR, 95% CI) from IHD (1.18, 1.13–1.24) and possibly from CeVD (1.09, 0.99–1.20) (967).

A cohort of Finnish men aged 25–64 years in 1980 was followed 1981–1994. Diesel exhaust exposed workers were compared with non-exposed workers. The RR (95% CI) for CVD mortality was 1.06 (1.00–1.14) and for CeVD mortality 1.12 (0.97–1.29). There was no difference between low-exposed workers (1.07, 0.95–1.20) and high-exposed workers (1.09, 0.95–1.24) regarding mortality from MI (1031).

A population-based case-control study of first-time MI conducted among Swedish citizens in the Stockholm County included 1 643 cases and 2 235 controls enrolled 1992–1994 (442). Working histories and data on potential confounders were collected by questionnaires and telephone interviews. Exposure to EC was assessed through a JEM. The risk of MI increased with maximum annual average exposure intensity (P for trend 0.034). The OR for MI among those with the highest average exposure intensity (> 42 µg EC/m^3, point estimate 87.5 µg/m^3) during the work history was 1.30 (95% CI 0.99–1.71), adjusted for smoking and alcohol habits. A series of parallel measurements of EC and $PM_{2.5}$ in motor exhaust exposed occupations in Stockholm (559) indicated that 87.5 µg EC/m^3 corresponds to around 330 µg/m^3 of $PM_{2.5}$. The risk decreased with time since cessation of exposure. Cumulative exposure of 0.2–0.7 mg EC/m^3-years (point estimate 0.42 mg/m^3-years) was associated with an OR of 1.25 (95% CI 0.96–1.63) for MI, adjusted for smoking and alcohol habits (442).

An increased mortality from IHD was observed among US transportation workers exposed to diesel engine exhaust in four trucking companies (SMR 1.49, 95% CI 1.40–1.59) (526). In an extension of this cohort, duration of employment correlated significantly with risk of death from IHD in long haul drivers and dockworkers. The trend was positive but less strong among pick-up and delivery drivers, mechanics, and hostlers, while it was negative among clerks (385).

A cohort of 62 800 men with self-reported occupational exposure to diesel exhaust was compared with 307 143 unexposed workers, all from the prospective American Cancer Society study, and was followed 1982–1984. The RRs were standardised by age, smoking and other occupational exposures. There was no increased risk for IHD (RR 0.98). There was a positive correlation between duration of exposure and the risk of CeVD; RRs (95% CIs) were 1.43 (0.89–2.29) for 1–15 years duration and 1.68 (1.06–2.66) for > 15 years duration (114).

A cohort of 12 315 workers exposed to diesel exhaust at eight US non-metal mining facilities was divided in 8 307 ever-underground workers and 5 848 surface-only workers. The mean respirable dust exposure was 1.9 mg/m^3 among underground workers and 0.7 mg/m^3 among surface workers. The corresponding mean exposures to respirable EC were 128 and 1.7 µg/m^3. State-based mortality rates were used for reference. The SMR (95% CI) for IHD was not increased among underground workers (0.97, 0.87–1.08) nor among surface workers (1.01, 0.88–1.14). The mortality from CeVD was not elevated. Exposure-response relationships were investigated for lung cancer only (52).

7.9.5 Previous evaluations

In 2016, NEG in cooperation with the Dutch Expert Committee on Occupational Safety (DECOS) evaluated diesel engine exhaust. The critical health effects were considered to be pulmonary inflammation and lung cancer. In addition, it was noted that human and animal inhalation studies showed an association between exposure to older technology diesel engine exhaust and CVD. Subjects with chronic CVD were regarded to be specifically sensitive to the health impacts of diesel exhaust exposure. Data from animal and human studies indicated that exposure to diesel engine exhaust may exacerbate pre-existing CVD, especially coronary artery disease (941).

The Swedish Agency for Health Technology Assessment and Assessment of Social Services recently reviewed the epidemiological literature on chemical occupational exposures and CVD (835). The reviewers concluded that there was moderately strong evidence for an association between occupational exposure to motor exhaust and development of heart disease.

7.9.6 Conclusion

In two controlled chamber studies, exposure for 1–2 hours to diesel engine exhaust containing 200–300 µg DEP/m^3 elicited a decrease in brachial artery diameter in healthy volunteers (736, 965), and exposure for 1 hour to diesel engine exhaust with 300 µg DEP/m^3 was associated with exercise-induced ST-segment depression in ECG among subjects with stable coronary artery disease (650). A transient increase in arterial stiffness was seen in healthy volunteers after 1 hour of exposure to 330 µg DEP/m^3 (585).

Out of five available cohort studies, four indicated an increased risk of CVD in association with exposure to diesel exhaust. A causal association is corroborated by a case-control study, showing an exposure-response association. Exposure to diesel exhaust of 87.5 µg EC/m^3 (LOAEC) or more was associated with an increased risk of MI (442). Based on parallel measurements by Lewné, this corresponds to around 330 µg/m^3 of $PM_{2.5}$ (LOAEC) (559). Human data are supported by animal studies showing that DEP exposure increases the formation of atherosclerotic plaques. Furthermore, DEP induce both acute phase response and pulmonary inflammation in mice.

Regarding CeVD, one study showed a significantly increased risk and two studies showed non-significant increased risks.

There is *moderately strong evidence* for an association between exposure to diesel engine exhaust and CVD.

7.10 Cooking fumes

7.10.1 General

Cooking, especially frying and grilling, generates air pollution, such as aerosol oil droplets, combustion products (including fine and ultrafine particles), organic gaseous pollutants and steam from the water contents of the food being cooked (165, 437, 875). A wide variety of organic compounds have been identified in cooking emissions, including alkanes, alkenes, acrolein, alkanoic acids, carbonyls, carboxylic acids, PAH and aromatic amines. Particles created during cooking may also have organic substances adsorbed on their surface, such as PAH (437). The levels and the chemical composition of cooking emissions vary depending on the cooking oils used, the temperature, the kind of food cooked, and the cooking method (228, 437, 874). Human exposure may occur by inhalation of cooking fumes, both in household and occupational cooking.

This presentation contains occupational studies among cooks and other restaurant workers. Studies on cooking at home were not included since they mainly investigated exposure from biomass and coal fuels for cooking and heating, which were not considered relevant with respect to occupational exposure to cooking fumes.

Epidemiological studies and risk estimates are presented in Appendix, Table A8.

7.10.2 Occupational epidemiological studies

In a Swedish cohort study (cohorts followed 1970–1995), an increased risk (SMR, 95% CI) due to IHD mortality was observed among both male (1.33, 1.12–1.56) and female (1.29, 1.20–1.37) cooks and cold buffet managers. An increased risk was also observed among male (1.55, 1.26–1.90) and female (1.21, 1.15–1.26) kitchen assistants as well as among male waiters and head waiters (1.23, 1.08–1.39), compared to all gainfully employed men or women. Waiters were identified as a similar socioeconomic group exposed to low levels of kitchen-generated air pollutants (880).

A case-control study in Sweden was carried out to estimate the RR (95% CI) of first MI in various occupational groups. Kitchen assistants were found to be one of ten occupations (in the 1970 and 1975 censuses) among Swedish women, but not men, with an increased incidence of MI (1.5, 1.0–2.1) during the period 1976–1984, compared to that of other employed. The excess risk did not persist after adjusting for socioeconomic group (1.4, 0.9–2.0). Female waitresses showed a decreased incidence of MI (377).

In a prospective cohort study of MI incidence among manual workers in the service sector in Sweden 1987–2005, female cooks, restaurant and kitchen assistants, and waiting staff all showed a statistically significant increase in risk (HR, 95% CI: 1.34, 1.21–1.48; 1.12, 1.03–1.21; and 1.25, 1.06–1.47, respectively). No increased risk was found among female cold-buffet managers. Among males, there was no statistically significant increase in risk for any of these occupations. The association was not more convincing for subjects working ≥ 5 years. Group level information on smoking habits showed a similar percentage of daily smokers among female cooks compared to female manual workers in general. The association with exposure to cooking fumes is uncertain because 1) no excess was found among male kitchen workers, and 2) female waiters showed a similar risk excess as female kitchen workers, although they were less exposed to cooking fumes (92).

In a Finnish study, the SMR (95% CI) for fatal MI 1971–1991 was increased among female (1.17, 1.06–1.31) but not male kitchen assistants, compared to other economically active women or men. The SMR (95% CI) for other IHD was increased for female, but not male, cooks and other kitchen staff (1.30, 1.11–1.54), kitchen assistants (1.40, 1.18–1.65) and restaurant waiters (1.54, 1.19–1.98). The mortality from CVD was increased among female kitchen assistants (1.13, 1.06–1.21) and female restaurant waiters (1.19, 1.07–1.33) (713).

A study on occupational mortality of women aged 15–59 years (in the period 1971–1981, related to their occupation as recorded in the 1971 census) in England and Wales showed an increased mortality of circulatory diseases among cooks compared to all employed women, as a result of a significant excess of mortality from IHD (SMR 3.60, 95% CI 1.55–7.09) (673).

Male British retired army cooks had elevated death rates (SMR, 95% CI) from IHD (1.42, 1.13–1.76) and CeVD (2.05, 1.22–3.24) compared to the national population, as well as compared to a referent group of other men retired from the army and supposed to have had a similar work situation regarding physical training and irregular hours (1.43, 1.01–2.02 and 2.17, 0.94–4.99, respectively) (183).

7.10.3 Conclusion

Most occupational studies supported a relationship between working as a cook or other kitchen worker and CVD, including MI or other IHD, but there was no evidence of exposure-response relationships. For CeVD, one study supported a relationship with exposure to cooking fumes and another did not.

There is *limited evidence* for an association between exposure to cooking fumes and CVD.

7.11 Second-hand smoke

7.11.1 General

Cigarette smoke contains at least 4 000 chemical compounds (890). Sidestream smoke may contain higher concentrations of some chemicals, e.g. aminophenyls, BaP and formaldehyde, than mainstream smoke (436). Exposure to second-hand smoke is sometimes referred to as environmental tobacco smoke (ETS) or passive smoking.

Smoking was recognised as a risk factor for CVD already in the 1950s. Most studies report a 1.5–2.5 times greater risk of CHD and stroke for smokers than for non-smokers (464).

The worldwide burden of disease from exposure to second-hand smoke was estimated from data from 192 countries. In 2004, 33% of male non-smokers and 35% of female non-smokers were exposed to second-hand smoke. This exposure was estimated to have caused 379 000 deaths from IHD and the loss of 2 836 000 disability-adjusted life-years in 2004 (1062).

7.11.2 Epidemiological studies

A US cross-sectional internet-based study (Health eHeart Study) comprised 4 976 participants from California, 2013–2014. Second-hand smoke was assessed through a validated questionnaire and prevalent atrial fibrillation was self-reported by 593 (11.9%) participants. Atrial fibrillation was validated by a subset review of electronic medical records. Participants who had a smoking parent during gestational development later showed an increased risk for atrial fibrillation (OR 1.37, 95% CI 1.08–1.73). Residing with a smoker during childhood was also associated with an increased risk of later atrial fibrillation (OR 1.40, 95% CI 1.10–1.79). These associations were more pronounced among patients without risk factors for atrial fibrillation (234).

7.11.3 Meta-analyses

A meta-analysis comprised 10 cohort and 8 case-control studies of non-smokers. The RR (95% CI) of CHD was 1.25 (1.17–1.32) among non-smokers exposed to second-hand smoke with no difference in risk between males and females. The risk of CHD was slightly higher after exposure to second-hand smoke at home (1.17, 1.11–1.24) than at work (1.11, 1.00–1.23) (392).

In all, 28 studies were included in a meta-analysis of second-hand smoke and stroke. Based on 39 sex-specific estimates, the meta-analysis gave an overall fixed-effect RR estimate of 1.23 (95% CI 1.16–1.31) with significant ($P < 0.05$) heterogeneity. There was no significant heterogeneity by sex, continent, fatality, disease endpoint or degree of adjustment for potential confounding factors. Risk estimates for stroke (RR, 95% CI) were less elevated in prospective studies (1.15, 1.06–1.24) than in case-control studies (1.44, 1.22–1.60) and cross-sectional studies (1.40, 1.21–1.61). A significant increase was not seen in studies that excluded smokers of any tobacco (1.07, 0.97–1.17), but was seen in studies that included pipe- or cigar-only smokers, occasional smokers or long-term former smokers. No elevation was

seen for haemorrhagic stroke. Eleven studies provided exposure-response estimates, the combined RR for the highest exposure level being 1.56 (95% CI 1.37–1.79). Many studies have evident weaknesses, recall bias and particularly publication bias being major concerns (547).

7.11.4 Previous evaluations

In 2010, a WHO working group concluded that it is a causal relationship between second-hand smoke and IHD, and suggested that an RR of 1.27 (95% CI 1.19–1.36) could be used to estimate the burden of disease caused by second-hand smoke exposure at home or at work. It was considered that stroke in relation to second-hand smoke exposure among non-smokers is biologically plausible, but that epidemiological evidence is currently inconsistent; the evidence of causality is less convincing than for IHD, but strongly suggestive (1061).

7.11.5 Conclusion

A large epidemiological database, including a WHO review (1061) and a meta-analysis (392), strongly supports an association between exposure to second-hand smoke and IHD. Another meta-analysis (547) supports an association between exposure to second-hand smoke and CeVD.

There is *strong evidence* for an association between exposure to second-hand smoke and CVD.

7.12 Firefighting and smoke from fires

7.12.1 General

Smoke from fires is composed of suspended liquid and solid particulate matter, gases and vapours generated from combustion or pyrolysis of various materials. The particles are initially microscopic in size (0.3–1.6 μm), but coalesce rapidly and thereby become visible. These particles have adsorbent properties and transport toxic compounds generated by combustion. Most polymers in buildings will burn or thermally degrade to more simple monomers during a fire. These monomers include e.g. ethene, acrylonitrile, styrene, methyl acrylate, ethyl acrylate, propene, vinyl chloride, vinyl acetate, chloroprene, phenol and isoprene. Burning of plastics produces large amounts of soot. Plastics generate higher levels of hydrogen cyanide, hydrochloric acid and acrolein than wood and fossil fuels in fires (438).

Particulate matter was generated during a peat wildfire event in eastern North Carolina, US. Wildland peat fires routinely produce high organic carbon levels (e.g. > 90% by mass of forest wildfire particulate matter). Because peat is made up of biologically decomposed organic materials, burning it produces organic aerosols that may include endotoxins and other biogenic substances (340).

Among firefighters, the exposure may vary widely depending on type of work activities, time spent at fires, and use of respiratory equipment. Firefighters are

exposed mainly by inhalation, but for some chemicals, such as PAH and PCBs, exposure through dermal absorption may also be important (438).

Carbon monoxide is a well-known constituent of smoke from fires and increased levels of COHb has consequently been found in the blood of non-smoking firefighters (574). Heart rate and COHb levels were monitored in firefighters during a search and rescue drill in a smoke-filled building. Carbon monoxide levels were 200–1 000 ppm. Heart rates increased to 90% of maximum for age within minutes, and COHb levels increased more than 1% per minute. The results show that exertion levels and therefore ventilatory rates may be so great during firefighting that COHb can rise to dangerous levels within minutes even at moderate or low levels of atmospheric carbon monoxide (353). Data on carbon monoxide are presented in Section 15.1.

7.12.2 Animal studies

Naeher *et al*. summarised animal studies and concluded that short-term inhalation of wood smoke can compromise pulmonary immune defence mechanisms important for maintaining host resistance against pulmonary infections. Moreover, a likely target for wood smoke induced immunotoxicity seems to be the alveolar macrophages. These immune cells, which serve as the primary defence of the deep lung, provide a link between the non-specific and specific defence systems of the respiratory tract (689).

Coarse particles obtained during the smouldering phase of a peat wildfire event induced strong lung inflammatory responses in mice as characterised by increases in bronchoalveolar lavage fluid proteins, cytokines, neutrophils and intracellular reactive oxygen species production. These responses were associated with organic coal and biological compounds [i.e. lipopolysaccharides (LPS) and endotoxins]. In contrast, ultrafine particles collected during the wildfire did not induce lung inflammation but caused cardiovascular effects in an ischaemia reperfusion injury model. These effects were associated with organic carbon content, because the ultrafine particles obtained during the smouldering, but not the glowing, phase had more than three times higher organic carbon content (340).

7.12.3 Epidemiological studies of firefighters

A cohort of 1 116 male firefighters employed for at least 1 year 1931–1983 in Stockholm, Sweden, was followed 1951–1986. The mortality (SMR, 95% CI) was lower than expected for circulatory diseases (0.84, 0.71–0.98), IHD (0.98, 0.81–1.17) and CeVD (0.71, 0.44–1.09). There were no clear relationships between years of employment or number of fires and IHD mortality. The mortality showed a tendency to be lower among firefighters with many episodes using self-contained breathing apparatus (970). Some years later, Swedish male firefighters were compared with other manual workers and the mortality from CVD tended to be lower than expected (1015).

A cohort of 11 691 male Danish firefighters was compared with a random sample from the employed population. The follow-up period started from the date of first

employment or 1 January 1977 and lasted until the end of 2014. Information on incidence of CVD was retrieved from the nationwide Danish National Patient Registry. The age- and calendar time-adjusted standardised incidence ratio (SIR, 95% CI) for CVD was increased (1.10, 1.05–1.15). The risk was also elevated for the most frequent outcomes, including angina pectoris (1.16, 1.08–1.24), acute MI (1.16, 1.06–1.26), chronic IHD (1.15, 1.06–1.24) and atrial fibrillation/flutter (1.25, 1.14–1.36). No significantly increased risks were observed for cerebral apoplexy (0.95, 0.86–1.05), transient ischaemic attack (1.12, 0.97–1.30), arteriosclerosis (1.02, 0.88–1.18) and arterial embolism/thrombosis (0.83, 0.58–1.19). Risks were almost always higher among full-time firefighters than among part-time/volunteer firefighters. The risks were lower during active employment as firefighters (733).

Employees of the city of Buffalo formed a cohort of 1 867 white male firefighters who had worked for at least 1 year 1950–1979 and were followed until 1979. Expected deaths were calculated from US national rates for white men. The mortality risks (SMR, 95% CI) were somewhat lower than expected for circulatory diseases (0.92, 0.81–1.04), atherosclerotic heart disease (0.92, 0.79–1.07) and all vascular lesions of the CNS (0.92, 0.64–1.27). By years of employment, SMRs for circulatory disease were 0.41 ($P < 0.05$), 0.71, 0.84, 1.00 and 1.10 after 1–9, 10–19, 20–29, 30–39 and ≥ 40 years of exposure, respectively. Corresponding SMRs for atherosclerotic heart disease were 0.51, 0.81, 0.83, 0.94 and 1.19 (1006).

US Boston firefighters, followed 1915–1975, showed a decreased mortality from circulatory diseases (SMR 0.86) (688). This finding was later confirmed by the longitudinal Normative Aging Study from Boston. Firefighters did not differ significantly from non-firefighters in the incidence of CHD (230).

US firemen, aged 25–59 years, from Connecticut, had an increased IHD mortality (SMR 1.52, 95% CI 1.23–1.81) (828). Also, firefighters from Philadelphia had an increased mortality from IHD (SMR 1.09, 95% CI 1.02–1.16) but not from CeVD. The IHD mortality tended to be higher among ladder company firefighters and among those hired before 1935 (62). Among firefighters from Florida, the mortality from CVD (SMR, 95% CI) was decreased in males (0.76, 0.66–0.86), but increased in females (3.85, 1.66–7.58) (592).

A cohort of 2 289 male firefighters employed by the Seattle Fire Department on or after 1 January 1945, and who had served for at least 1 year prior to 1 January 1980, was followed until the end of 1983. US white male rates were used for comparison because the large majority of the firefighters were white. There were 172 deaths from circulatory diseases (SMR 0.78, 95% CI 0.68–0.92). Except for firefighters with ≥ 30 years exposure, all subgroups had lower than expected mortality due to circulatory diseases. However, the SMRs increased uniformly with both time since first exposure and duration of exposure. Duration of exposure < 15, 15–29 and ≥ 30 years were associated with SMRs (95% CIs) of 0.63 (0.39–0.96), 0.75 (0.62–0.91) and 1.03 (0.75–1.38), respectively. After a restriction of the cohort to firefighters who had survived 30 years after first exposure, the positive relationship between duration of exposure and mortality due to circulatory diseases

remained; duration of exposure < 15, 15–29 and ≥ 30 years were associated with SMRs (95% CIs) of 0.56 (0.21–1.22), 0.80 (0.63–1.00) and 1.03 (0.75–1.38) (P trend < 0.10). The trend was also calculated with the lowest duration of exposure as referent; exposure durations of 15–29 years and ≥ 30 years were associated with risks (RR, 95% CI) of 1.42 (0.69–3.36) and 1.84 (0.87–4.41), respectively (403).

Totally 4 546 firefighters who were employed by the cities of Seattle, Tacoma, and Portland for at least 1 year between 1944 and 1979 were compared with US national rates. The mortality (SMR, 95% CI) due to IHD was less than expected based on US rates for white men. However, mortality due to diseases of the arteries, veins and pulmonary circulation was increased among firefighters who had worked for ≥ 30 years (1.33, 1.0–1.8) and among firefighters ≥ 65 years old (1.58, 1.1–2.1) (226).

Short-term death from CHD was studied among US firefighters from 1994 to 2004, excluding deaths associated with the terrorist attack on 11 September 2001. The odds of death from CHD during specific activities were compared with the odds during non-emergency duties. The ORs were 12.1–136 (sic) times higher during fire suppression, 2.8–14.1 times higher during alarm response, 2.2–10.5 times higher during alarm return, and 2.9–6.6 times higher during physical training. These ORs were based on three estimates of the time that firefighters spend on their specific duties and were all significant (P < 0.001) (474).

The mortality from circulatory diseases was increased among Toronto, Canada, firefighters aged 45–49 years (SMR 1.80, 95% CI 1.01–3.19) (69).

Eight Australian fire agencies supplied records of male paid firefighters from 1976 to 2003. The cohort included 17 394 full-time and 12 663 part-time firefighters and was compared with the mortality of the male Australian population. Follow-up lasted 1980–2011. The total cohort showed decreased mortality (SMR 95% CI) for all circulatory diseases (0.62, 0.55–0.70), IHD (0.68, 0.59–0.79) and CeVD (0.55, 0.39–0.77). There was no difference in mortality between full-time and part-time firefighters (343).

7.12.4 Exposure-response relationships

A cohort comprised 160 000 Australian male volunteer firefighters. Before joining as volunteer there was no formal fitness assessment and they were thus much less selected than paid firefighters. The volunteer firefighters had a reduced risk of mortality and cancer incidence compared with the general population, which is likely to be a result of a healthy-volunteer effect and, perhaps, lower smoking rates. However, volunteers who attended more than 576 fires had an increased relative mortality risk for IHD compared to volunteers who attended less than 220 fires (RR 1.86, 95% CI 1.07–3.23). The IHD mortality was also significantly increased for the sub-categories structural fires, landscape fires and vehicle fires (342).

7.12.5 Markers of effect

In a human experimental study, inhalation of wood smoke increased the levels of the inflammatory marker SAA, as well as factor VIII in plasma and the factor

VIII/von Willebrand factor ratio, indicating a disturbed balance of coagulation factors (64).

During the 1997 Southeast Asian forest fires, 30 males performing compulsory national service in Singapore were exposed to ~ 125 μg/m^3 of PM_{10} for 5 weeks. Their IL-1β and IL-6 levels in blood were increased compared with the post-fire period as an expression of an inflammatory response (937, 983).

Healthy conscripts, participating in a rescue educational course for firefighting, were primarily exposed to particulate matter in bystander positions. Firefighting training was associated with elevated urinary excretion of 1-hydroxypyrene, increased body temperature, decreased microvascular function and altered HRV. The authors concluded that altered effect markers were most likely due to complex effects from particle exposure, physical exhaustion and increased core body temperature (28).

7.12.6 Reviews

In 2011, the authors of a review of CVD in US firefighters concluded that CVD remains the leading cause of line of duty death among firefighters, 45% of on-duty fatalities. Firefighting activities include heavy physical exercise in combination with high ambient temperatures and exposure to air pollutants. Clinical epidemiological investigations have proven that on-duty CVD events occur almost exclusively among susceptible firefighters with underlying CVD. Consequently firefighters with known CHD or other clinically significant atherosclerotic endpoints should be restricted from participating in strenuous emergency duties (897) with or without heavy fire smoke exposure.

7.12.7 Epidemiological studies of the general population

Daily mortality and daily hospital admissions due to CVD were monitored in the Helsinki metropolitan area, Finland. Days significantly affected by smoke from vegetation fires between 2001 and 2010 were identified using air quality measurements at an urban background and a regional background monitoring station, and modelled data on surface concentrations of vegetation-fire smoke. Associations between daily $PM_{2.5}$ concentration and health outcomes were analysed using Poisson time series regression. All statistical models were adjusted for daily temperature and relative humidity, influenza, pollen and public holidays. On smoke-affected days, a 10-μg/m^3 increase in $PM_{2.5}$ was associated with a borderline statistically significant increase in CVD mortality among the total population at a lag of 3 days (12.4%, 95% CI -0.2% to 26.5%). In contrast, $PM_{2.5}$ on smoke-affected days was not associated with hospital admissions due to CVD. This study provides suggestive evidence for an association between exposure to long-range transported $PM_{2.5}$ from vegetation fires and CVD mortality. Hence, vegetation-fire originated air pollution may have adverse effects on public health over a distance of hundreds to thousands of kilometres from the fires (505).

The prolonged heat wave in Moscow, Russia, during the summer of 2010 triggered numerous wildfires leading to increased air pollution. The relative

increases in total mortality per 10-μg/m^3 increase of PM_{10} were 0.43% (95% CI 0.09–0.77%) at temperatures ≤ 18 °C, and 1.44% (95% CI 0.94–1.94%) at a temperature equal to 30 °C. CVD death was one of the pronounced proportions of total mortality (862).

In June 2008, burning peat deposits produced haze and air pollution, encroaching on rural communities of eastern North Carolina, US. A population-based study used emergency department visits as outcome parameter. Satellite data was used to determine a high-exposure window and distinguish counties most impacted by the dense smoke plume from surrounding referent counties. Poisson log-linear regression with a 5-day distributed lag was used to estimate changes in the cumulative RR. In the exposed counties, a significant increase in cumulative RR was observed for visits associated with heart failure (1.37, 95% CI 1.01–1.85) (773).

The relationship between particulate matter from forest fire smoke exposures, during a severe forest fire season in Melbourne, Victoria, Australia, and out-of-hospital cardiac arrest was studied. Totally, 174 "fire-hours" (i.e. hours during which Melbourne's air quality was affected by forest fire smoke) were identified during 12 days of the 2006/2007 fire season. There were 2 046 out-of-hospital cardiac arrests during the study period. During the fire season, men had greater increases in out-of-hospital cardiac arrests with interquartile range (IQR) increases in the 48-hour lagged $PM_{2.5}$ (8.1%, 95% CI 2.3–14.1%, IQR 6.1 μg/m^3) or PM_{10} (11.1%, 95% CI 1.6–21.5%, IQR 13.7 μg/m^3). There was no significant association between the rate of out-of-hospital cardiac arrests and air pollutants among women (229).

In another study of the wildfires in Victoria 2006/2007, $PM_{2.5}$ exposure was associated with increased risk of out-of-hospital cardiac arrests and IHD. After adjusting for temperature and relative humidity, an increase in IQR of 9.04 μg/m^3 in $PM_{2.5}$ over 2 days moving average (lag 0–1) was associated with a 7.0% (95% CI 1.0–13.3%) increase in risk of out-of-hospital cardiac arrests, with strong associations shown among men (9.1%, 95% CI 1.6–17.0%) and older adults (aged ≥ 65 years, 7.3%, 95% CI 0.2–14.8%). The increase in risk was 2.1% (95% CI 0.09–4.1%) for IHD-related emergency department attendance and 1.9% (95% CI 0.4–3.4%) for IHD-related hospital admissions at lag 2 days, with strong associations shown among women (3.2%, 95% CI 0.8–5.7%) and older adults (2.4%, 95% CI 0.8–5.7%) (372).

7.12.8 Conclusion

Several studies of health effects from wood fires in the general population showed short-term elevated mortality from CVD, and mechanistic studies showed effects on early markers of CVD.

Occupational studies of firefighters showed mixed results. The interpretation of occupational studies is hampered by potential confounding, both positive and negative. On one hand, firefighting is associated with high physical and ergonomic demands during rescue operations. The work can be mentally stressful and is often

associated with heat exposure. Many of these exposures are associated with CVD (358, 834). On the other hand, firefighters are often obliged to pass a regular physical examination test requiring a good cardiopulmonary capacity, see e.g. Tornling *et al*. (970).

The risk of CVD in Swedish firefighters was lower than expected (970, 1015), whereas a study of Danish firefighters showed an increased risk (733). Studies of firefighters from the US, Canada and Australia did not provide consistent evidence for an excess of CVD; several studies showed normal or low risks of CVD while increased risks were reported in five studies (69, 226, 474, 592, 828). A possible interpretation of the data is that a harmful effect of exposure to smoke is counter-balanced by a selection of physically fit individuals to the occupation.

There is *moderately strong evidence* for an association between exposure to smoke from fires and CVD.
There is *limited evidence* for an association between firefighting and CVD.

7.13 Other combustion-generated air pollutants

Estimations of quantitative data on personal exposure of combustion-generated respirable particles (other than motor exhaust) were used in a population-based case-control study of MIs 1992–1994 in Stockholm, Sweden. In total, 1 135 cases and 1 658 controls were identified. Lifetime history of occupations, work tasks, smoking and alcohol habits and several other potential confounding factors were obtained by questionnaire or telephone interview. Exposure to combustion-generated particles was assessed by an industrial hygienist, based on a JEM. ORs were adjusted for smoking and alcohol habits, hypertension, overweight, diabetes mellitus and physical inactivity at leisure time. The adjusted risk of MI increased monotonically and statistically significantly with both maximum and cumulative exposure to respirable combustion-generated particles. The second highest intensity of exposure to respirable particles (1.0–2.4 mg/m^3) during at least 1 year of work was associated with an increased risk (RR, 95% CI) of MI (1.42, 1.05–1.92) which increased further (2.11, 1.23–3.60) at the highest intensity of exposure ($\geq$ 2.5 mg/m^3). Trend analysis of exposure-response data revealed that an increase of respirable particle exposure with 1 mg/m^3 was associated with an increased risk of 1.24 (1.07–1.51). A cumulative exposure of $\geq$ 6.75 mg/m^3-years of respirable particles was associated with a significantly increased risk of MI (1.35, 1.02–1.79) (364).

The importance of particulate matter for CVD was demonstrated in a study evaluating the effect of a ban in 1990 on coal sales in Dublin, Ireland. Average black smoke concentrations in Dublin declined by 35.6 µg/m^3 (70%) and CVD mortality decreased by 10.3% (8–13%, P < 0.0001) after the intervention (173).

Exposure-response relationships for urban air pollution, second-hand smoke and active smoking (in terms of daily exposure of $PM_{2.5}$) and relative risk of CVD was presented by Pope *et al*. in 2009. The risk of CVD in the low-exposed (urban air

pollution and second-hand smoke) was considerably higher than that expected from linear extrapolation from the high-exposed (the active smokers). A log-transformation of exposure fitted the data much better. Thus, the study suggests that the exposure-response curve for combustion-generated particles is much steeper at low than at high exposures. Declining smoking-related risks among elderly participants were probably caused by competing risks and selection bias (756). It has been suggested that nicotine exposure contributes to down-regulation of inflammation via the cholinergic anti-inflammatory pathway (264).

7.14 Summary of exposure-response data

The epidemiological studies of occupational exposure to combustion-generated particles show partly inconsistent results.

The inconsistent findings cannot easily be explained by differences in exposure circumstances, because most occupations reviewed in this document represent occupations known to be associated with high exposure to combustion products and PAH. Possibly, the proportion of PAH present in the particle phase or gas phase is of importance. The evidence for causality is strengthened by the fact that studies using more detailed exposure estimates more often showed positive findings, and that several of these studies adjusted for smoking. Positive exposure-response relationships were demonstrated in a few studies.

An increased risk of IHD has repeatedly been reported among aluminium smelter workers. Positive finding were more consistently found in studies using personal exposure estimates, and several of the aluminium smelter studies presented smoking-adjusted risk estimates.

A large multicentre study of asphalt pavers using detailed exposure data found an increased risk of CVD and a clear exposure-response relationship (134).

Studies of coal gas production workers and chimney sweeps provide some (limited) support for an association between high exposure to PAH and IHD, while studies of coke plant and graphite electrode workers, roofers, tar workers or creosote workers do not.

Regarding exposure to motor exhaust (mainly diesel engine exhaust), the data show moderately strong evidence for a casual association with CVD, while studies of cooking fumes and firefighting, respectively, provide limited evidence for such an association.

Studies of exposure to second-hand smoke show strong evidence for an association with CVD.

A population-based case-control study demonstrated exposure-response pattern for occupational exposure to combustion products (other than motor exhaust) and MI, after adjustment for several relevant confounders including smoking. A cumulative exposure of ≥ 6.75 mg/m^3-years of respirable particles was associated with a significantly increased risk of MI (364). The average exposure in this exposure class can be estimated to 11.25 mg/m^3-years of respirable particles (982), which corresponds to an exposure level of 0.28 mg/m^3 over a 40-year working life.

Table 3. Summary of LOAECs from epidemiological and human experimental studies.

Exposure/effect	Estimated LOAEC			Reference
	BaP (µg/m^3)	$PM_{2.5}$ (mg/m^3)	EC (µg/m^3)	
Electrolytic aluminium smelting				
IHD mortality	2.78	0.86		(312, 702)
Asphalt paving				
CVD mortality	0.068–0.105			(134)
Diesel engine exhaust				
Decreased brachial artery diameter, 2-h exposure		0.2		(736, 965)
Exercise-induced ST-depression in subjects with stable coronary artery disease, 1-h exposure		0.30 [a]		(650)
Transient increase in arterial stiffness, 1-h exposure		0.33 [b]		(585)
MI incidence		~0.33 [c]	87.5	(442)
Combustion-generated particles (other than motor exhaust)				
MI incidence		0.28 (resp.)		(364)

[a] Median particle diameter 54 nm (range 20–120).
[b] Same engine, fuel and rotational speed as in previous study (650).
[c] Calculated based on Lewné *et al*. (559).
BaP: benzo(a)pyrene, CVD: cardiovascular disease, EC: elemental carbon, IHD: ischaemic heart disease, LOAEC: lowest observed adverse effect concentration, MI: myocardial infarction, $PM_{2.5}$: particulate matter with maximal aerodynamic diameter of 2.5 µm, resp.: respirable fraction.

There are data on levels of combustion-generated $PM_{2.5}$ from several epidemiological as well as experimental studies. These data show consistent LOAEC estimates, regardless of exposure source and study design. The human experimental studies indicate negative effects on the cardiovascular system starting at 0.2–0.3 mg/m^3 (584, 649, 735, 964). Also, two of the three epidemiological studies indicate a LOAEC of about 0.3 mg/m^3 (363, 441) while the third, addressing IHD mortality, indicate a LOAEC of 0.86 mg/m^3 (311, 701).

Taken together, both single human experimental exposures and epidemiological studies indicate that harmful effects from exposure to combustion-generated particles appear at 0.2–0.3 mg/m^3 as $PM_{2.5}$ (LOAEC). There were only two epidemiological studies using exposure estimates expressed as BaP (134, 311), and the relatively inconsistent findings allow no conclusions on LOAEC in terms of BaP exposure. LOAEC estimates are summarised in Table 3.

7.15 Conclusion

Several epidemiological and experimental studies show harmful effects on the cardiovascular system from exposure to combustion-generated particles ($PM_{2.5}$) at 0.2–0.3 mg/m^3.

There is *moderately strong evidence* for an association between exposure to combustion-generated particles and CVD.

8. Mineral dusts

8.1 Asbestos

8.1.1 General

The term asbestos includes a number of fibrous silicates. The two main groups are serpentine asbestos (curved fibres) comprising chrysotile, and amphibole asbestos (straight fibres) comprising crocidolite, amosite, antophyllite, tremolite and actinolite (432). All forms of asbestos cause mesothelioma and cancer of the lung, larynx and ovary (439). Non-asbestiform amphibole minerals are addressed separately (Section 8.1.9).

In Sweden, the import of asbestos rose sharply during the mid-1950s to a level of some 10 000 tonnes annually. The import continued to grow and a peak of 20 000 tonnes was reached in the early 1970s. There was a sharp and rapid decline in 1976 and a total ban of asbestos use was enforced in 1982 (253). All the Nordic countries banned asbestos before the year 2000 (475), the European Union (EU) in 2005 (19).

In 2018, the total mining production of asbestos worldwide was around 1.1 million tonnes. The leading producers were Russia (59%), China (9%), Brazil (9%) and Kazakhstan (20%) (975).

Epidemiological studies and risk estimates are presented in Appendix, Tables A9–A11, for asbestos cement workers, miscellaneous asbestos exposures and proxies for asbestos exposure (e.g. pleural plaques), respectively. Pleural plaques and diffuse pleural thickening are non-neoplastic abnormalities typically caused by asbestos exposure. The prevalence of pleural plaques was surveyed in the male adult populations in the 1970s and 1980s and were higher in Finland (6.8%) (1055) than in Uppsala County, Sweden (2.7%) (404) and Telemark, Norway (1.8%) (405).

8.1.2 Conversion of measurements of asbestos

With the exception of some of the earliest studies conducted for insulators, most of the measurement data presented below represent concentrations reported in units of fibres/cm^3 (ml). However, prior to around the late 1960s, the available analytical technologies were not capable of measuring asbestos fibres *per se*, but instead quantified total dust concentrations expressed as million particles per cubic foot (mppcf). These data represent collective counts of all fine, dry asbestos as well as non-asbestos particles such as other fibres and grains. Historical dust measurements were therefore likely to overestimate actual asbestos concentrations unless no other (non-asbestos) particles were present. Because the conversion of total dust particles to asbestos fibres could vary considerably, depending on the type of fibre and the kind of media from which the fibres were derived, no single conversion factor has been developed to compare these measures. In spite of this limitation, a widely used conversion factor when attempting to understand the significance of historical data is that 1 mppcf is approximately equal to 6 fibres/cm^3 (1023) (1 mppcf = 10^6 particles/cf = 10^6 particles/28 000 cm^3 = 36 particles/cm^3). This means that asbestos fibres constituted only a small fraction of the total dust.

Other conversion factors with ratios ranging from 1:1 to 1:10 (mppcf to fibres/cm^3) have been reported when working with different products or industries (1023). In a US study of workers manufacturing asbestos cement products from New Orleans, Louisiana, 1 mppcf corresponded to 1.4 fibres/cm^3 (427).

In order to study the relationship between count and mass, three industrial plants were investigated; an asbestos-cement sheet factory using chrysotile, an asbestos-cement pipe factory using chrysotile and crocidolite, and a chrysotile mining and milling plant. The gravimetric data for asbestos appeared to be largely dependent on the type of plant and, when a single plant was considered, on the working process involved. The highest values were generally found in the mining activities, the lowest in the production of asbestos-cement sheets. The conversion factors varied widely ranging from 400 to 4 900 fibres/µg (761).

In 1984, the US Committee on Nonoccupational Health Risks of Asbestiform Fibers presented relationships between different methods of measuring exposure to asbestos in the workplace. By light microscopy, 1 mg asbestos/m^3 corresponds to 30 fibres/cm^3, which is equivalent to 30 fibres/ng. By electron microscopy, 1 mg asbestos/m^3 corresponds to 2 000 fibres/cm^3 equivalent to 2 000 fibres/ng (188).

8.1.3 Animal studies

Atherosclerosis-prone ApoE-/- mice who inhaled around 5 mg/m^3 chrysotile asbestos fibres, 6 hours/day for 30 days had approximately 3-fold larger atherosclerotic lesions than similar asbestos-exposed ApoE-/-/CD4-/- double-knockout (DKO) mice. Lung inflammation and the magnitude of lung fibrosis assessed histologically were similar in asbestos-exposed ApoE-/- and DKO mice. Monocyte chemoattractant protein-1 (MCP-1) levels were increased in bronchoalveolar lavage fluid and plasma, and plasma concentrations correlated with lesion size ($P < 0.04$) in asbestos-exposed ApoE-/- mice. At 9 days, activator protein-1 (AP-1) and nuclear factor kappa B (NFκB), transcription factors linked to inflammation and found in the promoter region of the *MCP-1* gene, were increased in aortas of asbestos-exposed ApoE-/- but not DKO mice. The authors concluded that the degree of lung inflammation and fibrosis does not correlate directly with cardiovascular effects of inhaled asbestos fibres and that these findings support a critical role of CD4+ T-cells in linking fibre-induced pulmonary signalling to consequent activation of *NFκB*- and *AP-1*-regulated genes in atherogenesis (320).

Rats receiving two intratracheal instillations of 2 mg of amosite asbestos with an interval of 1 week showed marked perivascular and interstitial cardiac fibrosis after 6 months (119).

Libby amphibole asbestos (Montana, US) was intratracheally instilled in four strains of rats. Amphibole asbestos reduced adenosine diphosphate (ADP)-induced platelet aggregation and decreased circulating platelets in Wistar Kyoto (WKY) rats (1 mg/animal) and Fischer 344 rats (5 mg/animal) at the 3-month time-point but not in spontaneously hypertensive (SH) (1 mg/animal) or spontaneously hypertensive heart failure (SHHF) (1 mg/animal) rats. Aorta mRNA expression for biomarkers of oxidative stress (haem oxygenase-1 and lectin-like oxidised low-density

lipoprotein receptor-1), inflammation (macrophage inflammatory protein-2) and thrombosis (tissue plasminogen activator, plasminogen activator inhibitor-1 and von Willebrand factor) were increased at baseline in SHHF rats relative to WKY rats. The amphibole exposure upregulated several of these biomarkers and also those involved in aortic contractility of WKY rats at 3 months, suggesting thrombogenic, vasocontractile and oxidative stress-mediated impairments. The aorta changes in Fischer 344 rats were less remarkable than in WKY rats. The authors concluded that exposure to amphibole decreased circulating platelets and platelet coagulability while increasing the expression of oxidative stress, thrombosis and vasoconstriction biomarkers in the aorta of healthy rats. These changes were similar to those noted at baseline in SH and SHHF rats, suggesting that amphibole-induced pulmonary injury might increase the risk of developing CVD in healthy individuals (857).

8.1.4 Occupational epidemiological studies

8.1.4.1 Asbestos cement work

Mortality from CVD among asbestos cement workers has been studied in Sweden (14, 723), Denmark (767), England (326), Poland (934), Italy (579, 632, 765), Greece (865), the US (427) and Canada (293). Almost all studies compared the mortality of asbestos-exposed workers with national or regional rates. No significant increased risks of CVD were observed. No increased risk of heart disease and no clear exposure-response relationship were observed in a Swedish study comparing asbestos cement workers with industrial workers (14).

8.1.4.2 Miscellaneous asbestos exposures

In the Great Britain Asbestos Survey, mortality was studied during 1971–2005 among 98 117 asbestos workers undergoing regular medical examinations. The mortality was increased (SMR, 95% CI) due to IHD (1.40, 1.36–1.44) and CeVD (1.64, 1.54–1.74). The number of deaths from IHD was 4 183 (383). This cohort was further analysed and a significant relation was found between duration of exposure and IHD. The interaction between duration of exposure to asbestos and smoking implied that the mortality rate was positively associated with duration of exposure among never and former smokers, but there was a negligible increase in risk with duration of exposure among current smokers (382).

Asbestos stripping and removal workers were part of the British cohort described above, and 52 387 workers were followed 1971–2005. A subgroup of 31 302 stripping/removal workers completed a questionnaire and a positive exposure-response relationship was found between the number of weekly hours spent stripping and mortality (RR) from circulatory disease and IHD (317).

A cohort of 3 211 men first employed 1933–1974 at a Rochdale asbestos textile factory was followed until 1983. A small but not significantly increased mortality due to circulatory disease was observed when the cohort was compared with death rates for England and Wales (SMR 1.15) and for Rochdale (SMR 1.18) (744).

A cohort of 952 workers first employed 1930–1965 in a chrysotile asbestos mine in Northern Italy was followed until 1975. An increased mortality due to CVD was recorded (SMR 1.48, $P < 0.01$) when the cohort was compared with Italian national rates (806).

Enterline and coworkers reported the mortality of 1 074 white men who retired from a US asbestos company during the period 1941–1967. The participants were exposed during production or maintenance and were followed until 1980. An increased mortality due to CHD was observed (SMR 1.12, $P < 0.05$) when the cohort was compared with US national rates (259).

A US cohort of 1 130 former workers in Tyler, Texas, that manufactured asbestos pipe containing amosite insulation material was followed until 1993. An increased risk of CeVD mortality was found (SMR 2.21, 95% CI 1.17–3.77) (555).

Totally 5 770 US workers, employed 1950–1973 in any of four plants in North Carolina that produced asbestos textile products, were followed through 2003. An increased mortality due to diseases of the heart was found (SMR 1.32, 95% CI 1.22–1.42) compared to the national population (576).

An increased mortality due to diseases of the circulatory system was found among white male textile workers exposed to chrysotile in the US (SMR 1.25, $P < 0.05$). Smoking habits were about the same as in the control group of US men (224). The cohort was expanded to contain altogether 3 072 workers and was followed through 2001. Increased risks (SMR, 95% CI) of IHD (1.20, 1.10–1.32) and CeVD (1.29, 1.08–1.53) were observed (396).

Libby, Montana, US was the site of a vermiculite mining and processing operation from the 1920s to 1990. Although pure vermiculite causes no known adverse health effects, Libby vermiculite was contaminated with a mixture of amphibole fibres (mainly tremolite). By using a within-cohort comparison, a significantly increased CVD mortality was observed in workers exposed to levels ≥ 44 fibres/ml-year compared with workers exposed to < 1.4 fibres/ml-year (RR 1.5, 95% CI 1.1–2.0). Smoking status was an unmeasured confounder, but adjustment for assumed differences in smoking habits had a minimal effect on the risk estimate (539).

A cohort of 1 932 chrysotile asbestos miners in China who had worked at least 1 year 1981–1988 was followed until 1 June 2010. The cohort was divided in two groups, exposed (miners, blasters, mechanics, maintenance and transport workers) and controls (not directly asbestos exposed workers; management and service workers). The mortality due to CVD was slightly increased among the exposed when compared with national rates (SMR 1.27, 95% CI 0.96–1.63) and also when compared with internal controls (RR 1.30, 95% CI 0.79–2.14 after adjustment for gender and smoking habits). The corresponding CeVD mortality was increased compared with national rates (SMR 1.38, 95% CI 1.03–1.79) and also when compared with internal controls (RR 1.75, 95% CI 1.00–3.08 after adjustment for gender and smoking habits). Mortality from pulmonary heart disease was also significantly increased (SMR 2.70) (242).

A cohort of 586 male and 279 female workers from a Chinese chrysotile textile factory was prospectively followed for 37 years, 1972–2008. Vital status was identified, and the date and underlying cause of death were verified from death registry. Cause-specific SMRs by gender were computed with nationwide gender- and cause-specific mortality rates as reference. There were significant increases of asbestosis in both genders and a significant increase of lung cancer among male workers. Pulmonary heart disease was increased (SMR, 95% CI) among men (13.1, 9.5–18.1) and women (8.3, 2.3–30.4). There was no increased mortality from other diseases of the heart (men: 0.9, 0.5–1.4 or women: 1.0, 0.4–3.0) or from CeVD (men: 1.0, 0.7–1.5 or women: 0.3 based on 1 case) (987).

A total of 1 106 crocidolite-exposed workers were selected from the workforce of the asbestos industry in Western Australia. Pleural thickening was a risk factor for death from other causes than asbestos-related diseases (RR 1.5, 95% CI 1.3–1.8) and IHD formed the largest proportion of deaths from these other causes. Pleural thickening had a greater effect on mortality from diseases of other causes (IHD) than asbestos-related diseases (217).

Some studies applied pleural plaque or asbestosis as proxy for asbestos exposure (Appendix, Table A11). Calcified pleural plaques were more common among 148 coronary patients (35%) than among 100 lung cancer patients (19%) chosen as referents. The RR of calcified pleural plaques was 2.2 (95% CI 1.4–3.3) adjusted for age and gender (507).

IHD was studied in a cohort of 1 725 Swedish male shipyard workers exposed to asbestos. Men with pleural plaques had a non-significantly increased risk (RR, 95% CI) of IHD compared to men without pleural plaques (1.3, 0.8–2.0) after stratification for age and smoking habits. In addition, men with asbestosis or suspected asbestosis had a significantly higher risk of dying from IHD than men without asbestosis (3.1, 1.5–6.4), after stratification for age and smoking habits (825).

A cohort of about 11 000 men born 1891–1920 and employed for at least 1 month in the chrysotile mines and mills of Quebec was followed until 1988 (619). One part of this large cohort comprising 4 559 men was followed regarding radiological findings, and workers with abnormal signs were compared with workers with normal radiological examinations. Uncalcified pleural changes were associated with an increased mortality risk for diseases of the heart (RR 1.54, $P < 0.005$). Pleural calcifications were also associated with a somewhat increased risk of heart diseases (RR 1.34, $P < 0.10$) (564).

8.1.5 Case reports

Pericardial lesions including parietal pericardial plaques (212, 971) and constrictive pericarditis (212, 295) have been observed 20–30 years after asbestos exposure. One study indicated that non-ischaemic myocardial fibrosis is more common among patients with asbestosis (503).

8.1.6 Meta-analyses

Totally 16 studies were included in a meta-analysis of asbestos exposed cohorts investigating CVD. The combined result from all studies indicated an increased risk (SMR, 95% CI) for CVD (1.11, 1.01–1.22). The outcome varied between different subdiagnoses, namely pulmonary heart disease (2 studies; 4.13, 1.55–10.98), circulatory diseases (9 studies; 0.99, 0.88–1.11), all heart diseases (4 studies; 0.99, 0.86–1.14) and IHD (7 studies; 1.04, 0.82–1.32). The mortality from CVD varied with type of asbestos exposure. The SMRs (95% CIs) were increased among workers exposed to chrysotile (1.23, 1.07–1.41) and amphibole (1.26, 1.02–1.56) except among crocidolite exposed workers (0.80, 0.74–0.86). Among chrysotile exposed workers, the highest risks of CVD mortality were seen in asbestos textile workers, whereas miners and cement production workers had lower risks. Studies of chrysotile exposed workers in developing countries like South Africa and China showed higher SMRs than studies in Europe or North America. This difference reflects higher fibre concentrations in the work environment in developing countries. Many comparisons in this meta-analysis showed significant heterogeneities (795).

8.1.7 Exposure-response relationships

In the study reported by McDonald and coworkers, IHD was more common among those exposed to levels ≥ 300 mppcf-years of asbestos (SMR 1.24) than among those exposed to < 30 mppcf-years (SMR 0.92) (619). In approximately the same cohort, workers exposed to levels ≥ 300 mppcf-years had an increased mortality of heart disease compared to unexposed workers (RR 1.57, X^2 27.90, $P < 0.001$) (564).

In the cohort of British asbestos workers undergoing regular medical examinations, a significant relationship was found between duration of exposure and IHD (382). In a subgroup comprising stripping and removal workers, a relationship was found between the number of weekly hours spent stripping and mortality (RR) from circulatory disease and IHD (317).

Totally 1 862 Libby vermiculite workers were exposed to amphibole fibres, mainly tremolite because the vermiculite was contaminated with such fibres. By using a within-cohort comparison, a clear relationship was demonstrated between cumulative fibre exposure and CVD mortality. The mortality was significantly increased over the exposure groups 1.4 – < 8.6, 8.6– < 44.0 and ≥ 44 fibres/ml-year ($P = 0.067$) compared to workers exposed to < 1.4 fibres/ml-year. Risk estimates (RR, 95% CI) were 1.3 (1.0–1.6), 1.3 (1.0–1.6) and 1.5 (1.1–2.0) (539).

8.1.8 Markers of effect

Non-smoking patients with asbestosis were compared with healthy non-smoking controls. The asbestosis patients had significantly increased serum levels of the inflammatory markers CRP and IL-6 (551).

Among 505 asbestos-exposed construction workers, a slight but significant relationship was found between CRP and pleural calcifications, a marker of asbestos exposure (995).

Totally 584 asbestos-exposed construction workers were screened with computed tomography. Paraseptal emphysema and bullae in the lungs were both significantly associated with CVD (997). In a similar study, 633 asbestos-exposed workers were investigated with high-resolution computed tomography and followed on average 8 years. Emphysema and visceral pleural abnormalities were both significantly associated with CVD (996). The relationship between pleural plaques and CVD was probably not possible to investigate as almost all participants had parietal pleural abnormalities.

The cardiac autonomic nervous system was investigated by the time domain HRV and its correlation with lung function tests in patients with pleural disease caused by asbestos exposure. Patients with restrictive pulmonary disease had cardiac autonomic dysfunction, which correlated with the severity of restriction. This was thought to be the result of chronic hypoxia, pulmonary hypertension and right ventricular enlargement (734).

Human pulmonary epithelial cells cultured in the presence of asbestos crocidolite produced a dose-dependent increase in the secretion of IL-6 (590).

8.1.9 Taconite mining (non-asbestiform amphiboles)

Mining and processing of taconite iron ore result in potential exposure to non-asbestiform amphibole and non-amphibole elongate mineral particles (EMP), respirable silica (quartz) and dust. The term EMP refers to any mineral particle of inhalable size with a minimum aspect ratio of 3:1. Mortality was evaluated 1960–2010 in a cohort of Minnesota taconite mining workers employed by any of the seven companies in operation in 1983. The cohort including 31 067 workers with at least 1 year of employment was compared with the Minnesota population. Mortality (SMR, 95% CI) from CVD (1.10, 1.06–1.14), specifically for hypertensive heart disease (1.81, 1.39–2.33) and IHD (1.11, 1.07–1.16) was higher than expected. Also mortality from mesothelioma was found to be higher than expected (SMR 2.77, 95% CI 1.87–3.96) (18). Previous smaller cohort studies of Minnesota taconite miners and millers did not demonstrate increased risks of CVD (192).

8.1.10 Conclusion

Approximately ten epidemiological studies provide support for an association between asbestos exposure and CVD. Of these, two studies supported a relationship between asbestos exposure and pulmonary heart disease (*cor pulmonale*) (242, 987) and four cohorts demonstrated a relation to CeVD (223, 242, 383, 396, 555). A meta-analysis of 16 studies showed an increased risk of CVD (795).

Asbestosis or pleural plaques were significantly related to heart disease in five studies (159, 507, 564, 825, 996).

Two cohorts exhibited an exposure-response relationship between asbestos exposure and CVD (539, 564, 619) and the results from another cohort supported a relation between duration of exposure and IHD (382). A cumulative exposure of 1.4–8.6 fibres/ml-year was associated with an increased mortality from CVD (539).

This cumulative exposure corresponds to 0.04–0.2 fibres/ml during 40 years of exposure.

There is *strong evidence* for an association between exposure to asbestos and CVD.

8.2 Crystalline silica

8.2.1 General

Crystalline silica (silicon dioxide) is an abundant mineral that makes up the earth's crust. It is found in sand, rock and mineral ore. Inhalation of respirable crystalline silica dust such as quartz, cristobalite and tridymite can cause silicosis, a fibrotic lung disease. Occupational exposures to respirable-sized silica particles include mining, quarrying, drilling and sand-blasting activities (955).

8.2.2 Animal studies

Intratracheal instillation of quartz (0.125 mg) in rats induced a clear, transient pulmonary inflammation with a marked influx of cells. There was an increase of both pulmonary and plasma CRP levels and an impairment of fibrinolytic function (935). In hamsters, intratracheally instilled crystalline silica particles (0.02 and 0.2 mg) triggered pulmonary inflammation, together with stimulation of peripheral platelet-rich thrombus formation. This activation may predispose platelets to initiate thrombotic events on mildly damaged blood vessels (701).

8.2.3 Occupational epidemiological studies

Epidemiological studies and risk estimates are presented in subgroups of miners, coal miners, other crystalline silica-exposed workers and silicotics (Appendix, Tables A12–A13). Foundry workers have been excluded due to their complex exposure, including PAH, silica, carbon monoxide and noise.

Several studies of silica-exposed workers observed a decreased mortality of IHD (154, 177, 178, 349, 512). However, many other studies observed an increased mortality of IHD among miners and industrial sand workers, some of which compared to the general population.

8.2.3.1 Mining

A cohort from North Karelia in Finland comprised 597 miners employed for at least 3 years in a copper mine or a zinc mine. The excess mortality was mainly due to IHD; 44 observed deaths versus 22.1 and 31.2 expected, based on the general Finnish and the North Karelian ($P < 0.05$) male population, respectively (12).

Male miners, well borers, dressing plant workers, and other mine and stone workers were identified in the Swedish National Census of 1970. The cohort was followed from 1970 until the end of 1995 and linked to the Cause of Death Register. The referent group comprised all gainfully employed men identified in the same census. An increased IHD mortality (SMR, 95% CI) was observed among miners

(1.3, 1.2–1.4), well borers (1.3, 1.1–1.5), dressing plant workers (1.4, 1.2–1.7) and other mine and stone workers (1.4, 1.2–1.5) (1000).

A case-control study of 22 689 male patients with first MI in former West Germany showed an increased risk among miners (RR 1.97, $P < 0.001$) (117).

US gold miners (n = 3 328) in South Dakota who had worked underground for at least 1 year 1940–1965 were followed until 1990. They were exposed to silica and non-asbestiform amphibole minerals. Prior to 1950 the dust contained approximately 13% crystalline silica. There was a slightly decreased risk for IHD (SMR 0.94, 95% CI 0.85–1.03) when compared with US referent rates. However, in an analysis based on multiple cause mortality, an increased mortality due to myocardial degeneration was observed among workers hired prior to 1930 (SMR 9.2, 95% CI 5.1–15.2) (907).

Totally 3 971 white South-African gold miners at work on 1 January 1970 were identified and followed until the end of 1978. At entry in the study the age of the workers was 39–54 years. An increased mortality of IHD was found (SMR 1.15, 95% CI 1.00–1.32). A case-control analysis was conducted comprising the miners who had had at least 85% of their service in gold mines. Two referents per case were selected randomly from the miners born in the same year as the case and who survived the case. Ten years of underground mining was associated with an RR of 1.5 ($P = 0.004$) for IHD after adjustment for smoking, systolic blood pressure and BMI (1041). This cohort was enlarged to totally 4 925 white miners and was further followed until the end of 1989. The SMR for IHD mortality was now 1.24 (95% CI 1.15–1.34). However, the relationship between underground mining and IHD was no longer observed (776). With an increased follow-up time, the proportion of currently exposed miners will decrease due to retirement by age and the number of non-exposed will increase. This may explain the difference between short- and long-term follow-up. Such risk reduction would be analogues to the decreased risk for IHD observed among ex-smokers (237).

A large cohort comprised 68 241 metal miners as well as pottery workers from south central China who were employed 1972–1974 and followed until 1989. Age-, sex-, and cause-specific national death rates were used to calculate the expected numbers of death. There was an increased mortality (SMR, 95% CI) due to IHD (1.25, 1.05–1.45), hypertensive heart disease (3.30, 2.68–4.02) and pulmonary heart disease (5.81, 5.38–6.26). Smoking habits were unlikely responsible for this risk as the mortality from lung cancer was lower than expected (SMR 0.8, 95% CI 0.7–0.9) (155).

A subgroup of this cohort comprising 7 837 workers from four tin mines were followed through 1994. The SMRs (95% CIs) were 0.77 (0.65–0.90) for CVD and 1.15 (1.00–1.33) for CeVD. Cumulative dust-exposure did not show a clear relationship with the occurrence of CVD (164). In some mines, the dust contained arsenic which probably influenced the relationship between dust exposure and lung cancer and may also have confounded the relation with CVD.

8.2.3.2 Coal mining

Coal mining generates coal-containing particles but also quartz dust and nitrogen oxides from blasting operations (668). Some studies showed an increased risk of IHD among coal miners. Enterline reviewed data for American coal miners in 1972. Group life insurance data showed a higher mortality among workers in the coal mining industry than among workers in other mining industries. In 1967, the Society of Actuaries published SMRs from 44 industries and the highest total mortality was found among coal miners. In the three cohort studies mentioning CHD, increased SMRs (1.09–1.44) were observed (257). Working coal miners from US Appalachia had a decreased risk of IHD (SMR 0.69) based on regional rates, in contrast to non-working coal miners (SMR 1.02). The higher SMR for the latter may be explained by retirement because of ill health (198). This observation was, however, not supported in a study of 23 000 US coal miners covered by the United Mine Workers Health and Retirement Funds. Time of follow-up was 1959–1971. Non-pensioners and pensioners had SMRs due to major CVD of 1.00 and 0.92, respectively (788).

The mortality of coal miners and non-miners was studied in Rhondda Fach, Wales. Mortality due to IHD and other circulatory diseases was less common among miners with the most complicated coal workers' pneumoconiosis (Category A, B or C) than among workers with less severe pneumoconiosis, no pneumoconiosis or non-miners (179). In contrast, Dutch coal miners had an increased mortality due to IHD. These workers were rather heavily exposed as most of the miners had radiological manifestations of coal workers' pneumoconiosis (630). A later study of 17 820 coal workers from ten British collieries did not show any clear evidence of an association between exposure and IHD (646).

A more recent study comprised 8 971 US coal miners from anthracite and bituminous regions. In the anthracite region, the IHD risk was highest in the second quartile of cumulative exposure while the risk decreased in the highest quartile of exposure. This pattern was probably due to the effect of competing risk from pneumoconiosis mortality, which was much higher in the anthracite region than in the bituminous regions. The HR regarding IHD increased with increasing cumulative coal dust exposure in the bituminous regions, after adjustment for age, BMI and smoking. Cumulative coal dust exposures of 20–63.5, 63.6–97.4 and > 97.4 mg/m^3-years were associated with HRs (95% CIs) of 1.58 (1.09–2.30), 1.81 (1.23–2.66) and 1.92 (1.29–2.86), respectively (529).

8.2.3.3 Miscellaneous silica exposures

Out of 4 626 industrial sand workers exposed to crystalline silica, 330 died due to IHD. The calculated SMR was 1.22 (95% CI 1.09–1.36) (910). This increase seemed not to be explained by smoking (879).

A Swedish case-control study comprised 26 847 men with first MI. For each case, two controls were selected from the study base through random sampling, stratified by age, county and socioeconomic group. The occupation with the second highest

risk for a first MI was stonecutters and carvers (RR 1.9, 95% CI 1.1–3.4). This high risk could not be explained by differences in smoking habits alone (377).

In a cohort of 17 644 porcelain production workers in Germany, there was no increased mortality due to diseases of the circulatory system (SMR 1.00 for men and 0.83 for women). However, in a Bavarian subcohort, males had an increased risk (SMR 1.17, 95% CI 1.05–1.31), whereas females did not (SMR 1.03, 95% CI 0.85–1.23) (96).

Mortality was studied among 2 924 white male and 946 white female members of the International Brotherhood of Potters and Allied Workers in the US who died 1955–1977. These workers were exposed to dust particles during the production of ceramics. The basic raw materials used in the pottery industry contained quartz, silica, silicates, mica, feldspar, oxides of iron and carbonates of calcium and magnesium. During the latest 20–30 years the use of some fibrous materials such as talc increased. The PMR regarding IHD was significantly increased for both men (1.07, $P < 0.01$) and women (1.17, $P < 0.01$) (956).

Swedish construction workers exposed to inorganic dust showed an increased risk of IHD (RR 1.07, 95% CI 1.03–1.12) after adjusting for age, smoking, hypertension and BMI. However, the inorganic dust was a mixture of asbestos, cement dust, concrete dust, man-made mineral fibres (MMMF) and quartz (967).

8.2.3.4 Silicotics

An increased risk of atherosclerotic heart disease mortality was observed among 1 130 male silicotics identified in the Swedish Hospital Discharge Register (SMR 1.5, 95% CI 1.4–1.8) (130). Interestingly, 88% of the silicotics had the diagnosis of atherosclerotic heart disease prior to their first hospitalisation for silicosis. This fact does not immediately make this association non-causal as silicosis is a disease which will develop over decades of silica exposure. The disease will be manifest in X-ray investigations after more than 20 years of exposure (13).

Most studies of silicotics around the world did not demonstrate an increased risk of IHD mortality (Appendix, Table A13). However, a case-control study among 732 South African gold miners showed that extensive silicosis was clearly related to *cor pulmonale* (OR 4.95, 95% CI 2.92–8.38) at death, while age or smoking were not significant predictors of *cor pulmonale* (686).

Potential years of life lost (PYLL) because of pneumoconiosis was studied using data from the Nationwide Epidemiological Study on Pneumoconioses in China 1949–1986. Silicosis was the most common pneumoconiosis and comprised 44 108 subjects. Silicosis had the greatest mean PYLL with an average of 22.1 years. Deaths due to circulatory diseases contributed with more PYLL (19.8 years) than all cancers (18.2 years) and respiratory diseases (17.2 years). Among circulatory diseases, *cor pulmonale* was responsible for the highest PYLL (20.6 years) (1054).

Silicosis and constrictive pericarditis were observed in a male stone miner exposed for 10 years. An association between silica exposure and pericarditis was suggested as no other causing agent was identified (456).

8.2.3.5 Acute silicosis

In 1929, acute silicosis was recognised as a result of comparatively short exposure to alkaline silica mixtures in the manufacturing of scouring soaps (150). Two women aged 17 and 19 years who were packing a cleaning-powder in a London factory developed acute silicosis after an exposure period of less than 3 years and a little more than 4 years, respectively. Both died from their disease and the younger girl had a heart with recent fibrinous pericarditis (594).

Three men were mixing dry silica and soap at an open machine. All of them developed acute silicosis after 3–5 years of exposure and these were among the first cases identified in the US industry. One of the men developed right ventricular hypertrophy probably explained by the increased resistance and loss of elasticity in the pulmonary vessels (150).

One case report described a 19-year-old man who had worked as a silica powder packer in a stone-grinding workplace in Iran. After 18 months of exposure he died of cardiogenic shock, and autopsy revealed advanced silicotic masses in the lungs, pericardial effusion, and cardiomegaly associated with irregular plaque formation on the visceral layer of the pericardium (657).

8.2.4 Antineutrophil cytoplasmic antibodies associated vasculitis

Silica exposure has also been related to the development of antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV). In a meta-analysis of six studies, silica ever-exposure was associated with development of AAV, with a summary OR of 2.56 (95% CI 1.51–4.36). Despite moderate heterogeneity among studies, the totality of the evidence after the meta-analysis pointed to an association between silica exposure and risk for developing AAV (347). In a previous study, ANCA positivity was found less frequently (7%) in a group with history of silica exposure without signs of pronounced silicosis, than in groups with simple (30%) or complicated silicosis (36%). However, no typical AAV was present among the participants (67).

8.2.5 Exposure-response relationships

Quartz-exposed quarry and shed workers employed 1950–1982 in the Vermont granite industry were followed until 1996. Quartz exposure decreased by 80–90% after 1940. Mortality (SMR, 95% CI) from silicosis was higher among workers exposed before 1940 (27.4, 20.3–36.1) than among workers exposed after 1940 (3.98, 0.82–11.6). The corresponding SMR (95% CI) for circulatory disease decreased from 0.94 (0.86–1.03) to 0.63 (0.56–0.70) and for IHD from 0.89 (0.81–0.97) to 0.58 (0.51–0.65). Thus, the decreased quartz exposure resulted in decreased mortality from silicosis, circulatory disease and IHD (349). A decreased mortality from circulatory disease was also observed among US goldminers. The SMRs before 1930 and after 1951 were 0.98 and 0.63, respectively (129). The estimated crystalline silica exposure decreased from 0.15 mg/m^3 before 1930 to 0.02 mg/m^3 after 1950 (907).

The mortality of 13 621 male employees at the iron-ore mines in Malmberget and Kiruna, Sweden, was investigated. The cohort comprised men who had been employed for at least 1 year 1923–1996 and was followed 1952–2001. There were 1 477 cases of MI, resulting in an SMR (95% CI) of 1.12 (1.07–1.18). There was a positive trend between number of years of underground exposure and mortality of MI; exposure for 0–5 years, 5–15 years and > 15 years were associated with SMRs (95% CIs) of 1.03 (0.92–1.16), 1.13 (1.01–1.25) and 1.20 (1.08–1.32), respectively (98). The content of crystalline silica in the respirable fraction of the dust was estimated to 2.5%. There was a positive relationship between cumulative respirable silica exposure and mortality (HR, 95% CI) from MI among workers ≤ 60 years of age; ≤ 0.9, 0.9–2.5 and > 2.5 mg/m^3-years corresponded to HRs of 0.93 (0.71–1.23), 1.36 (1.01–1.84) and 1.82 (1.33–2.49), respectively (97). In the same cohort, an opposite trend was found between years of underground exposure and mortality of stroke and CeVD. Exposure for ≥ 15 years was associated with a lower RR (95% CI) for both stroke (0.52, 0.29–0.90) and CeVD (0.66, 0.49–0.89) (100).

In the large cohort comprising 68 241 metal miners as well as pottery workers from south central China (described in Section 8.2.3.1) (155), exposure was classified as high (mostly from underground open cast or separation jobs), medium, low or no dust-exposure. High- or medium-dust exposed workers were compared with low/no dust exposed workers. High-exposed workers had an increased mortality (RR, 95% CI) due to all heart disease (1.55, 1.3–1.8) and pulmonary heart disease (1.93, 1.6–2.4) with significant trends for both outcomes (P < 0.01). There was no significant trend regarding mortality (RR, 95% CI) due to IHD for medium dust-exposed workers (0.65, 0.3–1.3) and high dust-exposed workers (1.16, 0.7–1.9) (155).

A subcohort from the large Chinese cohort (155) consisting of 42 572 workers employed at 29 Chinese metal mines and pottery factories for ≥ 1 year 1960–1974 was followed until 2003 (570). A time-specific JEM was developed using all available total dust concentrations to estimate individual silica dust exposure. Total dust concentration was converted to a respirable silica concentration by a conversion factor (163). Positive cumulative silica exposure-response trends were observed for mortality from total heart disease (HRs for increasing quartiles of cumulative silica exposure compared with the unexposed group were 0.89, 1.09, 1.32, 2.10; P for trend < 0.001) and from pulmonary heart disease (0.92, 1.39, 2.47, 5.46; P for trend < 0.001). After dividing the workers in two groups based on lifetime highest silica exposure (> 0.1 mg/m^3 and ≤ 0.1 mg/m^3, respectively), the positive trends remained in both groups. There was also a positive trend for IHD among workers with lifetime highest exposure ≤ 0.1 mg/m^3 (P for trend < 0.001) and those with a cumulative exposure of 0.56–0.87 mg/m^3-years had a significantly increased risk of IHD mortality (HR 1.52, 95% CI 1.02–2.27) (Table 4) (570). This Chinese cohort was further analysed among participants with lifetime highest respirable crystalline silica exposure ≤ 0.05 mg/m^3. Workers with the highest cumulative silica exposure (> 0.67 mg/m^3-years) had an increased risk of IHD (HR 1.89, 95% CI 1.07–3.35) (Table 4) (571).

Table 4. Cumulative respirable crystalline silica exposure and hazard ratios (95% CI) for mortality from heart disease and silicosis (570, 571).

Diagnosis	Quartiles of cumulative exposure (mg/m^3-years)			
	Lifetime highest silica exposure > 0.1 mg/m^3 (570)			
	0.04–1.73	1.74–3.80	3.81–7.06	> 7.07
Total heart disease	0.98 (0.84–1.14)	1.15 (1.00–1.32)	1.63 (1.43–1.85)	2.14 (1.89–2.41)
Pulmonary heart disease	1.24 (0.95–1.63)	2.03 (1.61–2.55)	3.77 (3.06–4.65)	5.80 (4.75–7.07)
IHD	1.18 (0.87–1.59)	1.05 (0.78–1.43)	0.90 (0.65–1.24)	0.61 (0.42–0.89)
Silicosis	1.00	6.31 (4.86–8.21)	15.2 (11.8–19.5)	19.3 (14.9–25.0)
	Lifetime highest silica exposure ≤ 0.1 mg/m^3 (570)			
	0.01–0.33	0.34–0.55	0.56–0.87	> 0.87
Total heart disease	1.13 (0.85–1.49)	1.12 (0.82–1.53)	1.26 (0.97–1.62)	1.34 (1.04–1.72)
Pulmonary heart disease	1.46 (0.83–2.58)	1.51 (0.80–2.86)	1.29 (0.72–2.29)	2.40 (1.51–3.83)
IHD	1.04 (0.63–1.72)	1.13 (0.68–1.90)	1.52 (1.02–2.27)	1.60 (1.07–2.40)
Silicosis	1.00	0.43 (0.11–1.65)	1.12 (0.44–2.86)	1.60 (0.64–4.01)
	Lifetime highest silica exposure ≤ 0.05 mg/m^3 (571)			
	0.01–0.26	0.27–0.47	0.48–0.67	> 0.67
Pulmonary heart disease	0.71 (0.23–2.25)	1.64 (0.66–4.09)	1.17 (0.46–2.94)	1.25 (0.54–2.89)
IHD	0.81 (0.36–1.85)	1.15 (0.55–2.41)	1.61 (0.87–2.97)	1.89 (1.07–3.35)

CI: confidence interval, IHD: ischaemic heart disease.

Another subgroup of the previous cohort comprising 7 665 workers from one iron mine was followed 1960–2012. A relationship was observed between cumulative silica exposure and IHD mortality after adjustment for gender, year and age of hire and smoking. Exposure to 0.49–0.84 mg/m^3-years was associated with an HR for IHD of 1.54 (95% CI 1.06–2.23) (527).

8.2.6 Markers of effect

An increased plasma concentration of fibrinogen was observed among tunnel construction workers after a workshift with a respirable dust exposure of ≤ 2 mg/m^3 (406). Thus, signs of inflammation have been observed in relation to exposure to silica, however, the workers were also exposed to diesel exhaust. Furthermore, Spanish coal miners with pneumoconiosis had higher plasma levels of fibrinogen than coal miners without pneumoconiosis (284). Serum levels of CRP were also significantly higher among silicotics than among healthy subjects (185).

8.2.7 Conclusion

More than ten studies indicate a relationship between crystalline silica exposure and the occurrence of CVD (primarily IHD). No association between exposure and CeVD was observed.

Decreasing quartz exposures resulted in decreased mortalities from silicosis, circulatory diseases and IHD in Vermont, Canada (349). A Swedish study showed

a positive relationship between cumulative respiratory crystalline silica exposure and mortality from MI among workers ≤ 60 years of age (97). Chinese studies showed relationships between cumulative crystalline silica exposure and mortality from pulmonary heart disease (*cor pulmonale*) and IHD at lifetime highest silica exposures ≤ 0.1 mg/m^3 (570, 571). A cumulative silica exposure of 0.56–0.87 mg/m^3-years was associated with an increased IHD mortality (570). This exposure corresponds to 0.01–0.02 mg/m^3 during a working life of 40 years.

There is *strong evidence* for an association between exposure to crystalline silica and CVD.

8.3 Man-made vitreous fibres

8.3.1 General

Man-made vitreous fibres (MMVF) is a generic name used to describe an inorganic fibrous material manufactured primarily from glass, rock, minerals, slag and processed inorganic oxides. The produced MMVF are non-crystalline. Other names for MMVF include manufactured vitreous fibres, man-made mineral fibres (MMMF), machine-made mineral fibres and synthetic vitreous fibres (435).

8.3.2 Occupational epidemiological studies

Epidemiological studies and risk estimates are presented in Appendix, Table A14.

8.3.2.1 Nordic countries

A Swedish cohort of 2 807 workers employed for at least 1 year before 1972 and exposed to MMMF during insulation of prefabricated wooden houses was followed for mortality 1969–1988. It was not possible to distinguish exposure to glass wool from rock wool since most plants used both types of insulation materials during different time periods. Exposure was categorised in the following way: 0) No exposure to MMMF; 1) Mean background exposure level of 0.06 (range 0.02–0.08) fibres/ml; 2) Work periods with full-time employment in locations where MMMF were handled, but without direct handling of MMMF, mean exposure level of 0.09 (0.05–0.13) fibres/ml; and 3) Work periods with direct handling of MMMF during most of the working day associated with a mean exposure level of 0.11 (0.05–0.17) fibres/ml. The highest exposure in category 3 occurred 1975–1980 and was estimated as 0.20–0.25 fibres/ml. The total cohort had a lower than expected risk (SMR, 95% CI) for circulatory disease (0.84, 0.74–0.94), IHD (0.83, 0.72–0.95) and CeVD (0.77, 0.55–1.04). There was no clear exposure-response relationship for circulatory disease; the exposure categories 0, 1, 2 and 3 had SMRs of 0.77, 0.84, 0.97 and 0.78, respectively. Nor was there a clear relationship between duration of employment and the occurrence of circulatory disease; duration categories < 10 years, 10–19 years and ≥ 20 years had SMRs of 0.84, 0.91 and 0.75, respectively (363).

A cohort of 3 539 male and female MMVF production workers from three Swedish plants employed for at least 1 year before 1978 was followed for mortality 1952–1990. National and regional rates were used to calculate expected numbers. No increased risks (SMR, 95% CI) of circulatory disease (1.01, 0.91–1.12), IHD (0.95, 0.83–1.08) or CeVD (0.96, 0.73–1.24) were observed (753).

A cohort of 941 workers (616 males and 325 females) in the glass wool producing industry in Finland was identified. The group included workers employed in the Karhula plant 1941–1952, alive on January 1953, and who were employed at least 3 months 1953–1977. The period of follow-up was 1953–1981. There were no significantly increased mortality regarding circulatory diseases for men (SMR 1.31) or women (SMR 0.81) (948) compared to the general population.

8.3.2.2 Europe (non-Nordic countries)

The workforces from two factories producing MMMF in England and Northern Ireland were followed until 1984. The factory in England produced mainly glass wool and the cohort comprised 3 548 men and 1 186 women. The expected mortality was calculated using rates from England and Wales. The mortality (SMR, 95% CI) from circulatory diseases was not increased for males (1.04, 0.92–1.18) or females (0.92, 0.65–1.26). The factory in Northern Ireland (Dungannon district council area) produced mainly glass yarn from continuous filament and the cohort comprised 1 196 men and 714 women. The expected mortality was calculated using rates from Northern Ireland. The mortality (SMR, 95% CI) from circulatory diseases was not significantly increased for men (1.24, 0.95–1.58) or women (0.68, 0.27–1.40). Higher mortality from IHD (SMR 1.09) and CeVD (SMR 1.29) was observed among men 1979–1981 (327).

A German factory produced rock wool by a steam-blowing process 1942–1977. The exposed cohort of 2 096 male employees was compared with a reference cohort comprising 1 778 males selected from workers in cork and styropor panel production of the same company. The cohorts were followed until 1979. Mortality from circulatory disease was less common among the exposed than among referents (RR 0.70, 95% CI 0.51–0.97) (174). Basically the same cohorts of exposed (reduced to 2 092 men) and referents (reduced to 1 775 men) were followed until 1982. The mortality from circulatory diseases of the exposed workers was compared with national rates (SMR 0.90, 95% CI 0.73–1.11) and with the mortality of the referents (RR 0.74, 95% CI 0.60–0.92). The referents may have been exposed to coal tar, silica, urethane formaldehyde foam and polystyrene as these substances were used some time during the production processes. The referents had a higher overall mortality (SMR 1.22) and a significantly increased risk for circulatory diseases (SMR 1.31) (175).

A cohort was formed comprising 1 098 male workers from an Italian man-made glass-fibre industry producing glass wool and continuous filament. Workers employed for at least 1 year 1944–1974 were included and followed 1944–1983. The CVD mortality (SMR, 95% CI) was lower than expected when compared with both national rates (0.60, 0.37–0.92) and local rates (0.50, 0.31–0.76) (90).

8.3.2.3 North America

A cohort comprised 1 448 white male workers initially employed 1940–1949 in one major fibrous glass construction products manufacturing facility. Cohort participants were included when they achieved at least 5 years of employment in fibrous glass production, packing or maintenance activities. The cohort was followed until 1972. Expected deaths were calculated from rates of the general US white male population. The number of deaths from diseases of the heart was 163 (SMR 0.91) and 30 from vascular lesions affecting the CNS (SMR 0.91). The mean concentration of fibres was 0.08 fibres/ml. The median diameter and length of the fibres was 1.8 µm and 28 µm, respectively (72).

A cohort comprising 6 536 male employees that had been engaged in fibrous glass production for at least 10 years at any time during 1968–1977 was followed until 1978. Already in 1968, 4 046 workers were included in the cohort. Lists of eligible employees were developed by Owens-Corning Fibreglass from records at the company headquarters in Toledo and from records at the manufacturing plants. The majority of deceased individuals were white males and it was considered appropriate to use US white males as comparison group. The mortality due to circulatory diseases was not increased (SMR 0.84, based on 199 cases). The corresponding mortality in a subcohort comprising 1 240 workers with 20 years of employment and 30 years of latency was similar (SMR 0.73, based on 49 cases) (669). The mortality pattern from non-malignant respiratory diseases showed a clear healthy worker survivor effect.

Totally 596 male rock and slag mineral wool production workers were exposed at least 1 year 1940–1948 in a Midwestern plant. The cohort was followed until 1974. The observed number of deaths was compared with the expected number derived from the sex, age, race, calendar-time and cause-specific US mortality rates. The exposure to fibres was the following: until 1935, 1.2–2.5 fibres/ml; 1935–1948, 0.5–1.0 fibres/ml; 1948–1967, 0.1–0.3 fibres/ml; 1967–1974, 0.5–0.7 fibres/ml. The mortality (SMR, 90% CI) from diseases of the heart among men employed in rock and slag mineral wool production and manufacturing was not increased (0.97, 0.81–1.16). The mortality from heart disease was similar in a subcohort of mineral wool production workers (1.03, 0.84–1.24) (785).

A cohort of 16 661 MMMF workers employed for at least 1 year 1945–1963 at one or more of 17 US manufacturing plants were followed until 1982. The cohort comprised 14 815 workers from the fibrous glass plants and 1 846 workers from the mineral wool plant. At the end of 1982, one third of the cohort had died. Race information was unknown for over 30% of the total cohort and of those with known race whites constituted over 96%. National white male rates were used to calculate the expected number of deaths. In the total follow-up period 1946–1982, there were no increased risks regarding all heart disease, IHD and CeVD (SMRs 0.98, 0.99 and 1.00, respectively). In the later part of the follow-up period, 1979–1982, there was an increased risk for CeVD (SMR 1.27, $P < 0.05$) but not for all heart disease (SMR 1.06) and IHD (SMR 1.06) (260). This cohort was further followed 1983–1985. In the total follow-up period 1946–1985 there were no increased risks for all heart

disease (SMR 1.00) and CeVD (SMR 1.01). In the later part of the follow-up period, 1983–1985, there was an increased risk regarding all heart disease (SMR 1.15, $P < 0.05$) but not regarding CeVD (SMR 1.05) (604). This cohort was expanded to comprise 32 110 workers employed for at least 1 year 1945–1978 at any of ten US fibreglass manufacturing plants and followed until 1992. In the total follow-up period 1946–1992 there were no increased risks (SMR, 95% CI) regarding all heart disease (0.92, 0.88–0.95) and CeVD (0.86, 0.79–0.94). A comparison with local county rates showed approximately the same results (606).

Totally 4 008 female fibre glass workers, employed for at least 1 year 1945–1978 in production areas or maintenance in any of ten US fibreglass manufacturing plants, were followed until 1992. A majority of the women were hired in the 1940s and 1950s, two thirds were 20–39 years of age at the time of hire. The majority of the employed females (57%) worked for less than 5 years in the plants. A decreased mortality risk (SMR, 95% CI) of all heart disease (323 fatalities) was observed when the cohort was compared with national rates (0.77, 0.69–0.86) and local county rates (0.73, 0.65–0.82). Similar decreased mortality risks (SMR, 95% CI) were also observed for CeVD (82 fatalities) when the cohort was compared with national rates (0.74, 0.59–0.92) and local county rates (0.78, 0.62–0.97) (920).

Respirable glass fibres (also called Beta fibres) were produced at the Anderson plant, South Carolina, US, 1963–1968. Totally 2 933 white male workers who had worked for at least 1 year between the start of the plant in 1951 and the end of 1991 were followed until 1991. The mortality of the cohort was compared with the US national rates for white men. The majority of the continuous filament fibreglass produced had an average diameter of 10–12 μm or larger. The Beta fibres had an average diameter of 3.5 μm. There were no increased risks (SMR, 95% CI) of all heart disease (0.84, 0.70–1.00), IHD (0.83, 0.67–1.02) and CeVD (0.97, 0.54–1.60) (170). Further cohorts from the same plant included 1 074 white women, 130 non-white women and 494 non-white men who worked for a minimum of 1 year from the opening of the plant in 1951 through 1991. No significantly increased risks of all heart disease, IHD and CeVD were reported (994).

A cohort of 942 male workers with at least 1 year of employment producing refractory ceramic fibres in New York and Indiana was followed 1952–2000. The cohort comprised 446 former employees who terminated work before 1987 and 496 currently employed at that time or hired subsequently. In the 1950s, the maximum exposure estimate was 10 fibres/ml for carding in textile operation. Subsequent improvements reduced the exposure to < 10 fibres/ml. In 1987–1988, the time-weighted averages (TWAs) were 0.03–0.61 fibres/ml for dry fabrication, 0.01–0.27 fibres/ml for wet fabrication, 0.01–0.47 fibres/ml for furnace operations and 0.02–0.62 fibres/ml for maintenance. Subsequently, exposure levels remained relatively stable. The mortality of the cohort was compared with the US national rates and death rates between ethnic groups were analysed separately. There were no increased risks (SMR, 95% CI) for diseases of the heart (0.73, 0.48–1.06), IHD (0.85, 0.54–1.28) and CeVD (0.43 based on 2 cases) (552).

A cohort of 2 557 male insulating glass wool plant workers from Sarnia, Ontario, Canada, who had worked at least 90 days 1955–1977, was followed until 1984 and the mortality was compared with rates from Ontario. The total cohort was divided in three groups; those who had worked in the plant only; those who had worked in the office only; and those who had worked in both places. The mortality (SMR) from IHD was not increased in any of the three groups; for plant-only workers 0.82 (based on 38 cases); for office-only workers 0.81 (based on 4 cases); and for plant-office workers 1.29 (based on 8 cases). CeVD mortality only occurred among plant-only workers (SMR 1.32, based on 10 cases) (860). The cohort was further followed until 1997. There was no increased mortality (SMR, 95% CI) of IHD (0.81, 0.63–1.02) or CeVD (0.91, 0.50–1.52) among plant-only workers (858).

A cohort comprised 1 465 male and female glass filament producing workers from a Canadian plant in Guelph, Ontario. Workers who had worked at least 1 year 1951–1986 were included in the cohort. Mortality was compared with that of the general population of Ontario. The TWAs of exposure were 0.02–0.05 fibres/ml with the highest value observed being 0.91 fibres/ml. The mortality (SMR) for circulatory disease was decreased for males (0.65, $P < 0.05$, based on 29 cases) and slightly increased for females (1.89, $P = 0.07$, based on 8 cases) (859).

8.3.3 Pooled analyses

A European cohort comprised totally 21 967 MMMF-production workers (18 753 males and 3 214 females) from 13 plants in 7 countries including Denmark, Finland, Norway, Sweden, the United Kingdom, Germany and Italy. The rock wool – slag wool cohort contained 10 115 workers, the glass wool cohort contained 8 286 workers and the continuous filament cohort contained 3 566 workers. The cohort was followed until 1982 and the mortality reference rates were computed from the WHO mortality data bank. No increased mortality risks (SMR, 95% CI) were observed for diseases of the circulatory system (1.00, 0.94–1.07), IHD (1.03, 0.96–1.11) and CeVD (0.88, 0.75–1.02) (869, 870).

A European cohort of totally 11 373 male MMVF-production workers from 13 plants in 7 countries (same as above) who had worked at least 1 year during 1933–1977 was followed until 1990–1992. The mortality reference rates were computed from the WHO mortality data bank. Seven factories produced rock or slag wool, five factories produced glass wool, and two factories produced continuous filament. Mortality from IHD (SMR, 95% CI) was increased for continuous filament workers (1.43, 1.06–1.88) but not for rock or slag wool workers (0.97, 0.87–1.08) or glass wool workers (1.05, 0.95–1.15). A higher mortality of IHD (SMR, 95% CI) was found among glass wool workers (1.20, 1.06–1.35) and continuous filament workers (1.58, 1.13–2.14) from the UK. However, when adjusting for local variation in IHD mortality by applying the ratio of local versus national mortalities to expected deaths, the SMR in the UK glass wool worker subcohort decreased to 1.03 (0.91–1.16). In internal analyses, rock or slag wool and continuous filament workers with ≥ 30 years since first employment had a higher risk from IHD than workers with < 30 years since first employment. On the other

hand, analysis by duration of employment suggested a decreasing risk among rock or slag wool workers with increasing duration. Glass wool workers employed in the early technological phase (with presumed higher fibre concentrations) had an increased mortality from IHD (RR 1.6, 95% CI 1.0–2.5) compared with workers employed in the late phase. This trend was stronger among glass wool workers from the largest UK factory than among other factories. No excess mortality from CeVD was reported for type of production, country or technological phase (822).

8.3.4 Conclusion

In 14 cohort studies of workers exposed to MMVF, there were generally no increased risks of CVD when the mortality of exposed workers was compared with national or regional reference rates. In one US cohort, an increased mortality was found regarding CeVD (260) and heart disease (604) in later parts of the follow-up periods. In a joint European cohort comprising 11 373 male production workers, an increased risk from IHD was found among workers exposed to continuous filaments (822). A higher IHD mortality was found among glass wool workers and continuous filament workers from the UK (822).

There is *insufficient evidence* for an association between exposure to man-made vitreous fibres and CVD.

8.4 Carbon nanotubes

8.4.1 General

The toxicity of carbon nanotubes (CNTs) was evaluated by NEG in 2013 (395). CNTs can be seen as graphene sheets rolled to form cylinders and may be categorised as single- (SWCNT) or multi-walled (MWCNT). Due to the small size, the number of particles as well as the surface area per mass unit are extremely high. CNTs are highly diverse, differing with respect to e.g. diameter, length, chiral angles, chemical functionalisation, purity, stiffness and bulk density. Today, CNTs are utilised primarily for the reinforcement of composite polymers, but there is considerable potential for other applications. The rapidly growing production and use of CNTs increases the risk for occupational exposure. CNTs may be absorbed via inhalation and ingestion. Since CNTs in bulk form are of very low density and much dust is produced during their handling, exposure by inhalation appears to represent the greatest potential risk in the workplace (395).

8.4.2 Animal studies

Both SWCNTs and MWCNTs cause inflammation and fibrosis in the lungs of animals. Mild granulomatous inflammation in the lungs and lung-draining lymph nodes have been observed in rats exposed for 13 weeks to 0.1 mg/m^3 MWCNTs (LOAEC), with more pronounced inflammation in both mice and rats at higher exposures. Thus, inflammatory responses in the lungs may be considered as the critical effect (395). In addition, intratracheal and intrapharyngeal instillation

of CNTs led to accelerated plaque progression directly (143, 562), or indirectly through an induced acute phase response (757).

8.4.3 Occupational epidemiological studies

In a cross-sectional study, 22 workers in a company producing MWCNTs were compared with 42 gender- and age-matched unexposed participants. An upward trend was observed in the endothelial damage marker ICAM-1, indicating endothelial activation and an increased inflammatory state in workers exposed to MWCNTs. No consistent significant associations were found for 11 other cardiovascular markers (520). A similar group of 24 exposed workers and 43 controls from principally the same study base as above (520) was investigated regarding epigenetic alterations in blood cells. No difference in global methylation of the genomic DNA was observed but some significant changes in methylation of some sites in promoter regions were observed in the MWCNT-exposed group (334).

A cross-sectional study was performed among 108 workers at 12 US facilities using CNTs and nanofibres. Some statistically significant positive associations were reported. Systolic blood pressure was associated with exposure to fine particulate matter. Resting heart rate was associated with the concentration of EC, both the respirable and inhalable size fractions. Haematocrit was associated with the logarithmic mass concentration of CNTs, and nanofibre counts. However, most health outcomes were not associated with exposure measures. The authors concluded that the associations between exposure and resting heart rate and haematocrit counts may not be causal and require examination in other studies (843).

The industrial use of CNTs is rather new. Prospective long-term studies including occupationally exposed workers were not located.

8.4.4 Conclusion

No prospective long-term studies including occupationally exposed workers were located. A small cross-sectional study in the MWCNT production industry indicated endothelial damage and increased inflammation (520). Another cross-sectional study indicated effects on blood pressure, resting heart rate and haematocrit (843). Mechanistic and animal studies showed evidence for atherosclerotic effects of CNTs (143, 562, 757).

There is *insufficient evidence* for an association between exposure to carbon nanotubes and CVD.

9. Metals

9.1 Aluminium

9.1.1 General

Aluminium is the third most common element in the earth's crust and is found in several minerals such as feldspars, micas, cryolite and bauxite. Bauxite is the main raw material for aluminium production (517). Metallic aluminium is produced from bauxite in two stages. First alumina (Al_2O_3) is extracted from bauxite by a chemical process (Bayer process) followed by an electrolytic process; electrolytic aluminium production is described in Section 7.2. The present section covers health effects of exposure to alumina and aluminium powder (particulate aluminium).

9.1.2 Occupational epidemiological studies

In a cohort, comprising 5 770 male Australian bauxite miners and alumina refinery workers, there was an association between ever alumina exposure and mortality (RR, 95% CI) from CeVD based on 10 deaths (3.8, 1.1–13), but not from CVD (1.1, 0.7–1.8). There was some evidence of a relationship between cumulative alumina exposure and mortality from CeVD (P for trend 0.04) (314).

9.1.3 Exposure-response relationships

Australian gold miners who inhaled aluminium powder in order to prevent silicosis had a slightly increased CVD mortality compared to other gold miners (HR 1.02 per year of exposure, 95% CI 1.00–1.04). The authors remarked that duration of aluminium dust inhalation may not have been accurately assessed for all miners and observed trends were questionable. The actual exposure levels may have been lower given the aversion of the miners to the aluminium therapy. On the other hand, the comparison between miners ever and never exposed to aluminium dust was probably more reliable (HR 1.19, 95% CI% 0.99–1.44) (742).

9.1.4 Conclusion

The two epidemiological studies on aluminium exposed workers that were located showed increased risks of CeVD (alumina) (314) and CVD (aluminium powder) (742), respectively.

There is *insufficient evidence* for an association between exposure to particulate aluminium and CVD.

9.2 Arsenic

9.2.1 General

Arsenic (As) is a grey, crystalline solid with metallic lustre. Arsenic compounds are hygroscopic crystalline or amorphous substances, which occur in trivalent and pentavalent forms. Arsenic trioxide is the major arsenic compound regarding occupational exposures (304).

The most common sources of exposure to arsenic are contaminated drinking water and occupational exposure among primary copper smelter workers. CVD is one of several important outcomes of arsenic exposure and comprises peripheral vascular disease including blackfoot disease, IHD, stroke and hypertension (304).

In 1900, an epidemic of a multisystem disease occurred in the Manchester area in England, with over 6 000 cases and more than 70 deaths. This epidemic has been described as the first metal-induced cardiotoxic syndrome produced by intake of beer contaminated with arsenic (16). The syndrome included the usual signs and symptoms of arsenic poisoning and an unusual but prominent aspect in this epidemic was heart failure. The source of arsenic was contaminated sulphuric acid which was used to treat cane sugar. It was observed that some persons seemed to have a "peculiar idiosyncrasy" and "that many persons became ill who drank less beer than others who were not affected". The conclusion was drawn that arsenic predisposed susceptible persons develop alcoholic cardiomyopathy (497). Arsenic intoxication was associated with atypical ventricular tachycardia (346).

Epidemiological studies and risk estimates are presented in Appendix, Table A15.

9.2.2 Animal studies

Mice treated orally with sodium arsenite ($NaAsO_2$) for 2 days developed increased lipid peroxidation and abnormal ultra-structural changes in the cardiac tissue (600).

9.2.3 Occupational epidemiological studies

A Finnish cohort consisted of men who were in the same occupation in 1975 and 1980 and were 25–64 years old in 1980. CVD mortality was followed 1981–1994. Information on marital status, education and income was updated in 1985 and 1990. Working conditions were evaluated from a JEM comprising three categories of arsenic exposure: unexposed, low-exposed (three lowest quartiles of the exposed) and high-exposed (top quartile of the exposed). A fully adjusted Poisson regression model was applied which included age, period, marital status, professional status, education, income, occupational class and category, and working conditions. The top quartile was compared with the lower exposed and unexposed workers. The resulting RR for CeVD mortality was 1.04 (95% CI 0.75–1.45) (1031).

Low levels of arsenic are common in copper ore all over the world and primary copper smelter workers are exposed to arsenic but also to several other compounds like silica dust and sulphur dioxide (543).

A case-control study from a Swedish primary copper smelter demonstrated a significantly increased mortality from CVD. There was also a significant exposure-response relationship over increasing categories of arsenic exposure (56). A cohort of 3 916 male smelter workers from the same smelter showed a non-significantly increased mortality from IHD (SMR 1.07, 95% CI 0.97–1.17), but there was no exposure-response relationship (471).

A cohort of 8 047 white male workers from copper smelters in US Montana exposed to arsenic trioxide was followed until 1963. An increased mortality from heart disease compared with regional rates was observed (SMR 1.18, $P < 0.01$).

However, these smelter workers were also exposed to sulphur dioxide, silica and some of them also to lead (543). A subcohort of 1 800 men from the same smelter was followed until 1978. Ceiling exposure was based on the highest arsenic exposure category in which a man had spent at least 30 days. In the group with high ceiling exposure (0.5–4.9 mg/m^3), an increased SMR was found for IHD (1.59, $P < 0.01$), and in the group with very high ceiling exposure (≥ 5.0 mg/m^3) the SMR was higher (1.71, $P < 0.01$). There was also an increased risk for IHD (SMR 1.31, $P < 0.05$) among smokers exposed to TWAs below 0.1 mg/m^3 (1004). The total cohort now consisting of 8 045 arsenic exposed copper smelter workers, further followed until 1977, also had an increased mortality from heart disease (542). The cohort was further followed through 1990 with confounding control using parametric g-formula and the result indicated an exposure-response relationship (484).

Totally 2 802 white males were included in a cohort of US copper smelter workers in Tacoma, Washington. After adjustment for the healthy worker survivor effect, a significant increased mortality from CVD (RR 1.7, 95% CI 1.1–2.6) was observed after high cumulative exposure to arsenic (≥20 mg/m^3-years). After applying a 20-year lag, a cumulative exposure of 4–8 mg/m^3-years was associated with an increased CVD mortality (RR 1.5, 95% CI 1.1–2.1) (402).

9.2.4 Meta-analyses of epidemiological studies of the general population

A meta-analysis of environmental arsenic exposure included seven studies on CVD, eight studies on CHD and four on stroke. CHD was defined as non-fatal MI, angina, coronary revascularisation (i.e. percutaneous transluminal coronary angioplasty or coronary artery bypass surgery) or CHD death. Stroke comprised both fatal and non-fatal stroke. Subjects were divided in three exposure groups using data on drinking water, toenails and urine. Comparisons of outcomes were made between the highest and lowest exposure group. Risk estimates from separate studies were typically adjusted for basic demographics e.g. age, sex, systolic blood pressure, smoking and history of diabetes. The calculated RR (95% CI) was 1.30 (1.04–1.63) for CVD, 1.23 (1.04–1.45) for CHD and 1.15 (0.92–1.43) for stroke (172).

9.2.5 Pooled analyses of epidemiological studies of the general population

Several types of studies were included in a pooled analysis of groups exposed to arsenic in drinking water. In studies with multiple exposure categories, comparisons were made between high (> 50 µg/l) and low (< 50 µg/l) arsenic levels. The pooled RRs (95% CIs) for CVD, CHD, stroke, and peripheral arterial disease were 1.32 (1.05–1.67), 1.89 (1.33–2.69), 1.08 (0.98–1.19) and 2.17 (1.47–3.20), respectively (663).

In an analysis 5 years later, pooled log-linear and non-linear RRs for each end-point were estimated for drinking water arsenic concentrations of 20, 50, 100 and 200 µg/l, using 10 µg/l as reference. There were significant trends regarding arsenic concentrations and incidence and mortality of CVD and CHD in the log-linear model. The resulting RRs (95% CIs) for 20 µg/l were 1.09 (1.03–1.14) for CVD incidence, 1.07 (1.01–1.14) for CVD mortality, 1.11 (1.05–1.17) for CHD

incidence, 1.16 (1.07–1.26) for CHD mortality, 1.08 (1.00–1.17) for stroke incidence and 1.06 (0.93–1.20) for stroke mortality (664, 665).

9.2.6 Markers of effect

Available data suggest that arsenic causes a range of effects related to oxidative stress and vascular inflammation. Findings from mechanistic studies suggest that arsenic causes inflammation in vascular tissues and activates oxidative signalling (17). In individuals with arsenic-related skin lesions in Bangladesh, plasma levels of systemic inflammation and endothelial dysfunction markers (such as the soluble intercellular and soluble vascular cell adhesion molecules, ICAM-1 and VCAM-1) were positively associated with serum arsenic concentrations (166).

9.2.7 Previous evaluations

In 2011, WHO evaluated the relationship between long-term exposure to arsenic in drinking water and CVD (e.g. blackfoot disease, CHD, peripheral arterial disease, MI, stroke, and other cardiovascular endpoints such as increased blood pressure and prolonged QT interval of the ECG). An association between blackfoot disease and inorganic arsenic exposure had been confirmed by many studies, but the disease has been reported primarily in an area along the south-western coast of Taiwan, China, where arsenic contamination in well water is very high (170–880 µg/l). Except for blackfoot disease, however, reported associations between inorganic arsenic exposure and CVD and other cardiovascular endpoints currently were not considered sufficient evidence of causality and were not considered pivotal for the assessment (1013).

9.2.8 Conclusion

Several studies on arsenic exposed workers were found (overlapping cohorts), some of which showing an increased risk of CVD. An occupational cumulative arsenic exposure of 4–8 mg/m^3-years was associated with an increased mortality from CVD (402), which corresponds to 0.1–0.2 mg/m^3 arsenic during 40 years.

A meta-analysis showed an increased risk of CVD from environmental exposure (172). In a pooled analysis, 20 µg/l of arsenic in drinking water was associated with increased incidence and mortality from CVD (664, 665). Consumption of beer contaminated with arsenic has been associated with cardiomyopathy (16, 497).

Mechanistic data of oxidative stress and vascular inflammation from arsenic exposure provide further support for a link with CVD (17, 166).

There is *strong evidence* for an association between exposure to arsenic and CVD.

9.3 Beryllium

9.3.1 General

Beryllium is a steel-grey, shiny, hard and brittle metal. Beryllium is the lightest of all solid and chemically stable substances. It is lighter than aluminium, harder than steel and the melting point is unusually high (1 278 °C). Beryllium is found in rocks, coal, soil and volcanic dust. The overall market volume of beryllium is relatively small. Total world production of beryllium in 2008 was about 200 tonnes. Due to its unique combination of physico-chemical properties it is used in many specific industrial applications, such as medical diagnostics, nuclear fusion reactors, and aerospace applications where lightweight structures are required which are resistant to deformation under high stresses or high temperatures (848).

9.3.2 Occupational epidemiological studies

Some US cohort studies of beryllium exposed workers have reported heart diseases as an outcome. An early US cohort of 3 055 white male beryllium exposed workers employed in the Reading and Lorain plants sometime between 1942 and 1968 were followed until 1975. An increased risk of heart disease was observed (SMR 1.13, $P < 0.05$). Mortality due to heart disease differed between workers employed before 1950 (SMR 1.16, $P < 0.05$) and workers employed after 1950 (SMR 0.92). This decrease in mortality was similar to that due to non-neoplastic respiratory disease observed during the same period. The risk (SMR) regarding heart disease was 1.29 for workers exposed for > 5 years and 1.10 for workers exposed for < 5 years. Smoking habits was an unlikely cause of these increased risk estimates (978). It was estimated that air concentrations of beryllium in the 1940s frequently exceeded 1 mg/m^3 in these facilities (992).

A US cohort comprising 9 225 males who had worked between 1940 and 1969 was followed until 1988. The cohort members had worked in plants engaged in beryllium processing, including extraction of beryllium hydroxide from beryl ore, and production of beryllium oxide, pure beryllium metal, and beryllium copper alloy and machining of beryllium-containing products. Mortality from IHD was significantly increased in the total cohort (SMR 1.08, 95% CI 1.01–1.14). The Reading plant had a great impact on this result as it had an SMR of 1.12 ($P < 0.01$), whereas many of the other plants had SMRs around 1.0. Mortality from diseases of the arteries, veins and pulmonary circulation which includes *cor pulmonale* was increased only in the Lorain plant (SMR 1.78, $P < 0.05$) (992). The cohort was updated with quantitative exposure estimates and 9 199 workers were followed until December 2005. An increased mortality from *cor pulmonale* was reported (SMR 1.17, 95% CI 1.08–1.26). No risk estimate of mortality from IHD was reported (842).

9.3.3 Markers of effect

Chronic beryllium exposure may stimulate the acquired immune response to release mediators of chronic inflammation in the lung involving cellular and molecular components of innate immunity. This vicious cycle driven by beryllium results in

progressive impairment of lung function, granuloma formation and progression to lung fibrosis, berylliosis (832).

9.3.4 Exposure-response relationships

In the US cohort comprising 9 199 workers, three out of seven plants had air measurements of beryllium. The diagnosis *cor pulmonale* was included among diseases of the arteries, veins and pulmonary circulation and caused most of the deaths within the category. There was a positive relationship between maximum daily weighted average beryllium exposure and diseases of the arteries, veins and pulmonary circulation. The highest (≥ 70 μg/m^3) and second highest ($25–<70$ μg/m^3) exposure categories were associated with risk estimates (SMR, 95% CI) of 1.52 (1.23–1.85) and 1.31 (1.09–1.58), respectively, based on comparisons with the US population (842).

9.3.5 Conclusion

Few cohort studies were located. One of these demonstrated a marginal increase in IHD mortality (992). In an update of the same cohort, an increased mortality from diseases of the arteries, veins and pulmonary circulation (*cor pulmonale*) was observed at beryllium concentrations of $25–<70$ and ≥ 70 μg/m^3 (842).

There is *limited evidence* for an association between exposure to beryllium and pulmonary heart disease (*cor pulmonale*).

9.4 Cadmium

9.4.1 General

Cadmium is widely spread in the environment. Human exposure occurs by ingestion of food contaminated with cadmium, by smoking and in certain industrial settings. Smokers have approximately twice the body burden of cadmium compared to non-smokers. In non-smokers, the primary source of exposure is food (322). Regarding the effect of tobacco smoke on CVD, attempts have been made to discern the contribution from cadmium. It has been estimated that for the sum of acute MI, bypass grafts and percutaneous coronary intervention, and death in IHD, about half of the increased risk in current smokers was mediated via cadmium (560).

Exposure to cadmium has been associated with diseases of the cardiovascular system, bone, kidneys and lungs. The effects on the cardiovascular system have been suggested to be a result of the action on the cardiovascular endothelium and smooth muscle, mediated by generation of a proinflammatory state, endothelium dysfunction, increased oxidative stress, and down-regulation of the nitric oxide production (10, 17).

Epidemiological studies and risk estimates are presented in Appendix, Table A16.

9.4.2 Occupational epidemiological studies

In a mortality study, 869 Swedish battery workers exposed to nickel hydroxide and cadmium oxide (employed at least 1 year 1940–1980) were followed up until 1992. Compared with the general population, the SMRs (95% CIs) for IHD were 1.16 (0.96–1.40) in males and 0.75 (0.25–1.76) in females, and those for CeVD were 0.78 (0.47–1.21) in males and 1.34 (0.37–3.43) in females, after adjusting for smoking habits (470).

A Finnish cohort of men who were in the same occupation in 1975 and 1980 and were 25–64 years old in 1980 was followed for mortality 1981–1994. Information on marital status, education and income was updated in 1985 and 1990. Working conditions were evaluated from a JEM. A fully adjusted Poisson regression model was applied which included age, period, marital status, professional status, education, income, occupational class and category, and working conditions. The RRs (95% CIs) for cadmium-exposed workers compared with unexposed workers were 1.01 (0.93–1.10) for CVD mortality and 1.07 (0.91–1.24) for CeVD mortality (1031).

In a cohort from the UK, almost 7 000 male cadmium-exposed workers from five industries (primary production, copper-cadmium alloys, silver-cadmium alloys, pigments and oxide and stabilisers) who were exposed for more than 1 year during 1942–1970 were followed for mortality to the end of 1984. Compared to the general population there was no significant excess of death due to hypertensive disease (SMR 1.19, 95% CI 0.85–1.52) and the mortality from CeVD was significantly lower than expected (SMR 0.77, 95 % CI 0.66–0.89) (483).

The mortality of 347 male copper-cadmium alloy workers in the UK (first employed 1922–1978 and for at least 1 year) was investigated during the period 1946–1992. Compared to the general population there was no excess of mortality from diseases of the circulatory system (SMR 1.03, 95% CI 0.83–1.27) (896).

A cohort of 1 462 male workers at a UK tin smelter (employed for at least 1 year 1967–1995) was followed through 2001. Mortality (SMR, 95% CI) from diseases of the circulatory system showed a deficit compared to the national population (0.96, 0.82–1.11) and to the regional population (0.94, 0.80–1.09). Similar results were found for IHD, CeVD and hypertensive diseases (94).

A US cohort of 2 422 male workers (employed ≥ 3 years 1946–1996) exposed to arsenic, cadmium and other substances at a copper mine and smelter in Copperhill, Tennessee was followed-up through 2000. Based on national and local county comparisons there was no evidence of an increased mortality risk from CeVD, all heart disease or hypertension (605).

9.4.3 Epidemiological studies of the general population

In a cohort of 64-year-old Swedish women, cadmium levels in blood and urine were associated with the prevalence and future growth of atherosclerotic plaques in the carotid arteries (275), and with low ankle-brachial index as a measure of peripheral artery disease (276), after adjusting for smoking and other cardiovascular risk factors.

A prospective, population-based cohort study in the city of Malmö, Sweden, showed that blood cadmium levels were associated with increased incidence of heart failure. The HR (95% CI; 4th vs 1st quartile) was 2.64 (1.60–4.36) adjusted for age and 1.95 (1.02–3.71) after adjustment also for an extensive set of risk factors and biomarkers related to CVD. The blood cadmium level was not significantly associated with risk of incident atrial fibrillation (120).

Another study based on the same cohort showed an association between blood cadmium levels and incidence of several cardiovascular outcomes such as acute coronary event, acute MI, any stroke and ischaemic stroke as well as CVD mortality. An increased HR for all these outcomes was noted for participants in the highest quartile of blood cadmium levels (0.50–5.1 µg/l) compared with the first quartile (< 0.17 µg/l). An increased incidence of major adverse cardiac event was found also for participants in the third quartile of blood cadmium levels (0.26–0.50 µg/l). When the cohort was restricted to never-smokers, the same outcome was seen only for subjects in the highest quartile (0.50–5.1 µg/l), based on 8 cases (63).

Based on the same cohort, an association was observed between blood cadmium levels and incidence of ischaemic stroke, both independently and in interaction with carotid plaques. The HR (95% CI; 4th vs 1st quartile) was 1.91 (1.33–2.74) when adjusted for age and sex, and 1.66 (1.01–2.72) when adjusted for additional risk factors (121).

In a Belgian study, 480 subjects from a cadmium-contaminated area and 476 subjects from a reference area with lower cadmium levels were randomly recruited. The subjects were followed by monitoring of blood cadmium (1985–2003), urinary cadmium (1985–1996) and mortality (1985–2007). At baseline, blood cadmium (14.6 vs 10.2 nmol/l) and urinary cadmium (14.1 vs 8.6 nmol/24-hour) levels were higher in deceased than in survivors. The risk (HR, 95% CI) for CVD mortality associated with a doubling of baseline blood cadmium was 1.20 (0.90–1.60). The corresponding risk associated with a doubling of urinary cadmium was 1.07 (0.85–1.34). After adding 42 smelter workers to the study base, the calculated HRs (95% CI) for CVD were 1.29 (0.99–1.67) for a doubling of blood cadmium levels and 1.11 (0.89–1.38) for a doubling of urine cadmium levels (699).

Blood cadmium levels were associated with an increased prevalence of peripheral arterial disease (defined as a blood pressure ankle brachial index < 0.9 in at least one leg) in a representative sample (cross-sectional analysis) of the general US population (696). A strong positive association between urinary cadmium levels and peripheral arterial disease were seen in the same population. After multivariate adjustment (age, sex, race, education level and smoking status), subjects with peripheral arterial disease had 36% higher urinary cadmium levels than subjects without the disease (697). The results support a possible role for cadmium in atherosclerosis.

In another cross-sectional study of US adults (National Health and Nutrition Examination Survey, NHANES, 1999–2004), cadmium levels in blood, but not in urine, were associated with a modest elevation in blood pressure levels. The average differences in systolic and diastolic blood pressure, comparing participants in the

90th and 10th percentile of the blood cadmium distribution, were 1.36 mmHg (95% CI -0.28–3.00) and 1.68 mmHg (0.57–2.78), respectively. There was no association between cadmium levels and the prevalence of hypertension (945).

A cross-sectional sample of 4 912 participants 45–79 years old in the US NHANES III 1988–1994 was included in a study of MI. In logistic regressions by gender, only women showed a significant association between urinary cadmium levels and MI. Women with urinary cadmium levels ≥ 0.88 µg/g creatinine showed an OR of 1.80 (95% CI 1.06–3.04) compared to women with urinary cadmium levels < 0.43 µg/g creatinine. When the analysis was restricted to never-smokers (n = 2 187 men and women), subjects with urinary cadmium levels ≥ 0.88 µg/g creatinine had an OR for MI of 1.85 (95% CI 1.10–3.14) compared to never-smokers with urinary cadmium levels < 0.43 µg/g creatinine (272).

Cadmium levels in blood and urine in the general US population (NHANES 1999–2006) were positively associated with the risk of having a history of stroke or heart failure. Those with a history of stroke and heart failure had mean blood cadmium levels of 5.1 and 5.0 nmol/l compared to 3.8 nmol/l among those without disease. Corresponding urinary levels were 3.7 and 4.0 versus 2.6 nmol/l. After adjusting for demographic and cardiovascular risk factors, a 50% increase in blood cadmium corresponded to a 35% increased odds of a history of stroke (OR 1.35, 95% CI 1.12–1.65) and a 48% increased odds for history of heart failure (OR 1.48, 95% CI 1.17–1.87). A 50% increase in urinary cadmium corresponded to a 9% increase in odds for history of stroke (OR 1.09, 95% CI 1.00–1.19) and a 12% increase in odds for history of hypertension (OR 1.12, 95% CI 1.03–1.20) (741).

A prospective study of US adults (NHANES 1999–2004, 8 989 participants ≥ 20 years of age) showed that cadmium levels in blood and urine were associated with future CVD mortality, heart disease mortality, and for cadmium levels in urine also with IHD mortality, after adjusting for sociodemographic and cardiovascular risk factors, including smoking status, recent smoking dose and cumulative smoking dose. The adjusted HRs (95% CIs) for mortality, comparing the 80th and the 20th percentiles of blood cadmium level distributions were 1.69 (1.03–2.77) for CVD, 1.98 (1.11–3.54) for heart disease and 1.73 (0.88–3.40) for IHD. Corresponding adjusted HRs (95% CIs) for urinary cadmium level distributions were 1.74 (1.07–2.83), 2.53 (1.54–4.16) and 2.09 (1.06–4.13). The population attributable risks for CVD mortality associated with having concentrations above the 80th percentile of the blood (0.80 µg/l) and urine (0.57 µg/g creatinine) cadmium distributions were 7.5% and 9.2%, respectively (946).

A prospective cohort study of 3 348 American Indian adults 45–74 years of age showed that urine cadmium was associated with increased mortality and incidence of CVD. After adjusting for sociodemographic and cardiovascular risk factors, the HRs (95% CIs; 80th vs 20th percentile of urine cadmium concentrations) were 1.43 (1.21–1.70) and 1.34 (1.10–1.63) for CVD and CHD mortality, respectively. The corresponding HRs for incident CVD, CHD, stroke, and heart failure were 1.24 (1.11–1.38), 1.22 (1.08–1.38), 1.75 (1.17–2.59) and 1.39 (1.01–1.94), respectively (943).

A 15-year follow-up study among inhabitants of a cadmium-polluted area (Kakehashi River basin) in Japan showed that the mortality from heart failure was higher among subjects with high urinary cadmium (≥ 10 µg/g creatinine) than among those with moderate urinary cadmium (< 10 µg/g creatinine) levels, in both sexes after adjustment for age (690).

Another follow-up study among the inhabitants living in the cadmium-polluted area Kakehashi River basin in Japan was performed. An excess mortality due to heart failure and cerebral infarction in both sexes was shown, and nephritis and nephrosis in men with renal tubular dysfunction (urinary β_2-microglobulin > 1 000 µg/g creatinine). A significant increase in mortality risk for cerebral infarction in men was observed during the first 5-year observation period. The mortality risk for heart failure and cerebral infarction increased in proportion to the increased urinary β_2-microglobulin levels in both sexes (709).

A cross-sectional study (Korean NHANES 2008–2010) comprised 5 919 adults ≥ 20 years of age. A 2-fold increase in blood cadmium was associated with 0.76 and 1.01 mmHg increases in diastolic blood pressure in women and men, respectively. Increases of 2.24 and 1.98 mmHg in diastolic pressure in women and men, respectively, were observed when the highest quartile was compared with the lowest quartile of blood cadmium. Effects on systolic blood pressure were similar to those on diastolic pressure. Doubling of blood cadmium resulted in 18.6% and 31.5% increases in the risk of hypertension in women and men, respectively (545).

9.4.4 Meta-analyses of epidemiological studies of the general population

A meta-analysis of environmental cadmium exposure included in total eight studies, whereof six studies on CVD, five studies on CHD and three studies on stroke. CVD included CHD and stroke. CHD was defined as non-fatal MI, angina, coronary revascularisation (i.e. percutaneous transluminal coronary angioplasty or coronary artery bypass surgery) or CHD death. Stroke comprised both fatal and non-fatal stroke. Subjects were divided in three exposure groups using data on blood and urine cadmium concentrations. Comparisons of outcomes were made between the highest and lowest exposure groups. Risk estimates from separate studies were typically adjusted for basic demographics, e.g. age, sex, systolic blood pressure, lipids, smoking and history of diabetes. The calculated RRs (95% CIs) were 1.33 (1.09–1.64) for CVD, 1.29 (0.98–1.71) for CHD, and 1.72 (1.29–2.28) for stroke. There was a linear dose-response relationship between cadmium levels and CVD (172).

9.4.5 Pooled analyses

In a systematic review by Tellez-Plaza *et al*., the authors concluded that their pooled analysis (12 studies included) together with experimental evidence supported an association between cadmium exposure and CVD, especially CHD. The number of studies with stroke, heart failure and peripheral artery disease endpoints was small. Overall, the pooled RRs (95% CIs) for CVD, CHD, stroke and peripheral artery disease were 1.36 (1.11–1.66), 1.30 (1.12–1.52), 1.18 (0.86–1.59) and 1.49

(1.15–1.92), respectively. The pooled RRs for CVD in men, women and never-smokers were 1.29 (1.12–1.48), 1.20 (0.92–1.56) and 1.27 (0.97–1.67), respectively (944).

9.4.6 Dose-response relationships

Increased incidences of major adverse cardiac event were found in the two highest exposure quartiles (blood cadmium levels of 0.26–0.50 μg/l and 0.50–5.1 μg/l) after adjustment for sex, smoking, waist circumference, education, physical activity, alcohol intake, serum triglycerides, HbA1c (glycated haemoglobin), CRP, post-menopausal status, hormonal replacement, treatment for hypertension, diabetes mellitus, lipid-lowering medication, diastolic blood pressure, LDL and HDL cholesterol. Among never-smokers, an increased incidence was observed in the highest exposure quartile (0.50–5.1 μg/l) (63).

One study among American Indian adults showed dose-response relationships between urine cadmium concentrations and incidence and mortality due to CVD. Analyses with subjects divided in four groups depending on urinary cadmium levels (≤ 0.61, 0.62–0.92, 0.93–1.45, > 1.45 μg/g creatinine) showed a positive dose-response relationship between cadmium concentration and all CVD outcomes. LOAELs for increased incidence of CVD, CHD and heart failure, and stroke were 0.62–0.92, 0.93–1.45, and > 1.45 μg/g creatinine, respectively. The calculated HRs were adjusted for sex, postmenopausal status for women, education, BMI, total cholesterol, estimated LDL cholesterol, hypertension, diabetes, estimated glomerular filtration rate, smoking status and cumulative smoking dose (943).

Among inhabitants of a cadmium-polluted area there was a dose-response relationship between urinary cadmium and heart failure mortality (690). In the same area, among subjects with renal tubular dysfunction induced by cadmium, a urinary β2-microglobulin level of 300–1 000 μg/g creatinine was associated with an increased mortality from heart failure (women) and cerebral infarction (men) (709).

9.4.7 Conclusion

None of five occupational mortality studies showed an increased risk of CVD among cadmium-exposed workers (quantitative exposure data lacking), whereas 11 studies on the general population supported a relationship between blood or urine cadmium concentrations and the occurrence of CVD, IHD, arterial disease or hypertension and four of these also supported an association with stroke. Three of these studies showed dose-response relationships (63, 690, 943). The risk of CVD was increased for subjects with blood cadmium levels of 0.26–0.50 μg/l (2–4 nmol/l) compared to subjects with levels < 0.17 μg/l (63) and for subjects with urinary cadmium levels of 0.62–0.92 μg/g creatinine (0.62–0.93 μmol/mol creatinine) compared to those with levels ≤ 0.61 μg/g creatinine (LOAELs) (943).

The evidence from general population studies for a relationship between cadmium exposure and CVD is strong. However, the lack of positive findings in occupational studies and confounding from smoking weakens the relationship.

There is *moderately strong evidence* for an association between exposure to cadmium and CVD.

9.5 Chromium (VI)

9.5.1 General

Chromium (Cr) is found in nature primarily as chromite ore with chromium in the trivalent form. This form of chromium seems to be a nutritional supplement for humans and may play a role in the metabolism of glucose. Chromium is an important metal due to its high corrosion resistance and hardness. Steel can be highly resistant to corrosion by adding chromium to form stainless steel. Chromium can oxidise to form hexavalent chromium or chromate and this form of chromium can cause cancer in the respiratory organs after long-term inhalation (537).

9.5.2 Occupational epidemiological studies

In the early 1960s, the University of Pittsburgh was contracted to study the mortality among males born 1890 or later, employed in three US chromate producing plants 1937–1940 with follow-up through 1960. Arteriosclerotic heart disease mortality (SMR) was 1.93 in 1941–1945 and 0.64 in 1956–1960 (Table 5). A decreased mortality was also observed for stroke, but the number of cases was very small. During the initial period 1941–1945, death rates were very high for respiratory cancers. The decline in mortality due to respiratory cancer indicates a decreased exposure to a very potent carcinogen. The author suspected calcium chromate to be this carcinogenic agent in these old chromate producing plants. However, it was unknown if all of the excess deaths were related to exposures in chromate production (258).

A US cohort of 1 737 male workers employed at least 1 month 1940–1969 in a chromium pigment factory in New Jersey, was followed until 1982. The pigments contained both lead and zinc chromates. The SMR (95% CI) was 0.85 (0.71–1.00) due to IHD and 0.56 (0.35–0.84) due to vascular lesions of the CNS (391). Another cohort originating from New Jersey comprised 3 408 workers who had worked between 1937 and 1971 in former chromate producing plants in the northern part of

Table 5. Mortality among chromate production workers employed 1937–1940 and followed through 1960 (258).

Year	1941–1945		1946–1950		1951–1955		1956–1960	
Cause of death	Obs.	SMR	Obs.	SMR	Obs.	SMR	Obs.	SMR
All	59	1.58	55	1.26	75	1.35	57	1.00
Respiratory cancer	16	29.1	19	15.7	19	7.92	15	4.75
Arteriosclerotic heart disease	11	1.93	12	1.13	18	1.03	13	0.64
Stroke	2	1.21	2	0.78	1	0.26	3	0.80

Obs.: number of observed cases, SMR: standardised mortality ratio.

the state. The PMRs regarding arteriosclerotic heart disease were 0.97 for white men, 0.90 for black men and 1.19 (95% CI 0.73–1.83) for white women. There was no increase of vascular lesions of the CNS among white men (PMR 0.78) and black men (PMR 0.68) (799).

A cohort of 482 former US chromate production workers from Painesville, Ohio, was followed until 1997. Of these, 41% started working at the chromate plant during the 1940s, and 59% started before 1955. The average airborne concentration of hexavalent chromium in the indoor operating areas of the plant was 720 $\mu g/m^3$ during 1943–1948, 270 $\mu g/m^3$ during 1957–1964 and 39 $\mu g/m^3$ during 1965–1972. SMR (95% CI) for diseases of the heart was 1.13 (0.93–1.36) based on reference rates from Ohio and 1.21 (0.99–1.46) based on US reference rates. Corresponding SMRs for other circulatory diseases were 1.43 (0.96–2.04) and 1.51 (1.02–2.16) (205, 580).

A US chromate chemical manufacturing facility in Castle Hayne, North Carolina, was built in 1971 and designed to reduce the high levels of chromium exposure found at most older facilities. The cohort comprised 398 workers employed during 1971–1989 of which 45 had previously worked at the plant in Painesville, Ohio. More than 99% of the measurements of hexavalent chromium based on personal sampling were below 50 $\mu g/m^3$. The SMR regarding all heart diseases was 0.65 (90% CI 0.26–1.37) based on only 5 cases and North Carolina eight counties' rates (732).

A cohort was formed from two cohorts of chromate production employees constituting the current US chromium chemical industry, after major process changes. The exposure levels to hexavalent chromium at both plants were very low after changing from high-lime to no-lime processes. The geometric mean of personal air concentrations of hexavalent chromium remained $<< 1.5$ $\mu g/m^3$ for most years at both plants. The range of annual means was 0.36–4.36 $\mu g/m^3$ and the highest personal air sampling values were generally < 10 $\mu g/m^3$. The SMR for diseases of the heart was 0.59 (95% CI 0.24–1.21) based on 7 cases (581).

Totally 2 298 chromate producing workers were identified from three factories (Bolton, Rutherglen and Eaglescliffe) in the UK. The subjects had worked for at least 1 year 1950–1976 and were followed until 1988. One fifth were exposed before 1945, and 50% were exposed before the major process changes in the end of the 1950s which improved working conditions. During the follow-up, no significant increased risks were observed in the different factories for IHD (SMRs 1.03–1.12) and CeVD (SMRs 1.06–1.30) (215).

Two cohorts from two German chromate-producing factories comprised 1 417 workers and were followed until 1988. Both factories were originally high-lime facilities. The plant in Leverkusen completed the changeover to a no-lime process in 1958 and the plant in Uerdingen completed the changeover in 1964. The SMRs (95% CIs) due to CVD were 1.16 (0.97–1.39) in Leverkusen and 0.96 (0.78–1.15) in Uerdingen (506). In a later study, 901 workers exposed only after the changeover formed a new cohort which was followed until 1998. The exposure had declined from the mid-1970s judged from urinary chromium levels. A total of 264 employees

had at least one urinalysis exceeding 40 µg/l chromium (corresponding to 52 µg/m^3 of hexavalent chromium in air) and were considered to have had a peak exposure. Consequently most of the urinary concentrations did not exceed 40 µg/l. The SMR (95% CI) for diseases of the heart was 0.66 (0.45–0.93) and that for other diseases of the circulatory system was 1.00 (0.57–1.63). In this latter category, the SMR (95% CI) for CeVD was 0.84 (0.38–1.60) (95). A calculated SMR based on diseases of the heart (32 observed vs 48.55 expected) and other diseases of the circulatory system (16 observed vs 15.90 expected) would be 0.75 [(32 + 16) / (48.55 + 15.90)] which is lower than the previous SMRs from Leverkusen and Uerdingen.

A Japanese cohort study of 896 male workers manufacturing chromium compounds showed an increased risk for lung cancer (SMR 9.5) but not for heart disease (SMR 0.6) and CeVD (SMR 1.0) (831).

A cohort comprising 666 Japanese chromate pigment (including lead chromate) manufacturing workers employed at least 1 year 1950–1975 were followed until 1989. From 1976, the geometric mean of hexavalent chromium was 3–19 µg/m^3 at measurement sites in the factories. The number of observed deaths due to heart diseases was 5 versus 9.9 expected (SMR 0.50, 95% CI 0.16–1.18) (476).

9.5.3 Markers of effect

In a Chinese cross-sectional study, 86 male workers exposed to sodium dichromate were compared with 45 non-exposed referents. The air concentrations of chromium were < 50 µg/m^3. The exposed workers had significantly higher levels of white cells in the blood and also higher concentrations of serum CRP, as an expression of an unspecific inflammatory response (986).

9.5.4 Conclusion

Around ten cohorts from chromate producing industries were located. Most studies used national or regional rates to calculate expected deaths. Two of the studies demonstrated increased risks of circulatory diseases (205, 580) and arteriosclerotic heart disease (258). The latter study showed decreasing trends of arteriosclerotic heart disease mortality over time (258), which may be associated with improvements of the working environment and decreasing exposures.

Some other studies did not show increased risks of CVD mortality. However, most risk estimates were based on small numbers (< 10 cases) (476, 581) and exposures < 50 µg/m^3 (95, 732).

There is *insufficient evidence* for an association between exposure to hexavalent chromium and CVD.

9.6 Cobalt

9.6.1 General

Cobalt is the 33rd element in abundance in the earth's crust and an essential element which enters in the composition of vitamin B_{12} (540). Because of cobalt's practical

advantages of high melting point, strength and resistance to oxidation, about 70% of the cobalt consumed is used for the production of special alloys. Cobalt alloys include strong and corrosion-resistant superalloys used in components of gas turbines and jet engines; magnetic alloys used in telecommunications and for the manufacturing of special medical devices; cobalt-containing high-strength steels used in the aerospace and naval industries; electrodeposited alloys used in protective coatings, in recording systems and for computer applications; alloys with special properties such as for surgical and dental implants; and hard metal alloys (cemented carbides). The hard metal alloys were developed in Germany in the 1920s, using powder metallurgy (568).

In the early 1960s, cobalt chloride or cobalt sulphate was added to some brands of beer in order to stabilise the foam and as a result of this intervention heavy beer drinkers developed cardiomyopathy. However, it is likely that poor nutrition and ethanol played a synergistic role (540, 852). The cardiomyopathy among beer drinkers carried a high mortality rate (672). Cardiomyopathy was also described in two workers exposed to heavy dust concentrations from cobalt-containing ores for 2 months and 2 years, respectively (454) and after exposure to hard metal dust in a man responsible for weighing and mixing tungsten carbide and cobalt powder (486).

In 2016, Packer reviewed exposures behind the occurrence of cobalt cardio-myopathy. This condition is not common but has been described after cobalt treatment for anaemia, among nutritionally deficient drinkers of cobalt-fortified beer, in haemodialysis patients with end-stage renal disease, among cobalt exposed industrial workers and in patients with total metal hip replacement or arthroplasty. Despite a large number of exposed industrial workers, reports have been exceptionally rare, with only 7 cases over a 20-year period. The clinical emergence of cobalt cardiomyopathy requires the coexistence of one or more cofactors, particularly a low-protein diet, thiamine deficiency, alcoholism or hypothyroidism (730).

9.6.2 Animal studies

The bioavailability of cobalt increases in the presence of tungsten carbide. Intra-tracheal instillation of a tungsten carbide-cobalt mixture in rats caused severe alveolitis and fatal pulmonary oedema, whereas the corresponding dose of cobalt powder alone caused a moderate inflammatory response (540).

Mice exposed to 3 mg/m^3 of cobalt sulphate heptahydrate for 24 months (mass median aerodynamic diameter 1.5–1.8 μm) developed arteritis in the main coronary arteries (2/17 vs 0/18 in controls) and in other coronary arteries (2/48 vs 0/46). The number of animals with arteritis in the renal arteries was 5/48 versus 1/46. Overall, there was a significant increased risk of arteritis among the exposed ($P < 0.05$). Mice exposed to 30 mg/m^3 for 90 days did not develop arteritis (679).

9.6.3 Occupational epidemiological studies

In a cross-sectional study of 30 cemented tungsten carbide workers, a weak but significant inverse correlation was found between duration of cobalt exposure (mean 9.9 years) and resting left ventricular function. Nine workers with abnormal chest X-ray findings had relatively lower exercise right ventricular ejection fractions. Diminished right ventricular reserve was probably due to fibrotic lung disease and early *cor pulmonale*. Although overt left ventricular dysfunction was not present, prolonged exposure to industrial cobalt may have a weak cardio-myopathic effect (421).

A group of 31 hard metal workers in Italy were studied of which 20 were apparently healthy, 10 subjects presented pulmonary fibrosis of different degrees and 1 person had asthma. The average duration of exposure to cobalt containing dusts was 10.4 (range 1–30) years, while the air levels of cobalt ranged from 0.09 to 13.6 mg/m^3. Cardiac function was studied by ECG, exercise test, echocardiogram and radionuclide angiocardiography with ^{99}Tc. Within the group of patients with hard metal lung disease, cases of cardiomyopathy of doubtful aetiology were found. The cardiac indexes obtained through radionuclide angiocardiography showed ventricular dysfunction in the healthy hard metal workers which could be a manifestation of initial pulmonary artery hypertension or of an early incipient *cor pulmonale* due to an unknown fibrotic lung disease (208).

A higher pulse rate was recorded among 46 plate painters in a Danish porcelain factory exposed to cobalt blue dye compared with 51 top-glaze painters serving as referents (768).

In two studies of 870 French cobalt production workers (676) and 7 459 hard metal workers (678), no increased risks (SMR, 95% CI) of circulatory diseases were observed (0.80, 0.36–1.51 and 0.88, 0.75–1.03, respectively). In a later study, a cohort was formed comprising the largest production site which was in operation since the 1940s. The mortality (SMR, 95% CI) due to circulatory diseases was 0.91 (0.72–1.14) among men and 1.25 (0.75–1.95) among women. The IHD risks were similar. The overall smoking habits were close to a previous population survey (1022).

A Swedish cohort of 3 163 male hard metal workers was followed 1951–1982. The SMRs (95% CIs) regarding circulatory diseases and IHD were 0.97 (0.81–1.15) and 0.99 (0.80–1.21), respectively. In a subgroup of high and long-term (> 10 years) exposed workers, a higher SMR for IHD was observed (1.69, 95% CI 0.96–2.75) (415).

A later Swedish cohort of 15 633 white- and blue-collar workers in the hard metal industry was followed 1952–2012. Increased mortality (SMR, 95% CI) from IHD (1.22, 1.15–1.29) but not from CeVD (1.08, 0.97–1.19) was observed (1009). No exposure-response analysis was presented.

9.6.4 Conclusion

The majority of cohorts comprising cobalt-exposed hard metal workers did not exhibit an increased risk of circulatory diseases or IHD.

Cardiomyopathy has been described after intake of cobalt-containing beer and after inhalation of high cobalt dust concentrations. However, despite a large number of exposed industrial workers, such reports are exceptionally rare. Signs of *cor pulmonale* have been observed as a result of fibrotic lung disease.

There is *insufficient evidence* for an association between exposure to cobalt and CVD.

9.7 Lead

9.7.1 General

The general population may be exposed to lead from leaded gasoline, lead in paint and in soldered cans. Occupational exposures originate mainly from smelters, refineries, battery and paint production. Several mechanisms have been discussed to explain the observed increases of blood pressure associated with lead exposure, including impairment of renal function, and induction of oxidative stress, inflammation and endothelial dysfunction (694).

Around the year 2000, an estimated 2% of the total global burden of CVD was due to lead exposure (annually 229 000 deaths and 3.1 million disability-adjusted life years, i.e. the sum of years of life lost due to death and years of life with disability) (287).

9.7.2 Occupational epidemiological studies

In a study of male Swedish primary smelter workers, no increased risk of IHD or CeVD was observed in the total cohort of 3 979 subjects or in the highest exposed subgroup comprising 1 026 workers, respectively (587).

Among Swedish secondary lead smelter workers, an increased risk of IHD was found (SMR 1.72, 95% CI 1.20–2.42). The SMR did not increase with cumulative blood lead dose but was higher prior to 1969 which was the period with the highest exposure (329).

A Finnish cohort of men who were in the same occupation in 1975 and 1980 and who were 25–64 years old in 1980 was followed for CVD mortality 1981–1994. Information on marital status, education and income was updated in 1985 and 1990. Working conditions were evaluated from a JEM comprising three categories of lead exposure: unexposed, low-exposed (three lowest quartiles of the exposed) and high-exposed (top quartile). A fully adjusted Poisson regression model was applied which included age, period, marital status, professional status, education, income, occupational class and category, and working conditions. Compared to unexposed workers, the RR (95% CI) for CVD mortality was 1.00 (0.93–1.08) for low-exposed and 1.12 (1.03–1.23) for high-exposed. The corresponding RRs (95% CIs) for MI were 1.01 (0.93–1.10) and 1.13 (1.00–1.28). High-exposed workers had an increased risk of CeVD (1.24, 1.00–1.55) compared to low- and unexposed workers (1031).

In 1963, an increased mortality (SMR 2.6, P < 0.001) due to CeVD was reported among pensioners who died 1926–1961 and had worked in a British lead battery factory and were in the highest category of lead exposure (232). This population was later included in a study of 754 deaths 1925–1976 among workers from four battery factories. An increased mortality from CeVD was found again among workers in the highest category of lead exposure (232). The population was further enlarged with battery workers as well as non-lead exposed workers. This enlarged study base was used for a case-control study of 867 deaths 1926–1985 of men with relatively high occupational lead exposure (40–80 µg/100 ml blood) and 1 206 men with relatively low or absent lead exposure (< 40 µg/100 ml blood). CeVD fatalities were defined as cases, and fatalities from all other causes were defined as controls. A significant excess of deaths from CeVD was found 1946–1965 among the high lead-exposed workers, but no excess was found 1966–1985, due to assumed better working conditions (280).

An increased mortality from CeVD (SMR 4.1, P < 0.001) was found among 57 lead chromate pigment workers suffering from clinically diagnosed lead poisoning 1930–1945 (214).

Totally 1 990 male workers employed 1940–1965 at a US primary lead smelter in Idaho were followed until 1988. CeVD mortality was non-significantly elevated (SMR 1.05, 95% CI 0.82–1.32) with a tendency to increase with increasing duration of exposure (P = 0.07) (911).

Two US cohorts of male lead workers, 4 519 battery plant workers and 2 300 lead production workers, who had been employed for at least 1 year during the period 1946–1970 were followed until 1980. The cohort from Idaho (911) was not included in these cohorts. Among the battery plant workers, no increased mortality (SMR, 95% CI) of circulatory diseases was observed (1.00, 0.93–1.08), but a significantly increased mortality from other hypertensive diseases (mainly renal, 3.20, 1.97–4.89), and chronic or unspecified nephritis (2.22, 1.35–3.43). Likewise, lead production workers did not have any increased mortality from circulatory diseases (0.91, 0.79–1.03), whereas they exhibited an increased mortality from other hypertensive diseases (4.75, 2.18–9.02), hypertensive heart disease (2.03, 1.13–3.35) and chronic or unspecified nephritis (2.65, 1.14–5.22). The deaths from CeVD were not significantly increased in any of the cohorts, 0.93 (0.77–1.11) and 1.32 (0.98–1.75), respectively. There was no significant exposure-response relationship, as > 20 years of exposure was associated with SMRs for CeVD of 0.89 among the battery plant workers and 1.46 among the lead production workers. However, the distribution of CeVD was skewed against cerebral haemorrhage (45%) (193). This is a higher proportion than commonly reported including both haemorrhage in the brain tissue and the surrounding subarachnoid space (15%). Hypertension is closely related to intracerebral haemorrhage (1056).

Typographers are a group with historically lower exposure levels than most other lead-exposed groups. A decreased risk of arteriosclerotic heart disease was observed among 1 261 type setters from New York employed in 1961 and followed until 1984. However, there was an increased risk (SMR, 95% CI) of CeVD (1.35,

0.98–1.82), especially among workers exposed for ≥ 30 years (1.68, 1.18–2.31) (639).

A Russian study of printing workers comprised 1 423 men and 3 102 women. An increased risk of IHD was found among male typecasting machine operators (SMR 1.29, 95% CI 1.08–1.56). Information on exposure was based on an industrial hygiene survey and exposure duration in years. However, no exposure-response relationship was observed. In male and female manual typesetters and linotype operators, no increased risks of CeVD were observed (443).

Totally 241 smelter workers from the Broken Hill area, New South Wales, Australia, were diagnosed with lead poisoning 1928–1959. The proportionate death rates for 140 lead poisoned smelter workers were compared with the rates for 695 predominantly production workers free of known lead poisoning. An increased PMR was observed regarding chronic nephritis and cerebral haemorrhage, 3.06 and 1.99, respectively ($P < 0.05$) (626).

A cohort of male lead-exposed workers in Korea was followed 2000–2005. The HR for adjusted hospital admission due to CVD for each grade of blood lead level (10–20 and ≥ 20 µg/dl) was compared with that of the reference grade (< 10 µg/dl). The adjusted variables included age and exposure to other metals. HRs (95% CIs) of IHD (1.78, 1.17–2.72), angina pectoris (1.93, 1.13–3.29) and cerebral infarction (2.24, 1.14–4.39) were significantly higher among workers with a blood lead level ≥ 20 µg/dl than among those with a level < 10 µg/dl. The HR (95% CI) for CeVD was significantly higher among workers with a blood lead level of 10–20 µg/dl than among those with a level < 10 µg/dl (1.52, 1.00–2.31). IHD, CeVD, angina pectoris and cerebral infarction all showed a positive linear relationship with blood lead levels (652).

9.7.3 Pooled analyses of occupational epidemiological studies

Three cohorts of lead-exposed workers with blood lead level data from the US, Finland and the UK were pooled. The US cohort of 58 000 male workers was assembled from the Adult Blood Lead Surveillance (ABLES) programme. Blood lead levels were measured at different times in different states, but generally started in the early 1990s and went through 2007. Eleven states were included which had the majority of the ABLES data. Mortality was followed through 2010. The Finnish cohort of 21 000 workers (12% women) was created from those with documented blood lead level in the period 1973–1983, based on laboratory reports and employer data. Finnish labour law mandated that if the blood lead level of any worker at the workplace exceeded 42 µg/dl, then all workers in that workplace should have their blood lead level measured. Most blood samples came from the battery industry, lead smelting, metal foundries, railroad machine shops and chemical factories. The cohort was followed through 2013. The UK cohort numbered 9 000 (15% women), and was followed through 2011. Blood lead levels were measured in the period 1975–1979, as part of an effort to conduct a census of all workers exposed to lead. The principal industrial sectors included pottery and glaze (14%), lead battery (12%), lead smelting (10%) and demolition/scrap metal (9%). In the pooled

analysis, there was a positive dose-response relationship between blood lead levels and IHD (P for trend < 0.0001); HRs (95% CIs) were 1.14 (1.04–1.26), 1.16 (1.03–1.31) and 1.41 (1.28–1.57) for blood lead levels of 20– < 30, 30– < 40 and ≥ 40 µg/dl, respectively. There was also a relationship between blood lead levels and stroke (P for trend < 0.0002); HRs (95% CIs) were 1.24 (1.03–1.50), 1.49 (1.20–1.85) and 1.41 (1.16–1.72) for levels of 20– < 30, 30– < 40 and ≥ 40 µg/dl, respectively. Referents had a maximum blood lead level < 20 µg/dl and the HRs were adjusted for gender, birth year decade and country. No association between smoking and blood lead levels was found in a small subsample of the US cohort (n = 115) (905).

9.7.4 Epidemiological studies of the general population

Based on the US 2000 census and analysis of NHANES II, it was estimated that 29 million people (15% of the adult population older than 20 years) had blood lead levels of at least 1.0 µmol/l (207 µg/l) 1976–1980. A total of 4 292 persons aged 30–74 years with blood lead measurements were followed up through December 1992. After adjustments for potential confounders (age, sex, race, education, income, smoking, BMI, exercise and location), individuals with base line blood lead levels of 1.0–1.4 µmol/l had an increased mortality from circulatory diseases (RR 1.39, 95% CI 1.01–1.91) (589). Lead exposure declined dramatically beginning in the late 1970s largely because of the removal of lead from gasoline, from paint and, to a lesser extent, from solder used in cans. NHANES III comprised 9 757 participants and was conducted during 1988–1994 with follow-up to December 2000. Blood lead levels < 240 nmol/l were used as reference and an increased mortality (RR, 95% CI) due to CVD was found for levels of 240–450 nmol/l (50–90 µg/l) (1.20, 0.93–1.55) and ≥ 460 nmol/l (100 µg/l) (1.55, 1.16–2.07). A significant linear trend was also observed (841).

Navas-Acien and coworkers reviewed the literature regarding the relationship between lead exposure and CVD (694). The review comprised 12 studies of the general population; 5 prospective cohort studies, 1 cross-sectional study and 6 case-control studies. Lead exposure was positively associated with CVD in all studies. The evaluation also included 18 studies with occupational exposures from different industrial settings; battery, ceramic, refinery and smelter industries. Most of these were cohort studies in which external comparisons to the general population were used to derive SMRs. RR estimates varied widely. In two of three studies that reported associations by duration of employment, CeVD mortality was related to increasing duration of exposure (639, 911). Navas-Acien and coworkers concluded that the evidence was sufficient to infer a causal relationship between lead exposure and hypertension. They also concluded that the evidence was suggestive but not sufficient to infer a causal relationship between lead exposure and CVD (694).

After the review by Navas-Acien and coworkers some further studies have been published. Among 868 environmentally exposed men, lead levels in bone (patella and tibia) were measured and the average follow-up was 8.9 years. The highest tertile of lead in bone was compared with the lowest tertile. This comparison

resulted in significant increased mortalities (HR, 95% CI) regarding both CVD (2.5, 1.1–5.6) and IHD (8.4, 1.3–54.4) after adjustment for age, smoking and education (1001).

A total of 14 289 adults aged ≥ 20 years were enrolled in the US NHANES III 1988–1994 and followed to the end of 2011. The geometric mean concentration of lead in blood was 2.71 μg/dl and 3 632 (20%) participants had a concentration of lead in blood of at least 5 μg/dl (≥ 0.24 μmol/l). Subjects with a blood lead concentration of 6.7 μg/dl (0.324 μmol/l) had an increased mortality risk (HR, 95% CI) of CVD (1.70, 1.30–2.22) and IHD (2.08, 1.52–2.85) compared to those with a blood lead level of 1.0 μg/dl (0.048 μmol/l) (90^{th} vs 10^{th} percentile). The estimates were adjusted for age, sex, household income, ethnic origin, BMI, smoking, hypertension, urinary cadmium, alcohol consumption, physical activity in previous month, healthy eating index, serum cholesterol and glycated haemoglobin. The population attributable fraction of the concentration of lead in blood for all-cause mortality was 18.0% (95% CI 10.9–26.1), which is equivalent to 412 000 deaths annually. Respective fractions were 28.7% (15.5–39.5) for CVD mortality and 37.4% (23.4–48.6) for IHD mortality, which correspond to 256 000 deaths a year from CVD and 185 000 deaths a year from IHD. The authors concluded that low-level environmental lead exposure is an important, but largely overlooked, risk factor for CVD mortality in the US (538).

9.7.5 Meta-analyses of epidemiological studies

A meta-analysis focusing on blood lead levels and blood pressure comprised 31 studies and included 58 518 subjects, recruited from the general population in 19 surveys and from occupationally exposed groups in 12 studies. An association between blood lead levels and blood pressure was found in both men and women. A 2-fold increase of blood lead concentration was associated with a 1.0 mmHg (95% CI 0.5–1.4) rise in systolic blood pressure and with a 0.6 mmHg (0.4–0.8) rise in diastolic blood pressure (698). In another meta-analysis, three prospective studies and five cross-sectional studies had measurements of tibia lead levels. An increase of tibia lead levels by 10 μg/g bone was associated with a 0.26 mmHg (95% CI 0.02–0.5) rise in systolic blood pressure and the summary OR per 10 μg/g bone for hypertension was 1.04 (95% CI 1.01–1.07) (695).

A meta-analysis of environmental lead exposure included ten studies on CVD, eight studies on CHD and six studies on stroke. CVD included CHD and stroke. CHD was defined as non-fatal MI, angina, coronary revascularisation (i.e. percutaneous transluminal coronary angioplasty or coronary artery bypass surgery) or CHD death. Stroke comprised both fatal and non-fatal stroke. Subjects were divided in three exposure groups using data on blood concentrations. Comparisons of outcomes were made between the highest and lowest exposure tertile. Risk estimates from separate studies were typically adjusted for basic demographics, e.g. age, sex, systolic blood pressure, lipids, smoking and history of diabetes. The calculated RRs (95% CI) were 1.43 (1.16–1.76) for CVD, 1.85 (1.27–2.69) for

CHD, and 1.63 (1.14–2.34) for stroke. There was a linear relationship between blood lead levels and CVD (172).

9.7.6 Markers of effect

A total of 9 145 individuals ≥ 40 years of age participated in NHANES 1999–2004. No evidence of an association between blood lead levels and inflammatory markers such as CRP, fibrinogen and white blood cell count was observed (ORs around or below 1). Although men but not women appeared to be at increased risk of lead-induced inflammation, no consistent dose-response patterns were observed across blood lead level quintiles (895).

A group of 87 lead-exposed industrial workers and 61 controls were studied. The lead-exposed workers had significantly higher median blood lead levels than controls, 29.1 µg/dl (range 9.0–61.1) versus 8.3 µg/dl (1.0–21.7). CRP as a marker of inflammation was significantly increased ($P \leq 0.05$) among the exposed workers. Blood lead levels showed a significant positive correlation with CRP ($r = 0.75$) (490). However, smoking habits being a possible confounder was not taken into account.

9.7.7 Previous evaluations

In 2012, the US National Toxicology Program (NTP) reviewed the health effects of low-level of lead exposure. NTP declared that there is sufficient evidence that blood lead levels < 10 µg/dl (0.5 µmol/l) were associated with small but detectable increases in blood pressure and risk of hypertension. NTP concluded that there is limited evidence for increased CVD mortality at blood levels < 10 µg/dl. Lead levels in bone reflecting long-term lead exposure were more consistently associated with hypertension and CVD mortality (717).

9.7.8 Conclusion

The association between occupational and environmental exposure to lead and CVD has been extensively documented.

In a pooled analysis of Finnish, UK and US lead-exposed workers, there were significantly positive dose-response relationships between blood lead levels and IHD and stroke; blood lead levels of 20–30 µg/dl (0.97–1.45 µmol/l) were associated with increased risks (905).

In a US study of the general population (NHANES), subjects with a blood lead concentration of 6.7 µg/dl (0.324 µmol/l) had an increased mortality of CVD compared to those with a blood lead level of 1.0 µg/dl (0.048 µmol/l) (90^{th} vs 10^{th} percentile) (538).

There is *strong evidence* for an association between exposure to lead and CVD.

9.8 Manganese

9.8.1 General

Manganese is absorbed by ingestion and by inhalation after occupational exposure. Manganese ions may also be injected intravenously in order to use their strongly paramagnetic properties in magnetic resonance imaging. Cardiovascular magnetic resonance is an important diagnostic tool in cardiology. Manganese ions accumulate inside myocytes allowing for better imaging. In 15 healthy volunteers given manganese ($MnCl_2$) intravenously, there was a slight increase in systolic blood pressure and heart rate after 3 and 4 minutes of infusion with normalisation of these parameters thereafter. At follow-up 6 months after the investigation, no volunteer reported any neurological or cardiological adverse events or symptoms (283).

Manganese superoxide dismutase (MnSOD) is a member of the superoxide dismutase (SOD) family, which have antioxidant capacity. MnSOD may be the most important enzyme of the SOD family as it resides in mitochondria where cellular respiration takes place. One study demonstrated that *MnSOD* polymorphism (Ala16Val) may be associated with the development of type 2 diabetes among Japanese-Americans (691). Diabetes is an established risk factor for CVD (91).

9.8.2 Occupational epidemiological studies

Manganese exposed ferroalloy workers had decreased systolic blood pressure (829), whereas ferroalloy manufacturers in another investigation had higher systolic and diastolic blood pressure than non-exposed referents (202).

In 1955, an interesting observation was made by Rodier (790) when studying manganese-exposed Moroccan miners. The ore was very rich in manganese and neurological symptoms were common among the underground miners and 150 cases of poisoning were reported. Each year approximately 3.7% of the workers were affected with pneumonia. Death from heart failure could occur after a week with pneumonia or suddenly in patients regarded as cured. The manganese pneumonia was associated with a marked rise in erythrocyte sedimentation rate (790). The sedimentation rate can be influenced by several serum proteins, e.g. fibrinogen, haptoglobin, immunoglobulins and ceruloplasmin. Increased concentration of fibrinogen is an established risk factor for IHD (288) and has also been associated with sudden death (519). In another study of workers producing oxides and salts of manganese, the white blood cell count was significantly higher among exposed workers than among referents when smoking habits were taken into account (791). An increased white blood cell count is associated with an increased risk of CHD (1011).

In a study of Norwegian ferromanganese/silicomanganese furnace workers, 3 deaths due to pneumonia (411) and an increased mortality from sudden death (SMR 2.47, 95% 1.28–4.32) based on 12 cases were reported (410) during active employment. However, the workers were also exposed to other agents such as carbon monoxide and heat.

9.8.3 Epidemiological studies of the general population

In a Korean NHANES, 1 991 participants were studied in a cross-sectional design. Blood manganese concentration was positively and significantly associated with hypertension in this representative sample of the Korean adult population (544). A similar result was found among males from India (939).

In a US cross-sectional study of 639 older men in the Normative Aging Study, toenail concentrations of several metals including manganese were assessed. Manganese was negatively but not significantly associated with blood pressure. After adjusting for other metals, an increase in manganese was more strongly associated with decreased blood pressure (667).

9.8.4 Conclusion

The only longitudinal study on workers exposed to manganese that was located showed an increased risk of sudden death (410). A few environmental studies showed inconsistent results regarding manganese exposure and hypertension.

There is *insufficient evidence* for an association between exposure to manganese and CVD.

9.9 Mercury

9.9.1 General

Mercury vapours, mercuric salts and methylmercury behave differently regarding absorption, distribution and toxicity in the human body. Vapour inhalation is the most important occupational exposure route for mercury, typically occurring in mercury mining and in chloralkali factories. In the general public, fish consumption is an important source of methylmercury exposure (881).

9.9.2 Inorganic mercury

9.9.2.1 Animal studies

Two strains of mice were exposed to metallic mercury vapour at 6.6–7.5 mg/m^3 during 4 hours/day for 3 consecutive days. This exposure was lethal to over 60% of metallothionein (MT)-null mice but did not kill any wild-type mice. More severe pulmonary damage was found in MT-null mice than in wild-type mice by histopathological observation. MT levels in the lung were elevated in wild-type mice after mercury vapour exposure, and gel filtration of the lung cytosol revealed that most of the mercury was associated with MT. These findings suggest that MT plays a protective role against acute pulmonary toxicity (1046).

9.9.2.2 Case reports

Inhalation of large doses of elemental mercury vapour results in an influenza-like illness which will appear 1–4 hours after exposure. The fever is accompanied with severe pulmonary irritation, characterised by cough, dyspnoea and tightness in the chest (331, 651).

A 32-year-old woman broke a fluorescent lamp while trying to replace a damaged one. After one day she had malaise, fatigue, weakness of the lower and upper extremities, atypical chest pain and palpitation. ECG disclosed atrial fibrillation with T-wave inversion in lateral precordial leads. Analysis of biological media revealed a blood mercury level of 4.2 μg/l (reference value: < 10 μg/l), a spot urine mercury level of 61.3 μg/l (presumed reference value: < 10 μg/l) and a 24-hour urine mercury level of 344 μg/l (presumed reference value: < 15 μg/l). The woman was diagnosed with mercury poisoning and was given chelating therapy for 4 days. Her 24-hour urine mercury level normalised after 5 days. Neurological symptoms disappeared and ECG taken on the third day of admission showed sinus rhythm and normalisation of negative T-waves (477).

9.9.2.3 Occupational epidemiological studies

An increased CVD mortality was found among 1 190 male workers exposed to inorganic mercury from eight Swedish chloralkali plants compared with the national mortality rates and a latency time of ≥ 10 years (SMR 1.3, 95% CI 1.0–1.5) (65). In contrast, a similar study from Norway comprising 674 male workers from two chloralkali plants did not observe an increased CVD mortality (250). An American study of 2 133 male workers exposed to mercury vapours during production of nuclear weapons did not have an increased mortality due to vascular lesions of the CNS (203). Other vascular diseases were not reported.

No increase of CVD mortality was observed among workers compensated for mercury intoxication following exposure in the Italian fur hat industry. Mercury nitrate was used in fur carroting, a process where a mixture of mercury nitrate and nitric acid is applied to make the cut fur limp. The number of compensated women and men were 820 and 326, respectively (634).

Mortality was studied among 6 784 male workers from four mercury mines and mills in Italy, Slovenia, Spain and Ukraine. Increased mortalities (SMR, 95% CI) were found from hypertension (1.46, 1.08–1.93), heart disease other than ischaemic (1.36, 1.20–1.53) and pneumoconiosis (27.1, 23.1–31.6). Workers in the mines had the highest SMR for other diseases of the heart than IHD, and they were probably exposed to the highest levels of silica. There were no significant trends between duration of employment or estimated cumulative exposure (based on urinary mercury levels) and hypertension and other diseases of the heart, respectively (115). No conclusion can be drawn regarding mercury exposure and circulatory diseases.

In 2002, the first results were presented from the US Health Professionals Follow-up Study (HPFS), which is a cohort study of 33 737 men who supplied toenail clippings. The cohort was followed 1987–1992. Dentists had higher levels of mercury in their toenails (0.91 μg/g) than non-dentists (0.45 μg/g). The mercury levels were not significantly associated with CHD after adjustment for age, smoking and other risk factors (1047). The cohort was further followed and a female cohort from the Nurses' Health Study was added. Subjects with higher levels of mercury in their toenails did not have increased risks of CHD, stroke or total CVD. The

median mercury concentration was 0.23 µg/g among cases with CVD and 0.25 µg/g among control participants (680).

9.9.3 Methylmercury

Methylmercury exposure causes oxidative stress which is an early biological response that can produce vascular endothelial cell damage by promoting inflammation and vasoconstriction as well as lipid peroxidation via generation of reactive oxygen species (355).

9.9.3.1 Animal studies

Rats exposed by gavage to 100 µg/kg/day of methylmercury chloride for 100 days had increased systolic blood pressure, a decreased level of glutathione in the erythrocytes and an increased level of malondialdehyde (MDA) in plasma. There was a negative correlation between nitrite/nitrate plasma levels and systolic blood pressure and a positive correlation between MDA and systolic blood pressure, suggesting increased inhibition of nitric oxide (NO) formation with increase of hypertension. This study suggests that long-term exposure to methylmercury increases the systolic blood pressure, at least in part with increased production of radical oxygen species as judged by increased production of MDA and depressed NO availability (355).

9.9.3.2 Epidemiological studies of the general population

In the general population, mercury originates mainly from fish consumption. In a population-based nested case-control study from northern Sweden, 78 cases of first-ever MI were compared with 156 controls. High erythrocyte mercury levels or high plasma polyunsaturated fatty acids were associated with low risk of MI (375).

A case-control study from northern Sweden comprised 431 cases with MI and 499 controls. Mercury was measured in erythrocytes and the median level was 3.54 µg/l. An increased level of mercury in erythrocytes was associated with a lower risk of MI. The authors considered the mercury levels to be a biomarker of fish intake and that the results indicated a protective effect of fish consumption (1007).

In 1995, the first results were presented from the Finnish Kuopio Ischaemic Heart Disease (KIHD) study regarding a possible relation between mercury and heart disease. A total of 1 833 men were followed 1984–1991. Mercury was measured in hair, and men in the highest tertile (> 2.0 µg/g) had an increased mortality risk (RR, 95% CI) of acute MI (2.0, 1.2–3.1) and CVD (2.9, 1.2–6.6) compared with those with a lower mercury content (824). The study in eastern Finland was slightly enlarged to comprise 1 871 men who were followed 1984–1997. A 44% reduction of acute coronary events was observed when the highest 5th of the serum n-3 end-product fatty acids docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA) was compared with the lowest 5th of these fatty acids. Men in the highest 5th of the DHA + DPA who had a low hair content of mercury had a 67% reduced risk of acute coronary events (779). This cohort was further followed until 2002 and now men in the highest 3rd of hair mercury content (> 2.03 µg/g) had an increased risk (RR, 95% CI) of acute coronary events (1.60, 1.24–2.06), CVD (1.68, 1.15–2.44)

and CHD (1.56, 0.99–2.46). High mercury content in hair attenuated the protective effects of high-serum levels of DHA and DPA (1030). The mercury concentration of 2 μg/g hair corresponds to blood concentration of 15 ng/g erythrocytes. This level was exceeded by only 2 subjects in one of the Swedish studies above (375). The discrepancy of the results between the Finnish and the Swedish study may be explained by the higher dose in the Finnish study.

A case-control study conducted in eight European countries and Israel comprised 684 men with first MI and 724 referents. The toenail mercury levels were 0.27 μg/g among cases and 0.25 μg/g among referents. The risk-factor-adjusted OR for MI was 2.16 (95% CI 1.09–4.29) when the highest quintile of toenail mercury level (0.66 μg/g) was compared with the lowest quintile. The DHA levels in adipose tissue were also included in this adjustment (357).

Three out of four studies supported a link between methylmercury exposure and intima-media thickening of the carotid artery (793). In one of the studies comprising men from eastern Finland, a linear relationship was observed between their hair mercury concentration and plasma fibrinogen (823), indicating a possible weak inflammatory response.

Blood pressure was studied among Nunavik Inuit adults from northern Quebec, Canada. The mean age of the 732 participants was 34.4 years and the mean blood mercury level was 50.2 nmol/l (10 μg/l). Mercury was significantly associated with systolic blood pressure (979). Blood pressure was also investigated in a cross-sectional study among 1 240 US women in the NHANES 1999–2000. The mean concentration of mercury in blood was 1.8 μg/l. Fish consumers had a higher mean concentration than non-fish consumers, 2.3 and 0.8 μg/l, respectively. A significant relationship was found between blood mercury levels and systolic blood pressure among non-fish consumers but not among fish consumers. Intake of fish oils may counteract the harmful effects of mercury on blood pressure (1040).

Mercury exposure and oxidative stress were studied among fish-eating riparians living in the Brazilian Amazon. Both mercury in whole blood and in hair were significantly inversely related to several biomarkers of oxidative stress such as glutathione peroxidase, glutathione, catalase and δ-aminolevulinate dehydratase. These results further demonstrate a relation between mercury exposure and oxidative stress (356).

9.9.4 Meta-analysis of epidemiological studies of the general population

A meta-analysis of environmentally mercury-exposed subjects was conducted, based on four studies addressing CVD and five studies addressing CHD only. CHD was defined as non-fatal MI, angina, coronary revascularisation (i.e. percutaneous transluminal coronary angioplasty or coronary artery bypass surgery) or CHD death. Baseline (i.e. start of study) exposure estimates were derived from data on mercury levels in blood, hair and toenails. The calculations were based on a comparison between the top 3rd and the bottom 3rd of baseline levels of mercury. Risk estimates from separate studies were typically adjusted for basic demographics

e.g. age, sex, systolic blood pressure, smoking and history of diabetes. The RR (95% CI) was 0.94 (0.66–1.36) for CVD and 0.99 (0.65–1.49) for CHD (172).

9.9.5 Conclusion

Only one out of six occupational studies showed an increased risk of CVD after exposure to inorganic mercury (65).

Several population studies indicated a positive association between methylmercury exposure via fish consumption and MI. Animal data provide some support for oxidative stress and increased blood pressure caused by methylmercury.

There is *insufficient evidence* for an association between exposure to inorganic mercury and CVD.
There is *limited evidence* for an association between exposure to methylmercury and CVD.

9.10 Titanium dioxide

9.10.1 General

Titanium dioxide (TiO_2) is used in a wide variety of products including paints, plastics, rubber, ink and food products. The titanium-containing ore is mixed with either sulphuric acid or chlorine and subsequently heated or oxidised to produce titanium dioxide, which is then ground. Further treatments result in various grades of pigment. Titanium tetrachloride ($TiCl_4$) is produced as an intermediate in the chloride process (113). One commonly used welding electrode is coated with rutile (the most common crystal form of TiO_2) (877).

9.10.2 Animal studies

Atherosclerosis-prone ApoE-/- (knockout) mice were exposed to nanoparticles of titanium dioxide with diameters of 5–10 nm. The mice were divided into five groups and exposed groups were given tracheal instillations of nanoparticles at doses of 10, 50 or 100 µg, once per week for 6 weeks. One control group was given PBS vehicle intratracheally once weekly for 6 weeks, whereas the other control group received no tracheal instillation. After 6 weeks of exposure, there was a significant difference between the high-dose group and the PBS control group in terms of CRP, nitric oxide (NO), endothelial nitric oxide synthases (eNOS), total cholesterol and HDL cholesterol in serum. The results also showed significantly increased ratios of plaque area/luminal area and lipid-rich core area/plaque area in the mid- and high-dose groups. In summary, the study showed that tracheal instillation of nanoparticles induced considerable systemic inflammation, endothelial dysfunction and lipid metabolism dysfunction, contributing to the progression of atherosclerosis (162).

ApoE-/- mice were exposed to three different types of titanium dioxide particles (two nanosized and one fine sized). A single intratracheal instillation of one type of nanosized titanium dioxide particles (0.5 mg/kg bw) was associated with modest

plaque progression in the aorta while no effect on plaque progression was detected for the other types. No associations between the pulmonary titanium dioxide exposure and inflammation (influx of neutrophils) or vasodilatory dysfunction were detected (640).

Rats were exposed whole-body to 2.62 mg/m^3 of an aerosol of nanosized titanium dioxide for 2 hours, 1.72 mg/m^3 4 hours/day for 2 days or 3.79 mg/m^3 4 hours/day for 4 days. No significant pulmonary or cardiovascular changes were noted at low and middle exposure levels. However, the high exposure level caused significant increases in breathing rate, pulmonary inflammation and lung cell injury (623).

After a single intratracheal instillation of titanium dioxide nanoparticles (18, 54 and 162 µg) in mice, a dose-related increase of acute phase mRNA *Saa3* was observed. *Saa3* is expressed in various tissues in mice, including lung. In humans, *SAA3* is a pseudogene, i.e. is no longer coding for a protein (814).

9.10.3 Occupational epidemiological studies

A total of 15 017 workers (14 331 men and 686 women) were employed at least 1 month in 1 of 11 factories producing predominantly pigment-grade titanium dioxide in Europe. The period of follow-up ranged from 1950–1972 until 1997–2001. The SMRs (95% CIs) for IHD were 0.88 (0.81–0.95) for men and 0.63 (0.20–1.41) for women (113).

A US cohort comprised 4 241 workers employed at least 6 months at four titanium dioxide plants. All workers were employed on or after 1 January 1960 and were followed until 2000. The cohort was compared with the US population regarding mortality. The SMR (95% CI) was 0.9 (0.7–1.0) for all heart disease and 0.8 (0.5–1.2) for all CeVD. The RR (95% CI) regarding all heart disease did not increase with increasing cumulative exposure; lowest tertile 1.0 based on 22 cases, mid tertile 1.1 (0.7–1.8) based on 57 cases, and highest tertile 0.8 (0.5–1.4) based on 44 cases (319). Titanium dioxide was measured as total dust. Exact estimates of cumulative exposures were not presented.

Another US cohort comprising 3 607 workers employed at least 6 months in three DuPont titanium dioxide production facilities were followed 1935–2006. A larger proportion of workers was exposed to titanium dioxide (97%) than to titanium tetrachloride (81%) and 77% of the workers were exposed to both compounds. An internal analysis was performed and increased risk estimates for heart disease mortality and cumulative titanium dioxide exposure after a 10-year lag were observed, but without clear exposure-response relationships (Table 6). No increased risk was observed among workers exposed to titanium tetrachloride (251).

Exposure monitoring began around 1975 in the two US studies. Mean titanium dioxide exposures for packers, micronizers and addbacks were 6.2 mg/m^3 in the first study (319) and 8.1 mg/m^3 for packers and 8.46 mg/m^3 for grinders (i.e. micronizers) in the DuPont study (251). Similarly, mean exposure levels were 2.5 mg/m^3 (maintenance mechanics) (319) and 4.4 mg/m^3 (maintenance), respectively (251).

Table 6. Relative risk estimates for heart disease mortality and cumulative titanium dioxide exposure after a 10-year lag (251).

Cumulative TiO_2 exposure (mg/m^3-years)	RR (95% CI)
< 5	1
5–15	1.47 (1.02–2.11)
15–35	1.65 (1.16–2.34)
35–80	1.36 (0.92–2.00)
> 80	1.51 (1.00–2.25)

CI: confidence interval, RR: relative risk, TiO_2: titanium dioxide.

9.10.5. Conclusion

Three occupational cohort studies were found of which one showed an increased risk of heart disease mortality among titanium dioxide exposed workers (251). A few animal studies showed that pulmonary exposure to titanium dioxide nanoparticles induced modest plaque progression and increased the pulmonary acute phase *Saa3*-gene expression (162, 640, 814).

There is *insufficient evidence* for an association between exposure to titanium dioxide and CVD.

9.11 Zinc

9.11.1 General

Zinc is a bluish-white metal, which is stable in dry air but will be coated with zinc oxide in moist air. Zinc is used as protective coating for other metals (galvanised steel), in dye casting, in non-corrosive alloys and in brass. Inorganic zinc compounds are used in automotive equipment, storage and dry cell batteries, and dental, medical and household applications (826). Zinc chloride-based smoke bombs and screens have been used since World War II (249).

9.11.2 Human experimental studies

Human volunteers inhaling 2.5 and 5 mg/m^3 of zinc oxide fume for 2 hours exhibited mild fever and increased plasma concentrations of IL-6 (289). In a later study, sheet metal workers occupationally exposed to low levels of zinc oxide were experimentally exposed once to 5 mg/m^3 zinc oxide for 2 hours. Despite a mild clinical response, the mean plasma IL-6 levels increased significantly after exposure. In naïve subjects, the inflammatory response decreased during exposure for 3 successive days (290). These experiments indicate an adaptation with a milder inflammatory response after repeated exposures.

Sixteen healthy subjects were exposed to filtered air and nanosized zinc oxide particles (sham, 0.5, 1.0 and 2.0 mg/m^3) for 4 hours on 4 different days, including 2 hours of cycling at a low workload. Exposures were randomised and double-blinded, with the exception of the exposure to 2.0 mg/m^3, which was blinded according to instructions from the ethic committee. The effects were assessed before, immediately after, and about 24 hours after each exposure. Concentration-

dependent increases in symptoms, body temperature, acute phase proteins and neutrophils in blood were detected after zinc oxide inhalation. Significant effects were detected at concentrations ≥ 1.0 mg/m^3, with the most sensitive parameters being inflammatory markers in blood; CRP and SAA (659).

Twelve healthy subjects were exposed to filtered air and 0.5 mg/m^3 freshly generated zinc oxide in the fine or ultrafine fractions for 2 hours at rest. Exposure to zinc oxide did not cause any significant increase of symptoms, leukocyte surface markers, haemostasis, cardiac electrophysiology, IL-6, SAA or fibrinogen (78).

The different outcomes of these two last experiments (78, 659) may be explained by differences in exposure time (4 vs 2 hours) and workload (cycling vs rest).

9.11.3 Case reports

A case report described a 25-year-old male welder exposed to zinc fumes with metal fume fever together with aseptic meningitis, pericarditis, pleuritis and pneumonitis (387).

9.11.4 Occupational epidemiological studies

Welders are sometimes exposed to zinc oxide fume when welding in galvanised steel. In a survey, 31% of welders aged 20–59 years had experienced metal fume fever on at least one occasion (801). However, all metal fume fevers are not caused by zinc oxide.

Inhalation of zinc chloride smoke may cause airway irritation. Intoxication with clinical signs has mainly been associated with war situations and in military and fire emergency training sessions in enclosed spaces. Symptoms follow a biphasic course mainly characterised by dyspnoea, coughing and lacrimation, in the first 6 hours, followed by reappearance of early signs complemented with inflammation related signs and tachycardia from 24 hours onwards (249). Two soldiers were fatally injured by accidental inhalation of zinc chloride from a smoke bomb. Although exposure was relatively short, but to a high smoke concentration, acute injury was minor and for 10 days the patients were clinically satisfactory. Unexpectedly, both then rapidly developed features typical of severe adult acute respiratory distress syndrome (ARDS) with pulmonary hypertension. Lung vascular injury was assessed by angiography and morphometric techniques. Vessels showed a significant lumen reduction in vessel external diameter. In microvessels, there was obliteration and widespread occlusion by endothelial cell proliferation and clot (419).

9.11.5 Epidemiological studies of the general population

The California Teachers Study comprised approximately 45 000 women who were followed 2002–2007. Long-term airborne exposure to $PM_{2.5}$ doubled the mortality from IHD. Zinc exposure correlated with $PM_{2.5}$ exposure but had a much weaker effect (727).

In a joint analysis of 19 European cohorts, no statistically significant associations were found between zinc particulate ($PM_{2.5}$ and PM_{10}) exposure and CVD mortality (985).

9.11.6 Conclusion

Inhalation of zinc oxide can cause an inflammatory response with fever. Environmental zinc exposure was weakly associated with IHD in one study (727). No long-term occupational cohort studies of zinc exposed workers were identified.

In a human experimental study, inhalation of 1 and 2 mg/m^3 of zinc oxide nanoparticles for 4 hours induced increased plasma levels of the acute phase proteins SAA and CRP, which have been suggested as biomarkers of particle-induced CVD (659).

Inhalation of zinc chloride fume may affect the lung parenchyma and cause lung vascular injuries (249, 419).

There is *insufficient evidence* for an association between exposure to zinc and CVD.

10. Other dusts and fumes

10.1 Welding and soldering fumes

10.1.1 Welding fumes

10.1.1.1 General

Welding processes generate both respirable particles and gases. Welders are generally exposed to small particles of iron but also to many other particles of metal or non-metal origin (300). Most of the primary particles in welding aerosols have diameters of 5–40 nm. All types of primary particles have a tendency to form chainlike agglomerates and grow to sizes between 0.1 and 1 μm, regardless of the welding technique. A clear size dependence of the particle chemical composition was encountered in the case of manual metal arc welding aerosol. Small particles with diameters < 50 nm were mostly metal oxides in contrast to larger particles which also contained more volatile elements (87). Tungsten inert gas (TIG) welding generated the highest number of ultrafine particles (particles < 100 nm) but rather low mass concentrations expressed as mg/m^3 (550). During friction stir welding of aluminium, the number of airborne nanoparticles may reach the same levels as during TIG-welding (746).

The generation of fumes from different welding techniques and working conditions was studied. Flux cored arc welding generated more smoke than manual metal arc welding (mean 15 mg/m^3 vs 4 mg/m^3). In addition, welding in confined spaces was associated with higher levels of particles compared with welding in more open spaces or large workshops (mean 13 mg/m^3 vs 4 mg/m^3) (412).

Epidemiological studies and risk estimates are presented in Appendix, Table A17.

10.1.1.2 Animal studies

Atherosclerosis-prone ApoE-/- mice were exposed to 40 mg/m^3 of stainless steel welding fumes [generated from metal active gas (MAG) welding, with a shielding

gas containing 95% argon and 5% carbon dioxide], 3 hours/day for 10 days. Inflammatory serum proteins IL-1β and monocyte chemoattractant protein 3 were increased 2 weeks after welding fume exposure. Thus, the exposure caused systemic inflammation and in addition increased plaque progression (34, 262).

10.1.1.3 Occupational epidemiological studies

An increased mortality from IHD was observed in some studies among welders compared to the general population (441, 675, 705, 1039). Other cohort studies of welders did not demonstrate any significant differences regarding diseases of the circulatory system compared to the general population (75, 627, 641, 763, 868, 876, 904), and in one study a significantly decreased risk was observed (74). An increased CeVD incidence or mortality among welders was found in two out of four studies (422, 441, 627, 675).

Some cohort studies of welders with more adequate referent cohorts are available. In 2002, male welders were compared with gainfully employed men, and the SMRs regarding IHD were significantly increased; 1.06 in a long follow-up (25 years) and 1.35 in a short follow-up (5 years) (882). The different risk estimates between these follow-up periods may be explained by a larger proportion of retired and consequently non-exposed welders in the cohort with long-term follow-up. In 2012, Wiebert *et al*. compared welders with manual workers not exposed to particles. Welders had an increased risk of morbidity/ mortality due to MI with HRs of 1.19 and 1.29, for males and females, respectively (1015). This sequence of studies with improving quality supports an association between welding fume exposure and IHD.

A Swedish case-control study estimated the RR (95% CI) of first MI in various occupational groups. Male welders and flame cutters had an increased risk after adjustment for age, county and calendar year (1.1, 1.0–1.3), but not after adjustment for age, county and socioeconomic group (1.0, 0.9–1.2) (377).

Later studies were better designed and included both fatal and non-fatal cases of disease. In a Danish study, 8 376 male metal workers answered a questionnaire about welding experience and lifestyle. The cohort of 5 866 welders was followed from the start of 1987 (baseline) until the end of 2006. A JEM based on more than 1 000 measurements of ambient air particles in the workplace 1971–1985 was used to estimate the cumulative exposure to welding fume particles. Air samples had been collected on filters placed in the breathing zone inside welding helmets. Exposures before 1971 were estimated by extrapolation, assuming a declining trend in exposure in all welding processes during 1971–1985. Cumulative exposure after baseline was estimated by an average exposure for 1980–1985 multiplied by number of years in the welding industry after baseline. The mean cumulative estimated particulate exposure was 53.1 mg/m^3-years before baseline (1924–1986) and 8.7 mg/m^3-years after baseline (1987–2006). Information of CVD was retrieved from the Danish National Patient Registry. Increased risks (SIR, 95% CI) were observed regarding acute MI (1.1, 1.0–1.2), chronic IHD (1.2, 1.1–1.3) and cerebral infarction (1.2, 1.1–1.4) (441).

Gas welders are seldom separated from electric arc welders in epidemiological studies. However, one study showed a higher SMR regarding CVD in gas welders (SMR 1.22) than in electric arc welders (SMR 0.92) (763). This might be a chance finding, but gas welding in badly ventilated areas has been associated with high levels of carbon monoxide (35). A study of lung cancer found a higher risk among welders exposed for more than 25 years only to gas welding fumes than among welders exposed only to arc welding fumes (601). If this difference between gas and electric arc welders is real, agent(s) other than carbon monoxide must be responsible. There might be a common agent (e.g. PAH) causing both CVD and lung cancer among gas welders. A Finnish JEM presented associations between welding fume and PAH exposures particularly among smelters and foundry workers (866).

A cohort of 2 818 male welders employed before 1980 with at least 6 months employment in an iron-steel plant in Anshan, China, was followed until 1993. Non-exposed blue-collar workers from the same plant were used as referents. Increased mortality risks (SRR, 95% CI) were observed for acute MI (2.0, 1.1–3.6) and CeVD (1.3, 1.2–1.4) (422).

10.1.1.4 Meta-analysis of epidemiological studies

In a meta-analysis, 18 studies were identified with estimates of IHD morbidity or mortality among workers exposed to welding fumes. The weighted RR (95% CI) for IHD was 1.09 (1.00–1.19) based on 10 studies. The RR (95% CI) was 1.39 (0.96–2.02) among studies using an internal reference group and 1.08 (0.99–1.18) among studies with an external reference group. The heterogeneity of the effect estimates in these calculations was moderate to high (I^2: 65, 72 and 62%, respectively). An increased RR (95% CI) was observed for acute MI (1.69, 1.18–2.42) but not for other IHD (1.06, 0.98–1.14). The heterogeneity of the effect estimates in the calculation of acute MI was low (I^2: 0%). Information was lacking to evaluate risks related to specific welding characteristics (655). The study by Wiebert *et al.* (1015) was not included in this meta-analysis.

10.1.1.5 Exposure-response relationships

In a French study of 2 721 welders from 13 factories including 3 shipyards, a relationship was found between duration of employment and mortality from IHD. Employment for ≥ 20 years was associated with a significantly increased mortality from IHD (SMR 1.79, $P < 0.05$) (675).

The Danish study of welders, designed with internal comparisons of the cohort with adjustment for tobacco smoking, alcohol and hypertension medicines, showed a significantly increasing HR for chronic IHD and non-significant increases for acute MI, angina pectoris and cerebral infarction with increasing exposure to particles. Cumulative particulate exposures of 10–50, 50–100 and > 100 mg/m^3-years were associated with HRs (95% CIs) for chronic IHD of 2.51 (1.15–5.49), 2.79 (1.29–6.04) and 1.70 (0.78–3.72), respectively (441). The strength of this study is weakened by the low number of cases in the referent group (n = 7) and the broken

trend at the highest cumulative exposure, although the latter may be explained by the healthy worker survivor effect. The lowest cumulative exposure category of 10–50 mg/m^3-years of welding fumes corresponds to 0.25–1.25 mg/m^3 for 40 years.

10.1.1.6 Markers of effect

An increase of the inflammatory marker CRP was observed 16 hours after exposure among welders from an apprentice welding school who worked mainly in low-alloy steel one day with a mean exposure of 1.7 mg/m^3 measured as $PM_{2.5}$ (492).

Blood levels of acute phase proteins increased in a group of 15 human volunteers after experimental exposure for 6 hours to welding fumes containing copper and zinc (71).

10.1.2 Soldering fumes

The Copenhagen Male Study comprised 2 974 men in 1985–1986 when a new baseline or starting point was established. The cohort was followed until 1991. An increased incidence (RR, 95% CI) of IHD was found after 5–15 years of soldering fume exposure (2.0, 0.9–4.7) and after > 15 years of exposure (2.2, 1.2–4.0), after adjustment for age, smoking, alcohol, physical activity, systolic and diastolic blood pressure, hypertension, BMI, cholesterol, triglycerides and retirement status (923). A later study investigated lifetime prevalence of MI and incidence of IHD in an 8-year follow-up. More than 5 years exposure to soldering fumes among men with blood type O was associated with an increased prevalence of MI (OR 3.0, 95% CI 1.6–5.8). A similar but weaker association between blood type O and IHD incidence was found for those exposed more than 5 years to soldering fumes (OR 1.8, 95% CI 1.0–3.2) (924).

10.1.3 Conclusion

Epidemiological studies of welders with adequate referent groups showed increased risks of IHD. A meta-analysis demonstrated a significantly increased risk of IHD, from exposure to welding fumes. An increased risk of acute MI was also found, based on three studies, which was associated with low heterogeneity in effect estimates (655). One study of welders showed increasing risks for IHD with increasing cumulative particulate exposure, but the trend was broken at the highest level. A cumulative particulate exposure of 10–50 mg/m^3-years (the lowest exposure category) was associated with a significantly increased risk for chronic IHD. Exposure to 10–50 mg/m^3-years corresponds to 0.25–1.25 mg/m^3 for 40 years of welding fumes (441). There were four epidemiological studies on welders addressing CeVD, two of which showed an increased risk (422, 441).

An increased risk of IHD was reported in the only cohort located regarding exposure to soldering fumes (923, 924).

There is *moderately strong evidence* for an association between exposure to welding fumes and IHD.

There is *insufficient evidence* for an association between exposure to soldering fumes and CVD.

10.2 Metalworking fluids

10.2.1 General

Metalworking fluids are complex mixtures used as coolants, lubricants and anti-corrosives in a variety of industrial metal machining operations. Metalworking fluids may be petroleum- or water-based and are generally classified in three categories: straight (mineral oil), soluble and synthetic. Exposure to metalworking fluids is widespread throughout the world (168).

10.2.2 Animal studies

Rats were exposed nose-only to aerosols of metalworking fluid (10 mg/m^3) contaminated with endotoxins (0, 0.8, 1.6 and 3.2 μg/m^3) for 3 hours. There was a significant exposure-related increase of neutrophils in the bronchoalveolar lavage when the metal working fluid was contaminated with endotoxins over the whole exposure range (220).

Guinea pigs were exposed to neat (unused) or in-use metalworking fluids by inhalation. The animals exhibited significant inflammation resulting from metal-working fluids exposure marked by a change in neutrophils in bronchoalveolar lavage fluid from 3% among controls (neat) to 60–79% among those exposed (in-use). The in-use metal working fluid contained varying concentrations of endotoxins (960).

10.2.3 Occupational epidemiological studies

A cohort of 4 825 female autoworkers was followed 1980–2004 and compared with the mortality in Michigan. The SMR (95% CI) from IHD was 1.08 (0.93–1.24), based on 201 cases (311).

Hypersensitivity pneumonitis is a complex syndrome resulting from repeated exposures to a variety of organic particles (854). This type of pneumonitis has been observed in the automotive industry among metalworking fluid-exposed workers. Strong candidates for microbial aetiology are non-tuberculous mycobacteria and fungi (515). Acute hypersensitivity pneumonitis is characterised by an influenza-like syndrome occurring hours after substantial exposure. Acute or subacute episodes may evolve to chronic hypersensitivity pneumonitis. Pulmonary hyper-tension develops in approximately 20% of patients with chronic pneumonitis and is associated with an increased fatality rate (854).

10.2.4 Exposure-response relationships

A US cohort of 39 412 autoworkers (88% men) who had worked at least 3 years 1938–1985 in one of three Michigan automobile manufacturing plants was followed through 1994. The relationship between current or cumulative exposure to straight

Table 7. Cumulative exposures to straight metalworking fluid ($PM_{3.5}$) and hazard ratios for IHD mortality (200). [a]

Cumulative exposure (mg/m^3-years)	No. of cases	HR (95% CI)
0	214	1.0
< 0.06	67	1.42 (1.04–1.94)
0.07–0.22	69	1.13 (0.83–1.55)
0.23–0.68	68	0.88 (0.64–1.21)
0.68–2.77	68	1.29 (0.97–1.72)
> 2.77	67	1.53 (1.15–2.05)

[a] The exposure-response model was weighted by the stabilised inverse probability of staying at work. CI: confidence interval, HR: hazard ratio, IHD: ischaemic heart disease, $PM_{3.5}$: particulate matter with maximal aerodynamic diameter of 3.5 μm.

metalworking fluid as $PM_{3.5}$ and IHD mortality was investigated by Cox proportional hazard models. Age, calendar year of follow-up, sex, race and plant were included in each model. There was a U-shaped cumulative exposure-response curve with an elevated HR of 1.42 in the category with lowest exposure and of 1.53 in the category with highest exposure to straight metalworking fluid (Table 7). There was no clear association with current exposure. The authors concluded that the results provided modest evidence that occupational exposure to fine particulate matter from straight fluids, especially those with higher PAH content, increases the risk of IHD mortality. There was no relationship between cumulative exposure to soluble or synthetic fluids and IHD mortality (200). Chevrier *et al*. used the cohort of Michigan autoworkers to address the healthy worker survivor effect. The cohort of 38 747 workers, who had worked at least 3 years 1941–1982, was followed until 1994. After adjustment for the healthy worker survivor effect by g-estimation of accelerated failure-time models, 5 years of exposure was related to an increased risk of IHD (HR 1.15, 95% CI 1.11–1.19) (168).

A subcohort of US aluminium workers comprising 7 211 workers in aluminium fabrication, employed for more than 2 years 1996–2012, was followed 1998–2012. The $PM_{2.5}$ exposure was mostly composed of water-based metalworking fluids. The median $PM_{2.5}$ exposure was 0.20 mg/m^3 and the 10^{th} percentile was 0.06 mg/m^3. RRs were based on a comparison between exposures above and below these two concentrations. The RRs (95% CIs) regarding IHD at the cut-offs 0.20 mg/m^3 and 0.06 mg/m^3 were 1.14 (0.80–1.63) and 1.45 (1.13–1.86), respectively (127).

Another subcohort of US aluminium fabrication workers comprised 8 290 workers who were employed at least 2 years. Follow-up started in 1998 in some facilities and in 2005 in others and was ended in 2009. The HR for recent $PM_{2.5}$ exposure and incidence of IHD rose in fabrication to 1.5 at 1.25 mg/m^3 and was statistically significant throughout most of the exposure range (0.25–1.25 mg/m^3) (199).

10.2.5 Indirect evidence

Several studies showed increased rates of respiratory symptoms such as cough and phlegm among workers exposed to metalworking fluids (26, 472, 607, 782). Automobile workers at three General Motors facilities were studied by questionnaire for

possible respiratory effects resulting from airborne exposures to metalworking fluids. A total of 1 042 machinists worked at the time of the study and were exposed to one of three types of metalworking fluid aerosols; straight mineral oils, soluble oil emulsions or water-based synthetic fluids that contained no oils. Assembly workers (n = 769) without direct exposure served as an internal reference group. Several respiratory symptoms as well as physician-diagnosed chronic bronchitis were primary outcomes. Machinists as a whole had higher prevalence of cough, phlegm, wheezing and breathlessness than assembly workers. Increased levels of current exposure to straight oils were associated with higher prevalences of phlegm and wheeze, after adjusting for confounders. Increased current exposure levels of synthetic fluids were associated with cough, phlegm, wheeze, chest tightness and chronic bronchitis. In models that included both past and current exposure, only current exposures to straight and synthetic fluids were associated with current symptoms (351). These relationships between exposure to metalworking fluids and respiratory symptoms may be regarded as an indirect evidence of a relation between exposure and CVD, as chronic bronchitis is related to CVD (Section 4.1).

10.2.6 Conclusion

Among the few epidemiological studies that were located on metalworking fluid exposure, increased risks of IHD were shown in the automotive industry (200) as well as in aluminium fabrication (127, 199). One of these studies demonstrated a significantly increased risk of IHD from recent metalworking fluid exposure in the range 0.25–1.25 mg/m^3. Recent exposure to 1.25 mg/m^3 ($PM_{2.5}$) of metalworking fluid was associated with an HR of 1.5 (199).

There is *limited evidence* for an association between exposure to metalworking fluids and IHD.

10.3 Wood industry

10.3.1 General

Wood dust is a complex mixture, generated in the processing of wood. Its composition varies considerably depending on the species of tree being processed. Wood dust is composed mainly of cellulose (approximately 40–50%), polyoses, lignin and a large and variable number of substances of lower molecular mass which may significantly affect the properties of the wood (440).

Trees are characterised botanically as gymnosperms (principally conifers, generally referred to as softwoods) and angiosperms (principally deciduous trees, generally referred to as hardwoods). Softwood and hardwood are not botanical concepts, referring to the species of tree and not directly describing the hardness of wood (440).

In 2000–2003, about 3.6 million workers in the EU were occupationally exposed to inhalable wood dust. Of those, construction employed 1.2 million workers (33%), mostly construction carpenters. The proportions of exposed workers were 20% in

the furniture industry, 9% in the manufacture of builders' carpentry, 5% in sawmilling, 4% in forestry and less than 100 000 in other wood industries. About half of the workers (52%) were exposed to inhalable dust concentrations > 1 mg/m^3 and 16% were exposed to levels > 5 mg/m^3 (482). Airborne fungi or fungal spores have been present in sawmills (79, 274, 376).

Epidemiological studies and risk estimates are presented in Appendix, Table A18.

10.3.2 Occupational epidemiological studies

Two Swedish studies showed an increased risk of heart disease among wood dust exposed workers. A cohort of 20 854 wood dust exposed construction workers was compared with 71 778 unexposed controls. Exposed workers had a higher risk of IHD (RR 1.12, 95% CI 1.04–1.20) after adjustment for age, smoking, hypertension and BMI. The risk for CeVD was, however, not increased (967). A case-control study of MI revealed an increased risk (RR, 95% CI) among male frame and circular sawyers and planers (1.7, 1.0–3.0) and among female bench carpenters and cabinet makers (2.0, 1.0–3.9) after adjustment for age, county and socioeconomic group (377).

All economically active persons in Finland were included in a census study. Occupation was registered in 1970 and the follow-up period was 1971–1991. Increased risks regarding MI as well as CeVD were observed among both male and female forestry workers and log floaters (713).

A cohort of 10 322 male workers in woodworking industries was compared with 406 798 non-wood workers in the US. The study started in 1959 and the cohort was followed until 1972. No comparisons showed significantly increased risks of CHD among the wood workers (913).

A cohort of model and pattern makers in a German automobile company was formed 1960–1985 and was exposed to a wide variety of different materials including wood, stone powder, metals, plastics and organic solvents (76, 77). These studies are therefore not included in the overall evaluation.

Occupation and industry codes on death certificates from 19 US states were analysed to evaluate mortality risks among men and women usually employed in construction occupations and who died 1984–1986. There was a decreased PMR among white male carpenters for IHD (0.94, 95% CI 0.92–0.97) (784).

The relationship between carpentry and development of CHD, stroke and total mortality was examined among men of Japanese ancestry participating in the Honolulu Heart Program. After 18 years of follow-up, men who indicated that their present and usual occupation was carpentry had a significantly lower age-adjusted rate of definite CHD and a significantly lower total mortality rate compared to participants who were never occupied as carpenters. These results were unchanged when controlling for several cardiovascular risk factors and potentially confounding variables (647).

In general, a decreased risk of CVD was found in studies comparing a wood dust exposed group with national or regional populations (6, 644, 645, 726).

10.3.3 Pooled analyses

A combined cohort consisted of 28 704 persons from five cohorts: British furniture workers, members of the union representing US furniture workers, two cohorts of plywood workers and one of wood model makers (6, 105, 106, 644, 645, 783, 796). Pooled analyses carried out for all cohorts combined, the two furniture worker cohorts combined, and the two plywood workers cohorts combined, showed no increased mortality from circulatory diseases or IHD. For all cohorts combined, SMRs (95% CIs) were 0.8 (0.7–0.8) and 0.8 (0.7–0.8), respectively (225).

10.3.4 Indirect evidence

Cryptogenic fibrosing alveolitis, synonymous with idiopathic pulmonary fibrosis, is probably a disease entity of increasing frequency (425). Idiopathic pulmonary fibrosis has been associated with a prothrombotic state (693) and with various co-morbidities including cardiovascular manifestations such as pulmonary hypertension, heart failure, coronary artery disease and atrial arrhythmias (11). Idiopathic pulmonary fibrosis has been associated with occupational wood dust exposure (55, 359, 426, 448, 749).

10.3.5 Conclusion

Three studies from Sweden and Finland indicated a relationship between exposure in the wood industry and CVD, but no exposure-response information was found (377, 713, 967). A pooled analysis did not show increased risks for CVD (225).

There is *limited evidence* for an association between exposure in the wood industry and CVD.

10.4 Pulp and paper industry

10.4.1 General

Worldwide, the pulp and paper industry employs hundreds of thousands of workers. Production of pulp and paper is an important sector of Finnish, Norwegian and Swedish industries. The historical production was dominated by the sulphite process but today the sulphate process has taken the lead. The occupational chemical exposures in this industry comprise paper dust but also e.g. wood dust, calcium carbonate, chlorine, chlorine dioxide, formaldehyde, hydrogen sulphide, organic sulphides, sulphur dioxide, terpenes, and cutting and lubricating oils (31, 481, 508, 712, 738). The exposures vary considerably between processes and departments (969). Further exposures include microorganisms (388), noise, heat and shift work (508, 536).

Epidemiological studies and risk estimates are presented in Appendix, Table A19.

10.4.2 Occupational epidemiological studies

A Swedish cohort of 18 163 male and 2 291 female pulp and paper mill workers employed 1939–1999 and with more than 1 year of employment was followed 1952–2001. The total Swedish population served as referents. SMRs (95% CIs) for total mortality was 1.02 (0.98–1.06) among men in the sulphate mills and 0.93 (0.90–0.97) among men in the sulphite mills. Mortality (SMR, 95% CI) from acute MI was increased among both the sulphate (1.22, 1.12–1.32) and sulphite (1.11, 1.02–1.21) mill male workers. Male mortality was also increased due to the same diagnose in the department of sulphate pulping (1.29, 1.07–1.54), paper production (1.26, 1.06–1.49) and maintenance (1.16, 1.02–1.30). Mortality from CeVD was not increased in males. In female workers, there were no significantly increased risks (30).

The mortality pattern among Swedish pulp and paper mill workers was evaluated in a case-control study encompassing 4 070 men deceased 1950–1987. The subjects were identified from the register of deaths and burials in six parishes and 619 were identified as pulp and paper mill workers. No increased risks of IHD or CeVD were observed (1028).

In a Swedish case-control study, the risk of a first MI was estimated in various occupational groups. Totally 26 847 male cases were identified from both hospital discharge and death records. Two referents for each case were randomly selected from the study base. Increased risks (RR, 95% CI) were found among paper and paperboard workers (1.6, 1.0–2.7) and paper pulp workers (1.3, 1.0–1.7), after adjustment for age, county and socioeconomic group (377).

Mortality among workers in the Finnish pulp and paper industry was evaluated in a retrospective cohort study of 3 520 workers who had been employed continuously for at least 1 year 1945–1961. Mortality was followed up until 1981. National mortality rates were used for comparison. Overall mortality for the entire cohort did not differ from that expected (1 044 observed vs 1 029 expected, SMR 1.01), but there was an excess of deaths (SMR, 95% CI) from diseases of the circulatory system among men (1.21, 1.09–1.34). This was due to the excess of deaths from IHD found in the sulphite (1.31, 0.97–1.73), sulphate (1.42, 1.15–1.74) and paper (1.38, 0.95–1.93) mills and maintenance department (1.18, 1.01–1.38), but not in the saw mill. The existing smoking data did not explain the finding (467).

The previously described cohort was further analysed regarding sulphite mill workers exposed to sulphur dioxide and sulphate mill workers exposed to hydrogen sulphide and organic sulphides. Among those exposed to sulphur dioxide, an excess of CVD deaths was noticed among males (24 observed vs 19.4 expected, SMR 1.23) due to an excess of coronary deaths (18 observed vs 12.4 expected, SMR 1.45). The CVD mortality was not affected by the duration of occupational exposure or follow-up period. Among men exposed to hydrogen sulphide and organic sulphides, there was also an excess of CVD deaths (37 observed vs 24.7 expected, SMR 1.50) due to an excess of coronary deaths (25 observed vs 16.7 expected, SMR 1.50). These excesses increased with longer follow-up period. The increased CVD mortality in the sulphate mill cohort could not be explained by common cardiovascular risk

factors and may therefore have been associated with the occupational exposures (469).

All economically active persons in Finland were included in a census study. Occupations were registered in 1970 and the total cohort follow-up period was 1971–1991. Male pulp mill workers had an increased mortality caused by IHD other than MI (SMR 1.34, 95% CI 1.10–1.64) (713).

A total of 3 143 female pulp and paper workers first employed 1920–1993 were included in a Norwegian cohort. The follow-up period was 1951–2000. SMRs were calculated using the national female mortality rates as referents. Poisson regression analysis was used to examine internal relations between the duration of employment in paper departments and the risk of death from selected causes. The study showed increased risks (SMR, 95% CI) for CVD (1.17, 1.05–1.30), IHD (1.22, 1.03–1.43) and CeVD (1.16, 0.94–1.42). Analysis by department showed that paper department workers with short-term employment had the highest mortality risk. Internal analyses revealed a 5% increase in the risk of dying from IHD among paper department workers exposed to paper dust. The risk decreased with increasing duration of employment (536).

A cohort of 4 242 men and women employed at a Scottish paper mill between 1955 and 1992 was followed until 1994. No increased mortality (SMR, 95% CI) was found for CVD (1.00, 0.92–1.08), IHD (0.98, 0.88–1.09) and CeVD (1.12, 0.94–1.33) (184).

A French cohort comprising 5 529 male and 876 female pulp and paper mill workers employed in four factories was followed 1968–1992. The CVD mortality (SMR, 95% CI) was 0.80 (0.68–0.93) (1021).

Mortality was studied in a cohort of 3 241 workers employed 1970–1992 in four pulp and paper mills in Catalonia, Spain. SMRs were derived using mortality rates of Spain as the reference. For all workers, the SMR (95% CI) from CVD was 0.55 (0.39–0.74) (821).

There are several studies from the US including two proportionate mortality studies utilising death certificates and work histories. Solet and coworkers collected data from 1 010 decedent members of the United Paperworkers International Union who died 1970–1984. A total of 201 white men had worked in pulp and paper production. The PMR regarding arteriosclerotic heart disease was 1.00 (95% CI 0.78–1.26) (893). Another study comprised 2 113 US and Canadian members of the Pulp, Sulfite, and Paper Workers' Union, 1935–1964. There was a non-significantly increased risk of circulatory diseases (PMR 1.14) among pulp and paper workers. Similar risk estimates were observed in several subgroups (643). The US cohort studies of pulp and paper workers did not demonstrate any increased risks of CVD compared with national rates (398, 399, 609, 787, 1035). However, an internal comparison showed an increased risk of CVD in other chemical pulping processes, excluding sulphate (Kraft) and sulphite pulping (609).

A cohort study of 8 456 pulp and paper mill workers from New Zealand who worked at least 1 year between 1978 and 1990 did not show any increased mortality due to diseases of the circulatory system (SMR 0.78, 95% CI 0.64–0.93) (624).

10.4.3 Pooled analyses

A cohort comprised 57 613 pulp and paper workers (51 240 men and 6 373 women) who had worked at least 1 year in this industry in Brazil, Denmark, Finland, France, Japan, New Zealand, Norway, Poland, South Africa, Spain, Sweden or the US. The subgroup with high sulphur dioxide exposure did not exhibit an increased mortality of diseases of the circulatory system (SMR 0.96, 95% CI 0.86–1.07) (549).

10.4.4 Exposure-response relationships

The influence of exposure duration in the pulp and paper industry on the risk for CVD was addressed in a few studies, but no positive exposure-response relationships were observed (184, 469, 536, 1035).

10.4.5 Markers of effect

The relationship between several metrics of exposure and some traditional markers of inflammation in blood (CRP, SAA and fibrinogen) was studied among workers in a Swedish pulp and paper mill. The mean 8-hour TWA concentration of personal sampled inhalable dust was 0.30 mg/m^3 (range 0.005–3.3). Statistically significant relationships were found between personal sampled total dust exposure and the three inflammatory markers. There were also statistically significant relationships between inhalable dust levels (personal sampling) and levels of CRP and SAA. Exposure below 0.46 mg/m^3 was not related to CRP and SAA (1010).

10.4.6 Conclusion

Five studies from Finland, Norway and Sweden indicated a relationship between exposure in the pulp and paper industry and CVD mortality, but no positive relationships between exposure duration and CVD were observed (30, 377, 467, 536, 713). One study, however, showed a positive relationship between particle exposure and some inflammatory markers in the blood of pulp and paper mill workers (1010).

There is *moderately strong evidence* for an association between exposure in the pulp and paper industry and CVD.

10.5 Textile industry

10.5.1 General

Over 60 million people are employed in the textile or clothing industry worldwide (528). Textile workers are exposed to textile dusts, both natural and synthetic, throughout the textile manufacturing process. The largest single exposure in this industry is cotton dust. Airborne exposure to endotoxins occurs in cardrooms in the cotton industry and during wool carpet-weaving. Textile workers are also exposed to many chemicals which are used in dyeing processes and in crease-resistance and flame-retardant treatments (434).

In 1861, Greenhow was one of the first British observers to describe a respiratory disease in the cotton trade characterised by difficulty in breathing. It was recorded

that card room workers were apt to become asthmatic about middle life and that few were very long-lived. This disease was later referred to as "byssinosis" (837). Subjects exposed by inhalation to dust from cotton, flax or soft hemp may develop a characteristic feeling of chest tightness on Mondays accompanied by an impairment of respiratory function. This reaction is classically referred to as the first stage of byssinosis (839).

The first reference made to CVD mortality among cotton workers by the Registrar General is in the Annual Report from 1891. The mortality of cotton operatives from circulatory diseases showed an excess of one-fifth compared to occupied males. Also 10 years later, in 1901, the Registrar General recorded a slight excess in the death rates of cotton workers from circulatory diseases (837). Old reviews from the 1880–1932 Decennial Supplements to the Annual Report of the Registrar General of Births, Deaths and Marriages in England and Wales revealed increased overall mortality for employed males (particularly excesses among older cardroom and blowroom operatives) for CVD and respiratory diseases [cited in reference (633)].

Epidemiological studies and risk estimates are presented in Appendix, Table A20.

10.5.2 Occupational epidemiological studies

Two studies compared textile workers with gainfully employed or economically active persons. A Swedish study found an increased mortality among men due to IHD (SMR 1.15, 95% CI 1.08–1.22) based on 988 cases (888). A Finnish study showed an increased mortality due to CeVD among male weaving machine operators (SMR 2.05, 95% CI 1.02–3.70) based on only 11 cases (713).

A cohort of all people in Denmark aged 20–59 years in 1981 was followed up for 4 years for emigration, death and hospital admission for IHD as the primary diagnosis. The data set allowed tabulation of rates of hospitalisation by occupation, position and industry. A group at significant excess risk of IHD was e.g. self-employed males in the textile industry (standardised hospitalisation ratio 1.85, 95% CI 1.03–3.35) (973).

A Polish cohort of textile workers comprising 2 852 males and 4 693 females who had worked ≥ 10 years in one of the Lódź cotton plants 1964–1993 was followed through 1995. Polish national rates served to calculate SMR values. Male workers had an increased mortality (SMR, 95% CI) for atherosclerosis (1.45, 1.25–1.67) but not for circulatory diseases (0.99, 0.91–1.08), IHD (0.92, 0.78–1.08) or CeVD (0.81, 0.62–1.05). The highest risks were found for atherosclerosis in the weaving (1.41, 1.07–1.83) and spinning (1.75, 1.29–2.33) departments. Female workers had no significantly increased risk for any CVD diagnosis (933).

Occupational mortality data (1970–1972) for England and Wales showed an increased risk among male textile workers for circulatory disease (SMR 1.21) and CeVD (SMR 1.47). After social class standardisation, the SMRs decreased to 1.12 and 1.36, respectively (350).

Two proportional mortality studies with subjects from England and Wales (1979–2000), and Rhode Island, US (1968–1978), showed increased risks for IHD with the most consistent increases found among weavers (243, 1051), spinners and winders (1051).

A US cohort of 1 444 white workers (1 062 men and 382 women) employed at two cotton mills in North Carolina some time 1937–1940 was followed 1940–1975. There were increased mortalities from arteriosclerotic heart disease among males (SMR 1.37, $P < 0.01$) and females (SMR 1.58, $P < 0.02$) in the yarn processing (633).

Most studies focused on cotton textile workers but one cohort study investigated workers of a synthetic textiles plant in Quebec, Canada. The cohort consisted of 7 487 men and 2 724 women who had worked at least 1 year at the plant, and who were either working in 1947 or were newly employed between 1947 and 1977. The period of follow-up was 1947–1986. Relationships between duration of exposure and mortality were investigated by internal analyses. Among men, risks for IHD increased with length of service at the plant even though the SMRs were less than unity (overall SMR 0.76, 95% CI 0.70–0.83), whereas no trend was observed for women. SMRs and RRs were also calculated according to duration of employment in each processing unit; some associations of potential significance were observed (for IHD in the maintenance and janitor units and CeVD in the weaving unit) (344).

10.5.3 Meta-analyses

A meta-analysis comprised totally seven cohorts of cotton textile workers from the UK, Finland and the US. Comparisons were made with national or state standard populations. Risk estimates (meta-SMR, 95% CI) were not increased for circulatory system diseases for males (0.85 0.79–0.91) and females (0.94, 0.81–1.06) (922).

10.5.4 Exposure-response relationships

The mortality rates of cerebral vascular lesions were significantly higher among male strippers and grinders (6.4/1 000) compared with the general male population 55–64 years of age (2.0/1 000) according to the Registrar General's mortality figures for 1930–1932 in England and Wales. Strippers and grinders had the greatest dust exposure. Cotton spinners also had a significantly increased mortality (3.4/1 000) and their exposure may have been as high, as stripping dust may have reached the spinning rooms (837). No air levels were presented in the paper but photos illustrated a dusty work environment.

The mortality of 3 458 workers in the British cotton industry, originally enrolled in a study of respiratory symptoms in the period 1968–1970, was followed to the end of 1984. Total mortality and mortality from respiratory disease were less than expected, and both decreased as length of service increased. These patterns of mortality indicate a healthy worker survivor effect. An increased mortality from circulatory diseases was found among those exposed for 15–29 years (SMR 1.25, 95% CI 1.02–1.52). However, risk estimates were lower both for those with shorter exposure (SMR 0.88) and for those with longer exposure (SMR 0.79) (414).

Totally 267 400 female textile workers in Shanghai, China, were followed for CVD mortality 1989–2000. Factory exposures were approximated by sector classifications based on materials and processes. Quantitative endotoxin and cotton dust measures were available for a subcohort of 3 188 workers. Cox proportional hazards modelling was used to estimate risks. A slightly elevated mortality (HR, 95% CI) for the cotton sector was seen for haemorrhagic stroke (1.12, 1.02–1.23) but not for ischaemic stroke (1.12, 0.97–1.31). Increased cumulative endotoxin exposure expressed as endotoxin units/m^3-years tended to increase total stroke mortality, after adjustment for age and smoking (P for trend 0.09) (324).

10.5.5 Indirect evidence

A cohort of Chinese cotton textile workers was established in 1981 and followed for 20 years. These cotton workers had greater annual declines of FEV_1 compared with silk workers. Chronic loss in lung function was more strongly associated with exposure to endotoxins than with dust (988) (for a description of the association between lung function and CVD, see Chapter 4).

10.5.6 Conclusion

Most studies comparing cohorts of cotton textile workers with the general population showed a decreased mortality due to CVD, which was also confirmed by a meta-analysis (922) comprising seven cohort studies. Two studies showed an increased risk for CVD among textile workers compared to other workers (713, 888).

One study showed that the highest risk from CeVD was seen in the highest exposed cotton workers, i.e. strippers and grinders (837).

There is *limited evidence* for an association between exposure in the textile industry and CVD.

10.6 Agriculture

10.6.1 General

The proportion of individuals involved in farming has decreased regularly in populations worldwide in the last decades, from 50% in 1980 to 40% in 2010. During the same period, the absolute number rose from 1 billion to 1.3 billion. However, in high-income countries, the proportion as well as the number of individuals working in agriculture decreased drastically from 13% (71 million) in 1980 to 4% (26 million) in 2010 (554).

Agricultural workers and farmers are exposed to a mixture of dusts with widely varying constituents and concentrations. Dairy farmers are exposed to dust during tilling, harvesting, and feeding animals with hay, ensilage, crushed grain and supplements containing minerals and proteins. The aerosols contain varying amounts of highly immunogenic and toxic agents, such as allergens, microbial

antigens, endotoxins, mycotoxins and proteolytic enzymes. Airborne particles from mouldy materials contain spores from moulds and Gram-positive bacteria (599).

In 1555, Olaus Magnus, the last catholic archbishop in Sweden, wrote about threshing in winter time: "When separating the grain from the chaff, care must be taken to choose a time when there is a suitable wind which will sweep away the grain dust, so that it will not damage the vital organs of the threshers. This dust is so fine that it will almost unnoticeably penetrate into the mouth and accumulate in the throat. If this is not quickly dealt with by drinking fresh ale, the thresher may never again or only for a short period eat what he has threshed" (774). The pulmonary disorder known as farmer's or thresher's lung, due to the inhalation of the dust from mouldy hay, was first described in 1932 by Campbell in Britain (140). This disease is an example of hypersensitivity pneumonitis, also known as extrinsic allergic alveolitis, which is a syndrome caused by an exaggerated immune response to the inhalation of a variety of antigenic particles found in the environment (194).

Fatal cases of farmer's lung are rare; based on death certificates, 13 cases were identified in Finland 1980–1990. Compared with incidence data from the years 1980–1982, the mortality was estimated to be 0.7%. On average, death occurred 8 years after the diagnosis of farmer's lung. One patient died acutely after a heavy mould exposure. The other patients had chronic disease and the immediate cause of death was pneumonia in 7 patients, respiratory insufficiency in 4 patients, and pneumothorax in 1 patient. The majority of these cases had suffered from symptoms of farmer's lung for more than 1 year before the diagnosis was established and fibrotic changes were already visible in the chest radiograph at the time of the diagnosis. *Cor pulmonale* was diagnosed in 8 patients (504).

Epidemiological studies and risk estimates are presented in Appendix, Table A21.

10.6.2 Occupational epidemiological studies

Most epidemiological studies observed no association between the occupational entities agricultural workers or farmers and CVD when the mortality in these occupations was compared with that of the general population. However, some studies of livestock workers (889), animal caretakers (713) and livestock farmers (546) indicated increased risks.

10.6.3 Meta-analyses

A meta-analysis comprising 12 studies has been presented regarding the relationship between farming and the occurrence of CVD. The total number of deaths due to IHD was 65 898 and the meta-RR was 0.89 (95% CI 0.88–0.90). Two studies showed a non-significantly increased RR. Eight studies demonstrated an RR below 1.0, whereof six studies showed a significantly decreased risk (107, 216).

Acquavella and coworkers performed a meta-analysis comprising 14 studies of white male farmers from Finland, Iceland, Sweden, Italy, Canada and the US. The summary RR was 0.86 (95% CI 0.78–0.95) regarding IHD (7).

Potential health effects from exposure to crop protection chemicals were investigated through systematic review and meta-analysis of 37 separate cohorts of

workers in the crop protection product manufacturing industry. The meta-SMRs (95% CIs) for CVD, CHD and CeVD were 0.91 (0.84–0.99), 0.99 (0.9–1.10) and 1.05 (0.89–1.25), respectively (462).

10.6.4 Exposure-response relationships

The relationship between ambient $PM_{2.5}$ and CVD mortality was studied in the US Agricultural Health Study cohort. The cohort (n = 83 378) included farmers, their spouses and commercial pesticide applicators residing primarily in Iowa and North Carolina. Deaths occurring between enrolment (1993–1997) and 30 December 2009 were identified by record linkage. Six-year average (2001–2006) remote sensing-based estimates of ground-level $PM_{2.5}$ were assigned to participants' residences at enrolment, and Cox proportional hazards models were used to estimate HRs in relation to a 10-$\mu g/m^3$ increase in $PM_{2.5}$, adjusted for individual-level covariates. In total 1 967 deaths due to CVD occurred over a median follow-up time of 13.9 years. Positive associations were observed between ambient $PM_{2.5}$ and CVD mortality among men. These associations were strongest among men who did not move from their enrolment address (HR 1.63, 95% CI 0.94–2.84), and in particular, among non-moving participants with the most precise exposure geocoding (HR 1.87, 95% CI 1.04–3.36). The authors concluded that rural $PM_{2.5}$ may be associated with CVD mortality in men, however, similar associations were not observed among women (999).

10.6.5 Indirect evidence

An increased risk of hospitalisation for venous thromboembolism was presented among both male and female blue-collar workers and farmers. This disease is associated with an increased tendency for blood coagulation. The results were observed in a nationwide database constructed by linking Swedish census data to the Hospital Discharge Register 1990–2007 (1059).

10.6.6 Markers of effects

Previously unexposed volunteers who inhaled dust in a swine confinement building during 4 hours had increased levels of IL-6 and fibrinogen in blood after exposure (887). A similar but lower increase in blood IL-6 levels was observed when swine farmers were exposed to this environment (731).

Greenhouse workers, exposed to bioaerosols comprising e.g. bacteria and fungi, did not have higher serum levels of SAA and CRP than referents. However, endotoxin exposure was positively associated with serum concentrations of SAA and CRP (597).

Plasma levels of fibrinogen were studied in some gross occupational groups in the Kuopio region of eastern Finland. The concentrations of fibrinogen were significantly higher among farmers than among white-collar workers after adjustment for alcohol consumption, BMI, physical fitness, smoking, coffee consumption, HDL cholesterol, LDL cholesterol, blood leukocyte count and prevalent disease (at least one sign of IHD, hypertension, diabetes or previous stroke) (1025).

10.6.7 Conclusion

A meta-analysis did not demonstrate associations between farming and CVD (107, 216). However, a few studies of animal caretakers and livestock farmers indicated increased risks (546, 713, 889). There were no indoor exposure-response data for agricultural workers or farmers and CVD, but one study showed a relationship between rural environmental particle exposure and CVD.

Extreme exposures have caused hypersensitivity pneumonitis (farmer's lung) which has further developed into *cor pulmonale* (194, 504).

There is *insufficient evidence* for an association between agriculture work and CVD.

10.7 Cleaning

10.7.1 General

Cleaners constitute a significant proportion of the workforce. Cleaning is associated with several chemical agents such as surfactants, acidic and alkaline substances, water softeners, disinfectants and solvents. Some of these agents are administered as aerosols and some may evaporate from surfaces. Consequently cleaners can be exposed to aerosols as well as gases (708). In a Swedish survey, 37% of female cleaners reported exposure to air pollutants during at least one fourth of their working hours, compared with 18% of all participating women (692). In a Spanish study, the majority of cleaners reported respiratory symptoms (1057). Nose and throat symptoms were common among 775 Danish female cleaners (44%) and most of them reported improvement of symptoms during holidays and weekends. Furthermore, chronic bronchitis was more common among the cleaners who continuously used sprayers (OR 3.2, 95% CI 1.0–10.4) (708).

10.7.2 Mechanistic evidence

House dusts collected from carpet, bed, shelf and floor by vacuum cleaning were found to trigger the production of IL-6 and IL-8 in a dose-dependent manner in lung epithelial cells *in vitro*. The interleukin production was several-fold higher compared with that obtained after swine dust exposure (827). In the Copenhagen School Study, dusts from schools with a high prevalence of building-related symptoms (e.g. eye, nose and throat irritation, nasal congestion, headache, fatigue and difficulties in concentration) had a higher potency to stimulate IL-8 secretion in lung epithelial cells compared with dusts from schools with a low prevalence of building-related symptoms (20).

10.7.3 Occupational epidemiological studies

A Swedish case-control study comprised 9 755 women with MIs. For each case two controls were selected from the study base through random sampling, stratified by age, county and socioeconomic group. An increased risk (RR, 95% CI) was found among female cleaners (1.2, 1.0–1.5), after adjustment for age, county and calendar

year. The risk decreased after adjustment for socioeconomic group (1.1, 0.9–1.4) (377).

Three cohorts of female cleaners based on Swedish census information on gainfully employed women were followed until 31 December 1995: 1) all cleaners in the 1970 census, 2) all cleaners in the 1980 census who were also recorded as cleaners in the 1970 census, and 3) all cleaners in the 1990 census. These cohorts were not independent as one individual might belong to one, two or all three cohorts. Mortality (SMR, 95% CI) due to IHD was higher in all cohorts of cleaners; the 1st cohort (1.25, 1.21–1.28), the 2nd cohort (1.34, 1.22–1.46) and the 3rd cohort (1.25, 1.02–1.51) (883).

A later Swedish cohort included all manual workers identified from the Swedish national census in 1980 who were alive as of 1 January 1987. First time events of ischaemic or haemorrhagic stroke during the period 1987–2005 were identified through linkage to the Hospital Discharge Register and the National Cause of Death Register. An increased risk (HR, 95% CI) of ischaemic stroke (1.11, 1.07–1.14) and haemorrhagic stroke (1.14, 1.05–1.23) was found among women exposed to low levels of large particles (> 1 μm). The dominant occupation in this group of women was cleaners (96%) (886).

All economically active persons were included in the Finnish census of 1970 and followed until 1991 regarding mortality. CVD was more common among female cleaners and cleaning supervisors than in the reference population (SMR 1.10 based on 4 064 deaths). It is worth noting that younger persons (25–44 years in 1970; SMR 1.39, 95% CI 1.25–1.54) had a higher risk than older persons (45–64 years in 1970; SMR 1.07, 95% CI 1.04–1.11). The same pattern was demonstrated for MI as well as CeVD (713). This result might be explained by a higher proportion of individuals who were retired and therefore not exposed during the whole follow-up period.

An occupational study in the Nordic countries was based on censuses and their linkage to mortality statistics. The survey population consisted of individuals aged 20–64 years around the first of January 1971. The follow-up period was 10 years, 1971–1980. The reference population consisted of all economically active persons. The total number of deaths due to diseases of the circulatory system and "sudden death" among female cleaners was 4 046 with an SMR of 1.19. National SMRs were 1.48 (Finland), 1.16 (Denmark), 1.11 (Norway) and 1.06 (Sweden) (711).

Occupational information was obtained from the 1971 census records of women in the Longitudinal Study carried out by the Office of Population Censuses and Surveys comprising a sample of 1% of the population of England and Wales. The analysis was based on 77 081 women aged 15–59 years. Charwomen, office cleaners and window cleaners had a non-significantly increased SMR for IHD of 1.35, based on 10 deaths (673).

The mortality of 53 140 male and 96 914 female cleaners aged 30–60 years selected from the 1991 census was compared with the mortality of the total non-manual Belgian working population (854 540 men and 654 287 women). The population was followed until 2011. Male and female cleaners had smoking-

adjusted SMRs (95% CIs) for IHD of 1.22 (1.13–1.31) and 1.40 (1.25–1.57), respectively. Smoking-adjusted SMRs (95% CIs) for CeVD mortality were also increased among male (1.20, 1.06–1.35) and female (1.13, 1.00–1.27) cleaners (981).

10.7.4 Conclusion

Six studies indicated an increased risk of CVD among female cleaners (377, 711, 713, 883, 886, 981). No meta-analyses or exposure-response studies were found.

There is *limited evidence* for an association between cleaning and CVD.

11. Non-chlorinated organic solvents

Organic solvents refer to chemicals with an ability to dissolve fats, resins, lipids and polymers. These compounds are generally colourless, liquid at room temperature and have high evaporating rates. Most solvents have a faint or pleasant odour. Styrene is a plastic monomer with similar properties often categorised as solvent although not strictly so. Mixtures of solvents are used in several occupations for many purposes as degreasant, thinner, solvent and extractant. Occupations associated with organic solvent exposures are painters, varnishers and carpet layers. (57). Chlorinated solvents are presented in Chapter 12.

11.1 Carbon disulphide

11.1.1 General

The worldwide production capacity of carbon disulphide is approximately 1 million tonnes; most of it used in the production of viscose fibre and cellophane film. Carbon disulphide is also released as a by-product in oil and gas processing. Additional industrial releases result from its use in the chemical industry and tire manufacturing. Virtually all anthropogenic and natural releases are to air. Carbon disulphide is also produced naturally by soil and sediment microorganisms, vegetation, forest and grass fires, and volcanoes. Worldwide, at least 40% and possibly as much as 80% of releases are a result of natural or biogenic activity (447).

Carbon disulphide is extensively absorbed by inhalation, but also via the skin. It is biotransformed to several metabolites, of which 2-thiothiazolidine-4-carboxylic acid is used for biomonitoring of exposure at the workplace (447).

Available data to assess the potential of carbon disulphide to induce irritancy or sensitisation are limited. Inhalation in viscose rayon plants is irritating to the mucous membranes, including the respiratory system, but the role of concomitant exposure to hydrogen sulphide and sulphuric acid in induction of these effects is unknown (447).

Based on the results of studies of workers exposed to carbon disulphide and supporting data from animal experiments, the nervous system appears to be the critical target for carbon disulphide-induced toxicity. Other effects for which there

is considerable weight of evidence in humans exposed to carbon disulphide include alterations in serum lipids and blood pressure that are associated with increased risk of CVD, systemic ophthalmological effects (including those on colour vision and damage to the blood vessels of the retina) and with higher exposures increased mortality from heart disease (447).

Vigliani described 43 carbon disulphide poisonings during the period 1946–1953 from four Italian plants producing artificial textile fibres by the viscose process. Cerebral arteriography of several cases and necropsy of 3 cases revealed that the encephalopathy was vascular in nature and due to a sclerosis of the small arteries and capillaries of the brain and spinal medulla. During the period 1938–1944 the concentrations of carbon disulphide were higher than 200–300 mg/m^3 (60–90 ppm) in some departments of the factories. Vascular lesions have also been observed in animal studies (1019).

11.1.2 Occupational epidemiological studies

The CVD mortality of a cohort of 343 Finnish men exposed for at least 5 years to carbon disulphide in a viscose rayon plant was followed 1967–1982. There was an increased mortality among the exposed (RR 1.6, 95% CI 1.0–2.6) compared to that in an equally large cohort of male paper mill workers (718).

A UK cohort of viscose rayon workers, previously described by Tiller *et al*. (961), was reconstructed and followed to the end of 1982. The cohort now comprised totally 2 848 men (930). The spinners, the workers most heavily exposed to carbon disulphide, had a significantly higher mortality from IHD (SMR 1.72). The IHD mortality tended to increase with increasing exposure score. However, over the age of 65 years mortality tended to decline with increasing exposure. This was contrary to expectation under the hypothesis that carbon disulphide promotes atherosclerosis. Instead it suggests that carbon disulphide has some type of reversible, direct cardiotoxic or thrombotic effect. This was supported by the findings that there was a strong significant trend for IHD mortality to increase with increasing exposure in the previous 2 years. Further, IHD mortality showed a highly significant trend with exposure among current workers but no such trend among workers who had left the industry (930).

A Polish cohort of 2 085 male workers with a diagnosed chronic occupational carbon disulphide poisoning during 1970–1990 was followed until 1992. Increased mortalities (SMR, 95% CI) were observed for diseases of the circulatory system (1.39, 1.25–1.54), IHD (1.37, 1.14–1.64) and CeVD (1.88, 1.43–2.42). Increased mortality due to IHD was observed in the ages 40–59 years and due to CeVD in the ages 50–69 years (735).

A cohort of 10 418 men employed 1957–1979 at four US rayon plants was followed until 1983. The national US population served as referents. There was a non-significantly increased mortality (SMR, 95% CI) due to all circulatory diseases (1.04, 0.98–1.10), arteriosclerotic heart disease (1.04, 0.97–1.12) and CeVD (1.08, 0.90–1.28). When the cohort was restricted to 4 448 workers with intermediate or heavy exposure (based on job titles), the corresponding SMRs increased regarding

circulatory diseases (1.14, $P < 0.05$) and arteriosclerotic heart disease (1.24, $P < 0.01$), whereas the SMR for CeVD decreased to 1.03. Within the restricted group, men exposed for 15 years had increased mortalities (SMRs) from arteriosclerotic heart disease when starting exposure both prior to 1945 (1.38, $P < 0.05$) and 1945–1949 (1.92, $P < 0.01$), whereas there were no significant increases among men starting exposure after 1950 (596).

Liss *et al*. investigated the proportional mortality in a viscose rayon plant in Ontario, Canada, with 279 deaths recorded. The general population in Ontario contributed with reference mortality numbers. In a subgroup of highly exposed carbon disulphide workers, mortality from IHD was less than expected (PMR 0.82), whereas mortality from stroke was greater than expected (PMR 2.07, $P < 0.05$). The excess was confined to workers who died at an age ≥ 65 years (PMR 2.29, $P < 0.01$), but workers who died at an age < 65 years (PMR 1.01) comprised only one fatality. In addition, highly exposed workers had an increased mortality from CeVD (OR 4.92, 1.66–14.65) compared to viscose rayon workers with lower exposure (569).

Nishiwaki and coworkers studied male workers from 11 Japanese rayon factories. The cohort comprised 217 exposed, 125 ex-exposed and 324 referent workers. All participants were investigated by magnetic resonance imaging (MRI) of the brain at base-line and after 6 years. Signs of hyperintensive spots were evaluated and may indicate silent cerebral infarctions. There was a significant increase of hyperintensive spots (OR 2.27, 95% CI 1.37–3.76) during the 6-year follow-up after adjustment for age, smoking, alcohol consumption, BMI, education, systolic blood pressure and HDL cholesterol. The geometric mean exposures of carbon disulphide and the biomarker 2-thiothiazolidine-4-carboxylic acid in urine during this period were 4.87 ppm [standard deviation (SD) 1.91] and 1.60 mg/g creatinine (SD 1.91), respectively. No exposure-response relationships were observed among the exposed workers. The authors concluded that exposure to carbon disulphide below 10 ppm might increase the number of hyperintensive spots in brain MRI (710).

11.1.3 Meta-analyses

In 2002, Tan and coworkers performed a meta-analysis of 11 cohort studies on carbon disulphide exposed workers. The RR for CVD was 1.56 (95% CI 1.12–2.1) (938), however the Finnish cohort was included three times in the analysis (three follow-ups published).

11.1.4 Exposure-response relationships

In the UK cohort, there was a strong significant trend for IHD mortality to increase with increasing exposure score to carbon disulphide in the 2 years prior to death (930).

The results from the first 5 years of follow-up of a Finnish cohort of carbon disulphide exposed workers showed a 4.7-fold (95% CI 1.4–16.1) excess mortality for CHD compared with a referent cohort of paper mill workers (962). After 1972, a preventive intervention programme instituted at the rayon plant included removing all workers with coronary risk factors from exposure. Exposure levels

were reduced after 1972 and complied with the occupational exposure limit (OEL) of 10 ppm. These measures were reflected in a normalisation of the mortality from IHD, with an RR of 1.0 in the period after the intervention (718).

Among Japanese rayon factory workers, hyperintensive spots (may indicate silent cerebral infarctions) were observed on MRI of the brain after 6 years exposure to carbon disulphide concentrations around 5 ppm (710).

11.1.5 Conclusion

Several epidemiological studies showed a relationship between carbon disulphide exposure and CVD, including exposure-response relationships (718, 930). In one of the studies, compliance with the OEL of 10 ppm normalised the risk of IHD mortality (718). Hyperintensive spots, which may indicate silent cerebrovascular infarctions, were observed on MRI of the brain after 6 years exposure to carbon disulphide concentrations around 5 ppm (710). The increased risk of IHD caused by exposure to carbon disulphide may decrease when exposure ceases. It is not known if the occurrence of CeVD behaves in the same way.

There is *strong evidence* for an association between exposure to carbon disulphide and CVD.

11.2 Styrene

11.2.1 General

Styrene is a component of several types of resins used in the manufacture of a wide range of products. The six most common resins are polystyrene (building material, packaging material), styrene-butadiene rubber (tires and other vehicle components), unsaturated polyester resins in fibreglass-reinforced plastic (boats, storage tanks, bathtubs/shower stalls), styrene-butadiene latex (backings for floor coverings and paper), acrylonitrile-butadiene styrene (household and office equipment) and styrene-acrylonitrile (household products, battery casings) (661).

11.2.2 Occupational epidemiological studies

Mortality due to arteriosclerotic heart disease and CeVD was lower among US workers who developed and manufactured styrene-based products than among unexposed workers from the Michigan manufacturing location, with RRs (95% CIs) of 0.86 (0.76–0.98) and 0.95 (0.70–1.29), respectively (118).

A cohort of 5 204 persons who produced plastic boats in two companies in the US 1959–1978 was followed until 1998 and was compared with Washington State rates. At one company, average styrene exposure was 42.5 ppm in the fibreglass department, and at the other company, average exposure was 71.7 ppm in the laminating department. These were the high-exposure departments. Workers in these departments did not show a significant elevation in risk for diseases of the heart or other diseases of the circulatory system. High-exposed workers were identified from air sampling results and from discussions at the plant. The high-

exposed workers employed for more than 1 year had a mortality risk (SMR, 95% CI) of 1.39 (0.78–2.30) for IHD, and the mortality for IHD among low-exposed workers was 0.77 (0.58–0.99) (811). When the cohort was further followed until 2011, the SMR (95% CI) for IHD was 1.15 (0.77–1.67) among high-exposed workers and 0.77 (0.62–0.94) among low-exposed workers. A comparison between high-exposed and low-exposed workers revealed a standardised relative risk (SRR) of 1.03 (95% CI 0.36–2.94). Mortality from CeVD was also presented. High- and low-exposed had SMRs (95% CIs) of 1.36 (0.59–2.68) and 1.06 (0.71–1.51), respectively. When comparing high-exposed and low-exposed the SRR (95% CI) was 1.15 (0.48–2.75). Mortality from cardiomyopathy showed significant increases with increasing levels of exposure, but numbers were small and not presented (809).

A total of 15 826 people worked for at least 6 months with production of reinforced styrene plastic in 30 US factories during the years 1948–1977. Styrene exposure ranged from 1 to 200 ppm. The cohort was followed until 1989 (1036) and further followed until 2008 (186). Causes of death were compared with national mortality rates. None of these plants had been included in previous styrene studies. In 1977, the average exposure was 25 ppm and a decade earlier it was 35 ppm. The estimated TWA for all exposure was 28 ppm and the mean duration of exposure to styrene was 4.3 years. In the total cohort, an increased mortality (SMR, 95% CI) was observed for all heart diseases (1.05, 1.00–1.11) and IHD (1.08, 1.02–1.15) but not for CeVD (1.07, 0.94–1.22). There was an inverse trend between estimated cumulative styrene exposure and mortality by all heart diseases, but this trend was not reflected in the internal analysis (186).

In a US case-cohort study, 498 fatal cases of IHD were compared with 997 randomly selected persons employed 1943–1984 in two styrene-butadiene rubber plants. Both styrene and butadiene exposures were estimated, and ranked from 0 to 10 in a JEM containing 579 job assignments (610). Exposure levels of styrene and butadiene decreased in these types of industries between the 1940s and the early 1990s. Average exposure decreased, for styrene from 2.2 to 0.2 ppm and for butadiene from 5.9 to 0.8 ppm (593). Mortality (HR, 95% CI) due to acute IHD was elevated among those who had been exposed to styrene during the preceding 2 years (4.99, 1.07–23.34) but not among those exposed 2–5 years ago (0.95, 0.82–1.09), after adjustment for butadiene exposure (610).

A later study examined the mortality due to IHD in a total of 16 579 men who worked in six styrene-butadiene rubber plants in the US and Canada. This study also included the two production plants from the previous study (610). No significant correlation between styrene exposure during the previous 2 years and mortality due to acute IHD could be observed in this study. There was, however, a correlation between average lifetime styrene exposure and chronic IHD for persons < 55 years of age but not among workers ≥ 55 years of age (222). The previous study raised the suspicion of a connection between IHD and exposure to styrene (610), but this later, larger study with similar design was unable to confirm such a connection. One possible explanation for this discrepancy may be that the previous

study reporting an elevated risk (610) included all employees, whereas the later study (222) included only persons who had been employed for at least 1 year.

A cohort comprised 4 863 women employed for at least 1 day at eight styrene-butadiene rubber plants in the US and Canada. The average follow-up time was 37 years. A decreased mortality was observed regarding circulatory diseases (SMR 0.87, 95% CI 0.79–0.95) (830).

In a cross-sectional study of the US population during 1999–2004 (NHANES) comprising 3 408 subjects, a relationship was found between blood concentrations of styrene and several alkylbenzenes and reported physician-diagnosed CVD. Occupational exposure was not reported in the questionnaire (1043).

11.2.3 Pooled analyses

A pooled analysis included 40 688 persons who worked with reinforced plastic in Denmark, Finland, Norway, Sweden, Italy and the UK. Causes of death were compared with rates for the national populations. Mortality due to circulatory disease was lower than expected, SMRs for different job-categories ranged from 0.91 to 0.97 (502).

11.2.4 Exposure-response relationships

A cohort of workers engaged in the development or manufacturing of styrene-based products in Dow Chemical Company plants in the US, 1940–1986, was followed until 1986. In a subcohort of workers exposed to a TWA of ≥ 5 ppm of styrene and ethylbenzene, an increased mortality from arteriosclerotic heart disease was found (SMR 1.34, 95% CI 1.04–1.71). The heart disease excess was concentrated primarily among the workers with relatively short (≤ 4 years) duration of exposure. The majority of deaths occurred many years after the workers had left their exposed work (118).

In the US case-cohort study, 498 fatal cases of IHD were compared with 997 randomly selected persons employed 1943–1982 in two rubber plants. There was a relationship between cumulative styrene exposure (ppm-years) and acute IHD mortality (HR 1.07, 95% CI 1.02–1.13), after adjustment for butadiene exposure. The relationship between styrene exposure the most recent 2 years and acute IHD mortality was estimated among workers employed 2 years or more. Recent TWA styrene exposures of < 0.1, 0.1–< 0.2, 0.2–< 0.3 and ≥ 0.3 ppm were associated with acute IHD mortality with risk estimates (HR, 95% CI) of 1.0, 1.24 (0.36–4.33), 2.95 (1.02–8.57) and 4.30 (1.56–11.84), respectively (610). However, potential confounding exposures (e.g. butadiene) were not taken into account.

11.2.5 Markers of effect

A group of 29 hand lamination workers and sprayers exposed to styrene at 139.5 mg/m^3 (32 ppm) was compared with 19 clerks. An increased expression of ICAM-1 on surfaces of lymphocytes, monocytes and granulocytes was observed. ICAM-1 is responsible for cell-cell contact and for adhesion to endothelial cells and fibrinogen. There was a significantly lower level of soluble ICAM-1 in serum in the exposed group than in controls but no difference in the serum L-selectin level. The

authors concluded that the results indicate that styrene exposure activates the immune system and alters leukocyte adherence (450).

11.2.6 Conclusion

Four out of six longitudinal cohorts, including a subcohort, demonstrated an increased risk of IHD mortality among styrene exposed workers (118, 186, 222, 610). In a subcohort of US workers, manufacturing styrene-based products and exposed to a TWA of ≥ 5 ppm of styrene and ethylbenzene, an increased mortality from arteriosclerotic heart disease was found (118). A cohort (222) and a subcohort (610) indicated an increased risk associated with recent styrene exposure. A correlation was observed between average lifetime styrene exposure and chronic IHD mortality among persons below the age of 55 years but not among those 55 years and older (222), i.e. at a life period with a higher probability of retirement. Elevated acute IHD mortality was seen among workers recently exposed to styrene (0–2 years) but not among those exposed 2–5 years ago (610). These two studies indicated that an exposure free period decrease IHD mortality.

A large pooled analysis showed no increased risk of CVD mortality among styrene-exposed workers producing reinforced plastic (502).

There is *limited evidence* for an association between exposure to styrene and CVD.

11.3 Dimethylformamide

11.3.1 General

N,N-Dimethylformamide (DMF) is a solvent used in factories handling polyurethane materials and acrylic fibres. DMF is also utilised in the pharmaceutical industry, in pesticide formulation and in the production of synthetic leathers, surface coatings, films and fibres. This colourless solvent is miscible with water and most organic liquids. DMF can be absorbed by inhalation and also through dermal contact (493).

11.3.2 Animal studies

Rats, mice, rabbits, guinea pigs and dogs were exposed to DMF for 58 days (5 days/week, 6 hours/day of which 5.5 hours at 23 ppm followed by 0.5 hour at 426 ppm). No clinical signs of toxicity were observed in rats, mice, rabbits and guinea pigs. All 4 exposed dogs showed degenerative anatomical changes in the heart muscle (176).

Within the US NTP, rats were exposed to DMF levels of 0, 50, 100, 200, 400 and 800 ppm 6 hours/day, 5 days/week during 13 weeks. All rats survived the exposures. Body weight gains were reduced by 50–65% in rats exposed at 800 ppm and to a lesser extent in the 400-ppm group. Evidence of hepatocellular injury was noted as early as day 4, based on increases in activities of liver-specific enzymes in serum in both sexes exposed at 200–800 ppm. Serum cholesterol levels were increased at all exposure concentrations. Relative liver weights were increased in

males exposed at 100–800 ppm, and in females at all concentrations. Minimal to moderate centrilobular hepatocellular necrosis was seen in rats of both sexes exposed at 400 and 800 ppm; the lesion was more severe in females. Decreased absolute heart weights were observed at 400 and 800 ppm in both sexes, but there was no change regarding relative heart weights. Overall, the ECG changes were subtle, were not increased in incidence or severity by increased DMF exposure, and were not accompanied by any gross or microscopic evidence of cardiotoxicity, although they occurred in groups that also showed increases in serum creatine phosphokinase activity (591).

11.3.3 Occupational epidemiological studies

A cohort of 2 530 workers with potential exposure to DMF in the period 1950–1970 was followed for mortality 1950–1982. Observed numbers of death were compared with the expected numbers based on Du Pont Company, national US and South Carolina rates. There was an increased mortality due to IHD among wage employees when compared with the Du Pont Company rates (62 observed vs 40.3 expected, $P < 0.01$). A significant increase of IHD was also found when the cohort was compared with US rates, but not when compared with regional rates. There was no increased mortality regarding CeVD. The potential exposure for each job was ranked according to exposure level, but the exposure data were not used further in the analysis of mortality (156, 157).

11.3.4 Conclusion

The only cohort study located showed an increased risk of IHD mortality in workers with potential exposure to dimethylformamide, compared with national rates but not compared with local rates (157).

There is *insufficient evidence* for an association between exposure to dimethylformamide and CVD.

11.4 Mixed organic solvents

11.4.1 Occupational epidemiological studies

Totally 1 292 male painters who worked in a dockyard for ≥ 12 months 1950–1992 were followed for mortality 1960–1994. PMRs were calculated for the total cohort. A subcohort of 309 painters born 1900–1929 was followed 1975–1994 and compared with the male Scottish population. The solvents used were mainly white spirit, xylene, trimethylbenzene, *n*-butanol, trichloroethylene, naphtha and cumene. The total cohort had an increased risk (PMR, 95% CI) for IHD (1.32, 1.05–1.64), but not for CeVD (0.67, 0.35–1.17). No significant results were obtained for the subcohort (160).

Painters from the International Brotherhood of Painters and Allied Trades in the US comprised 42 170 males with at least 1 year of union membership, born before 1940 and alive at the end of 1975. The cohort was followed until 1994 and the

mortality of the painters was compared with US rates. Turpentine was used before World War II and was later replaced by organic solvents. The main solvents were toluene, xylene, ketones, alcohols, esters and glycol ethers. Metals in paint pigments included titanium oxide, chromium and iron compounds. The mortality (SMR, 95% CI) was assessed regarding IHD (0.97, 0.95–1.00), cardiomyopathy (1.17, 0.99–1.37) and hypertension with heart disease (1.19, 1.01–1.39). Based on a previous survey of painters in construction and maintenance, current smoking (48.9%) was more common in this occupation than in the entire male US population (36.3%) (908).

A cohort of workers employed for at least 1 year at a large aircraft manufacturing facility in California since 1960 was followed until 1996. A subcohort of 9 201 workers exposed to mixed solvents was compared with the general population in California for white workers and with the US general population for non-white workers. There was decreased mortality (SMR, 95% CI) regarding all heart disease (0.90, 0.85–0.96) and CeVD (0.77, 0.65–0.90). Among factory workers exposed to mixed solvents on a routine basis, no significant increases of any cause of death were found. Analyses were also conducted of workers routinely exposed to any mixed solvent excluding trichloroethylene and perchloroethylene. Fewer observations resulted in increased instability of the SMRs, but the pattern mirrored the previous presentations (116).

11.4.2 Meta-analyses

A meta-analysis included 55 published mortality studies of solvent exposed workers. There was a great variation of work titles (e.g. shoe manufactures, dry cleaners, painters, chemical and rubber industry workers) and of exposures (e.g. benzene, carbon disulphide, dichloromethane, DMF, dioxane, styrene and trichloroethylene). The calculated risk (SMR, 95% CI) regarding circulatory diseases was 0.85 (0.81–0.90) (161).

11.4.3 Exposure-response relationships

A Swedish case-control study (1 335 cases and 1 658 referents) identified first-time, non-fatal MI among men and women 45–70 years of age in the Stockholm County 1992–1994. Referent subjects were selected from the population to match the demographic characteristics of the cases. A lifetime history of occupations with descriptions and durations of work tasks and specific occupational solvent exposures was obtained by questionnaire. The RRs were adjusted for age, sex, year of enrolment, hospital catchment area, smoking, alcohol drinking, hypertension, diabetes mellitus, overweight and physical inactivity at leisure time. There was no clear exposure-response relationship between solvent exposure and MI; risk estimates are presented in Tables 8–9 (364).

Table 8. Risk estimates for non-fatal myocardial infarction according to highest intensity of solvent exposure during at least 1 year of work (364).

Exposure (hygienic effect [a])	Crude RR (95% CI)	Adjusted RR (95% CI)
Unexposed	1	1
≤ 0.19	1.32 (1.08–1.61)	1.26 (1.02–1.55)
0.2–0.5	1.13 (0.82–1.55)	1.05 (0.76–1.47)
≥ 0.5	1.60 (1.04–2.48)	1.49 (0.94–2.35)

[a] The sum of fractional contributions from different organic solvents in relation to their respective occupational exposure limit in 1993.
CI: confidence interval, RR: relative risk.

Table 9. Risk estimates for non-fatal myocardial infarction according to cumulative solvent exposure (364).

Exposure (hygienic effect-years [a])	Crude RR (95% CI)	Adjusted RR (95% CI)
Unexposed	1	1
> 0–0.55	1.50 (1.16–1.95)	1.50 (1.14–1.96)
0.56–1.9	1.09 (0.82–1.44)	1.00 (0.74–1.34)
≥ 2.0	1.31 (1.01–1.69)	1.20 (0.92–1.58)

[a] The product of the average hygienic effect (see Table 8) during the exposure period and the exposure duration in years.
CI: confidence interval, RR: relative risk.

The Copenhagen Male Study comprised 2 974 males aged 53–75 years free from overt CVD at baseline (1985–1986) which were followed until December 1991. Adjustment was made for potential confounders including alcohol consumption, physical activity, tobacco smoking, serum cotinine, serum lipids, serum selenium, BMI, blood pressure, hypertension, social class and retirement status. There was an increased risk (RR, 95% CI) for first IHD event among workers exposed to organic solvents for ≥ 16 years (2.2, 1.2–3.9, P for trend 0.04) but not for 5–15 years (1.0, 0.4–2.5) (923).

Totally 7 540 middle-aged Japanese-American men participated in the Honolulu Heart Program during 1965–1968. The cohort was followed until 1998. Industrial hygienists assessed the participants' potential for exposure to solvents based on their primary job. A cumulative exposure intensity score was calculated by multiplying the estimated exposure score (0, 1, 2 and 3) with the number of years of exposure for each individual. Cumulative exposure scores were categorised as none, low, medium and high, and were calculated as 0, 1–39, 40–79 and ≥ 80. All associations were assessed using Cox proportional hazards models and adjustments were made for education, smoking, triglycerides, physical activity, alcohol intake and systolic blood pressure. There was an increased risk for CHD in the highest exposure category with 15-year lag (151) (Table 10).

Table 10. Adjusted hazard ratios regarding cause-specific mortality by latency 1965–1998 (151).

Disease	Exposure	0-year lag HR (95% CI)	15-year lag HR (95% CI)
Circulatory diseases	None	1.0	1.0
	Low	0.83 (0.72–0.95)	0.88 (0.77–1.00)
	Medium	0.97 (0.81–1.15)	1.09 (0.86–1.39)
	High	1.05 (0.83–1.32)	1.76 (0.99–3.12)
		P for trend 0.526	*P for trend 0.052*
CHD	None	1.0	1.0
	Low	0.83 (0.68–1.02)	0.79 (0.65–0.96)
	Medium	0.81 (0.61–1.06)	1.15 (0.81–1.62)
	High	1.06 (0.75–1.48)	2.27 (1.07–4.84)
		P for trend 0.959	*P for trend 0.333*
Stroke	None	1.0	1.0
	Low	0.89 (0.71–1.13)	1.01 (0.82–1.23)
	Medium	1.11 (0.84–1.46)	1.12 (0.76–1.67)
	High	1.15 (0.80–1.67)	1.18 (0.38–3.71)
		P for trend 0.394	*P for trend 0.083*

CHD: coronary heart disease, CI: confidence interval, HR: hazard ratio.

11.4.4 Conclusion

The data base on mixed organic solvent exposure comprises seven epidemiological studies and a meta-analysis. Out of these, two studies with internal referents demonstrated an increased risk for CVD. One of these showed a significantly increased risk for IHD after ≥ 16 years of organic solvent exposure (923). Another study with semi-quantitative exposure estimates showed an increased CHD mortality at the highest exposure (151).

There is *limited evidence* for an association between exposure to mixed organic solvents and CVD.

12. Halogenated hydrocarbons

12.1 General

Halogenated hydrocarbons are widely used as aerosol propellants, refrigerants, solvent cleaners, foam-blowing and fire-extinguishing agents and as anaesthetics. Stable fluorine-containing derivatives of methane and ethane often contain chlorine in addition to fluorine and sometimes bromine (408, 1020). These chlorofluoro-carbons or freons are given names according to a system used worldwide. Some common groups are hydrofluorocarbons (HFC), hydrochlorofluorocarbons (HCFC) and chlorofluorocarbons (CFC); with “H” for hydrogen, the first “C” for chlorine, “F” for fluorine, and the last “C” for carbon. The following numbers denotes the number of atoms; the rightmost value is fluorine atoms, the next value to the left is hydrogen atoms +1 and the next value is carbon atoms -1. For the methanes there

is one single carbon (only two numbers), e.g. HCFC-22, chlorodifluoromethane. To identify isomers, letters are added after the numbers, e.g. HFC-134a and 1,1,1,2-tetrafluoroethane. Refrigerants can also be named with the prefix R, followed by a number e.g. R-22 (109).

A Finnish cohort of workers exposed to unspecified chlorinated hydrocarbon solvents comprised men who were in the same occupation in 1975 and 1980 and were 25–64 years old in 1980. The mortality for CVD was followed 1981–1994. Information on marital status, education and income was updated in 1985 and 1990. Working conditions were evaluated from a JEM comprising three categories: unexposed, low-exposed (three lowest quartiles of the exposed) and high-exposed (top quartile of the exposed). A fully adjusted Poisson regression model was applied which included age, period, marital status, professional status, education, income, occupational class and category, and working conditions. When high-exposed workers were compared with low- and unexposed workers, the RR (95% CI) for MI and CeVD mortality was 1.09 (0.95–1.25) and 1.11 (0.92–1.35), respectively (1031).

12.2 Chemicals causing cardiac sensitisation to catecholamines

12.2.1 General

Already in 1911, Levy and Lewis reported that cats light anaesthetised with chloroform were unexpectedly sensitive to injected adrenaline, manifested as disturbances in heart rhythm (124). The tendency of volatile anaesthetic agents such as cyclopropane, chloroform, halothane, methoxyflurane and enflurane to sensitise the heart to the arrhythmogenic action of various catecholamines (monoamine neurotransmitters such as adrenaline, also called epinephrine) has been investigated in animal studies and in clinical human studies (424, 459). As an example of a clinical human study, Johnston *et al*. gave submucosal injections of adrenaline in saline solution during halothane or enflurane anaesthesia to 25 patients undergoing transsphenoidal removal of pituitary tumours. Positive evidence of ventricular irritability was given by the appearance of ≥ 3 premature ventricular contractions during or following injection. Positive or negative responses were plotted against the total dose of epinephrine. From these data, the effective doses for 50% of the exposed group (ED_{s50}) were 2.1 µg/kg bw for halothane and 10.9 µg/kg bw for enflurane (459). Later studies have confirmed these results (408).

Abusive sniffing of high concentrations of volatile halocarbons and hydrocarbons has been associated with sudden deaths. These chemicals involve aerosol products and propellants as well as industrial solvents. They include chemicals such as trichlorofluoromethane (CFC-11), dichlorodifluoromethane (CFC-12), chlorodi-fluoromethane (HCFC-22), 1,1,1-trichloroethane, trichloroethylene, toluene and petrol (68, 124). Between 1959 and 1966 excess mortality among young asthmatic persons in England and Wales was associated with the use of fluorocarbon-containing aerosols carrying sympathomimetic drugs (exogenous, e.g. isoprenaline,

and endogenous, e.g. adrenaline, stimulant agonists of the sympathetic nervous system) (245).

12.2.2 Animal studies

Evidence of cardiac sensitisation to catecholamines has been shown in dogs (Table 11) (408, 812).

12.2.3 Human experimental studies

In this section, common names are used. For corresponding chemical names, see Table 11.

Two volunteers were exposed to air, 1 000 ppm and 10 000 ppm CFC-12 for 2.5 hours without knowing the order of exposure. ECG was continuously monitored and did not reveal any abnormalities (59).

Healthy adult male and female volunteers were exposed in small groups (2–8 subjects) to CFC-11 or CFC-12 in series of single exposures to 0, 250, 500 and 1 000 ppm for periods of 1 minute to 8 hours. As there were no untoward health effects the subjects were then repeatedly exposed 5 days/week for 2–4 weeks to 1 000 ppm CFC-11 or CFC-12. The concentrations of gases were recorded

Table 11. Cardiac sensitisation to catecholamines in dogs after exposure to halogenated hydrocarbons (408, 812).

Chemical name	Common name	Cardiac sensitisation to catecholamines, % in air (LOAEC) [a]
Trichloromethane, chloroform	–	0.5–2.0
Trichloroethylene	–	0.7–1.0
Trichlorofluoromethane	CFC-11	0.5
Dichlorodifluoromethane	CFC-12	5.0 and 20
Chlorodifluoromethane	HCFC-22	5.0
Bromochlorodifluoromethane	Halon 1211	1.0
Bromotrifluoromethane	Halon 1301	7.5
Bromochlorotrifluoroethane, halothane	Halon 2311	0.1–0.5
Trichlorotrifluoroethane	CFC-113	0.5
Dichlorotetrafluoroethane	CFC-114	2.5
Chloropentafluoroethane	CFC-115	15
Dichlorotrifluoroethane	HCFC-123	2.0
Chlorotetrafluoroethane	HCFC-124	2.5
Pentafluoroethane	HFC-125	10
Tetrafluoroethane	HFC-134a	7.5–8.0
Dichlorofluoroethane	HCFC-141b	0.5–1.0
Chlorodifluoroethane	HCFC-142b	5
Trifluoroethane	HFC-143a	30
Difluoroethane	HFC-152a	15
Heptafluoropropane	HFC-227ea	10.5
Hexafluoropropane	HFC-236fa	15
Pentafluoropropane	HFC-245ea	2

[a] 1% equals 10 000 ppm.

LOAEC: lowest observed adverse effect concentration.

continuously in the chamber atmosphere. A 12-lead ECG was performed pre-exposure and after the last exposure. During exposure, left precordial ECG (lead V_5) was monitored continuously. Single exposures for 1 minute to 8 hours did not produce any untoward effects on ECG monitoring. Repeated exposures were not associated with alterations of cardiac rhythm. However, male subjects repeatedly exposed to 1 000 ppm CFC-11 had significant decrements in cognitive test performance (914).

One study describes ECG measurements in 10 volunteers after 15–60 seconds of controlled exposure to CFC-11, CFC-12, CFC-114 and mixtures thereof (976). The reported exposure concentrations are highly improbable (in the sub-ppb range), therefore the study is disregarded.

Healthy volunteers (4/sex) were exposed in two separate double-blind chamber studies. The volunteers were exposed for 1 hour on 8 separate occasions, once weekly, first to air and then to ascending concentrations of either HFC-134a or HFC-227 (1 000, 2 000, 4 000 and 8 000 ppm), interspersed with a second air exposure and two CFC-12 exposures (1 000 and 4 000 ppm). Exposures did not result in any adverse effects on pulse, blood pressure or ECG (252).

Ten healthy firefighters, aged 40–50 years, were exposed to 1 000 ppm Halon 1211 and humidified air while exercising, in a double-blind crossover experiment, and were monitored during and after exposure. Two subjects displayed increased ventricular ectopy during Halon exposure. One subject had increased ventricular premature beats/hour during and 8 hours post-exposure to Halon compared to air exposure (49.5 vs 8.7 beats/hour). In addition, 8 of the 10 subjects had a smaller systolic blood pressure rise during Halon exposure than during air exposure. None of the observed differences were statistically significant. The authors pointed out that these results were consistent with findings in other investigations, suggesting that occupational fluorocarbon exposures may be cardiotoxic in certain individuals, although the small sample sizes used in this and other studies have resulted in limited statistical power to demonstrate such effects (479).

12.2.4 Occupational studies

In this section, common names are used. For corresponding chemical names, see Table 11.

One fatality after occupational exposure to CFC-11 has been reported. However, hypoxemic asphyxiation may have contributed to death (354).

One case report describes a 56-year old man with tachycardia with supra-ventricular and ventricular extrasystoles. The man was admitted to hospital due to dyspnoea and returned to work after a month. At check-up, 1.5 months later, he had no symptoms and his ECG was normal with no arrhythmias. He had been exposed to CFC-12 during filling and adjusting air-conditioning systems in cars. The average 8-hour TWA was always below 500 ppm, but during adjustments, concentrations were above 750 ppm several times (averages during 15 minutes). Breaking a valve resulted in levels around 6 000 ppm during the first 15 minutes (1060).

Totally, 27 refrigeration repair workers exposed to different fluorocarbons and their thermal decomposition products were investigated and compared with 14 non-exposed workers. Heart palpitations were more common among the exposed workers (26% vs 0%, $P < 0.05$). Standard 12-lead ECGs were all within normal limits (139).

Ambulatory ECG were studied among 6 refrigeration repair workers (age 31–56, mean 46 years) exposed to CFC-12 and HCFC-22 and a control group of 6 plumbers (age 29–54, mean 45 years). The ambulatory ECGs were recorded for 24 hours on a day of exposure and on a control day. The ECG tapes were automatically analysed and all aberrant complexes recorded by the machine were checked. One person read all the tapes without knowledge of exposure. The number of ventricular ectopic beats was compared between the day of exposure and the control day and with the tape of the control. In addition, the number of ventricular ectopic beats during exposure was compared with the number occurring during the rest of the day. The concentrations of fluorocarbons were measured in four instances. High peak fluorocarbons levels (1 300–10 000 ppm) were measured during refrigerator repair work. No clear connection between fluorocarbons and cardiac arrhythmia was found, although one subject had several ventricular ectopic beats which may have been connected with exposure (36).

In a cross-sectional study, 23 apparently healthy male workers at the refrigeration services workshop were compared with 23 unexposed healthy male security employees from the Suez Canal Authority. The refrigeration workers were exposed to CFC-12 and HCFC-22 and the average concentrations in the breathing zone were 5 720 mg/m^3 (1 140 ppm) and 4 310 mg/m^3 (1 200 ppm), respectively. The results of ECG Holter monitoring revealed a significantly higher number of atrio-ventricular arrhythmias in exposed than in non-exposed workers. Among the exposed workers, there was also a significantly higher number of arrhythmias during an exposed day than during a non-exposed day. Serum cholesterol levels were also raised (816).

Totally 89 refrigerator repairmen were exposed to a number of fluorocarbons from leaking compressors or from emptying or refilling the systems. Most cooling systems (89%) contained CFC-12 or HCFC-22. The concentrations of fluoro-carbons in the breathing zones and the heart activity were recorded simultaneously. The highest level recorded in one minute was 14 000 ppm and the highest 8-hour TWA was 280 ppm. Low-, medium- and high-exposure categories were based on the length of time that the levels exceeded 750 ppm [(Swedish 15-minute short-term exposure limit (STEL)] as well as the peak level. Exposure never exceeding 750 ppm was categorised as minimal. The ECGs were analysed blindly by a cardiologist. Two types of arrhythmia were recorded, ectopic beats and sudden bradycardia. A within-subject comparison design was applied and the main parameter was the difference in arrhythmia frequencies between exposed and unexposed periods. No appreciable differences between exposed and unexposed periods and no consistent exposure-effect relationships were observed, although subjects in the medium exposure category showed a difference of borderline

significance (Wilcoxon's test: P = 0.05, one tailed). It was not possible to investigate the impact of specific fluorocarbons. Subjects with medium or high exposure to HCFC-22 tended to have the highest absolute differences of ectopic beats when comparing exposed and unexposed periods (P = 0.05). Of the men, 6 had peak exposures exceeding 10 000 ppm; 4 were exposed to CFC-12 and 2 were exposed to HCFC-22. For 5 of the 6 men, there were no differences between exposed and unexposed periods regarding arrhythmia. One subject exposed to the lowest peak CFC-12 (11 400 ppm) had an ectopic beat within 8 minutes after the peak exposure and no arrhythmia when unexposed. Regarding sudden bradycardia there was an increased frequency during exposed periods, but the difference was of borderline significance. The authors concluded that misclassification of the exposure and the possible confounding effect of physical workload and psychological strain may have obscured a causal relation and therefore a minor effect could not be ruled out. The results did not support the notion that fluorocarbons induce cardiac arrhythmia in occupationally exposed refrigerator repairmen (246). One drawback of the study is the lack of data for individual fluorocarbons.

Totally 118 employees at the pathology department were exposed to fluorocarbons including HCFC-22 when spraying frozen tissues with an aerosol preparation. The employees were compared with 85 participants from the radiological department. Heart palpitations were reported in a questionnaire. Half of the employees exposed to HCFC-22, 35% of those exposed to other fluorocarbons and 53% of those exposed to both preparations had onset of palpitation versus 14% of the employees in the radiological department. There was also an exposure-response relationship between the numbers of treated frozen sections each week and episodes of palpitations (P < 0.03). Two subjects proceeded to use HCFC-22 in a manner similar to the general processing of tissues. A 2-minute sample was collected while two 10-second blasts were expelled over the tissue. The average exposure of HCFC-22 was 300 ppm during the 2-minute period (898).

Freons such as HCFC-22 can be decomposed to phosgene and many other chlorinated or non-chlorinated hydrocarbons such as aldehydes and hydrochloric acid by electric arc welding. After occupational exposure to decomposed HCFC-22, a 65-year-old man developed respiratory symptoms such as cough, blood-stained sputum, and increasing dyspnoea. Three weeks later, his family doctor diagnosed infectious bronchitis. Another week later he died due to MI. Inhalation of these highly irritative chemicals from decomposed freon may start an inflammatory process eventually leading to MI (884). However, this case is not an example of catecholamine sensitisation but rather an inflammatory process.

A 16-year old male collapsed after cleaning a subfloor pit containing waste and spill material, including CFC-113. He became unconscious and had ventricular tachycardia and fibrillation, which did not respond to medical intervention. He died one hour after collapsing (622). Several young men, 19–32 years old, died during excessive occupational exposure to CFC-113 (480, 612). Two cases of atrial fibrillation and one case of sudden death occurred in workers exposed to CFC-113 used for degreasing of the interior of military tanks. All three men were exposed

inside these tanks (480). Measurements performed inside a tank 24 hours after exposure showed a level of 7 600 ppm (737).

Healthy workers were exposed to CFC-113 during cleaning rocket and ground support equipment for the National Aeronautic and Space Administration (NASA) programmes. Exposure and ambulatory ECG monitoring data were evaluated on 16 workers, each of whom was examined on exposed and low-exposed workdays. The mean full-shift TWA exposure was 442 ppm during an exposed day and 64 ppm during a low-exposed day. There was no difference between exposed and low-exposed days regarding rate of ventricular and supraventricular premature beats, or heart rate. However, an episode of sinus rhythm bradycardia for less than 15 minutes occurred during a short-term exposure of 600 ppm (248).

A 40-year old man collapsed after cleaning a degreasing tank. At autopsy, high concentrations of HCFC-141b were found in his blood (14 mg/l) and tissues (51).

12.2.5 Conclusion

There is strong evidence that inhalation of high concentrations of several volatile halocarbons and hydrocarbons induce cardiac arrhythmias in combination with catecholamines (surrogates for stress induction, e.g. adrenaline).

This has been shown in humans for anaesthetics (cyclopropane, chloroform, halothane, methoxyflurane and enflurane) during general anaesthesia (424, 459).

Additional similar substances (Table 11) induce arrhythmogenic action in combination with catecholamines in animals (408, 812) and have been associated with sudden deaths in humans after abusive sniffing or asthma treatment with fluorocarbon containing aerosols (68, 124, 245).

Some human experimental and occupational studies were located, the latter in particular on refrigeration repair workers. Selected substances were studied, in single and combined exposures. Results were mostly negative. Overall, the support for cardiac sensitisation at occupationally realistic exposure levels is inconclusive.

There is *insufficient evidence* for an association between CVD and occupational exposure to chemicals known to cause cardiac arrhythmias at very high exposure levels, e.g. during asthma treatment and general anaesthesia.

12.3 Methyl chloride

12.3.1 General

Methyl chloride is a colourless gas at ambient temperatures. It can be compressed to a liquid, which has a weak ethereal smell. In industry, methyl chloride is used in the production of silicones, as methylating agent, as solvent in the production of plastic and synthetic rubber, and as a refrigerant (446).

12.3.2 Animal studies

Fischer 344 rats and B6C3F1 mice were exposed to 0, 50, 225 or 1 000 ppm methyl chloride 6 hours/day, 5 days/week for 2 years. Mouse survival was low in the 1 000-ppm exposure group compared with control animals. The relative heart weight was

increased in female mice and male and female rats at 1 000 ppm. Also, changes in relative or absolute kidney, liver and brain weights were seen at 1 000 ppm in both species (446).

12.3.3 Occupational epidemiological studies

A cohort comprised 852 male workers employed for at least 1 month 1943–1978 in a synthetic rubber manufacturing plant in Baton Rouge, Louisiana. Methyl chloride was one of the substances in the manufacturing process. The mortality of the cohort was compared with US national cause-specific death rates. No increased mortality regarding diseases of the circulatory system was observed in a subcohort of 661 white male workers (SMR 0.97, 95% CI 0.76–1.23). However, a tendency to an exposure-response relationship was observed when methyl chloride exposure was estimated with a subjective procedure. SMRs were 0.48 (3 observed vs 6.3 expected) among low exposed workers, 0.91 (10 vs 11.0) among medium exposed and 1.08 (43 vs 40.0) among high exposed (418).

In 1963 on board an Icelandic trawler, methyl chloride was leaking from the refrigerator. Methyl chloride was refilled several times during the fishing trip, which lasted 4 days. One deckhand died from an acute intoxication on the second day. The total crew comprised 29 men, and 13 of these were hospitalised due to severe symptoms of methyl chloride intoxication. The exposed cohort comprised 27 men (as one deckhand died and another returned to his native country) and was compared with an external referent group. Five referents were selected to each crew member from three different registers of seamen. These men were not more than two years older or younger than the crew member. The inclusion criterion for the referents was that they had all been active seamen or fishermen in 1963 or earlier. The 135 referents were categorised as deckhands or officers. The cohorts were followed 1963–2010. Based on previous knowledge, the exposure was roughly estimated to be in the order of 100–1 000 ppm. There were increased risks (HR, 95% CI) for all causes of deaths (2.10, 1.28–3.46), all CVD events (2.06, 1.02–4.15), acute CHD (3.12, 1.11–8.78) and CeVD (5.35, 1.18–24.35) (770).

12.3.4 Conclusion

One occupational cohort study (418) and a follow-up after an accident (770) indicated an increased CVD risk after methyl chloride exposure.

There is *insufficient evidence* for an association between exposure to methyl chloride and CVD.

12.4 Dichloromethane

12.4.1 General

Dichloromethane (methylene chloride) is a colourless liquid with a sweet and pleasant odour. Dichloromethane has been used as a solvent in paint strippers and removers, in adhesives, as a propellant in aerosols, as a solvent in manufacture of

pharmaceuticals and drugs, in chemical processing, as a metal cleaning and finishing solvent, and in urethane foam blowing. This chemical has also been used as a solvent in the production of triacetate fibres and in film processing (716). Dichloromethane is a reproductive toxin and probably carcinogenic to humans. In 1993, it was banned in consumer products in Sweden and in 1996 the ban also comprised industrial use, with some exceptions (662).

Epidemiological studies and risk estimates are presented in Appendix, Table A22.

12.4.2 Human experimental studies

Inhalation of dichloromethane results in an increase of COHb due to biotransformation of dichloromethane to CO. This increase reduces the transport capacity of oxygen in the blood. COHb levels around 20% may be lethal for patients with IHD (918). Data on COHb levels obtained after experimental CO exposure (Section 15.1) have therefore been included in this section.

Non-smoking volunteers were exposed for 7.5 hours to dichloromethane levels of 50, 100, 150 and 200 ppm. At the end of exposure, the COHb levels were 1.9, 3.4, 5.3 and 6.8%, respectively. Repeated exposures to dichloromethane for 7.5 hours/day for 5 consecutive days produced slightly higher blood concentrations of COHb than those found for single exposures (233).

In controlled exposures of healthy volunteers to CO, COHb levels up to 5.1% have been related to effects on exercise performance but were not observed to induce myocardial ischaemia or cardiac arrhythmias (9, 496).

In a controlled exposure study of patients with coronary artery disease, CO exposures resulting in COHb concentrations of 2.4% and 4.7% significantly reduced the time to onset of angina symptoms and of ST-segment changes of the ECG during exercise in a dose-dependent manner (21, 22). Other studies on patients also showed that CO exposure (COHb 2.9–5.9%) aggravated exercise-induced myocardial ischaemia including decreased time to onset of angina symptoms, decreased time to onset of ST-segment changes and increased duration of angina symptoms (8, 29, 499). In another study on patients, no change in time to onset of angina and of ST-segment changes were observed at a COHb of 3.8% (863). At a COHb level of 5.9%, but not at 4.0%, an increase in the number of ventricular arrhythmias was reported (864). In contrast, no such effect was seen in another study on patients at the same COHb level (5.8%) (409).

12.4.3 Occupational epidemiological studies

Cohorts of workers exposed to dichloromethane have been identified in plants manufacturing photographic film base and textile fibres. Workers manufacturing photographic film base in the UK (963, 964) and the US (309, 393, 394) did not have increased risks of CVD mortality, nor did US textile fibre workers (336, 531, 728).

12.4.4 Pooled analyses

All the cohorts of photographic film base workers (394, 964) and textile fibre workers (336, 531) were pooled and comprised totally 6 964 participants. The

calculated SMR for IHD was 0.89 (95% CI 0.81–0.97) based on 500 deaths. When only active workers were included the SMR was 0.76 (95% CI 0.59–0.97) (394).

12.4.5 Exposure-response relationships

The UK cohort of 1 473 male workers employed 1946–1988 producing cellulose triacetate film in Brantham was followed until 2006. The relationship between cumulative exposure to dichloromethane and IHD mortality was analysed with Cox regression. The estimated RR (95% CI) for lifetime cumulative exposure to 1 000 ppm-years was 1.47 (0.91–2.39) (963). Other studies did not show positive tendencies between cumulative dichloromethane exposures and IHD (336, 394).

12.4.6 Markers of effect

Fifty employees of two fibre production plants were selected for study, 24 of whom were occupationally exposed to dichloromethane. All the participants were white males between the ages of 37 and 63 years. Eleven of the men had reported a history of heart disease. Under the conditions of this study, neither an increase in ventricular or supraventricular ectopic activity nor episodic ST-segment depression was associated with exposure to dichloromethane that ranged from 60 ppm to approximately 475 ppm as TWAs (728).

12.4.7 Conclusion

A pooled analysis of four cohorts of workers exposed to dichloromethane in plants manufacturing photographic film base or textile fibres did not show increased risks of CVD (394). Exposure-response analyses did not show relationships between cumulative exposures to dichloromethane and CVD (393, 394, 963).

Inhalation of dichloromethane results in an increase of COHb due to bio-transformation of dichloromethane to CO. Among healthy volunteers, COHb blood levels up to 5.1% did not induce myocardial ischaemia or cardiac arrhythmias (918). However, among patients with coronary artery disease (IHD), CO exposures resulting in COHb concentrations of 2.4% and 4.7% induced angina pectoris symptoms. COHb levels around 20% may be lethal for patients with IHD. Exposure of non-smoking volunteers to dichloromethane for 7.5 hours at 50, 100 and 150 ppm resulted in post-exposure COHb-values of 1.9, 3.4, and 5.3%, respectively (233). Thus, exposure to 50–150 ppm of dichloromethane may induce angina pectoris symptoms in subjects with IHD.

There is *moderately strong evidence* for an association between exposure to dichloromethane and angina pectoris symptoms in subjects with previous angina pectoris (IHD).

12.5 Trichloroethylene

12.5.1 General

Trichloroethylene (TCE, TRI) is a colourless liquid with a characteristic odour similar to chloroform. The chemical is absorbed by inhalation and also by dermal

exposure. TCE is rapidly oxidised by cytochrome P450 (mainly CYP2E1), via the respective epoxide, to trichloroacetaldehyde (chloral). This metabolite is further metabolised to trichloroethanol as well as trichloroacetic acid (846).

In 1996, occupational use of TCE was banned in Sweden. During 2015–2016, the total registered use was 7–28 tonnes/year and country in Denmark, Finland and Sweden (data from Norway were confidential) (899). Within the EU REACH legislation (Registration, Evaluation, Authorisation and Restriction of Chemicals), TCE is identified as a substance of very high concern requiring authorisation before use since 2016 (244).

TCE is one of the halogenated hydrocarbons that has been associated with cardiac sensitisation to catecholamines among dogs (Table 11, Section 12.2).

12.5.2 Occupational epidemiological studies

During 1930–1986, one plant in central Sweden produced TCE for the whole domestic market. TCE is sensitive to photochemical degradation and consequently various stabilisers were added to the commercial product. The producer provided two TCE formulas on the market; *Standard TRI* and *TRI-plus*. *Standard TRI,* the bulk TCE product, was stabilised with diisopropylamine and thymol. *TRI-plus* contained butylene oxides and epichlorohydrin as stabilisers. It is likely that *standard TRI* was the dominating product to which the cohort was exposed. The cohort of 1 670 persons (1 421 men and 249 women) was followed 1955–1986. National mortality rates were used for comparison. The mortality (SMR, 95% CI) due to circulatory diseases was significantly increased among males (1.17, 1.00–1.37) but not among females (2.02, 0.97–3.71). Estimations of exposure were based on urinary levels of trichloroacetic acid. A slightly higher point estimate regarding circulatory disease was observed at the highest urinary concentration when a latency time of 10 years and an exposure time of at least 2 years were applied (58). In summary, no clear dose-response relationship was observed.

A cohort study of workers employed for at least 1 year at a large US aircraft manufacturing facility in California since 1960 was followed until 1996. The primary organic solvent used in vapour degreasers until 1966 was TCE, when it was replaced by tetrachloroethylene. The mortality of a subcohort comprising 2 267 TCE-exposed workers was compared with that of the general population in California for white workers and with the US general population for non-white workers. There was decreased mortality (SMR, 95% CI) regarding all heart disease (0.85, 0.78–0.94) and CeVD (0.66, 0.50–0.85). Analyses were also conducted of workers routinely exposed to TCE but not tetrachloroethylene. Fewer observations resulted in increased instability of the SMRs, but the pattern mirrored the previous presentations. Over 70% of the workers exposed to TCE were also estimated to have had exposure to compounds containing chromate (116).

A retrospective cohort study comprised 14 457 workers at a US aircraft maintenance facility at Hill Air Force Base, Utah, 1952–1956. The study group consisted of all civilian employees who had worked for at least 1 year and the cohort was followed up through 1982. Observed deaths among white people were compared

with the expected number of deaths, based on the Utah white population. Significant deficits occurred for mortality from IHD (SMR 0.93, 95% CI 0.88–0.98). Detailed analysis of the 6 929 employees occupationally exposed to TCE (the most widely used solvent at the base during the 1950s and 1960s) did not show any significant increases (SMR, 95% CI) for men regarding IHD (0.98, 0.90–1.07) and CeVD (0.83, 0.66–1.03), or for women regarding IHD (0.90, 0.67–1.17) and CeVD (0.83, 0.52–1.25). Cumulative exposure categories were derived by cumulatively multiplying the exposure index assigned to each job by the time exposed at that level. Among white males, the SMRs for IHD were 0.94, 0.94 and 1.05 for cumulative exposures of < 5, 5–25 and > 25, respectively. There was no significant trend (900). This cohort was further followed (102, 764) (Section 12.5.3).

12.5.3 Exposure-response relationships

In total, 4 733 aircraft manufacturing workers (2 555 males and 2 178 females) in Arizona, employed for at least 6 months 1950–1985, and exposed to TCE mainly during degreasing 1952–1977, were followed through 1993. US rates were used for comparison. Jobs were classified in exposure categories of high, medium, low or none. The highest rating involved work on degreaser machines with an estimated TCE exposure of 50 ppm. Jobs with medium rating were near the degreasing area with more than occasional contact with TCE. A low exposure rating was given jobs away from the degreasing area, but with occasional TCE contact. All other jobs were assigned no exposure to TCE. Exposure scores were assigned 0 for no, 1 for low, 4 for medium and 9 for high exposure. The score 0 was given to those with less than 6 months of TCE-exposure. For each job, the number of months with exposure to TCE was multiplied with the score 0, 1, 4 or 9. An individual cumulative exposure score was then calculated as the sum of months × score of all jobs of that individual. The exposed workers were categorised in low- or high-exposed groups based on the cumulative exposure score, with the low-exposed group including those with low-exposed rating and up to 5 years of exposure or medium-exposed rating for at most 1.4 years. Mortality (SMR, 95% CI) from all heart disease was significantly decreased both among high-exposed workers (0.85, 0.74–0.97) and among low-exposed workers (0.56, 0.44–0.70), although it seems to be higher among high-exposed. Corresponding SMRs (95% CIs) for mortality from CeVD were 0.55 (0.35–0.83) and 0.66 (0.39–1.06), respectively (670).

The US cohort of workers at an aircraft maintenance facility (900) (Section 12.5.2) was further followed until 1990. Based on a Poisson model, an increased mortality (RR, 95% CI) was observed for IHD (1.1, 1.0–1.3) but not for CeVD (1.0, 0.8–1.3) among TCE-exposed workers compared to referents with no chemical exposure. An exposure score for TCE was assigned to each job based on possible exposure intensity, frequency and duration of peak exposures from vapour degreasing and of low-level exposures at the work bench. Information from two surveys in the 1960s and 1970s on work practices at vapour degreasers and other potential exposures was used to create an intensity index of exposure to TCE

Table 12. Relative risks (95% CI) among workers with or without exposure to TCE followed through 1990. Cohort members with no chemical exposures as referents (102).

Group	No TCE exposure	Cumulative TCE exposure		
		< 5 unit-years	5–25 unit-years	> 25 unit-years
Men				
IHD	1.1 (1.0–1.3)	1.0 (0.9–1.2)	1.1 (1.0–1.4)	1.2 (1.0–1.4)
CeVD	1.2 (0.9–1.6)	0.7 (0.5–1.1)	0.6 (0.4–1.0)	1.2 (0.8–1.7)
Women				
IHD	1.3 (1.0–1.8)	1.1 (0.7–1.5)	0.6 (0.3–1.1)	1.2 (0.9–1.6)
CeVD	1.5 (0.9–2.7)	0.5 (0.2–1.3)	1.0 (0.4–2.8)	1.8 (1.1–2.9)

CeVD: cerebrovascular disease, CI: confidence interval, IHD: ischaemic heart disease, TCE: trichloroethylene.

Table 13. Hazard ratios (95% CI) among workers exposed to TCE and followed through 2000. Cohort members with no chemical exposures as referents (764).

Group	Cumulative TCE exposure		
	< 5 unit-years	5–25 unit-years	> 25 unit-years
Men			
IHD	0.98 (0.85–1.13)	1.11 (0.95–1.30)	1.15 (1.00–1.33)
CeVD	0.85 (0.63–1.16)	0.68 (0.47–0.99)	1.17 (0.87–1.56)
Women			
IHD	1.17 (0.88–1.56)	0.70 (0.42–1.62)	1.11 (0.86–1.44)
CeVD	0.84 (0.50–1.41)	1.23 (0.67–2.28)	1.32 (0.90–1.94)

CeVD: cerebrovascular disease, CI: confidence interval, IHD: ischaemic heart disease, TCE: trichloroethylene.

for various periods (600 for the years 1939–1954, 400 for 1955–1967 and 200 for 1968–1978). These scores provide an indication of the relative exposures over time but should not be viewed as ppm. After 1978, TCE in the degreasers was replaced by 1,1,1-trichloroethane. Mortality from IHD was significantly increased in this follow-up. Small but significant excesses of IHD occurred among men exposed to TCE. A significant excess of CeVD occurred among the women with highest cumulative exposure (Table 12) (102). The cohort was further followed until 2000 and exposure-response relationships were derived from a Cox model (Table 13). Exposure was also categorised as low-intermittent, low-continuous, peak-infrequent and peak-frequent. The only significant mortality was found for CeVD among women at peak-frequent exposure (HR 1.50, 95% CI 1.05–2.13) (764).

12.5.4 Conclusion

Four occupational cohorts were found. One study of TCE-exposed workers showed an increased mortality from circulatory diseases among males (58). Another cohort study, with several follow-up periods, showed significant increases of IHD mortality among males in the highest cumulative exposure category and of CeVD mortality among females exposed to frequent peaks or high cumulative levels (102, 764).

There is *limited evidence* for an association between exposure to trichloroethylene and CVD.

12.6 Tetrachloroethylene

12.6.1 General

Tetrachloroethylene, often called perchloroethylene, is a solvent mainly used for cleaning and for degreasing in metal cleaning (218).

12.6.2 Occupational epidemiological studies

The mortality patterns of 671 US female laundry and dry cleaning workers for the period 1963–1977 were analysed using Wisconsin death certificate data. The PMR for IHD was significantly increased (1.13, $P < 0.05$), but there was no significant increase for other CVD (PMR 1.03). When lower wage occupations were used as controls, no significant increased IHD risk was observed (PMR 1.05) (478).

A US cohort was formed from four labour unions and included 1 690 dry cleaning workers exposed to tetrachloroethylene. The participants had worked at least 1 year prior to 1960 and were followed until 1982. The mortality from diseases of the circulatory system was decreased (SMR 0.70, 95% CI 0.60–0.82) (128).

A retrospective cohort mortality study was conducted of workers employed for at least 1 year since 1960 at a large aircraft manufacturing facility in California. The cohort was followed until 1996. A subcohort of 2 631 tetrachloroethylene-exposed workers was identified. The mortality of the subcohort was compared with the mortality rates in the general population. There was no increased mortality (SMR, 95% CI) regarding all heart disease (0.84, 0.71–0.99) and CeVD (0.86, 0.56–1.27) among these workers. The primary organic solvent used in vapour degreasers until 1966 was TCE, when it was replaced by tetrachloroethylene. Analyses were also conducted of workers routinely exposed to tetrachloroethylene but not to TCE. Fewer observations resulted in increased instability of the SMRs, but the pattern mirrored the previous presentations. Over 70% of the workers exposed to tetrachloroethylene were also estimated to have had exposure to compounds containing chromate (116).

A US cohort of 5 369 members of a dry cleaning union in St. Louis (entering 1948–1979) was followed until December 1993. A number of organic solvents has been used by the dry cleaning industry over the years and tetrachloroethylene became the solvent of choice in the 1960s. An increased risk of IHD (SMR 1.1, 95% CI 1.0–1.3) was observed for one of the follow-up periods (1979–1991) but not for an earlier follow-up period (103).

Totally 1 708 workers identified from dry cleaning union records from four US cities (San Francisco, Chicago, Detroit and New York) who had worked for at least 1 year prior to 1960 in shops using tetrachloroethylene as the primary cleaning solvent were followed until December 1996. The SMR in the entire cohort due to IHD was 1.01 (95% CI 0.89–1.15). In a subcohort containing 625 subjects who had worked only in shops where tetrachloroethylene was the primary cleaning solvent

the SMR was 1.27 (95% CI 1.02–1.55) (810). The same cohort now comprising 1 704 workers was later followed until December 2004. The SMR in the entire cohort due to IHD was 1.10 (95% CI 0.99–1.22). In the subcohort now containing 618 subjects who had worked only in shops where tetrachloroethylene was the primary cleaning solvent the SMR was 1.21 (95% CI 1.03–1.48). There was an increased risk of hypertensive end-stage renal disease in the subcohort (SIR 2.66, 95% CI 1.15–5.23). Vascular disease of the kidney can both cause and arise from hypertension. However, it is thought that most hypertensive end-stage renal disease is caused by hypertensive nephrosclerosis, which is a consequence of hypertension (137).

12.6.3 Markers of effect

In a cross-sectional study of dry cleaners, two subgroups exposed to mean levels of 70 and 335 mg/m^3 of tetrachloroethylene (range 11–750 mg/m^3) had a higher total leukocyte count compared with blood donors, a possible expression of an inflammatory process (33). An increased total leukocyte count is an established risk indicator for IHD (209).

12.6.4 Conclusion

The results from two cohorts (103, 137, 810) out of four occupational cohorts indicated an increased risk for IHD in tetrachloroethylene exposed workers.

There is *limited evidence* for an association between exposure to tetrachloroethylene and IHD.

12.7 Vinyl chloride and polyvinyl chloride production

12.7.1 General

Vinyl chloride (monomer), a colourless gas with a faintly sweet odour, is used for the production of polyvinyl chloride (PVC) resins, a widely used plastic material (558).

In 1988, Richard Doll reviewed the literature regarding occupational exposures to vinyl chloride. Air concentrations around 10 000 ppm induced unconsciousness and cardiac arrhythmia, while prolonged exposures to concentrations an order of magnitude lower was associated with a specific pathological syndrome. This syndrome was characterised by four cardinal signs: enlargement of the liver and spleen with specific histological appearance, patchy infiltration of the skin resembling scleroderma, bony changes in the tips of the fingers described as acroosteolysis, and peripheral circulatory changes identical with the classical picture of Raynaud's disease. These disturbances could be avoided if air exposure never exceeded the level of a few hundred ppm, which is the level to which exposures were generally reduced in the mid-1960s (235).

12.7.2 Animal studies

Wistar rats were exposed to 5 000 ppm vinyl chloride 7 hours/day, 5 days/week during 52 weeks. Focal myodegeneration of the heart was more frequent in males (3/9 vs 0/10 controls) and females (8/10 vs 1/10 controls). Also thickened walls of the heart arteries was increased in males (2/9 vs 0/10 controls) and females (4/10 vs 0/10) (285).

12.7.3 Occupational epidemiological studies

A Swedish factory started its production of vinyl chloride and PVC at the end of World War II. The cohort included totally 750 vinyl chloride-exposed workers who did not emigrate during the period of follow-up ending at October 1974. The level of exposure to vinyl chloride and PVC in the past was unknown. However, episodes of unconsciousness had occurred among autoclave cleaners during the 1950s, which indicated vinyl chloride concentrations of at least 10 000–15 000 ppm. The cohort mortality was compared with the general Swedish population. There were increased risks (SMRs) of circulatory diseases (1.53, based on 28 cases, $P = 0.02$), MI (1.64, 15 cases, $P = 0.046$) and cerebral haemorrhage (1.48, 5 cases, $P = 0.018$). The authors pointed out that vascular deaths is noteworthy as other disorders observed in vinyl chloride exposed workers like acroosteolysis, Raynaud's phenomenon and angiosarcomas are all associated with the vessels (136).

Totally 2 073 workers from four PVC-processing industries in Sweden with at least 3 months of exposure 1945–1974 were included in a cohort. Different subcohorts were followed 1969–1976 and national mortality rates were used as referents. The RRs were 0.91 for CVD and 1.49 for MI for workers exposed for at least 6 months, including those who stopped working before 1961 ($n = 1\,771$). The RRs were approximately the same for workers exposed for at least 6 months from 1961 or later ($n = 1\,428$), 0.99 for CVD and 1.25 for MI. The RRs were higher for workers exposed at least 2 years and followed up to 5 years after the end of exposure ($n = 1\,155$), 1.18 ($P < 0.05$) for CVD and 2.03 ($P < 0.05$) for MI. When the follow-up was extended to 10 years after the end of exposure, the RRs were 1.01 and 1.82 ($P < 0.05$), respectively (658). The decreased risks after a longer period of non-exposure may indicate reversibility of a causal effect when exposure cease.

Workers from one of the Swedish PVC factories were further followed. Totally 2 042 male workers employed at least 3 months in the period 1945–1980 were followed 1961–1985. The records contained no data on workers who had left the employment or died before 1961. The expected mortality was based on male rates from the Blekinge County. There were totally 60 CVD deaths (SMR 1.00, 95% CI 0.77–1.29) and 44 IHD deaths (SMR 1.00, 95% CI 0.73–1.35). After a latency-period of 10 years there were totally 47 CVD deaths (SMR 1.08, 95% CI 0.80–1.45) and 36 IHD deaths (SMR 1.11, 95% CI 0.79–1.56) (370).

Workers from three of the four previously mentioned Swedish PVC factories (658) were further followed. Totally 717 male workers employed at least 3 months 1964–1974 were followed 1964–1986. The calculated expected mortality was based on national male rates. There were totally 49 deaths from circulatory diseases (SMR

1.0, 95% CI 0.7–1.3) and 38 IHD deaths (SMR 1.0, 95% CI 0.7–1.4). Among 198 immigrant workers (mostly from Finland), there was an increased mortality (SMR, 95% CI); 15 deaths from circulatory diseases (2.5, 1.4–4.1) and 13 deaths from IHD (3.0, 1.6–5.1). The observed deaths among the immigrants were probably close to what should have been expected if the Finnish male population had constituted the reference category. Consequently the increased risks among the immigrants were not caused by occupational exposure (583).

A cohort comprised totally 12 700 male workers from 19 vinyl chloride/PVC factories in Italy, Norway, Sweden (cohorts described above) and the UK. The cohort was followed until 1997 and the mortality was compared with the respective national rates. There was a decreased risk from diseases of the circulatory system (SMR 0.83, 95% CI 0.78–0.88) based on 1 136 fatalities. However, there was an increased risk from liver cancer as a possible expression of vinyl chloride exposure (991).

A cohort included 1 658 male workers employed in a vinyl chloride production and polymerisation facility in Porto Marghera, Italy [subcohort of the previously described European cohort (991)]. All subjects working in the plant in 1956 or hired thereafter until end of 1985 were included and followed until 2017. The mortality of the cohort was compared with regional rates. A JEM was constructed and the cumulative exposure was categorised as 0–733, 734–2 378, 2 379–5 187 and ≥ 5 188 ppm-years. Overall, there were decreased mortalities (SMR, 95% CI) from diseases of the circulatory system (0.66, 0.57–0.77) and IHD (0.66, 0.53–0.82), but no exposure-response analysis was presented (282).

A proportionate mortality study was performed based on 4 341 deaths among current and former employees of 17 US PVC fabricators during 1964–1973. Sex-race-cause-specific PMRs were computed using the corresponding US mortality as the standard. No angiosarcomas were found. There were no excesses of diseases of the circulatory system among men (PMR 1.05) or women (PMR 0.91). The mortality pattern for CeVD was about the same (PMR males 0.99 and females 0.92) (169).

A US cohort consisted of 10 173 men employed during or after 1942 at 37 plants belonging to 17 companies. The men had been exposed to vinyl chloride at least 1 year prior to December 1972 and were followed 1942–1982. The observed mortality, by cause, was compared with US mortality rates, standardised for age, race and calendar time. There were decreased SMRs (95% CIs) regarding diseases of the circulatory system (0.88, 0.81–0.95), atherosclerotic heart disease (0.82, 0.75–0.89) and vascular lesions of the CNS (0.76, 0.60–0.96). The SMRs were higher when the duration of exposure was 10–20 years compared to < 10 years (Table 14). The SMRs were also higher when first exposure occurred before 1950 compared with later (1037). The pattern of low–normal–low SMR with increasing duration of exposure may be explained by an exposure-response relationship (first phase) combined with a healthy worker survivor effect (second phase).

The previous US cohort (now comprising 9 951 men) was further followed through 2013. Liver cancer was elevated and strongly associated with cumulative

Table 14. Mortality (SMR) from CVD in vinyl chloride exposed men (1037).

Mortality cause	Duration of exposure (no. of cases)		
	< 10 years	10–20 years	> 20 years
Diseases of circulatory system	0.82 [a] (335)	1.07 (216)	0.75 [a] (84)
Atherosclerotic heart disease	0.78 [a] (259)	1.02 (172)	0.60 [a] (57)
Vascular lesions of the CNS	0.75 (39)	0.74 (19)	0.85 (12)
	Year of first exposure (no. of cases)		
	< 1950	1950–1959	≥ 1960
Diseases of circulatory system	0.98 (398)	0.80 [b] (170)	0.65 [b] (67)
Atherosclerotic heart disease	0.85 [b] (284)	0.84 [a] (150)	0.63 [b] (54)
Vascular lesions of the CNS	0.81 (46)	0.71 (17)	0.62 (7)

[a] $P < 0.01$, [b] $P < 0.05$.

CNS: central nervous system, CVD: cardiovascular disease, SMR: standardised mortality ratio.

vinyl chloride exposure. Mortality (SMR, 95% CI) due to diseases of the heart (0.86, 0.82–0.90) and CeVD (0.83, 0.73–0.94) was not increased (683).

12.7.4 Conclusion

Two Swedish cohort studies provided support for a relationship between exposure in the vinyl chloride/PVC industry and CVD mortality (136, 658), whereas a pooled European cohort (991) and a US cohort (683, 1037) did not show increased risks for CVD. In one of the positive studies, there was a tentative decrease of incidence after exposure cessation (658).

Prolonged exposure to vinyl chloride at high levels (approximately 1 000 ppm) is clearly associated with peripheral circulatory changes identical with the classical picture of Raynaud's disease (235). However, such levels are far above current occupational exposure levels.

There is *insufficient evidence* for an association between exposure to vinyl chloride/polyvinyl chloride and CVD.

12.8 Dioxins and dioxin-like compounds

12.8.1 General

Dioxins (polychlorinated dibenzo-*p*-dioxins) are unwanted contaminants formed during the combustion or production of chlorinated compounds. 2,3,7,8-Tetra-chlorodibenzo-*p*-dioxin (TCDD) is considered the most toxic of the dioxin congeners. TCDD has been a contaminant in e.g. phenoxy acid herbicides and chlorophenols (1005). Dioxins are highly persistent and bioaccumulative with biological half-times of 5–10 years (332). Dioxin-like compounds comprise polychlorinated dibenzofurans (which tend to co-occur with dioxins) and some polychlorinated biphenyls (PCBs) (190). Data on PCBs are presented in Section 12.9.

12.8.2 Mechanistic evidence

The aryl hydrocarbon receptor (AHR) is believed to play an important role in the development and function of the cardiovascular system, based on observations in *AhR* knockout mice which develop cardiac hypertrophy, abnormal vascular structure in multiple organs and altered blood pressure (1052). Several persistent substances activate *AHR* signalling, including PAH and halogenated aromatic hydrocarbons such as TCDD.

12.8.3 Occupational epidemiological studies

The epidemiological studies originate from accidents, manufacturing chlorinated compounds and handling or spraying TCDD-contaminated phenoxy acid herbicides (Appendix, Table A23).

12.8.3.1 Accidents

In 1953, an uncontrolled decomposition reaction occurred in a trichlorophenol production unit owned by BASF AG in Ludwigshafen, Germany. Totally 243 male workers were engaged in clean up, repair and demolition after the accident. The cohort was followed almost 40 years, until 1992. There was no increased mortality (SMR, 95% CI) regarding circulatory diseases (0.8, 0.6–1.2) or IHD (0.7, 0.4–1.1) and no dose-response relationships were observed (729).

In 1963, an uncontrolled reaction occurred in the autoclave where 2,4,5-trichlorophenol was synthesised. An explosion followed and dioxins, including TCDD, and polychlorinated dibenzofurans were released. A group of 140 exposed male workers were followed until 1991 and was compared with the general male population in the Netherlands. The mortality (SMR, 95% CI) was not significantly increased for circulatory diseases (1.1, 0.6–1.7) or for IHD (1.5, 0.8–2.5). However, an increased mortality from IHD was observed among 29 workers with chloracne (3.7, 1.4–8.1) (420).

In 1976, an accident occurred in a chemical plant manufacturing 2,4,5-trichlorophenol in Seveso, Italy. An uncontrolled exothermic reaction in a production kettle caused a sudden surge in temperature and pressure that blew a safety device. The reactor content, a fluid mixture containing some 2 900 kg of organic matter, released substantial amounts of TCDD into the air through an exhaust pipe. The blood concentration of TCDD in 7 subjects from the most contaminated area, nearly 20 years after the accident, was 53.2 pg/g (ppt) blood lipids (geometric mean). The mortality (RR, 95% CI) due to circulatory diseases, 1976–1991, was increased for males (1.6, 1.1–2.5) but not for females (1.0, 0.6–1.7) (740).

12.8.3.2 Manufacture of chlorinated compounds

Totally 1 189 male chemical workers in Hamburg, Germany, employed for at least 3 months, produced phenoxy herbicides 1952–1984, when the plant was closed. Concentrations of dioxins and polychlorinated dibenzofurans were measured in blood and the levels at the end of exposure were estimated based on half-times from an elimination study of workers in this cohort. The cohort was followed until 1992. There were significant dose-response relationships regarding both CVD and IHD

and the dose-response patterns were more pronounced for toxic equivalency (TEQ, a sum of individual toxic equivalency factors, TEF) than for TCDD alone (299). The cohort, now comprising 1 191 male workers and 398 female workers, was further followed until 2007. During the follow-up, there were increased mortality risks (SMR, 95% CI) for men regarding circulatory diseases (1.16, 1.02–1.31) and CeVD (1.57, 1.19–2.05) but not for women (0.74, 0.56–0.94 and 0.64, 0.32–1.15, respectively). The median estimated cumulative job exposure to TCDD was 77.4 ppt (ng/kg) for men and 19.5 ppt for women, based on blood fat; no dose-response relationships were observed (602). Increasing time of follow-up since last exposure is likely associated with a decreasing total body burden of TCDD and consequently lower risks for CVD.

A cohort of 562 workers were exposed to phenoxy herbicides or chlorophenols. In 1950, the factory started production of chlorophenoxy herbicides in the Netherlands, the main product being 2,4,5-trichlorophenoxyacetic acid. The production was contaminated with TCDD, other dioxins and polychlorinated dibenzofurans. In 1969, synthesis of phenoxy herbicides was ended and the last TCDD-contaminated process ended in 1976. Based on extrapolated TCDD levels measured in a subset of the cohort, TCDD levels were predicted at the time of maximum exposure. The cohort was followed until 1991 and exposed workers were compared with non-exposed workers. Workers in the highest category of exposure (serum levels > 124 ppt TCDD, lipid adjusted) had increased mortality (RR, 95% CI) from circulatory diseases (2.3, 1.2–4.3) and IHD (3.1, 1.4–6.5) (420).

The cohort was further followed, now comprising 1 020 male workers (both exposed and non-exposed) from the same factory as above and a second group of 1 036 male workers from another factory. This new cohort was followed until 2006. Exposure assessment was based on a predictive model for TCDD plasma levels at the time of assumed last exposure. The estimated highest exposure (≥ 9.9 ppt) was associated with an increased mortality from IHD (HR 2.6, 95% CI 1.6–4.3) (112).

A cohort of 5 132 chemical workers from 12 US plants manufacturing products 1942–1984 that were contaminated with TCDD was followed until 1993. In a restricted subcohort comprising 3 538 workers, there was a clear and positive relationship between cumulative TCDD exposure score and IHD mortality (909).

12.8.3.3 Chlorophenoxy herbicide spraying and application

A cohort of 1 909 male chlorophenoxy herbicide applicators that had worked between 1955 and 1971 was followed until 1989. No increased mortality regarding IHD or CeVD was observed compared to the male Finnish population (50).

Large amounts of herbicides were used in the Vietnam War by US forces for defoliation 1962–1971. An increased mortality from circulatory disease was observed among exposed US veterans compared with non-exposed veterans (RR 1.3, 95% CI 1.0–1.6) (489). In a similar study of Korean Vietnam veterans, an increased risk regarding circulatory mortality was observed when exposure was presented as a continuous variable (HR 1.02, 95% CI 1.00–1.04) (1045).

12.8.4 Pooled analyses

An IARC multicentre cohort comprised 21 863 phenoxyacid herbicide and chlorophenol production workers and sprayers from 36 cohorts in 12 countries. An increased mortality risk (RR, 95% CI) from circulatory disease was observed among exposed workers compared to non-exposed workers (1.51, 1.17–1.96). The risk for IHD was approximately the same (1.67, 1.23–2.26). The risk for CeVD was not increased (1.54, 0.83–2.88). An increased risk (RR, 95% CI) from circulatory disease was also observed when workers exposed for 10–19 years were compared with non-exposed workers (1.28, 1.05–1.55). However, there was no increased mortality among workers exposed for ≥ 20 years (1005).

12.8.5 Reviews

In a systematic review of dioxin exposure, cohorts were excluded that were exposed either primarily to PCBs or in the leather and perfume industries, which include other cardiotoxic co-exposures. Totally 12 cohorts were included of which 10 comprised occupationally exposed workers. The analyses were divided according to two well-recognised criteria of epidemiological study quality: the accuracy of the exposure assessment, and whether the exposed population was compared with an internal or an external reference group. In the highest-quality group, consistent and significant dose-related increases in IHD mortality and more modest associations with CVD mortality were observed. The primary limitation of the studies was a lack of adjustment for potential confounding by the major cardiovascular risk factors (428).

Within the US National Academy of Medicine (NAM), a part of the National Academies of Sciences, Engineering, and Medicine, the Committee to Review the Health Effects in Vietnam Veterans of exposure to herbicides concluded in 2012 that there is sufficient evidence to place hypertension, IHD and stroke in the limited or suggestive category (445).

12.8.6 Dose-response relationships

Three accidents have been reported. The Seveso accident (740) had the shortest mortality follow-up time, less than 20 years, and the other two had follow-up periods of 28 years or longer (420, 729). Only the Seveso study presented a significant effect, a higher mortality from circulatory diseases for males. One aspect of a longer follow-up is a likely lower body burden of TCDD as the half-time of serum levels is 5–7 years.

Dose-response relationships have been observed between exposure among workers manufacturing products contaminated with TCDD in Germany (299), the Netherlands (112) and the US (909), and IHD. Plasma levels ≥ 9.9 ppt (ng/kg) TCDD were associated with an increased risk of IHD (HR 2.60, 95% CI 1.57–4.31) (112).

12.8.7 Conclusion

The epidemiological data on dioxins and dioxin-like compounds originate from accidents, manufacture of chlorinated compounds and spraying and applying

chlorophenoxy herbicides. A pooled IARC multicentre study comprising 36 occupational cohorts showed increased mortality for circulatory disease and IHD, but not for CeVD (1005). Three studies demonstrated positive dose-response relationships between TCDD exposure and IHD (112, 299, 909). In two of these, plasma levels of TCDD were used as dose estimates (112, 299). Plasma levels ≥ 9.9 ppt (ng/kg) TCDD were associated with an increased risk of IHD (112).

There is *strong evidence* for an association between exposure to dioxins and dioxin-like compounds and IHD.

12.9 Polychlorinated biphenyls

12.9.1 General

Polychlorinated biphenyls (PCBs) are a class of 209 congeners in which 1–10 chlorine atoms are attached to biphenyl in different combinations. The PCBs have been commercially produced as complex mixtures since 1929. Because of the chemical and physical stability and electrical insulating properties, PCBs have had a variety of uses in industry. However, due to their harmful effect on the environment, the production and use of PCBs is banned or restricted worldwide. Nowadays, PCBs are mainly regarded as ubiquitous environmental pollutants, but they can still occur in work environments, especially when renovating and demolishing buildings and in recycling and waste management (567). PCBs may be divided in dioxin-like PCBs (e.g. PCBs 74, 118, 126, 156, 169) and non-dioxin-like PCBs (e.g. PCBs 99, 138, 153, 170, 180 and 187) (366).

PCBs, like many chlorinated compounds, are poorly metabolised and thus persistent (half-times in humans approximately 4–40 years) (567). The half-time generally increases with number of chlorine atoms, but other factors like the chlorine positions on the biphenyl also influence the half-time (145).

12.9.2 Mechanistic evidence

Co-planar or dioxin-like PCBs are AHR agonists and may compromise the normal functions of vascular endothelial cells by activating oxidative stress-sensitive signalling pathways and subsequent proinflammatory events critical in the pathology of atherosclerosis and CVD (400).

12.9.3 Animal studies

Female Harlan Sprague Dawley rats were exposed to the dioxin-like PCB 126 (3,3',4,4',5-pentachlorobiphenyl) in an NTP study. The animals were gavaged 5 days/week with up to 1 000 ng/kg bw/day of PCB 126 for up to 2 years. The control animals received a corn oil/acetone vehicle. After a full necropsy of all animals, a complete set of tissues was examined microscopically. PCB 126 was associated with exposure-related increases in the incidences of degenerative cardiovascular lesions. Cardiomyopathy and chronic active arteritis increased in an

exposure-related manner in all exposed groups (460). PCB 126 also increased heart weight, serum cholesterol levels and blood pressure in rats (565).

Mice (LDLR-/-) fed a low-fat atherogenic diet were given 0 or 1 μmol/kg PCB 126 twice (at week 2 and week 4) by gavage, and were sacrificed 8, 10 or 12 weeks post-exposure. Mice exposed to PCB 126 exhibited significantly increased plasma levels of inflammatory cytokines, increased circulating biomarkers of CVD, altered platelet and red blood cell counts, increased accumulation of hepatic fatty acids and accelerated atherosclerotic lesion formation in the aortic root. PCB 126 also increased circulating neutrophils, monocytes and macrophages as determined by flow cytometry analysis. Thus, exposure to the dioxin-like PCB 126 increased inflammation and accelerated atherosclerosis in mice (745).

12.9.4 Occupational epidemiological studies

A Swedish cohort of 242 male capacitor manufacturing workers exposed to PCBs for at least 6 months 1965–1978 was followed 1965–1991 and compared with national death rates. High-exposed workers had a higher risk for circulatory diseases (SMR 3.28, 95% CI 1.07–7.66, based on 5 cases) after at least 5 years of work and at least 20 years since first exposure, but this was not observed for IHD (361).

In a study by Broding *et al*., 562 subjects who had worked for an average of 14.7 years in a PCB-contaminated building in Germany scored significantly higher than the control group in subscale "cardiac complaints" on the 24-item Giessen Subjective Complaints List (GSCL-24). The subscale scores were, however, low in both groups. Multivariate analysis confirmed that work in the contaminated building influenced the intensity of complaints, although overall, thorough statistical analysis revealed no correlation between symptoms on the GSCL-24 scale and current PCB congener plasma concentrations. The median sum of PCBs in air was 1.8 μg/m^3. The median sum of PCBs in plasma (PCBs 28, 52, 101, 138, 153, 180) in the exposed group was 2.3 μg/l (mean 2.6; 10th and 90th percentiles: 1 and 4.6 μg/l). For PCBs 28 and 52, the mean plasma concentrations in the control group were about 20% of those in the exposed group (0.023 vs 0.117 μg/l and 0.004 vs 0.019 μg/l). Several confounding variables (e.g. socioeconomic status, medication) were not controlled for (125).

Between 1946 and 1977, the General Electric Company manufactured small and large capacitors using PCBs as dielectric fluid in two production plants located one mile apart in upstate New York. Large capacitors were filled manually with PCBs 1946–1960 resulting in excessive spillage. In the mid-1960s, the filling process was automated. Small capacitors were impregnated by flooding racks of capacitors with heated PCBs under vacuum in large ovens. Upon removal of the capacitors from the ovens, a fog of condensed PCBs dispersed throughout the plant. Following impregnation, the capacitors dripping with PCBs were moved to the sealing station where the filling ports were soldered shut. Salvage and repair of large capacitors were also performed. It involved draining the PCBs, milling off the seal cover and manually removing and repairing the wet components. All of these activities

including cleaning the outside of the capacitors entailed significant direct dermal and inhalation exposure. Exposed surfaces in the plants were coated with PCBs. Totally 7 061 (4 056 male and 3 005 female) PCB capacitor workers were followed through 2008 (mean follow-up 41 years). National US and New York State rates were used for comparison. There was a decreased mortality (SMR, 95% CI) from heart disease (0.88, 0.82–0.94) and CeVD (0.81, 0.68–0.95) compared to the US population. However, there was an increased risk of cardiomyopathy among females based on 12 cases (1.95, 1.01–3.40) in the comparison with the New York State population (494).

A cohort was formed of workers manufacturing electric capacitors employed for at least 90 days at a New York plant 1946–1977 (plant 1) or at a Massachusetts plant 1939–1976 (plant 2). The cohort comprised 2 572 workers who held jobs identified as having the highest exposure to PCBs (e.g. impregnation, sealing and testing capacitors). The death rates were compared with death rates from the state of New York (excluding New York City) and Massachusetts. The SMR (95% CI) regarding IHD was 1.12 (0.98–1.28) for the total cohort and 1.44 (1.06–1.91) for those with 5–9 years of employment, but lower for those with longer employment (0.97, 0.80–1.18) (758). The cohort was enlarged to comprise 14 458 PCB-exposed workers employed ≥90 days 1939–1977 and followed 1940–1998. Commercial PCB mixes, 41–54% chlorine, were used at both plants, with less chlorinated varieties used at a later period. At any given time, more than one mix was likely in use. NIOSH conducted exposure surveys in the spring 1977. TWAs for air samples were 24–476 μg/m^3 at plant 1 and 50–1 260 μg/m^3 at plant 2. The IHD mortality (SMR, 95% CI) was 0.97 (0.90–1.03) for the total cohort, and 0.87 (0.79–0.96) and 1.07 (0.97–1.17) in plant 1 and 2, respectively (759).

Totally 2 885 white electrical capacitor workers were exposed to PCBs and other chemicals 1944–1977 in a US plant in La Salle, Illinois. Before 1952, chlorinated naphthalenes were used as a dielectric and, in 1952, PCBs were introduced and were used in large capacitors until 1979. The main exposure to PCBs was through skin contact but airborne exposure occurred in one special department where heat volatilised the oil. The cohort was followed through 2000. When the IHD death rate of the cohort was compared with US standard rates, the SMR (95% CI) was 1.14 (0.96–1.34) for white males and 0.96 (0.83–1.12) for white females (598).

Totally 3 588 electrical capacitor workers exposed to PCBs 1957–1977 at an Indiana facility were followed until 1986. Mean levels of PCBs (with ≤ 4 chlorine atoms per molecule) varied between 100 and 760 μg/l serum. The comparison group was the US population and the SMR (95% CI) for diseases of the heart was 0.7 (0.5–0.9) (873). The cohort comprising 3 569 workers was further followed through 1998. Cumulative PCB exposure was calculated for each worker based on job titles, job codes and era of employment. The cumulative PCB exposure was 10–1 218 590 unit-days (median 16 860 unit-days; 11 000 and 90 000 unit-days defined cut-points of tertiles). The overall mortality from IHD (SMR, 95% CI) was 0.84 (0.7–1.0). The IHD mortality in the highest tertile of exposure (0.88, 0.7–1.1) was similar to

that of the middle tertile of exposure (0.94, 0.7–1.2) but was slightly higher than that of the lowest tertile of exposure (0.72, 0.5–1.0) (808).

A cohort was formed of 138 905 PCB-exposed men who had been employed full time (continuously for ≥ 6 months) at any of five US electric utility companies at any time in the period 1950–1986. Women were excluded because they rarely worked in jobs with exposures of interest. The mortality of the cohort was compared with that of the US population. The SMR (95% CI) for diseases of the heart was 0.76 (0.74–0.78) (575).

12.9.5 Epidemiological studies of the general population

Fish consumption may promote cardiovascular health. The role of major food contaminants, such as PCBs common in fatty fish, was studied in the population-based Swedish Mammography Cohort comprising 33 446 middle-aged and elderly women, free from CVD at baseline 1997. Validated estimates of dietary PCB exposure and intake of fish fatty acids (eicosapentaenoic acid and docosahexaenoic acid; EPA-DHA) were obtained via a food frequency questionnaire at baseline. The cohort was followed for 12 years. Women in the highest quartile of dietary PCB exposure (median 286 ng/day) had multivariable-adjusted RRs (95% CIs) of MI before and after adjusting for EPA-DHA intake of 1.21 (1.01–1.45) and 1.58 (1.10–2.25), respectively, compared to women in the lowest quartile (median 101 ng/day). Stratification by low and high EPA-DHA intake resulted in RRs (95% CIs) of 2.20 (1.18–4.12) and 1.73 (0.81–3.69), respectively, comparing the highest PCB tertile with the lowest. The intake of dietary EPA-DHA was inversely associated with risk of MI after but not before adjusting for dietary PCB (85). The same cohort of 34 591 women was followed for 12 years. There were 2 015 incident cases of total stroke (1 532 ischaemic strokes, 216 intracerebral haemorrhages, 94 sub-arachnoid haemorrhages and 173 unspecified strokes). Multivariable-adjusted risk estimates (RR, 95% CI), controlled for known stroke risk factors and fish consumption, were 1.67 (1.29–2.17) for total stroke, 1.61 (1.19–2.17) for ischaemic stroke and 2.80 (1.42–5.55) for haemorrhagic stroke for women in the highest quartile of dietary PCB exposure (median 288 ng/day) compared to women in the lowest quartile (median 101 ng/day) (86).

A Swedish population-based cohort comprised 36 759 men free from CVD at baseline 1997. Validated estimates of dietary PCB exposure and intake of fish fatty acids were obtained via a food frequency questionnaire at baseline. During 12 years of follow-up, 3 005 incident cases of MI and 654 fatal cases of MI were observed. RRs were adjusted for known cardiovascular risk factors, long-chain omega-fatty acids and methylmercury exposure. Compared to men in the lowest quintile of dietary PCB exposure (median 113 ng/day), men in the highest quintile (median 436 ng/day) had multivariable-adjusted RRs (95% CIs) of 1.74 (1.30–2.33; P trend < 0.001) and 1.97 (1.42–2.75; P trend < 0.001) for total, and non-fatal MI, respectively (84).

Blood pressure was measured in 758 residents in Anniston, Alabama. Rates of hypertension increased significantly with age and concentration of serum PCBs.

Among 394 persons not on antihypertensive medication, linear regression analysis demonstrated a significant positive relation between serum PCB levels and both systolic and diastolic blood pressure. After adjustment for potentially confounding variables, logistic regression gave increased ORs (95% CIs) for both systolic (3.82, 1.1–12.8) and diastolic hypertension (4.15, 1.4–11.6) when comparing those in the highest and the lowest tertiles of total serum PCBs (348). Fasting serum samples were obtained from 575 Anniston residents who were not on any lipid-lowering medication. Serum concentrations of total PCBs were significantly associated with elevated serum levels of total lipids, total cholesterol and triglycerides but not with levels of LDL and HDL after adjustment for age, gender, race, BMI, smoking and exercise. The PCBs with the strongest associations were those with 3, 4 or ≥ 8 total chlorine atoms (27).

Results from NHANES 1999–2002 (final sample size 889 persons) indicated an association between serum concentrations of five dioxin-like PCBs (PCBs 74, 118, 126, 156, 169) and six non-dioxin-like PCBs (PCBs 99, 138, 153, 170, 180, 187) and the prevalence of self-reported diagnosis of CVD, but only among females. Adjustment was made e.g. for age, BMI, total cholesterol, HDL cholesterol, triglycerides, CRP, hypertension, smoking and exercise. Adjusted ORs (95% CIs) for quartiles compared to a reference category (lowest quartile) were 0.9 (0.2–3.5), 2.0 (0.5–7.6) and 5.0 (1.2–20) for the sum of the dioxin-like PCBs (significant concentration-response relationship among the four quartiles, P for trend < 0.01). The highest ORs (95% CIs) were seen for PCB 156, i.e. 9.2 (2.1–39) and 10.4 (2.3–47) in the two highest quartiles (P for trend < 0.01). For the sum of non-dioxin-like PCBs, the adjusted ORs (95% CIs) were 1.2 (0.4–4.0), 1.2 (0.4–4.2) and 3.8 (1.1–13) with P for trend of 0.02. ORs (95% CIs) in the highest quartile for PCBs 138, 153 and 170 were 13.4 (1.6–115; P for trend < 0.01), 10.4 (1.1–94; P for trend < 0.01) and 9.2 (1.0–84; P for trend 0.01), respectively. The median concentrations in serum in the highest quartiles were 21, 91, 127 and 36 ng/g lipid, respectively, for PCBs 156, 138, 153 and 170. The authors emphasised that their results must be interpreted with caution, because of the cross-sectional design and use of self-reported CVD (366).

The same team reported suggestive associations between hypertension in men (but not in women) and both dioxin-like and non-dioxin-like PCBs when NHANES 1999–2002 data were used (524 participants). Risks (OR, 95% CI) in the highest tertiles were 2.3 (0.8–6.6) and 2.8 (0.9–8.5), respectively. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Treated hypertensives were excluded (367).

Another cross-sectional study using NHANES 1999–2002 investigated the association between 11 PCBs in serum and hypertension. Persons were assigned to the hypertensive category if a doctor had told them that they were hypertensive, if they were on antihypertensive drugs or had a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. After adjustment (e.g. for age, gender, BMI, smoking, total cholesterol), several PCBs (PCBs 74, 99, 118, 126, 138/158, 170, 187) remained significantly associated with hypertension (gender data were not

reported). The strongest adjusted associations were found for the dioxin-like PCBs 118 and 126. The group with serum levels of PCB 118 > 27.5 ng/g lipid had an OR of 2.30 when compared with the group with levels < 12.5 ng/g lipid. In the group with concentrations of PCB 126 > 59.1 pg/g lipid, the OR was 2.45 (comparison group ≤ 26.1 pg/g lipid) (273).

12.9.6 Conclusion

Some studies of the general population suggest a relationship between PCB exposure and hypertension (273, 348, 367). These studies must be interpreted with caution because of their cross-sectional design. The possible relationship between PCB exposure and IHD has been investigated in a number of occupational cohort studies, but the results are inconsistent and dose-estimates are crude. Animal data support a relationship between exposure to the dioxin-like PCB 126 and CVD (460, 565, 745).

There is *limited evidence* for an association between exposure to PCBs and CVD.

12.10 Per- and polyfluoroalkyl substances

12.10.1 General

Per- and polyfluoroalkyl substances (PFAS) are a group of man-made chemicals with extreme persistence in the environment, and potential risk to human health and ecosystems. PFAS have been produced since the 1950s and are used in multiple products and for industrial purposes due to their favourable properties such as repellence towards fat, dirt and water, temperature resistance and film-forming capacity (929). Application areas for PFAS are e.g. as ingredients in firefighting foams, impregnation of clothing and textiles, paint, wax, insecticides, detergents and food packaging. Occupational exposure is likely in relation to production and use of a multitude of PFAS-containing products.

The most well-known PFAS (out of 4 700 identified varieties) are perfluoro-octanesulphonic acid (PFOS) and perfluorooctanoic acid (PFOA), both also called C8. Due to the increased concern of environmental and human adverse effects, they are gradually substituted to shorter chain alternatives (722). The European Food Safety Authority (EFSA) recently performed an updated risk assessment opinion for PFOS and PFOA in food (247). This section is mainly based on the EFSA report.

Mean estimated half-times (95% CIs) for PFOS and PFOA were 3.4 (3.1–3.7) and 2.7 years (2.5–2.9), respectively. There was a marked sex difference with more rapid elimination in women for PFOS, but only marginally for PFOA (561).

In animal studies, the liver, one of the major sites of cholesterol synthesis, is the target organ. Human studies provide strong support for causal associations between exposure to PFOS and PFOA and increased serum concentrations of cholesterol (247, 263, 328, 700). The traditional view of a causal link between high cholesterol serum levels and CVD is under debate (775).

12.10.2 Occupational epidemiological studies

Ammonium perfluorooctanoate (APFO) has been used in industry mainly as a polymerisation aid in the production of fluoropolymer high-performance materials. In the presence of water, APFO dissociates readily to PFOA. The latter compound has been found in serum of exposed production workers at concentrations of 0–100 ppm (0–100 μg/ml), with the majority residing under 20 ppm. In 1948, the Washington Works (DuPont) started production of polymers in West Virginia. In a longitudinal study of 454 PFOA-exposed workers in this plant, blood was sampled at least twice 1979–2004. The mean serum PFOA level over the study period was 1.13 (0–22.7) ppm. Serum PFOA levels were positively associated with total cholesterol levels, with an increase of 1.06 mg/dl of cholesterol for each 1 ppm increase of PFOA (P = 0.011). Serum PFOA concentrations were not significantly associated with triglycerides, LDL or HDL (819).

A cross-sectional study in the same industry comprised 1 025 active workers with potential exposure to APFO. The serum PFOA concentrations were 0.005–9.55 ppm, with the highest levels found in those currently working in APFO areas (median serum PFOA 0.49 ppm) and the lowest in the non-exposed areas (median serum PFOA 0.11 ppm). Serum PFOA levels were significantly associated with three of five lipid outcomes (cholesterol and two fractions of LDL, but not with HDL or triglycerides). An increase of 1 ppm PFOA in serum was associated with a total cholesterol increase of 4.04 mg/dl (818).

Totally 6 027 men (81%) and women who had ever worked at the Washington Works plant facility in Parkersburg, West Virginia 1948–2002 (see above), were included in a cohort and these years delimit the mortality follow-up period. SMRs were estimated by comparing observed numbers of deaths with expected numbers derived from mortality rates from the US population, the West Virginia state population and a regional DuPont reference worker population. Most SMR estimates based on US and state populations were below 1. Comparison with the employee population also resulted in many SMR estimates at or near a no-effect level. Relative to the regional worker population, the SMR for CVD among men was 1.10 (95% CI 0.98–1.23). Mortality from diabetes was significantly increased among male workers compared to the regional worker population (SMR 1.83, 95% CI 1.12–2.83) (553).

A cohort of 4 747 employees who had ever worked in the Washington Works plant 1948–2002 was followed until 2002. Time-dependent APFO-exposures were estimated from detailed work histories for all employees using an exposure reconstruction model based on occupational information and PFOA serum data. RR estimates, based on Cox proportional hazards regression models, indicated no statistically significant increased mortality risk for IHD associated with estimated cumulative exposure. A positive trend was observed at an exposure lag of 10 years, but not at no lag or other lag calculations. The authors concluded that there was no convincing evidence of increased IHD mortality for APFO-exposed workers (820).

The same cohort was enlarged and further followed. It included all workers with at least one day of work 1948–2002. Overall, 5 791 workers had work histories

with sufficient detail to allow estimation of PFOA serum levels over time. PFOA was used in the plant from 1950 onwards, with a peak in the 1990s and a sharp decline of usage and emissions after 2001. Referents were obtained from DuPont plants in the Appalachian region. The follow-up period was 1952–2008. The median serum PFOA concentration of the exposed workers was much higher than that of the general US population (400 vs 4 µg/l). Cumulative doses were categorised in quartiles: 0 – < 904, 904 – < 1 520, 1 520 – < 2 700 and ≥ 2 700 ppm-years; the SMRs (95% CIs) for IHD were 1.07 (0.85–1.32), 1.02 (0.80–1.28), 0.87 (0.67–1.11) and 0.93 (0.72–1.19), respectively. The corresponding SMRs (95% CIs) for stroke were 0.63 (0.85–1.32; mismatch between SMR and CI), 0.78 (0.39–1.39), 1.34 (0.82–2.07) and 0.69 (0.32–1.31), respectively. No cumulative dose-response trend was seen for CVD mortality (912).

In 1947, production of APFO started at the 3M Company manufacturing facility in Cottage Grove, Minnesota. A cohort of 3 993 employees was followed until 2002. The eligibility criterion was a minimum of 365 days employment prior to 1997. Cox regression models were used to estimate the risks, using an internal-cohort of non-exposed workers as referents. Moderate and high APFO-exposures were positively associated with CeVD (HR, 95% CI: 1.8, 0.9–3.7, 19 cases and 4.6, 1.3–17.0, 3 cases, respectively). There was no relationship regarding moderate or high exposures and IHD (HR, 95% CI: 1.2, 0.9–1.7 and 0.9, 0.4–2.1, respectively). Risk estimates were adjusted for sex and birth year. Including wage type and smoking habits in the model did not alter the results. High exposure was characterised as definite exposure ≥ 6 months and moderate exposure included definite exposure < 6 months or ever working in areas with probable occupational exposure. Comprehensive biological monitoring data were not available, but serum PFOA concentrations were collected from 131 employees. Subjects working in areas where jobs were classified as having definite or probable exposure had median serum concentrations in the range 2.6–5.2 ppm and 0.3–1.5 ppm, respectively (586).

Perfluorooctanesulphonyl fluoride (POSF) has been produced almost exclusively at one facility in the US and one in Belgium. In the US, the manufacturing started in 1961 in Decatur, Alabama, and consisted of a film plant and a chemical plant. The 2 083 participants of the cohort had worked at least 1 year by the end of 1997 and were followed until 1998. The mortality of the cohort was compared with the rates in Alabama. POSF can be degraded or metabolised to PFOS. Biological monitoring of serum PFOS levels was performed among 232 randomly selected employees to estimate occupational exposure to POSF. The geometric mean serum PFOS concentrations at the film and chemical plant were 0.1 and 0.9 ppm, respectively. Because production processes remained constant over time, a simple JEM was developed based on work histories and job specific serum PFOS levels. Workplace exposure was characterised as no, or potentially low or high. The mortality (SMR, 95% CI) for all heart disease and CeVD among workers employed for at least 1 year in a high-exposed job were 0.61 (0.32–1.07) and 0.93 (0.11–3.37), respectively. There was no indication of dose-response relationships (15).

12.10.3 Epidemiological studies of the general population

A subgroup of 560 US adults from The C8 Short-Term Follow-up Study, exposed from public drinking water contaminated with PFOA, was studied in 2005–2006 and followed until 2010. The serum concentrations of PFOA and PFOS fell by half from initial geometric means of 74.8 and 18.5 ng/ml, respectively, with little corresponding change in LDL cholesterol levels. However, participants with greater declines in serum PFOA or PFOS had greater decreases in LDL cholesterol. For a person whose serum PFOA fell by half, the predicted fall in LDL cholesterol was 3.6% (95% CI 1.5–5.7%). For PFOS, the decrease in LDL cholesterol was even stronger, 5% (95% CI 2.5–7.4%). The corresponding decreases of total cholesterol were smaller for both PFOA and PFOS, 1.7 and 3.2%, respectively (296).

Totally 32 254 participants from two US sources, the community-based C8 Health Project 2005–2006 and the cohort of 3 713 workers from Leonard *et al*. (553), completed surveys in 2008–2011 regarding medical histories of stroke. In a cross-sectional retrospective study, year-by-year serum PFOA concentration estimates were based on information on residential history, drinking water habits and sources, and public water supply maps. Cumulative PFOA serum levels for each year were calculated as the sum of the serum concentration estimate that year and all previous years. Compared to the lowest quintile of cumulative dose, subsequent quintiles in the retrospective analysis had risk estimates (HR, 95% CI) of 1.39 (1.11–1.76), 1.36 (1.08–1.71), 1.45 (1.15–1.82) and 1.13 (0.90–1.44). The cumulative doses in these categories (quintiles 2–5) were > 178–319, > 319–912, > 912–4 490 and > 4 490 µg/l, respectively. Tests for trend with linear or log-transformed cumulative dose were not significant (P = 0.52 and 0.59, respectively). The failure to incorporate those who died from stroke before 2005–2006 could bias the result of the retrospective analysis. A restriction of the analysis to earlier calendar time provided some suggestion that this could be the case, since dose-response trends were consistently more pronounced and significant in earlier calendar periods than in later ones. A second prospective study included only participants from the C8 Health Project 2005–2006 followed until 2008–2011. The result of this follow-up did not indicate a positive trend. The authors concluded that the data provided modest evidence of an association between PFOA exposure and stroke incidence (871).

A US NHANES cross-sectional study comprised 1 216 participants from the 1999–2000 and 2003–2004 surveys. Serum PFOA levels were presented in quartiles and the outcomes were self-reported CVD including physician-diagnosed CHD, heart attack and stroke, and objectively measured peripheral arterial disease, defined as an ankle-brachial blood pressure index < 0.9. Increasing serum PFOA levels were positively associated with CVD and peripheral arterial disease, independent of confounders such as age, sex, race/ethnicity, smoking status, BMI, diabetes mellitus, hypertension, and serum cholesterol level. Compared to subjects among quartile 1 (reference) of PFOA level, the OR (95% CI) among subjects in quartile 4 was 2.01 (1.12–3.60; P for trend 0.01) for CVD and 1.78 (1.03–3.08; P for trend 0.04) for peripheral arterial disease (856).

A Swedish population-based cohort included farmers and rural residents. Totally 1 782 males participated in the base-line examination (1990–1991) and 1 587 took part in the second examination 2002–2003. The examinations included questionnaires, physical measurements and blood sampling. The total cohort was followed 1992–2009 and CHD diagnoses were retrieved from the National Cause of Death Register and Patient Register. Conditional logistic analyses were used to investigate the relationship between levels of PFAS and CHD. Eight different PFAS were analysed, e.g. PFOA, PFOS and perfluoroheptanoic acid (PFHpA). All PFAS were significantly correlated with each other. Most PFAS increased between base-line and the second examination but PFOA and PFOS decreased. There was a significant association between PFHpA and CHD (OR, 95% CI) for the 3rd and 4th quartile (2.72, 1.52–4.84 and 2.45, 1.40–4.29) compared to the lowest quartile. After adjustment for BMI, systolic blood pressure, total cholesterol, HDL and tobacco use, the risk estimates were slightly attenuated. There were no statistically significant associations between the concentrations of the other seven PFAS at baseline and CHD. The authors suggested that the association observed was probably a chance finding (611).

In the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study, 1 016 individuals were investigated at age 70 years of which 826 were reinvestigated at age 75 and 602 at age 80 years. The carotid artery intima-media thickness increased 0.058 mm during the 10-year period ($P < 0.0001$). Following adjustment for baseline values of PFAS and sex, the changes in plasma levels of six of the eight measured PFAS (including PFOS) were significantly positively related to the change in intima-media thickness over the 10-year follow-up period. Further adjustment for traditional cardiovascular risk factors (HDL and LDL cholesterol, smoking, systolic blood pressure, statin use, fasting glucose and serum triglycerides) affected these relationships only marginally (566). Furthermore, 801 subjects was also studied with a cross-sectional design. Left ventricular geometry was determined with echocardiography. Increased levels of several PFAS were associated with increased left ventricular end-diastolic diameter and decreased relative wall thickness, which was calculated from interventricular septum and posterior wall thickness. These associations were mainly found for the longer-chained PFAS (654).

12.10.4 Reviews

In 2018, the EFSA Panel on Contaminants in the Food Chain evaluated the risks to human health related to the presence of PFOS and PFOA in food. The derivation of a health-based guidance value was based on human epidemiological studies. For PFOS, the increase in serum total cholesterol in adults, and the decrease in antibody response at vaccination in children were identified as the critical effects. For PFOA, the increase in serum total cholesterol was the critical effect (247).

12.10.5 Dose-response relationships

Serum concentrations of PFOS (247) or PFOA (818, 819) were positively related to concentrations of cholesterol. In a prospective study of seniors (PIVUS) there was a positive relationship between the changes in plasma levels of several PFAS (including PFOS) and the change in intima-media thickness over the 10-year follow-up period (566). In an NHANES cross-sectional study, serum PFOA levels were positively associated with peripheral arterial disease, defined as an ankle-brachial blood pressure index, and with self-reported CVD (856).

Workers exposed to APFO ≥ 6 months had an increased CeVD mortality (586). In a cross-sectional study on stroke, dose-response trends among PFOA-exposed subjects were more pronounced in earlier calendar periods than during later calendar periods. A prospective design, did not reveal any dose-response relationship (871). There were significantly increased CHD risks at the two highest quartiles of PFHpA serum levels, but the increase was not continuous (611).

12.10.6 Conclusion

Human studies provide strong support for associations between exposure to PFOS or PFOA and increased serum concentrations of cholesterol (247).

Some studies of occupationally exposed workers and non-occupationally exposed subjects have demonstrated relationships between PFAS exposure and CVD (586, 611, 856, 871). However, two of the studies had a cross-sectional design (856, 871), one study did not demonstrate clear dose-response relationships (611) and the remaining study had a low number of participants in the high-exposed group (586).

There is *insufficient evidence* for an association between exposure to per- and polyfluoroalkyl substances (PFAS) and CVD.

13. Nitrated explosives

13.1 General

Nitroglycerine (glyceryl trinitrate), a highly explosive substance, was synthesised by the Italian chemist Ascanio Sobrero in 1847. Alfred Nobel added silica guhr to nitroglycerine to make it a stable explosive. In 1879, nitroglycerine was introduced as treatment for angina pectoris (416). It has also been used in rocket propellants. Nitroglycerine is often mixed with ethylene glycol dinitrate (nitroglycol) to make dynamite. Propylene glycol dinitrate is the principal constituent in Otto fuel II, a torpedo propellant. The vapour pressures of ethylene and propylene glycol dinitrates are more than 100 times higher than the corresponding vapour pressure for nitroglycerine (2-4). Dinitrotoluene has principally been used as intermediate in the production of toluene diisocyanate. It has also been a component in the production of dyes, explosives and propellants (556).

Nitroglycerine (341), ethylene glycol dinitrate (417, 458) and propylene glycol dinitrate (458) are easily absorbed through the skin. The skin permeability of both 2,4-dinitrotoluene and 2,6-dinitrotoluene was categorised as moderate (458).

Symptoms among workers exposed to nitroglycerine and other organic nitrates are often developing in three stages. The first stage is characterised by vasodilation and workers experience headaches, flushes and palpitations. After days, weeks or months, a second stage comes into play comprising compensatory responses of vasoconstriction. This phase is manifested by an increase in diastolic blood pressure, a decrease in pulse pressure, and the relief of headaches or other first stage symptoms. A third stage relates to the withdrawal of nitroglycerine exposure. Withdrawal from the sustained vasodilatory effects over a 48–72 hour period leaves the more persistent vasoconstrictor response unopposed. This response results in general arteriolar constriction clinically manifest in cutaneous and coronary arteries. Intermittent chest pain can be relieved by nitroglycerine. Coronary insufficiency or acute MI may develop. This period of vasoconstriction subsides after 96–120 hours (534). This third stage has been called *Monday morning angina* or *Monday morning death* (518).

13.2 Nitroglycerine and ethylene glycol dinitrate

Cases of angina pectoris and sudden death following withdrawal from occupational exposure to nitroglycerine and ethylene glycol dinitrate have been reported from Norway (93), Sweden (582), Germany (932), France (532), Italy (66), Israel (82), the US (144) and South Africa (760).

The most obvious symptom is a pain resembling that of angina pectoris which starts as a rule 1–3 days after interruption of exposure to nitroglycerine or ethylene glycol dinitrate (582).

The relationship between occupational exposure to nitroglycerine and ethylene glycol dinitrate and cardiovascular disturbances has been reviewed and established by many authors (518, 522) and committees (2-4, 584).

13.3 Propylene glycol dinitrate

In a chamber experiment, volunteers were exposed to propylene glycol dinitrate. Exposure to 0.2 ppm for 2–8 hours caused headache in 7 out of 9 volunteers. Both frequency and intensity of headaches decreased dramatically after repeated daily exposures to 0.2 ppm (915).

Propylene glycol dinitrate has been used as a torpedo propellant in the US Navy. Forman *et al*. studied 1 352 torpedomen exposed to propylene glycol dinitrate from 1970 through 1979. The average yearly strength was 822 persons. The control group comprised 14 336 torpedomen unexposed to propylene glycol dinitrate, with an average yearly strength of 4 906. A second control group comprised 29 129 fire control technicians with an average yearly strength of 11 198. The peak airborne exposures were 0.00–0.22 ppm, with 88% of grab samples (short duration) $\leq$ 0.1 ppm and 50% of grab samples $\leq$ 0.05 ppm. Measured 8-hour TWAs were

< 0.05 ppm. Incident cases of MI and angina pectoris were recorded during the 10-year period. After age-adjustment, the RRs (95% CIs) for MI were 2.22 (0.74–6.72) and 2.61 (1.33–5.14), compared to unexposed torpedomen and fire control technicians, respectively. The corresponding risks (RR, 95% CI) regarding angina pectoris were 3.77 (0.43–32.11) and 3.77 (1.01–14.10). When MI and angina pectoris were added together, the risks (RR, 95% CI) were 2.60 (1.11–6.12) and 2.93 (1.71–5.03) (302).

13.4 Dinitrotoluene

Headache and weakness was common (50%) among workers exposed to dinitrotoluene during the first year of production during World War II in the US. After 1942, the prevalence of symptoms was reduced to around 10% after improved ventilation, training, protective equipment, job rotation and medical surveillance (621).

Workers at two US ammunition plants (Joliet, Illinois and Radford, Virginia) were exposed to dinitrotoluene. Cohorts of 156 and 301 men who had worked at least 1 month during the 1940s and 1950s at jobs with opportunity for substantial dinitrotoluene exposure were followed through the end of 1980. Numbers of expected deaths were calculated using rates of US white males as the standard. When combining the two cohorts, there was an increased SMR of circulatory diseases (1.40, $P < 0.01$) and IHD (1.41, $P < 0.01$) but not of CeVD (1.00). Deaths from IHD remained high (1.37, $P = 0.05$) even when the combined cohort was compared with expected numbers derived from rates of the counties in which the plants were located. Additional analyses revealed evidence of a 15-year latency period and suggested a relationship with duration of exposure. More than 5 months of exposure was associated with an SMR for IHD of 1.68 ($P < 0.001$), whereas the SMR for < 5 months of exposure was 1.03. Mortality from lung cancer, a marker of smoking habits, was less than expected (556).

A later US study comprised 4 989 white male munitions workers from Radford, Virginia, with probable exposure to dinitrotoluene (903). This cohort included workers from a later time-period (1949–1980) than the previous study (556). All workers had been employed for at least 5 months. A non-exposed comparison group comprised 5 136 white male workers. The cohorts were followed until December 1982. There were no increased risks regarding mortality due to IHD and CeVD when dinitrotoluene-exposed workers were compared with US national rates (SMR 0.98 and 0.95, respectively) and with unexposed workers (SRR 0.99 and 0.89, respectively). An excess in mortality from CeVD was observed in the 55–59-year age group when dinitrotoluene-exposed workers were compared with unexposed workers (SRR 4.46, 95% CI 1.11–17.84). There was an inverse trend between duration of dinitrotoluene exposure and IHD mortality ($P = 0.003$) (903).

13.5 Conclusion

Nitroglycerine and *ethylene glycol dinitrate* both have established acute and chronic effects on the cardiovascular system. The acute symptoms result from blood vessel dilation and consist primarily of headache, heart palpitations, dizziness and nausea (2-4, 518, 522, 584).

The two studies located for *propylene glycol dinitrate* showed an increased risk of CVD among torpedomen (302) and headache in volunteers chamber exposed to 0.2 ppm (915).

Three occupational cohorts exposed to *dinitrotoluene* were found. One of these showed an increased risk of CVD (556), and headache was observed in a cross-sectional study (621).

The data on propylene glycol dinitrate and dinitrotoluene are meagre, but the association with CVD is strengthened by similarities with the other nitrated explosives regarding chemical structure and properties, and in reported health effects.

There is *strong evidence* for an association between exposure to nitroglycerine and ethylene glycol dinitrate and CVD. There is *limited evidence* for an association between exposure to propylene glycol dinitrate and dinitrotoluene and CVD.

14. Irritant gases

14.1 Formaldehyde

14.1.1 General

Formaldehyde is a colourless gas with a pungent odour. The substance is extremely reactive and is easily polymerised. It is also flammable, and can form explosive mixtures with air. Formaldehyde is a component of normal human metabolism and occurs naturally in fruits and other foods. The substance is also formed e.g. in decomposition or incineration of organic materials. The primary industrial use of formaldehyde is for production of resins; phenol, urea and melamine are used as adhesives and binders in paper and wood products, in production of plastics and in surface treatments of textiles. Polyacetal resins are used mostly in production of plastics. Formaldehyde occurs in manufacture of various types of plywood, particle board, medium-density fibreboard, etc. It is formed by acid-cured varnishes during the curing process, although the varnishes themselves contain very little formaldehyde. Formaldehyde or formaldehyde-releasing substances are often used as preservatives in products such as cutting fluids and water-based paints, and are also widely used as preservatives in cosmetics, hygiene products and foodstuffs. In addition, formaldehyde is used in pathology and cytology laboratories and for embalming. According to the Scientific Committee on Occupational Exposure Limits (SCOEL), formaldehyde is a genotoxic carcinogen, with a mode of action

including inflammation and cellular proliferation, for which a practical threshold is supported (849).

14.1.2 Occupational epidemiological studies

The mortality of a cohort of 4 512 British pathologists who were members of the Royal College of Pathologists 1974–1987 was compared with the general mortality in England and Wales. There were totally 91 deaths from diseases of the circulatory system and the SMR was 0.46 (95% CI 0.37–0.56) (374).

A cohort containing 14 014 men employed after 1937 at six British factories where formaldehyde was produced or used was followed 1941–2000. The mortality was compared with the expected numbers of deaths for the national population. Identification data and occupational histories were abstracted from employment records, and each job was classified as belonging to one of five categories of formaldehyde exposure (background, low, moderate, high or unknown). No measurements of formaldehyde had been performed before 1970, but from later measurements and from workers' recall of irritant symptoms, it was estimated that background exposure corresponded to TWA concentrations < 0.1 ppm; low exposure to 0.1–0.5 ppm; moderate exposure to 0.6–2.0 ppm; and high exposure to > 2.0 ppm. Some of the exposures may have occurred through inhalation of paraformaldehyde particles or particles of formaldehyde-based products. The mortality (SMR, 95% CI) from circulatory diseases among high-exposed men and in the total cohort was 1.04, (0.97–1.11, 849 deaths) and 0.98 (0.94–1.02, 2 266 deaths), respectively (182).

A proportionate mortality study compared the causes of death among embalmers in California with those of the general US population. The study group consisted of embalmers who were first licensed to practice in California 1916–1978 and who died 1925–1980. There were totally 1 007 fatalities among white male embalmers. There was an increased mortality ratio from IHD (PMR 1.19, $P < 0.05$) but not from CeVD (PMR 0.94). Smoking was an unlikely explanation as mortality from lung cancer was not increased (PMR 0.96). The same pattern of IHD mortality was observed in a parallel study of totally 1 132 fatalities among white male embalmers from New York (PMR 1.12, $P < 0.05$) (980).

The proportional mortality was studied among 3 649 white and 397 non-white male US embalmers and funeral directors who had died 1975–1985. Comparisons were based on the US general population. Increased mortality ratios (PMR, 95% CI) were observed from IHD among whites (1.13, 1.07–1.19) and non-whites (1.45, 1.22–1.72) but not from vascular lesions of the CNS among whites (1.02, 0.90–1.15) and non-whites (0.90, 0.61–1.27). The corresponding PMRs for lung cancer were 0.97 and 0.75, respectively (390).

A cohort of 1 477 male Ontario undertakers first licensed during 1928 through 1957 was followed until 1977. Numbers of observed and expected deaths were determined for the period 1950–1977, using rates of Ontario men as the standard. Mortality ratios were not significantly increased for circulatory diseases (SMR 1.07), IHD (SMR 1.07) and CeVD (SMR 0.78). However, the mortality from

cirrhosis of the liver was increased (SMR 2.38, P < 0.001), which suggests that the undertakers had consumed more alcoholic beverages than the general population. This may explain the small increases of circulatory disease mortality (557).

In a cohort study, mortality was evaluated among 26 561 workers employed in ten US formaldehyde-producing or -using facilities. The cohort was composed of all workers first employed at the selected plants before 1966, and was followed through 1980. Among white men, there was no exposure-response relationship for atherosclerotic heart disease. At cumulative formaldehyde exposures of 0, ≤ 0.5, 0.51–5.5 and > 5.5 ppm-years, the SMRs (95% CIs) were 0.97 (0.80–1.16), 1.15 (1.05–1.26), 0.94 (0.86–1.03) and 0.90 (0.79–1.01), respectively (105). This cohort was further followed through 1994. The mortality risk (SMR, 95% CI) for circulatory diseases was lower than expected for both exposed workers (0.88, 0.85–0.91) and non-exposed workers (0.77, 0.72–0.83). The use of slightly different categories of formaldehyde exposure resulted in SMRs for circulatory diseases of 0.97, 1.00, 0.98 and 1.05 at cumulative exposures of 0, > 0–< 1.5, 1.5–< 5.5 and ≥ 5.5 ppm-years, respectively. There was no significant exposure-response trend (389).

A cohort of 3 929 male workers was exposed to formaldehyde and employed at an automotive iron foundry for at least 6 months 1960–1987, when the foundry was permanently closed. The exposed workers were compared with the US population and an internal population of 2 032 men who had worked in the same foundry during the same time period but not in formaldehyde-exposed jobs. Only workers in the core making and related operation were exposed to formaldehyde. The highest levels of formaldehyde exposure were experienced by workers operating the two-stage core machines with predicted mean breathing zone concentrations of 2.6 ppm through 1978, 1.8 ppm 1978–1983 and 1.2 ppm from 1984. The follow-up continued through 1989. Compared to the general population, the SMR (95% CI) for IHD for formaldehyde-exposed workers and non-exposed foundry workers was 0.97 (0.82–1.14) and 0.87 (0.73–1.04), respectively. Corresponding figures for CeVD were 1.10 (0.81–1.48) and 1.07 (0.73–1.50) (32). It should be mentioned that foundry workers have many confounding exposures such as noise, silica and PAH.

A cohort of 11 039 workers was exposed to formaldehyde for ≥ 3 months in three garment plants in Georgia and Pennsylvania. Formaldehyde was first introduced in 1955 in one plant and in 1959 in the other plants. The cohort was followed through 1998. These garment facilities produced shirts from fabrics which were treated with formaldehyde resins to impact crease resistance. The mean TWA formaldehyde exposure at the plants in the early 1980s was 0.15 ppm, but past exposures may have been substantially higher. The expected numbers of death were based on rates from the US population. There was no increased mortality (SMR, 95% CI) from heart disease (0.96, 0.89–1.04) and IHD (0.95, 0.86–1.03), but an increased mortality from cardiomyopathy, conductive disorders and other heart diseases (1.17, 1.00–1.36). When duration of exposure (< 3 years, 3–9 years and ≥ 10 years) was related to mortality, there was a significantly negative trend regarding heart disease and IHD. Mortality from cardiomyopathy, conductive disorders and other

heart diseases had the highest SMR at the lowest duration (1.45, 99% CI excluded 1.0). With year of first exposure categorised as prior to 1963, 1963–1970 and 1971 or later, SMRs for heart disease were 0.93, 1.04 and 1.14, respectively. The corresponding numbers for IHD were 0.90, 1.05 and 1.40 (750). This pattern may reflect a high SMR when there is a short time period between exposure and outcome. A longer period between exposure and outcome may increase the likelihood for a longer non-exposure period due to movement to other employment or retirement.

14.1.3 Conclusion

One occupational cohort of formaldehyde exposed workers presented an increased mortality regarding cardiomyopathy, conductive disorders and other heart diseases (750). In addition, two proportionate mortality studies reported an increased risk for IHD among embalmers (390, 980). The remaining five cohort studies did not show increased CVD risks.

There is *insufficient evidence* for an association between exposure to formaldehyde and CVD.

14.2 Phosgene

14.2.1 General

Phosgene ($COCl_2$) was used during World War I in chemical warfare. In chemical industry it is used as an agent for direct chlorination (766).

14.2.2 Occupational epidemiological studies

A cohort of 694 male chemical workers was exposed to low levels of phosgene while working at a uranium processing plant in Tennessee 1943–1945. The expected numbers of deaths were based on rates for US white males. The total number of deaths due to diseases of the circulatory system was 101 (SMR 0.86, 95% CI 0.70–1.04). The SMR was slightly higher among 106 workers with acute exposure to high levels of phosgene (SMR 1.06, 95% CI 0.63–1.67). On the basis of reported symptoms most of the 106 workers had been exposed to around 50 ppm-minutes (754).

14.2.3 Conclusion

The only located occupational study on phosgene did not show an increased risk for CVD (754).

There is *insufficient evidence* for an association between exposure to phosgene and CVD.

14.3 Sulphur dioxide

14.3.1 General

Exposure to sulphur dioxide (SO_2) is prevalent in many occupational settings, e.g. paper and pulp factories, smelters, steel works and chemical industries (254). Ambient sulphur dioxide remains a major air pollutant in many parts of the world.

14.3.2 Human experimental studies

Healthy volunteers and patients with stable angina pectoris, multivessel coronary artery disease (i.e. IHD) and good left ventricular function (20/group) were exposed to 200 ppb (540 $\mu g/m^3$) sulphur dioxide and air for 1 hour. Baseline concentrations of CRP were higher in patients with IHD than in healthy subjects. There were no changes in CRP, fibrinogen or D-dimer during exposure. A significant reduction in HRV was observed 4 hours post-exposure in volunteers, but not in patients (805).

14.3.3 Occupational epidemiological studies

A group of 400 male workers were employed for at least 6 months during the period 1961–1981 in a Swedish sulphuric acid factory. The cohort was followed until 1985 and mortality was compared with rates from the regional county. The relative SMR for CVD was 1.33 (22 cases, P = 0.17) which increased to 1.51 (22 cases, P = 0.05) after a latency period of at least 5 years. The SMRs increased slightly with time of employment (254) (Table 15).

The mortality of Finnish sulphite mill workers employed for at least 1 year during 1945–1961 was followed until 1981. Among those exposed to sulphur dioxide (2 268 person-years), a non-significantly increased mortality (SMR, 95% CI) was observed from CVD (1.23, 0.79–1.84) and IHD (1.45, 0.86–2.29) (469).

A cohort comprised 1 096 male workers from a plant producing sulphuric acid, in Tuscany, Italy. The workers had been employed at least 1 year at the plant in the period 1962–1997 and were followed until 2000. The mortality from circulatory diseases was decreased (SMR 0.64, 95% CI 0.49–0.84) (739).

14.3.4 Epidemiological studies of the general population

Epidemiological evidence about the health effects in the general population of sulphur dioxide exposure is not abundant.

Table 15. Relationship between time of employment and risk of CVD mortality (latency time ≥ 5 years) among workers in a sulphuric acid factory (254).

< 2 years employment			2–5 years employment			> 5 years employment		
Observed	SMR	SSMR	Observed	SMR	SSMR	Observed	SMR	SSMR [a]
3	1.29	1.29	6	1.50	1.72	13	1.57	1.82

[a] P for trend > 0.5.

CVD: cardiovascular disease, SMR: standardised mortality ratio, SSMR: SMR standardised to the age distribution in the group with < 2 years employment.

During 2000–2007, the CVD mortality was investigated in Seoul, Korea, with a time-stratified case-cross-over design. The mean daily sulphur dioxide concentration was 5.4 ppb (14 μg/m^3) (SD 2.4 ppb). An interquartile increase of sulphur dioxide concentration was associated with an increased risk (OR, 95% CI) of CVD mortality (3.64, 1.46–5.87). The CVD mortality was higher for males than for females (1.05, 1.01–1.09) and higher for manual than for professional occupations (1.19, 1.03–1.37) (894).

A nationwide time-series analysis was conducted in China during 2013–2015 including 272 major cities. The annual-mean of sulphur dioxide concentrations was 29.8 μg/m^3. The associations between exposure and daily cause-specific mortality were investigated with the 2-day moving average of the present and previous day concentrations of sulphur dioxide. Risk estimates were adjusted for age, sex and educational level. A 10-μg/m^3 increase in sulphur dioxide concentration was associated with an increment in mortality of 0.70% (95% CI 0.49–0.91%) from CVD, 0.64% (95% CI 0.30–1.58%) from hypertension disease, 0.65% (95% CI 0.42–0.89%) from CHD and 0.58% (95% CI 0.33–0.84%) from stroke. The risk estimates did not change after adjusting for fine particulate matter, carbon monoxide and ozone, but decreased substantially after adjusting for nitrogen dioxide. However, the estimate regarding CVD was still increased after adjusting for nitrogen dioxide (0.97%, 95% CI 0.45–1.49%). The authors concluded that the associations might not be independent from nitrogen dioxide (984).

14.3.5 Conclusion

Two occupational cohort studies showed non-significant increases of CVD among workers exposed to sulphur dioxide (254, 469), whereas two environmental studies showed positive associations between ambient sulphur dioxide exposure and risk for CVD (894, 984).

There is *limited evidence* for an association between exposure to sulphur dioxide and CVD.

14.4 Nitrogen dioxide

14.4.1 General

Nitrogen dioxide (NO_2) is formed when nitrogen in the air is oxidised by electrical discharges or combustion, notably in internal combustion engines and around welding. These processes create mostly nitrogen monoxide (NO), which is then oxidised to nitrogen dioxide. Nitrogen dioxide occurs in the general environment in concentrations around 0.01–0.05 ppm (1 ppm = 2 mg/m^3). In Sweden, the major source is diesel engine exhaust. Nitrogen dioxide is also formed during combustion of bottled gas and city gas for cooking and heating, and in vehicles run on liquefied petroleum gas (LPG). In indoor arenas where LPG-powered ice machines are used, nitrogen dioxide levels are commonly around 0.1–0.8 ppm with peaks approaching 3–4 ppm, but considerably higher concentrations have been measured under special

circumstances. Tobacco smoking also contributes to the occurrence of nitrogen dioxide (660).

Occupational exposures to very high levels of nitrogen dioxide can occur in enclosed areas, notably during gas welding, work in fodder silos, and dynamiting in mines. The most common source of exposure is diesel engine exhaust, particularly in enclosed, poorly ventilated locations such as tunnels and mines (660).

Studies from Norway and Sweden in 1996–2004 among tunnel construction workers showed nitrogen dioxide concentrations of 0.2–0.9 ppm. A more recent study from Norway conducted in 2010–2011 indicated a decrease in diesel exhaust emissions, reflected as a lowered nitrogen dioxide concentration of 0.09 ppm. In seven non-metal mining facilities in the US in 1998–2001, the average nitrogen dioxide exposure was 0.1–0.6 ppm among underground workers and 0.01–0.06 ppm among surface workers (941).

14.4.2 Human experimental studies

Healthy, non-smoking subjects were exposed to air and 2 ppm nitrogen dioxide for 4 hours in random order on separate occasions. Endobronchial biopsies and bronchial washing were done 1.5 hour or 6 hours after exposure. The nitrogen dioxide exposure induced a 1.5-fold increase in IL-8 ($P < 0.05$) at 1.5 hour and a 2.5-fold increase in neutrophils ($P < 0.01$) at 6 hours in the bronchial washing. Immunohistological examination of bronchial biopsy specimens showed no signs of upregulation of adhesion molecules, and failed to reveal any significant changes in inflammatory cells at either time-point after nitrogen dioxide exposure. The increase in neutrophils may be a consequence of the enhanced IL-8 secretion observed 1.5 hour after exposure (110).

Ten healthy male volunteers were exposed to 4 ppm nitrogen dioxide or filtered air for 1 hour during intermittent exercise in a randomised double-blind crossover study. Bilateral forearm blood flow and fibrinolytic markers were measured before and during unilateral intrabrachial infusion of bradykinin, acetylcholine, sodium nitroprusside or verapamil 4 hours after the exposure. Inhalation of nitrogen dioxide did not impair vascular vasomotor or fibrinolytic function (535).

Twenty-one healthy volunteers were exposed on separate occasions to air and 0.6 and 1.5 ppm nitrogen dioxide for 3 hours with intermittent moderate exercise. Respiratory symptom scores were generally highest after exposure to 1.5 ppm, but differences between exposures to nitrogen dioxide and air were not significant for any single symptom. In an analysis of variance, haematological results revealed a 4.1% exposure-related decrease in haematocrit ($P = 0.003$). Also circulating total lymphocytes ($P = 0.024$) and T-lymphocytes ($P = 0.049$) decreased with nitrogen dioxide exposure. Exposure to nitrogen dioxide increased the blood lymphocyte $CD4^+$-to-$CD8^+$ ratio from 1.74 to 1.85 in males but decreased the ratio from 1.88 to 1.78 in females ($P < 0.001$ for gender difference). Polymorphonuclear leukocytes in bronchial lavage increased with nitrogen dioxide exposure ($P = 0.003$). Thus, these levels of exposure caused mild airway inflammation (307).

14.4.3 Occupational epidemiological studies

A cohort consisting of 53 814 men employed in 1985 at four US trucking companies was followed until 2000. Using an exposure model, each worker was assigned a unique annual exposure based on his address. Time-varying variables for years employed and years off work were used to adjust for a healthy worker survivor effect. HRs were calculated in units of the interquartile range. There was a 10.9% (95% CI 2.7–19.8%) increased risk of CVD mortality when the average ambient nitrogen dioxide exposure increased 8 ppb in the single pollutant model. In the multi-pollutant model, including PM_{10} and sulphur dioxide, the risk was attenuated to 8.3% (95% CI -2.5–20.4%). There were no increased risks regarding PM_{10} or sulphur dioxide (384).

14.4.4 Epidemiological studies of the general population

It has been suggested that previous associations between environmental nitrogen dioxide exposure and CVD do not reflect adverse health effects of nitrogen dioxide itself but rather that of other air pollutants, mainly particulate matter or other components of the complex mixture of traffic-related air pollutants. Primarily, this is due to the strong correlations between nitrogen dioxide and other combustion-derived air pollutants, especially particulate matter (649).

A total of 11 428 patients with ST-elevation MI (STEMI) were included in a Belgian study 2009–2013. Each 10-μg/m^3 increase in ambient nitrogen dioxide was associated with an increased OR of STEMI of 1.05 (95% CI 1.02–1.08), which was higher than the increase associated with particulate exposure. Among subjects ≤ 54 years old the corresponding OR was 1.07 (95% CI 1.01–1.14) (42).

14.4.5 Meta-analyses

A meta-analysis of ten studies estimated an increased risk of death from CVD of 1.07% (95% CI 0.43–1.72%) per 10-μg/m^3 increase in 24-hour nitrogen dioxide. All the studies also had exposure information on particulate matter. Following adjustment for particulate matter, the estimate was attenuated to 0.82% (95% CI 0.22–1.42%). The results support an association between short-term nitrogen dioxide exposure and adverse health outcome that is largely independent of particulate matter mass (649).

Another meta-analysis comprised four studies and involved 461 441 participants. The studies included environmental air pollutants from particles and gases (ozone, carbon monoxide, sulphur dioxide and nitrogen dioxide) and investigated the association with atrial fibrillation. There was a statistically significant association between atrial fibrillation development and all gaseous pollutants as well as $PM_{2.5}$. Nitrogen dioxide was the most frequently studied gaseous pollutant and an increase of 10 ppb was associated with an increased risk of atrial fibrillation (1.19%, 95% CI 0.70–1.67%). The authors suggested that gaseous or particulate pollutants are associated with an increased risk of atrial fibrillation (861).

14.4.6 Conclusion

Experimental human studies have shown inflammatory responses after nitrogen dioxide exposure (110, 307). There is also some evidence from meta-analyses of relationships between ambient nitrogen dioxide exposure and CVD mortality (649) and atrial fibrillation (861). However, the environmental exposures always occur together with other particulate and gaseous exposures.

There is *limited evidence* for an association between exposure to nitrogen dioxide and CVD.

14.5 Ozone

14.5.1 General

Ozone (O_3) is both a source of protection and risk for all species. In the stratosphere, where the majority of atmospheric ozone is found, ozone plays an important role in preventing harmful ultraviolet radiation from reaching the surface of the earth. At ground level, ozone was first identified as a component of photochemical pollution in the Los Angeles' basin in the 1940s (681).

Exposure of humans to ozone, either during an air pollution episode or under controlled chamber conditions, has elicited a wide spectrum of responses. These effects include subjective perceptions of respiratory discomfort (substernal soreness and pain on deep inspiration), putative alterations in lung function, development of airway inflammation, as well as tissue injury. Generally these responses have been studied over relatively short periods (681).

High concentrations of ozone may occur in aircraft cabins (50–100 ppb, 100–200 $\mu g/m^3$) as a consequence of compressed ambient air from high altitudes. Use of air cleaning devices and photocopiers in offices may add substantially to the background level (1033). Metal inert gas (MIG) welding of aluminium generates a characteristic UV-irradiation which produces ozone from oxygen. Ozone concentrations up to 250 $\mu g/m^3$ have been observed during this type of welding (386). In the early 1990s, pulp mills in the Nordic countries started to use ozone as a bleaching agent (968).

14.5.2 Human experimental studies

Male and female volunteers were exposed to 0, 100 and 200 ppb ozone (200 and 400 $\mu g/m^3$) in random order for 4 hours with intermittent exercise. Inhalation of ozone induced exposure-dependent adverse changes in the frequency domains of HRV across exposures, consistent with increased sympathetic tone and an exposure-dependent increase in serum CRP levels across exposures at 24 hours. Changes in HRV and CRP did not correlate with ozone-induced local lung inflammatory responses (granulocytes, IL-6 or IL-8 in BAL). According to the authors, inhalation of ozone caused adverse systemic inflammatory and cardiac autonomic effects that may contribute to the CVD mortality associated with short-term exposure (43).

Obese and non-obese non-smoking women were exposed to 400 ppb (800 µg/m^3) ozone and air for 2 hours with intermittent light exercise. The pre- to post-exposure decrease in forced vital capacity from ozone was significantly greater in the obese group. Plasma IL-6 levels were significantly increased at 4 hours post-exposure in both groups and had returned to pre-exposure levels 20 hours post-exposure (83).

14.5.3 Epidemiological studies of the general population

Associations between daily ozone concentrations and mortality during 1990–2010 among persons with and without previous CVD hospitalisation were analysed with a generalised additive model adjusted for time trend, influenza and weather. An average 10-µg/m^3 increase in the same and preceding day was associated with an increased mortality of 1.72% (95% CI 0.44–3.02%) in those with prior admission for acute MI, which was more than 3 times higher than for those with no previous acute MI (0.50%, 95% CI 0.10–0.89%) (88).

No effect of ozone was observed in the previously referred Belgian study on STEMI patients (Section 14.4.4) (42).

14.5.4 Meta-analyses

A meta-analysis of associations between ambient ozone exposure and mortality from CVD comprised totally 12 studies, published 1988–2013. The CVD mortality was non-significantly higher for older persons than for younger persons. The increase in risk for a 10-ppb increase in daily 8-hour ozone concentration was 0.73% (95% CI 0.43–1.04) for older persons and 0.53% (95% CI 0.20–0.86) for younger persons (80).

14.5.5 Conclusion

Experimental human studies have shown inflammatory responses after ozone exposure (43, 83).

One meta-analysis (80) and one further study (88) demonstrated relationships between ambient ozone exposure and CVD mortality. However, ambient ozone exposure always occur in combination with other particulate and gaseous exposures. Long-term occupational cohort studies of ozone-exposed workers are lacking.

There is *limited evidence* for an association between exposure to ozone and CVD.

15. Asphyxiants

15.1 Carbon monoxide

15.1.1 General

Carbon monoxide (CO) is a colourless and odourless gas. It is an atmospheric pollutant in urban areas, chiefly from exhaust of combustion engines, but also from incomplete burning of other fuels. CO is an important constituent of tobacco smoke.

Exposure to CO is common in many occupational areas, mainly in those associated with exhaust emissions. CO is also an important industrial gas, which is used for the production of chemical intermediates (918).

The main mechanism behind CO-induced toxicity is the binding of CO to haemoglobin, resulting in COHb formation and hypoxia. COHb levels around 20% may be lethal for patients with IHD. This short review is mainly based on a previous criteria document on carbon monoxide from NEG (918).

15.1.2 Human experimental studies

In controlled exposure studies of healthy volunteers, COHb levels up to 5.1% have been related to effects on exercise performance but not to myocardial ischaemia or cardiac arrhythmias (9, 496).

In controlled exposures of patients with coronary artery disease, CO exposures resulting in COHb concentrations of 2.4% and 4.7% significantly reduced the time to onset of angina symptoms and of ST-segment changes of the ECG during exercise in a dose-dependent manner (21, 22). Other studies on patients with angina pectoris have also shown that CO exposure (COHb 2.9–5.9%) aggravated exercise-induced myocardial ischaemia including decreased time to onset of angina symptoms, decreased time to onset of ST-segment changes and increased duration of angina symptoms (8, 29, 499). In another study on patients with angina pectoris, no changes in time to onset of angina symptoms and of ST-segment changes were observed at a COHb level of 3.8% (863). At a COHb level of 5.9%, but not at 4.0%, an increase in number of ventricular arrhythmias was reported among patients with coronary artery disease (IHD) (864). No such effect was seen in another study on such patients at a similar COHb level (5.8%) (409).

15.1.3 Occupational epidemiological studies

IHD mortality was studied among 931 male foundry workers in Finland who participated in a health examination in 1973. The workers were followed up to 1993 through registers and by using a questionnaire (513). In 1973, the systolic and diastolic blood pressures of workers exposed to CO were slightly higher than those of unexposed workers. The prevalence of angina pectoris was associated with occupational CO exposure and smoking, separately and combined (401). In the 1987 follow-up, the RR for IHD mortality was estimated as 4.4 for CO-exposed smokers compared to unexposed non-smokers. The IHD mortality in 1973–1993 was analysed by the Cox proportional hazards model. A statistically significant relationship was found between regular CO exposure and IHD mortality (HR 2.15, 95% CI 1.00–4.63). The HR decreased slightly when age and smoking were taken into account (513).

15.1.4 Conclusion

The established mechanism behind CO-induced toxicity is COHb formation leading to hypoxia. The evaluation of the association between exposure to CO and CVD is entirely based on evidence from controlled human exposure studies.

Among healthy volunteers, COHb levels up to 5.1% did not induce myocardial ischaemia or cardiac arrhythmias. However, among subjects with coronary artery disease (IHD), CO-exposures resulting in COHb concentrations of 2.4% and 4.7% significantly reduced the time to onset of angina pectoris symptoms and of ST-segment changes of the ECG during exercise. COHb levels around 20% may be lethal for subjects with IHD (918). Two occupational studies support an association between CO exposure and CVD, but exposure-response data are lacking (401, 513).

There is *strong evidence* for an association between exposure to carbon monoxide and angina pectoris symptoms among subjects with previous angina pectoris (IHD).

15.2 Cyanide

15.2.1 General

Cyanide originates from both natural sources and chemical manufacture with the highest exposure occurring in the latter. Manufacture of products used in building construction and transportation vehicle interiors as well as in residential and commercial building interiors and furnishings accounts for the majority of the use of cyanide. Cyanide is also used in the manufacture of e.g. nylon, rayon, PVC, modacrylic, polyurethane foam, polyester wadding, neoprene foam, rubber, plastics and adhesive resins (840). Cyanide as lixiviant for gold has been utilised in the mining industries for more than one century. It has also been used to recover gold and other metals from electronic waste (206). The salts of cyanide are commonly used in the jewellery industry (180).

Acute cyanide poisoning in humans is predominantly caused by inhalation of smoke from fires (303). Cyanide has been assumed to be a likely terrorist weapon (840).

Cyanide poisoning produces rapid blockage of cellular respiration due to binding to cytochrome a3, resulting in accumulation of lactate. Lactic acidosis is a recognised hallmark of acute cyanide poisoning in humans (180).

15.2.2 Accidents

Medical records were reviewed of 161 fire survivors with suspected or confirmed cyanide poisoning. Cardiac arrest was common; 58 asystole and 3 ventricular fibrillation. Cardiac rhythm disorders were almost as common with 56 supra-ventricular tachycardias. Twelve repolarisation disorders and five intracardiac conduction disorders were observed. Of the 161 patients, 26 displayed no cardiac disorder. Of the patients initially in cardiac arrest, 30 died at the scene, 24 died in hospital and 5 survived without cardiovascular sequelae. Cardiac disorders improved with increasing doses of hydroxocobalamin, and higher doses of the antidote seem to be associated with a superior outcome in patients with initial cardiac arrest (303).

15.2.3 Conclusion

Acute cyanide poisoning is often associated with cardiotoxic effects such as cardiac arrest and cardiac rhythm disorders (303). However, supraventricular tachycardias may be an expression of increased circulatory demands. No epidemiological studies were located on the relationship between long-term exposure to cyanides and CVD.

There is *insufficient evidence* for an association between exposure to cyanide and CVD.

15.3 Hydrogen sulphide

15.3.1 General

Hydrogen sulphide is a gas found in volcanic gases, swamps, and sulphur springs. It is produced by bacterial processes during the decay of both plant and animal protein (e.g. in sewage water) or through the direct reduction of sulphate. Generation of hydrogen sulphide can be expected whenever oxygen is depleted and organic material containing sulphur is present. Hydrogen sulphide occurs in most petroleum and natural gas deposits and in mines where sulphur is present. Occupational exposure to hydrogen sulphide is primarily a problem in the "sour gas" segment of the natural gas industry, where natural gas with a high concentration of sulphur is processed (931).

There have been several reports of accidental deaths and injuries at a number of work situations and workplaces such as flat fish farming, asphalt roofing, liquid manure pits in farming, oil fields, oil refineries and sewage handling. Hydrogen sulphide is formed in manufacturing processes whenever elemental sulphur or sulphur compounds are present with organic chemicals at high temperatures. Examples of industries where this gas can be generated include petroleum refineries, natural gas plants, petrochemical plants, coke oven plants, kraft paper mills, viscose rayon manufacture, sulphur production, iron smelters, food processing plants and tanneries (931).

15.3.2 Mechanistic evidence

Hydrogen sulphide inhibits cytochrome oxidase, which is an important mitochondrial enzyme. Upon binding to cytochrome oxidase, hydrogen sulphide prevents the enzyme from combining electrons with oxygen and thus prevents the reduction of oxygen to water, creating chemical suffocation and preventing ATP (adenosine triphosphate) formation (666). A direct toxic action of sulphide on the heart has been associated with various arrhythmias, disorders of conduction and disorders of ventricular repolarisation (430, 485, 917).

Hydrogen sulphide is endogenously produced in small amounts and plays a role as a secondary messenger in cellular signalling. Hydrogen sulphide is considered a gasotransmitter, a signalling gas, together with carbon monoxide and nitrogen oxide. Like nitrogen oxide, hydrogen sulphide causes smooth muscle relaxation (666).

15.3.3 Accidents

From 1980 through 2013, there were 35 accidents in the Netherlands with manure storage involving 56 adults with hydrogen sulphide intoxication. The survival rate was 43% as 24 patients survived. Of the 8 patients with documented cardiopulmonary resuscitation on the scene, 6 survived without neurological complications. The authors pointed out that this survival rate (75%) is far better than the survival rates after out-of-hospital cardiac arrest (5–8%). The authors concluded that manure related hydrogen sulphide intoxication is associated with a high mortality, although in some cases, recovery appears to be far more favourable than the initial presentation would suggest. Possibly, protection from hypoxic injury due to induction of a suspended animation-like state (a state in which life is temporarily slowed down or stopped) by hydrogen sulphide may be responsible (666).

15.3.4 Occupational epidemiological studies

A cohort comprising men employed continuously for at least 1 year 1945–1961 at three pulp and paper mills in south eastern Finland was followed until 1981. A subcohort of men exposed to hydrogen sulphide and organic sulphides contained 4 179 person-years. There was an increased mortality (SMR, 95% CI) due to CVD (1.50, 1.05–2.06) and IHD (1.50, 0.97–2.22). The CVD mortality (SMR, 95% CI) was higher among men with a work duration of 1–4 years (2.16, 0.99–4.10) than among those with a work duration of ≥ 5 years (1.36, 0.91–1.97). The IHD mortality (SMR, 95% CI) was also higher among workers with a short work duration (2.54, 1.02–5.23) than among those with a longer work duration (1.29, 0.77–2.05). There was also an increased CVD mortality (SMR, 95% CI) among workers who had worked ≥ 5 years and had been followed > 15 years (1.73, 1.09–2.62). The corresponding mortality for IHD was 1.62 (0.88–2.72) (469).

15.3.5 Conclusion

Hydrogen sulphide poisoning is associated with fatal cardiotoxic effects. One epidemiological study provides some weak support for a relationship between occupational hydrogen sulphide exposure and CVD, but no exposure-response relationships were presented (469).

There is *insufficient evidence* for an association between exposure to hydrogen sulphide and CVD.

15.4 Phosphine

15.4.1 General

Aluminium phosphide is a cheap solid fumigant and highly toxic pesticide which is commonly used for grain preservation in many Asian countries. The compound has currently aroused interest due to increasing number of intoxications in the past four decades when used for agricultural and non-agricultural purposes. Upon contact

with moisture, aluminium phosphide undergoes a chemical reaction yielding phosphine gas (PH_3). Phosphine inhibits cellular oxygen utilisation and can induce lipid peroxidation. The specified fatal dose of aluminium phosphide when ingested is 0.15–0.5 g. The average time interval between ingestion and death is 3 hours (1–48 hours), 95% of the patients die within 24 hours and the commonest cause of death is cardiac dysrhythmia (656).

Phosphine can inhibit cytochrome c oxidase *in vitro* but has much less activity *in vivo*. It can rapidly perturb mitochondrial conformation and inhibit oxidative respiration (656).

15.4.2 Accidents

Two children and 29 of 31 crew members aboard a grain freighter became acutely ill after inhaling the fumigant phosphine; one child died. Predominant symptoms were headache, fatigue, nausea, vomiting, cough and shortness of breath. Abnormal physical findings included jaundice, paraesthesia, ataxia, intention tremor and diplopia. Focal myocardial infiltration with necrosis, pulmonary oedema and widespread small-vessel injury were found at post-mortem examination of the 2-year-old child. The surviving 4-year-old child showed several signs indicating myocardial injury, including ECG and echocardiographic changes and transient elevation of the MB (myocardial band) fraction of serum creatinine phosphokinase (a marker of acute MI). Four crew members were hospitalised and three had experienced shortness of breath and substernal burning. Illness was significantly associated with living or working amidships or on the forward deck areas of the vessel. The highest concentration of phosphine (20–30 ppm) was measured in a void space of the main deck adjacent to the air intake system for ventilation amidships. Substantial phosphine leakage (7.5–10 ppm) was noted around one hatch on the forward deck and at an air intake ventilator aft of the main house (12 ppm). Levels of 0.5 ppm of phosphine gas were measured in some of the living quarters amidships (1024).

In 2008, 80 000 tonnes of peas were treated with 1–1.5 g/m^3 of aluminium phosphide on board a bulk carrier with 13 seafarers. A 56-year-old seafarer with intense abdominal and chest pains, associated with dizziness, was rescued by helicopter and admitted rapidly to hospital. His heart rate decreased and the respiratory distress increased. He finally died of pulmonary oedema, major metabolic acidosis and acute multiorgan failure. The following day, a 41-year-old man turned ill also with abdominal pain, vomiting and dizziness. The ECG only revealed type 1 Brugada syndrome (abnormal electrical activity of the heart). Of the 11 other seafarers evacuated for observation, 3 showed clinical abnormalities. One crew member had a right bundle branch block which spontaneously improved after several hours of monitoring. The authors concluded that the seafarers were poisoned by phosphine gas spreading through cabins above the hold (573). No measurements of phosphine were performed.

15.4.3 Occupational epidemiological studies

A cross-sectional study investigated 22 Indian workers engaged in fumigation of stored grains and exposed to phosphine. The mean age of the workers was 48 years and the mean duration of exposure was 11.1 years (range 0.5–29). The workers placed aluminium phosphide tablets on the stacks of grains and covered it with a gas-proof plastic cover. After fumigation, they reported symptoms which included cough (18%), dyspnoea (32%), tightness around the chest (27%) and headache (32%). The symptoms lasted for 10 minutes to 3 hours. The abnormal physical signs included bilateral diffuse rhonchi and absent ankle reflex each occurring in one worker. Phosphine concentrations in the work environment ranged from 0.17 to 2.11 ppm. The workers were also exposed to other pesticides but not during the last 4 weeks (653).

Aluminium phosphide was used for fumigation of bulk wheat in country storages in New South Wales, Australia. Exposures to phosphine occurred over a wide range of concentrations, from zero when adding tablets to 35 ppm when shipping. In all, 67 men were interviewed and the majority stated that they were aware of the odour of phosphine most of the time. The most common symptoms were headache (83%), diarrhoea (82%), nausea (73%) and epigastric pain (65%). Cardio-respiratory symptoms were slightly less common; tightness of chest (52%), breathlessness (34%), soreness or pain in chest (29%), palpitations (27%) and severe retrosternal pain (6%) (461).

15.4.4 Conclusion

Phosphine inhibits mitochondrial cytochrome oxidase and cellular oxygen utilisation. It is well established that excessive exposure to phosphine causes fatal cardiac dysrhythmias (573, 656). The epidemiological data on phosphine exposure and CVD are meagre.

There is *insufficient evidence* for an association between exposure to phosphine and CVD.

16. Evaluation of human health risks

16.1 Assessment of health risks

The evaluations on occupational chemical exposures in relation to CVD were categorised according to the strength of evidence (Chapter 6) as:
1. Strong, 2. Moderately strong, 3. Limited, or 4. Insufficient.

Summary of evaluations, categorisations of strength of evidence and critical exposure-response data are presented in Tables 16–17. In the text below, agents with strong or moderately strong evidence for an association with CVD are presented. The categorisations were mostly based on epidemiological data on workers or the general population, but in some cases on human experimental data. Effects only seen at excessive concentrations (e.g. during anaesthesia or during

occupational conditions no longer valid) were not considered relevant for the categorisation.

In subjects with previous angina pectoris (IHD), exposure to dichloromethane and carbon monoxide have elicited angina pectoris symptoms. Such subjects may well be part of the work force. These findings were therefore considered relevant for occupational exposure and have driven the assessment of the strength of evidence for these substances.

16.1.1 Combustion-generated air pollutants

Exposure occurs in many industrial processes and occupational activities (e.g. electrolytic aluminium smelting, coke and graphite electrode production, coal gasification, chimney sweeping, asphalt paving, tar distillation) and includes many sources of air pollutants (e.g. diesel engine exhaust, cooking fumes, second-hand smoke and smoke from fires).

It should be noted that air pollution generated from different types of combustion processes differ in composition, and that the content of several active agents used as indicators of exposure (e.g. PAH, BaP and EC) varies. Therefore, e.g. air concentrations of BaP from different types of combustion-generated processes are not directly comparable.

Overall, there is moderately strong evidence for an association between exposure to *combustion-generated particles* and CVD. $PM_{2.5}$ exposure around 0.2–0.3 mg/m^3 to different combustion-generated particles (e.g. diesel engine exhaust) was associated with effects on blood vessels or the heart in human experimental (585, 650, 736, 965) and epidemiological (364, 442) studies.

16.1.2 Mineral dusts

Asbestos, crystalline silica, MMVF and CNTs were evaluated.

There is strong evidence for an association between exposure to *asbestos* and CVD. An exposure of 0.04–0.2 asbestos fibres/ml for 40 years was associated with an increased mortality from CVD (539).

Evidence is also strong for an association between exposure to *crystalline silica* and CVD. Exposure at 0.01–0.02 mg/m^3 of respirable crystalline silica for 40 years was associated with an increased mortality from IHD (570).

16.1.3 Metals

Totally 11 metals were evaluated.

There is strong evidence for an association between *arsenic* exposure and CVD. Exposure to arsenic air concentrations of 0.1–0.2 mg/m^3 for 40 years was associated with an increased mortality from CVD (402).

Evidence is also strong for an association between *lead* exposure and CVD. A blood lead level of 6.7 µg/dl (0.32 µmol/l) was associated with an increased CVD mortality (538).

There is moderately strong evidence for an association between *cadmium* exposure and CVD. Blood cadmium levels of 0.26–0.50 µg/l (2–4 nmol/l) were associated with an increased risk of major adverse cardiac events (63) and urinary

cadmium levels of 0.62–0.92 µg/g creatinine (0.62–0.93 µmol/mol creatinine) were associated with CVD (943).

16.1.4 Other dusts and fumes

There is moderately strong evidence for an association between exposure to *welding fumes* and IHD; exposure to 0.25–1.25 mg/m^3 for 40 years was associated with an increased risk of chronic IHD (441).

Evidence is also moderately strong for an association between exposure in the *pulp and paper industry* and CVD.

16.1.5 Pulmonary heart disease

Some dusts and metals cause pneumoconiosis (e.g. asbestosis, silicosis and berylliosis) and extrinsic allergic alveolitis (metalworking fluids, wood dust and agricultural dust), which may lead to pulmonary arterial hypertension (pulmonary heart disease or *cor pulmonale*).

The evidence for an association between *crystalline silica* and *cor pulmonale* is strong. Occupational exposure-response relationships were observed for crystalline silica and beryllium, respectively, and pulmonary heart disease.

16.1.6 Non-chlorinated organic solvents

Some organic solvents, including mixed solvent exposures, were evaluated.

For *carbon disulphide,* the evidence is strong for an association between exposure and CVD.

16.1.7 Halogenated hydrocarbons

There is moderately strong evidence that exposure to *dichloromethane* elicits angina pectoris symptoms in subjects with previous IHD.

There is strong evidence for a relationship between exposure to *dioxins and dioxin-like compounds* and IHD; plasma levels ≥9.9 ppt (ng/kg) TCDD were associated with an increased risk (112).

16.1.8 Nitrated explosives

Strong evidence supports an association between exposure to both *nitroglycerine* and *ethylene glycol dinitrate* and CVD. Some of the explosives are easily absorbed through the skin (nitroglycerine, ethylene glycol dinitrate and propylene glycol dinitrate), thus the unprotected skin may be the major route of exposure.

16.1.9 Asphyxiants

For *carbon monoxide*, there is strong evidence for a relationship between exposure and angina pectoris symptoms among subjects with previous IHD; COHb concentrations of 3–5% reduced the time to onset of angina symptoms (918).

Table 16. Evaluations of chemical exposures associated to CVD by strength of evidence.

Chemical agent	Strength of evidence for CVD			
	Strong	Moderately strong	Limited	Insufficient
Combustion-generated particles				
Overall evaluation [a]		x		
Mineral dusts				
Asbestos	x			
Crystalline silica	x			
Man-made vitreous fibres				x
Carbon nanotubes				x
Metals				
Aluminium				x
Arsenic	x			
Beryllium			x [b]	
Cadmium		x		
Chromium (VI)				x
Cobalt				x [c]
Lead	x			
Manganese				x
Mercury (inorganic)				x
Methylmercury			x	
Titanium dioxide				x
Zinc				x
Other dusts and fumes				
Welding fumes		x		
Soldering fumes				x
Metalworking fluids			x	
Wood industry			x	
Pulp and paper industry		x		
Textile industry			x	
Agriculture work				x [d]
Cleaning			x	
Non-chlorinated organic solvents				
Carbon disulphide	x			
Styrene			x	
Dimethylformamide				x
Mixed organic solvents			x	
Halogenated hydrocarbons				
Chemicals causing cardiac sensitisation to catecholamines				x [e]
Methyl chloride				x
Dichloromethane		x [f]		
Trichloroethylene			x	
Tetrachloroethylene			x	
Vinyl chloride/polyvinyl chloride (PVC)				x [g]
Dioxins and dioxin-like compounds	x			
Polychlorinated biphenyls (PCBs)			x	

Table 16. Evaluations of chemical exposures associated to CVD by strength of evidence.

Chemical agent	Strength of evidence for CVD			
	Strong	Moderately strong	Limited	Insufficient
Per- and polyfluoroalkyl substances (PFAS)				x
Nitrated explosives				
Nitroglycerine	x			
Ethylene glycol dinitrate	x			
Propylene glycol dinitrate			x	
Dinitrotoluene			x	
Irritant gases				
Formaldehyde				x
Phosgene				x
Sulphur dioxide			x	
Nitrogen dioxide			x	
Ozone			x	
Asphyxiants				
Carbon monoxide	x[f]			
Cyanide				x[h]
Hydrogen sulphide				x[h]
Phosphine				x[h]

[a] Including data from electrolytic aluminium smelting, coke production, coal gasification, graphite electrode production, chimney sweeping, asphalt paving, tar distillation work, roofing and creosote work, diesel engine exhaust, cooking fumes, second-hand smoke, firefighting and smoke from fires.

[b] Beryllium: Pulmonary heart disease *(cor pulmonale)*.

[c] Cobalt: For cardiomyopathy (a rare condition after probably high exposures), *limited evidence*.

[d] Agriculture work: After extreme exposures, *moderately strong evidence* for *cor pulmonale*.

[e] Chemicals causing arrhythmia due to cardiac sensitisation to catecholamines:
During anaesthesia, *strong evidence* for an association with cardiac arrhythmia (cyclopropane, chloroform, halothane, methoxyflurane, enflurane);
At high levels (1 000–100 000 ppm), *moderately strong evidence* for an association between inhalation of some other volatile halocarbons and hydrocarbons and cardiac arrhythmia (Table 11, Section 12.2).

[f] Dichloromethane and carbon monoxide: In subjects with previous angina pectoris (IHD).

[g] Vinyl chloride: After exposure to several hundreds of ppm, *strong evidence* for Raynaud's disease.

[h] Cyanide, hydrogen sulphide, phosphine: After excessive exposure, *strong evidence* for fatal cardiotoxicity.

CVD: cardiovascular disease, IHD: ischaemic heart disease.

Table 17. Summary of critical exposure levels and corresponding occupational exposure limits and biological limit values.

Agent or occupation	Evaluation of evidence	Critical effects (CVD, or more specific sub-diagnosis)	Critical exposure levels	Corresponding OELs/BLVs in the Nordic countries and the EU [a]
Combustion-generated air pollutants				
Combustion-generated particles (overall)	Moderately strong	Increased risk of CVD.	0.2–0.3 mg/m^3 of $PM_{2.5}$ (364, 442, 585, 650, 736, 965) [b, c].	3–5 mg/m^3 organic dust, total (DK, NO) (38, 39). 5 mg/m^3 organic dust, inh. (FI, SE) (40, 892). – (EU).
Electrolytic aluminium smelting	Moderately strong	Increased risk of IHD.	0.26–1.47 mg/m^3 of $PM_{2.5}$; 0.86 mg/m^3, class midpoint (702).	See organic dust above.
		Increased risk of IHD.	111 µg/m^3-y of BaP (312); 2.78 µg/m^3 for 40 y.	2–10 µg/m^3 BaP (FI, SE) (40, 892). – (DK, NO, EU).
Asphalt paving	Limited	Increased risk of CVD.	68–105 ng/m^3 of BaP (134).	See BaP above.
Diesel engine exhaust	Moderately strong	Decreased brachial artery diameter.	200–300 µg DEP/m^3 (736, 965) [b].	See organic dust above. 1 µg DEP/m^3 ~ 1 µg/m^3 of $PM_{2.5}$, since nearly all of the mass emitted by diesel engines is in the fine particle range (< 2.5 µm) (495).
		Exercise-induced ST-segment depression in ECG in subjects with stable coronary artery disease.	300 µg DEP/m^3 (650) [b].	
		Transient increase in arterial stiffness.	330 µg DEP/m^3 (585) [b].	
		Increased risk of MI.	87.5 µg EC/m^3 (442) [c]; ~330 µg/m^3 of $PM_{2.5}$ (559).	0.05 mg EC/m^3 (EU, from Feb 2023 [d]) (270). – (DK, FI, NO, SE). 1 µg DEP/m^3 ~ 0.75 µg EC/m^3 (0.30–0.90) for older technology heavy-duty diesel engines (941).

Table 17. Summary of critical exposure levels and corresponding occupational exposure limits and biological limit values.

Agent or occupation	Evaluation of evidence	Critical effects (CVD, or more specific sub-diagnosis)	Critical exposure levels	Corresponding OELs/BLVs in the Nordic countries and the EU [a]
Mineral dusts				
Asbestos 1321-21-4	Strong	Increased CVD mortality.	1.4–8.6 f/ml-y (539); 0.04–0.2 f/ml for 40 y.	0.1 f/cm^3 (DK, FI, NO, SE) (38-40, 892). 0.1 f/cm^3 (EU) (269).
Crystalline silica 14808-60-7	Strong	Increased IHD mortality.	0.56–0.87 mg/m^3-y (570); 0.01–0.02 mg/m^3 for 40 y.	0.05–0.1 mg/m^3, resp. (DK, FI, NO, SE) (38-40, 892). 0.1 mg/m^3, resp. (EU) (268). < 0.05 mg/m^3, resp. (SCOEL) (845). 0.025 mg/m^3, resp. (ACGIH) (5).
Metals				
Arsenic 7440-38-2	Strong	Increased risk of CVD.	4–8 mg/m^3-y (402); 0.1–0.2 mg/m^3 for 40 y.	0.01 mg/m^3, total (DK, NO, SE) (38-40). 0.01 mg/m^3, inh. (FI) (892). 0.01 mg/m^3, inh. (EU, from July 2021 [e]) (271).
Beryllium 7440-41-7	Limited	Diseases of the arteries, veins and pulmonary circulation; most of the deaths due to *cor pulmonale*.	25–< 70 µg/m^3 (842).	0.1–2 µg/m^3 (DK, FI, NO, SE) (38-40, 892). 0.6 µg/m^3, inh. (EU, July 2021–July 2026 [f]) (271). 0.02 µg/m^3, inh. (SCOEL) (848). 0.05 µg/m^3, inh. (ACGIH) (5).
Cadmium 7440-43-9	Moderately strong	Increased risk of CVD.	0.26–0.50 µg/l blood (63); 2–4 nmol/l.	50 nmol/l blood (5.6 µg/l) (SE) (41). 5 µg/l blood (ACGIH) (5).
		Increased risk of CVD.	0.62–0.92 µg/g creatinine in urine (943); 0.62–0.93 µmol/mol creatinine.	20 nmol/l urine (FI) (892). 2 µg/g creatinine, urine (SCOEL) (847). 5 µg/g creatinine, urine (ACGIH) (5).
Lead 7439-92-1	Strong	Increased risk of CVD.	6.7 µg/dl blood (538); 0.324 µmol/l.	20 µg/100 ml (DK) (39). 1.4 µmol/l (FI) (892). 0.5 µmol/l, fertile women (NO, SE) (38, 41). 1.5 µmol/l, men/non-fertile women (NO, SE) (38, 41). 70 µg/100 ml (EU) (201). 30 µg/100 ml (SCOEL) (844).

Table 17. Summary of critical exposure levels and corresponding occupational exposure limits and biological limit values.

Agent or occupation	Evaluation of evidence	Critical effects (CVD, or more specific sub-diagnosis)	Critical exposure levels	Corresponding OELs/BLVs in the Nordic countries and the EU [a]
Other dusts and fumes				
Welding fumes	Moderately strong	Increased risk of IHD.	10–50 mg/m^3-y, resp. (441); 0.25–1.25 mg/m^3 for 40 y.	0.5–1.7 mg/m^3, welding process dependent [g] (DK) (39). 5 mg/m^3, unspecified, total (NO) (38). 2.5 mg/m^3, inorganic dust, resp. (SE) (40). 5–10 mg/m^3, inorganic dust, inh. (FI, SE) (40, 892). – (EU).
Metalworking fluids	Limited	Increased risk of IHD.	0.25–1.25 mg/m^3 of $PM_{2.5}$ (199).	0.2 mg/m^3, inh., guidance value (SE) (40). – (DK, FI, NO, EU).
Organic solvents				
Carbon disulphide 75-15-0	Strong	Hyperintensive spots indicating silent cerebral infarction.	5 ppm (710).	5 ppm, 15–16 mg/m^3 (DK, FI, NO, SE) (38-40, 892). 5 ppm, 15 mg/m^3 (EU) (266). 1 ppm (ACGIH) (5).
Halogenated hydrocarbons				
Dichloromethane 75-09-2	Moderately strong	Increased COHb in blood, which may elicit angina symptoms in subjects with previous angina pectoris (observed after exposure to carbon monoxide, see below).	50–150 ppm; resulted in 1.9–5.3% COHb in blood after 7.5 h exposure (233) [b].	15–50 ppm, 50–177 mg/m^3 (DK, FI, NO, SE) (38-40, 892). 100 ppm, 353 mg/m^3 (EU) (267). BLVs for COHb: see “Carbon monoxide” below.
Vinyl chloride 75-01-4	Strong	Peripheral circulatory changes (Raynaud’s disease).	~1 000 ppm (235).	1 ppm, 2.5–3 mg/m^3 (DK, FI, NO, SE) (38-40, 892). 1 ppm, 2.6 mg/m^3 (EU, from Feb 2021) (270).
Dioxins and dioxin-like substances	Strong	Increased risk of IHD.	≥9.9 ppt (ng/kg) TCDD in plasma (112).	–

Table 17. Summary of critical exposure levels and corresponding occupational exposure limits and biological limit values.

Agent or occupation	Evaluation of evidence	Critical effects (CVD, or more specific sub-diagnosis)	Critical exposure levels	Corresponding OELs/BLVs in the Nordic countries and the EU [a]
Asphyxiants				
Carbon monoxide 630-08-0	Strong	Reduced time to onset of angina symptoms and of ST-segment changes of the ECG during exercise in subjects with previous angina pectoris.	2.4% and 4.7 % COHb in blood (2.4% COHb ~ 14 ppm CO) (21, 22) [b].	4% COHb, end of shift (FI) (892). 4% COHb (SCOEL) (851). 3.5% COHb, end of shift (ACGIH) (5). – (DK, NO, SE, EU).

[a] SCOEL and ACGIH limit values added only if being below the corresponding limit values of the Nordic countries and the EU.
[b] Human experimental studies.
[c] Epidemiological studies.
[d] For underground mining and tunnel work from February 2026.
[e] For copper smelting sector from July 2023.
[f] 0.2 µg/m^3 from July 2026.
[g] Includes electric-arc welding, MAG/MIG/TIG welding and flame cutting.
ACGIH: American Conference of Governmental Industrial Hygienists, BaP: benzo(a)pyrene, BLV: biological limit value, CO: carbon monoxide, COHb: carboxyhaemoglobin, CVD: cardiovascular disease, DEP: diesel exhaust particles, DK: Denmark, EC: elemental carbon, ECG: electrocardiography, EU: European Union, FI: Finland, IHD: ischaemic heart disease, inh.: inhalable fraction, MAG: metal active gas, MI: myocardial infarction, MIG: metal inert gas, NO: Norway, OEL: occupational exposure limit, $PM_{2.5}$: particulate matter with maximal aerodynamic diameter of 2.5 µm, resp.: respirable fraction, SCOEL: Scientific Committee on Occupational Exposure Limits, SE: Sweden, TCDD: tetrachlorodibenzo-*p*-dioxin, TIG: tungsten inert gas.

16.2 Groups at extra risk

This section presents some data of sensitive groups and cardiovascular risk factors which need further attention regarding possible interactions with occupational chemical exposures.

16.2.1 Women

There is some evidence that women may be more prone to CVD from particulate air pollution. Among Swedish manual workers occupationally exposed to particles, the risk of acute MI was somewhat higher in women than in men (1015). Based on the same cohort, there was also a higher risk of MI in women than in men associated to occupational exposure to respirable silica dust (1016). Another Swedish study showed a statistically significantly increased risk of MI among female (but not male) cooks, restaurant and kitchen assistants, and waiting staff exposed to cooking fumes or second-hand smoke (92). There was an association between ambient particulate air pollution and fatal CHD in women but not in men in a cohort of non-smoking Californian adults (158). Another Californian study reported an association between ambient $PM_{2.5}$ exposure and atherosclerosis (carotid intima-media thickness), with larger effects in women than in men (525). There is also some evidence that women may be more sensitive than men to tobacco smoking regarding CHD and stroke (369, 433).

16.2.2 Blood group O

It has been recognised that individuals with non-O blood groups may be at elevated risk of venous thromboembolic events, MI, cerebrovascular ischaemic events, and peripheral vascular disease compared with individuals with blood group O; this risk increase has been attributed to higher concentrations of factor VIII and von Willebrand factor (993).

In The Copenhagen Male Study, a cohort of 3 321 men without overt CVD was followed for 8 years. Among men with blood group O, 4.7% had a history of MI compared with 5.7% among men with other blood phenotypes. However, long-term occupational exposure (> 5 years of exposure) to various airborne pollutants, soldering fumes, welding fumes and plastic fumes was associated with a significantly increased lifetime prevalence of MI among men with blood group O. The ORs (95% CIs) for these exposures were 3.0 (1.6–5.8), 2.1 (1.05–4.2) and 8.3 (2.6–27.0), respectively. The corresponding incidence odds of IHD during a 8-year follow-up was lower but still significantly increased for soldering fumes (OR 1.8, 1.0–3.2). No increased risks were observed among occupationally exposed men with other blood groups (924). No other studies focusing on the possible relation between chemical occupational exposures, blood groups and CVD were located. Thus, occupational chemical exposures may be associated with increased risks for CVD among workers with blood group O.

16.2.3 Shift workers

A review showed limited evidence for relationships between shift work and stroke and between night work and IHD (834, 953).

Interaction between shift work and exposure to carbon disulphide was suggested in a cohort study of 1 873 workers at a New York manufacturing plant. The CHD mortality was significantly higher among workers with ≥ 4 years of exposure to both shift work and carbon disulphide than among workers with < 4 years of exposure to both shift work and carbon disulphide. Mortality was not higher among workers with ≥ 4 years of just one of the two exposures (146).

16.2.4 Smokers

Smoking is an established risk factor for CVD (464). Adjustment for smoking is a standard procedure in many epidemiological studies, in order to exclude the confounding effect of smoking. Information about the interaction between smoking and many occupational chemical exposures is scarce.

16.2.5 Diabetics

Diabetes is an established risk factor for CVD (91). Diabetic patients have shown evidence of proinflammatory response to both recent and chronic exposure to environmental air pollution (449).

There is a potential interaction between exposure to second-hand smoke and diabetes regarding MI. As many as half of the non-fatal MIs were associated with exposure to second-hand smoke among diabetics in a case-control study of never-smokers (798). A Canadian cohort study compared the CVD mortality among diabetics and non-diabetics regarding ambient exposure to $PM_{2.5.}$ Among subjects with diabetes on the death certificate, the HR (95% CI) for CVD mortality from $PM_{2.5}$ exposure was 1.51 (1.39–1.65) per 10 μg/m^3 versus 1.20 (1.16–1.25) among subjects without diabetes (748).

16.2.6 Obesity

Epidemiological evidence suggests that obesity may increase the susceptibility to CVD from ambient $PM_{2.5}$ exposure (998). Studies regarding the possible interaction between obesity and occupational chemical exposures and CVD were not found.

16.2.7 Chronic bronchitis

Chronic bronchitis is defined as cough and sputum for at least 3 months a year (1012). An association has been reported between chronic bronchitis and MI after adjustment for age, gender, smoking, diabetes mellitus, systolic blood pressure, angina pectoris and total cholesterol (371). Chronic bronchitis was also associated with IHD among men and women after adjustment for smoking, systolic blood pressure and cholesterol (465). Furthermore, chronic non-productive cough was associated with increased plasma levels of fibrinogen (371).

Chronic bronchitis was a significant predictor of IHD among granite workers (RR 2.2, 95% CI 1.5–3.3), foundry workers (RR 2.3, 95% CI 1.6–3.4) and iron foundry workers (RR 2.0, 95% CI 1.4–3.0) (514).

16.2.8 Previous heart disease

Subjects with CHD may experience angina symptoms from CO exposure. Smokers have higher levels of COHb as a consequence of inhalation of cigarette smoke and smokers with CHD may experience angina symptoms at even lower levels of CO exposure (918).

Exposure to 300 µg DEP/m^3 for 1 hour was associated with exercise-induced ST-segment depression in ECG among subjects with stable coronary artery disease (650).

Subjects with previous acute MI had a 3-fold increased acute MI mortality associated with a 10-µg/m^3 increase of ozone exposure compared with persons without previous infarction (88). Consequently persons with previous heart disease may have a higher risk regarding CVD related to air pollutant exposures.

17. Recommendation for revision of occupational exposure limits

Among the evaluations presented in this document, some agents have been strongly or moderately strongly associated with CVD (summarised in Table 16), in some cases at levels near or below current OELs. A re-assessment of the OELs for these agents should be considered. The agents of concern are briefly described and compared to existing OELs below and in Table 17. For more detailed descriptions, see Chapters 7–15.

17.1 Strong evidence for cardiovascular disease

Asbestos: Exposure at 0.04–0.2 fibres/ml for 40 years, estimated from cumulative exposure data, was associated with CVD (Section 8.1). This range is similar to the binding OEL in the EU and the TLV set by the American Conference of Governmental Industrial Hygienists (ACGIH) of 0.1 fibres/ml.

Respirable crystalline silica: Exposure at 0.01–0.02 mg/m^3 for 40 years, estimated from cumulative exposure data, was associated with IHD (Section 8.2). This range is clearly below the binding OEL in the EU of 0.1 mg/m^3 and the TLV of 0.025 mg/m^3 set by ACGIH.

Lead: A blood concentration of 6.7 µg/dl (0.324 µmol/l) was associated with increased CVD mortality (Section 9.7). These data indicate effects well below current biological exposure limits in the Nordic countries (0.5–1.5 µmol/l and 20 µg/100 ml).

Carbon disulphide: Exposure around 5 ppm was associated with an increase of hyperintensive spots indicating silent cerebral infarctions (Section 11.1). These data suggest effects at the same level as the Nordic and EU OELs.

Carbon monoxide: In subjects with previous IHD, blood concentrations of 2.4% and 4.7% COHb reduced the time to onset of angina pectoris symptoms (Section 15.1). The data suggest effects around the biological exposure limit/index of Finland and ACGIH of 3.5–4% COHb. Also SCOEL considered 4% COHb a level that should not be exceeded.

17.2 Moderately strong evidence for cardiovascular disease

Combustion-generated particles: Exposure has been associated with CVD and especially IHD. Experimental and epidemiological data, predominantly on diesel engine exhaust, indicate that 0.2–0.3 mg/m^3 of $PM_{2.5}$ (respirable dust) generated from combustion is associated with an increased risk of IHD. The OELs for organic dusts in the Nordic countries are far higher, 3–5 mg/m^3. Elemental carbon (EC) has been suggested as a better marker for diesel engine exhaust. One of the epidemiological studies on diesel engine exhaust measured EC, and exposure to 87.5 µg EC/m^3 was associated with an increased risk of MI (Chapter 7). In the EU, a binding OEL for diesel engine exhaust emissions of 50 µg/m^3 measured as EC applies from the year 2023.

Cadmium: Levels of 0.26–0.50 µg/l (2–4 nmol/l) in blood and 0.6–0.9 µg/g (0.6–0.9 µmol/mol) creatinine in urine in environmental studies were associated with increased risks for major adverse cardiac events (Section 9.4). The effect concentrations are clearly below current biological exposure limits, e.g. 20 and 50 nmol/l blood in Finland and Sweden, respectively, and the value of 2 µg/g creatinine in urine recommended by SCOEL.

Welding fumes: Exposure of 0.25–1.25 mg/m^3 for 40 years, estimated from cumulative exposure data, has been associated with IHD (Section 10.1). These levels are similar to the Danish OELs for welding fumes (0.5–1.7 mg/m^3) and lower than the Nordic OELs for inorganic dust.

Dichloromethane: In subjects with previous IHD, angina pectoris symptoms developed at blood COHb levels of 3–5%, which corresponds to dichloromethane exposure at 50–150 ppm (Section 12.4). The effect concentration is similar to the OELs in the Nordic countries of 15–50 ppm and biological exposure limits of 4% COHb (Finland, SCOEL).

18. Research needs

Little is known about *gender differences* in susceptibility to CVD from chemical exposures (Section 16.2.1). Occupations with identical chemical exposures among women and men should therefore be studied. Further, there are gender differences regarding exposures. One women dominated occupation is cleaning. In a recent study, women cleaning at home or working as occupational cleaners had an accelerated decline in lung function. Both work with cleaning sprays and other cleaning agents were associated with accelerated FEV_1 decline (928). Decreased lung function is associated with CVD (872), but evidence is limited for an association between cleaning and CVD (Section 10.7). Studies to explore the relation between specific cleaning agents and CVD are needed.

The relationship between *occupational air pollutants and atrial fibrillation* needs to be further explored. Almost 1% of the male population in Sweden younger than 60 years of age has experienced atrial fibrillation. The occurrence of this arrhythmia is lower among women. Among smokers, the disease is twice as common compared

to non-smokers (148). There is also an established relationship between atrial fibrillation and the occurrence of stroke (463).

CeVD is generally less studied than IHD in relation to occupational chemical exposures. Consequently both fatal and non-fatal CeVD should be studied. A recent study of Swedish foundry workers found an elevated morbidity and mortality from stroke, but not from MI (278). Ischaemic and haemorrhagic stroke should be separated as the mechanisms behind these diseases may be different.

Diseases such as diabetes, obesity and chronic bronchitis have been associated with an increased risk of CVD. Diabetes and obesity are common conditions and the relationships between these conditions in combination with occupational chemical exposures and CVD need to be further explored. It is also important to increase the knowledge regarding the susceptibility of persons with previous CVD who return to their previous work.

Interactions between chemical and non-chemical occupational exposures needs to be studied, as there are many non-chemical aspects of work that are related to CVD. The Swedish Agency for Health Technology Assessment and Assessment of Social Services evaluated contributions of the work environment from non-chemical occupational exposures to IHD. There was moderately strong evidence for a relationship between job strain and small decision latitude on one hand and IHD incidence on the other. Limited evidence was found for iso-strain, pressing work, effort-reward imbalance, low support, lack of justice, lack of skill discretion, insecure employment, night work, long working week and noise in relation to IHD (834, 953).

The transition from exposure to non-exposure may have consequences regarding further development of CVD and needs to be investigated. Studies on smoking cessation have given some experiences regarding further development of heart disease. A meta-analysis including 20 studies showed a 36% reduction in crude RR of mortality for patients with CHD who quit smoking compared with those who continued smoking (204). Levels of inflammatory markers such as fibrinogen decrease after smoking cessation, but it takes more than 10 years to reach the level of non-smokers (990). Leaving an occupational exposure may be associated with a decreased risk of CVD. The effect of disease progression or regression from cessation of exposure may vary between different chemical exposures.

Exposed groups of workers may be studied by *biomarkers of inflammation* in a cross-sectional design, as several inflammatory markers such as IL-6, CRP, SAA, fibrinogen and leukocyte cell count are related to CVD (209-211). The cross-sectional design may be adequate when prospective cohort studies are impossible to perform.

19. Summary

Sjögren B, Bigert C, Gustavsson P. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals*. 153. Occupational chemical exposures and cardiovascular disease. Arbete och Hälsa 2020;54(2):1–428.

This document reviews and evaluates the scientific literature on the association between occupational chemical exposures and cardiovascular disease (CVD), with emphasis on epidemiological data. Exposures – chemical agents, industries and occupational activities – were divided in four categories according to the strength of the scientific evidence for an association between exposure and CVD as follows:

1. *Strong evidence:* asbestos, crystalline silica, arsenic, lead, carbon disulphide, dioxins and dioxin-like compounds, nitroglycerine, ethylene glycol dinitrate and carbon monoxide.
2. *Moderately strong evidence:* combustion-generated particles, cadmium, dichloromethane, welding fumes, and pulp and paper industry.
3. *Limited evidence:* beryllium, methylmercury, styrene, mixed organic solvents, trichloroethylene, tetrachloroethylene, polychlorinated biphenyls (PCBs), propylene glycol dinitrate, dinitrotoluene, sulphur dioxide, nitrogen dioxide, ozone, metalworking fluids, cleaning, and textile and wood industries.
4. *Insufficient evidence:* man-made vitreous fibres, carbon nanotubes, aluminium, chromium (VI), cobalt, manganese, inorganic mercury, titanium dioxide, zinc, dimethylformamide, methyl chloride, vinyl chloride, per- and polyfluoroalkyl substances (PFAS), formaldehyde, phosgene, cyanide, hydrogen sulphide, phosphine, soldering fumes, work in agriculture, and chemicals causing cardiac arrhythmias, e.g. during asthma treatment and general anaesthesia.

Combustion-generated air pollutants present a special challenge. The evidence is *strong* for second-hand smoke, *moderately strong* for electrolytic aluminium smelting, diesel engine exhaust, smoke from fires, and *limited* for coal gasification, chimney sweeping, asphalt paving, cooking fumes and firefighting. The different evidence levels are likely due to differences in number and size of studies as well as differences in exposure levels and chemical composition. The mode of action is likely the same or similar for all subcategories of combustion generated particles.

When possible, lowest observed adverse effect concentrations (LOAECs) for CVD were identified for each agent and compared with corresponding occupational exposure limits (OELs) or biological limit values (BLVs) in the Nordic countries and the EU. LOAECs suggesting CVD below current limit values were found for combustion-generated particles, crystalline silica, cadmium, lead and welding fumes. LOAECs close to current limit values were found for asbestos, carbon disulphide, dichloromethane and carbon monoxide. A reassessment of these limit values should be considered.

Keywords: biological limit value, cardiovascular disease, chemical, occupational exposure limit, review, risk assessment, toxicity.

20. Summary in Swedish

Sjögren B, Bigert C, Gustavsson P. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals*. 153. Occupational chemical exposures and cardiovascular disease. Arbete och Hälsa 2020; 54(2):1–428.

Detta dokument utvärderar den vetenskapliga litteraturen om sambandet mellan kemisk exponering i arbetsmiljön och hjärtkärlsjukdom, med tyngdpunkt på epidemiologiska studier. Exponeringarna – kemiska ämnen, industrier och yrkesaktiviteter – delades in i fyra kategorier baserat på styrkan i det vetenskapliga underlaget (graden av evidens) enligt följande:

1. *Stark evidens:* asbest, kristallin kvarts, arsenik, bly, koldisulfid, dioxin och dioxinlika föreningar, nitroglycerin, etylenglykoldinitrat och kolmonoxid.
2. *Måttligt stark evidens:* förbränningspartiklar, kadmium, diklormetan, svetsrök och pappers- och pappersmassaindustri.
3. *Begränsad evidens:* beryllium, metylkvicksilver, styren, organiska lösningsmedel, trikloretylen, tetrakloretylen, polyklorerade bifenyler (PCB), propylenglykoldinitrat, dinitrotoluen, svaveldioxid, kvävedioxid, ozon, skärvätskor, städning, textilindustri och skogsindustri.
4. *Otillräcklig evidens:* mineralfibrer, kolnanorör, aluminium, kobolt, krom (VI), mangan, oorganiskt kvicksilver, titandioxid, zink, dimetylformamid, metylklorid, vinylklorid, per- och polyfluorerade alkylsubstanser (PFAS), formaldehyd, fosgen, cyanid, svavelväte, fosfin, lödrök, jordbruksarbete och ämnen som orsakar hjärtarytmier vid astmabehandling och under narkos.

Luftföroreningar som bildas vid förbränning innebär en speciell utmaning. Evidensen är *stark* för passiv rökning, *måttligt stark* för elektrolytisk aluminiumsmältning, dieselavgaser och brandrök, och *begränsad* för gasframställning från stenkol, sotning, asfaltsläggning, matlagningsrök och brandbekämpning. Variationen i evidensstyrka beror sannolikt på skillnader i studiernas antal och storlek samt på skillnader i exponeringsnivåer och kemisk sammansättning. Mekanismen är sannolikt densamma eller likartad för alla partiklar som bildas vid förbränning.

När det var möjligt jämfördes de lägsta observerade effektnivåerna (LOAEC) för hjärtkärlsjukdom med gällande hygieniska luftgränsvärden eller biologiska gränsvärden i Norden och i EU. Förbränningspartiklar, kristallin kvarts, bly, kadmium och svetsrök hade lägsta effektnivåer under aktuella hygieniska/biologiska gränsvärden. För asbest, koldisulfid, kolmonoxid och diklormetan låg de lägsta effektnivåerna nära respektive gränsvärde. En översyn av dessa gränsvärden bör övervägas.

Nyckelord: biologiska gränsvärden, hjärtkärlsjukdom, hygieniska gränsvärden, kemisk exponering, riskbedömning, toxicitet, översikt.

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22. Data bases used in search of literature

A complete search for literature based on PubMed and Embase, covering the period 1970–2016, was performed in January 2017 (835). Supplementary searches in PubMed were performed in 2018.

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Appendix A. Tables on chemical exposures and cardiovascular disease (selected agents)

For abbreviations used in tables, see the list of abbreviations and acronyms following the main table of contents.

Table A1. Electrolytic aluminium smelting.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Nordic countries							
Cohort: 2 264 males employed > 6 mo 1942–1987 at a primary aluminium smelter. *Referents:* Swedish national, regional (northern Sweden), and local (Västernorrland County) male rates.	1952–2004	Mortality (ICD-7) from MI (420.0–420.2) and CeVD (330–334).	*MI* National rates Regional rates Local rates Employment 0.5–≤ 2 y 2–10 y > 10 y *CeVD* National rates Regional rates Local rates Employment 0.5–≤ 2 y 2–10 y > 10 y	 157 37 43 77 54 14 16 24	SMR 0.97 (0.83–1.14) 0.87 (0.74–1.02) 0.73 (0.62–0.85) HR 1.00 0.99 (0.64–1.54) 1.15 (0.77–1.74) SMR 1.14 (0.86–1.49) 1.00 (0.75–1.31) 0.89 (0.67–1.17) HR 1.00 0.94 (0.46–1.93) 0.89 (0.45–1.77)	No exposure information. P(trend): 0.37. P(trend): 0.78.	(99)
Cohort: 1 085 male smelter workers employed ≥ 6 mo 1922–1975 using prebaked electrodes. *Referents:* Norwegian national male rates.	1962–1991	Mortality (ICD-9) from IHD (410–414), CeVD (430–438), peripheral arterio-sclerosis (440, 444) and sudden death (798). All atherosclerotic disease: IHD,	*Employment < 3 y* IHD CeVD Peripheral arterioscler. Sudden death *Employment* ≥ 3 y IHD CeVD Peripheral arterioscler. Sudden death *All atherosclerotic disease*	 46 11 4 6 94 36 9 10	SMR 1.00 (0.73–1.33) 0.80 (0.40–1.43) 3.08 (0.84–7.88) 1.26 (0.46–2.75) 0.88 (0.71–1.07) 1.01 (0.72–1.43) 2.61 (1.19–4.95) 0.93 (0.45–1.72)	Cumulative exposure: Intensity by a semi-quantitative scale (0–1.0) × years of exposure. Cumulative CTPV exposure (cum exp) was calculated for 661 smelter workers with ≥ 3 y employment. Restricted time window for exposure before observation; 0–19 y (RE0–19), 20–39 y (RE20–39) and ≥ 40 y (RE40).	(813)

Table A1. Electrolytic aluminium smelting.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
		peripheral arterio-sclerosis and sudden death.	RE0–19, cum exp 0 < 3 ≥ 3 RE20–39, cum exp 0 < 3 ≥ 3 RE40, cum exp 0 < 3 ≥ 3 RE40, cum exp 0 < 3 ≥ 3	 46 14 9 64 12 16 47 11 13 47 11 13	 0.80 1.47 1.00 0.90 0.80 1.17 0.93 1.40 1.71 RR 1.0 1.7 (0.9–3.2) 1.8 (1.0–3.3)	 RE0–19, P(trend): 0.21. RE20–39, P(trend): 0.47. RE40, P(trend): 0.03. RE40, P(trend): 0.03.	
Cohort: 10 857 male smelter workers from 6 plants employed ≥ 3 y before 1962 or 1962–1996. *Referents:* Norwegian national male rates.	1962–1996	Mortality (ICD-9) from circulatory disease (390–459), IHD (410–414), CeVD (431–438), arteriosclerosis (440, 444, 785), hypertensive disease (401–405) and sudden death (798).	Circulatory disease IHD CeVD Arteriosclerosis Hypertension Sudden death	1 618 986 307 34 46 115	SMR 0.95 (0.91–1.00) 0.92 (0.86–0.98) 0.94 (0.84–1.05) 1.01 (0.70–1.41) 1.17 (0.85–1.56) 1.03 (0.86–1.24)	No association between cumulative PAH exposure and mortality from IHD.	(794)

Table A1. Electrolytic aluminium smelting.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Europe (non-Nordic)							
Cohort: 6 455 male smelter workers from 11 plants employed ≥ 1 y 1950–1976. *Referents:* French national male rates.	1950–1976	Mortality (ICD-8) from circulatory disease (390–458).	*Circulatory disease* Electrolysis Maintenance Smelting Employment at electrolysis < 10 y 10–20 y > 20 y As above and 20 y since first exposure < 10 y 10–20 y > 20 y	 101 62 23 24 39 32 	SMR 0.89 (0.74–1.04) 0.83 (0.66–1.02) 0.90 (0.61–1.22) 0.90 (0.63–1.23) 1.30 (0.95–1.67) 0.81 (0.58–1.07) 0.78 (0.48–1.21) 1.29 (0.92–1.75) 0.83 (0.57–1.17)	Two thirds of the workers were hired before 1960. The majority had worked with the Söderberg process, which was later replaced by the prebake process. The percentage of smokers was 64% among electrolytic workers exposed < 10 y, 55% among workers exposed 10–20 y and 75% among workers exposed > 20 y.	(685)
Cohort: 2 133 male smelter workers from 1 plant employed ≥ 1 y 1950–1994 (423 workers active 1950 and 1 710 workers first employed 1950–1994). *Referents:* French national male rates.	1968–1994	Mortality (ICD-8–9) from circulatory disease, hyper-tensive disease, IHD, cardiac arrhythmias, CeVD and heart failure.	Circulatory disease Hypertension IHD Arrhythmias CeVD Heart failure	93 3 39 3 14 12	SMR 0.81 (0.65–0.99) 1.05 (0.22–3.08) 0.97 (0.69–1.33) 0.43 (0.09–1.25) 0.47 (0.26–0.79) 0.88 (0.46–1.54)	A follow-up of 1 plant of the above described cohort.	(674)

Table A1. Electrolytic aluminium smelting.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
North America							
Cohort: 2 103 male aluminium workers from a prebake-type reduction plant in Washington state, employed ≥ 3 y and ≥ 1 y 1946–1962. *Referents:* US national male population.	Until 1976	Mortality (ICD-7) from circulatory disease (400–468).	 *Circulatory disease* Exposed Non-exposed Employment duration 3–4 y 5–9 y 10–14 y 15–19 y 20–24 y ≥ 25 y Years between hire and death 3–4 y 5–9 y 10–14 y 15–19 y 20–24 y ≥ 25 y	 162 66 96 14 40 30 49 19 10 4 13 21 46 38 38	SMR 0.77 (P < 0.05) 0.77 (P < 0.05) 0.76 (P < 0.05) 0.41 (P < 0.05) 0.86 0.70 0.96 0.67 1.13 0.27 (P < 0.05) 0.46 (P < 0.05) 0.49 (P < 0.05) 0.88 0.78 1.56 (P < 0.05)	Jobs were categorised in 5 exposed and 14 non-exposed, based on air sampling. Most workers were characterised as non-exposed. 519 workers were hired in 1946 when the plant changed ownership.	(642)
Cohort: 21 829 aluminium workers from 14 reduction plants employed ≥ 5 y 1946–1977. *Referents:* US national male population.	Until 1977	Mortality from major CVD (ICD-7).	*CVD* White Non-white Horizontal Söderberg pot Vertical Söderberg pot Prebake Remainder	 1 850 243 363 53 1 352 325	SMR 0.92 (P < 0.01) 0.71 (P < 0.01) 0.80 (P < 0.01) 0.58 (P < 0.01) 0.97 0.78 (P < 0.01)	SMR was increased for *all other heart disease* for white workers in the Söderberg process (SMR 1.60, P < 0.05). Most death certificates listed heart failure as the cause of death.	(789)

Table A1. Electrolytic aluminium smelting.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 11 966 aluminium workers from 8 US plants (2 194 smelters, 8 290 fabricators, 960 refinery workers and 522 other workers) enrolled in the primary insurance plan and employed ≥ 2 y. Almost 70% of the cohort and 90% of the cases were employed in 1996 at study start.	1998–2009	Incident IHD cases from health insurance claims (ICD-9, 410–414).	*IHD* Recent $PM_{2.5}$, mg/m^3 (restricted to exposures measured with high confidence) ≤ 0.05 > 0.05–0.16 > 0.16–0.37 > 0.37–1.47 > 1.47	 15 132 148 139 143	HR 1 1.58 (0.88–2.63) 1.78 (1.02–3.11) 1.48 (0.83–2.66) 1.48 (0.77–2.85)	To exclude prevalent cases a 2-y wash-out period without IHD claims was required. In fabricators, PM was composed of water-based metalworking fluids (soluble or synthetic). In smelters, PM was composed of inorganic materials and CTPV. HRs adjusted for age, race, gender, calendar year, smoking, facility type, BMI, job grade, and past exposure. No relationship with cumulative exposure.	(199)
Cohort: 12 949 aluminium workers from 11 US plants of 5 555 smelters and 7 349 fabricators, enrolled in the primary insurance plan and employed ≥ 2 y. Extension of the study above (199). Subjects were enrolled either at the start of follow-up or on their dates of hire.	1998–2012	Incident IHD cases from health insurance claims (ICD-9, 410–414; ICD-10, I20–I25).	*IHD* Smelters Fabricators Smelters, $PM_{2.5}$, mg/m^3 < 0.26 (10th percentile) 0.26–1.46 1.47–1.95 1.96–2.58 ≥ 2.59 < 0.26 (10th percentile) 0.26–1.46 1.47–1.95		HR, Cox MSM 1.98 (1.18–3.32) 1.38 (0.98–1.94) HR, Cox standard 1.00 1.51 (0.98–2.37) 1.73 (1.06–2.86) 1.53 (0.97–2.45) 1.53 (0.97–2.46) HR, Cox MSM 1.00 2.00 (1.16–3.45) 1.97 (1.06–3.67)	To exclude prevalent cases a 2-y wash-out period without IHD claims was required. Standard Cox proportional hazard regression to estimate HR for $PM_{2.5}$ exposure and incident IHD. Marginal structural model (MSM) and inverse probability weighting was used to adjust for a time-varying confounder (feature of	(702)

Table A1. Electrolytic aluminium smelting.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			1.96–2.58 ≥ 2.59		1.78 (1.00–3.18) 1.77 (1.01–3.11)	healthy worker survivor effect).	
Case-control study *Cases:* 306 males (150 anginas and 156 MI) from a large primary aluminium production complex. *Controls:* 575 controls; 2 per case from the same plant, matched for birth date, hiring date and length of service (within 5 y), with no known IHD or peripheral vascular disease.	1975–1983	Episodes of IHD (angina and MI).	*IHD* Reduction workers Söderberg Prebake *Years in reduction plant* < 1 y 1–4 y 5–9 y 10–14 y 15–19 y ≥ 20 y	Cases/refs 182/257 137/192 67/71 70/135 44/49 31/42 19/31 13/41 75/94	OR 1.72 (1.09–2.97) 1.71 (1.07–2.72) 2.26 (1.27–4.02) 1.00 2.22 (1.17–4.20) 1.98 (0.92–4.28) 1.39 (0.62–3.13) 0.80 (0.36–1.80) 1.86 (1.05–3.28)	OR was calculated by conditional logistic regression.	(954)
Cohort: 6 423 male workers at an aluminium smelter or its power-generating station in British Columbia employed ≥ 3 y 1954–1997.	1954–1999	Mortality from acute MI (ICD-9, 410).	*Acute MI*	184	RR (only presented in figures).	Roughly monotonically increasing risk for acute MI with increasing cumulative exposure for both BaP and benzene-soluble material in categorical analyses. The slopes of the exposure-response relationships were not significant.	(313)
Cohort: 6 423 male and 603 female workers at an aluminium smelter in British Columbia employed ≥ 3 y 1954–1997. Same male cohort as above.	1954–1999	Mortality (ICD-9) from IHD (410–414, 429.2), acute MI (410), CeVD (430–438) and other circulatory	*Males* IHD Acute MI CeVD Other circulatory disease *Females*	 281 184 58 63	SMR 0.90 (0.80–1.01) 1.00 (0.88–1.13) 0.89 (0.68–1.15) 0.89 (0.68–1.14)	Smoking information from 88% of the cohort.	(312)

Table A1. Electrolytic aluminium smelting.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Referents: British Columbia, Canada, population.		disease (399–400, 406–409, 415–423.9, 424.4–429.1, 429.3–429.9, 439–459, 480–486).	IHD	8	0.84 (0.39–1.59)		
			Acute MI	7	1.27 (0.60–2.40)		
			CeVD	8	1.64 (0.71–3.23)		
			Other circulatory disease	4	1.08 (0.30–2.82)		
			Males, IHD				
			Cum exposure 5-y lag		HR	Cumulative BaP exposure (cum exposure) expressed as µg/m^3-y. Smoking-adjusted HRs.	
			0	56	1		
			> 0–7.78	56	1.11 (0.76–1.62)		
			7.79–24.2	57	1.48 (1.01–2.17)		
			24.3– 66.6	56	1.28 (0.86–1.91)		
			≥ 66.7	56	1.62 (1.06–2.46)	P(trend): 0.053.	
			Continuous	281	1.002 (1.000–1.005)		
			Cum exposure recent 5 y				
			0	221	1		
			> 0–0.14	15	1.03 (0.61–1.75)		
			0.15–2.85	15	0.77 (0.44–1.36)		
			2.86–10.4	15	1.02 (0.56–1.87)		
			≥ 10.5	15	1.09 (0.57–20.9)	P(trend): 0.61.	
			Males, acute MI				
			Cum exposure 5-y lag				
			0	35	1		
			> 0–7.50	37	1.14 (0.71–1.82)		
			7.51–27.6	37	1.21 (0.75–1.96)		
			27.7–67.3	38	1.36 (0.84–2.22)		
			≥ 67.4	37	1.46 (0.87–2.45)	P(trend): 0.19.	
			Continuous	184	1.001 (0.997–1.005)		
			Cum exposure recent 5 y				
			0	144	1		
			> 0–0.03	10	1.19 (0.62–2.28)		

Table A1. Electrolytic aluminium smelting.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			0.04–2.14	10	0.77 (0.39–1.55)		
			2.15–9.18	10	0.96 (0.46–2.00)		
			≥ 9.19	10	0.98 (0.44–2.19)	P(trend): 0.92.	
			Males, CeVD				
			Cum exposure 5-y lag				
			0	15	1		
			> 0–11.3	14	0.88 (0.42–1.83)		
			11.4–76.7	15	0.65 (0.31–1.34)		
			≥ 76.8	14	1.42 (0.67–2.99)	P(trend): 0.20.	
			Males, IHD, actively employed				
			Cum exposure 5-y lag				
			< 8.75	16	1		
			8.75–35.6	12	1.88 (0.84–4.19)		
			35.7–76.9	12	1.99 (0.85–4.65)		
			≥ 77.0	12	2.39 (0.95–6.05)	P(trend): 0.10.	
			Continuous	56	1.002 (0.995–1.009)		
			Current exposure				
			0	22	1		
			> 0–4	19	0.84 (0.43–1.64)		
			≥ 5	11	1.25 (0.51–3.04)		
			Males, acute MI, actively employed				
			Cum exposure 5-y lag				
			< 9.18	10	1		
			9.18–41.3	8	1.59 (0.60–4.22)		
			41.4–75.9	8	1.95 (0.71–5.40)		
			≥ 76.0	8	1.87 (0.62–5.60)	P(trend): 0.29.	
			Continuous	34	1.001 (0.993–1.010)		

Table A1. Electrolytic aluminium smelting.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			Current exposure				
			0	16	1		
			> 0–4	11	0.63 (0.27–1.44)		
			≥ 5	7	1.39 (0.44–4.33)		
Cohorts: Cohorts of Quebec male aluminium smelter workers. A: 5 285 men employed 1950. B: 529 men employed 1951. C: 163 men employed 1950. *Referents:* Quebec male population.	1950–1999	Mortality (ICD-9) from circulatory disease (390–459), IHD (410–414, 429.2) and CeVD (430–438).	*Circulatory disease*		SMR		(337)
			Cohort A	1 686	0.95 (0.91–1.00)		
			Cohort B	141	0.87 (0.73–1.02)		
			Cohort C	42	0.79 (0.57–1.07)		
			Cohort A+B+C	1 869	0.94 (0.90–0.98)		
			IHD				
			Cohort A	1 095	0.94 (0.88–0.99)		
			Cohort B	90	0.82 (0.66–1.01)		
			Cohort C	28	0.79 (0.53–1.15)		
			Cohort A+B+C	1 213	0.92 (0.87–0.98)		
			CeVD				
			Cohort A	274	1.10 (0.97–1.23)		
			Cohort B	33	1.52 (1.05–2.14)		
			Cohort C	10	1.35 (0.65–2.49)		
			Cohort A+B+C	317	1.14 (1.01–1.27)		
			CeVD				
			Cumulative BaP exposure, µg/m^3-y			Calculations based on cohort A+B+C.	
			0	32	0.98 (0.67–1.38)		
			< 20	154	1.09 (0.93–1.28)		
			20–	23	1.31 (0.83–1.97)		
			40–	24	1.06 (0.68–1.58)		
			80–	43	1.54 (1.11–2.07)		
			160–	31	0.91 (0.62–1.29)		
			320–	10	2.79 (1.34–5.13)	P(trend): 0.16.	

Table A1. Electrolytic aluminium smelting.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			Cumulative exposure to benzene soluble matter, mg/m^3-y			Calculations based on cohort A+B+C.	
			0	32	0.98 (0.67–1.39)		
			< 2	106	1.07 (0.87–1.29)		
			2–	37	1.01 (0.71–1.40)		
			4–	43	1.39 (1.01–1.87)		
			8–	41	1.29 (0.91–1.72)		
			16–	45	1.18 (0.86–1.57)		
			32–	14	1.42 (0.78–2.39)	P(trend): 0.2.	
Cohorts: Quebec aluminium smelter workers. A: 6 697 men and 588 women employed after 1950. B: 1 082 men and 56 women employed after 1951. C: 1 379 men and 42 women employed after 1950. D: 568 men and 42 women only employed at prebake technology plant. *Referents:* Quebec population.	1950–1999	Mortality (ICD-9) from circulatory disease (390–459), IHD (410–414, 429.2) and CeVD (430–438).	*Circulatory disease*		SMR		(339)
			Cohort A+B+C	322	0.89 (0.80–0.99)		
			Cohort A	202	0.97 (0.84–1.11)		
			Cohort B	19	0.70 (0.42–1.10)		
			Cohort C	101	0.81 (0.66–0.98)		
			Cohort D	3	0.65 (0.14–1.91)		
			IHD				
			Cohort A+B+C	221	0.87 (0.75–0.99)		
			Cohort A	148	1.00 (0.84–1.17)		
			Cohort B	12	0.63 (0.33–1.10)		
			Cohort C	61	0.69 (0.53–0.89)		
			Cohort D	3	0.93 (0.19–2.71)		
			CeVD				
			Cohort A+B+C	47	1.13 (0.83–1.50)		
			Cohort A	25	1.05 (0.68–1.55)		
			Cohort B	3	0.96 (0.20–2.81)		
			Cohort C	19	1.29 (0.78–2.02)		
			Cohort D	0	0.5 expected		
			CeVD				

Table A1. Electrolytic aluminium smelting.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			Cumulative BaP exposure, µg/m^3-y			Calculations based on cohort A+B+C.	
			0	5	1.25 (0.41–2.91)		
			< 20	19	0.91 (0.55–1.41)		
			20–	6	1.53 (0.56–3.33)		
			40–	6	1.56 (0.57–3.40)		
			80–	4	0.76 (0.21–1.95)		
			160–	6	2.29 (0.84–4.98)		
			320–	1	1.01 (0.03–5.64)	P(trend): > 0.2.	
			CeVD				
			≥ 20 y since first exposure			Calculations based on cohort A+B+C.	
			1950–1959	29	1.17 (0.79–1.69)	The corresponding risk	
			1960–1969	5	1.70 (0.55–3.96)	estimate for the cohorts	
			1970–1979	2	1.34 (0.16–4.84)	employed pre-1950 was	
			1950–1999	36	1.24 (0.87–1.71)	1.18 (1.05–1.33).	
Quebec aluminium reduction plant workers. *Fixed cohorts:* A: 5 285 at work in 1950. B: 529 at work in 1951. C: 163 at work in 1950. *Dynamic cohorts:* A: 6 751 hired since 1950. B: 1 132 hired since 1951. C: 1 401 hired since 1950. *Referents:* Quebec population.	1950–2004	Mortality (ICD-10) from IHD (I20–I25, I51.6, 429.2) and CeVD (I60–I69).	*IHD* Fixed cohorts 1950–1999 2000–2004 Dynamic cohorts 1950–1999 2000–2004 *CeVD* Fixed cohorts 1950–1999 2000–2004 Dynamic cohorts	 1 213 81 221 54 317 20	 0.92 (0.87–0.98) 0.83 (0.66–1.04) 0.87 (0.75–0.99) 0.83 (0.62–1.08) 1.14 (1.01–1.27) 0.69 (0.42–1.06)	Plants A and B started before the 1930s with prebake lines, changed to Söderberg lines around early 1940s. Plant C started in 1943 with Söderberg lines exclusively.	(338)

Table A1. Electrolytic aluminium smelting.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			1950–1999	47	1.13 (0.83–1.50)		
			2000–2004	8	0.61 (0.26–1.20)		
Australia							
Cohort: 4 396 male workers who had worked in 2 Australian prebake aluminium smelters ≥ 3 mo. *Referents:* Australian population.	1983–2002	Mortality from circulatory disease, CVD and CeVD (ICD-codes not given).	*All smelters*		SMR	The cohort comprised three groups: 1. Subjects participating in health survey 1995/1996 (36%). 2. Subjects starting employment after 1995/1996 (8%). 3. Subjects employed on or after 1983 and who left before 1995/1996 (56%). The PAH exposure is known to be lower for prebake smelters than for Söderberg smelters.	(867)
			Circulatory disease	86	0.87 (0.70–1.07)		
			CVD	68	0.88 (0.69–1.12)		
			CeVD	13	0.91 (0.53–1.56)		
			Ever production				
			Circulatory disease	59	0.94 (0.73–1.22)		
			CVD	49	1.00 (0.76–1.32)		
			CeVD	7	0.78 (0.37–1.65)		
			Ever maintenance				
			Circulatory disease	19	0.71 (0.46–1.12)		
			CVD	14	0.68 (0.40–1.14)		
			CeVD	4	1.02 (0.38–2.71)		
			Duration in production or maintenance				
			Circulatory disease				
			3 mo–< 10 y	21	0.92 (0.60–1.42)		
			10–20 y	39	0.93 (0.68–1.28)		
			> 20 y	11	0.6 (0.33–1.08)		
			CVD				
			3 mo–< 10 y	17	0.96 (0.60–1.54)		
			10–20 y	32	0.98 (0.70–1.39)		
			> 20 y	8	0.55 (0.28–1.10)		
			CeVD				
			3 mo–< 10 y	1	3.3 expected		
			10–20 y	6	0.98 (0.44–2.19)		
			> 20 y	3	1.19 (0.39–3.70)		

Table A1. Electrolytic aluminium smelting.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 4 316 male workers who had worked in 2 prebake aluminium smelters ≥ 3 mo. Same cohort as above (867) comprising ever- and never-exposed to CTPV and inhalable dust.	1983–2002	Mortality from circulatory disease (ICD-9, 390–459; ICD-10, I00–I99), CVD (ICD-9, 410–429; ICD-10, I20–I52), and CeVD (ICD-9, 430–432.8; ICD-10, I60–I69).	*Ever- vs never-exposed* Circulatory disease CTPV Inhalable dust CVD CTPV Inhalable dust CeVD CTPV Inhalable dust *Medium-high vs low-unexposed* CeVD	 30/55 63/22 21/46 50/17 6/7 9/4 	RR 0.7 (0.4–1.1) 0.7 (0.4–1.2) 0.6 (0.3–1.0) 0.7 (0.4–1.2) 1.1 (0.4–3.3) 0.6 (0.2–1.8) 1.8 (0.5–5.8)	56% were exposed to CTPV and 85% to inhalable dust. *Median and maximum cumulative exposures* 0.18 and 90 µg/m^3-y for BaP-exposed workers, 0.08 and 30 mg/m^3-y for workers exposed to the benzene-soluble fraction, 12 and 750 mg/m^3-y for inhalable dust-exposed workers.	(310)

Table A2. Coke production.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Nordic countries							
Cohort: 888 male workers employed ≥ 1 y in a coke plant operating 1964–1988. *Referents:* Norwegian national male rates.	1962–1993	Mortality (ICD-9) from IHD (410–414), CeVD (431–438) and sudden death (798).	IHD CeVD Sudden death *Cumulative PAH exposure, µg/m³-y* IHD Unexposed < 50 50–149 ≥ 150 IHD + sudden death Unexposed < 50 50–149 ≥ 150 IHD + sudden death, 15 y latency Unexposed < 50 50–149 ≥ 150	47 3 4 29 9 4 5 32 10 4 5 35 11 2 3	SMR 1.09 (0.80–1.45) 0.33 (0.07–0.97) 0.88 (0.24–2.26) 1.06 1.18 1.04 1.19 1.06 1.29 0.95 1.08 0.96 1.76 0.71 1.38	Smoking habits were lower than in the general Norwegian population; 24–56% lower depending on age group. No significant trends for cumulative PAH exposure but a significant trend (P = 0.01) for peak CO exposure and IHD, 3 y before death.	(135)
Europe (non-Nordic)							
Cohort: 610 UK male coke oven workers employed 1954. *Referents:* rates from England and Wales.	1954–1965	Mortality from CVD.	CVD	29	45.5 expected		(213)

Table A2. Coke production.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort I: 2 753 male workers employed in coke work January 1966–July 1967 by the British Steel Corporation. *Cohort II:* 3 855 male workers employed January 1967 by the National Smokeless Fuel Limited. *Referents:* rates from Scotland, England and Wales.	Cohort I: 12 y Cohort II: 13 y	Mortality (ICD-8) from IHD (410–414) and CeVD (430–438).	IHD CeVD *IHD, age at death* < 45 y 45–54 y 55–64 y ≥ 65 y *IHD, cohort I* Non-oven Part oven Oven *IHD, cohort II* Non-oven Part oven Oven *IHD by years of oven work, subcohort (91%) of cohort I* < 5 y 5–9 y ≥ 10 y	 409 81 18 74 166 151 26 32 88 136 23 94 16 25 34	SMR/rSMR 0.91/1.02 0.71/0.80 Expected 11.9 72.5 178.1 188.4 SMR 0.97 0.92 1.04 0.96 0.73 1.19 0.99 1.36 0.88	rSMR (relative SMR) means cause-specific SMR/SMR all causes. The proportion of smokers among coke workers was similar to that among other manual workers in Britain. The SMR for all oven workers was 1.11 (P = 0.06). The healthy worker survivor effect was discussed.	(429)
Cohort: 5 639 male Dutch coke plant workers employed ≥ 6 mo 1945–1969. Subcohorts of coke oven and by-product workers. *Referents:* national Dutch male rates.	Until 1984	Mortality from circulatory disease (ICD-9).	*Circulatory disease* Coke oven work By-product work	 186 338	SMR 0.98 0.94		(926)

Table A2. Coke production.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 536 male coke oven plant workers in Lorraine Collieries, retired 1963–1982. *Referents:* French national male rates.	1963–1987	Mortality from CVD (ICD-9, 390–459).	*CVD* Entire cohort Ovens All Non-smokers Smokers Near ovens All Non-smokers Smokers Non-exposed All Non-smokers Smokers	 64 6 2 3 22 7 12 23 8 14	SMR 1.33 (P < 0.05) 1.23 1.72 1.02 1.55 (P < 0.05) 2.24 (P < 0.05) 1.34 1.79 (P < 0.01) 2.35 (P < 0.05) 1.69 (P < 0.05)	Exposure classification: *Ovens*, constant presence on coke ovens. *Near ovens*, near ovens or intermittent presence on coke ovens. *Non-exposed*, administrative personnel, time keeper, maintenance workers without direct contact with ovens.	(152)
Cohort: 538 male workers employed at a coke plant in Carrara 1960–1985. *Referents:* Italian national and regional Tuscany male rates.	1960–1990	Mortality from circulatory disease.	*Circulatory disease* National rates Regional rates	 37 37	SMR 0.74 (0.52–1.02) 0.88 (0.62–1.21)		(308)
North America							
Cohort: 3 530 male coke plant workers (2 369 white and 1 161 non-white) employed 1953 or before. *Referents:* total population of steel workers, 58 828 males from several plants in the US.	1953–1961	Mortality from heart disease and vascular lesions of CNS.	*All* Heart disease Vascular CNS lesions White workers Heart disease Vascular CNS lesions Non-white workers Heart disease Vascular CNS lesions	 111 28 87 17 24 11	SMR 0.98 1.15 1.07 1.11 0.76 1.22		(572)

Table A2. Coke production.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			Coke oven workers, all				
			Heart disease	49	0.80		
			Vascular CNS lesions	15	1.06		
			White workers				
			Heart disease	29	0.86		
			Vascular CNS lesions	6	0.94		
			Non-white workers				
			Heart disease	20	0.72		
			Vascular CNS lesions	9	1.15		
			Non-oven workers, all				
			Heart disease	62	1.20		
			Vascular CNS lesions	13	1.29		
			White workers				
			Heart disease	58	1.22		
			Vascular CNS lesions	11	1.24		
			Heart disease				
			Coke oven, all	49	0.80		
			Side oven	34	0.85		
			Partial topside	5	0.46		
			Full topside	10	0.94		
			Coke oven employment				
			< 5 y	24	0.93		
			≥ 5 y	25	0.70		

Table A3. Coal gasification.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Nordic countries							
Cohort: 295 gas production workers employed ≥ 1 y 1965–1972. *Referents:* rates from occupationally active and employed in Greater Stockholm or from the general population of Greater Stockholm.	1966–1986	Mortality (ICD-8) from circulatory disease (390–458), IHD (410–414) and CeVD (430–438).	*Cohort vs general pop.* Circulatory disease IHD CeVD *Cohort vs employed* Circulatory disease IHD CeVD *Years since first employment* 1–19 y Circulatory disease IHD 20–39 y Circulatory disease IHD ≥ 40 y Circulatory disease IHD *30 y after first employment* Employed 1–29 y Circulatory disease IHD Employed ≥ 30 y Circulatory disease IHD	 39 28 6 39 28 6 9 7 15 11 15 10 7 5 16 11	SMR 1.09 (0.77–1.48) 1.09 (0.73–1.58) 1.25 (0.46–2.72) 1.27 (0.90–1.74) 1.25 (0.83–1.81) 1.52 (0.56–3.31) 1.38 (0.63–2.52) 1.49 (0.60–3.07) 0.93 (0.52–1.53) 0.91 (0.46–1.64) 1.89 (1.06–3.12) 1.76 (0.85–3.25) 0.84 (0.34–1.74) 0.81 (0.26–1.90) 1.75 (1.00–2.84) 1.67 (0.83–2.99)	*Mean (range) exposure to BaP measured on top of ovens* 1964: 4.3 µg/m^3 (0.007–33). 1965: 0.52 µg/m^3 (0.021–1.29). 52% of workshop and maintenance workers were daily smokers. In a sample of the Swedish population 56–57% were daily smokers.	(365)

Table A3. Coal gasification.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Europe (non-Nordic)							
Cohort: 11 499 male production workers from 4 UK Gas Boards employed ≥ 5 y or in receipt of pension 1953. *Referents:* national rates from England and Wales.	1953–1961	Mortality from arteriosclerotic and degenerative heart disease (ICD-7).	*Exposure category* A. Heavy B. Intermittent C. Less/minimal/no Referents		Annual death rate/1 000 men 3.34 3.53 3.68 4.48	A: Coal carbonising process workers. B: Periodic entry into gas-producing plant and other process workers.	(236)
Cohort I: same as above. *Cohort II:* 4 687 male workers from 4 additional Gas Boards. *Referents:* national rates from England and Wales.	Cohort I: 1953–1965 Cohort II: 1957–1965	Mortality from arteriosclerotic and degenerative heart disease (ICD-7).	*Cohort I* Exposure category A. Heavy C. Less/minimal/no Referents *Cohort II* Exposure category A. Heavy B. Intermittent C. Less/minimal/no Referents	 119 27 47 59 70 	Annual death rate/1 000 men 4.63 3.54 5.41 5.65 5.09 4.81 5.00	Exposure categories as above.	(238)
North America							
Cohorts: 51 899 male workers employed ≥ 6 mo in Pacific Gas and Electric Company before 1986 and alive 1971. 513 male gas generator workers. *Referents:* US national and Californian male rates.	Until 1997	Mortality from heart disease and CeVD.	*All workers* Heart disease CeVD *Gas generator workers* Heart disease CeVD	 3 472 608 29 6	SMR [a] 0.86 (0.83–0.89) 0.91 (0.84–0.98) 0.74 (0.50–1.06) 1.06 (0.38–2.30)	*Employment start before 1970* All workers: 60% Gas generator workers: 49%. [a] Californian rates.	(111)

Table A4. Graphite electrode production.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Nordic countries							
Cohort: 901 Swedish electrode manufacturing workers (807 men, 94 women) employed > 3 mo 1968–1988. *Referents:* Swedish national rates standardised for age, gender, calendar time and geographical region.	1969–1989	Mortality (ICD-8) from circulatory disease (390–458), IHD (410–414) and CeVD (430–438).	Circulatory disease IHD CeVD *IHD, cumulative BaP exposure, µg/m³-y* 0–5 5–10 > 10	11 7 2 4 0 3	SMR 0.95 (0.47–1.69) 0.87 (0.35–1.80) 1.03 (0.12–3.70) 0.86 – 1.21	BaP was measured on six occasions 1974–1989 (n = 164). In the highest cumulative exposure group, the mean was 3 µg/m³. Smoking habits in 1990 among 181 male workers: current smokers 22%, ex-smokers 42% and non-smokers 35%. Corresponding figures for males in the county were 28%, 30% and 41%.	(360)
Europe (non-Nordic)							
Cohort: 1 115 male carbon electrode manufacturers employed on January 1957 in a French factory. *Referents:* French national population.	1957–1984	Mortality from circulatory disease (ICD-8, 390–458).	Circulatory disease	40	SMR 0.71 (0.51–0.97)	Mean BaP exposure: 170 ng/m³ (range 15–740), measured 1983–1984.	(677)
Cohort: 1 291 male graphite electrode manufacturing workers employed ≥ 1 y 1950–1989 in Brescia, Italy. *Referents:* Italian national and regional male rates (1970–1997).	1950–1997	Mortality (ICD-9) from circulatory disease (390–459) and silicosis (500, 502).	Circulatory disease Silicosis *Circulatory disease* Time since first employment < 10 y	126 79 4	SMR 0.88 (0.73–1.05) 66.4 (52.6–82.7) 0.86 (0.23–2.20)	The rods were baked at 850–1 200 °C in pit furnaces fed by naphtha and filled with a coke siliceous sand stuffing. The siliceous sand was replaced with rice husks in 1967.	(635)

Table A4. Graphite electrode production.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			10–19 y > 19 y Length of employment < 10 y 10–19 y > 19 y	23 99 21 42 63	1.48 (0.94–2.22) 0.81 (0.65–0.98) 0.92 (0.57–1.41) 0.83 (0.60–1.12) 0.90 (0.69–1.15)	All deaths from silicosis occurred among workers hired before 1967.	
Cohort: 1 006 male carbon (graphite) electrode manufacturing workers employed ≥ 1 y 1945–1971 in Umbria region, Italy. *Referents:* Italian national male population.	1955–1996	Mortality from circulatory disease (ICD-8, 390–459).	Circulatory disease	181	SMR 0.91 (0.78–1.06)	About half of the workers had been substantially exposed to PAH.	(240)
North America							
Cohorts: 2 219 white male workers employed in carbon based electrode and specialty products operations on 1 Jan 1974 and ≥ 10 y service in Union Carbide. *Referents:* US national white male rates.	1974–1983	Mortality (ICD-8) from circulatory disease and CeVD.	Circulatory disease CeVD *Circulatory disease* Supervisory, office employee Crafts Operators, labour Years of employment 10–19 y 20–29 y ≥ 30 y	91 11 24 18 49	SMR 0.60 (0.48–0.74) 0.67 (0.33–1.19) RR 0.8 1.4 1.0 0.5 1.1 1.1 P(trend):0.02	Conditional RRs were calculated.	(949)

Table A4. Graphite electrode production.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Asia							
Cohorts: 332 male workers employed in graphite electrode manufacturing plant > 5 y 1951–1974. *Referents:* rates from Vital Statistics of Japan.	1951–1988	Mortality (ICD-9) from CVD (420–438) and CeVD (430–438).	CVD CeVD	7 2	SMR 1.13 (0.46–2.33) 0.14 (0.02–0.50)	Mean BaP exposure: 32.2 and 55.7 µg/m^3 (highest 102 µg/m^3). Documents from 200 workers who resigned from the plant 1965–1969; 121 (60%) left the plant by the end of the 2nd year of employment. 166 worked with graphite electrode manufacturing, and 38 (23%) reported improper working environment and serious concern about health conditions as reason for resignation.	(671)

Table A5. Chimney sweeping.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Nordic countries							
Cohort: 6 374 male chimney sweeps from Swedish nationwide trade union records 1918–2006. *Referents:* Swedish national male rates.	1952–2006	Mortality (ICD-6–10) from circulatory disease, IHD and CeVD.			SMR		(453)
			Circulatory disease	724	1.18 (1.10–1.27)		
			IHD	462	1.20 (1.10–1.32)		
			Years of employment				
			> 0–9.9 y	95	1.29 (1.05–1.58)		
			10–19.9 y	89	1.40 (1.13–1.73)		
			20–29.9 y	64	1.07 (0.82–1.37)		
			≥ 30 y	214	1.14 (1.00–1.31)		
			CeVD	99	0.96 (0.78–1.16)		
			Years of employment				
			> 0–9.9 y	20	1.05 (0.64–1.62)		
			10–19.9 y	21	1.26 (0.78–1.92)		
			20–29.9 y	17	1.09 (0.63–1.74)		
			≥ 30 y	41	0.79 (0.56–1.07)		
Cohort: 4 436 male chimney sweeps from nationwide trade union records 1918–2006. *Referents:* skilled manual workers in the service sector in Sweden.	1991–2005	Lethal and non-lethal first-time MI (ICD-6–10).			SIR	Dust levels 3–19 mg/m^3 during most common work operations 1985–1986. Sweeping in private homes was associated with inhalable dust levels of 3.8 mg/m^3 and sweeping in industrial settings could exceed 1 000 mg/m^3. Exposure comprised dust, PAH and metals.	(362)
			MI	318	1.39 (1.24–1.55)		
			Years of employment				
			> 0–9 y	137	1.53 (1.28–1.81)		
			10–19 y	67	1.28 (0.99–1.63)		
			20–29 y	45	1.18 (0.86–1.59)		
			≥ 30 y	69	1.39 (1.08–1.76)		
			Years since 1st employment				
			20–29 y		1.54 (1.03–2.23)		
			≥ 30 y		1.36 (1.21–1.53)		
Males from Danish census 1970. *Cohort:* 713 chimney sweeps. *Referents:* employed.	1970–1975	Mortality from IHD (ICD-8, 410–414).	IHD	12	SMR 2.21, P < 0.05	No exposure information.	(381)

Table A6. Asphalt paving.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Pooled analysis *Cohort:* 12 367 male asphalt workers from 217 companies in Denmark, Finland, France, Germany, Israel, the Netherlands and Norway employed ≥ 1 work season in asphalt paving 1913–1999.	Earliest follow-up started 1953 and latest ended 2000.	Mortality (ICD-9) from circulatory disease (390–459) and IHD (410–414).	*Circulatory, average BaP exposure, ng/m³*		RR	Differences in smoking habits were an unlikely explanation for the observed exposure-response relationships.	(134)
			0–68	128	1.00		
			68–105	142	1.30 (1.01–1.67)		
			106–146	143	1.55 (1.18–2.05)		
			147–272	139	1.45 (1.09–1.93)		
			≥ 273	108	1.58 (1.16–2.15)	P(trend): < 0.001.	
			Circulatory, cumulative BaP exposure, ng/m³-y				
			0–189	137	1.00		
			189–501	145	1.08 (0.85–1.38)		
			502–931	118	1.06 (0.80–1.42)		
			932–2 012	132	1.24 (0.89–1.71)		
			≥ 2 013	128	1.42 (0.96–2.09)	P(trend): 0.09.	
			IHD, average BaP exposure, ng/m³				
			0–68	83	1.00		
			68–105	83	1.13 (0.82–1.55)		
			106–146	83	1.33 (0.94–1.90)		
			147–272	86	1.20 (0.84–1.71)		
			≥ 273	83	1.64 (1.13–2.38)	P(trend): 0.02.	
			IHD, cumulative BaP exposure, ng/m³-y				
			0–189	83	1.00		
			189–501	83	0.99 (0.72–1.36)		
			502–931	84	1.22 (0.86–1.74)		
			932–2 012	83	1.24 (0.82–1.85)		
			≥ 2 013	85	1.58 (0.98–2.55)	P(trend): 0.06.	

Table A7. Tar distillation work, roofing and creosote work.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Europe (non-Nordic)							
Cohort: 255 male tar distillery workers at 4 distillation plants, employed January 1967. *Referents:* regional population of England and Wales.	1967–1983	Mortality (ICD-8) from circulatory disease (390–458), IHD (410–414), CeVD (430–438), and diseases of arteries, arterioles, capillaries and veins (440–458).	*Circulatory disease* IHD CeVD Vessels *IHD, age at death* ≤ 54 y 55–64 y ≥ 65 y *IHD, time at death since joining tar plant* ≤ 19 y 20–39 y ≥ 40 y	45 29 7 5 8 9 12 17 10 2	SMR 1.19 (P = 0.14) 1.14 (P = 0.26) 1.03 2.42 (P = 0.06) 2.06 (P = 0.04) 1.06 0.93 1.69 (P = 0.03) 0.89 0.5	No exposure information.	(595)
Cohort: 907 male tar distillery workers and 866 male roofers employed ≥ 0.5 y 1947–1980. *Referents:* Dutch national male rates.	1947–1988	Mortality from circulatory disease (ICD-9).	*Circulatory disease* Tar workers Roofers	 119 114	SMR 0.78 (0.65–0.94) 1.00 (0.83–1.20)	No exposure information.	(927)

Table A7. Tar distillation work, roofing and creosote work.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
North America							
Cohort: 5 939 active, probational and retired males, members ≥ 9 y of a union of roofers and waterproofers in 1960. *Referents:* US national male rates.	1960–1971	Mortality from heart disease and cerebral vascular lesions (CeVD).	*Heart disease* Years since joining union 9–19 y ≥ 20 y *CeVD* Years since joining union 9–19 y ≥ 20 y	 179 518 27 101	SMR 0.95 0.99 0.84 0.88	No smoking information. Mean exposure was 1.4–53 µg BaP per 7-h working day.	(378)
Cohort: 2 179 employees (2 010 males, 169 females) at 11 wood-treating plants in the US using creosote-based preservatives 1979–1999. *Referents:* US national male rates.	1979–2001	Mortality (ICD-8) from all heart disease, IHD, chronic endo-cardial disease, all other heart disease, and CeVD.	*All cohort* All heart disease IHD Endocardial disease Other heart disease CeVD *Hourly employed* All heart disease IHD Endocardial disease Other heart disease CeVD *All heart disease* Length of employment < 15 y 15.0–24.9 y 25.0–34.9 y ≥ 35 y Time since first employment < 15 y	 88 52 5 29 14 81 47 5 27 13 40 13 18 10 15	SMR 0.91 (0.73–1.13) 0.73 (0.54–0.95) 1.15 (0.37–2.69) 1.16 (0.78–1.67) 0.89 (0.49–1.50) 0.96 (0.76–1.19) 0.76 (0.56–1.00) 1.30 (0.42–3.03) 1.21 (0.80–1.76) 0.93 (0.49–1.58) 1.34 0.56 (P < 0.05) 0.95 0.80 0.93	Approximately 90% of the employees were hourly salaried and with a generally higher exposure.	(1034)

Table A7. Tar distillation work, roofing and creosote work.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			15.0–24.9 y	29	1.20		
			25.0–34.9 y	18	0.82		
			≥ 35 y	19	0.85		
			IHD				
			Length of employment				
			< 15 y	21	0.98		
			15.0–24.9 y	8	0.46 (P < 0.05)		
			25.0–34.9 y	12	0.84		
			≥ 35 y	6	0.65		
			Time since first employment				
			< 15 y	7	0.62		
			15.0–24.9 y	15	0.85		
			25.0–34.9 y	11	0.67		
			≥ 35 y	14	0.83		

Table A8. Cooking fumes.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Nordic countries							
Manual workers in the service sector identified in the Swedish national census 1985. *Cohorts:* cooks (12 398 females and 3 779 males), cold buffet managers (1 948 and 17), waiting staff (4 532 and 2 218) and restaurant and kitchen assistants (15 049 and 1 331). *Referents:* skilled manual workers (for cooks, cold-buffet managers and waiting staff), and unskilled manual workers (for restaurant and kitchen assistants).	1987–2005	Incidence of first MI (ICD-9, 410; ICD-10, I21).	*Cooks* Males Females *Cold buffet managers* Males Females *Waiting staff* Males Females *Restaurant and kitchen assistants* Males Females	 201 609 2 56 110 167 86 595	HR 1.09 (0.94–1.27) 1.34 (1.21–1.48) 3.28 (0.82–13.12) 1.19 (0.91–1.55) 1.02 (0.84–1.24) 1.25 (1.06–1.47) 1.14 (0.93–1.41) 1.12 (1.03–1.21)	Adjustment for age, hypertension and diabetes.	(92)
All gainfully employed men and women identified in the Swedish national census 1970. *Cohorts:* cooks and cold buffet managers (12 348 females and 3 051 males), kitchen assistants (34 609 and 924) and waiting staff (27 802 and 3 745). *Referents:* all gainfully employed.	1970–1995	Mortality from IHD (ICD-7 and ICD-8, 410–414).	*Cooks and cold buffet managers* Males Females *Kitchen assistants* Males Females *Waiting staff* Males Females	 142 852 96 1 905 243 1 343	SMR 1.33 (1.12–1.56) 1.29 (1.20–1.37) 1.55 (1.26–1.90) 1.21 (1.14–1.26) 1.23 (1.08–1.39) 1.01 (0.95–1.06)	No smoking adjustment. An increased risk of IHD among male and female kitchen workers with the same occupation in both 1970 and 1980 was observed.	(882)

Table A8. Cooking fumes.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Case-control study: 26 847 Swedish men with first MI, 2 controls for each case.	Stockholm County: 1976–1984 Other counties: 1976–1981	Incidence of first MI, mortality (ICD-8, 410) and hospital discharges (410.00, 410.99).	*Kitchen assistants* Males Females *Waitresses* Males Females	 – – – –	RR No incr. or decr. [a] 1.4 (0.9–2.0) No incr. or decr. [a] 0.8 (0.6–0.9)	Adjustment for age, county and socio-economic group. [a] RR not shown.	(377)
All economically active men and women identified in the Finnish censuses 1970, 1975, 1980, 1985 and 1990. *Cohorts:* restaurant and kitchen workers. *Referents:* all economically active men and women 25–64 y of age in 1970, including nearly 6 million residents.	1971–1991	Mortality from CVD, MI, IHD other than MI, and CeVD.	*CVD* Restaurant service work, males Kitchen assistants, females Head waiters, restaurant waiters, females *MI* Kitchen assistants, females *IHD other than MI* Cooks and kitchen staff, females Kitchen assistants, females Head waiters, restaurant waiters, females *CeVD* All occupations in restaurants, males or females	 64 822 346 347 151 142 62 –	SMR 1.35 (1.04–1.72) 1.13 (1.06–1.21) 1.19 (1.07–1.33) 1.17 (1.06–1.31) 1.30 (1.11–1.54) 1.40 (1.18–1.65) 1.54 (1.19–1.98) No increased risk (SMRs not shown)	Adjustment for age.	(713)

Table A8. Cooking fumes.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Europe (non-Nordic)							
Study base: 77 081 women aged 15–59 y in 1971, comprising a 1% sample of the population of England and Wales. *Cohort:* cooks. *Referents:* all employed women.	1971–1981	Mortality from circulatory disease and IHD.	*Female cooks* Circulatory disease IHD	 8 8	SMR 1.80 3.60 (1.55–7.09)		(673)
Cohort: 1 798 male cooks who had retired from the Royal Army Catering Corps, UK, and were at the reserve list at any time 1974–1984. *Internal referents:* 1 310 referents retired from the Royal Army Pay Corps. *External referents:* national population.	1974–1989	Mortality from CVD, IHD and CeVD.	*National rates* CVD IHD CeVD *Internal referents* CVD IHD CeVD	 110 83 18 110 83 18	SMR 1.45 (1.19–1.75) 1.42 (1.13–1.76) 2.05 (1.22–3.24) SMR [a] 1.45 (1.07–1.96) 1.43 (1.01–2.02) 2.17 (0.94–4.99)	[a] Poisson regression analysis.	(183)

Table A9. Asbestos cement.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CIs)	Confounder adjustments and comments	Ref.
Nordic countries							
Cohort: 1 176 male asbestos cement workers employed > 3 mo 1943–1976. *Referents:* Swedish national male rates.	1951–1982	Mortality from circulatory disease.	Circulatory disease *Duration of exposure* Latency time 0 y < 2 y 2–4.9 y ≥ 5 y Latency time 20 y < 2 y 2–4.9 y ≥ 5 y	103	SMR 1.05 1.11 1.24 0.94 1.31 1.00 0.88	Fibre concentrations averaged 1 f/ml based on several hundred samples from five investigations 1970–1976. During earlier decades ventilation was inferior and the fibre concentration was estimated to have been 2 f/ml in accordance with total dust measurements. The vast majority of asbestos used was chrysotile, but 630 tons of amosite were used 1949–1951 and 400 tons of crocidolite in 1962.	(723)
Cohort: 1 929 male Swedish asbestos cement workers registered in the company personnel records 1907–1977 employed ≥ 3 mo. *Referents:* 1 233 Swedish industrial workers.	1927–1986	Mortality from heart disease (ICD-8, 410–429).	Heart disease *Latency time 20 y, cum exp, f/ml-y* < 15 15–39 ≥ 40	219	RR 1.1 (0.86–1.4) 1.1 (0.87–1.5) 0.9 (0.6–1.4) 1.2 (0.8–1.9) P(slope): 0.7	Estimated median cumulative exposure: 2–3 f/ml-y (median 1–2 f/ml, predominantly chrysotile). 13 cases of mesothelioma.	(14)
Cohort: 7 996 male Danish asbestos cement workers employed 1928–1984. *Referents:* Danish national male rates.	1943–1984	Mortality from circulatory disease (ICD-6–8, 410–429).	Circulatory disease	489	SMR 1.01 (0.92–1.11)	*Year and no. of particles (f/ml)* 1948: 50–800 1957: 10–100 1973: 41% of measurements > 2.	(767)

Table A9. Asbestos cement.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CIs)	Confounder adjustments and comments	Ref.
Europe (non-Nordic)							
Cohort: 1 510 men and 657 women employed 1941–1983 at an asbestos cement factory in England. *Referents:* national rates and local rates from the Tamworth Municipal Borough.	1941–1984	Mortality from circulatory disease (ICD-9, 390–459).	Circulatory disease *Males* National rates Local rates *Females* National rates Local rates	 172 54 	SMR 0.87 (0.74–1.01) 1.18 1.16 (0.87–1.51) 1.19	Measured personal airborne fibre concentrations available since 1970 showed mean levels < 1 f/ml. No excess of lung cancer and one case of mesothelioma.	(326)
Cohort: 2 525 male and 591 female asbestos cement workers employed ≥ 3 mo 1959–1980. *Referents:* Polish general population.	Until 1991	Mortality (ICD-9) from circulatory disease (390–459), IHD (410–414) and CeVD (430–438).	*Males* Circulatory disease IHD CeVD *Females* Circulatory disease CeVD	 148 65 17 8 2	SMR 0.83 (0.78–0.98) 0.96 (0.74–1.22) 0.77 (0.45–1.23) 0.69 (0.30–1.36) 0.85 (0.10–3.07)	Mainly chrysotile. 1970–mid 1980 20% of the asbestos was crocidolite and amosite. An excess of mesothelioma was found, 7 vs 0.2 expected.	(934)
Cohort: 200 male and 62 female asbestos cement workers employed in 1963 and newly employed 1963–1981 in a Carrara plant, Italy. *Referents:* general population of Toscana, Italy.	1963–2003	Mortality from CVD (ICD-9, 390–458).	*CVD* Males Females	 30 8	SMR 0.96 (0.65–1.37) 0.62 (0.27–1.21)	Exposure was to a mixture of chrysotile and crocidolite asbestos in a ratio of 2:5. An excess of pleura tumours was found, 4 vs 0.16 expected.	(765)
Cohort: 2 712 male and 646 female asbestos cement workers 1952–1987 from 10 plants in Emilia-Romagna, Italy.	1952–1998	Mortality from CVD (ICD-9, 390–459).	CVD	164	SMR 0.99 (0.84–1.15)	This cohort was previously followed until 1989. Asbestos concentrations were up to 40 f/ml prior to 1975 and < 0.5 f/ml in the late 1980s (335).	(579)

Table A9. Asbestos cement.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CIs)	Confounder adjustments and comments	Ref.
Referents: general population of Emilia-Romagna, Italy.						An excess of pleura tumours was found, 18 vs 0.94 expected.	
Cohort: 1 247 male asbestos cement workers employed 1950–1986 in a plant in Naples, Italy. *Referents:* general population of the Campania Region, Italy.	1965–2005	Mortality (ICD-9) from CVD (390–459) and IHD (410–414).	CVD IHD *CVD, latency time* 0–19 y 20–29 y 30–39 y ≥ 40 y	124 41 10 28 40 46	SMR 0.57 (0.48–0.68) 0.47 (0.34–0.64) 0.51 (0.25–0.94) 0.65 (0.43–0.94) 0.62 (0.44–0.84) 0.51 (0.38–0.68)	An excess of pleura tumours was found, 24 vs 0.9 expected. In 1979, total asbestos concentrations were 0.03–1.033 f/ml, while crocidolite concentrations were 0.250–0.526 f/ml.	(632)
Cohort: 317 asbestos cement workers exposed ≥ 5 y 1968–2006 in a plant near Thessaloniki, Greece. *Referents:* Greek male population.	1968–2006	Mortality from circulatory disease.	Circulatory disease	23	SMR 0.77 (0.49–1.16)	*Asbestos fibre concentrations (f/ml)* Before 1980: 3.5–6.5 1981–1983: 1.1–1.7 After 1983: < 1.	(865)
North America							
Cohort: 6 931 males employed ≥ 1 mo before 1970 in 2 asbestos cement products manufacturing plants in New Orleans, Louisiana. *Referents:* US and Louisiana male populations.	1970–1982	Mortality from CVD (ICD-8, 390–448).	*CVD* ≥ 20 y after initial exposure	638	SMR 0.88	Employed after 1942 in plant A and after 1937 in plant B. *Mean exposure (mppcf-y)* Plant A: 7.8 Plant B: 7.5.	(427)

Table A9. Asbestos cement.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CIs)	Confounder adjustments and comments	Ref.
Cohort: 535 asbestos-exposed workers from an asbestos-cement factory in Ontario, Canada. Hired before 1960 and employed ≥ 1 y. *Internal referents:* 205 non-exposed workers from the same factory. *External referents:* Ontario male population.	1960–1981	Mortality from IHD (ICD-8, 410–414).	*IHD, y since first exposure* 10–14 y Production workers Factory controls 15–19 y Production workers Factory controls 20–34 y Production workers Factory controls *20 y latency from first exposure* Factory controls Production workers Cum exposure, f/ml-y ≤ 30 30.1–75 75.1–105 105.1–150 > 150	 4 1 7 4 10 11 11 10 1 1 3 4 1	SMR 0.86 0.35 0.98 1.00 0.58 1.06 Rate/1000 man-y 6.4 1.0 1.5 6.7 17.8 2.4	This study is also presented in reference (292). Exposure sampling started in 1969. Exposures were assumed to be the same 1962–1970, 30% higher 1955–1961, and twice as high 1948–1954. There were exposure-response relationships regarding both lung cancer and mesothelioma. Mortality rate/1 000 man-y, standardised to the age and latency distribution of the cohort as a whole for the period beyond 20 y from first exposure. P(trend): > 0.3.	(293)

Table A10. Miscellaneous asbestos exposures.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Nordic countries							
Cohort: 238 (192 men, 46 women) quarry workers employed ≥ 1 y. *Referents:* Finnish population.	1923–1980	Mortality from CVD (ICD-8, 390–458).	*CVD, all* Males Females *CVD, highest exposures* Males Females	 40 9 28 4	SMR 1.01 0.99 1.10 1.33	Exposure was to wollastonite fibres which are similar to amphibole asbestos fibres in form, length and diameter but mineralogically different. Highest exposures: drilling, transport and crushing.	(431)
Europe (non-Nordic)							
Cohort: 878 asbestos textile workers in Rochdale, UK. *Referents:* national rates from the Registrar-General.	1916–1966	Mortality from circulatory disease (ICD-codes 400–468, according to classification at relevant period).	*Circulatory disease, men* Exposure duration, > 20 y, > 10 y before 1933 (57 men) > 20 y, < 10 y before 1933 (63 men) > 20 y, 0 y before 1933 (136 men) 10–19 y, 0 y before 1933 (538 men)	 13 8 9 24	 5.33 expected (P: 0.003) 5.66 expected (P: 0.211) 4.03 expected (P: 0.022) 22.6 expected (P: 0.412)	Chrysotile was predominantly used, but also small amounts of crocidolite. In 1933, ventilation was introduced in carding and weaving. *Exposure concentrations* 1961: 2–8 f/ml 1966: 1–8 f/ml.	(501)
Cohorts: asbestos textile workers in Rochdale, UK. Same factory as above. A: 145 men employed ≥ 20 y, including some time before 1933. B: 283 women first employed 1933–1962, total employment ≥ 10 y,	Until 1983	Mortality from circulatory disease (ICD-codes not given).	Circulatory disease (vs national rates) *Cohort A* ≥ 10 y before 1933 < 10 y before 1933 *Cohort B* Employed 1933–1950 Employed 1950–1974 *Cohort C*	 26 23 10 0	SMR 1.94 1.22 0.81 3.29 expected	Conditions were much dustier before 1933 than after. *Exposure 1951–1955* 157–978 particles/ml (5–28 f/ml). *Exposure 1956–1960* 153–978 particles/ml (4–28 f/ml). *Exposure 1961–1970*	(744)

Table A10. Miscellaneous asbestos exposures.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
C: 3 211 men employed 1933–1974. *Referents:* national rates from England and Wales, and local Rockdale rates.			Exposure < 10 y Exposure ≥ 10 y	407 129	1.16 1.10	2.5–20 f/ml. *Exposure 1971–1974* 2.5–7.5 f/ml.	
Cohort: 94 403 men and 4 509 women from the 1971 Asbestos Workers Survey in Great Britain. Main activities were manufacturing and removal. *Referents:* national rates from Great Britain.	1971–2005	Mortality from IHD (ICD-9, 410–414; ICD-10, I20–I25) and CeVD (ICD-9, 430–438; ICD-10, I60–I69).	*IHD* Males Females Exposure duration < 10 y 10–19 y 20–29 y 30–39 y ≥ 40 y *CeVD* Males Females Exposure duration < 10 y 10–19 y 20–29 y 30–39 y ≥ 40 y	 3 870 175 933 90 	SMR 1.28 (1.24–1.32) 1.61 (1.38–1.87) RR 1 1.16 (1.03–1.30) 1.10 (0.98–1.24) 1.15 (1.02–1.30) 1.25 (1.10–1.42) SMR 1.51 (1.42–1.61) 1.86 (1.49–2.28) RR 1 1.20 (0.93–1.56) 1.05 (0.80–1.37) 1.04 (0.79–1.38) 1.22 (0.93–1.62)	Adjustment for age and smoking. Duration of exposure was significantly related to IHD. Lack of information regarding individual exposure. The model included job, year of birth, duration of exposure, sex, age attained, and smoking status.	(382, 383)
Cohort: 31 302 stripping/ removal workers from the 1971 Asbestos Workers Survey in Great Britain. *Referents:* national rates from England, Wales and	1971–2005	Mortality from circulatory disease, IHD and CeVD.	Weekly hours stripping *Circulatory disease* < 10 h 10–<20 h 20–<30 h 30–<40 h	 133 16 28 32	RR 1.0 0.8 (0.5–1.4) 1.1 (0.7–1.6) 1.4 (0.9–2.1)	RR adjusted with Poisson regression for age, calendar period and sex.	(317)

Table A10. Miscellaneous asbestos exposures.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Scotland.			≥ 40 h	47	1.7 (1.2–2.4)		
			IHD				
			< 10 h	86	1.0		
			10–<20 h	12	1.0 (0.5–1.8)		
			20–<30 h	16	0.9 (0.6–1.6)		
			30–<40 h	24	1.6 (1.0–2.6)		
			≥ 40	32	1.9 (1.2–2.8)		
			CeVD				
			< 10 h	21	1.0		
			10–<30 h	10	1.4 (0.6–2.9)		
			30–<40 h	10	1.2 (0.6–2.7)		
			≥ 40 h	–			
Cohort: 933 male chrysotile asbestos miners employed ≥ 30 d 1930–1965 in Balangero, North Italy. *Referents:* Italian national rates.	1946–1975	Mortality from CVD (ICD-7, 400–468).	*CVD*	122	SMR 1.48 (P < 0.01)	When cumulative exposure ≥ 101 f/ml-y was compared with ≤ 100 f/ml-y, the RR was 1.27.	(806)
			Years since 1st exposure				
			≤ 19 y	22	1.49		
			≥ 20 y	100	1.48 (P < 0.01)		
Cohort: 1 058 male chrysotile asbestos miners who had worked ≥ 1 y 1946–1987 in Balangero, North Italy. *Referents:* Italian national rates.	1946–1987	Mortality from unspecified CVD, IHD and stroke.	CVD	100	SMR 1.63	No relationship with duration of exposure.	(751)
			IHD	37	0.8		
			Exposure duration				
			< 10 y	16	0.8		
			10–20 y	11	1.1		
			> 20 y	10	0.6		
			Stroke	31	1.0		
			Exposure duration				
			< 10 y	20	1.4		

Table A10. Miscellaneous asbestos exposures.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			10–20 y > 20 y	2 9	0.3 0.9		
Cohort: 1 056 male chrysotile asbestos miners who had worked ≥ 1 y 1930–1975 in Balangero, North Italy. *Referents:* Italian national rates before 1981 and regional rates from the province of Turin 1981–2001.	1946–2003	Mortality from circulatory disease (ICD-9, 390–459), IHD and CeVD.	Circulatory disease IHD CeVD	212 59 38	SMR Not given [a] 0.93 (0.71–1.20) 0.90 (0.64–1.24)	Workers employed 1930–1945 who did not survive until January 1946 were excluded. The mine was closed in 1990. [a] The excess mortality from circulatory disease contributed an important no. of excess deaths (no expected numbers presented). Excessive alcohol intake might explain some of the excess; SMR for liver cirrhosis 2.9 (2.2–3.8).	(752)
Cohort: 1 534 male railway carriage construction workers employed 1970 or hired 1970–1989. *Referents:* regional male rates from Regione Campania, Italy.	1970–1989	Mortality from circulatory disease.	Circulatory disease	58	SMR 0.64 (0.51–0.80)	3 cases of pleural cancer: SMR 4.72 (1.3–12.2).	(631)
Cohort: 734 workers in railway carriage construction and repair employed 1945–1969. *Referents:* regional rates from Tuscany Region, Italy.	1970–1997	Mortality from circulatory disease (ICD-8 and ICD-9).	Circulatory disease	55	SMR (90% CI) 0.73 (0.58–0.92)	5 cases of malignant pleural neoplasms: SMR 13.3 (90% CI 5.23–27.9) of which 4 were confirmed cases of mesothelioma.	(70)

Table A10. Miscellaneous asbestos exposures.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
North America							
Cohort: 3 641 men employed ≥ 1 mo 1938–1958 in a plant producing friction materials and packings in Connecticut. *Referents:* regional rates from Connecticut, US.	Until 1977	Mortality (ICD-7) from heart disease (400–443) and CeVD (330–334).	*Heart disease 20 y after first employment* Duration of service < 1 y 1–< 5 y 5–< 20 y ≥ 20 y *CeVD 20 y after first employment* Duration of service < 1 y 1–< 5 y 5–< 20 y ≥ 20 y *Heart disease 20 y after first employment, cum exp, mppcf-y* < 10 10–< 2 20–< 40 40–< 80 ≥ 80 *CeVD 20 y after first employment, cum exp, mppcf-y* < 10 10–< 20 20–< 40	 322 99 79 44 100 67 18 14 15 20 60 14 13 18 13 43 8 7	SMR 1.03 1.25 1.05 0.84 0.93 1.20 1.38 1.08 1.43 1.02 1.02 0.84 0.77 1.06 0.93 1.23 1.02 1.18	Until 1957, only chrysotile was used in the production and after that also a little anthophyllite. No cases of mesothelioma. SMR for respiratory cancer was 1.49 for the total cohort, 1.67 for men with exposure < 10 mppcf-y and 1.63 for men with exposure 40–80 mppcf-y. The authors considered the possibility that the short-term employees had worked in other hazardous industries before or after employment in the asbestos plant. This appeared to explain nearly all deaths from pneumoconiosis. Of 12 deaths from pneumo-coniosis all but 2 were ascribed to anthraco-silicosis or silicosis and none to asbestosis.	(615)

Table A10. Miscellaneous asbestos exposures.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			40–< 80	5	1.17		
			≥ 80	4	1.35		
Cohort: 4 137 men employed ≥ 1 mo 1938–1959 in a plant manufacturing mainly textiles but also friction products and packings in Pennsylvania. *Referents:* regional rates from Pennsylvania, US.	Until 1977	Mortality (ICD-7) from heart disease (400–443) and CeVD (330–334).	*Heart disease 20 y after first employment*	385	SMR 1.09	Chrysotile was the main type of asbestos used; 3 000–6 000 tons annually. Crocidolite and amosite were used from 1924 onwards for making insulation blankets, for locomotives and turbines and equipment for chemical factories and paper mills. In 1943, the use of amosite reached a peak of 600 tons. About 1939, exhaust ventilation was installed in the textile mill. 14 mesothelioma cases (10 pleural, 4 peritoneal). The SMR for respiratory cancer was 1.05 for all the cohort, but risk rose linearly from 0.67 for men with <10 mppcf-y to 4.16 for those with ≥80 mppcf-y.	(614)
			Duration of service				
			< 1 y	77	0.93		
			1–< 5 y	77	1.25		
			5–< 20 y	78	1.00		
			≥ 20 y	153	1.16		
			CeVD 20 y after first employment	47	0.81		
			Duration of service				
			< 1 y	7	0.55		
			1–< 5 y	10	1.07		
			5–< 20 y	10	0.78		
			≥ 20 y	20	0.88		
			Heart disease 20 y after first employment, cum exp, mppcf-y				
			< 10	221	1.03		
			10–< 20	41	0.89		
			20–< 40	60	1.31		
			40–< 80	34	1.31		
			≥ 80	29	1.09		
			CeVD 20 y after first employment, cum exp, mppcf-y				
			< 10	27	0.78		
			10–< 20	1	0.13		

Table A10. Miscellaneous asbestos exposures.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			20–<40 40–<80 ≥ 80	10 8 1	1.34 1.87 0.29		
Cohort: 820 male amosite asbestos factory workers in Paterson, New Jersey, recruited 1941–1945. *Referents:* white male population of New Jersey, US.	1945–1982	Mortality from CVD (ICD-7–9).	*Years since first exposure* 5–9 y 10–14 y 15–19 y 20–24 y 25–29 y 30–34 y 35–39 y	 16 29 41 47 49 29 21	SMR 0.64 0.92 1.11 1.30 1.44 (P < 0.05) 1.10 1.14	Underlying cause of death coded according to best evidence available. Amosite was used virtually exclusively; no crocidolite, very little chrysotile. Estimated median fibre exposure; 50 f/ml. 17 mesothelioma cases (8 pleural, 9 peritoneal). SMR for respiratory cancer significantly increased after 10 y since onset of work.	(853)
Cohort: 406 vermiculite mine workers in Libby, Montana, employed ≥ 1 y before 1963. *Referent:* US white male population.	1963–1999	Mortality from circulatory disease (ICD-9, 390–459).	Circulatory disease	104	SMR 0.95 (0.77–1.15)	The miners were exposed to fibrous tremolite, an amphibole asbestiform mineral. Before 1970, fibre concentrations were very high at many locations, especially in the dry mill, where they were estimated to > 100 f/ml. After that levels fell and by 1980 almost all were < 1 f/ml.	(618)

Table A10. Miscellaneous asbestos exposures.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
						There was a significantly increased risk of respiratory cancers.	
Cohort: 1 862 vermiculite workers exposed to Libby amphibole ≥ 6 mo before the mine closed 1990. *Referent:* US national rates.	Until 2006	Mortality from heart disease (ICD-9–10), IHD (ICD-9, 410–414, 429.2; ICD-10, I20–I22, I24–I25, 151.3, 151.6), other heart disease (ICD-9, 420–423, 428, 429.0–429.1, 429.3–429.9), diseases of the circulatory system (ICD-9, 430–438, 401, 403, 405, 415–417, 440–459), hypertension without heart disease (ICD-9, 401, 403, 405), diseases of arteries, veins or lymphatic vessels (ICD-9, 415–417, 440–459) and CVD (ICD-9,	*Heart disease* IHD Other heart disease *Circulatory disease* Hypertension Vessels *CVD with 20-y lag, cum exp, f/ml-y* < 1.4 1.4–< 8.6 8.6–< 44.0 ≥ 44.0	552 247 120 258 42 136 97 125 107 114	SMR 0.9 (0.9–1.0) 0.7 (0.6–0.8) 1.5 (1.2–1.8) 1.4 (1.2–1.6) 1.7 (1.2–2.4) 1.7 (1.4–2.0) RR 1.0 1.3 (1.0–1.6) 1.3 (1.0–1.6) 1.5 (1.1–2.0) Model P-value 0.0067	Libby vermiculite also contains actinolite and unregulated asbestos-like fibres, including winchite and richterite. 19 cases of mesothelioma. Lung cancer RRs increased monotonically with cumulative fibre exposure. Smoking was an unmeasured confounder for much of this cohort. Based on smoking data available for 336 workers who participated in a screening, the proportion of smokers was 50–66% among the unexposed and 66–85% among the exposed. With a Monte Carlo-approach the adjusted and unadjusted RRs for CVD were 1.5 and 1.6, respectively.	(539)

Table A10. Miscellaneous asbestos exposures.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
		410–414, 426–438, 440–448; ICD-10, I25, I70–I79).					
Cohort: 5 770 asbestos textile workers (3 975 males, 1 795 females) from 4 plants in North Carolina, exposed ≥ 1 d 1950–1973. *Referents:* US national population.	1950–2003	Mortality (ICD-6–10) from diseases of the heart and other circulatory disease.	Heart disease Other circulatory disease	730 229	SMR 1.32 (1.22–1.42) 1.47 (1.29–1.66)	Only chrysotile was used except for one plant in which limited amounts of amosite was used around 1963–1976. Mean cumulative exposure: 17.1 f/ml-y (range < 0.1–2 943). Increased risk of mesothelioma based on 4 cases (SMR 10.9, 95% CI 3.0–28.0). 36 deaths from asbestosis.	(576)
Cohort: 1 261 white male chrysotile textile workers from South Carolina, exposed ≥ 1 mo 1940–1965. *Referents:* US population.	1940–1975	Mortality (ICD-7) from diseases of the circulatory system (400–468) and vascular lesions of the CNS (330–334, 345).	Circulatory disease Vascular CNS lesions *Circulatory disease, cum exposure, f/ml-d* < 1 000 1 000–10 000 10 000–40 000 40 000–100 000 > 100 000	105 15 34 24 24 8 2	SMR 1.25 (P < 0.05) 1.37 1.39 1.12 1.58 (P < 0.05) 1.23 1.57	Only 1 mesothelioma (peritoneal) was observed. Several deaths from cancer of the abdomen (suspected mesothelioma, but no autopsies were performed). An exposure-response relationship was found for lung cancer.	(224)
Cohort: 3 022 chrysotile textile workers from South Carolina, exposed ≥ 1 mo	1940–1990	Mortality (ICD-9) from heart disease (390–398, 402,	*Heart disease* All White males	 414 226	SMR (90% CI) 1.22 (1.12–1.32) 1.41 (1.26–1.58)	Chrysotile was the only type of asbestos processed as raw fibre. Crocidolite yarn was	(223)

Table A10. Miscellaneous asbestos exposures.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
1940–1965. *Referents:* US population.		404, 410–414, 420–429), IHD (410–414) and CeVD (430–438).	White females Black males *IHD* All White males White females Black males *CeVD* All White males White females Black males	106 82 321 188 76 57 75 31 22 22	1.13 (0.95–1.32) 0.96 (0.79–1.16) 1.25 (1.13–1.37) 1.43 (1.26–1.61) 1.10 (0.90–1.33) 1.02 (0.81–1.27) 1.12 (0.91–1.35) 1.50 (1.08–2.02) 0.93 (0.63–1.32) 0.93 (0.66–1.40)	used in small quantities (~ 2 000 pounds crocidolite and 6–8 million pounds/y of chrysotile) from 1950s until 1975. Crocidolite was never carded, spun, or twisted: thus, the predominant exposure by far was to chrysotile asbestos. Most changes to control dust exposures were in place by 1940 and processes remained fairly constant from 1940 until production ceased in the late 1970s. Median cumulative exposures for white males, white females and black males were 1 462, 1 531 and 5 316 f/ml-d, respectively. 2 cases of mesothelioma (white males). The lung cancer risk increased by 2% for each f/ml-y.	
Cohort: 3 072 chrysotile textile workers from South Carolina, exposed ≥ 1 mo 1940–1965. In principle the same cohort as above (223).	1940–2001	Mortality (ICD according to the revision at the time of death) from heart disease, IHD, other disease of	Cohort vs US rates *Heart disease* All White males Non-white males Females *IHD*	 594 295 101 198	SMR 1.20 (1.10–1.30) 1.38 (1.23–1.55) 0.95 (0.77–1.15) 1.12 (0.97–1.29)	3 cases of mesothelioma. A strong exposure-response relationship between estimated chrysotile exposure and lung cancer mortality.	(396)

Table A10. Miscellaneous asbestos exposures.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Referents: US and South Carolina populations.		the heart, other disease of the circulatory system, and CeVD.	All White males Non-white males Females *Other heart disease* All White males Non-white males Females *Other circulatory disease* All White males Non-white males Females *CeVD* All White males Non-white males Females	469 250 70 149 81 28 20 33 185 65 42 78 131 49 28 54	1.20 (1.10–1.32) 1.39 (1.22–1.58) 0.92 (0.72–1.17) 1.11 (0.94–1.30) 1.27 (1.01–1.58) 1.28 (0.85–1.86) 1.16 (0.71–1.78) 1.34 (0.92–1.88) 1.28 (1.10–1.47) 1.46 (1.12–1.86) 1.11 (0.80–1.50) 1.25 (0.99–1.56) 1.29 (1.08–1.53) 1.70 (1.25–2.24) 1.03 (0.69–1.49) 1.19 (0.90–1.56)		
Cohort: 1 130 former workers of a plant in Tyler, Texas, manufacturing asbestos pipe insulation materials containing amosite 1954–1972. The mortality analysis included 753 men ≥ 10 y since first employment. Black men and women	Until 1993	Mortality (ICD-9) from all heart disease and CeVD.	All heart disease CeVD	60 13	SMR 1.18 (0.90–1.52) 2.21 (1.17–3.77)	81% current or ex-smokers. Duration of employment: 1 d to 17.3 y, mean (median) 12.7 (1.6) mo. Exposure levels measured in 1967, 1970 and 1971 were 15.9–91.4 f/ml. 6 mesothelioma cases (4 pleural and 2 peritoneal).	(555)

Table A10. Miscellaneous asbestos exposures.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
were excluded. *Referents:* US population.							
Cohort: 2 833 white men who worked in the US asbestos products industry 1948–1951. Most men worked in the asbestos textile industry. *Referents:* US white male population.	1948–1963	Mortality (ICD-7) from CVD (400–468), heart disease (400–443), CHD (420), hyper-tensive heart disease (440–443) and stroke (330–334).	 CVD Heart disease CHD Hypertension Stroke	 130 122 87 14 9	SMR 1.18 1.19 1.04 2.41 (P < 0.05) 0.68	There was a significantly increased risk for respiratory cancers (24 vs 11.9 expected).	(256)
Cohort: 1 464 men retired from the US asbestos industry during 1941–1967 (1 026 production workers and 438 maintenance-service workers). *Referents:* US white male population.	1941–1969	Mortality (ICD-7) from all heart disease (400–443), CHD (420), all other heart disease, and stroke (330–334).	 *All heart disease* Cum exposure, mppcf-y < 125 125–249 250–499 500–749 ≥ 750 *CHD* Cum exposure, mppcf-y < 125 125–249 250–499 500–749 ≥ 750 *All other heart disease* Cum exposure, mppcf-y < 125	 362 168 72 75 36 11 275 129 59 55 24 8 87 39	SMR 1.08 1.04 1.10 1.02 1.53 (P < 0.05) 0.89 1.04 1.03 1.13 0.95 1.28 0.81 1.20 1.07	Other heart diseases included *cor pulmonale*. Average duration of employment 25 (3–51) y. Historical exposure levels sometimes > 50 mppcf. 6.4% of production workers and 4.3% of maintenance service workers had retired due to disability. There was almost a linear relationship between asbestos exposure and respiratory cancer. 1 case of mesothelioma.	(255)

Table A10. Miscellaneous asbestos exposures.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			125–249 250–499 500–749 ≥ 750 *Stroke* Cum exposure, mppcf-y < 125 125–249 250–499 500–749 ≥ 750	13 20 12 3 68 31 14 15 5 3	0.98 1.29 2.55 (P < 0.05) 1.25 0.80 0.74 0.86 0.82 0.89 1.00		
Cohort: 1 074 white men retired from a US asbestos company 1941–1967. *Referents:* US white male population.	1941–1980	Mortality (ICD-7) from all heart disease (400–443), CHD (420), other heart disease, and stroke (330–334).	All heart disease CHD Other heart disease Stroke	395 315 53 85	SMR 1.12 (P < 0.05) 1.12 (P < 0.05) 1.13 0.92	Average duration of employment: 25 (3–51) y. The relationship between asbestos exposure and respiratory cancer was linear. 8 mesothelioma cases.	(259)
Cohort: 17 800 male members of the International Association of Heat and Frost Insulators and Asbestos Workers in the US and Canada. *Referents:* 73 763 white male workers with a history of occupational exposure to dust, fumes, vapours, gases, chemicals	1967–1976	CVD mortality	*CVD* Referent workers Referent workers US rates US rates	 638 566 638 566	RR 0.97 DC 0.86 BE 0.85 DC 0.75 BE	Cause of death according to: DC: death certificate BE: best evidence available.	(379)

Table A10. Miscellaneous asbestos exposures.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
or radiation, and US white male national rates.							
Cohort: 11 000 men born 1891–1920 and employed ≥ 1 mo in the chrysotile mines and mills of Quebec. Follow-up of 5 335 men alive in 1976 and ≥ 55 y old. *Referents:* Quebec male rates.	1976–1988	Mortality (ICD 8–9) from all IHD (410–413), other heart disease (391, 392.0, 402, 415–429) and CeVD (430–438).	IHD Other heart disease CeVD *IHD ≥ 20 y after first employment, cum exp, mppcf-y* < 30 30–< 100 100–< 300 ≥ 300 *CeVD, cum exp, mppcf-y* < 30 30–< 100 100–< 300 ≥ 300	 828 185 225 302 155 166 181 81 32 44 59	SMR 1.02 1.00 1.06 0.92 0.97 1.09 1.24 0.89 0.79 1.16 1.62	No adjustment for smoking habits. 25 cases of mesothelioma.	(619)
Australia							
Cohort: 6 498 males who had worked at the Wittenoom crocidolite mine and mill in Australia at any time 1943–1966. *Referents:* male rates from Western Australia.	Until 2000	Mortality from circulatory disease (ICD-7–10).	Circulatory disease	699	SMR 0.79 (0.73–0.85) [a] 1.35 (1.25–1.45) [b]	[a] Lost to follow-up assumed alive at 2000. [b] Lost to follow-up censored at their date last known to be alive. 316 mesothelioma cases (190 pleural and 32 peritoneal).	(687)

Table A10. Miscellaneous asbestos exposures.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 411 women employed in the mining and milling of crocidolite at Wittenoom 1943–1966. *Referents:* female rates from Western Australia.	Until 1980	Mortality from circulatory disease (ICD-codes not given).	Circulatory disease	6	SMR 0.60 (0.27–1.32) [a] 1.03 (0.46–2.29) [b]	[a] Lost to follow-up assumed alive at 1980. [b] Lost to follow-up censored at their date last known to be alive.	(46)
Asia							
Cohort: 1 932 chrysotile asbestos miners in China who worked ≥ 1 y 1981–1988. Exposed: miners, blasters, mechanics, and maintenance and transport workers. Not directly exposed (internal referents): management and service workers. *Referents:* Chinese national rates.	1981–2010	Mortality from CVD and CeVD.	*National rates* CVD CeVD *Internal referents* CVD CeVD	 56 50 56 50	SMR 1.27 (0.96–1.63) 1.38 (1.03–1.79) RR 1.30 (0.79–2.14) 1.75 (1.00–3.08)	In 2009, dust concentrations were 4.3–196.7 mg/m^3. There was a significantly increased risk for pulmonary heart disease, SMR 2.70. The RR was adjusted for gender and smoking habits. No cases of mesothelioma.	(242)

Table A11. Asbestosis and pleural plaques as proxies for asbestos exposure.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Nordic countries							
Cohort: 1 725 male shipyard workers born 1910–1929, exposed to asbestos in Sweden, 80 died from IHD. Indicators of exposure were asbestosis or pleural plaques. *Internal comparison (referents):* men with asbestosis or suspected asbestosis vs men without asbestosis. Men with pleural plaques vs men without pleural plaques.	1977–1988	Mortality from IHD (ICD-8, 410–414).	*IHD* Asbestosis or suspected asbestosis Pleural plaques		RR 3.1 (1.5–6.4) 1.3 (0.8–2.0)	Adjustment for age and smoking habits.	(825)
Case-control study *Cases:* 148 patients (101 men, 47 women) referred to Helsinki hospital for coronary angio-graphy. *Controls:* 100 lung cancer patients (72 men, 28 women) from the same hospital.		Patients referred to hospital for coronary angio-graphy.	*Prevalence of calcified pleural plaques* Cases, 35 % Controls, 19%	 52 19	RR 2.19 (1.44–3.32)	Adjustment for age and gender.	(507)
Cohort: 584 (574 men, 10 women) asbestos-exposed construction workers screened with computed tomography (CT), 1996–1997.	Until 2007–2008	Mortality from CVD (ICD-10, I00–I99).	*CVD* Paraseptal Emphysema bullae	64	HR 1.32 (1.11–1.56) 1.19 (1.01–1.41)	85 workers had asbestosis and probably all had pleural plaques.	(997)

Table A11. Asbestosis and pleural plaques as proxies for asbestos exposure.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 633 (627 men, 6 women) asbestos-exposed workers investigated with HRCT. Workers participating in a screening program 1990–1992, and workers with asbestosis or asbestos-related pleural pathology visiting clinics in Helsinki or Tampere, Finland.	Until 2013	Mortality from CVD (ICD-10, I00–I99).	*CVD* Emphysema Visceral pleural abnormalities Bronchial wall thickening	38	HR 1.09 (1.02–1.12) 2.36 (1.16–4.80) 1.69 (0.80–3.54)	HRCT: high-resolution computed tomography. Cox regression with adjustment for age, sex, smoked pack-years and asbestos exposure index. Almost all had parietal pleural abnormalities.	(996)
Europe (non-Nordic)							
Cohort: 233 asbestos cement workers employed by a company in Bari, Italy, and compensated for asbestosis. *Referents:* regional population of Apulia Region, Italy.	1979–1997	Mortality from circulatory disease (ICD-9).	Circulatory dis.	18	SMR (90% CI) 0.64 (0.41–0.95)	Criteria for compensation were not described and changed over time (presented in Italian). Mortality (observed vs expected): Pneumoconiosis: 14 vs 0.12 Pleural tumours: 4 vs 0.16.	(81)
Cohort: 631 Italian women compensated for asbestosis. *Referents:* Italian female population.	1980–1997	Mortality (ICD-9) from circulatory disease (390–459), hypertension (401–404), IHD (410–414) and CeVD (430–438).	Circulatory dis. Hypertension IHD CeVD	77 10 12 25	SMR 0.89 (0.70–1.12) 1.47 (0.70–2.70) 0.53 (0.28–0.93) 0.87 (0.56–1.28)	Subjects may have been diagnosed with asbestosis according to different criteria, as diagnostic procedures and standards for evaluation have evolved over time. Mortality (SMR): Pneumoconiosis: ~41 Pleural tumours: 64.	(330)

Table A11. Asbestosis and pleural plaques as proxies for asbestos exposure.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
North America							
Cohort: 4 559 male chrysotile miners and millers in Quebec born 1891–1920 who worked ≥ 1 mo. Last radiograph 1967. Workers with abnormal radiological signs were compared with workers with normal radiological examinations.	Until 1975	Mortality (ICD-7) from diseases of the heart (400–443) and CeVD (330–334).	*Heart diseases* Normal Less than normal Small opacities Large opacities PC UPC *CeVD* Normal Less than normal	566 331 235 62 39	RR 1 1.53 (X^2 25.25) 1.71 (X^2 27.92) 1.12 (X^2 0.05) 1.34 (X^2 2.25) 1.54 (X^2 13.96, P < 0.005) 1 1.17 (X^2 0.59)	Chest radiographs were read by six experienced readers. PC: Pleural calcification. UPC: Uncalcified pleural changes.	(564)
Australia							
Cohort: 354 male claimants for compensation for asbestosis 1947–1982 among former workers of the Wittenoom crocidolite mine and mill in Western Australia. *Referents:* male rates from Western Australia.	Until 1982	Mortality from IHD (ICD-9, 410.0–414.9).	IHD	22	SMR 1.43 (P = 0.065)	No smoking information.	(191)
Cohort: Plain chest radiographs from a 1/6 random sample of the workforce, 1 106 men, of the asbestos industry at Wittenoom, Western Australia 1943–1966 were classified for degree of profusion and pleural thickening.	Until 1986	Mortality from other causes, in which IHD formed the largest proportion.	Pleural thickening		RR 1.5 (1.3–1.8)		(217)

Table A11. Asbestosis and pleural plaques as proxies for asbestos exposure.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Asia							
Cohort: 124 male workers with asbestosis in Hong Kong 1981–2008. Asbestosis defined as positive radiographic findings of the lungs (profusion on small opacities of ≥ 1/0). *Referents:* Hong Kong male population.	1981–2008	Mortality (ICD-9) from heart disease (410–414, 428), acute MI (410) and chronic IHD (414).	Heart disease Acute MI Chronic IHD	7 4 2	SMR 3.24 (1.30–6.67) 4.32 (1.17–11.1) 3.12 (0.37–11.3)	Indirect smoking adjustment: 2.32 (0.93–4.79) 3.10 (0.84–7.94).	(159)

Table A12. Crystalline silica.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Nordic countries							
Case-control study: 26 847 men with first MI, 2 controls for each case.	Stockholm County: 1976–1984 Other counties: 1976–1981	Incidence of first MI, mortality (ICD-8, 410) and hospital discharges (410.00, 410.99).	*First MI* Stonecutters and carvers		RR 2.0 (1.2–3.6) 1.9 (1.1–3.4)	 Adjustment for age, county and calendar year. Adjustment for age, county and socioeconomic group.	(377)
All gainfully employed men identified in the Swedish census 1970. *Cohort:* 6 814 miners, 1 369 well borers, 743 dressing plant workers and 2 970 other male mine and stone workers. *Referents:* 2 million gainfully employed men.	1970–1995	Mortality from IHD (ICD-8–9, 410–414).	*IHD* Miners Well borers Dressing plant Other workers All workers	 886 141 107 298 1 432	SMR 1.29 (1.21–1.38) 1.28 (1.08–1.51) 1.40 (1.15–1.69) 1.35 (1.20–1.51) 1.31 (1.24–1.38)	No adjustment for smoking habits or socioeconomic status.	(1000)
Cohort: 13 621 male miners from Malmberget and Kiruna employed ≥ 1 y 1923–1996 and living in Sweden 1952. *Referents:* Swedish northern regional male population.	1952–2001	Mortality (ICD-10) from CVD (I00–I99) and MI (I20–I24).	*CVD* Surface work Underground work Exposure duration 0–5 y 5–15 y > 15 y *MI < 60 y of age* Surface work Underground work Exposure duration 0–5 y	 651 1 589 450 552 587 115 256 88	SMR 1.04 (0.96–1.12) 1.04 (0.99–1.09) 1.02 (0.93–1.12) 1.07 (0.98–1.16) 1.02 (0.94–1.11) 1.47 (1.21–1.76) 1.30 (1.15–1.48) 1.21 (0.97–1.50)		(98)

Table A12. Crystalline silica.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			5–15 y	84	1.23 (0.98–1.52)		
			> 15 y	84	1.51 (1.21–1.87)		
			MI > 60 y of age				
			Surface work	307	1.02 (0.91–1.14)		
			Underground work	799	1.08 (1.00–1.16)		
			Exposure duration				
			0–5 y	189	0.97 (0.83–1.11)		
			5–15 y	272	1.10 (0.97–1.23)		
			> 15 y	338	1.14 (1.02–1.26)		
Cohort: 13 621 male miners from Malmberget and Kiruna employed ≥ 1 y 1923–1996 and living in Sweden in 1952 (same as above).	1952–2001	Mortality from MI (ICD-6–10)	*Respirable dust, mg/m^3-y*		RR	The content of crystalline silica dioxide in the respirable fraction dust was estimated to 2.5%.	(97)
			Not exposed	311	1		
			> 0–35	361	0.98 (0.85–1.15)		
			> 35–100	355	1.21 (1.03–1.40)		
			> 100	450	1.31 (1.13–1.52)		
			Age ≤ 60 y				
			Not exposed	89	1		
			> 0–35	114	0.93 (0.71–1.23)		
			> 35–100	85	1.36 (1.01–1.84)		
			> 100	83	1.82 (1.33–2.49)		
			Age > 60 y				
			Not exposed	222	1		
			> 0–35	247	1.04 (0.87–1.25)		
			> 35–100	270	1.12 (0.94–1.34)		
			> 100	367	1.16 (0.98–1.37)		

Table A12. Crystalline silica.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 94 talc-exposed male miners employed ≥ 1 y 1944–1972, and 295 male millers employed ≥ 2 y 1935–1972. *Referents:* national Norwegian male rates.	1953–1987	Mortality (ICD-7) from circulatory diseases (400–468) and IHD (420–422).	Circulatory disease IHD	68 44	SMR 0.86 (0.67–1.10) 0.85 (0.62–1.14)	Exposure was to non-asbestiform talc with low quartz content. Silicosis was mentioned twice and talcosis once as contributory causes of death.	(1008)
Cohort: 1 026 granite workers in quarries and processing yards employed ≥ 3 mo 1940–1971. *Referents:* Finnish national male rates.	Until 1981	Mortality (ICD-8) from CVD and CHD.	*CVD/CHD* Time since entry into exposure 0 y 5 y 10 y 15 y 20 y 25 y 30 y	*CVD/CHD* 100/60 98/59 88/56 71/46 47/29 24/12 12/7	SMR 0.87/0.79 0.95/0.86 1.02/1.00 1.12/1.12 1.13/1.09 1.00/0.78 1.17/1.09	The cohort seems to contain both prevalently exposed workers 1940 and incidentally exposed workers 1940–1971. 7% had been employed in other industrial work. However, in 1981 only 15% of the cohort could be followed at least 20 y. Smoking habits similar to other male workers in Finland.	(510)
Cohort: 1 026 granite workers in quarries and processing yards entering work 1940–1971 and employed at least 3 mo. *Referents:* Finnish national rates.	Until 1985	Mortality from CVD (ICD-8).	*CVD* 1972 1975 1981 1985	 128	SMR 0.71 (P < 0.05) 0.70 (P < 0.05) 0.87 0.95	62% smokers 1970–1972.	(511)
Same cohort as above.	Until 1989	Mortality (ICD-8) from CVD and IHD.	CVD IHD	162 97	SMR 0.94 0.82		(512)

Table A12. Crystalline silica.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohorts: 597 miners first employed 1954–1973 who had worked ≥ 3 y under-ground, and 338 surface workers first employed 1954–1973. *Referents:* Finnish national and North Karelian male rates.	1954–1986	Mortality (ICD-8) from CVD and IHD.	*Miners, CVD* national rates regional rates *Miners, IHD* national rates regional rates *Surface workers, CVD* national rates regional rates *Surface workers, IHD* national rates regional rates	55 44 35 26 	SMR 1.79 (P < 0.05) 1.28 1.99 (P < 0.05) 1.41 (P < 0.05) 1.32 1.03 1.38 1.08	Exposure in the old mine during dry drilling: > 50 mg/m^3 total dust > 2 mg/m^3 respirable silica. Wet drilling decreased exposure and total dust was < 10 mg/m^3 after 1948. Highest exposure to respirable silica during loading in the new copper mine (mg/m^3): 1954–1965: 0.8 1966–1975: 0.5 1975–: 0.15. Other exposures were discussed such as nitroglycerine, noise, vibration and heavy work.	(12)
All gainfully employed men identified in the Finnish census 1970. *Cohort:* male miners and quarry workers. *Referents:* gainfully employed men.	1971–1991	Mortality (ICD-9) from CVD, other IHD (except MI) and MI.	*Age 25–64 y* CVD IHD (except MI) MI	 444 102 235	SMR 1.23 (1.11–1.35) 1.50 (1.23–1.83) 1.20 (1.06–1.37)	The SMRs in the age interval 25–44 y were always higher than in the interval 45–64 y. No adjustment for socioeconomic status.	(713)

Table A12. Crystalline silica.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Europe (non-Nordic)							
Cohort: 1 333 male Cornish tin miners retrieved from the National Health Service Central Register 1939. *Referents:* rates from England and Wales.	1939–1976	Mortality from circulatory diseases (ICD-8, 390–458).	Circulatory disease	378	SMR 0.99	12.5% of the cohort was ≥ 65 y of age in 1939.	(305)
Cohort: 3 010 male miners from 2 tin mines employed ≥ 1 y 1941–1984. *Referents:* rates from England and Wales.	1941–1986	Mortality from IHD (ICD-5–9).	IHD	208	SMR 1.08		(413)
Cohort: non-coal miners and quarrymen age 15–64 y from the Registrar General for England and Wales. *Referents:* men in the same social classes.		Mortality from CeVD.	*CeVD* Surface workers	32	PMR 1.02		(352)
Cohort: 4 093 male pottery workers retrieved 1970–1971 from 40 potteries in the UK. *Referents:* national and local rates.	1970–1985	Mortality from circulatory diseases.	*Circulatory disease* Local rates National rates Time since entering employment, local rates 0–19 y 20–39 y 40– y	205 40 77 88	SMR 1.04 1.14 0.9 1.1 1.1		(1029)

Table A12. Crystalline silica.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 4 822 male workers from pottery, refractory and sandstone industries first employed 1929–1992. *Referents:* national and Stoke-on-Trent rates.	1985–1992	Mortality (ICD-9) from heart disease (391–429) and CeVD (430–438).	*Stoke-on-Trent rates* Heart disease CeVD *National rates* Heart disease CeVD	 171 17 171 17	SMR 0.98 (0.83–1.13) 0.80 (0.46–1.28) 1.36 (1.16–1.58) 0.91 (0.53–1.46)	Respirable dust exposure: 0–0.8 (mostly 0.05–0.2) mg/m^3.	(167)
Cohort: 2 703 subjects (2 365 men, 338 women) in UK silica sand producing quarries employed ≥ 1 y 1950–1986. *Referents:* rates from Scotland, England and Wales.	1950–2001	Mortality (ICD-7–10) from circulatory diseases, IHD and other heart disease.	*Men* Circulatory disease IHD Other heart disease *Women* Circulatory disease IHD Other heart disease	 334 231 103 17 7 10	SMR 0.90 (0.80–1.00) 0.93 (0.82–1.06) 0.82 (0.67–1.00) 0.82 (0.48–1.32) 0.67 (0.27–1.38) 0.98 (0.47–1.80)	Geometric mean cumulative respirable crystalline silica exposure: 0.31 (0.01–23.2) mg/m^3-y.	(131)
Cohorts: 725 slate exposed and 530 non-slate exposed workers, North Wales.	1975–1981	Mortality from CVD (ICD-8).	*CVD* Slate exposed Non-slate exposed	 61 41	 65.1 expected 36.9 expected		(725)
Cohorts: 726 slate exposed and 529 non-slate exposed workers, North Wales. Same cohort as above.	1975–1998	Mortality from IHD and stroke.	*Slate exposed* IHD Stroke *Non-slate exposed* IHD Stroke	 110 33 70 21	Rate/1 000 person-y 8.8 2.6 7.1 2.1		(141)

Table A12. Crystalline silica.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Study base: distribution of miners among 22 689 males with first MI, aged 35–64 y participating in a rehabilitation program 1977–1978, compared with distribution of miners in the total male working population in West Germany.		Incidence of first MI (ICD-410).	*Miners* MI	 340	OR 1.97 (P < 0.001)		(117)
Cohort: males employed ≥ 1 y 1953–1985 from 9 slate quarries in the German Democratic Republic. Silicotics excluded. *Referents:* national rates.	1970–1985	Mortality from circulatory diseases (ICD-8, 390–458).	Circulatory disease	120	SMR 0.86 (0.71–1.03)		(628)
Cohort: 19 827 male construction workers with health examination 1986–1992. *Referents:* rates from Baden-Württemberg.	Until 1998–2000	Mortality (ICD-9) from circulatory diseases (390–459), IHD (410–414), other heart disease (420–429), CeVD (430–438) and pneumoconiosis (500–508).	 Circulatory disease IHD Other heart disease CeVD Pneumoconiosis	 185 109 29 22 3	SMR 0.59 (0.51–0.68) 0.61 (0.50–0.74) 0.55 (0.37–0.80) 0.45 (0.28–0.68) 2.30 (0.48–6.74)	Asbestos exposure reported by 7.5% and silica exposure by 2.4%. Smoking data available from 84% and 57% were smokers.	(48)
Cohort: 17 644 German porcelain production workers (8 288 men, 9 356 women) included in medical	Until 2005	Mortality (ICD-10) from circulatory diseases, I00–	*All men* Circulatory disease Silicosis *All women*	 371 5	SMR 1.00 (0.90–1.11) 7.20 (2.32–16.8)	The preparation department was the work area with highest potential crystalline silica exposures over time.	(96)

Table A12. Crystalline silica.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
surveillance program 1985–1987. Subcohort of 15 045 Bavarian porcelain workers (7 001 men, 8 044 women). *Referents:* national rates from Western Germany 1985–1997 and total Germany 1998–2005 and regional rates from Bavaria.		I99) and silicosis (J62).	Circulatory disease Silicosis *Bavarian men* Circulatory disease Silicosis *Bavarian women* Circulatory disease Silicosis *Bavarian men, exposed in preparation* Circulatory disease Silicosis *Never exposed in preparation* Circulatory disease Silicosis	125 0 315 5 119 0 37 3 278 2	0.83 (0.69–0.98) – 1.17 (1.05–1.31) 11.4 (3.66–26.5) 1.03 (0.85–1.23) – 1.40 (0.99–1.93) 67.2 (13.5–196) 1.15 (1.02–1.29) 5.06 (0.57–18.3)		
Study base: proportion of deaths among 1 067 iron ore miners in Lorraine compared with that in the French population.	1960–1976	Mortality from circulatory diseases (ICD-8, 390–458).	*Circulatory disease* Age at death < 40 y 40–49 y 50–59 y 60–69 y 70–79 y > 80 y	294 6 20 42 95 88 43	PMR 0.83 1.43 1.26 1.10 0.86 0.70 0.70		(684)

Table A12. Crystalline silica.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 1 173 iron mine workers aged 35–55 y in 1975 (185 surface workers) with normal chest X-ray. *Referents:* French population.	1975–1980	Mortality from CVD.	CVD	6	SMR 0.5 (0.2–1.1)	The number of deaths from lung cancer was higher (n = 13) than from CVD. The proportion of smokers was higher among miners (66%) than in the French male general population (52%). Diesel engines were used after 1970.	(747)
Cohort: 231 workers actively employed in 1960 in a refractory brick plant; sub-cohort of 95 non-silicotics. *Referents:* regional rates from the male population of Genoa, Italy.	1960–1979	Mortality from CVD (ICD-8, 390–429, 439–458).	*CVD* All workers Non-silicotics	 25 6	SMR 1.32 (0.85–1.95) 0.74 (0.27–1.61)	Geometric mean of respirable dust concentrations for the total cohort: 0.20–0.56 mg/m^3. Geometric mean of crystalline silica content: 6–21%. Silicotics are described in Table A13.	(762)
Cohort: 1 022 male workers actively employed 1954–1977 in a refractory brick plant in Genoa, Italy. *Referents:* Italian male rates.	1954–1986	Mortality from CVD (ICD-9, 390–459).	*CVD* All Employed ≤ 1957	 80 62	SMR 0.93 (0.74–1.15) 1.14 (0.87–1.46)	Geometric mean respirable dust concentrations: 0.20–0.56 mg/m^3. Maximum percentage of crystalline silica: 30–65%.	(636)
Cohort: 1 346 male talc miners and 438 millers who worked ≥ 1 y 1921–1950 in Germanasca and Chisone Valley, Italy. *Referents:* the population of town Alba with similar	1921–1974	Mortality from CVD.	*Cum exposure, mppcf-y* Miners 566–1 699 1 700–5 665 5 666–12 750 Millers	 66 71 71	RR 1.04 1.23 (P < 0.01) 0.82 (P < 0.05)	Increased risk of silicosis among miners after latency, but not among millers. The mineral contained quartz. Small amounts of tremolite was detected.	(807)

Table A12. Crystalline silica.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
ethnic, social and economic conditions.			25–141 142–424 425–906	28 20 24	1.05 1.32 0.79	No cases of mesothelioma among exposed.	
Cohort: 1 795 male talc miners and millers who worked ≥ 1 y 1946–1995 in Val Chisone, Italy. *Referents:* Italian national and regional rates.	1946–1995	Mortality from CVD, IHD and CeVD.	 CVD IHD CeVD *CVD, exposure duration* < 10 y 10–19 y 20–29 y ≥ 30 y Miners only < 10 y 10–20 y > 20 y	 288 88 60 66 70 108 44 43 45 89	SMR 0.93 (0.83–1.05) 0.87 (0.70–1.07) 0.67 (0.51–0.86) 1.13 (0.88–1.44) 1.07 (0.84–1.35) 0.91 (0.75–1.10) 0.66 (0.48–0.88) 1.24 (0.89–1.67) 1.04 (0.76–1.39) 0.78 (0.62–0.95)	The current talc was free from asbestiform fibres. Excess mortality from respiratory diseases was mainly silicosis.	(181)
Cohort: 4 740 male miners employed 1932–1971 and still employed 1960 or ≥ 1 y 1960–1971, from 2 mines in Sardinia, Italy. > 65% were hired before 1960. *Referents:* Italian national and regional rates.	1960–1988	Mortality from CVD (ICD-9, 390–459.9).	*CVD* All Underground Surface Underground Mine A Mine B Surface Mine A Mine B	 258 160 88 86 74 67 21	SMR 0.63 (0.56–0.72) 0.66 (0.56–0.77) 0.57 (0.46–0.71) 0.75 (0.60–0.92) 0.58 (0.45–0.73) 0.65 (0.51–0.83) 0.41 (0.26–0.63)	*Dust exposure mine A and B* 1945–1960: 3–5 mg/m^3 1962–1970: 2.5–2.6 mg/m^3 1971–: 1.6–1.8 mg/m^3 Surface exposure: < 1 mg/m^3. *Median quartz proportion of dust* 1.2% in mine A and 12.8% in mine B. 65% smokers in mine A, 67% in mine B, versus 63% in Sardinia.	(177)

Table A12. Crystalline silica.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
						Diesel transport started in the early 1970s. In mine B, the lower SMR may be explained by a more effective medical selection. No deaths from diabetes vs 7.8 expected. In mine A, 10 deaths from diabetes vs 12.5 expected.	
Cohort: 483 female workers employed ≥ 1 y 1932–1971 in ore screening in Sardinian lead and zinc mines. 310 belt pickers. *Referents:* Italian national rates.	1951–1988	Mortality from CVD.	*CVD* Total cohort Belt pickers Mine A Mine B Both mines ≥ 6 y employed	 70 44 23 21 11	SMR 0.70 (0.54–0.88) 0.65 (0.47–0.87) 0.81 (0.51–1.21) 0.53 (0.33–0.81) 0.64 (0.32–1.15)	Belt pickers exposed to silica. Average silica exposure: 0.007 mg/m^3 in mine A 0.09 mg/m^3 in mine B.	(178)
North America							
Cohort: 5 414 male quarry and shed workers employed 1950–1982 in Vermont granite industry. *Referents:* US white male rates.	1950–1983	Mortality (ICD-8) from circulatory diseases (390–458), athero-sclerotic heart disease (410–413) and silicosis (515.0).	 Circulatory disease Heart disease *Year of hire* < 1930 Circulatory disease Heart disease Silicosis 1930–1939 Circulatory disease Heart disease Silicosis 1940–1949	 711 482 424 282 36 93 69 4	SMR 0.75 (0.69–0.80) 0.75 (0.68–0.82) 0.85 (P < 0.01) 0.88 (P < 0.05) 9.99 (P < 0.01) 0.70 (P < 0.01) 0.73 (P < 0.01) 4.30 (P < 0.05)	Dust exposure prior to 1940 was 10 times higher than after 1940. Preliminary results were presented by Costello and Graham 1986 (196).	(197)

Table A12. Crystalline silica.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			Circulatory disease	133	0.79 (P < 0.01)		
			Heart disease	91	0.76 (P < 0.01)		
			Silicosis	1	0.95		
			1950–1959				
			Circulatory disease	46	0.41 (P < 0.01)		
			Heart disease	31	0.38 (P < 0.01)		
			Silicosis	0	–		
			1960–1969				
			Circulatory disease	12	0.35 (P < 0.01)		
			Heart disease	7	0.27 (P < 0.01)		
			Silicosis	0	–		
Cohort: 5 408 male quarry and shed workers employed 1950–1982 in Vermont granite industry. *Referents:* US white male rates.	Until 1996	Mortality (ICD-9) from all circulatory diseases (390–459), IHD (410–414) and silicosis (502).			SMR	Quartz exposure decreased by 80–90% after 1940. *Quartz exposure before 1940* General stone shed air contained ~ 0.2 mg/m^3, and pneumatic chisel workers were exposed on average to 0.6 mg/m^3. *Quartz exposure after 1940 (average)* 0.05–0.06 mg/m^3.	(349)
			Circulatory disease	842	0.79 (0.74–0.85)		
			IHD	710	0.74 (0.69–0.80)		
			Silicosis	53	20.6 (15.4–26.9)		
			Exposure				
			Before 1940				
			Circulatory disease	520	0.94 (0.86–1.03)		
			IHD	443	0.89 (0.81–0.97)		
			Silicosis	50	27.4 (20.3–36.1)		
			After 1940				
			Circulatory disease				
			IHD	322	0.63 (0.56–0.70)		
			Silicosis	267	0.58 (0.51–0.65)		
				3	3.98 (0.82–11.6)		
Cohort: 7 052 male workers in Vermont granite industry 1947–1998.	Until 2004	Mortality (ICD-9) from all heart disease, CeVD and silicosis.			SMR	71% of the cohort were born before 1940. 24% of the cohort were exposed before 1940.	(976)
			All heart disease	1 219	0.89 (0.84–0.94)		
			CeVD	217	1.02 (0.89–1.16)		
			Silicosis	55	59.1 (44.6–77.0)		

Table A12. Crystalline silica.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Referents: US white male rates.						Most deaths from silicosis occurred in men who began to work before 1940, prior to implementation of dust control.	
Cohort: 10 403 white male Minnesota iron-ore miners employed ≥ 1 y before 1966. *Referents:* US and St. Louis County white male rates.	1937–1978	Mortality (ICD-8) from arterio-sclerotic heart disease (410–413) and vascular lesions of CNS (430–438).	*All miners* Heart disease Vascular CNS lesions *Underground* Heart disease Vascular CNS lesions *Aboveground* Heart disease Vascular CNS lesions *Heart disease* Native born All foreign born Finnish born	 1 783 405 1 020 260 763 145 1 034 749 194	SMR 1.02 0.91 1.01 0.92 1.03 0.89 SMR/SMR [a] 1.07 [b]/0.96 0.97/0.81 [c] 1.26 [c]/1.05	Aboveground miners were basically not exposed to underground mining while underground miners included persons working in both areas. 39% of underground miners and 12% of aboveground miners were foreign born. ~ 8% silica in the ore. Strict smoking prohibition underground. Absence of underground diesel fuel. [a] US rates/St Louis County rates. [b] $P < 0.05$. [c] $P < 0.01$.	(541)
Cohort: 1 321 male gold miners, members of the Homestake Veterans Association who worked ≥ 21 y in Homestake, South Dakota. *Referents:* US or South Dakota male rates.	1937–1973	Mortality (ICD-7) from heart diseases (400–443), vascular lesions of CNS (330–334), pneumoconiosis (523–524) and	*1937–1955* Heart disease Vascular CNS lesions Respiratory cancer *1956–1973* Heart disease Vascular CNS lesions Respiratory cancer *Heart disease*	 107 24 6 157 40 11	SMR 1.41 1.06 1.76 1.01 0.99 0.84	The ore contained crystalline cummingtonite-grunerite, which when crushed divides by cleavage into fragments defined as fibres. These resemble amosite fibres but lack their strength and elasticity.	(617)

Table A12. Crystalline silica.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
		respiratory cancer (160–164).	Exposure			Silicosis was stated as the cause in 35 of 37 pneumoconiotic deaths.	
			Very low	39	0.83		
			Low	108	0.96		
			Moderate	34	1.03	One case of mesothelioma which may have been caused by exposure outside the mine.	
			High	34	0.99		
			Very high	56	1.28		
			Vascular CNS lesions				
			Exposure				
			Very low	6	0.49		
			Low	39	1.31		
			Moderate	4	0.58		
			High	5	0.76		
			Very high	11	1.18		
			Pneumoconiosis				
			Exposure				
			Very low/low	3	0.14		
			Moderate	2	0.39		
			High/very high	35	2.71		
			Respiratory cancer				
			Exposure				
			Very low/low	7	0.78		
			Moderate	3	1.30		
			High/very high	7	1.21		
Cohort: 3 328 white male gold miners who worked underground ≥ 1 y 1940–1965 in Homestake, South Dakota.	1941–1977	Mortality from circulatory diseases (ICD-7, 400–468).	Circulatory disease	285	SMR 0.84 (0.75–0.95)	30% of the cohort worked before 1940.	(129)
			Year of first employment			Smoking was prohibited in the mine from early 1930s until 1952.	
			–1930	117	0.98		
			1930–1934	50	0.82		

Table A12. Crystalline silica.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Referents: US white male rates.			1935–1939 1940–1944 1945–1949 1950–1954 1955–1959 1960–1964	30 20 38 21 6 3	0.56 0.82 0.90 0.87 0.65 0.72	Based on pathological reports at least two-thirds of the miners who died from non-malignant respiratory disease had silicosis.	
Cohort: 3 328 male gold miners who worked underground ≥ 1 y 1940–1965 in South Dakota, same as above. *Referents:* US white male rates.	1941–1990	Mortality (ICD-9) from IHD (410–414), CeVD (430–438), diseases of arteries, veins, circulation (415–417, 440–459), other myocardial degeneration (429.0, 429.1) and pneumoconiosis and other respiratory disease (470–478, 494–519).	IHD *Multiple cause mortality from 1960* IHD CeVD Vessels Other myocardial degeneration Respiratory disease *Employed, –1930* Other myocardial degeneration	431 527 128 180 20 251 15	SMR 0.94 (0.85–1.03) 0.88 (0.80–0.95) 0.95 (0.75–1.18) 1.19 (1.02–1.38) 3.03 (1.85–4.68) 2.08 (1.82–2.35) 9.20 (5.14–15.2)	Exposure to silica and to non-asbestiform amphibole fibres (cummingtonite-grunerite, 69%, tremolite-actinolite, 15%, and other non-asbestiform varieties, 16%). Median silica exposure estimation, mg/m^3: –1930: 0.15 1930–1950: 0.07 1950–: 0.02. 9% of all death certificates mentioned silicosis. 1 death of pneumoconiosis was asbestosis. Current smoking was more common among miners (65%) than among US males (57%).	(907)

Table A12. Crystalline silica.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 2 570 white male workers employed ≥ 12 mo and who worked ≥ 1 d 1942–1987 in the diatomaceous earth mining and processing industry, Lompoc California. *Referents:* US white male rates.	1942–1987	Mortality from IHD and CeVD (ICD-5–9).	IHD CeVD	159 30	SMR 0.85 (0.72–0.99) 0.97 (0.66–1.39)		(153)
Cohort: 2 342 white male workers employed ≥ 12 mo and who worked ≥ 1 d 1942–1987 in the diatomaceous earth mining and processing industry, Lompoc California. *Referents:* US white male rates.	1942–1994	Mortality from IHD and CeVD (ICD-5–9).	IHD CeVD	191 34	SMR 0.82 (0.71–0.95) 0.86 (0.60–1.20)	Same cohort as above except for exclusion of men from a smaller plant.	(154)
Cohort: same as above.	1942–2011	Mortality (ICD-8–10) from IHD, CeVD, and pneumoconiosis and other respiratory disorders.	*1942–1992* IHD CeVD Respiratory disease *1993–2011* IHD CeVD Respiratory disease	 203 34 28 112 17 15	SMR 0.83 (0.72–0.96) 0.86 (0.60–1.20) 3.96 (2.63–5.72) 0.71 (0.58–0.85) 0.46 (0.27–0.74) 1.12 (0.63–1.84)	About 88% of the cohort had ceased working by 1994.	(323)

Table A12. Crystalline silica.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Study base: proportion of deaths among miners compared with that among 10 million deaths aged 18–64 y in 550 occupations in the National Occupational Mortality Surveillance system in 30 US states.	1985–1999, 2003–2004, 2007	Mortality from acute MI (ICD-10, I21).	Acute MI *Mining* Black males *Coal mining* White males Black males	 73 1 794 36	PMR 1.63 (1.29–2.06) 1.21 (1.16–1.26) 1.67 (1.19–2.35)	Adjustment for age and smoking.	(786)
Cohort: 3 246 male workers employed ≥ 1 y 1940–1980 in 20 crush stone operations in US. *Referents:* US white and non-white male rates.	1940–1980	Mortality (ICD-8) from circulatory diseases (390–458) and arteriosclerotic heart disease (410–413).	*Whites and non-whites* Circulatory disease Heart disease	 294 198	SMR 0.84 (0.75–0.94) 0.86 (0.75–0.99)		(195)
Cohort: 2 670 male sand workers employed ≥ 3 y 1909–1979, of which ≥ 1 mo 1940 or later. 7 plants in the US and 1 in Canada. *Referents:* US white male rates.	Until 1994	Mortality from heart disease (ICD) and CeVD.	*Time since first exposure* < 20 y Heart disease CeVD ≥ 20 y Heart disease CeVD	 93 12 300 37	SMR 0.98 0.90 1.05 0.79	About 10% of the cohort was hired before 1940. 41% (15/37) of silicosis occurred in this group.	(616)
Cohort: 2 452 male sand workers, same as above excluding the Canadian plant. *Referents:* US male rates.	Until 2000	Mortality from all heart disease (ICD-9, 380.0–389.9, 402.0–402.9, 404.0, 410.0–519.9).	*All heart disease, ≥ 20 y since first exposure* –1994 1995–2000	 297 72	SMR 1.06 1.36		(620)

Table A12. Crystalline silica.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 4 626 industrial sand workers employed ≥ 1 wk from 18 plants in 11 US states. Cohort based on records of former and current workers collected 1987–1988. *Referents:* US national rates.	1960–1996	Mortality (ICD-9) from IHD (410–414) and silicosis (502).	*IHD* Based on underlying cause Based on multiple causes *Silicosis*	 330 474 11	SMR 1.22 (1.09–1.36) 1.22 (1.11–1.33) 66.3 (33.1–119)	Geometric mean silica exposure in breathing zone 1974–1996: 26 μg/m^3. Smoking was slightly more common among sand workers than among US referents.	(910)
Study base: proportion of deaths among pottery workers (International Brotherhood of Potters and Allied Workers; 2 924 white males, 946 white females) compared with the proportion among US white males and females.	1955–1977	Mortality (ICD-8) from circulatory diseases (390–458), arteriosclerotic heart disease (410–413) and vascular lesions of CNS (430–438).	*Males* Circulatory disease Heart disease Vascular CNS lesions *Females* Circulatory disease Heart disease Vascular CNS lesions	 1 657 1 199 233 559 342 114	PMR 0.99 1.07 (P < 0.01) 0.88 1.06 1.17 (P < 0.01) 0.94	< 20% of the pottery workers were < 55 y at death. Among males, 96 out of 268 respiratory disease deaths were diagnosed as pneumoconiosis due to silica and silicates. The corresponding proportion among females was 3 out of 45. Some fibrous material such as talc was introduced 20–30 y before the investigation; asbestos was not mentioned. 2 workers died from mesothelioma. Talc workers were sometimes also exposed to asbestos e.g. tremolite and anthophyllite (498).	(956)

Table A12. Crystalline silica.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 2 055 white male pottery workers employed ≥ 1 y, 1939–1966 in 3 US plants. *Referents:* US white male rates.	1940–1980	Mortality (ICD-8) from IHD (410–413) and vascular lesions of CNS (430–438).	IHD Vascular CNS lesions	231 34	SMR 1.04 0.74	The workers were exposed to silica dust and non-fibrous (non-asbestiform) talc in the production of ceramic plumbing fixtures.	(957)
Africa							
Cohort: 3 971 white miners, born 1916–1930, who attended the Medical Bureau for Occupational Diseases in 1969 for a certificate of fitness. *Referents:* South African white male rates. *Case-control study* *Cases:* 166 cases of IHD *Controls:* 2/case randomly selected from miners born in the same year as the case and who survived the case. Cases and controls were miners who had spent ≥ 85% of their service in gold mines.	1970–1978	Mortality (ICD-8) from IHD (410–414) and CeVD (430–438).	IHD CeVD IHD	203 23 166	SMR 1.15 (1.00–1.32) 0.89 (0.56–1.33) RR [a] 1.54 (1.04–2.28)	[a] In the case-control study, exposure was defined as 10 y of underground gold mining service. P = 0.004 after adjustment for smoking, systolic blood pressure and BMI.	(1041)

Table A12. Crystalline silica.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 4 925 white miners who attended the Medical Bureau for Occupational Diseases in 1969 for a certificate of fitness. *Referents:* South African white male rates. *Case-control study* *Cases:* 484 cases of IHD. *Controls:* 1/case randomly selected from miners born in the same year as the case and who survived the case. Cases and controls were miners who had spent ≥ 85% of their service in gold mines.	1970–1989	Mortality (ICD-9) from IHD (410–414), *cor pulmonale* (416) and CeVD (430–438).	IHD *Cor pulmonale* CeVD IHD	687 22 109 484	SMR 1.24 (1.15–1.34) 3.32 (2.08–5.03) 1.09 (0.89–1.31) RR [a] 0.97 (0.83–1.1) 0.98 (0.83–1.2) [b]	[a] In the case-control study, exposure was defined as 10 y of underground gold mining service (2 400 shifts) 5 y before death. The lag period of 5 y decreased exposure and may have weakened possible relationships. [b] Adjusted for smoking.	(776)
Asia							
Cohort: 68 241 workers (85% men) in employment records ≥ 1 y from mines and pottery factories [a], 1972–1974. 52% begun employment 1950–1959. *Referents:* Chinese national rates. [a] 28 442 in tungsten mines, 18 231 in copper/iron mines, 7 849 in tin mines, and 13 719 pottery workers.	1972–1989	Mortality from heart disease (IHD, hypertensive and pulmonary heart disease) and CeVD.	IHD Hypertensive heart Pulmonary heart disease CeVD *Exposure category* Heart disease Medium High IHD	152 99 695 730	SMR 1.25 (1.05–1.45) 3.30 (2.68–4.02) 5.81 (5.38–6.26) 0.77 (0.72–0.83) RR [b] 1.03 (0.9–1.2) 1.55 (1.3–1.8) P(trend): < 0.01	*Average annual exposure, mg/m³* Tungsten: 6.1 (2.0–26.3) Copper/iron: 5.6 (3.8–16.1) Tin: 7.7 (3.4–29.7) Pottery: 11.4 (9.4–23.8). *Exposure categories* High (mostly from underground open cast or separation jobs), medium, low, and not dust-exposed. [b] High or medium vs low/none.	(155)

Table A12. Crystalline silica.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			Medium High Hypertension Medium High Pulmonary heart disease Medium High CeVD Medium High		0.65 (0.3–1.3) 1.16 (0.7–1.9) 0.99 (0.6–1.7) 1.38 (0.9–2.0) 1.27 (1.0–1.6) 1.93 (1.6–2.4) P(trend): < 0.01 0.99 (0.8–1.2) 0.92 (0.8–1.1)		
Cohort: 7 837 workers in employment records ≥ 1 y from 4 tin mines, 1972–1974 (4 629 dust-exposed miners and 3 208 non-exposed workers). *Referents:* Chinese national rates.	1972–1994	Mortality from CVD and CeVD.	CVD CeVD *Cum dust exposure, mg/m^3-y* CVD < 0.1 0.1–29 30–69 ≥ 70 CeVD < 0.1 0.1–29 30–69 ≥ 70	151 188 42 25 24 60 70 22 30 66	SMR 0.77 (0.65–0.90) 1.15 (1.00–1.33) 0.65 [a] 0.94 0.75 0.83 1.35 [a] 1.11 1.16 1.01	Increased mortality among dust-exposed miners vs non-exposed for CeVD (RR 1.75, P < 0.01). [a] 95% CI of SMR excludes 1.00.	(164)

Table A12. Crystalline silica.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 4 851 workers in employment records ≥ 1 y from 3 ceramic factories in Jingdezhen city, 1972–1974. *Referents:* Chinese national rates.	1972–2003	Mortality from CVD and CeVD.	CVD CeVD *Cum dust exposure, mg/m³-y* CVD 0.1–119 120–219 ≥ 220 CeVD 0.1–119 120–219 ≥ 220	294 221	SMR 1.06 (0.94–1.19) 0.81 (0.71–0.93) RR 0.5 (0.4–0.8) 0.8 (0.6–1.1) 1.0 (0.7–1.3) 0.8 (0.6–1.2) 0.8 (0.5–1.1) 1.1 (0.7–1.5)	*Total dust exposure* ~ 15–28 mg/m³ 1950–1960s, 10–12 mg/m³ 1970–1980s after ventilation was improved. In the late 1980s, gas and electricity was used instead of coal as main energy, and dust exposure was lowered to 2–5 mg/m³ in 1990s and 1.6 mg/m³ in 2003.	(1053)
Australia							
Cohort: 1 974 Kalgoorlie gold miners identified in a survey 1961–1962. *Referents:* Western Australia male rates.	1961–1975	Mortality (ICD-8) from IHD (410–414) and CeVD (430–438).	IHD CeVD	178 40	SMR 1.0 1.0	57% worked > 10 y under-ground. 66% smoked among miners vs 53% among referents.	(47)

Table A13. Silicotics.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Nordic countries							
Cohort: 1 130 Swedish male silicotic patients identified in the Hospital Discharge Register in 1965–1983. Silicotics had ICD-codes; ICD-7, 523.00 and ICD-8, 515.00, 515.01, 515.05 and 515.09. The cohort was linked to the Swedish Registry of Causes of Death. *Referents:* Swedish national rates.	Until 1989	Mortality from circulatory disease, arteriosclerotic heart disease, other heart disease, CeVD and arterial disease.	Circulatory dis. Heart disease Other heart dis. CeVD Arterial disease	324 235 29 32 16	SMR 1.4 (1.3–1.6) 1.5 (1.4–1.8) 1.8 (1.2–2.6) 0.9 (0.6–1.2) 1.2 (0.7–1.9)	Approximately 70% of the cohort was deceased, with a median age at death of 74 y. 88% of the silicotics with arteriosclerotic heart disease had this diagnosis prior to their first hospitalisation in which silicosis was recorded. Because only hospitalised patients were included, the study population probably had a disproportionate number of silicotics with more advanced disease that required hospital admission. The diagnosis of heart disease prior to silicosis does not exclude a causal relation between silica dust exposure and IHD because silicosis will occur after decades of silica exposure.	(130)
Cohort: 961 diagnosed cases of silicosis in Finnish men 1935–1977. *Referents:* Finnish national male rates.	Until 1982	Mortality from CVD (ICD-8, 390–458).	CVD	203	SMR (99% CI) 1.11 (0.90–1.31)		(521)

Table A13. Silicotics.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 163 male silicotics visiting the Finnish Institute of Occupational Health, 1967–1985. *Referents:* Finnish national male rates.	Until 1994	Mortality from circulatory diseases.	Circulatory	30	SMR 1.0 (0.7–1.4)	Adjustment for age and calendar year. Mean duration of exposure: 24 (9–43) y.	(724)
Europe (non-Nordic)							
Cohort: males employed ≥ 1 y during 1953–1985 from 9 slate quarries in the German Democratic Republic, divided in non-silicotics and silicotics (retrieved from a silicosis register). *Referents:* German national rates.	1970–1985	Mortality from circulatory diseases (ICD-8, 390–458).	*Circulatory* Silicotics Non-silicotics	 34 120	SMR 0.75 (0.52–1.05) 0.86 (0.71–1.03)		(628)
Cohort: 440 male silicotics compensated during 1988–2000 from stone and quarry industry in Germany. *Referents:* German national rates.	Until 2001	Mortality (ICD-9) from circulatory diseases (390–459) and IHD (410–414).	Circulatory IHD	29 9	SMR 0.89 (0.59–1.28) 0.55 (0.25–1.04)	Median cumulative exposure: 18.9 mg/m^3-y (range 0.79–55.5). Average median exposure: 0.58 mg/m^3 (range 0.10–1.5).	(974)
Cohort: 1 796 male silicotics from metallurgical and foundry workers in Poland. Silicosis diagnosed 1970–1985. *Referents:* Polish national	Until 1991	Mortality (ICD-9) from circulatory diseases (390–459), hypertensive disease (401–405), IHD (410–414), CeVD	Circulatory Hypertension IHD CeVD Atherosclerosis	227 6 69 16 45	SMR 0.99 (0.87–1.13) 0.67 (0.25–1.46) 0.92 (0.72–1.16) 0.56 (0.32–0.91) 0.82 (0.60–1.10)		(902)

Table A13. Silicotics.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
male rates.		(430–438) and atherosclerosis (440).					
Cohort: 1 439 male silicotics from refractory materials, china, ceramics and quarry workers in Poland. Silicosis diagnosed 1970–1985. *Referents:* Polish national male rates.	Until 1991	Same as above.	Circulatory IHD CeVD Atherosclerosis	181 56 17 37	SMR 0.91 (0.78–1.05) 0.88 (0.66–1.14) 0.69 (0.40–1.11) 0.77 (0.54–1.06)	The proportion of ever-smokers was 78% and non-smokers 22%. During the observation period, the proportion of ever-smokers to non-smokers in the Polish general male population was 75% and 25%, respectively.	(902)
Cohort: 231 workers actively employed in 1960 in a refractory brick plant. 136 workers received compen-sation for silicosis as they were at least 21% disabled. *Referents:* regional male rates from Genoa, Italy.	Until 1979	Mortality from CVD (ICD-8, 390–429, 439–458).	*CVD* Silicotics Non-silicotics	 19 6	SMR 1.73 (1.04–2.69) 0.74 (0.27–1.61)	Exposure concentrations (geometric mean), total cohort: respirable dust concentrations 0.20–0.56 mg/m^3. Proportion of crystalline silica 6–21%.	(762)
Cohort: 520 silicotics diagnosed 1961–1980 at the San Martino Hospital, Genoa, Italy. *Referents:* Italian national and regional Genoa male rates.	Until 1981	Mortality from CVD (ICD-9, 390–458.9).	CVD	28	SMR 0.80 (0.27–0.58)[a] [a] Mismatch between SMR and CI.	The proportion of smokers among the silicotics and the male population of Genoa were 47% and 49%, respectively. 52 subjects lost to follow-up. The majority of participants was the same as in (638) (below).	(637)

Table A13. Silicotics.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 450 silicotics (with complete data) diagnosed 1961–1980 at the San Martino Hospital, Genoa, Italy. *Referents:* Italian national and regional Genoa male rates.	Until 1987	Mortality from CVD (ICD-9, 390–459).	CVD	35	SMR 0.51 (0.36–0.71)	The proportion of smokers among the silicotics and the Italian male population were 49% and 46%, respectively. The majority of participants was the same as in (637).	(638)
Cohort: 14 929 (14 098 men and 831 women) compensated for silicosis 1946–1979 in Tuscany, Italy. *Referents:* regional Tuscany rates.	1980–1999	Mortality (ICD-9) from CVD (390–459), hypertension (401–405), IHD (410–414) and CeVD (430–438).	*Males* CVD Hypertension IHD CeVD *Females* CVD Hypertension IHD CeVD	 2 526.5 64.5 868.0 811.2 160.6 15.4 49.5 42.9	SMR 0.65 (0.63–0.68) 0.54 (0.43–0.69) 0.70 (0.65–0.75) 0.65 (0.61–0.70) 0.74 (0.63–0.86) 1.60 (0.98–2.62) 0.98 (0.74–1.29) 0.54 (0.40–0.73)	Causes of death were ascertained for 7 724 out of 8 521 deceased subjects and calculated for the remaining 797 subjects according to the distribution among the ascertained subjects.	(603)
Cohort: 1 313 men compensated for silicosis 1959–1963 in Veneto region, Italy. *Referents:* Italian national male rates.	Until 1984	Mortality from circulatory diseases (ICD-8, 390–458).	Circulatory	181	SMR 1.07 (0.92–1.23)	Out of 1 225 members of the cohort with known smoking habits, 975 (80%) were current smokers at the time of the claim for compensation. For a previous follow-up until 1980, see (1049).	(1050)
Cohort: 595 men compensated for silicosis 1946–1984 in Latium region, Italy.	1969–1984	Mortality from circulatory diseases (ICD-8, 390–458).	Circulatory	165	Mortality odds ratio (MOR) 0.81 (0.69–0.94)		(301)

Table A13. Silicotics.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Referents: regional male Latium population (1969–1979).							
Cohort: 2 043 men compensated for silicosis 1943–1986 in Latium region, Italy. *Referents:* regional male Latium rates.	1987–2006	Mortality (ICD-9) from CVD (390–459), hypertension (401–405), IHD (410–414) and CeVD (430–438).	CVD Hypertension IHD CeVD	366.2 15.0 131.3 100.4	SMR 0.81 (0.73–0.89) 0.45 (0.27–0.75) 0.73 (0.61–0.86) 0.91 (0.75–1.10)	Causes of death were ascertained for 1 173 out of 1 258 deceased subjects and calculated for the remaining 85 subjects according to the distribution among the ascertained subjects.	(836)
Cohort: 714 silicotics diagnosed 1964–1970 in Sardinia, Italy. *Referents:* regional Sardinian rates.	1964–1997	Mortality from cardiocirculatory disease (ICD-9, 390–459.9).	Cardiocirculatory	112	SMR 0.94 (0.78–1.13)		(147)
North America							
Cohort: 1 190 miners compensated for silicosis 1940–1975 and 289 surface workers compensated 1940–1984 in Ontario, Canada. *Referents:* regional Ontario rates.		Mortality from IHD (ICD-8, 410–414).	*IHD* Miners Surface workers Silica brick Ceramics Granite quarry Other	 131 48 3 22 16 7	SMR 0.74 1.28 0.42 1.72 1.25 1.49	The surface worker cohort comprised 13 women. All but two worked in ceramics. The percentage of current and former smokers among surface workers was 85%.	(291)

Table A13. Silicotics.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 523 silicotic and 1 568 non-silicotic workers from the Ontario Silicosis Surveillance Registry, first exposed 1950 or later and still employed 1979 or later. *Referents:* regional rates from Ontario, Canada.	1974–1992	Mortality from IHD.	*IHD* Silicotics Non-silicotics	 5 25	SMR 0.31 0.51	Differences in smoking habits likely accounted for only a small part of the difference in incidence of lung cancer between the two groups. Consequently the effect on IHD is even smaller.	(294)
Cohort: 1 072 male silicotics compensated 1938–1985 in Quebec, Canada. *Referents:* regional Quebec rates.	Until 1986	Mortality from circulatory diseases (ICD-9, 390–459).	Circulatory	130	SMR 0.98 (0.90–1.08)	Deaths after 85 y of age were not included. The percentage of smokers was 50% based on 860 workers.	(444)
Cohort: 288 silicotics from New Jersey (1979–1992) and 372 silicotics from Michigan, US (1988–1992). *Referents:* US male population.	Until 1992	Mortality from circulatory diseases (ICD-9, 390–459).	Circulatory	80	PMR 0.54 (0.44–0.68)	The analysis was limited to black and white men.	(800)
Cohort: 760 silicotics (655 whites and 105 non-whites) diagnosed 1940–1983 in North Carolina, US. *Referents:* US national rates 1940–1983 and North Carolina rates from 1950.	Until 1983	Mortality (ICD-8) from circulatory diseases (390–398, 400.1–400.3, 400.9, 401–404, 410–414, 420–438, 440–444.1, 444.3–458) and IHD (410–413).	*Whites* Circulatory IHD *Non-whites* Circulatory IHD	 150 93 17 13	SMR 1.2 1.1 1.3 2.1 [a]	Published also in condensed form, see (24). [a] Comparison with US rates for white males, $P < 0.05$.	(25)

Table A13. Silicotics.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 590 (5 women) silicotic claims from California Workers' Compensation 1945–1975, US. *Referents:* US male national rates.	1946–1991	Mortality (ICD-9) from all heart diseases (390–398, 402, 404, 410–429), IHD (410–414) and CeVD (430–438).	 All heart disease IHD CeVD	 97 80 16	SMR 0.68 (0.55–0.83) 0.66 (0.53–0.83) 0.58 (0.33–0.95)	55% current smokers from a sample of 70%.	(345)
Africa							
Case-control study: study base comprised white South African gold miners aged ≥ 45 y with necropsy 1974–1988. 391 cases with *cor pulmonale*. 341 controls without *cor pulmonale*.		Determinants: Silicosis and thromboembolic disease	 *Silicosis* Extensive Moderate Slight *Thromboembolic disease*	Cases/ controls 30/7 47/26 123/98 57/12	 OR 4.95 (2.92–8.38) 1.63 (0.93–2.84) 1.46 (1.03–2.08) 1.92 (1.37–2.69)	The risk for *cor pulmonale* increased with the severity of silicosis.	(686)
Asia							
Cohort: 3 335 male hospitalised pneumoconiosis patients (1 941 silicosis, 1 278 anthracosilicosis and 22 asbestosis). *Referents:* Japanese national rates.	1979–1983	Mortality (ICD-8) from IHD (410–414) and CeVD (430–438).	*All* IHD CeVD *Silicosis only* IHD CeVD	 8 28 3 18	SMR 0.50 (0.00–1.00) 0.66 (0.36–0.97) 0.32 (0.00–0.97) 0.73 (0.33–1.14)	The first year following the diagnosis (pneumoconiosis) was excluded in the calculation of mortality to avoid the inclusion of cases with already diagnosed serious disease.	(171)

Table A13. Silicotics.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 1 827 male silicotics employed as refractory brick workers before 1962 and diagnosed 1963–1985. *Referents:* 1 470 male workers from 10 rough rolling steel mills.	Until 1985	Mortality from CHD, pulmonary heart disease and CeVD (according to Chinese classification, similar to ICD-7).	 CHD Pulmonary heart CeVD *Pulmonary heart* Silicosis grade I Silicosis II Silicosis III	 8 71 20 39 21 11	SRR 0.73 3.08 (P < 0.01) 0.43 2.85 (P < 0.01) 3.04 (P < 0.01) 4.45 (P < 0.01)		(241)
Cohort: prevalent cases of silicosis in 1972 and incident cases through 1989. Almost 6 500 silicotics (85% males). *Referents:* other miners and pottery workers (totally 68 241) in south central China.	1972–1989	Mortality from total heart disease, hyper-tensive heart disease, IHD, pulmonary heart disease and CeVD (according to the Chinese Health Ministry coding system).	 Total heart disease Hypertensive IHD Pulmonary heart CeVD		RR 2.74 (2.4–3.1) 1.17 (0.8–1.8) 1.10 (0.7–1.8) 4.92 (4.1–5.8) 0.77 (0.6–0.9)		(155)
Cohort: 932 cases of silicosis out of 7 837 tin miners from the cohort above retrieved 1972–1974. *Referents:* Chinese national rates.	Until 1994	Mortality from CVD (according to the Chinese Health Ministry coding system).	*CVD* Silicotics Non-silicotics		SMR 1.07 0.66	The highest prevalence of silicotics was found in the Limu mine which had the highest cumulative dust exposure and the lowest amount of arsenic in the ore.	(164)
Cohort: 4 372 silicotic males from 47 metallurgical mines and plants in China, diagnosed and alive before January 1980. *Referents:* Chinese national rates.	Until 1989	Mortality (ICD-9) from IHD (410–414), hypertensive heart disease (402) and CeVD (430–438).	 IHD Hypertensive CeVD	 28 13 91	SMR 0.40 (0.28–0.57) 1.41 (0.75–2.62) 0.49 (0.40–0.60)		(989)

Table A13. Silicotics.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 1 419 male silicotics registered in 1980 in the Hong Kong Silicosis Register. *Referents:* Hong Kong male population.	Until 1986	Mortality (ICD-9) from CVD (390–459), IHD (410–414) and pulmonary heart disease (415–417).	CVD IHD Pulmonary heart	25 7 13	SMR 0.74 (0.48–1.09) 0.63 (0.25–1.30) 2.58 (1.37–4.41)	More than half of the registered had tuberculosis (56%).	(707)
Cohort: 1 490 male silicotics registered in 1981–1996 in the Hong Kong Silicosis Register. *Referents:* Hong Kong male population.	Until 1997	Mortality (ICD-9) from CVD (390–459), IHD (410–414) and pulmonary heart disease (415–417).	CVD IHD Pulmonary heart	29 10 11	SMR 0.79 (0.53–1.14) 0.73 (0.35–1.34) 5.45 (2.72–9.76)	Subjects with concomitant asbestos or PAH exposure from iron foundries were excluded. The proportion of ever-smokers were 91% among silicotics and 49% among referents.	(149)
Cohort: 2 789 cases of silicosis in Hong Kong diagnosed 1981–1998. *Referents:* Hong Kong male population.	Until 1999	Mortality (ICD-9) from circulatory diseases (390–459), IHD (410–414), pulmonary heart disease (415–417) and CeVD (430–438).	Circulatory IHD Pulmonary heart CeVD	77 26 14 25	SMR 0.71 (0.56–0.89) 0.60 (0.39–0.88) 4.33 (2.37–7.27[a]) 0.65 (0.42–0.96) [a] calculated by B. Sjögren (author of the present document).	*Pulmonary heart disease* Surface construction workers: SMR 3.46 (1.49–6.81), 8 cases Caisson workers: SMR 8.84 (2.38–22.64), 4 cases Other workers: SMR 4.31 (0.48–15.57), 2 cases. Mean dust exposure: 0.45 mg/m^3. Cumulative mean dust exposure: 10.9 mg/m^3-y. History of tuberculosis 49%.	(1048)

Table A14. Man-made vitreous fibres.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Nordic countries							
Cohort: 2 807 male workers employed ≥ 1 y before 1972, from 11 Swedish companies manufacturing wooden houses. 1 068 were exposed to MMMF. *Referents:* Swedish male population.	1969–1988	Mortality (ICD-8) from circulatory diseases (390–458), IHD (410–414) and CeVD (430–438).	Circulatory disease IHD CeVD *Circulatory disease* Exposure, f/ml 0 0.06 (0.02–0.08) 0.09 (0.05–0.13) 0.11 (0.05–0.1) with a peak 1975–1980 of 0.20–0.25 Duration of employment < 10 y 10–19 y ≥ 20 y	288 208 40 152 23 49 29 105 70 89	SMR 0.84 (0.74–0.94) 0.83 (0.72–0.95) 0.77 (0.55–1.04) 0.77 0.84 0.97 0.78 0.84 0.91 0.75	Smoking data obtained from 73% of the cohort: 45% current or former smokers. According to a national survey, 50% were current smokers in ages 18–49 y in corresponding geographical areas. Most plants had used both rock wool and glass wool.	(363)
Cohort: 3 539 male and female MMVF production workers employed ≥ 1 y before 1978, at 1 fibre glass plant and 2 rock wool plants in Sweden. *Referents:* Swedish regional rates.	1952–1990	Mortality (ICD-8) from circulatory diseases (390–458), IHD (410–414) and CeVD (430–438).	Circulatory disease IHD CeVD	371 228 60	SMR 1.01 (0.91–1.12) 0.95 (0.83–1.08) 0.96 (0.73–1.24)	Adjustment for age, gender, calendar year and geographic region.	(753)
Cohort: 941 workers (616 males, 325 females) employed ≥3 mo 1941–1952 and alive 1 January 1953 in glass wool	1953–1981	Mortality from circulatory diseases (ICD-8, 390–458).	*Circulatory disease* Males Females	 42 14	SMR 1.31 0.81	Adjustment for age, gender and calendar year.	(948)

Table A14. Man-made vitreous fibres.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
producing industry in Finland. *Referents:* Finnish population.							
Europe (non-Nordic)							
Cohort I: 3 548 male and 1 186 female workers manufacturing glass fibre and employed 1946–1978 in England. *Cohort II:* 1 196 male and 714 female workers producing glass yarns from continuous filaments employed 1956–1978 in Northern Ireland. *Referents:* national rates from England and Wales, and Northern Ireland. Local rates from St Helens County Borough, England.	Until 1984	Mortality from circulatory diseases (ICD-8, 390–458).	*Cohort I* Males National rates Local rates Females National rates Local rates *Cohort II* Males Females	 252 39 64 7	SMR 1.04 (0.92–1.18) 1.13 0.92 (0.65–1.26) 1.10 1.24 (0.95–1.58) 0.68 (0.27–1.40)	Adjustment for age, gender and calendar year.	(327)
Cohort: 2 096 male rock wool production workers 1942–1977. *Referents:* 1 778 male workers from cork and styropor panel production.	Until 1979	Mortality from circulatory diseases (ICD-8, 390–458).	Circulatory disease	70	RR 0.70 (0.51–0.97)		(174)
Cohort: 2 092 male rock wool production workers 1942–1977. *Internal referents:* 1 775 male workers recruited from cork and styropor panel production.	Until 1982	Mortality from circulatory diseases (ICD-8, 390–459).	*Circulatory disease* National rates Internal rates	 89 90	SMR 0.90 (0.73–1.11) RR 0.74 (0.60–0.92)	Adjustment for age, gender and calendar year. Internal referents were sometimes exposed to coal tar, silica, urethane formaldehyde foam and	(175)

Table A14. Man-made vitreous fibres.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Basically the same cohorts as above. *Referents:* national rates from the Federal Republic of Germany.						polystyrene. They had a significantly higher mortality for circulatory disease, SMR 1.31.	
Cohort: 1 098 male glass-fibre production workers employed ≥ 1 y 1942–1977. *Referents:* Italian national and local rates.	1944–1983	Mortality from CVD (ICD-8, 390–458).	*CVD* National rates Local rates	21	SMR 0.60 (0.37–0.92) 0.50 (0.31–0.76)	Adjustment for age and calendar year. *Exposure characteristics across job categories* Mean conc. of resp. fibres: 0.005–0.027 f/ml. Median length: 3.7–7.5 µm. Median diameter: 0.3–0.7 µm.	(90)
Cohort: 21 967 MMMF production workers (18 753 males and 3 214 females) from 13 plants in 7 countries. Rock wool/slag wool cohort: 10 115, glass wool cohort: 8 286, continuous filament cohort: 3 566. *Referents:* national rates.	1981–1983	Mortality (ICD-8) from circulatory diseases (390–459), IHD (410–414) and CeVD (430–438).	Circulatory disease IHD CeVD *Circulatory disease, exposure duration* < 1 y ≥ 1 y	1 043 722 178 216 827	SMR 1.00 (0.94–1.07) 1.03 (0.96–1.11) 0.88 (0.75–1.02) 1.10 and 1.13 [a] 0.98	[a] Risk estimates differ between publications.	(869, 870)
Cohort: 11 373 male MMVF production workers from 13 plants in 7 countries, who had worked ≥ 1 y 1933–1977. *Referents:* national rates.	1990–1992	Mortality (ICD-10) from circulatory diseases (I00–I99), IHD (I20–	*Circulatory disease* All workers Rock/slag wool Glass wool Continuous filament *IHD*	 1 208 519 623 66	SMR 1.03 (0.97–1.09) 0.99 (0.91–1.08) 1.05 (0.97–1.14) 1.22 (0.94–1.55)	7 factories produced rock or slag wool, 5 factories glass wool and 2 factories continuous filament.	(822)

Table A14. Man-made vitreous fibres.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
		I25) and CeVD (I60–I69).	All workers	813	1.03 (0.96–1.11)		
			Rock/slag wool	335	0.97 (0.87–1.08)		
			Glass wool	427	1.05 (0.95–1.15)		
			Continuous filament	51	1.43 (1.06–1.88)		
			CeVD				
			All workers	214	1.01 (0.88–1.16)		
			Rock/slag wool	91	0.95 (0.77–1.17)		
			Glass wool	112	1.05 (0.86–1.26)		
			Continuous filament	11	1.21 (0.60–2.16)		
			IHD, duration of employment				
			Rock/slag wool				
			1–4 y	152	1		
			5–9 y	67	1.0 (0.7–1.3)		
			10–19 y	71	0.9 (0.6–1.2)		
			≥ 20 y	45	0.7 (0.5–1.0)	P(trend): 0.07.	
			Glass wool				
			1–4 y	184	1		
			5–9 y	84	0.8 (0.7–1.1)		
			10–19 y	99	1.0 (0.8–1.4)		
			≥ 20 y	60	1.2 (0.8–1.7)	P(trend): 0.5.	
			Continuous filament				
			1–4 y	12	1		
			5–9 y	17	1.3 (0.6–2.9)		
			10–19 y	18	2.5 (1.0–6.2)		
			≥ 20 y	4	1.6 (0.3–8.7)	P(trend): 0.1.	
			Technological phase at first employment				
			Rock/slag wool				

Table A14. Man-made vitreous fibres.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			Late Intermediate Early Glass wool Late Intermediate Early	225 59 51 88 222 117	1 1.0 (0.7–1.4) 1.0 (0.7–1.5) 1 1.3 (0.9–1.9) 1.6 (1.0–2.5)	 P(trend): 0.9. P(trend): 0.04.	
North America							
Cohort: 1 448 white males employed 1940–1949 in a fibrous glass production plant and with ≥ 5 y employment. *Referents:* US white male rates.	Until 1972	Mortality (ICD-7) from diseases of the heart (400–443) and vascular lesions affecting CNS (330–334).	Heart disease Vascular CNS lesions	163 30	SMR 0.91 0.91	Adjustment for age and calendar year. Mean concentrations: 0.3 mg/m^3 (dust) 0.08 f/ml. Median fibre dimensions: 1.8 µm (diameter) 28 µm (length).	(72)
Cohort: 6 536 males employed in fibre glass production ≥ 10 y any time 1968–1977. *Referents:* US white male rates.	Until 1978	Mortality from all diseases of the circulatory system (ICD-8).	*Circulatory disease* All workers Workers with ≥20 y of employment and ≥30 y latency	 199 49	SMR 0.84 0.73	Already in 1968, 4 046 workers were included in the cohort.	(669)
Cohort: 596 male rock and slag workers exposed ≥ 1 y 1940–1948. *Referents:* US white male rates.	Until 1974	Mortality from diseases of the heart (ICD-8, 400–443).	*Heart diseases* All workers Subcohort of mineral wool production workers	 93 77	SMR (90% CI) 0.97 (0.81–1.16) 1.03 (0.84–1.24)	The average historical air-borne fibre concentration probably did not exceed 2.5 f/ml before 1935 and 1.0 f/ml after 1935.	(785)

Table A14. Man-made vitreous fibres.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 16 661 MMMF-workers employed ≥ 1 y (0.5 y in 2 plants) 1945–1963 in 17 US manufacturing plants. 14 815 fibrous glass plant + 1 846 mineral wool plant workers. *Referents:* US white male rates.	Until 1982	Mortality (ICD-8) from all heart diseases (380–398, 400.1, 402, 404, 410–429), IHD (410–413) and CeVD (430–438).	*All heart diseases* 1946–1982 1946–1977 1978–1982 *IHD* 1946–1982 1946–1977 1978–1982 *CeVD* 1946–1982 1946–1977 1978–1982	 2 008 1 521 487 1 749 1 347 402 326 244 82	SMR 0.98 0.96 1.06 0.99 0.97 1.06 1.00 0.94 1.27 (P < 0.05)	Race information was unknown for more than 30% of the participants. Whites constituted > 96% of those with known race information.	(260)
Cohort: same as above.	Until 1982	Mortality (ICD-8) from all heart diseases (380–398, 400.1, 402, 404, 410–429) and CeVD (430–438).	*All heart diseases* 1946–1985 1946–1977 1978–1982 1983–1985 *CeVD* 1946–1985 1946–1977 1978–1982 1983–1985	 2 343 1 516 495 332 368 248 81 39	SMR 1.00 0.95 (P < 0.05) 1.07 1.15 (P < 0.05) 1.01 0.95 1.25 1.05		(604)
Cohort: 32 110 workers employed ≥ 1 y 1945–1978 in 10 fibre-glass manufacturing plants in US (same as above but expanded). *Referents:* US national and local county rates.	Until 1992	Mortality (ICD-8) from all heart diseases (390–398, 400.1, 402, 404, 410–414, 420–429) and CeVD (430–438).	*All heart diseases* National rates Local rates *CeVD* National rates Local rates	 3 518 3 237 547 501	SMR 0.92 (0.88–0.95) 0.88 (0.85–0.91) 0.86 (0.79–0.94) 0.86 (0.78–0.93)		(606)

Table A14. Man-made vitreous fibres.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 4 008 female fibre glass workers employed ≥ 1 y (0.5 y in 2 plants) 1945–1978 in 10 US manufacturing plants. *Referents:* US national and local county rates.	Until 1992	Mortality (ICD-8) from all heart diseases (390–398, 400.1, 400.9, 402, 404, 410–414, 420–429) and CeVD (430–438).	*All heart diseases* National rates Local rates *CeVD* National rates Local rates	 323 323 82 82	SMR 0.77 (0.69–0.86) 0.73 (0.65–0.82) 0.74 (0.59–0.92) 0.78 (0.62–0.97)	More than half of the women (57%) worked in the plants for < 5 years.	(920)
Cohort: 2 933 white male workers employed ≥ 1 y 1951–1991 at the Anderson Plant, South Carolina. *Referents:* US white male rates.	Until 1991	Mortality (ICD-7–9) from all heart diseases, IHD and CeVD.	All heart diseases IHD CeVD	122 96 15	SMR 0.84 (0.70–1.00) 0.83 (0.67–1.02) 0.97 (0.54–1.60)	Average diameter of the majority of the continuous fibre glass products: ≥ 10–12 µm. Respirable glass (Beta) fibres were produced 1963–1968 with an average diameter of 3.5 µm.	(170)
Cohort: 1 074 white female, 130 non-white female and 494 non-white male workers employed ≥ 1 y 1951–1991 at the Anderson Plant, South Carolina. *Referents:* US national rates.	Until 1991	Mortality (ICD-7–9) from all heart diseases, IHD and CeVD.	*White women* All heart diseases IHD CeVD *Non-white women* All heart diseases IHD CeVD *Non-white men* All heart diseases IHD CeVD	 18 7 9 1 1 2 12 9 2	SMR 0.68 (0.41–1.08) 0.39 (0.16–0.80) 1.40 (0.64–2.65) 0.57 (0.01–3.17) 1.06 (0.03–5.92) 3.23 (0.39–11.68) 0.54 (0.28–0.95) 0.67 (0.31–1.27) 0.41 (0.05–1.47)		(994)

Table A14. Man-made vitreous fibres.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 942 male workers employed ≥ 1 y producing refractory ceramic fibres in New York and Indiana (446 former employees who terminated work before 1987 and 496 employed 1987 or after). *Referents:* US national rates.	1952–2000	Mortality from all heart diseases, IHD and CeVD (according to ICD in effect at time of death).	 Heart diseases IHD CeVD	 27 23 2	SMR 0.73 (0.48–1.06) 0.85 (0.54–1.28) 0.43 (0.05–1.54)	In the 1950s, the maximum exposure estimate was 10 f/ml for carding in textile operations. Subsequent improvements reduced exposure to < 10 f/ml. *1987–1988 TWAs (f/ml)* 0.03–0.61 dry fabrication 0.01–0.27 wet fabrication 0.01–0.47 furnace operations 0.02–0.62 maintenance.	(552)
Cohort: 2 557 male insulating glass wool plant workers employed ≥ 90 d 1955–1977, Sarnia, Ontario, Canada. *Referents:* Ontario male rates.	Until 1984	Mortality from circulatory disease, IHD and CeVD (ICD-codes not given).	 Circulatory disease IHD CeVD	 57 38 10	SMR 0.91 0.82 1.32		(860)

Table A14. Man-made vitreous fibres.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: same as above. *Referents:* same as above.	Until 1997	Mortality (ICD-9) from circulatory disease (390.0–459.9), IHD (410.0–414.9) and CeVD (430.0–438.9).	Circulatory disease IHD CeVD *Year of first employment* IHD –1960 1960–1970 1970– CeVD –1960 1960–1970 1970–	111 72 14 59 7 6 11 2 1	SMR 0.90 (0.74–1.09) 0.81 (0.63–1.02) 0.91 (0.50–1.52) 0.88 0.42 (P < 0.05) 1.00 0.92 0.80 0.94	The factory closed 1991. Average exposure to glass fibres 1977–1990: 0.03 (0.01–0.32) f/ml.	(858)
Cohort: 1 465 male and female glass filament producing workers employed ≥ 1 y 1951–1986 from Guelph, Ontario, Canada. *Referents:* rates from Ontario.	Until 1986	Mortality from circulatory disease.	*Circulatory disease* Men Women	 29 8	SMR 0.65 (P < 0.05) 1.89 (P = 0.07)	*Exposure concentrations* 0.02–0.05 f/ml (TWAs) 0.91 f/ml (highest value).	(859)

Table A15. Arsenic.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Nordic countries							
Case-control study Totally 369 deaths recorded in men aged 30–74 y in the parish around a Swedish copper smelter factory. *Controls:* subjects who had died from all remaining causes of death after exclusion of unclear diagnoses, mental deficiency, diabetes, all malignant disease, and cirrhosis of the liver.	1960–1976	Mortality (ICD-8) from CVD (410–412, 427–428) and CeVD (430–438).	 *CVD* Cases, 129 Controls, 74 *CeVD* Cases, 34 Controls, 73	Exposed/ non-exposed 53/76 18/56 12/22 18/55	RR (90% CI) based on Mantel-Haenszel 2.1 (1.2–3.5) 1.6 (0.7–3.4)		(56)
Cohort: 3 916 male Swedish smelter workers employed ≥ 3 mo 1928–1967. *Referents:* local county rates.	Until 1981	Mortality (ICD-8) from IHD and CeVD.	*Cum arsenic exposure, mg/m³-y* IHD < 25 0.25–< 1 1–< 5 5–< 15 15–< 50 50–< 100 ≥ 100 All CeVD < 25 0.25–< 1 1–< 5 5–< 15 15–< 50	 67 53 96 71 111 19 20 437 19 19 24 15 37	 SMR 1.00 (0.78–1.27) 1.15 (0.86–1.50) 0.98 (0.79–1.19) 1.02 (0.80–1.29) 1.13 (0.93–1.36) 1.57 (0.94–2.45) 1.12 (0.68–1.72) 1.07 (0.97–1.17) 1.08 (0.65–1.68) 1.61 (0.97–2.52) 0.93 (0.60–1.38) 0.71 (0.40–1.17) 1.22 (0.86–1.68)		(471)

Table A15. Arsenic.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			50– < 100	5	1.43 (0.46–3.34)		
			≥ 100	4	0.69 (0.19–1.78)		
			All	123	1.06 (0.88–1.26)		
Cohort: arsenic exposed Finnish men who were in the same occupation in 1975 and 1980 in Finland, and who were 25–64 y old in 1980. *Referents:* non-exposed men. In total, 507 000 men in both groups.	1981–1994	Mortality from CeVD (ICD-9, 430–438).	CeVD		RR 1.04 (0.75–1.45)		(1031)
North America							
Cohort: 8 047 white male Anaconda smelter workers in Montana, who had worked ≥ 1 y before December 1956. *Referents:* white male rates in Montana, US.	1938–1963	Mortality from disease of the heart (ICD-6, 400–443).	Heart disease	725	SMR 1.18 (P < 0.01)		(543)
Cohort: 1 800 men sampled from the cohort above. *Referents:* as above.	1938–1978	Mortality (ICD-8) from IHD (410–413) and vascular lesions of CNS (430–438).	*IHD*		SMR		(1004)
			Heavy exposure	53	1.77 (P < 0.01)		
			Other exposure	199	1.37 (P < 0.01)		
			Vascular CNS lesions				
			Heavy exposure	6	0.87		
			Other exposure	55	1.48 (P < 0.01)		
			IHD, exposure, μg/m³				
			< 100	72	1.26 (P < 0.05)		
			100–499	67	1.35 (P < 0.01)		
			500–4 999	88	1.69 (P < 0.01)		

Table A15. Arsenic.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			≥ 5 000	25	1.48 (P < 0.05)		
			Smokers				
			< 100	51	1.31 (P < 0.05)		
			100–499	42	1.31		
			500–4 999	63	1.77 (P < 0.01)		
			≥ 5 000	19	1.48		
			Ceiling value			The ceiling value was	
			< 100	48	1.08	based on the highest	
			100–499	28	1.26	exposure category in	
			500–4 999	129	1.59 (P < 0.01)	which a man had spent	
			≥ 5 000	47	1.71 (P < 0.01)	at least 30 d.	
			Ceiling value smokers				
			< 100	33	1.09		
			100–499	18	1.13		
			500–4 999	88	1.65 (P < 0.01)		
			≥ 5 000	36	1.82 (P < 0.01)		
Cohort: 8 014 white male Anaconda smelter workers in Montana who had worked ≥ 1 y 1938–1956.	1938–1990	Mortality from heart disease (ICD-8, 410–414, 420–429).	*TWA arsenic conc., mg/m³, age 60 y*		Excess death/1 000		(484)
			0.29 (light)		4.1 (-0.4–8.4)		
			0.58 (medium)		8.7 (1.4–16)		
			11.4 (heavy)		18 (2.8–34)		
Cohort: 2 802 white male smelter workers from a copper smelter in Tacoma, Washington, who had worked ≥ 1 y 1940–1964.	1940–1976	Mortality (ICD-8) from circulatory disease (390–458), CVD (410–414, 420–429) and CeVD (430–438).	*Cum arsenic exposure, µg/m³-y*		RR	Adjustment for healthy worker survivor effect.	(402)
			Circulatory disease	525			
			< 750		1.0		
			750–1 999		0.97 (0.68–1.4)		
			2 000–3 999		1.0 (0.73–1.5)		
			4 000–7 999		1.2 (0.83–1.7)		
			8 000–19 999		1.2 (0.81–1.7)		

Table A15. Arsenic.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			≥ 20 000		1.3 (0.87–1.9)		
			CVD	394			
			< 750		1.0		
			750–1 999		0.92 (0.60–1.4)		
			2 000–3 999		1.1 (0.72–1.6)		
			4 000–7 999		1.3 (0.89–2.0)		
			8 000–19 999		1.5 (0.99–2.3)		
			≥ 20 000		1.7 (1.1–2.6)		
			CeVD	91			
			< 750		1.0		
			750–1 999		0.88 (0.41–1.9)		
			2 000–3 999		0.84 (0.39–1.8)		
			4 000–7 999		0.64 (0.28–1.4)		
			8 000–19 999		0.40 (0.17–0.99)		
			≥ 20 000		0.58 (0.23–1.5)		
			20-year lag				
			Circulatory disease				
			< 750		1.0		
			750–1 999		0.98 (0.73–1.3)		
			2 000–3 999		1.2 (0.91–1.6)		
			4 000–7 999		1.3 (1.0–1.8)		
			8 000–19 999		1.6 (1.2–2.1)		
			≥ 20 000		1.5 (1.0–2.3)		
			CVD				
			< 750		1.0		
			750–1 999		0.94 (0.66–1.3)		
			2 000–3 999		1.2 (0.85–1.7)		
			4 000–7 999		1.5 (1.1–2.1)		

Table A15. Arsenic.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			8 000–19 999		1.9 (1.3–2.7)		
			≥ 20 000		1.7 (1.1–2.8)		
Cohort: 2 422 male workers employed ≥ 3 y in smelter, mill, or sulphur operations 1946–1996 in Copperhill, Tennessee. *Referents:* US national rates and local rates from the 3-county area in which Copperhill workers largely resided.	*External comparison* 1960–2000 *Internal comparison* 1946–2000	Mortality (ICD-9) from all heart disease (390–398, 402, 404, 410–429), IHD (410–414) and CeVD (430–438).	*All heart disease*		SMR	The authors concluded that possible alternative explanations to the increased risk of CeVD included chance alone and uncontrolled confounding or effect modification by co-exposures or other factors correlated with arsenic exposure and unique to the Copperhill facility.	(605)
			US rates	326	0.73 (0.66–0.82)		
			Local rates	314	0.76 (0.68–0.85)		
			IHD				
			US rates	272	0.79 (0.70–0.89)		
			Local rates	262	0.80 (0.70–0.90)		
			CeVD				
			US rates	72	0.93 (0.73–1.17)		
			Local rates	68	1.07 (0.83–1.36)		
			CeVD, cum arsenic exposure, µg/m^3-y				
			US rates		SMR		
			Unexposed	43	0.93 (0.67–1.25)		
			< 0.046	6	1.02 (0.37–2.22)		
			0.046–0.413	6	1.55 (0.57–3.37)		
			0.414–0.721	7	4.04 (1.62–8.32)		
			≥ 0.722	6	1.22 (0.45–2.65)		
			Internal rates		RR		
			Unexposed	47	1.00		
			< 0.046	6	1.08 (0.46–2.52)		
			0.046–0.413	6	1.46 (0.62–3.46)		
			0.414–0.721	7	3.70 (1.65–8.30)		
			≥ 0.722	6	1.33 (0.56–3.13)		

Table A15. Arsenic.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Meta-analysis							
CVD: 7 studies of which 3 based on water, 2 studies based on toenails, 1 based on urine concentrations and 1 with un-specified matrix. CHD: 8 studies of which 4 studies based on water, 1 study based on toenails, 2 studies based on urine concentrations and 1 study with un-specified matrix. Stroke: 4 studies of which 1 study based on water, 1 study based on toenails, 1 study based on urine concentrations and 1 study with un-specified matrix.	Varying	Incidence of or mortality from CVD, CHD and stroke.	*Top vs bottom tertile of different exposure levels* CVD CHD Stroke	 3 208 4 640 961	RR 1.30 (1.04–1.63) 1.23 (1.04–1.45) 1.15 (0.92–1.43)		(172)

Table A16. Cadmium.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Nordic countries							
Cohort: 869 Swedish workers employed ≥ 1 y in a nickel-cadmium battery factory 1940–1980. *Referents:* regional rates from Kalmar County, Sweden.	1951–1992	Mortality from IHD and CVD.	*Battery workers, males* IHD CVD *Battery workers, females* IHD CVD	 115 19 5 4	SMR 1.16 (0.96–1.40) 0.78 (0.47–1.21) 0.75 (0.24–1.76) 1.34 (0.36–3.43)	Smoking data were not used in the epidemio-logical analyses.	(470)
Cohort: 599 women, 64-y old, in Gothenburg, Sweden, identified in the County Register and invited 2001–2003. Stratified, random selection to groups with normal glucose tolerance, impaired glucose tolerance and diabetes, as assessed in a population-based screening examination.	Follow-up examination after a median time of 5.4 y.	Prevalence of large atherosclerotic plaques in the carotid arteries.	*Quartiles (Q) of baseline B-Cd* Q1 Q2 Q3 Q4 *Quartiles (Q) of baseline U-Cd (creatinine)* Q1 Q2 Q3 Q4	 104 120 108 91 102 111 101 92	OR 1 2.6 (1.1–6.5) 3.9 (1.6–9.7) 4.6 (1.7–12.9) P(Q4:Q1): 0.003 1 1.2 (0.6–2.5) 1.8 (0.9–3.9) 2.7 (1.2–6.1) P(Q4:Q1): 0.018	*Baseline cadmium* 0.34 µg/l (0.14–1.69) in blood, 0.35 µg/g creatinine (0.14–1.01) in urine. Adjustment for pack-years of smoking, HbA1c, systolic blood pressure, ICAM-1, apolipoprotein B/A-1, statin treatment, BMI, high-sensitivity CRP and plaque status at baseline.	(275)
Cohort: same as above.	Follow-up examination after a median time of 5.4 y.	Peripheral artery disease measured as low ankle-brachial index (ratio of systolic blood pressure in tibial and brachial arteries ≤ 0.9 in any artery).	*Tertiles (T) of baseline B-Cd, µg/l* T1: 0.08–0.25 T2: 0.25–0.44 T3: 0.44–4.07 *Tertiles (T) of baseline U-Cd, µg/g creatinine* T1: 0.06–0.28 T2: 0.29–0.46	440	OR 1 0.6 (0.2–1.6) 2.4 (0.9–6.3) P(T3:T1): 0.068 1 0.8 (0.3–1.8)	Adjustment for pack-years of smoking, current smoking, systolic blood pressure, HbA1c, apo-lipoprotein B/A-1, statin treatment, stratification group at baseline (normal glucose tolerance, im-paired glucose tolerance,	(276)

Table A16. Cadmium.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			T3: 0.46–2.06		2.5 (1.1–5.8) P(T3:T1): 0.037	diabetes).	
Case-control study 30 447 men and women from the Malmö Diet and Cancer cohort with baseline examination 1991–1996. *Cases:* 302 subjects with abdominal aortic aneurysm. *Controls:* 2/case randomly selected from the study base.	Until 2009	Diagnose of abdominal aortic aneurysm from the Swedish Inpatient Register and Cause of Death Register (ICD 8–10).	*Tertiles of B-Cd, µg/l* < 0.17 0.17–0.31 > 0.31	Cases/ controls 26/183 50/179 197/184	RR 1 1.5 (0.8–2.8) 2.5 (1.3–5.0) P(trend): 0.018	Adjustment for sex, age, smoking, low level of education, low physical activity, hypertension, diastolic blood pressure and apolipoprotein.	(277)
Cohort: population-based cohort from the city of Malmö, Sweden (4 378 participants aged 46–67 y) with baseline examination 1992–1994.	Until 2010	Incidence of heart failure (ICD-8, 427.00, 427.10, and 428.99; ICD-9, 428; ICD-10, I50 and I11) and atrial fibrillation (ICD-8, 427.92; ICD-9, 427D; ICD-10, I48).	Quartiles (Q) of B-Cd (Q4: men 0.49–5.07 µg/l, women 0.49–4.83 µg/l). *Heart failure* Q1 Q2 Q3 Q4 *Atrial fibrillation* Q1 Q2 Q3 Q4	143 22 38 33 50 83 90 122 90	HR 1.00 1.59 (0.92–2.72) 1.04 (0.59–1.84) 1.95 (1.02–3.72) P(trend): 0.21 1.00 0.98 (0.73–1.33) 1.19 (0.89–1.59) 1.02 (0.69–1.51) P(trend): 0.45	Adjustment for age, systolic blood pressure, use of blood pressure- or lipid-lowering drugs, presence of diabetes mellitus, history of a coronary event, waist circumference, smoking status, alcohol intake, LDL, HDL, high-sensitivity CRP, plasma creatinine, marital and educational status.	(120)
Cohort: as above, 4 819 participants aged 45–64 y with baseline examination 1991–1994, of which 1 793	Until 2010	*Incidence* Acute coronary event (ICD-9, 410, 412, 414; ICD-10,	Quartiles of B-Cd, µg/l *Acute coronary event* All < 0.17	 80	HR 1	*All:* Adjustment for sex, smoking, waist circum-ference, education, physical activity,	(63)

Table A16. Cadmium.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
never-smokers.		I21, I22, I23, I25), acute MI (ICD-9, 410; ICD-10, I21), major adverse cardiac event (acute coronary event, coronary artery bypass graft, percutaneous coronary inter-vention), any stroke (ICD-9, 430, 431, 434, 436; ICD-10, I60, I61, I63, I64), ischaemic stroke (ICD-9, 434; ICD-10, I63) *Mortality* CVD (ICD-9, 390–459; ICD-10, I00–I99).	0.17–0.259 0.26–0.499 0.50–5.1 Never-smokers < 0.17 0.17–0.259 0.26–0.499 0.50–5.1 *Acute MI* All < 0.17 0.17–0.259 0.26–0.499 0.50–5.1 Never-smokers < 0.17 0.17–0.259 0.26–0.499 0.50–5.1 *Major adverse cardiac event* All < 0.17 0.17–0.259 0.26–0.499 0.50–5.1 Never-smokers < 0.17 0.17–0.259	81 88 128 47 31 26 7 75 77 79 113 44 31 24 7 96 193 122 158 57 39	1.0 (0.7–1.4) 1.2 (0.8–1.6) 1.9 (1.2–2.9) 1 0.9 (0.6–1.5) 1.0 (0.6–1.6) 2.3 (1.0–5.1) 1 1.0 (0.7–1.5) 1.1 (0.8–1.6) 1.8 (1.2–2.8) 1 1.0 (0.6–1.5) 1.0 (0.6–1.6) 2.4 (1.1–5.4) 1 1.1 (0.9–1.5) 1.4 (1.0–1.9) 1.9 (1.3–2.8) 1 1.0 (0.7–1.5)	alcohol intake, serum triglycerides, HbA1c, CRP, postmenopausal status, hormonal replacement, treatment for hypertension, diabetes mellitus, lipid-lowering medication, diastolic blood pressure, LDL and HDL cholesterol. *Never-smokers:* Adjustment for sex, smoking, waist circum-ference, education, physical activity, alcohol intake, serum triglycerides, HbA1c and CRP.	

Table A16. Cadmium.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			0.26–0.499	32	1.1 (0.7–1.7)		
			0.50–5.1	8	2.2 (1.0–4.6)		
			Any stroke				
			All				
			< 0.17	76	1		
			0.17–0.259	71	0.8 (0.6–1.2)		
			0.26–0.499	74	0.9 (0.7–1.4)		
			0.50–5.1	115	2.1 (1.3–3.2)		
			Never-smokers				
			< 0.17	41	1		
			0.17–0.259	32	1.0 (0.6–1.6)		
			0.26–0.499	31	1.2 (0.7–2.0)		
			0.50–5.1	7	2.2 (1.0–4.8)		
			Ischaemic stroke				
			All				
			< 0.17	63	1		
			0.17–0.259	58	0.8 (0.6–1.2)		
			0.26–0.499	59	0.9 (0.6–1.3)		
			0.50–5.1	98	2.1 (1.3–3.3)		
			Never-smokers				
			< 0.17	32	1		
			0.17–0.259	25	1.0 (0.6–1.7)		
			0.26–0.499	22	1.1 (0.6–2.0)		
			0.50–5.1	6	2.5 (1.0–6.0)		
			CVD, mortality				
			All				
			< 0.17	45	1		
			0.17–0.259	57	1.2 (0.8–1.9)		
			0.26–0.499	66	1.3 (0.9–2.1)		

Table A16. Cadmium.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			0.50–5.1 Never-smokers < 0.17 0.17–0.259 0.26–0.499 0.50–5.1	89 22 26 16 5	1.9 (1.1–3.2) 1 1.4 (0.8–2.6) 1.1 (0.6–2.2) 2.6 (1.0–6.9)		
Cohort: 4 156 subjects without history of stroke from the Malmö Diet and Cancer cohort with baseline examination 1991–1994.	2010	Incidence of ischaemic stroke (ascertained by linkage to the Swedish Hospital Discharge Register and the Stroke Register of Malmö).	*Quartiles (Q) of B-Cd* Q1 Q2 Q3 Q4 (men 0.47–5.07 µg/l; women 0.49–4.83 µg/l).	 47 46 48 80	HR 1.00 0.91 (0.60–1.37) 0.84 (0.56–1.28) 1.66 (1.01–2.72) P(trend): 0.04	Adjustment for age, sex, waist circumference, smoking status, diabetes mellitus, systolic blood pressure, use of blood pressure-lowering or lipids-lowering drugs, LDL, HDL and CRP. The association between B-Cd and stroke was evident, independently of, and in synergistic interaction with, carotid plaques.	(121)
Cohort: Cd-exposed men who were in the same occupation in 1975 and 1980 in Finland, and were 25–64 y old in 1980. *Referents:* non-exposed men. In total, 507 000 men in both groups.	1981–1994	Mortality (ICD-9) from CVD (390–459) and CeVD (430–438).	 CVD CeVD		RR 1.01 (0.93–1.10) 1.07 (0.91–1.24)	Working conditions were evaluated from a JEM. Adjustment for age, marital status, period, professional status, education, income, socioeconomic and job exposure variables.	(1031)

Table A16. Cadmium.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Europe (non-Nordic)							
Cohorts: 480 subjects from high-exposure areas and 476 subjects from low-exposure areas, from north-eastern Belgium (environmentally exposed), randomly recruited 1985–1989. The last Cd-producing plant in the high-exposure areas closed in 2002. In a second analysis, 42 smelter workers were added.	B-Cd until 2003, 24-h U-Cd until 1996, mortality until 2007.	Mortality from CVD, cardiac disease and CeVD.	*Original cohorts* B-Cd CVD Cardiac disease CeVD U-Cd CVD Cardiac disease CeVD *Inclusion of 42 workers* B-Cd CVD Cardiac disease CeVD U-Cd CVD Cardiac disease CeVD	High-/ low-exposure areas 50/38 33/23 9/12 50/38 33/23 9/12 60/38 41/23 10/12 60/38 41/23 10/12	HRs for a doubling of the internal Cd dose at baseline. 1.20 (0.90–1.60) 1.19 (0.84–1.71) 0.83 (0.46–1.49) 1.07 (0.85–1.34) 1.05 (0.79–1.40) 0.70 (0.59–0.98) 1.29 (0.99–1.67) 1.31 (0.95–1.81) 0.85 (0.49–1.47) 1.11 (0.89–1.38) 1.09 (0.83–1.43) 0.61 (0.37–0.99)	Adjustment for sex, age BMI, smoking status, γ-glutamyltransferase as index of alcohol intake and socioeconomic status.	(699)
Cohort: 347 male copper-cadmium alloy workers from 2 factories in Great Britain, first employed 1922–1978 and for a minimum of 1 y. *Referents:* general population of England and Wales.	1946–1992	Mortality from circulatory disease (ICD-8, 398–458).	Circulatory disease	88	SMR 1.03 (0.83–1.27)	Adjustment for age and calendar year.	(896)

Table A16. Cadmium.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 1 462 males employed ≥ 1 y 1967–1995 at a tin smelter complex in North Humberside, UK, and potentially exposed to a number of substances, including lead, arsenic, cadmium and natural-series radionuclides. *Referents:* national and regional populations.	1982–2001	Mortality from circulatory disease, IHD, CeVD and hypertensive diseases.	*Tin smelter workers* vs national rates Circulatory disease IHD CeVD Hypertension vs regional rates Circulatory disease IHD CeVD Hypertension	 175 104 32 7 175 104 32 7	SMR 0.96 (0.82–1.11) 0.83 (0.68–1.01) 1.07 (0.73–1.51) 2.37 (0.95–4.89) 0.94 (0.80–1.09) 0.77 (0.63–0.94) 1.04 (0.71–1.47) 3.66 (1.47–7.53)	Adjustment for sex, age and calendar year.	(94)
Cohort: almost 7 000 male cadmium-exposed workers born before 1940 and exposed to cadmium for > 1 y 1942–1970. *Referents:* population of England and Wales.	1943–1984	Mortality (ICD-8) from CVD (430–438) and hyper-tensive diseases (400–404).	*Exposure* CVD Total Ever high Ever medium Always low Hypertension Total Ever high Ever medium Always low	 178 2 23 153 49 1 8 40	SMR 0.77 (0.66–0.89) 0.42 (0.05–1.51) 0.79 (0.50–1.19) 0.78 (0.66–0.90) 1.19 (0.85–1.52) 1.24 (0.03–6.92) 1.68 (0.72–3.31) 1.12 (0.77–1.47)	SMR values calculated in 5-y age and calendar strata. Jobs were classified according to past Cd exposure (high, medium or low). Years at risk divided based on these categories into "ever high" (at least 1 y), "ever medium" (at least 1 y) and "always low".	(483)
North America							
Cross-sectional study: 2 125 participants ≥ 40 y of age from NHANES 1999–2000, selected to represent the US population.	1999–2000	Peripheral arterial disease defined as an ankle brachial index < 0.9 in at least one leg.	*Quartiles of B-Cd, nmol/l* ≤ 3.56 3.57–5.33 5.34–6.23 > 6.23	 27 20 32 60	OR 1.00 0.96 (0.41–2.25) 1.17 (0.61–2.25) 2.42 (1.13–5.15) P(trend): 0.02	Adjustment for age, sex, race, education, BMI, alcohol intake, hyper-tension, diabetes, hyper-cholesterolaemia, glomerular filtration rate,	(696)

Table A16. Cadmium.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
						CRP, self-reported smoking status, serum cotinine and lead.	
Cross-sectional study: 790 participants ≥ 40 y of age from NHANES 1999–2000.	1999–2000	As above.	75th vs 25th percentile of the U-Cd distribution.	49	OR 3.05 (0.97–9.58)	Adjustment for age, sex, race, education, smoking status and urinary creatinine.	(697)
Cross-sectional study: 4 912 individuals 45–79 y old in NHANES III (1988–1994) of which 2 187 (653 male and 1 534 female) never-smokers. When weighted, participants represented 52 234 055 Americans.	1988–1994	MI, determined by ECG.	*Tertiles (T) of U-Cd, µg/g creat.* All men T1: < 0.43 T2: 0.43–0.87 T3: ≥ 0.88 All women T1: < 0.43 T2: 0.43–0.87 T3: ≥ 0.88 Never-smokers T3:T1	451	OR 1.00 1.09 (0.60–2.00) 1.26 (0.71–2.26) 1.00 1.27 (0.77–2.09) 1.80 (1.06–3.04) 1.85 (1.10–3.14)	Adjustment for the Framingham risk score (age, total cholesterol, smoking status (yes vs no), HDL cholesterol, systolic blood pressure, and treatment for hyper-tension, pack-years of smoking, race-ethnicity, family history of heart attack and diabetes.	(272)
Cohort: 2 422 male workers employed ≥ 3 y in smelter, mill or sulphur operations 1946–1996, Copperhill, US. *Referents:* US national and local county rates.	1949–2000	Mortality (ICD-9) from CeVD (430–438), all heart disease (390–398, 402, 404, 410–429), IHD (410–414), chronic disease of endocardium and other myocardial	*CeVD* National rates Local rates *All heart disease* National rates Local rates *IHD* National rates Local rates *Chronic disease of*	72 326 272 9	SMR 0.93 (0.73–1.17) 1.07 (0.83–1.36) 0.73 (0.66–0.82) 0.76 (0.68–0.85) 0.79 (0.70–0.89) 0.80 (0.70–0.90)	SMRs computed for the total cohort and subgroups defined by work area within the Copperhill facility (smelter, acid, mill/mine, and mixed areas), race, year of hire, duration of employment, and the time since first employment.	(605)

Table A16. Cadmium.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
		insufficiency (424, 428), hypertension with heart disease (402, 404), all other heart disease (415–417, 420–423, 425–427, 429) and hypertension without heart disease (401, 403, 405).	*endocardium and other myocardial insufficiency* National rates Local rates *Hypertension with heart disease* National rates Local rates *All other heart disease* National rates Local rates *Hypertension without heart disease* National rates Local rates	 6 37 2 	 0.56 (0.26–1.07) 0.58 (0.27–1.11) 0.37 (0.13–0.80) 0.67 (0.22–1.57) 0.59 (0.41–0.81) 0.61 (0.43–0.84) 0.36 (0.04–1.29) 0.49 (0.06–1.75)	Historical exposures estimated for lead, SO_2, arsenic, cadmium, dust and cobalt.	
Cross-sectional study: 12 049 participants aged ≥ 30 y from NHANES 1999–2006 selected to represent the US population (of which all were analysed for B-Cd and 3 909 for U-Cd).	1999–2006	Stroke and congestive heart failure, self-reported.	*Stroke* B-Cd (5.1 vs 3.8 nmol/l) U-Cd (3.7 vs 2.6 nmol/l) *Congestive heart failure* B-Cd (5.0 vs 3.8 nmol/l) U-Cd (4.0 vs 2.6 nmol/l)	 492 171 471 135	OR for a 50% increase in Cd 1.38 (1.14–1.67) 1.10 (1.00–1.20) 1.48 (1.17–1.87) 1.12 (1.04–1.21)	Adjustment for age, sex, race/ethnicity, education, BMI, poverty income ratio, alcohol consumption, smoking status, diabetes, hypertension, hyper-cholesterolaemia, chronic kidney disease, and CHD. CHD was omitted in congestive heart failure analyses. U-Cd analyses were also adjusted for creatinine.	(741)

Table A16. Cadmium.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cross-sectional study: 15 332 adults > 20 y of age with determinations of Cd in blood (n = 10 991) and urine (n = 3 496) participating in the US NHANES 1999–2004.	1999–2004	Systolic and diastolic blood pressure levels, and hypertension.	*Quartiles of B-Cd, nmol/l* Systolic blood pressure ≤ 1.78 1.78–3.56 3.56–6.23 > 6.23 90th vs 10th percentile Diastolic blood pressure ≤ 1.78 1.78–3.56 3.56–6.23 > 6.23 90th vs 10th percentile *Quartiles of U-Cd, nmol/l* Systolic blood pressure ≤ 1.51 1.51–2.93 2.93–5.51 > 5.51 90th vs 10th percentile Diastolic blood pressure ≤ 1.51	 2 508 3 394 2 821 2 268 2 508 3 394 2 821 2 268 852 895 881 868 852	Blood pressure change (95% CI), mmHg 0.00 0.72 (-0.11–1.57) 1.85 (0.52–3.19) 1.50 (-0.24–3.24) P(trend): 0.116 1.36 (-0.28–3.00) 0.00 1.00 (0.28–1.71) 2.01 (0.86–3.15) 1.23 (0.10–2.35) P(trend): 0.006 1.68 (0.57–2.78) 0.00 -0.89 (-2.47–0.69) -0.55 (-3.03–1.93) -2.05 (-5.11–0.99) P(trend): 0.251 -1.78 (-4.76–1.19) 0.00	Adjustment for age, sex, race/ethnicity, education, smoking status (never, former, current), cotinine, alcohol intake, BMI, menopause status, anti-hypertensive medication), blood lead. The association between B-Cd and blood pressure was stronger among never-smokers. All models for U-Cd were also adjusted for creatinine levels.	(945)

Table A16. Cadmium.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			1.51–2.93	895	-0.26 (-1.28–0.75)		
			2.93–5.51	881	0.26 (-0.94–1.48)		
			> 5.51	868	-0.45 (-2.34–1.44)		
					P(trend): 0.565		
			90^{th} vs 10^{th} percentile		-0.44 (-1.94–1.05)		
			Hypertension				
			B-Cd, nmol/l		OR		
			≤ 1.78	819	1.00		
			1.78–3.56	1 419	0.98 (0.80–1.19)		
			3.56–6.23	1 452	1.25 (0.98–1.59)		
			> 6.23	979	1.03 (0.77–1.36)		
					P(trend): 0.303		
			90^{th} vs 10^{th} percentile		1.14 (0.89–1.45)		
			U-Cd, nmol/l				
			≤ 1.51	301	1.00		
			1.51–2.93	369	0.80 (0.54–1.21)		
			2.93–5.51	430	1.02 (0.66–1.58)		
			> 5.51	415	0.72 (0.43–1.21)		
					P(trend): 0.170		
			90^{th} vs 10^{th} percentile		0.66 (0.37–1.17)		
Cohort: 8 989 participants ≥ 20 y of age in the US NHANES 1999–2004.	Until 2006	Mortality (ICD-10) from CVD (I00–I78), heart disease (I00–I09, I11, I13, I20–I51) and IHD (I20–I25).	*B-Cd*		HR	Adjustment for sex, education, annual household income and race/ ethnicity, postmenopausal status, BMI, blood lead, CRP, total cholesterol, HDL cholesterol,	(946)
			80^{th} vs 20^{th} percentile (0.80 vs 0.22 µg/l)				
			CVD	191	1.69 (1.03–2.77)		
			Heart disease	113	1.98 (1.11–3.54)		
			IHD	88	1.73 (0.88–3.40)		
			U-Cd				

Table A16. Cadmium.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			80^{th} vs 20^{th} percentile (0.57 vs 0.14 µg/g creat.) CVD Heart disease IHD	 191 113 88	 1.74 (1.07–2.83) 2.53 (1.54–4.16) 2.09 (1.06–4.13)	cholesterol lowering medication, hypertension, diabetes, estimated glomerular filtration rate, smoking status, cumulative smoking dose and serum cotinine.	
Cohort: 3 348 American Indian men and women 45–74 y of age from 13 American Indian communities in Arizona, Oklahoma, and North and South Dakota, who participated in the Strong Heart Study in 1989–1991.	*Mortality* until 2008 *Incidence* from clinic visits 1993–1995, 1998–1999	Mortality from, and incidence of, CVD, CHD, heart failure and stroke.	U-Cd, µg/g creatinine *Mortality* CVD ≤ 0.61 0.62–0.92 0.93–1.45 > 1.45 CHD ≤ 0.61 0.62–0.92 0.93–1.45 > 1.45 *Incidence, fatal and non-fatal* CVD ≤ 0.61 0.62–0.92 0.93–1.45 > 1.45 CHD ≤ 0.61 0.62–0.92	 90 101 94 115 79 71 78 79 249 263 269 303 193 182	HR 1.0 1.33 (0.99–1.79) 1.37 (1.00–1.88) 1.87 (1.34–2.60) P(trend): < 0.001 1.0 1.09 (0.78–1.53) 1.32 (0.93–1.87) 1.51 (1.04–2.20) P(trend): < 0.005 1.0 1.20 (1.00–1.44) 1.30 (1.07–1.58) 1.48 (1.21–1.80) P(trend): < 0.001 1.0 1.13 (0.92–1.40)	Follow-up was 99.8% complete for mortality 99.2% complete for morbidity events. Adjustment for sex, postmenopausal status, education, BMI, total cholesterol, estimated LDL cholesterol, hypertension, diabetes, estimated glomerular filtration rate, smoking status and cumulative dose.	(943)

Table A16. Cadmium.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			0.93–1.45	198	1.31 (1.05–1.63)		
			> 1.45	193	1.33 (1.05–1.68)		
			Heart failure		P(trend): 0.002		
			≤ 0.61	60	1.0		
			0.62–0.92	81	1.40 (0.99–1.99)		
			0.93–1.45	87	1.52 (1.06–2.18)		
			> 1.45	100	1.61 (1.10–2.36)		
			Stroke		P(trend): 0.01		
			≤ 0.61	51	1.0		
			0.62–0.92	51	1.21 (0.81–1.80)		
			0.93–1.45	53	1.11 (0.73–1.69)		
			> 1.45	89	1.87 (1.22–2.86)		
					P(trend): 0.03		
Asia							
Cohort: 3 119 inhabitants (1 403 men, 1 716 women) of the Cd-polluted Kakehashi River basin in Japan, who participated in a health impact survey conducted by Ishikawa Prefecture in 1981–1982. The subjects amounted to 89% of all inhabitants ≥ 50 y old living in this area at that time. *Referents:* inhabitants living in a reference area.	Until 1996	Mortality (ICD-9) from heart failure, CeVD and cerebral infarction.	U-Cd, high [a] vs moderate [b] (≥ 10 vs < 10 µg/g creat.)		HR	Adjustment for age group. [a] 11.0% of men and 28.7% of women. [b] upper limit of referents.	(690)
			Heart failure				
			Men	13	1.97 (1.06–3.66)		
			Women	36	1.59 (1.03–2.46)		
			CeVD				
			Men	11	1.01 (0.53–1.91)		
			Women	30	1.22 (0.78–1.91)		
			Cerebral infarction				
			Men	10	1.32 (0.67–2.62)		
			Women	19	1.18 (0.67–2.09)		
Cohort: 3 178 inhabitants (1 424 men, 1 754 women) who participated in a health	Until 1996	Mortality (ICD-9) from heart failure and cerebral	U-β2 µ-globulin, µg/g creatinine		HR	Adjustment for age group.	(709)
			Heart failure, men				

Table A16. Cadmium.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
impact survey 1981–1982, amounting to 91% of all residents ≥ 50 y old, living in the Cd-polluted Kakehashi River basin in Japan.		infarction.	< 300 300–1 000 1 000–10 000 ≥ 10 000 *Heart failure, women* < 300 300–1 000 1 000–10 000 ≥ 10 000 *Cerebral infarction, men* < 300 300–1 000 1 000–10 000 ≥ 10 000 *Cerebral infarction, women* < 300 300–1 000 1 000–10 000 ≥ 10 000	29 9 14 8 16 25 26 20 18 13 22 6 12 11 21 10	1 0.88 (0.41–1.89) 1.45 (0.74–2.84) 3.69 (1.62–8.39) 1 1.94 (1.08–3.48) 3.05 (1.73–5.35) 3.19 (1.19–5.52) 1 2.4 (1.15–4.98) 4.48 (2.29–8.78) 5.36 (2.04–8.78) 1 1.88 (0.82–4.29) 3.58 (1.71–7.51) 3.19 (1.29–7.88)		
Cross-sectional study: 5 919 inhabitants ≥ 20 y of age (2 957 men, 2 962 women) who participated in the Korean NHANES 2008–2010, selected to represent the adult South Korean population.	2008–2010	Hypertension defined as ≥ 90 mmHg diastolic or ≥ 140 mmHg systolic blood pressure, or self-reported current use of an anti-hypertensive	*Per doubling of B-Cd* Men Women *B-Cd quartiles, µg/l* Men ≤ 0.62 > 0.62–0.93 > 0.93–1.33 > 1.33		OR 1.32 (1.15–1.50) 1.19 (1.00–1.41) 1 1.23 (0.91–1.67) 1.66 (1.22–2.28) 1.83 (1.32–2.52)	Adjustment for sex, age, residence area, education level, smoking and drinking status, serum creatinine, haemoglobin, BMI and diabetic status. ORs for having hyper-tension with doubling of the blood metal levels	(545)

Table A16. Cadmium.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
		medication.	Women ≤ 0.73 > 0.73–1.11 > 1.11–1.57 > 1.57		 1 1.34 (0.82–2.19) 1.27 (0.81–2.01) 1.47 (0.95–2.26)	were calculated using log_2-transformed blood Cd as an independent continuous variable.	
Meta-analysis							
CVD: 4 studies based on blood and 2 studies based on urine concentrations. CHD: 3 studies based on blood and 2 studies based on urine concentrations. Stroke: 2 studies based on blood and 1 study based on urine concentrations.	Varying	Incidence of, or mortality from, CVD, CHD and stroke.	*Top vs bottom tertile of blood or urine levels.* CVD CHD Stroke	 3 756 1 654 601	RR 1.33 (1.09–1.64) 1.29 (0.98–1.71) 1.72 (1.29–2.28)		(172)

Table A17. Welding fumes.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Nordic countries							
Total male population in the Swedish national census 1960. *Cohort:* 23 464 male welders and gas cutters. *Referents:* total male population.	1961–1970	Mortality from IHD (ICD-8, 410–414).	IHD	252	SMR 0.99		(876)
All gainfully employed men identified in the Swedish national censuses 1970 and 1990, respectively. *Cohorts:* male welders and gas cutters. *Referents:* all gainfully employed men.	1970–1995, 1990–1995	Mortality from IHD (ICD-7–8, 410–414).	*IHD* Census 1970 Census 1990	 2 156 102	SMR 1.06 (1.02–1.11) 1.35 (1.10–1.64)	The increased SMR in the census 1990 is unlikely explained by smoking habits.	(882)
Case-control study: 26 847 Swedish men with first MI, 2 controls/case.	Stockholm County: 1976–1984 Other counties: 1976–1981	Incidence of first MI, mortality (ICD-8, 410) and hospital discharges (410.00, 410.99).	*First MI* Male welders and flame cutters		RR 1.1 (1.0–1.3) 1.0 (0.9–1.2)	 Adjustment for age, county and calendar year. Adjustment for age, county and socioeconomic group.	(377)
All manual workers (984 040 males, 741 631 females) from the Swedish national census in 1980 who were alive on 1 January 1987. *Cohort:* welders. *Referents:* manual workers with no exposure to particles.	1987–2005	First-time events of acute MI (ICD-9, 410; ICD-10, I21) and other IHD (ICD-9, 411–414; ICD-10, I20, I22–I25).	*Males* Acute MI Other IHD *Females* Acute MI Other IHD	 3 368 4 499 110 162	HR 1.19 (1.13–1.25) 1.18 (1.13–1.23) 1.29 (1.07–1.56) 1.14 (0.98–1.33)	Morbidity and mortality was retrieved from the Hospital Discharge Register and the National Cause of Death Register.	(1015)

Table A17. Welding fumes.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort I: 233 male welders working on stainless steel ≥ 5 y 1950–1965. *Cohort II:* 208 male railway track welders working ≥ 5 y 1950–1965. *Referents:* Swedish national male rates.	Until 1992	Mortality from IHD (ICD-9, 410–414).	*IHD* Cohort I Cohort II	 24 35	SMR 0.92 (0.59–1.37) 0.89 (0.62–1.24)	*Chromium exposure, µg/m³* Cohort I: 10–750 (range) Cohort II: 10 (geometric mean).	(641)
Cross-sectional study *Cohort:* 236 men < 70 y of age who worked > 1 y 1960–1993 in a welding factory. Main tasks were stainless steel welding and grinding. *Referents:* 989 men randomly chosen from the general population matched for age with ≥ 5 y occupational activity after 1960.	1993	Morbidity of MI and angina pectoris.	*MI* All ≥ 10 y employment *Angina pectoris* All ≥ 10 y employment *Specific activities* Grinding MI Angina pectoris Welding MI Angina pectoris		OR 2.4 (1.1–4.9) 1.3 (1.0–1.7) 2.5 (1.1–5.8) 1.1 (0.7–1.7) 2.5 (1.1–5.9) 3.3 (1.3–8.5) 1.8 (0.7–4.4) 1.4 (0.5–4.2)	72% of the exposed and 74% of the referents answered a standardised questionnaire. The question on MI was validated and the sensitivities were 100% in the exposed group and 90% in the referent group. The corresponding specificities were both 90%. Multiple logistic regression (OR) adjusted for age, smoking, education and first degree relatives with CVD.	(407)

Table A17. Welding fumes.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 3 321 survivors from the Copenhagen Male Study (started in 1970) with baseline established 1985–1986. Exposed were compared with unexposed.	Until 1993	Prevalence of MI.	*≥ 5 y exposure* Blood group O Welding Soldering Other blood group Welding Soldering		 OR 2.1 (1.05–4.3) 3.0 (1.6–5.8) 0.8 (0.4–1.9) 0.7 (0.3–1.7)	ABO blood groups have been discussed as a genetic risk factor for IHD. In a further analysis, all participants with overt CVD at baseline (1985–1986) were excluded and the cohort was followed until 1993. Calculated ORs were based on logistic regression analysis and adjustments were made for smoking habits, serum lipids, BMI, blood pressure, hypertension, leisure time activities and alcohol habits. One possible explanation for the discrepancy between historical IHD and the prospective follow-up is a larger proportion of older (mean age 63 y), retired and consequently now non-exposed subjects in the second analysis.	(924)
		Incidence of IHD (ICD-8, 410–414).	*≥ 5 y exposure* Blood group O Welding Soldering Other blood group Welding Soldering		 OR 1.1 (0.6–2.2) 1.8 (1.0–3.2) 1.0 (0.5–2.1) 1.05 (0.5–2.2)		
Cohort: 5 866 male Danish welders employed ≥ 1 y 1964–1984. *External referents:* national male rates of CVD diagnosis calculated from the Danish National Patient Registry.	1986–2006	Incidence of acute MI (ICD-8, 410; ICD-10, I21), angina pectoris (ICD-8, 413; ICD-10, I20), other acute	Cumulative particle exposure, mg/m^3-y *Acute MI, all* 0–10 10–50 50–100 > 100	 377 11 40 80 76	SIR 1.12 (1.01–1.24) 1.26 (0.63–2.26) 0.94 (0.94[a]–1.28) 1.26 (1.00–1.57) 0.98 (0.77–1.23)	Shipyards were excluded in order to exclude asbestos exposure. [a] Mismatch between SMR and CI.	(441)

Table A17. Welding fumes.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Internal referents: 3 499 welders.		IHD (ICD-8, 411; ICD-10, I24), chronic IHD (ICD-8, 412; ICD-10, I25), cardiac arrhythmias (ICD-8, 427; ICD-10, I48–49), cardiac arrest (none; ICD-10, I46), heart failure (none; ICD-10 I50) and cerebral infarction (ICD-8, 433–434; ICD-10, I63).	*Angina pectoris, all*	437	1.11 (1.01–1.22)		
			0–10	9	0.80 (0.36–1.52)		
			10–50	65	1.13 (0.87–1.44)		
			50–100	87	1.06 (0.85–1.31)		
			> 100	101	1.12 (0.91–1.36)		
			Chronic IHD, all	326	1.17 (1.05–1.31)		
			0–10	5	0.68 (0.22–1.59)		
			10–50	42	1.14 (0.82–1.55)		
			50–100	68	1.23 (0.95–1.56)		
			> 100	65	1.00 (0.77–1.27)		
			Cerebral infarct., all	169	1.24 (1.06–1.44)		
			0–10	2	0.58 (0.07–2.10)		
			10–50	21	1.26 (0.78–1.92)		
			50–100	30	1.17 (0.79–1.67)		
			> 100	46	1.43 (1.05–1.91)		
			Other acute IHD	14	1.08 (0.59–1.80)		
			Cardiac arrhythmias	237	1.01 (0.89–1.15)		
			Cardiac arrest	32	0.95 (0.65–1.34)		
			Heart failure	157	1.05 (0.90–1.23)		
			Internal comparison, cumulative particle exposure, mg/m^3-y				
			Acute MI		HRR	HRR (hazard rate ratio) adjusted for calendar year, smoking, alcohol consumption and use of anti-hypertensive or "heart" medicine.	
			0–10	17	1		
			10–50	67	1.11 (0.65–1.89)		
			50–100	96	1.43 (0.85–2.41)		
			> 100	80	1.03 (0.61–1.74)		
			Angina pectoris				
			0–10	17	1		

Table A17. Welding fumes.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			10–50	80	1.23 (0.73–2.08)		
			50–100	107	1.41 (0.84–2.36)		
			> 100	95	1.21 (0.72–2.03)		
			Chronic IHD				
			0–10	7	1		
			10–50	61	2.51 (1.15–5.49)		
			50–100	83	2.79 (1.29–6.04)		
			> 100	60	1.70 (0.78–3.72)		
			Cerebral infarction				
			0–10	7	1		
			10–50	32	1.32 (0.58–3.01)		
			50–100	32	1.17 (0.52–2.67)		
			> 100	52	1.54 (0.70–3.39)		
Europe (non-Nordic)							
Cohort: 1 000 welders employed at a shipyard in England 1940–1968. *Referents:* national rates from England and Wales.	Until 1982	Mortality from IHD (ICD-8, 400–414).	IHD	66	SMR (90% CI) 1.30 (1.04–1.56)	Mean iron oxide levels: 13.6 (< 0.1–60) mg/m^3 (personal sampling).	(705)
Study base: proportion of deaths among male welders compared with that of other male workers (boilermakers, shipwrights, painters, electrical fitters and joiners) employed at HM Dockyard Devonport ≥ 6 mo 1955–1974. Totally 656 deaths, 52 among welders.	Until 1975	Mortality (ICD-9) from CVD, MI and CeVD.	CVD MI CeVD	25 18 4	PMR 0.90 1.06 0.79		(627)

Table A17. Welding fumes.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 1 213 welders and 1 688 turners who had worked ≥ 6 mo 1950–1970 in the German metal industry. *Referents:* rates from the Federal Republic of Germany.	1989–1995	Mortality from circulatory diseases (ICD-9, 390–459).	*Circulatory disease* Welders Turners Welders/turners *Welding* Coated electrodes MIG, MAG, TIG Mixed *Effective welding period per day* > 25% ≤ 25%	 94 196 53 11 27 37 57	SMR 0.83 (0.67–1.02) 0.92 (0.79–1.05) RR 0.86 (0.68–1.11) SMR 1.10 (0.82–1.44) 0.71 (0.36–1.28) 0.60 (0.40–0.87) 0.71 (0.50–0.98) 0.94 (0.71–1.21)	Arc welders exposed to fumes containing chromium and nickel. Welding with coated electrodes produce much higher levels of fumes containing chromium and nickel than other techniques such as metal inert gas (MIG), metal active gas (MAG) or tungsten inert gas (TIG) welding.	(75)
Cohort: 2 721 male welders from 13 factories including 3 shipyards. *Referents:* French national male rates.	1975–1988	Mortality (ICD-8) from circulatory diseases (390–459), IHD (410–414) and CeVD (430–438).	 Circulatory disease IHD CeVD *IHD* Employment duration < 10 y 10–19 y ≥ 20 y Time since first employment < 10 y 10–19 y ≥ 20 y	 47 28 9 0 4 24 1 4 23	SMR 1.09 (0.80–1.45) 1.51 (1.00–2.18) 0.93 (0.42–1.76) – 1.00 1.79 (P < 0.05) 0.55 0.95 1.84 (P < 0.05)	Materials most commonly used were mild steel and low alloyed steel. The main welding techniques were manual metal arc welding and oxyacetylene welding to a lesser extent.	(675)

Table A17. Welding fumes.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 267 male electric arc welders and 228 male gas welders ever employed in a shipyard 1960–1981, Italy. *Referents:* Italian regional male rates from Genoa.	1960–1996	Mortality from CVD (ICD-9, 390–459).	*CVD* Electric arc welders Gas welders	 40 47	SMR 0.91 1.22	Electric arc welders were mainly exposed to fumes containing nickel and chromium. Gas welders used oxyacetylene torchers and were exposed to hydrocarbon vapours, during cutting inside oil and petroleum ship holds.	(763)
North America							
Cohort: 3 247 US male welders employed ≥ 1 d 1950–1973 and who worked ≥ 3 y. *Referents:* US male rates.	Until 1976	Mortality from circulatory diseases (ICD-7, 400–468).	Circulatory disease	204	SMR 0.76 (P < 0.01)		(74)
Cohort: 4 459 male mild steel welders with ≥ 2 y of welding heavy equipment at 3 plants in the Midwestern US. The plants started operation 1951–1957. *Referents:* US male rates.	1988–1998	Mortality from IHD (ICD-9, 410–414).	IHD	203	SMR 0.99 (0.86–1.14)	The welders were not exposed to asbestos (typical of shipyard welders), chromium or nickel (present in stainless steel). In 1974–1987, concentrations of dust were 6–7 mg/m^3 and iron oxide concentrations were 3–4 mg/m^3 (906).	(904)
Asia							
Cohort: 2 818 male welders employed before 1980 with ≥ 6 mo employment in an iron-steel plant, Anshan, China. *Referents:* Non-exposed blue-collar workers from the same	1980–1993	Mortality (ICD-9) from circulatory disease except CeVD (390–429, 440–459), acute MI (410), IHD	Circulatory disease except CeVD Acute MI IHD except acute MI CeVD	20 12 3 52	SRR 1.31 (1.14–1.50) 2.04 (1.14–3.63) 0.95 (0.86–1.03) 1.28 (1.19–1.40)		(422)

Table A17. Welding fumes.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
plant.		except acute MI (411–412), CeVD (430–439), intracranial (431–432) and cerebral infarction (434).	Intracranial infarction Cerebral infarction	31 19	1.24 (1.13–1.37) 1.59 (1.22–2.05)		
Cohort: 2 826 male flame cutters employed from around 1975 in shipbreaking operations in Taiwan. *Referents:* Taiwanese population.	1985–2008	Mortality from CVD (ICD-9, 390–459), arteriosclerotic heart disease (410–414, 429) and vascular lesions of CNS (430–438).	CVD Heart disease Vascular CNS lesions	68 27 26	SMR 1.14 (0.88–1.44) 1.63 (1.07–2.37) 0.94 (0.61–1.37)	Shipbreaking operations included exposure to asbestos, heavy metals and other toxic materials, e.g. PCBs.	(1039)
Pooled analysis							
Cohort: 11 092 male welders from 9 European countries. *Referents:* national rates.	Varying	Mortality from circulatory disease (ICD-8, 390–458).	Circulatory disease	469	SMR 0.94 (0.86–1.03)	Cohorts from Denmark, England, Finland, France, Germany, Italy, Norway, Scotland and Sweden.	(868)
Meta-analysis							
10 studies.	Varying	Morbidity and mortality from IHD.	*IHD* All studies Internal referents External referents Acute MI Other IHD		RR 1.09 (1.00–1.18) 1.39 (0.96–2.02) 1.08 (0.99–1.18) 1.69 (1.18–2.42) 1.06 (0.98–1.14)	 10 studies 4 studies 7 studies 3 studies 10 studies	(655)

Table A18. Wood industry.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Nordic countries							
Cohort: 20 854 male Swedish workers exposed to wood dust out of totally 248 087 construction workers. The database included records of medical examinations 1971–1993. *Referents:* 71 778 unexposed construction workers.	1971–2001	Mortality from IHD (ICD-9, 410–412; ICD-10, I21–I25) and CeVD (ICD-9, 430–438; ICD-10, I60–I69).	IHD CeVD	786 201	RR 1.12 (1.04–1.20) 0.91 (0.79–1.04)	Adjustment for age, smoking, hypertension and BMI.	(967)
Case-control study*:* 26 847 men and 9 755 women (Swedish) with first MI, 2 controls for each case.	Stockholm County: 1976–1984 Other counties: 1976–1981	Mortality from MI (ICD-8, 410) and hospital discharges (410.00, 410.99).	Male frame and circular sawyers and planers Female bench carpenters and cabinet makers	– –	RR 1.7 (1.0–3.0) 2.0 (1.0–3.9)	Adjustment for age, county and socio-economic group.	(377)
All economically active males and females identified in the Finnish national census 1970. *Cohort:* forestry workers, log floaters, plywood and fibreboard workers and timber workers. *Referents:* all economically active males and females.	1971–1991	Mortality from CVD, MI, other IHD than MI, and CeVD.	*CVD* Males Forestry workers and log floaters Plywood and fibre-board workers Timber workers Females Plywood and fibre-board workers *MI* Males Forestry workers and log floaters Females	 4 357 351 1 112 273 2 391	SMR 1.21 (1.17–1.24) 1.19 (1.07–1.32) 1.07 (1.01–1.14) 1.18 (1.04–1.33) 1.23 (1.19–1.28)		(713)

Table A18. Wood industry.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			Forestry workers and log floaters	11	2.14 (1.07–3.85)		
			Other IHD than MI				
			Males				
			Plywood and fibre-board workers	79	1.42 (1.13–1.78)		
			Females				
			Plywood and fibre-board workers	46	1.42 (1.05–1.91)		
			CeVD				
			Males				
			Forestry workers and log floaters	646	1.16 (1.08–1.26)		
			Females				
			Forestry workers and log floaters	10	2.90 (1.39–5.37)		
Cohort: male members of the Danish carpenters and cabinet makers' trade union on 1 January 1971. *Referents:* Danish national male rates.	1971–1976	Mortality from diseases of the heart (ICD-8, 390–429).	*Heart disease* Age 20–64 y	211	SMR 0.81 (0.70–0.92)		(726)
Europe (non-Nordic)							
Cohort: 5 108 male workers born < 1940 and employed < 1968 in the Buckinghamshire furniture industry. *Referents:* from England and Wales as a whole and an area correction to adjust for local mortality 1968–1978.	Until 1982	Mortality from heart disease (ICD-9, 400–405, 410–414, 428–429).	Heart disease	499	SMR 0.69 (0.63–0.75)		(6)

Table A18. Wood industry.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
North America							
Cohort: 10 322 US male workers in woodworking industries (7 157 carpenters and joiners, 2 409 workers in lumber and sawmill and 735 in furniture cabinetry). *Referents:* 406 798 US non-wood workers.	1959–1972	Mortality from CHD (ICD-7).	*CHD* All woodworkers Carpenters and joiners Lumber and sawmill Furniture cabinetry	 1 008 706 228 73	SMR 0.95 (P < 0.05) [a] 0.93 (P < 0.05) 1.00 1.04	[a] SMR 0.95 (P = 0.045) after adjustment for age and smoking.	(913)
Cohort: 8 579 US white male wood furniture plant workers identified among 36 622 first employed 1946–1962 and members of the United Furniture Workers of America. *Referents:* US national rates.	Until 1979	Mortality (ICD-8) from arterio-sclerotic heart disease (410–413) and CeVD (430–438).	*All* Heart disease CeVD *≥ 20 y since first exposure* Heart disease CeVD	 519 69 193 28	SMR 0.7 (0.7–0.8) 0.5 (0.4–0.7) 0.8 (0.7–1.0) 0.6 (0.4–0.9)	Adjustment for age, race, sex and calendar time.	(645)
Cohort: 10 497 US white and black male and female wood furniture plant workers. Follow-up of the study above (645).	Until 1984	Mortality (ICD-8) from arterio-sclerotic heart disease (410–413) and CeVD (430–438).	*≥ 20 y since first exposure* Heart disease CeVD	 527 106	SMR 0.9 (0.9–1.0) 0.9 (0.8–1.1)		(644)
Study base: proportion of deaths among white male carpenters compared with that of 61 682 white men employed in construction occupations who died 1984–1986 in 19 US states.	1984–1986	Mortality from IHD (ICD-9, 410–414).	*IHD* Carpenters	 4 302	PMR 0.94 (0.92–0.97)		(784)

Table A18. Wood industry.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
The Honolulu Heart Program Cohort established in 1965. All were residents on Oahu at the time of baseline (1965–1968). *Cohort:* 685 present and usual carpenters + 365 usual carpenters of Japanese ancestry, born 1900–1919. *Referents:* 6 458 male never carpenters of Japanese ancestry born 1900–1919.	Until 1986	Incidence of definite CHD included non-fatal MI, CHD death and sudden death within 1 h. Thromboembolic or haemorrhagic stroke defined by a trained neurologist.	*Present and usual carpenters* CHD Stroke *Usual carpenters* CHD Stroke *Never carpenters* CHD Stroke		Rate/1 000 40.1 (P < 0.05) 23.1 55.5 39.1 62.4 34.4	Adjustment for age, lung function, BMI, serum cholesterol, systolic blood pressure, smoking, physical activity and alcohol consumption.	(647)
Pooled analysis							
Cohort: 28 704 persons combined from 5 studies: British furniture workers, members of the union representing furniture workers in the US, 2 cohorts of plywood workers and 1 cohort of wood model makers. Pooled analyses were carried out for all cohorts combined, the 2 furniture worker cohorts combined and the 2 plywood workers cohorts combined. *Referents:* national or regional rates.	Varying	Mortality (ICD-9) from circulatory diseases (390–459) and IHD (410–414).	*All wood workers* Circulatory disease IHD *Furniture workers* Circulatory disease IHD *Plywood workers* Circulatory disease IHD	 3 699 2 535 2 355 1 578 446 305	SMR 0.8 (0.7–0.8) 0.8 (0.7–0.8) 0.7 (0.7–0.8) 0.7 (0.7–0.8) 0.8 (0.8–0.9) 0.9 (0.8–1.0)	Included studies: (6, 105, 106, 644, 645, 783, 796).	(225)

Table A19. Pulp and paper industry.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Nordic countries							
Cohort: 18 163 men and 2 291 women from 8 Swedish mills employed 1939–1999 and with > 1 y of employment. *Referents:* Swedish national rates.	1952–2001 (acute MI from 1969)	Mortality (ICD-9) from diseases of the circulatory system, (390–459), IHD (410–414), acute MI (410) and CeVD (430–438).	*Sulphate mills, males* Circulatory disease IHD Acute MI CeVD *Sulphate mills, females* Circulatory disease IHD Acute MI CeVD *Sulphite mills, males* Circulatory disease IHD Acute MI CeVD *Sulphite mills, females* Circulatory disease IHD Acute MI CeVD *Sulphate pulping, males* Circulatory disease IHD Acute MI CeVD *Sulphite pulping, males* Circulatory disease IHD	 1 518 969 580 244 84 42 32 24 1 387 902 556 232 69 41 24 15 319 216 121 46 325 233	SMRs 1.11 (1.05–1.16) 1.09 (1.02–1.16) 1.22 (1.12–1.32) 1.06 (0.93–1.20) 0.94 (0.75–1.16) 0.97 (0.70–1.30) 1.25 (0.85–1.76) 1.05 (0.67–1.56) 0.95 (0.90–1.00) 0.96 (0.89–1.02) 1.11 (1.02–1.21) 0.94 (0.83–1.07) 0.84 (0.65–1.06) 1.00 (0.72–1.36) 1.07 (0.68–1.59) 0.72 (0.40–1.19) 1.12 (1.00–1.25) 1.17 (1.02–1.34) 1.29 (1.07–1.54) 0.95 (0.70–1.27) 0.94 (0.84–1.04) 1.03 (0.90–1.17)	Exposure levels as AM, GM (range) expressed as mg/m^3: *Sulphate pulping,* total dust: 3.6, 1.5 (0.1–64). *Sulphite pulping,* SO_2: 9.5, 4.5 (< 0.01–160). *Wood preparation,* wood dust: 2.0, 1.1 (0.1–15). *Paper production,* paper dust: 0.63, 0.41 (0.07–4.4). Possible confounders such as shift work and noise were not taken into account.	(30)

Table A19. Pulp and paper industry.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			Acute MI	143	1.16 (0.98–1.37)		
			CeVD	47	0.81 (0.59–1.08)		
			Wood preparation, males				
			Circulatory disease	345	0.98 (0.88–1.09)		
			IHD	217	0.96 (0.83–1.09)		
			Acute MI	122	1.04 (0.86–1.24)		
			CeVD	49	0.82 (0.61–1.08)		
			Paper production, males				
			Circulatory disease	343	1.11 (0.99–1.23)		
			IHD	225	1.12 (0.98–1.27)		
			Acute MI	137	1.26 (1.06–1.49)		
			CeVD	58	1.13 (0.85–1.46)		
Study base: 4 070 men deceased 1950–1987 and ≥ 20 y old at the time of death (of which 616 paper and paper mill workers) in 6 rather rural parishes in southeast Sweden.	1950–1987	Mortality (ICD-8) from IHD (410–414) and CeVD (430–438).	*Pulp and paper mill workers*		OR (90% CI)	Causes of death excluded among the referents: [a] Malignant causes. [b] Malignant causes, diabetes mellitus, obstructive lung disorders, pulmonary emboli and accidents. A previous smoking survey indicated an equal prevalence of smokers among subjects with and without a history of employment in paper mills (959).	(1028)
			IHD	207	0.9 (0.8–1.0) [a] 0.9 (0.8–1.1) [b]		
			CeVD	94	0.9 (0.8–1.2) [a] 1.0 (0.9–1.1) [b]		

Table A19. Pulp and paper industry.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Case-control study: 26 847 Swedish men with first MI. 2 controls for each case.	Stockholm County: 1976–1984 Other counties: 1976–1981	Incidence of first MI, mortality (ICD-8, 410) and hospital discharges (410.00, 410.99).	*First MI* Paper and paperboard workers Paper pulp workers		RR 1.6 (1.0–2.7) 1.3 (1.0–1.7)	Adjustment for age, county and socio-economic group.	(377)
Cohort: 3 520 paper and pulp industry workers employed for at least 1 y 1945–1961. *Referents:* Finnish national rates.	Until 1981	Mortality (ICD-8) from diseases of circulatory system (390–458) and IHD (410–414).	*All men* Circulatory disease IHD *All women* Circulatory disease IHD *Sulphite mill, men* Circulatory disease IHD *Sulphate mill, men* Circulatory disease IHD *Paper mill, men* Circulatory disease IHD *Board mill, men* Circulatory disease IHD *Maintenance, men* Circulatory disease IHD *Power plant, men*	 489 332 89 35 69 50 143 96 53 34 111 81 252 170	SMR 1.21 (1.09–1.34) 1.28 (1.14–1.44) 1.05 (0.84–1.29) 0.97 (0.68–1.35) 1.14 (0.89–1.44) 1.31 (0.97–1.73) 1.40 (1.16–1.70) 1.42 (1.15–1.74) 1.32 (0.99–1.73) 1.38 (0.95–1.93) 0.98 (0.80–1.22) 1.09 (0.87–1.36) 1.12 (0.98–1.29) 1.18 (1.01–1.38)	The observed excess of heart disease mortality could not be explained by differing smoking habits (468).	(467)

Table A19. Pulp and paper industry.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			Circulatory disease	93	1.45 (1.17–1.78)		
			IHD	67	1.58 (1.22–2.00)		
Subcohorts: Finnish sulphate and sulphite mill workers from the study above (467).	Until 1981	Mortality (ICD-8) from diseases of circulatory system (390–458) and IHD (410–414).	*Circulatory disease*		SMR	Exposure to hydrogen sulphide and organic sulphides.	(469)
			Exposure duration < 5 y	9	2.16 (0.99–4.10)		
			Exposure duration ≥ 5 y	28	1.36 (0.91–1.97)		
			Followed > 15 y	22	1.73 (1.09–2.62)		
			IHD				
			Exposure duration < 5 y	7	2.54 (1.02–5.23)		
			Exposure duration ≥ 5 y	18	1.29 (0.77–2.05)		
			Followed > 15 y	14	1.62 (0.88–2.72)		
All economically active males, 25–64 y, identified in the Finnish national census 1970. *Cohort:* male pulp mill workers. *Referents:* all economically active males.	1971–1991	Mortality from IHD other than MI.	IHD other than MI	101	SMR 1.34 (1.10–1.64)		(713)
Cohort: 3 143 female pulp and paper workers employed at least 1 y 1920–1993. *Referents:* Norwegian national rates and internal referents.	1951–2000	Mortality (ICD-9) from CVD (390–459), IHD (410–414) and CeVD (430–438).			SMR	The women were unlikely exposed to microorganisms as they were not working with fresh logs or wet part of the paper mills. Only a small number of women had been shift workers.	(536)
			CVD	315	1.17 (1.05–1.30)		
			IHD	147	1.22 (1.03–1.43)		
			CeVD	95	1.16 (0.94–1.42)		
			Tenure in paper department				
			< 3 y				
			CVD	54	1.33 (1.00–1.74)		
			IHD	32	1.73 (1.18–2.44)		
			CeVD	10	0.83 (0.40–1.52)		
			≥ 3 y				
			CVD	261	1.14 (1.01–1.29		

Table A19. Pulp and paper industry.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			IHD CeVD *Internal referents* CVD 1–2 y 3–14 y ≥ 15 y IHD 1–2 y 3–14 y ≥ 15 y	115 85	1.12 (0.94–1.35) 1.22 (0.97–1.51) RR 1.00 (0.70–1.44) 0.96 (0.73–1.28) 1.02 (0.74–1.39) 1.56 (0.97–2.52) 1.07 (0.70–1.63) 1.21 (0.77–1.90)	No information on smoking habits.	
Europe (non-Nordic)							
Cohort: 4 242 male and female paper mill workers employed at least 1 y 1955–1992. *Referents:* Scottish national rates.	Until 1994	Mortality (ICD-9) from CVD (390–459), IHD (410–414) and CeVD (430–438).	*All* CVD IHD CeVD *Tenure ≥ 10 y* CVD IHD CeVD	 554 351 136 381 237 95	SMR 1.00 (0.92–1.09) 0.98 (0.88–1.09) 1.12 (0.94–1.33) 1.04 (0.94–1.15) 1.00 (0.88–1.14) 1.16 (0.94–1.42)		(184)
Cohort: 5 529 male and 876 female pulp and paper mill workers employed in 4 factories. *Referents:* French national rates.	1968–1992	Mortality from CVD.	CVD	168	SMR 0.80 (0.68–0.93)		(1021)
Cohort: 2 502 male and 739 female pulp and paper mill workers employed ≥3 mo in	1970–1992	Mortality from CVD (ICD-9, 390–459).	*CVD* All	42	SMR 0.55 (0.39–0.74)		(821)

Table A19. Pulp and paper industry.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
4 factories in Catalonia 1970–1992. *Referents:* Spanish national rates.			Men Women	39 3	0.57 (0.40–0.78) 0.37 (0.07–1.10)		
North America							
Study base: proportion of deaths among 210 white male decedent members of the United Paperworkers International Union who had worked ≥ 10 y compared with that in the US population.	1970–1984	Mortality from arteriosclerotic heart disease (ICD-8, 410–414).	Heart disease	71	PMR 1.00 (0.78–1.26)	Adjustment for race, age at death and calendar year of death.	(893)
Study base: proportion of deaths among 2 113 decedent members of the US and Canadian Pulp, Sulfite and Paper Workers' Union compared with the proportion in the US population.	1935–1964	Mortality from diseases of circulatory system (ICD-8, 390–458).	*Circulatory disease* Sulphite, plus others Sulphate, plus others Sulphite, not sulphate, plus others Sulphate, not sulphite, plus others Paper, plus others, neither sulphite nor sulphate	1 110 722 444 413 135 121	PMR 1.14 1.14 (P < 0.05) 1.21 (P < 0.05) 1.07 (P < 0.05) 1.15 1.13		(643)
Cohort: 3 572 white male pulp and paper mill workers employed for at least 1 y 1945–1955. *Referents:* US national rates.	Until 1977	Mortality (ICD-7) from diseases of circulatory system (400–468) and vascular lesions of	Circulatory disease Vascular CNS lesions	432 72	SMR (90% CI) 0.81 (0.75–0.88) 0.85 (0.69–1.03)		(783)

Table A19. Pulp and paper industry.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
		CNS (330–334).					
Cohort: 883 white males of which 297 sulphite pulp mill and 376 paper mill workers, enrolled for a respiratory study 1961–1985, employed ≥ 1 y in a paper company in Berlin, New Hampshire. *Referents:* US national rates. A previous cohort was followed until 1973 (286).	Until 1985	Mortality (ICD-8) from diseases of circulatory system (390–458) and IHD (410–414).	*All* Circulatory disease IHD *Circulatory disease* Sulphite pulp mill Paper mill	 220 145 73 89	SMR 0.91 (0.80–1.04) 0.89 (0.75–1.05) 0.91 (0.72–1.15) 1.02 (0.82–1.26)		(398)
Cohort: same as above.	Until 1992	Mortality from all heart disease (no ICD-code given).	All heart disease	199	SMR 0.87 (0.75–1.00)	Over 80% of the cohort were cigarette smokers.	(399)
Cohort: 11 178 employees from 7 pulp and paper mills (9 358 males, 1 820 females) who worked ≥ 1 y 1975–1992. *Referents:* US national rates.	Until 1992	Mortality (ICD-9) from all heart disease, IHD, all other heart disease and CeVD.	*Tenure ≥ 1 y* All heart disease IHD All other heart disease CeVD *Tenure ≥ 30 y* All heart disease IHD All other heart disease CeVD	 276 222 43 32 170 139 24 17	SMR 0.75 (0.66–0.84) 0.80 (0.70–0.91) 0.67 (0.48–0.90) 0.84 (0.58–1.19) 0.80 (P < 0.01) 0.87 0.65 (P < 0.05) 0.77		(1035)

Table A19. Pulp and paper industry.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 63 025 pulp and paper mill workers from 51 mills employed 1970–1991 for ≥ 10 y. *Referents:* US national and regional rates and also internal comparisons.	Until 1991	Mortality (ICD-9) from diseases of circulatory system and CVD.	 Circulatory disease, US rates CVD, US rates *CVD, white males* US rates State rates County rates *CVD, white males* US rates Kraft (sulphate) Sulphite Other chemical pulping Other pulping *Heart disease, white males* Internal comparison Kraft (sulphate) Sulphite Other chemical pulping Other pulping	 3 259 2 243 1 999	SMR 0.75 (0.72–0.78) 0.74 (0.71–0.77) 0.75 (0.71–0.78) 0.80 (0.76–0.83) 0.86 (0.82–0.89) 0.75 (0.71–0.78) 0.78 (0.71–0.84) 0.77 (0.72–0.83) 0.71 (0.65–0.77) RR 0.96 (0.84–1.10) 1.06 (0.96–1.17) 1.12 (1.03–1.23) 0.91 (0.83–1.01)	Adjustment for race and sex.	(609)
New Zealand							
Cohort: 8 456 pulp and paper mill workers who worked ≥ 1 y 1978–1990. *Referents:* New Zealand national rates.	Until 1992	Mortality from diseases of circulatory system (ICD-9, 390–459).	Circulatory disease	119	SMR 0.78 (0.64–0.93)		(624)

Table A19. Pulp and paper industry.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Pooled analysis							
Cohort: 57 613 pulp and paper workers (51 240 men, 6 373 women) who worked ≥ 1 y in Brazil, Denmark, Finland, France, Japan, New Zealand, Norway, Poland, South Africa, Spain, Sweden and the US. *Referents:* national rates.		Mortality from diseases of circulatory system (ICD-9, 390–459).	*Circulatory disease* Never exposed Ever exposed High exposed	 1 438 3 660 342	SMR 0.92 (0.87–0.96) 0.94 (0.91–0.97) 0.96 (0.86–1.07)	SMRs by SO_2 exposure.	(549)

Table A20. Textile industry.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Nordic countries							
All gainfully employed identified in the Swedish national censuses 1970 and 1980. *Cohorts:* textile workers I: 1970 (7 419 men, 9 157 women) II: 1970 and 1980 (1 620 men, 1 772 women). *Referents:* all gainfully employed: I: 2 047 861 men, 1 260 583 women II: 645 393 men, 370 903 women.	1970–1995, 1980–1995	Mortality from IHD (ICD 7–8, 410–414).	*Cohort I* Males Females *Cohort II* Males Females	 988 434 114 35	SMR 1.15 (1.08–1.22) 1.08 (0.98–1.18) 1.34 (1.11–1.62) 1.35 (0.94–1.88)	No socioeconomic adjustment.	(888)
Cohort: 1 065 women exposed to raw cotton for ≥ 5 y and hired 1950–1971. *Referents:* Finnish female national rates. *Cross-sectional study* *Cohort:* same as above (still alive or next of kin), questionnaire study regarding previous disease; response rate 73%. *Referents:* 398 female paper box assembly workers, response rate 77%.	1950–1985 1985	Mortality (ICD-8) from CVD, IHD and CeVD. Morbidity from heart diseases, CeVD and hypertension.	 CVD IHD CeVD Heart diseases CeVD Hypertension	 37 16 13	SMR 0.77 0.74 0.91 OR 1.0 1.3 0.8	Mean dust levels: 1.8–3.3 mg/m^3 (highest levels for carding) measured in 5 mills in 1972.	(509)
All economically active males identified in the Finnish national census 1970. *Cohort:* male weaving machine operators.	1971–1991	Mortality from CeVD.	*CeVD* Age 25–64 y	 11	SMR 2.05 (1.02–3.70)	No socioeconomic adjustment.	(713)

Table A20. Textile industry.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Referents: all economically active males.							
Cohort: 353 self-employed males in textile industry identified in the Central Population Register of Denmark. *Referents:* all economically active persons 20–59 y old on 1 January 1981, identified in the Register.	Until 1984	Hospitalisations from IHD (ICD-8, 410–414).	IHD	11	SHR 1.85 (1.03–3.35)	SHR: standardised hospitalisation ratio.	(973)
Europe (non-Nordic)							
Registrar General reports for England and Wales, 1930–1932. *Cohort:* cotton weavers, spinners, strippers and grinders. *Referents:* all males aged 55–64 y.	1930–1932	Mortality from cerebral vascular lesions.	*Cerebral vascular lesions* Referents Social class III Cotton weavers Cotton spinners Strippers and grinders	 10 621 4 503 60 49 13	Rate/1 000 2.0 2.0 2.4 3.4 (P = 0.02) 6.4 (P = 0.02)	Strippers and grinders were those most exposed to fine dust in the card rooms. Spinning rooms were sometimes continuous with card rooms. Weavers had little contact with fine cotton dust.	(837)
Cross-sectional study (first) *Cohort:* 103 male card- and blow-room cotton workers, England. *Referents:* 93 male weavers and warehousemen. Participants were 35–65 y of age and had worked ≥ 10 y in the respective departments. *Cross-sectional study (second)*	Not given. Year of publication 1952.	Casual blood pressure taken in the beginning of the examination. Lowest blood pressure taken after lying down in silence.	*Mean blood pressure* First study Casual, systolic Lowest, systolic Casual, diastolic Lowest, diastolic Second study	Exp/ refs	Exp/refs (mmHg) 141.1/141.5 127.7/127.7 87.6/84.7 [a] 82.0/80.3	[a] P = 0.04.	(838)

Table A20. Textile industry.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 59 male card- and blow-room workers. *Referents:* 50 male weavers and warehousemen, all aged 50–59 y.		Hypertension defined as lowest pressures ≥ 150/90.	Systolic Diastolic *Hypertension*	 15/4 [b]	137.9/129.9 [b] 84.9/81.6	[b] P < 0.05.	
Study base: proportion of deaths among 1 429 dyers, bleachers and textile workers (Bradford National Union, membership for ≥ 1 y before 1936) compared with the proportion in the general population.	1957–1968	Mortality from CVD (ICD-8).	CVD	728	PMR 1.03	The principle jobs in the industry were dyeing, finishing, bleaching and printing.	(704)
Cohort: 1 586 workers (663 men, 923 women) seen at least once 1963–1966 in 16 Lancashire mills; 1 359 in mills processing cotton and 227 in mills processing man-made fibres. *Referents:* national rates from England and Wales.	1967–1977 (90% of the group) 1967–1979 (10% of the group)	Mortality (ICD-8) from IHD, CeVD and other cir-culatory disease.	*Cotton mills* Women IHD CeVD Other circulatory disease Men IHD CeVD Other circulatory disease *Man-made fibre mills* All circulatory disease Women Men	 11 4 7 16 8 1 2 5	SMR Crude (adjusted) 0.84 (0.75) 0.5 (0.4) 1.4 (–) 0.72 (0.63) 1.3 (1.0) 0.2 (–) 0.4 (0.4) 0.8 (0.7)	Adjustment for region of the mills. Mean dust levels: 1.0 mg/m^3 in card-rooms of cotton mills.	(89)
Cohorts: *Main study group:* 3 458 cotton workers (with at least 1 medical examination) enrolled in a study of respiratory symptoms 1968–1970.	Until 1984	Mortality (ICD 8–9) from circulatory disease, IHD and CeVD.	*Main study group* Circulatory disease IHD CeVD *Circulatory disease by*	 298 174 69	SMR 0.91 (0.81–1.02) 0.90 (0.77–1.05) 0.95 (0.74–1.20)	SMR by follow-up < 5 y ≥ 5 y 0.50 1.00 0.44 (P < 0.01) 1.01 0.75 1.00	(414)

Table A20. Textile industry.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Second group: 340 workers with no medical examination data. *Referents:* national rates from England and Wales.			*years of cotton exposure* Men < 15 y 15–29 y ≥ 30 y Women < 15 y 15–29 y ≥ 30 y *Circulatory disease by byssinosis* Men With byssinosis Without byssinosis Women With byssinosis Without byssinosis *Second group* Circulatory disease IHD	 23 62 82 3 39 89 Smoker Yes/No 44/2 85/22 21/7 55/45 36 22	 0.96 1.16 0.72 (P < 0.01) 0.53 1.42 (P < 0.01) 0.86 Smoker Yes/No 0.97/0.24 [a] 0.97/0.75 1.71 [a]/0.45 [a] 1.44 [a]/0.71 [a] 1.63 (1.14–2.26) 1.78 (1.11–2.69)	Percentage of smokers consuming < 15 cig/day in the cohort vs in the general population: males: 52% vs 35% females: 62% vs 62%. [a]P < 0.05 SMR by follow-up < 5 y ≥ 5 y 2.87 (P < 0.01) 1.24 3.64 (P < 0.01) 1.17	
Study base: proportion of deaths among textile and fabric workers compared with the proportion among 3.5 million deaths in England and Wales.	1979–2000	Mortality from IHD (ICD-9, 410–414).	IHD *Males* 1979–1990 1991–2000 *Females* 1979–1990 1991–2000	 8 271 2 808 7 125 3 711	PMR 1.11 (1.09–1.13) 1.13 (1.08–1.17) 1.06 (1.04–1.09) 1.03 (0.99–1.06)	Adjustment for age and social class. Increased risks for weavers, spinners and winders. An increased PMR of diabetes among male textile and fabric workers.	(1051)

Table A20. Textile industry.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 7 545 cotton industry workers (2 852 men, 4 693 women) employed 1964–1993 and working ≥ 10 y. *Referents:* Polish national rates.	Until 1995	Mortality (ICD-9) from diseases of the circulatory system (390–459), hypertensive disease (401–405), IHD (410–414), CeVD (430–438) and athero-sclerosis (440).	*Men*		SMR	The authors point out that the determination of specific diseases of the circulatory system in Poland is not reliable. Cotton was the basic material, but during some periods other types of fibre were also processed: polyester: 1973–1993 polyamide: 1983–1990 rayon: 1983–1993 acrylics: 1991–1993. Mean dust concentrations: 1.8 (carding machine operators) to 11.7 µg/m^3 (cotton waste baling press operators); 11.4 µg/m^3 (weaving room operators). (Units probably mg/m^3).	(933)
			Circulatory disease	562	0.99 (0.91–1.08)		
			Hypertension	29	1.35 (0.90–1.94)		
			IHD	156	0.92 (0.78–1.08)		
			CeVD	58	0.81 (0.62–1.05)		
			Atherosclerosis	195	1.45 (1.25–1.67)		
			Spinning department				
			Circulatory disease	127	1.15 (0.96–1.37)		
			Hypertension	10	2.39 (1.15–4.40)		
			IHD	25	0.76 (0.49–1.12)		
			CeVD	15	1.07 (0.60–1.76)		
			Atherosclerosis	47	1.75 (1.29–2.33)		
			Weaving department				
			Circulatory disease	142	0.86 (0.72–1.01)		
			Hypertension	8	1.29 (0.55–2.52)		
			IHD	40	0.82 (0.59–1.12)		
			CeVD	14	0.68 (0.37–1.14)		
			Atherosclerosis	56	1.41 (1.07–1.83)		
			Women				
			Circulatory disease	378	0.84 (0.76–0.93)		
			Hypertension	24	0.73 (0.47–1.09)		
			IHD	64	0.74 (0.57–0.94)		
			CeVD	55	0.67 (0.50–0.87)		
			Atherosclerosis	145	1.17 (0.99–1.38)		
			Spinning department				
			Circulatory disease	144	0.90 (0.76–1.06)		
			Hypertension	8	0.70 (0.30–1.38)		
			IHD	26	0.86 (0.56–1.26)		
			CeVD	19	0.65 (0.39–1.02)		

Table A20. Textile industry.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			Atherosclerosis	59	1.29 (0.98–1.66)		
			Weaving department				
			Circulatory disease	163	0.77 (0.66–0.90)		
			Hypertension	12	0.75 (0.39–1.31)		
			IHD	24	0.57 (0.37–0.85)		
			CeVD	24	0.61 (0.39–0.91)		
			Atherosclerosis	60	1.09 (0.83–1.40)		
Cohort: 2 916 male synthetic spinning plant workers working ≥ 6 mo 1968–1984. *Referents:* regional rates from Franche-Comté, France.	Until 1999	Mortality from diseases of the circulatory system (ICD-9, 390–459).	Circulatory disease	134	SMR 0.71 (0.60–0.85)	Exposure included heat-transfer fluids, mineral fibres, textile lubricants, dusts and degradation products of hot polymers.	(423)
Cohort: 3 961 cotton mill workers from 4 textile industries in Vicenza, Italy, working some time 1946–85. *Referents:* regional rates from Veneto, Italy.	1970–1994	Mortality from diseases of the circulatory system (ICD-9).	Circulatory disease	213	SMR 1.06 (0.93–1.22)		(608)
North America							
Study base: proportion of deaths among 6 113 male textile workers compared with the proportion among 45 482 male deaths in Rhode Island, US.	1968–1978	Mortality (ICD-8) from diseases of the circulatory system (390–458), IHD (410–414) and CeVD (430–438).			PMR	Stratification by 5-y age groups. The years of death strata were 1968–1973 and 1974–1978. Only whites and blacks included.	(243)
			Circulatory disease	3 726	1.03 (1.01–1.05)		
			IHD	2 870	1.06 (1.03–1.09)		
			CeVD	499	1.01 (0.93–1.09)		
			IHD				
			Weavers	486	1.10 (1.03–1.17)		
			Miscellaneous textile finishing operatives	164	1.18 (1.05–1.32)		
			Dyeing and finishing	608	1.07 (1.01–1.13)		

Table A20. Textile industry.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 1 062 white men and 382 white women employed at 2 cotton mills in North Carolina some time during 1937–1940. *Referents:* US general population.	1940–1975	Mortality (ICD-8) from arterio-sclerotic heart disease and other diseases of the heart.	Employment duration *Heart disease, males* All jobs < 20 y 20–29 y ≥ 30 y Yarn processing < 20 y 20–29 y ≥ 30 y *Other heart diseases, males* All jobs < 20 y 20–29 y ≥ 30 y Yarn processing < 20 y 20–29 y ≥ 30 y *Heart disease, females* All jobs < 20 y 20–29 y ≥ 30 y Yarn processing < 20 y 20–29 y ≥ 30 y	 199 64 67 68 68 32 19 17 20 11 5 4 5 3 1 1 35 13 13 9 27 12 10 5	SMR 1.03 0.86 1.20 1.09 1.37 (P < 0.01) 1.30 1.69 (P < 0.02) 1.23 2.12 (P < 0.01) 2.70 (P < 0.01) 1.88 1.48 2.15 2.44 1.91 1.72 1.28 1.03 1.52 1.47 1.58 (P < 0.02) 1.29 2.18 (P < 0.02) 1.54		(633)

Table A20. Textile industry.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohorts: white male cotton textile workers from 3 cotton textile mills in Georgia, US. *Cohort I:* 5 822 subjects working 1938–1941. *Cohort II:* 6 316 subjects working 1948–1951. *Referents:* white male population from Georgia, US.	Cohort I: 1938–1963 Cohort II: 1948–1963	Mortality (ICD-7) from heart disease (400–443), CHD (420) and stroke (330–334).	*Cohort I* Heart disease CHD Stroke *Cohort II* Heart disease CHD Stroke	 294 224 64 197 165 37	SMR 0.76 0.82 0.73 0.84 0.90 0.79		(397)
Study base: proportion of deaths among yarn, thread and fabric mill workers compared with the proportion among 10 million decedents aged 18–64 y in the National Occupational Mortality Surveillance system in 30 US states.	1985–1999, 2003–2004, 2007	Mortality from acute MI (ICD-10, I21).	*Yarn, thread and fabric mills* White males White females Black males Black females	 2 420 761 448 197	PMR 1.22 (1.17–1.26) 1.38 (1.29–1.49) 1.32 (1.20–1.44) 1.22 (1.06–1.40)	Adjustment for age and smoking.	(786)
Cohorts: 7 487 male and 2 724 female workers in a synthetic textile plant, who had worked ≥ 1 y in 1947 or were newly employed 1947–1977. *Referents:* regional rates from Quebec and from 2 subregions of the province.	1947–1986	Mortality originally according to ICD 5–9. Underlying cause of death re-classified according to a scheme by Laboratory Center for Disease Control.	*Circulatory diseases* Males Females *IHD, males* Exposure duration 1–4 y 5–9 y 10–19 y ≥ 20 y *IHD, females* Exposure duration 1–4 y	 834 65 101 92 117 258 15	SMR 0.75 (0.70–0.80) 0.59 (0.46–0.76) RR 1 1.16 (0.87–1.55) 1.13 (0.85–1.48) 1.40 (1.10–1.79) RR 1		(344)

Table A20. Textile industry.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			5–9 y	7	0.63 (0.25–1.56)		
			10–19 y	6	0.79 (0.29–2.14)		
			≥ 20 y	13	1.41 (0.61–3.23)	P(trend): 0.003.	
			IHD, maintenance unit, males				
			Exposure duration		RR		
			0 y	411	1		
			> 0–4 y	63	1.00 (0.75–1.30)		
			5–9 y	32	1.27 (0.86–1.83)		
			10–19 y	28	1.26 (0.83–1.84)		
			≥ 20 y	34	1.65 (1.13–2.34)	P(trend): 0.002.	
			IHD, janitor unit, females				
			Exposure duration		RR		
			0 y	33	1		
			> 0–4 y	3	1.53 (0.29–4.89)		
			5–9 y	0	0.00 (0.00–9.57)		
			10–19 y	3	3.02 (0.58–9.62)		
			≥ 20 y	2	9.57 (1.03–37.4)	P(trend): 0.037.	
			CeVD, weaving unit, males				
			Exposure duration		RR		
			0 y	67	1		
			> 0–4 y	6	0.72 (0.26–1.66)		
			5–9 y	4	0.88 (0.23–2.36)		
			10–19 y	5	0.77 (0.24–1.88)		
			≥ 20 y	19	2.14 (1.21–3.60)		
Asia							
Cohort: 267 400 female textile workers in Shanghai, China, active or retired 1989–1991.	1989–2000	Mortality (ICD-9) from IHD (410–414), ischaemic	*Endotoxin exposure* IHD Exposed	 184	HR 1.00 (0.84–1.21)	Adjustment for age and smoking.	(324)

Table A20. Textile industry.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cumulative exposures were analysed in a subcohort of 3 128 workers. *Exposure to endotoxins* during cotton spinning, weaving and knitting. *Exposure to particulates* during cotton, wool, mixed fibre or synthetic spinning, weaving and knitting. *Referents:* females from all other textile sectors.		stroke (434) and intracerebral haemorrhage (431).	Referents Ischaemic stroke Exposed Referents Haemorrhagic stroke Exposed Referents *Particulate exposure* IHD Exposed Referents Ischaemic stroke Exposed Referents Haemorrhagic stroke Exposed Referents *Subcohort* All stroke, cum endotoxin exposure, EU/m^3-y Unexposed > 0–2 275 > 2 275–2 944 > 2 944–5 168 > 5 168	310 287 412 711 1 104 312 182 463 236 1 190 625 20 10 10 10 10	 1.12 (0.97–1.31) 1.12 (1.02–1.23) 0.99 (0.82–1.18) 1.08 (0.92–1.26) 1.12 (1.02–1.24) 1.00 0.71 (0.33–1.53) 1.07 (0.49–2.32) 0.91 (0.43–1.95) 1.52 (0.72–3.24) P(trend): 0.09	Mortality rate/100 000: *IHD* 6.5 never-smokers 20.6 ever-smokers *Ischaemic stroke* 8.3 never-smokers 15.9 ever-smokers *Haemorrhagic stroke* 23.9 never-smokers 92.9 ever-smokers Adjustment for age and smoking. P(trend): 0.35 for cumulative cotton dust exposure.	

Table A20. Textile industry.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Australia							
Cohort: 7 684 workers from the Textile, Clothing and Footwear Union. *Referents:* Australian population.	1988–1999	Mortality from CVD (ICD-9, 390–459).	*CVD* Males Females	 14 7	SMR 0.91 (0.50–1.53) 1.21 (0.49–2.50)		(315)
Meta-analysis							
Meta-analysis of 6 cohorts: (89, 397, 414, 509, 633).	Varying	Mortality from circulatory system diseases.	*Circulatory disease* Males Females	 1 010 228	SMR 0.85 (0.79–0.91) 0.94 (0.81–1.06)		(922)

Table A21. Agriculture.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Nordic							
All economically active persons identified in the Swedish census 1960 and born in Sweden 1896–1940. *Cohort:* agricultural workers. *Referents:* all economically active persons; 1.9 million men and 0.7 million women.	1961–1968	Mortality (ICD-7) from CHD (420), MI (420.1), CNS vascular disease (330–334) and cerebral haemorr-hage (331).	*Males* Self-employed agricultural CHD MI Vascular CNS lesions Cerebral haemorrhage Manual agricultural CHD MI Vascular CNS lesions Cerebral haemorrhage *Females* Self-employed agricultural CHD MI Vascular CNS lesions Cerebral haemorrhage Manual agricultural CHD MI Vascular CNS lesions Cerebral haemorrhage	 2 820 2 319 932 532 1 225 1 020 351 170 90 68 82 47 22 17 25 15	SMR 0.87 (0.84–0.90) 0.87 (0.84–0.91) 0.96 (0.90–1.02) 0.98 (0.90–1.07) 0.90 (0.85–0.95) 0.91 (0.86–0.97) 0.88 (0.79–0.98) 0.77 (0.66–0.90) 0.91 (0.73–1.12) 0.90 (0.70–1.14) 1.07 (0.85–1.33) 1.10 (0.81–1.46) 0.75 (0.47–1.13) 0.75 (0.44–1.20) 1.07 (0.69–1.58) 1.16 (0.65–1.91)	Adjustment for age and urbanisation. Farmers and agricultural workers had a low mortality compared to other self-employed or manual workers. Smoking habits were likely to contribute to these differences.	(1042)

Table A21. Agriculture.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
All economically active persons identified in the Swedish census 1980. *Cohort:* 60 515 farmers (39 386 males, 21 129 females). *Referents:* 2 843 237 economically active persons (1 470 293 males, 1 372 944 females).	The cohort was linked to the national hospital care registry 1978–1983.	Morbidity (ICD of 1965) from CVD, IHD, MI, hyper-tension and CeVD.	*Males* CVD IHD MI Hypertension CeVD *Females* CVD	 1 969 322 393 93 334 732	SMR 0.74 (0.70–0.77) 0.66 (0.59–0.74) 0.64 (0.58–0.71) 0.70 (0.57–0.86) 1.03 (0.92–1.18) 1.01 (0.90–1.13)		(951)
Cohort: 1 220 male farmers born 1930–1949, living in nine rural municipalities and identified in the Swedish Farm Register in 1989. *Urban referents:* 1 087 males randomly sampled from the population of the county where the farmers lived.	Mortality 1989–2001 Morbidity 1990–2002 (admissions to hospitals, Hospital Patient Registry).	Mortality and morbidity from CVD, IHD and stroke according to ICD-9–10. ICD-10 diagnoses were transformed to ICD-9 diagnoses.	*Mortality* CVD IHD CeVD *Morbidity* CVD IHD CeVD	 26 15 3 238 104 27	HR 0.60 (0.36–0.99) 0.55 (0.29–1.04) P = 0.71 OR 0.72 (0.59–0.87) 0.66 (0.50–0.86) 0.46 (0.29–0.74)	Farmers were defined as persons who owned or rented a farm and who spent at least 25 h/wk farming. Farm labourers were not included. Female farmers were excluded due to small numbers. The cohort was previously followed until 1996 (916).	(952)
Case-control study: 26 847 Swedish men with first MI. 2 controls for each case.	Stockholm County: 1976–1984 Other counties: 1976–1981	Incidence of first MI, mortality (ICD-8, 410) and hospital discharges (410.00, 410.99).	*First MI* Farm managers and supervisors Agricultural/livestock workers		RR 1.6 (1.0–2.6) 0.8 (0.7–1.0)	Adjustment for age, county and socio-economic group.	(377)

Table A21. Agriculture.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
All males identified in the Swedish censuses 1960, 1970, 1980 and 1985. *Cohorts:* males employed in agriculture. *Referents:* all males 1986–1990.	Each cohort was followed 5–10 y.	Mortality from CVD (ICD-8, 390–458).	*CVD* 1961–1965 1966–1970 1971–1975 1976–1980 1981–1986 1986–1990		RR 0.97 0.98 1.08 1.09 1.11 0.93	Age-standardised mortality RR, adjusted for the healthy worker effect, for ages 45–69 y in Sweden 1961–1990.	(231)
All gainfully employed males and females identified in the Swedish national census 1970. *Cohort:* agricultural (22 663 males, 36 080 females) and livestock (3 015 males, 6 242 females) workers. *Referents:* all gainfully employed (2 047 861 males, 1 260 583 females).	1970–1995	Mortality from IHD (ICD-7–8, 410–414).	*Males* Agricultural work Livestock work *Females* Agricultural work Livestock work	 2 122 353 1 791 305	SMR 1.00 (0.96–1.05) 1.06 (0.95–1.18) 0.98 (0.94–1.03) 1.10 (0.98–1.23)	Agricultural and livestock workers smoke less than the general population. Thus, the crude SMR may underestimate the risk by ca. 9% for men and 5% for women.	(889)
Case-control study: all patients 30–72 y of age, residents in province Halland, Sweden, with first time acute MI, treated in two hospitals. Totally 4 737 cases (3 514 men, 1 223 women). 3 controls/case randomly selected from the register of the total population matched for sex, age and municipality.	1980–1992	Incidence of acute MI (ICD 8–9).	*Males* Self-employed farmers Agricultural employees *Females* Self-employed farmers Agricultural employees	 396 94 127 25	RR 0.67 (0.59–0.75) 0.92 (0.72–1.16) 0.94 (0.75–1.17) 1.05 (0.66–1.68)	Fatal cases not treated in the hospitals were excluded.	(60)

Table A21. Agriculture.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 213 self-employed females 20–59 y old in other agricultural occupations identified in the Central Population Register of Denmark. *Referents:* all economically active persons 20–59 y old on 1 January 1981 and identified in the Register.	Until 1984	Hospitalisations from IHD (ICD-8, 410–414).	IHD	2	SHR 4.55 (1.14–18.2)	SHR: standardised hospitalisation ratio.	(973)
Cohort: male farmers from the Finnish Farm Register identified in 1978. All persons owing a farm were included in the register. *External referents:* all economically active men in Finland. *Internal referents:* male farmers with no animals.	1979–1983	Mortality from CVD (ICD-8, 390–459).	CVD External rates *Internal rates* Type of farm No animals Dairy farms Pig farms Poultry farms Other animal husbandry	2 491 637 1 554 58 89 153	SMR 0.96 (0.94–0.98) RR [a] RR [b] 1.00 1.00 0.86 0.89 0.66 0.72 0.92 0.96 0.81 0.85	*Ever-smokers (%)* Farmers: 68.9 Industrial workers: 82.7 Service sector workers: 75.6. [a] Adjustment for age and location of farms. [b] Adjustment for age, location and size of farms. The authors discussed the problem of selection. In livestock production, farmers were probably more exposed to organic and microbial dusts, but the respiratory mortality of farmers with animals was not higher than among farmers with no animals.	(715)

Table A21. Agriculture.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
						This might be explained by the fact that animal farmers with respiratory problems changed their type of production, e.g. from dairy farming to grain crops.	
Cohort: female farmers and spouses to farmers, actively insured in the Farmers' Social Insurance Institution identified in the Finnish Farm Register in 1978.	1979–1985	Mortality from CVD (ICD-8, 390–459).	*CVD, type of farm* No animals Dairy farms Pig farms Poultry farms Other animal husbandry *CVD, farm size, hectare* 20– 15–19.9 10–14.9 5–9.9 1–4.9	 104 202 9 14 21 72 122 56 45 55	RR 1.00 0.76 0.59 0.84 0.78 1.00 1.13 0.88 1.16 1.18	Adjustment for age and location of farm. No significant differences observed. The larger area of land under cultivation the more likely a farmer was to own a dust respirator. Smoking habits could not explain minor differences.	(714)
All economically active males and females identified in the Finnish national census 1970. *Cohort:* agricultural workers and animal caretakers. *Referents:* all economically active males and females.	1971–1991	Mortality (ICD-9) from CVD and MI.	*CVD, males* 25–64 y 25–44 y 45–64 y *MI, males* 25–64 y 25–44 y 45–64 y *MI, females* [a]	 1 057 534 2 775	 1.19 (1.12–1.27) 1.47 (1.29–1.67) 1.13 (1.06–1.21) 1.13 (1.04–1.23) 1.48 (1.23–1.77) 1.05 (0.95–1.16) 1.07 (1.04–1.12)	[a] Entrepreneurs.	(713)
Cohort: 2 497 male and 1 956 female farmers born 1913–	13 y or until endpoint	Mortality from coronary disease	*Coronary death,* IHD Males		RR 0.86 (0.65–1.16)	Adjustment for age, smoking, serum	(465, 466)

Table A21. Agriculture.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
1947 in the eastern provinces of Finland. The cohort was surveyed in 1972 and 1977. *Referents:* white collar workers.		and incidence of non-fatal acute MI (ICD-8–9, 410–411).	Females *First coronary event* Males Females	115 32 259 75	1.67 (1.03–2.75) 0.87 (0.72–1.06) 1.07 (0.81–1.42)	cholesterol and systolic blood pressure.	
Cohort: 5 923 Icelandic farmers who were either registered in the Farmers' Pension Fund in 1977 or became members before 1984. *Referents:* Icelandic male rates.	1977–1985	Mortality (ICD-7) from IHD (420) and CeVD (330–334).	 IHD CeVD	 106 21	SMR 0.55 (0.45–0.67) 0.67 (0.42–1.03)	Probably male farmers but not clearly stated.	(769)
Cohorts: farm workers, farmers and farm managers in the Nordic countries identified around 1971. *Referents:* all economically active persons in the Nordic countries.	1971–1980	Mortality (ICD-8) from diseases of the circulatory system (390–458) and sudden death (782.4, 795).	*Male farm workers* Denmark Finland Norway Sweden Total *Male farmers and farm managers* Denmark Finland Norway Sweden Total *Female farm managers and farm workers* Denmark	 945 716 527 1 383 3 571 3 991 10 957 3 251 4 747 22 946 477	SMR 0.81 1.53 0.84 0.83 0.91 0.66 1.34 0.76 0.71 0.91 0.83		(711)

Table A21. Agriculture.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			Finland Norway Sweden Total	2 460 771 696 4 404	1.37 0.85 0.89 1.08		
Europe (non-Nordic)							
Cohort: 62 960 certified pesticide users included in the Pesticide Users' Health Study (PUHS) 1987–2003, Great Britain. *Referents:* rates from Scotland, England and Wales.	1987–2005	Mortality from diseases of the circulatory system (ICD-9, 390–459; ICD-10, I00–I99), IHD (ICD-9, 410–414; ICD-10, I20–I25) and CeVD (ICD-9, 430–438; ICD-10, I60–I69).	*Males* Circulatory disease IHD CeVD *Females* Circulatory disease IHD CeVD	 530 335 89 4 1 2	SMR 0.58 (0.53–0.63) 0.54 (0.48–0.60) 0.66 (0.54–0.82) 0.43 (0.16–1.14) 0.27 (0.04–1.90) 0.71 (0.18–2.85)		(316)
Irish males (15–64 y of age) identified in the census 1981. *Cohort I:* farmers, relatives assisting and farm managers. *Cohort II:* farm labourers and fishermen. *Referents:* all Irish males.	1986–1991	Mortality from circulatory diseases (ICD 8–9).	*Circulatory disease* Cohort I Cohort II		SMR 0.89 (P < 0.01) 0.94		(720)
Cohort: Irish farmers and agricultural workers. *Referents:* Irish national rates, using the WHO European standard population.	2000–2006	Mortality from circulatory diseases (ICD-9, 390–459).	*Circulatory disease* Farmers Agricultural workers		SMR 2.16 (2.02–2.30) 2.26 (1.93–2.60)	Linear regression showed an upward trend 2000–2006 for farmers, P < 0.04. No significant trend for agricultural workers. The inclusion of fishermen in	(891)

Table A21. Agriculture.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
						agricultural workers may have raised the SMR.	
Cohort: 567 157 farm owners and workers were invited and 180 060 (97 833 males, 82 227 females) answered a questionnaire 2005–2007. *Referents:* French general population.	Until 2009	Mortality (ICD-10) from diseases of the circulatory system (I00–I99), ischaemic cardiopathy (I20–I25), other cardiopathy (I30–I33, I39–I52) and CeVD (I60–I69).	*Males* Circulatory disease Ischaemic cardiopathy Other cardiopathy CeVD *Females* Circulatory disease Ischaemic cardiopathy Other cardiopathy CeVD	 1 998 598 528 432 1 653 391 507 370	SMR 0.68 (0.65–0.71) 0.65 (0.60–0.70) 0.66 (0.60–0.72) 0.71 (0.65–0.78) 0.73 (0.70–0.77) 0.78 (0.71–0.87) 0.73 (0.67–0.80) 0.67 (0.60–0.74)	An excess of total deaths among non-participants compared with participants. *Males:* SMR 1.06 (1.04–1.07) vs 0.68 (0.67–0.70). *Females:* SMR 1.03 (1.01–1.04) vs 0.71 (0.69–0.73).	(554)
Skilled male workers, 30–59 y old, identified in the 1982 and 1990 censuses, based on three registers from the WHO-MONICA project in France (Lille, Strasbourg and Toulouse). *Cohort:* male farmers and agricultural workers. *Referents:* skilled male workers.	1985–1989	Incidence (ICD-9) of CHD (410–414), sudden death (797–799), arterial hypertension (401–405), other heart diseases (420–429), CeVD (430–438), disease of the arteries, arterioles, and capillaries (440–447), shock (785.5), pulmonary embolism (415) and heart failure (428).	*Farmers* Acute MI, incidence All coronary events, incidence mortality *Agricultural workers* Acute MI, incidence All coronary events, incidence mortality		OR 0.76 (0.58–1.00) 0.79 (0.64–0.97) 1.39 (0.86–2.26) 1.16 (0.72–1.89) 1.43 (1.03–1.99) 1.54 (0.73–3.26)	ORs calculated by multiple logistic regression analysis with age, occupational categories and region as independent variables. A cross-sectional study showed the following proportion of smokers: farmers 38%, unskilled and agricultural workers 47% and skilled workers 47%.	(533)

Table A21. Agriculture.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: economically active males in agricultural and related occupations 25–64 y at death in France and Spain. *Referents:* professional, technical, administrative and managerial workers 25–64 y at death in France and Spain.	1980–1982, 1988–1990	Mortality (ICD-9) from IHD (410–414) and CeVD (430–438).	*IHD, France* Age 25–44 y 1980–1982 1988–1990 Age 45–64 y 1980–1982 1988–1990 *IHD, Spain* Age 25–44 y 1980–1982 1988–1990 Age 45–64 y 1980–1982 1988–1990 *CeVD, France* Age 25–44 y 1980–1982 1988–1990 Age 45–64 y 1980–1982 1988–1990 *CeVD, Spain* Age 25–44 y 1980–1982 1988–1990 Age 45–64 y 1980–1982 1988–1990	3 052 853 1 671 468 	RR 0.53 (0.41–0.70) 1.21 (0.96–1.53) 0.48 (0.45–0.51) 1.25 (1.16–1.35) 1.27 (0.69–2.33) 2.10 (1.02–4.33) 0.51 (0.42–0.63) 1.25 (0.98–1.60) 1.12 (0.84–1.48) 1.80 (1.28–2.54) 0.90 (0.82–0.99) 1.88 (1.66–2.12) 0.89 (0.65–1.21) 2.99 (0.84–10.6) 0.82 (0.60–1.13) 1.68 (1.14–2.47)	The almost consistently lower RRs in 1980–1982 than in 1988–1990 represent the shift from low to high disease occurrence in low socio-economic groups due to smoking and other lifestyle factors.	(577)

Table A21. Agriculture.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 23 401 male farmers from Asti, Alessandria and Cuneo, Italy, licensed during 1970–1974 to use pesticides in agriculture. *Referents:* regional rates from Piedmont, and provincial rates from Asti, Alessandria and Cuneo.	Until 1986	Mortality from CVD (ICD-8).	*CVD* Regional rates Provincial rates	1 080	SMR 0.52 (0.49–0.56) 0.58 (0.55–0.61)		(966)
Cohorts: 1 701 male and 426 female farmers or farm workers identified in the 1971 census. Each subject was considered from January 1972 or from the date of first arrival to the cohort. *Referents:* Italian general population.	Until 1988	Mortality (ICD-8) from diseases of the circulatory system (390–458), hypertensive disease (400–404) and IHD (410–414).	*Males* Circulatory disease Hypertension IHD *Females* Circulatory disease	 188 18 50 15	SMR 0.79 (0.69–0.92) 1.53 (0.91–2.43) 0.57 (0.42–0.75) 0.63 (0.35–1.05)	The cohort composition was mainly of a cross-sectional design and the mortality of those who retired before 1971, or even during the study period, is missing.	(281)
Cohort: 1 493 male rice farming owners and workers registered in 1988 in Novara province, Italy. *Referents:* Italian general population.	1957–1992	Mortality from MI, other IHD and stroke (ICD-codes not reported).	 MI Other IHD Stroke	 67 72 155	SMR 0.72 (0.56–0.92) 0.41 (0.32–0.52) 0.96 (0.81–1.12)	The study has a systemic error by counting person-years prior to the date of cohort formation.	(325)
North America							
Cohort: 18 811 male farm owners and operators members ≥ 1 y of the New York State Farm Bureau 1973–1979.	1973–1984	Mortality from diseases of the circulatory system (ICD-8, 390–458;	 Circulatory disease IHD CeVD	 814 569 102	SMR 0.68 (P < 0.005) 0.65 (P < 0.005) 0.72 (P < 0.005)	Overall and cause-specific mortality rates by single years of age were calculated for the referents.	(901)

Table A21. Agriculture.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Referents: 747 128 males, identified in the US census 1980, who resided in upstate New York State, excl. New York City.		ICD-9, 390–459), IHD (ICD 8–9, 410–414) and CeVD (ICD 8–9, 430–438).					
Cross-sectional study Participants identified by a health census form mailed to every permanent residents in the Otsego County, New York State in 1999. *Cohort:* 1 140 male farmers. *Referents:* 10 132 male non-farmers.		Prevalence of heart disease, hyper-tension and diabetes.	Heart disease Hypertension Diabetes		OR 0.67 (0.40–1.12) 0.83 (0.72–0.96) 0.86 (0.70–1.05)	Multiple logistic regression adjusted for age, smoking and BMI. The OR for heart disease was also adjusted for hypertension, diabetes and high cholesterol.	(455)
Cohort: 35 972 deceased white male farmers in Wisconsin, US. *Referents:* deceased white male non-farmers in Wisconsin.	1968–1976	Mortality (ICD-8) from diseases of the circulatory system, all arteriosclerotic heart disease, and all vascular lesions of CNS.	Circulatory disease All arteriosclerotic Vascular CNS lesions	23 045 15 143 4 344	PMR 1.02 (P < 0.05) 1.00 1.05 (P < 0.05)	Adjustment for age and calendar year of death. There was a deficit of smoking- and alcohol-related diseases due to less prevalent use of tobacco and alcohol by farmers.	(817)
Study base: farmers compared with other occupations from the male population ≥ 35 y of age in the 6-county area around Grand Forks, North Dakota, US, approximately 20 000 subjects.	1957	Reported cases. Diagnosis made by review committee: angina pectoris, coronary in-sufficiency, MI, sudden death, other	*All CHD* Farmers Others *MI* Farmers Others *CHD without previous*	 101 127 42 59	Rate/1 000 9.60 13.64 3.99 6.34		(1058)

Table A21. Agriculture.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
		manifestations of CHD.	*manifestations* Farmers Others	 70 90	 6.65 9.67		
All males aged 20–64 y from the Iowa censuses 1960 and 1970. *Cohort:* male farmers (totally 6 960 deaths). *Referents:* all males (totally 31 310 deaths).	1964–1970, 1971–1978	Mortality from IHD, hypertensive heart disease and CeVD.	*1964–1970* IHD Hypertension CeVD *1971–1978* IHD Hypertension CeVD		SMR 0.89 (P < 0.001) 0.82 0.89 (P < 0.05) 0.93 (P < 0.001) 0.97 0.91	A cross-sectional study was presented in the same paper. Current smoking was less common among farmers (19%) than among non-farmers (46%) and regular physical activity was twice as common among farmers.	(755)
Study base: white male farmers and farm managers compared with non-farmers, all 20–64 y of age in Iowa, US.	1971–1978	Mortality from diseases of the circulatory system (ICD-8).	*Circulatory disease* Farmers Non-farmers	Rate/ 100 000 248 322	RR 0.77 (P < 0.01)		(133)
Cross-sectional study Subjects ≥ 65 y old from 2 counties in Iowa were interviewed in their homes. *Cohort:* 696 male and 591 female farm workers with > 25 y of exposure to farm work. *Referents:* 146 males and 379 females who had never worked on a farm.	December 1981–July 1982	Anamnestic history of heart attacks, stroke and blood pressure.	*Heart attacks* Males Retired Working Females Retired Working *Stroke* Males Retired Working	Exp/refs % 23.1/16.9 17.7/12.8 7.7/8.8 6.4/7.4 7.9/2.8 5.1/1.8		Standardised to age 75 y, non-smoker, non-drinker, using individual logistic regression models. Male farm workers had more frequently (P < 0.05) a history of stroke and higher diastolic blood pressure.	(1044)

Table A21. Agriculture.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			Females Retired Working	 5.7/7.0 1.1/1.3			
Study base: proportion of deaths among 9 245 white and 3 508 non-white male farmers who died in North Carolina, US, 1976–1978 compared with that among other male decedents in the state.	1976–1978	Mortality from diseases of the circulatory system (ICD-8, 390–458).	*Circulatory disease* Whites Non-whites	 5 606 1 866	PMR 1.0 (1.0–1.1) 1.0 (1.0–1.1)		(221)
Cohort: 52 393 private licensed pesticide applicators (51 034 men, 1 359 women), almost entirely farmers, recruited 1994–1997 to the Agricultural Health Study in Iowa and North Carolina, US. *Referents:* Iowa and North Carolina general populations.	Until 2000	Mortality from CVD (ICD-9).	CVD *All* Farm growing corn Yes No Farm with animals Yes No	 537 315 222 215 322	SMR 0.5 (0.5–0.6) 0.5 [a] 0.6 [a] 0.5 [a] 0.6 [a]	Adjustment for age, calendar year of death, state, race and gender. [a] 95% CI did not include 1.0.	(104)
Cohort: same as above (now containing 52 394 subjects) was further followed. *Referents:* Iowa and North Carolina general populations.	Until 2007	Mortality (ICD-9 or 10) from heart disease (divided in IHD, chronic diseases of the endocardium, cardiomyopathy and conductive disorder) and other circulatory diseases (divided in	*Heart disease* IHD Endocardial disease Cardiomyopathy Conductive disorder *Other circulatory dis.* CeVD Vessels	1 376 1 099 32 75 61 376 236 125	SMR 0.54 (0.51–0.56) 0.52 (0.49–0.55) 0.64 (0.44–0.90) 0.69 (0.54–0.87) 0.59 (0.45–0.75) 0.51 (0.46–0.57) 0.52 (0.45–0.59) 0.54 (0.45–0.64)	Adjusted for age, calendar year, state, race and gender. A comparable occupational population in Iowa and North Carolina would be a preferred reference group, but such a group did not exist. An alternative was to calculate the	(977)

Table A21. Agriculture.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
		CeVD and diseases of arteries/veins/ lymphatic vessels).	*Heart disease* IHD Endocardial disease Cardiomyopathy Conductive disorders *Other circulatory dis.* CeVD Vessels	 1 376 1 099 32 75 61 376 236 125	rSMR 0.99 (0.93–1.06) 0.96 (0.90–1.03) 1.18 (0.84–1.68) 1.29 (1.03–1.62) 1.09 (0.85–1.40) 0.95 (0.86–1.06) 0.96 (0.84–1.09) 1.00 (0.84–1.20)	relative SMR (rSMR) defined as the ratio of the cause-specific SMR to the SMR for all other causes, omitting the cause of interest (i.e. $rSMR_x = SMR_x/SMR_{not\ x}$). Some diagnoses were omitted. Rates of death from chronic lung and liver diseases commonly associated with tobacco and alcohol use were significantly lower.	
Cohort: 83 378 farmers, their spouses and commercial pesticide applicators residing primarily in Iowa and North Carolina, US, and enrolled 1993–1997 to the Agricultural Health Study. Deaths were identified via annual linkage with death registries in Iowa and North Carolina as well as the National Death Index.	Until 2009	Mortality from CVD (ICD-9, 400–440; ICD-10, I10–I70), IHD (ICD-10, I25) and CeVD (ICD-10, I60–I69).	*CVD, all* Men Women *CVD, all non-movers* Men Women *IHD* *CeVD*	1 055 786 269 801 592 209 213 242	HR 1.31 (0.84–2.04) 1.66 (1.00–2.78) 0.62 (0.25–1.55) 1.33 (0.80–2.23) 1.87 (1.04–3.36) 0.45 (0.16–1.29) 2.68 (1.04–6.87) 1.78 (0.72–4.42)	HR mortality per 10-$\mu g/m^3$ increase of satellite-based estimates of ambient $PM_{2.5}$ in fully adjusted models. $PM_{2.5}$ levels were assigned to each enrolment address, which was based on geo-coding. Air levels reflected 6-y mean (2001–2006) of combined daily aerosol optical depth retrievals.	(999)
Study base: proportion of deaths among farmers and farm operators compared with the proportion among the US	1984–1988	Mortality (ICD-8, recoded from ICD-9) from all disease of the circulatory	*Circulatory disease* White males US referents Alabama referents		PMR 0.99 1.05 ($P < 0.05$)		(54)

Table A21. Agriculture.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
population in 1985 and the Alabama population in 1984–1988.		system (390–458) and IHD (410–413).	White females US referents Alabama referents Non-white males US referents Alabama referents Non-white females US referents Alabama referents *IHD* White males US referents Alabama referents White females US referents Alabama referents Non-white males US referents Alabama referents Non-white females US referents Alabama referents		 0.97 0.99 1.05 (P < 0.05) 1.06 (P < 0.05) 1.02 1.03 0.76 (P < 0.05) 1.03 0.71 0.97 0.69 (P < 0.05) 1.09 (P < 0.05) 0.53 (P < 0.05) 0.88		
Study base: odds of mortality among farmers compared with those among non-farmers. Data from the Georgia Office of Vital Statistics, US, 1985–1994.	1985–1994	Mortality (ICD-9) from circulatory disease (390–459), hypertensive diseases (401–405), IHD (410–414), other heart disease	*White male farmers* Circulatory disease Hypertension IHD Other heart disease CeVD *Black male farmers*	 3 493 78 1 746 923 569	OR 1.11 (1.08–1.15) 0.94 (0.80–1.10) 1.06 (1.02–1.09) 1.08 (1.02–1.13) 1.17 (1.10–1.24)		(942)

Table A21. Agriculture.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
		(415–429) and CeVD (430–438).	Circulatory disease Hypertension IHD CeVD	4 091 218 1 598 877	1.16 (1.11–1.21) 0.75 (0.65–0.87 1.21 (1.14–1.29) 1.27 (1.18–1.38)		
Study base: proportion of deaths among 7 504 deceased farm workers and 7 404 deceased farm owners/ managers obtained from California Department of Health Services' Center compared with the proportion of deaths in California, US, 1975.	1978–1979	Mortality (ICD-8) from circulatory disease (390–458), arteriosclerotic heart disease (410–413) and vascular CNS lesions (430–438).	*Farm workers* White males Circulatory disease Heart disease Vascular CNS lesions White females Circulatory disease Heart disease Vascular CNS lesions Non-white males Circulatory disease Heart disease Vascular CNS lesions Non-white females Circulatory disease Heart disease Vascular CNS lesions *Farm owners/managers* White males Circulatory disease Heart disease Vascular CNS lesions White females Circulatory disease Heart disease		PMR 0.87 (P < 0.01) 0.61 (P < 0.01) 0.82 (P < 0.01) 0.94 0.75 (P < 0.01) 0.90 0.96 0.67 (P < 0.01) 0.96 1.02 0.64 (P < 0.01) 1.14 0.95 (P < 0.01) 0.67 (P < 0.01) 0.85 (P < 0.01) 0.88 (P < 0.01) 0.61 (P < 0.01)	Mexican-Americans (36% of the deceased farm workers) belonged to the category of whites.	(921)

Table A21. Agriculture.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			Vascular CNS lesions Non-white males Circulatory disease Heart disease Vascular CNS lesions Non-white females Circulatory disease Heart disease Vascular CNS lesions		0.85 0.99 0.66 (P < 0.01) 1.09 1.30 (P < 0.05) 0.75 1.88 (P < 0.05)		
Participants, 16–64 y old, derived from the California Occupational Mortality Study (US). *Cohort:* white male farm workers and farmers. *Referents:* white male workers from all occupations.	1979–1981	Mortality from IHD, CeVD, other circulatory disease and hypertension.	*Farm workers* IHD CeVD Other circulatory Hypertension *Farmers* IHD CeVD Other circulatory Hypertension	 347 87 132 17 257 20 77 9	SMR 1.03 (0.92–1.14) 1.43 (1.14–1.76) 0.93 (0.78–1.11) 0.72 (0.42–1.16) 1.24 (1.09–1.40) 0.69 (0.42–1.06) 1.08 (0.85–1.35) 0.72 (0.33–1.36)	Adjustment for age, smoking, alcohol and socioeconomic status.	(73)
Cohort: 1 428 white male farm owners and managers from the California Agricultural Statistics Service, randomly sampled and interviewed in 1993. *Referents:* white male population in California, US.	1993–2004	Mortality from heart disease and CeVD.	Heart disease CeVD	81 4	PMR 0.96 0.31 (P < 0.004)	Adjustment for age and year. The smoking rate in 1993 was 11% which was approximately half the rate in the general population.	(44)
Cohort: 20 505 male private and farmer pesticide appli-	1975–1993	Mortality from circulatory disease,	Circulatory disease	686	SMR 0.87 (0.81–0.94)	Adjustment for age and calendar year.	(297)

Table A21. Agriculture.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
cators licensed in Florida, US, 1975–1993. *Referents:* male population in Florida.		atherosclerotic heart disease with congestive heart failure and vascular disease in CNS.	Atherosclerotic heart Vascular CNS lesions	446 79	0.99 (0.90–1.09) 0.81 (0.64–1.01)		
Study base: proportion of deaths among farmers compared with that among occupation-coded death certificates from 23 US states.	1984–1988	Mortality from arteriosclerotic heart disease, vascular lesions of the CNS and hypertension.	Farmers *White men* Heart disease Vascular CNS lesions Hypertension *White women* Heart disease Vascular CNS lesions Hypertension *Non-white men* Heart disease Vascular CNS lesions Hypertension *Non-white women* Heart disease Vascular CNS lesions Hypertension	 39 032 9 874 1 162 718 237 25 2 850 1 275 303 533 338 80	PMR 1.02 (1.01–1.03) 1.15 (1.13–1.17) 0.92 (0.87–0.98) 0.96 (0.89–1.04) 0.91 (0.79–1.03) 0.63 (0.41–0.93) 1.03 (0.99–1.06) 1.38 (1.30–1.46) 0.90 (0.80–1.01) 0.96 (0.88–1.04) 1.38 (1.23–1.53) 0.91 (0.72–1.13)	Adjustment for age at death.	(101)
Cohort: 2 681 white male farmers sampled from the US population and interviewed within the National Health Interview Survey. *Referents:* 113 377 currently employed white men.	1986–1990	Diseases were classified as CVD, IHD (ICD-9, 413–414) and hyper-tension (401–405).	CVD IHD Hypertension	116 29 84	Prevalence risk ratio (PRR) 1.3 (1.0–1.7) [a] 1.3 (0.7–1.9) 1.4 (1.0–1.7)	Adjustment for age. [a] $P < 0.05$.	(123)

Table A21. Agriculture.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Study base: proportion of deaths among farmers and workers in agriculture (age ≥ 25 y) compared with registered deaths in the 1986 US National Mortality Followback Survey.	1986	Mortality (ICD-9) from MI (410), IHD (414), other heart disease (429.2) and CeVD (436).	*Farmers*		PMR	Smoking is an unlikely factor behind increased risks as the PMRs for lung cancer were low among farmers and workers in agriculture, 0.59 and 0.61 respectively.	(777)
			MI	12 719	1.11		
			IHD	8 241	0.98		
			Other heart disease	3 733	1.25		
			CeVD	4 946	1.41		
			Workers in agriculture, crops				
			MI	13 535	1.06		
			IHD	10 672	1.14		
			Other heart disease	3 419	1.04		
			CeVD	5 087	1.31		
Study base: proportion of deaths among farm workers compared with the proportion among occupation-coded death certificates from 24 US states.	1984–1993	Mortality from diseases of the circulatory system, arteriosclerotic heart disease, hypertension and CeVD.	Farm workers		PMR	Adjustment for age.	(187)
			White men				
			Circulatory disease	5 773	0.96 (0.94–0.99)		
			Heart disease	3 646	0.95 (0.92–0.98)		
			Hypertension	118	0.85 (0.71–1.02)		
			CeVD	808	1.05 (0.98–1.13)		
			White women				
			Circulatory disease	421	0.94 (0.85–1.04)		
			Heart disease	233	0.96 (0.84–1.09)		
			Hypertension	18	1.22 (0.72–1.93)		
			CeVD	77	0.91 (0.72–1.14)		
			Non-white men				
			Circulatory disease	2 987	1.06 (1.02–1.09)		
			Heart disease	1 450	1.01 (0.96–1.07)		
			Hypertension	191	0.91 (0.78–1.04)		
			CeVD	620	1.24 (1.15–1.34)		
			Non-white women				
			Circulatory disease	1 660	1.08 (1.03–1.14)		

Table A21. Agriculture.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			Heart disease	730	1.02 (0.95–1.10)		
			Hypertension	160	1.24 (1.05–1.44)		
			CeVD	411	1.26 (1.14–1.39)		
Study base: proportion of deaths among 222 549 crop farmers and 44 930 livestock farmers compared with the proportion among occupation-coded death certificates from 26 US states.	1984–1993	Mortality (ICD-9) from acute MI (410), CeVD (430–438) and diseases of arteries, arterioles and capillaries (440–448).	*Crop farmers*		PMR	White male crop farmers 15–64 y of age at death had a higher PMR for acute MI (1.23, 1.20–1.27) than older farmers (1.18, 1.17–1.19). This was not consistent for livestock farmers or other diagnoses.	(546)
			White men				
			Acute MI	31 596	1.18 (1.17–1.19)		
			CeVD	15 284	1.16 (1.14–1.17)		
			Vessels	4 927	0.97 (0.94–0.99)		
			White women				
			Acute MI	557	1.04 (0.93–1.15)		
			CeVD	467	1.01 (0.92–1.10)		
			Vessels	152	1.21 (1.03–1.42)		
			Black men				
			Acute MI	2 650	1.22 (1.19–1.26)		
			CeVD	2 411	1.37 (1.33–1.42)		
			Vessels	421	1.10 (1.00–1.21)		
			Black women				
			Acute MI	481	1.06 (0.97–1.16)		
			CeVD	661	1.37 (1.27–1.48)		
			Vessels	93	0.96 (0.77–1.18)		
			Livestock farmers				
			White men				
			Acute MI	7 209	1.20 (1.18–1.22)		
			CeVD	3 153	1.08 (1.05–1.12)		
			Vessels	1 139	1.01 (0.95–1.07)		
Cohort: 9 471 pesticide-exposed workers (9 293 farmers, 178 pesticide applicators) identified in the	Until 1997	Mortality from CVD, follow-up performed through linkage with the	CVD	231	RR 1.4 (1.2–1.7)	Adjustment for age. All participants were included at ≥ 18 y of age.	(298)

Table A21. Agriculture.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
US National Health Interview Survey (NHIS) 1986–1994. *Referents:* 438 228 non-pesticide exposed in other occupations from the same source, NHIS.		National Death Index.				No excess of respiratory cancers (RR 1.0, 0.8–1.4) indicates no bias from smoking habits.	
Study base: proportion of deaths among farmers and agricultural workers compared with that among 550 occupations in the National Occupational Mortality Surveillance system in 30 US states, based on 10 million deaths aged 18–64 years.	1985–1999, 2003–2004, 2007	Mortality from acute MI (ICD-10, I21).	Acute MI *Farmers* White males Black males *Agricultural workers* Black females Hispanic males	 4 678 506 83 117	PMR 1.49 (1.46–1.52) 1.45 (1.32–1.58) 1.35 (1.08–1.68) 1.24 (1.03–1.50)	Adjustment for age and smoking.	(786)
Cohort: 155 547 male farmers aged ≥ 35 y from Alberta, Saskatchewan, Manitoba, assembled by linking data from the Canadian Censuses of Agriculture and Population 1971. *Referents:* male population from these areas.	1971–1987	Mortality from circulatory disease (ICD-9).	Circulatory disease	15 219	SMR 0.73 (0.72–0.74)	In a previous estimation, up to 10–15% of deaths were missed because of limitations in record linkage. A previous study of Saskatchewan farmers showed the same result (1018).	(855)
Australia/Asia							
Cohort: Australian male farmers and farm managers aged 25–74 y. *Referents:* general male	1999–2002	Mortality from circulatory disease (ICD-10, I00–I99), IHD and other	Circulatory disease IHD Other circulatory	1 251 823 428	SMR 1.40 (1.23–1.59) 1.39 (1.18–1.63) 1.42 (1.13–1.72)	The higher all-cause mortality in farmers supports other Australian data illustrating that	(306)

Table A21. Agriculture.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
population, from the Australian Population Census 2001.		circulatory disease.	disease			mortality rates rise as remoteness increases in rural populations. In another study, farming men and women exhibited an increased prevalence of CVD risk factors (132).	
Cohort: male agricultural workers in Hong Kong. *Referents:* general male population in Hong Kong.	1979–1983	Mortality from circulatory disease (ICD-9, 359–390).	Circulatory disease	346	SMR 0.77 (0.69–0.85)		(706)
Cohort: agricultural workers in Korea. *Referents:* manual and non-manual workers in Korea. *Cross-sectional:* Participants collected from the 2005 Korean NHANES. *Cohort:* agricultural workers. *Referents:* manual and non-manual workers.	2004–2008 2005	Mortality (ICD-10) from hypertension (I10–I15), IHD (I20–I25) and CeVD (I60–I69). Prevalence of hypertension, IHD and CeVD.	*Mortality* Hypertension IHD CeVD *Prevalence* Hypertension IHD CeVD	 1 940 6 475 16 635 406 37 56	SMR 0.72 (0.65–0.80) 0.77 (0.73–0.82) 0.89 (0.86–0.92) OR 0.9 (0.7–1.1) 1.3 (0.6–2.7) 1.4 (0.7–2.9)	The agricultural workers included about 4.4% fishery and 0.2% forestry workers. ORs adjusted for age, education, marriage, smoking and drinking. Mental health was an important health issue in agricultural workers as suicide was more common.	(548)

Table A22. Dichloromethane (DCM).

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Europe							
Cohort: 1 473 male workers employed 1946–1988 producing cellulose triacetate film in Brantham, UK. *Referents:* national rates from England and Wales.	Until 1994	Mortality (ICD-9) from all heart disease (390–398, 402, 404, 410–429), IHD (410–414) and CeVD (430–438).	 All heart disease IHD CeVD *IHD, cumulative exposure, ppm-y* < 400 400–799 > 800 *IHD, time since first exposure* < 20 y 20–30 y > 30 y	 124 114 16 47 13 10 28 47 39	SMR 0.88 (0.74–1.05) 0.92 (0.76–1.10) 0.50 (0.29–0.82) 0.79 1.06 1.22 0.73 1.16 0.86	 P(trend): 0.11.	(964)
Follow-up of the previous cohort.	Until 2006	As above.	 All heart disease IHD CeVD *IHD, cumulative exposure, ppm-y* < 400 400–799 > 800 *IHD, continuous exposure, ppm-y* 1 000	 178 156 29 68 15 15 	SMR 0.88 (0.75–1.02) 0.88 (0.75–1.03) 0.59 (0.39–0.84) 0.78 (P < 0.05) 0.93 1.17 RR 1.47 (0.91–2.39)	Mean exposure (8-h TWA): 19 ppm for 9 y. P(trend): 0.20.	(963)

Table A22. Dichloromethane (DCM).

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
North America							
Study base: all death certificates of Kodak Park male employees who died in 1956–1976. *Cohort:* all 751 males hourly employed in 1964 and DCM exposed. *Internal referents (I):* other non-exposed males at Kodak Park. *External referents (E):* New York State males (exclusion of New York City).	1956–1976	Mortality (ICD-8) from circulatory diseases (390–458) and IHD (410–414).			PMR	Air concentrations (ppm) of DCM 1959–1976 as mean (range); no. of samples: 1959: 79.4 (9–350); 188 1966: 118.8 (100–150); 4 1973: 90.5 (41–188); 28 1975: 40.3 (0–250); 57.	(309)
			Circulatory disease	200	1.00		
			IHD	129	0.95		
	Until 1976	Mortality (ICD-8) from circulatory diseases (390–458), hypertension (400–404), IHD (410–414) and CeVD (430–439).			SMR (I ref; E ref)		
			Circulatory disease	45	1.17; 0.73		
			Hypertension	4	3.91[a]; 2.72		
			IHD	33	1.15; 0.70 [a]		
			CeVD	5	1.56; 0.75		
			≥ 20 y exposure			[a] $P < 0.05$.	
			Circulatory disease	24	0.96; 0.59 [a]		
			Hypertension	2	2.99; 2.08		
			IHD	19	1.03; 0.61 [a]		
			CeVD	1	0.46; 0.22		
Cohort: 1 013 male workers employed in the Roll Coating Division, Kodak for ≥ 1 y 1964–1970 (expansion of previous cohort). *Internal referents (I):* 40 000 non-exposed males at Kodak. *External referents (E):* New York State males (exclusion of New York City).	Until 1984	Mortality from circulatory diseases, IHD and CeVD. ICD-8 until 1978 and ICD-9 from 1979.			SMR (I ref; E ref)	Mean exposure 26 ppm.	(393)
			Circulatory disease	90	0.83; 0.68		
			IHD	69	0.90; 0.70		
			CeVD	8	0.65; 0.53		
			IHD, cumulative exposure, ppm-y				
			< 350	19	1.23; 0.95		
			350–749	22	0.79; 0.61		
			≥ 750	28	0.84; 0.66		

Table A22. Dichloromethane (DCM).

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 1 013 male workers (same as above) employed in the Roll Coating Division, Kodak for ≥ 1 y 1964–1970. *Internal referents (I):* non-exposed males at Kodak. *External referents (E):* New York State males (exclusion of New York City).	Until 1994	As above.	Circulatory disease IHD CeVD *IHD, cumulative exposure, ppm-y* < 400 400–799 800–1 199 ≥ 1 200	171 122 19 34 38 33 17	SMR (I ref; E ref) 0.95; 0.84 1.00; 0.85 0.90; 0.87 RR (I ref; E ref) 1.19; 1.17 0.84; 0.83 1.18; 1.03 0.85; 0.85	Mean exposure: 26 ppm for 24 y.	(394)
Cohort: 1 311 male workers (1 070 in the Roll Coating Division and 241 in the Dope and Distilling Departments) employed at Kodak Rochester for ≥ 1 y 1946–1970. This and the previous cohort overlapped. Of 1 617 unique employees, 707 (44%) were members of both cohorts. *Internal referents (I):* Expected numbers based on intracohort distribution of person-years. *External referents (E):* New York State males residing outside New York City 1945–1990.	Until 1994	As above.	Circulatory disease IHD CeVD *IHD, cumulative exposure, ppm-y* < 150 150–349 350–799 ≥ 800	166 117 20 34 22 33 28	SMR (vs E ref) 0.86 (0.74–1.01) 0.86 (0.71–1.03) 1.06 (0.65–1.63) RR (I ref; E ref) 1.12; 0.91 0.92; 0.76 1.03; 0.90 0.91; 0.83	Mean exposure: 39 ppm for 17 y.	(394)

Table A22. Dichloromethane (DCM).

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 3 211 white workers (2 187 men, 1 024 women) at the Amcelle textile manufacturing plant in Cumberland, Maryland, US, who worked ≥ 3 mo 1970–1981 when the plant closed. *Referents:* regional rates from Allegany County.	Until 1989	Mortality from IHD (ICD-9, 410–414).	*Exposure* Men High Low None Women High Low None High exposed men, by exposure duration < 10 y 10–19 y 20 y–	 98 96 41 0 32 2 33 45 20	SMR 0.92 (0.75–1.12) 0.96 (0.78–1.17) 0.99 (0.71–1.34) – 0.70 (0.48–0.99) 0.41 (0.05–1.49) 1.30 (0.89–1.82) 0.84 (0.61–1.13) 0.72 (0.44–1.11)	*Exposure categories* High: 350–700 ppm Low: 50–100 ppm.	(336)
Cohort: 1 271 workers (white and non-white men and women) in the preparation or extrusion areas of a textile manufacturing plant in Rock Hill, South Carolina who worked ≥ 3 mo 1954–1977. *Internal referents (I):* 948 workers from a referent plant. *External referents (E):* US national rates.	Until 1977	Mortality from diseases of the circulatory system and IHD.	*Circulatory disease* White men White women Non-white men *IHD* White men White women Non-white men	 11 3 4 10 2 2	SMR (E); HR (I) 0.79 (E); 1.9 (I) 0.81 (E) 1.82 (E) 0.95 (E); 2.6 (I) 1.25 (E) 1.82 (E)		(728)

Table A22. Dichloromethane (DCM).

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 1 271 workers (same as above). *Referents:* local rates from York County, US.	Until 1990	Mortality from IHD and CeVD.	IHD CeVD	43 7	SMR 0.90 (0.65–1.21) 0.54 (0.22–1.11)	By including only active workers, the SMR for IHD decreased to 0.67. A previous follow-up until 1986 gave similar results (530).	(531)
Pooled analysis							
Cohorts: 6 964 photographic film base workers, ref. (394, 964) and textile fibre workers, ref. (336, 531).	Varying	Mortality from IHD (ICD-9, 410–414).	IHD All workers Only active workers	 500 66	SMR 0.89 (0.81–0.97) 0.76 (0.59–0.97)		(394)

Table A23. Dioxins and dioxin-like compounds.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Nordic countries							
Cohort: 1 909 male chlorophenoxy herbicide applicators 1955–1971. *Referents:* Finnish male population.	1972–1989	Mortality from IHD, other heart disease and hypertension, and CeVD.	 IHD Other heart disease and hypertension CeVD	 148 20 26	SMR 0.94 (0.80–1.10) 1.03 (0.63–1.59) 0.73 (0.48–1.04)	4/5 preparations of 2,4,5-trichlorophenoxyacetic acids used in Finland during the 1960s contained 0.1–0.95 mg/kg TCDD; in 1 preparation the TCDD content was below the detection limit. Neither sentinel tumours nor overall cancer were increased.	(50)
Europe (non-Nordic)							
Cohort: 1 189 male chemical workers producing phenoxy herbicides in Hamburg, employed ≥ 3 mo 1952–1984. *Referents:* 2 528 gas workers from the same German region with comparable socio-economic status.	1952–1992	Mortality (ICD-9) from CVD (390–459) and IHD (410–414).	*TCDD, ng/kg blood fat* CVD 0–2.8 2.81–14.4 14.5–49.2 49.3–156.7 156.8–344.6 344.7–3 890.2 IHD 0–2.8 2.81–14.4 14.5–49.2 49.3–156.7 156.8–344.6 344.7–3 890.2	 157 76 	RR 1.22 (0.81–1.83) 0.88 (0.54–1.44) 1.35 (0.91–2.01) 1.64 (1.12–2.39) 1.53 (0.95–2.44) 1.96 (1.15–3.34) 1.43 (0.83–2.44) 0.81 (0.41–1.61) 1.18 (0.65–2.16) 0.90 (0.47–1.75) 1.61 (0.85–3.04) 2.48 (1.32–4.66)	RR = 1 refers to a TCDD level below the median among the referents. P(trend): 0.01. P(trend): < 0.01.	(299)

Table A23. Dioxins and dioxin-like compounds.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 1 191 male and 398 female chemical workers in Hamburg employed ≥ 3 mo 1952–1984 producing phenoxy herbicides. The same cohort as (299). *Referents:* regional rates from Hamburg, Germany.	1952–2007	Mortality (ICD-9) from circulatory disease (390–459) and CeVD (430–438).	*Men* Circulatory disease CeVD *Women* Circulatory disease CeVD *Circulatory disease, cumulative TCDD exposure, ppt (sic)* Men > 0– < 13.1 13.1– < 77.4 77.4– < 334.5 ≥ 334.5 Women 0 > 0–19.5 > 19.5–78.3 > 78.3	 251 54 58 11 55 63 70 63 10 11 18 19	SMR 1.16 (1.02–1.31) 1.57 (1.19–2.05) 0.74 (0.56–0.94) 0.64 (0.32–1.15) 1.14 (0.86–1.49) 1.20 (0.92–1.53) 1.20 (0.94–1.52) 1.08 (0.83–1.39) 0.65 (0.35–1.20) 0.79 (0.39–1.41) 0.78 (0.46–1.23) 0.73 (0.44–1.15)	The plant closed in June 1984. Median estimated cumulative job exposure to TCDD: 77.4 (0–16 514) ppt (men) 19.5 (0–15 195) ppt (women). The concentrations were based on blood fat.	(602)
Cohort: 243 male workers engaged in clean up, repair and demolition after an accident. *Referents:* male rates from the former West Germany.	1953–1992	Mortality (ICD-9) from circulatory disease and IHD.	*Circulatory disease* TCDD, µg/kg bw < 0.1 0.1–0.99 ≥ 1 *IHD* TCDD, µg/kg bw < 0.1	37 13 11 13 16 7	SMR 0.8 (0.6–1.2) 0.8 (0.4–1.4) 1.0 (0.5–1.7) 0.8 (0.4–1.3) 0.7 (0.4–1.1) 0.9 (0.3–1.8)	In 1953, an uncontrolled decomposition reaction occurred in the trichlorophenol production unit in Ludwigshafen, Germany.	(729)

Table A23. Dioxins and dioxin-like compounds.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			0.1–0.99	4	0.7 (0.2–1.7)		
			≥ 1	5	0.6 (0.2–1.3)		
Cohort: 562 workers (549 males, 13 females) classified as exposed to phenoxy herbicides or chlorophenols 1955–1985. *External referents:* gender-specific Dutch national rates. *Internal referents:* 567 non-exposed workers (482 males, 85 females).	1955–1991	Mortality (ICD-9) from circulatory disease (390–459), IHD (410–414), and CeVD (430–438).	*All males* Circulatory disease IHD CeVD *140 males exposed at accident* Circulatory disease IHD *501 medium or high exposed vs 530 low/non-exposed, TCDD exposure* Circulatory disease Medium High IHD Medium High CeVD Medium High	 45 33 9 15 14 	SMR 1.0 (0.8–1.4) 1.2 (0.8–1.6) 1.4 (0.6–2.6) 1.1 (0.6–1.7) 1.5 (0.8–2.5) RR [a] 1.5 (0.8–2.8) 1.5 (0.8–2.9) 1.5 (0.7–3.6) 2.3 (1.0–5.0) 2.0 (0.5–8.2) 0.8 (0.2–4.1)	Production of chlorophenoxy herbicides started in 1950 and ended in 1969. In 1963, an un-controlled reaction occurred in the autoclave where 2,4,5-trichloro-phenol was synthesised. An explosion followed and TCDD was released. The last TCDD contaminated process ended in 1976. [a] Adjustment for age, calendar period and time since first exposure. Medium: $TCDD_{max}$ 7.7–124.1 ppt, lipid adjusted. High: $TCDD_{max}$ 124.2–7 308 ppt, lipid adjusted.	(420)

Table A23. Dioxins and dioxin-like compounds.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 1 020 male workers from factory A (same factory as above) employed 1965–1986. *Referents:* non-exposed male workers from factories A and B, including all 1 036 workers of the latter.	1955–2006	Mortality (ICD-10) from circulatory disease (I00–I99), IHD (I20–I25) and CeVD (I60–I67).			HR	Exposure assessment was based on a predictive model for TCDD plasma levels at the time of assumed last exposure. Half-time estimate: 7.1 y.	(112)
			Circulatory disease	182	1.07 (0.98–1.16)		
			IHD	93	1.19 (1.08–1.32)		
			CeVD	39	0.98 (0.83–1.16)		
			IHD, TCDD, based on occupational history, ppt				
			≤ 0.4	35	1.0		
			0.4–1.9	16	1.17 (0.65–2.09)		
			1.9–9.9	14	1.00 (0.54–1.85)		
			≥ 9.9	28	2.60 (1.57–4.31)		
			IHD, TCDD, based on a priori assumed exposure status, ppt				
			≤ 0.4	33	1.0		
			0.4–1.9	21	1.02 (0.60–1.76)		
			1.9–9.9	20	1.25 (0.72–2.18)		
			≥ 9.9	19	2.78 (1.57–4.91)		
North America							
Cross-sectional study *Cohort:* 281 workers from 2 US factories producing trichloro-phenol or derivatives employed > 15 y earlier. *Referents:* 260 subjects with no self-reported occupational exposure to TCDD.	1987	Reported MI, angina pectoris, arrhythmia and hypertension.	Serum TCDD, pg/g lipid		OR	Matching for age, race and gender.	(138)
			MI				
			< 238	20	1.28 (0.67–2.45)		
			≥ 238	9	1.91 (0.84–4.38)		
			Angina pectoris				
			< 238	15	0.84 (0.43–1.67)		
			≥ 238	6	1.10 (0.43–2.83		
			Arrhythmia				
			< 238	25	0.89 (0.51–1.53)		

Table A23. Dioxins and dioxin-like compounds.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			≥ 238	8	0.91 (0.40–2.07)		
			Hypertension				
			< 238	93	1.14 (0.79–1.66)		
			≥ 238	34	1.46 (0.84–2.52)		
Cohort: 5 132 chemical workers from 12 US plants producing TCDD-contaminated products 1942–1984, of which 608 with chloracne and 3 538 with cumulative exposure estimates. *Referents:* US national population.	Until 1993	Mortality (ICD-9) from IHD (410–414) and CeVD (430–438).	*Total cohort*		SMR	Exposure score based on the following: 1) the concentration of TCDD (mg/g) in process materials. 2) the fraction of the day the worker worked on the specific process. 3) a qualitative contact level (0.01–1.5) based on estimates of the amount of TCDD contamination reaching exposed skin areas or the potential for inhalation of TCDD-contaminated dust. The trend for IHD was strengthened with the use of the logarithm of cumulative exposure.	(909)
			IHD	456	1.09 (1.00–1.20)		
			CeVD	69	0.96 (0.74–1.21)		
			Workers with chloracne				
			IHD	92	1.17 (0.94–1.44)		
			IHD by cumulative exposure score		RR		
			0– < 19		1.00		
			19–139		1.23 (0.75–2.00)		
			139– < 581		1.34 (0.83–2.18)		
			581– < 1 650		1.30 (0.79–2.13)		
			1 650– < 5 740		1.39 (0.86–2.24)		
			5 740– < 20 200		1.57 (0.96–2.56)		
			≥ 20 200		1.75 (1.07–2.87)		
					P(trend): 0.05		

Table A23. Dioxins and dioxin-like compounds.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Cohort: 1 262 male US veterans of Operation Ranch Hand exposed to herbicides 1962–1971 in Vietnam, of which 587 enlisted ground crew. *Referents:* 19 078 male US veterans who flew or serviced other aircrafts in Southeast Asia, of which 10 724 enlisted ground crew.	Until 1999	Mortality (ICD-9) from circulatory disease (390–459), atherosclerotic heart disease (410– 412, 414.0, 414.8, 414.9, 428.4, 440.9, 444), CeVD (430, 431, 432.9, 434.0, 434.9, 436, 442.8, 437.9) and hypertensive disease (401.9, 402.9, 437.2, 441.0, 441.1, 441.2, 441.3, 441.5).	*All cohort* Circulatory disease *Enlisted ground crew veterans* Circulatory disease Heart disease CeVD Hypertension *2 452 veterans with dioxin assay results* Circulatory disease 1 436 referents 442 background 287 low 287 high	Exp/refs 66/745 40/393 28/281 5/34 2/15 31 8 12 9	RR 1.3 (1.0–1.6) 1.7 (1.2–2.4) 1.7 (1.1–2.5) 2.3 (0.9–6.0) 2.5 (0.6–10.8) 1.0 0.8 (0.4–1.8) [a] 1.8 (0.9–3.5) [a] 1.5 (0.7–3.3) [a] P(trend): 0.07	[a] Adjustment for military occupation, birth year, smoking and family history of heart disease. *Dioxin exposure categories* Background: Ranch Hand veterans ≤ 10 ppt. Among veterans with exposure > 10 ppt the level at the end of service in Vietnam was estimated with a 1st order kinetics model (half-time 7.6 y). Low: initial level ≤ 117.6 ppt. High: initial level > 117.6 ppt.	(489)
Cross-sectional study 1 469 male US veterans from Army Chemical Corps with minimum 18 mo service 1965–1973 in Vietnam. Agent Orange was sprayed 1965–1970. *Cohort:* 907 herbicide sprayers. *Referents:* 562 non-sprayers.	2013	Self-reported physician-diagnosed hypertension.	*Hypertension* Herbicide sprayers Non-sprayers	 740 (81.6%) 406 (72.2%)	OR 1.77 (1.35–2.30)	Blood samples of TCDD 1999–2000. Serum TCDD concentrations mean (range), lipid corrected: *361 sprayers* 3.5 (0.5–30.6) ppt *192 non-sprayers* 2.5 (0.7–17.7) ppt P = 0.0001.	(207)

Table A23. Dioxins and dioxin-like compounds.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
Asia							
Cohort: 180 639 Korean Vietnam veterans who served in Vietnam 1964–1973.	1992–2005	Mortality (ICD-10) from circulatory disease (I00–I99), hypertension (I10–I13), IHD (I20–I25), angina pectoris (I20), acute MI (I21), chronic IHD (I25), CeVD (I60–I69), intracerebral haemorrhage (I61–I62), cerebral infarction (I63) and aortic aneurysm (I71).	*Circulatory disease*		HR	An Agent Orange exposure index was based on a geographical information system model. Exposure was presented as a continuous variable and as a comparison between high- and low-exposure groups.	(1045)
			Continuous exp.	3 180	1.02 (1.00–1.04)		
			High vs low exp.	1 716/1 464	1.04 (0.97–1.12)		
			Hypertension				
			Continuous exp.	192	1.06 (0.99–1.14)		
			High vs low exp.	110/82	1.18 (0.88–1.58)		
			IHD				
			Continuous exp.	843	0.99 (0.96–1.03)		
			High vs low exp.	437/406	0.99 (0.86–1.14)		
			Angina pectoris				
			Continuous exp.	60	1.22 (1.05–1.41)		
			High vs low exp.	43/17	2.34 (1.32–4.15)		
			Acute MI				
			Continuous exp.	699	0.98 (0.95–1.02)		
			High vs low exp.	352/347	0.93 (0.80–1.09)		
			Chronic IHD				
			Continuous exp.	82	0.97 (0.88–1.08)		
			High vs low exp.	41/41	0.92 (0.59–1.44)		
			CeVD				
			Continuous exp.	1 618	1.01 (0.99–1.04)		
			High vs low exp.	879/739	1.01 (0.92–1.12)		
			Intracerebral haemorrhage				
			Continuous exp.	758	1.03 (0.99–1.07)		
			High vs low exp.	407/351	1.05 (0.90–1.22)		
			Cerebral infarction				
			Continuous exp.	309	0.99 (0.94–1.05)		
			High vs low exp.	167/142	0.96 (0.76–1.20)		

Table A23. Dioxins and dioxin-like compounds.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			Aortic aneurysm				
			Continuous exp.	29	1.05 (0.88–1.26)		
			High vs low exp.	17/12	1.26 (0.59–2.66)		
Pooled studies							
IARC multicentre cohort: 21 863 phenoxyacid herbicide and chlorophenol production workers and sprayers from 36 cohorts in 12 countries (of which 13 831 exposed, 7 553 non-exposed and 479 with unknown exposure). *External referents:* national rates from the respective countries. *Internal referents:* 7 553 non-exposed workers.	1939–1992	Mortality (ICD-9) from circulatory disease (390–459), IHD (410–414), CeVD (430–438) and other diseases of the heart (415–429).	*Circulatory disease*		SMR	HCD: higher chlorinated dioxins.	(1005)
			Males	1 738	0.91 (0.87–0.95)		
			Females	48	1.00 (0.73–1.32)		
			IHD				
			Males	1 179	0.92 (0.87–0.98)		
			Females	24	1.07 (0.68–1.59)		
			CeVD				
			Males	254	0.86 (0.76–0.97)		
			Females	9	0.73 (0.33–1.38)		
			Other heart disease				
			Males	166	1.11 (0.95–1.29)		
			Females	6	0.92 (0.34–2.00)		
			Workers exposed to TCDD/HCD		SMR		
			Circulatory disease	1 170	0.94 (0.88–0.99)		
			IHD	789	0.97 (0.90–1.04)		
			CeVD	162	0.84 (0.71–0.98)		
			Other heart disease	138	1.20 (1.01–1.42)		
			Internal referents, exposure duration		RR		
			Circulatory disease	1 151/582	1.51 (1.17–1.96)		
			< 1 y	248	1.00		
			1–4 y	370	1.16 (0.98–1.38)		
			5–9 y	220	1.32 (1.08–1.60)		
			10–19 y	233	1.28 (1.05–1.55)		

Table A23. Dioxins and dioxin-like compounds.

Study group and design	Time of follow-up	Outcome (diagnose)	Categories of exposure	No. of cases	Risk estimates (95% CI)	Confounder adjustments and comments	Ref.
			≥ 20 y	80	0.96 (0.73–1.27) P(trend): 0.19		
			IHD	775/391	1.67 (1.23–2.26)		
			< 1 y	187	1.00		
			1–4 y	236	1.05 (0.86–1.29)		
			5–9 y	135	1.17 (0.92–1.48)		
			10–19 y	158	1.21 (0.96–1.53)		
			≥ 20 y	59	0.98 (0.70–1.36) P(trend): 0.29		
			CeVD	161/95	1.54 (0.83–2.88)		
			< 1 y	31	1.00		
			1–4 y	54	1.13 (0.70–1.82)		
			5–9 y	38	1.39 (0.83–2.32)		
			10–19 y	34	1.22 (0.72–2.08)		
			≥ 20 y	4	0.30 (0.10–0.91) P(trend): 0.51		

Appendix B. Previous NEG criteria documents

NEG documents published in the scientific serial Arbete och Hälsa (Work and Health).

Substance/Agent	Arbete och Hälsa issue
Acetonitrile	1989:22, 1989:37*
Acid aerosols, inorganic	1992:33, 1993:1*
Acrylonitrile	1985:4
Allyl alcohol	1986:8
Aluminium and aluminium compounds	1992:45, 1993:1*, 2011;45(7)*D
Ammonia	1986:31, 2005:13*
Antimony	1998:11*
Arsenic, inorganic	1981:22, 1991:9, 1991:50*
Arsine	1986:41
Asbestos	1982:29
Benomyl	1984:28
Benzene	1981:11
1,2,3-Benzotriazole	2000:24*D
Boric acid, Borax	1980:13
1,3-Butadiene	1994:36*, 1994:42
1-Butanol	1980:20
γ-Butyrolactone	2004:7*D
Cadmium	1981:29, 1992:26, 1993:1*
7/8 Carbon chain aliphatic monoketones	1990:2*D
Carbon monoxide	1980:8, 2012;46(7)*
Carbon nanotubes	2013;47(5)*
Ceramic Fibres, Refractory	1996:30*, 1998:20
Chloramines, Inorganic	2019;53(2)
Chlorine, Chlorine dioxide	1980:6
Chloromequat chloride	1984:36
4-Chloro-2-methylphenoxy acetic acid	1981:14
Chlorophenols	1984:46
Chlorotrimethylsilane	2002:2
Chromium	1979:33
Cobalt	1982:16, 1994:39*, 1994:42
Copper	1980:21
Creosote	1988:13, 1988:33*
Cyanoacrylates	1995:25*, 1995:27
Cyclic acid anhydrides	2004:15*D
Cyclohexanone, Cyclopentanone	1985:42
n-Decane	1987:25, 1987:40*
Deodorized kerosene	1985:24
Diacetone alcohol	1989:4, 1989:37*
Dichlorobenzenes	1998:4*, 1998:20
Diesel engine exhaust	2016;49(6)*D

NEG documents published in the scientific serial Arbete och Hälsa (Work and Health).

Substance/Agent	Arbete och Hälsa issue
Diesel exhaust	1993:34, 1993:35*
Diethylamine	1994:23*, 1994:42
2-Diethylaminoethanol	1994:25*N
Diethylenetriamine	1994:23*, 1994:42
Diisocyanates	1979:34, 1985:19
Dimethylamine	1994:23*, 1994:42
Dimethyldithiocarbamates	1990:26, 1991:2*
Dimethylethylamine	1991:26, 1991:50*
Dimethylformamide	1983:28
Dimethylsulfoxide	1991:37, 1991:50*
Dioxane	1982:6
Endotoxins	2011;45(4)*D
Enzymes, industrial	1994:28*, 1994:42
Epichlorohydrin	1981:10
Ethyl acetate	1990:35*
Ethylbenzene	1986:19
Ethylenediamine	1994:23*, 1994:42
Ethylenebisdithiocarbamates and Ethylenethiourea	1993:24, 1993:35*
Ethylene glycol	1980:14
Ethylene glycol monoalkyl ethers	1985:34
Ethylene oxide	1982:7
Ethyl ether	1992:30* N
2-Ethylhexanoic acid	1994:31*, 1994:42
Flour dust	1996:27*, 1998:20
Formaldehyde	1978:21, 1982:27, 2003:11*D
Fungal spores	2006:21*
Furfuryl alcohol	1984:24
Gasoline	1984:7
Glutaraldehyde	1997:20*D, 1998:20
Glyoxal	1995:2*, 1995:27
Halothane	1984:17
n-Hexane	1980:19, 1986:20
Hydrazine, Hydrazine salts	1985:6
Hydrogen fluoride	1983:7
Hydrogen sulphide	1982:31, 2001:14*D
Hydroquinone	1989:15, 1989:37*
Industrial enzymes	1994:28*
Isoflurane, sevoflurane and desflurane	2009;43(9)*
Isophorone	1991:14, 1991:50*
Isopropanol	1980:18
Lead, inorganic	1979:24, 1992:43, 1993:1*
Limonene	1993:14, 1993:35*

NEG documents published in the scientific serial Arbete och Hälsa (Work and Health).

Substance/Agent	Arbete och Hälsa issue
Lithium and lithium compounds	2002:16*
Manganese	1982:10
Mercury, inorganic	1985:20
Methacrylates	1983:21
Methanol	1984:41
Methyl bromide	1987:18, 1987:40*
Methyl chloride	1992:27*D
Methyl chloroform	1981:12
Methylcyclopentadienyl manganese tricarbonyl	1982:10
Methylene chloride	1979:15, 1987:29, 1987:40*
Methyl ethyl ketone	1983:25
Methyl formate	1989:29, 1989:37*
Methyl isobutyl ketone	1988:20, 1988:33*
Methyl methacrylate	1991:36*D
N-Methyl-2-pyrrolidone	1994:40*, 1994:42
Methyl-tert-butyl ether	1994:22*D
Microbial volatile organic compounds (MVOCs)	2006:13*
Microorganisms	1991:44, 1991:50*
Mineral fibers	1981:26
Nickel	1981:28, 1995:26*, 1995:27
Nitrilotriacetic acid	1989:16, 1989:37*
Nitroalkanes	1988:29, 1988:33*
Nitrogen oxides	1983:28
N-Nitroso compounds	1990:33, 1991:2*
Nitrous oxide	1982:20
Occupational exposure to chemicals and hearing impairment	2010;44(4)*
Occupational skin exposure to chemicals	2018;52(3)*
Oil mist	1985:13
Organic acid anhydrides	1990:48, 1991:2*
Ozone	1986:28
Paper dust	1989:30, 1989:37*
Penicillins	2004:6*
Permethrin	1982:22
Petrol	1984:7
Phenol	1984:33
Phosphate triesters with flame retardant properties	2010;44(6)*
Phthalate esters	1982:12
Platinum	1997:14*D, 1998:20
Polychlorinated biphenyls (PCBs)	2012;46(1)*
Polyethylene,	1998:12*
Polypropylene, Thermal degradation products in the processing of plastics	1998:12*

NEG documents published in the scientific serial Arbete och Hälsa (Work and Health).

Substance/Agent	Arbete och Hälsa issue
Polystyrene, Thermal degradation products in the processing of plastics	1998:12*
Polyvinylchloride, Thermal degradation products in the processing of plastics	1998:12*
Polytetrafluoroethylene, Thermal degradation products in the processing of plastics	1998:12*
Propene	1995:7*, 1995:27
Propylene glycol	1983:27
Propylene glycol ethers and their acetates	1990:32*N
Propylene oxide	1985:23
Refined petroleum solvents	1982:21
Refractory Ceramic Fibres	1996:30*
Selenium	1992:35, 1993:1*
Silica, crystalline	1993:2, 1993:35*
Silicon carbide	2018;52(1)*
Styrene	1979:14, 1990:49*, 1991:2
Sulphur dioxide	1984:18
Sulphuric, hydrochloric, nitric and phosphoric acids	2009;43(7)*
Synthetic pyretroids	1982:22
Tetrachloroethane	1996:28*D
Tetrachloroethylene	1979:25, 2003:14*D
Thermal degradation products of plastics	1998:12*
Thiurams	1990:26, 1991:2*
Tin and inorganic tin compounds	2002:10*D
Toluene	1979:5, 1989:3, 1989:37*, 2000:19*
1,1,1-Trichloroethane	1981:12
Trichloroethylene	1979:13, 1991:43, 1991:50*
Triglycidyl isocyanurate	2001:18*
n-Undecane	1987:25, 1987:40*
Vanadium	1982:18
Vinyl acetate	1988:26, 1988:33*
Vinyl chloride	1986:17
Welding gases and fumes	1990:28, 1991:2*
White spirit	1986:1
Wood dust	1987:36
Xylene	1979:35
Zinc	1981:13

*: in English, remaining documents are in a Scandinavian language.
D: collaboration with the Dutch Expert Committee on Occupational Safety (DECOS).
N: collaboration with the US National Institute for Occupational Safety and Health (NIOSH).

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