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Cardiovascular diseases and the work environment

A critical review of the epidemiologic literature on chemical factors

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KRISTENSEN TS. Cardiovascular diseases and the work environment: a critical review of the epidemiologic literature on chemical factors. *Scand J Work Environ Health* 1989;15:245—264. This is the second of two articles reviewing the epidemiologic research on cardiovascular diseases (CVD) and the work environment. It deals with chemical factors, ie, lead, cadmium, cobalt, arsenic, carbon monoxide, passive smoking, organic solvents, carbon disulfide, nitroglycerin, nitroglycol, and others. The epidemiologic literature relating to each is assessed on the basis of a number of methodological criteria, and the need for future research, the methodology of literature reviews, and preventive implications and perspectives are discussed. It is concluded that the causal relationship between two of the chemicals, carbon disulfide and nitroglycerin/nitroglycol, and CVD is very well documented. For lead and passive smoking a causal relation to CVD is likely. More research is needed concerning cobalt, arsenic, antimony, and other chemical compounds. Exposure to carbon monoxide increases the acute risk of CVD but has probably no lasting atherosclerotic effect. Cadmium and organic solvents are probably not causally related to CVD.

Key terms: antimony, arsenic, beryllium, cadmium, carbon disulfide, carbon monoxide, chemicals, cobalt, combustion products, dinitrotoluene, hypertension, ischemic heart disease, lead, nitroglycerin, nitroglycol, occupation, organic solvents, organophosphates, passive smoking.

This is the second of two articles on the work environment and cardiovascular diseases (CVD). It reviews the epidemiologic literature on occupational chemical factors and CVD. The results of the review are compared with those of earlier reviews in this field (1—13).

As in the previous article (14), I have dealt with occupational factors, but not with individual habits or characteristics. Thus, for example, I discuss passive but not active smoking, lead and cadmium but not soft water. To facilitate the best possible clarification of the occupational factors considered, I have also included investigations which are not strictly occupational because most of the exposures are also found outside the work environment.

The objectives of this article are the same as those of the previous one, ie, (i) to record and integrate the epidemiologic literature on CVD and the work environment; (ii) to evaluate the research with the objective of elucidating possible causalities between occupational factors and CVD; (iii) if possible, to point out areas where enough is known to start employing the research results for the purpose of prevention, and (iv) to point out defects and deficiencies in existing research with the objective of strengthening and improving future research efforts.

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Materials and methods

The criteria for collecting and evaluating the epidemiologic literature have been described in detail in the previous article (14). The objective has been to include all epidemiologic studies on the exposures in English, German or the Scandinavian languages (or which have summaries in one of these languages). That objective has not been fully realized, although this review is more comprehensive than earlier reviews on the same topic. To give the readers an opportunity to supplement the review of the individual exposures, some special reviews from recent years have also been included. They contain extensive lists which also cover the nonepidemiologic literature.

The most important objective of the review has been to identify causal risk factors for CVD. With this in mind, I have evaluated the following five central methodological points for each study: (i) the time dimension, (ii) confounding, (iii) selection, (iv) measurement of exposure and disease, and (v) adequate design and statistical analysis. On the basis of this critical evaluation, each study has been given a score between "x" and "xxxxx" for methodological quality. (For more details of this scoring system, see reference 14.)

It should be emphasized that, when I refer to "study" in the following discussion, I do not necessarily mean an "article" or "paper." An article may contain two or more studies, eg, when the same hypothesis has been tested on two different populations, such as men and women or inhabitants of two different cities. If the analyses are published in such a way that the results for each individual group can be iden-

Table 1. Results of 63 epidemiologic studies of cardiovascular diseases (CVD) and lead exposure according to the methodological quality of the studies. The table is based on references 28, 33—107

Degree of relationship[a]	Methodological quality[b]									
	x		xx		xxx		xxxx		x—xxxx	
	N	%	N	%	N	%	N	%	N	%
−	—	0	1	5.3	—	0	—	0	1	1.6
(−)	—	0	—	0	—	0	—	0	—	0
0	8	44.4	6	31.6	6	25.0	—	0	20	31.7
(+)	5	27.8	2	10.5	2	8.3	—	0	9	14.3
+	3	16.7	9	47.4	16	66.7	2	100	30	47.6
?	2	11.1	1	5.3	—	0	—	0	3	4.8
Total	18	100	19	100	24	100	2	100	63	100

[a] − = negative relationship between lead exposure and CVD/blood pressure, (−) = slight or inconsistent negative relationship, 0 = no relationship, (+) = slight or inconsistent positive relationship, + = positive relationship, and ? = uncertain relationship.
[b] The criteria for methodological quality are explained in the text. No studies had xxxxx for quality.

tified, they have been regarded as separate studies. On the other hand, the same research project is often published in several articles, eg, in prospective studies, in which successive results are published as the cohort grows older. In such cases, all articles have been evaluated as a whole with regard to study outcome and methodological quality.

Results

Lead

Many epidemiologic studies have been published on lead and CVD. Nonetheless, the topic is treated very superficially in the general reviews on the relationship between environmental exposures and CVD. In several more recent reviews, lead is not mentioned at all (3, 4, 7, 8), while the topic is treated very briefly with a maximum of three references in others (1, 2, 5, 9, 12). Only in the early review by Warshaw from 1960 (13), in Kurppa et al's review of 1984 (6), and in the reports of Rosenman (10, 11) is a reasonably thorough discussion of the possible lead-CVD relationship included. These authors give six to twelve empirical references. The general conclusion drawn by the authors who mention the topic is that further research is necessary.

In the more specific literature on lead, trace metals, or trace elements, similar divergencies are found. There are examples of CVD not being mentioned in reviews on lead and health (15) and of lead not being mentioned in reviews on trace metals and CVD (16—18). However, the most common conclusion in these reviews is again that further research is necessary (19—24). Some reviews do, however, conclude that lead has been shown to increase the risk of CVD, eg, Teleky's review from 1937 (25) and Stöfen's review from 1974, which primarily deals with German and East European studies (26).

In 1987 and 1988, two reviews were published which marked a new departure in this field of research. One is the comprehensive review by Sharp et al (27) on epidemiologic, clinical, and toxicologic studies concerning low-level lead exposure and blood pressure. The other is a special issue of *Environmental Health Perspectives* (1988, volume 78), which contains papers and discussions from an international symposium on the relationships between lead and blood pressure. This issue contains several reviews of both experimental and observational investigations (28—32). The conclusion from these comprehensive reports is that it must be considered probable, though not yet definitively proved, that low-level lead exposure increases blood pressure and consequently the risk of CVD.

In the present review, 63 empirical studies have been evaluated (table 1). The empirical research in the field can be said to fall into three periods, ie, 1920—1962, 1963— 1980, and 1980—the present. In the first period several studies were published on the topic, especially on the relationship between occupational lead exposure and blood pressure. The methodology of most of these studies is, naturally, rather primitive, but there are exceptions — for example, Vigdortchik's remarkable study from 1935 (51). I have included six of the investigations from this early period in my review. The second period, 1963—1980, was heralded by Dingwall-Fordyce & Lane's historical prospective mortality study from 1963 (64, 66). During this period, at least one investigation was published on the topic every year, but, as suggested earlier, these studies did not arouse any particular attention. From 1980 on, the situation has changed dramatically. Many more studies have been published (38 of the 63 investigations in table 1 are from the 1980s), and also interest is sharply rising in the possible relationship between lead and blood pressure at very low-level lead exposures, corresponding to those levels that the general population is exposed to from leaded gasoline, food, water, etc.

Table 1 reveals five features. First, many empirical investigations have been conducted. Second, virtually all the studies have a low or medium score for epidemiologic quality. Third, 30 investigations (48 %) show a clear positive relationship between lead exposure and CVD (or blood pressure), while nine (14 %) show a positive tendency. Fourth, a very clear relationship exists between study quality and study outcome. The percentage of positive studies increases as one moves from "x" to "xxxx" as follows: 17, 47, 67, and 100 %. Fifth, there is only one study which shows a negative relationship between lead exposure and CVD (33).

The large number of positive studies and the positive correlation between study quality and study outcome supports the hypothesis of a causal relationship between lead exposure and CVD.

A more-detailed examination of the 63 studies indicates that they are very different with regard to study design, study end points, and intensity of exposure. Many of the studies are, eg, cross-sectional investigations of the relationship between rather low levels of lead in blood and blood pressure, while others are historical prospective studies of mortality among

heavily exposed workers. However, further analysis shows that both the share of positive studies and the positive trend with increasing study quality are virtually the same when the different types of studies are analyzed separately.

While the relationship between low-level lead exposure and blood pressure-hypertension has been dealt with in detail in the earlier mentioned reviews from 1987 and 1988 (27—32), studies of lead workers with considerably higher levels of exposure have not. As these studies are of particular interest for occupational medicine, I have included six dealing with mortality in my review.

Dingwall-Fordyce & Lane (64, 66) found increasing cerebrovascular mortality with increasing lead exposure. The standardized mortality ratio (SMR) values were 94, 98, and 160 for employed lead workers as exposure increased and 76, 176, and 258 for retired lead workers, respectively. A later follow-up study showed the same trend, but — as expected — converging SMR values (65).

Cooper and his co-workers (57—59) found moderately elevated or normal SMR values for cerebrovascular mortality in two lead-exposed cohorts (SMR 132 and 93) but elevated values for "other hypertensive diseases" (SMR 475 and 320) and "hypertensive heart diseases" (SMR 203 and 128).

McMichael & Johnson (86) compared the mortality of workers with previous lead poisoning with the mortality of other lead workers and Australian men in general. Using proportionate mortality ratios, they found twice as many deaths due to cerebral hemorrhage and 24 % more deaths due to other cerebrovascular diseases among the formerly lead-poisoned workers than among the other lead workers. In a comparison with Australian men, the differences were even greater.

Davies (62) also studied men with previously registered lead poisoning and found an SMR of 410 for cerebrovascular diseases.

Selevan et al (93, 94) found fewer cerebrovascular deaths than expected (SMR 84), but even in this "negative" study the SMR values for cerebrovascular deaths increased with increasing exposure (< 5 years: SMR 47; 5—19 years: SMR 75; ≥ 20 years: SMR 146).

Finally, Gerhardsson et al (40) found an SMR of 130 for cerebrovascular diseases among lead workers. Internal comparisons showed a positive correlation between both the mean blood-lead level and the peak blood-lead level and cerebrovascular mortality.

These six mortality studies of lead-exposed workers all have a medium level of epidemiologic quality. However, when the problems associated with historical prospective mortality studies are taken into consideration, the investigations show a rather consistent pattern with increased cerebrovascular or hypertensive mortality in the highly exposed groups. In addition, most of the studies showed an increased mortality as a result of chronic renal disease.

Even though studies with high methodological quality ("xxxx" or "xxxxx") are few, the following conclusions seem reasonable on the basis of the existing epidemiologic literature: (i) there is a causal relationship between lead exposure and blood pressure even at low exposure levels corresponding to blood-lead levels below 30 µg/dl (27, 28, 31, 70, 73, 74, 106), and, even if the relationship is weak, this relationship may have considerable public health implications due to the widespread lead exposure throughout the industrialized world (32, 72); (ii) there is an increased incidence of cerebrovascular diseases among workers who have been occupationally exposed to lead, but the clarification of the dose-response relationship is not possible on the basis of the existing studies; (iii) no studies have been found in which the incidence of ischemic heart disease (IHD) increased as a result of lead exposure.

Cadmium

The relationship between cadmium and CVD has been treated with considerable variability in general reviews on environmental exposures and CVD. A few authors dealt with the topic rather extensively (6, 10, 11, 13), but none gave more than 10 references. Others mentioned the possible relationship between cadmium and CVD but treated the topic very superficially (1, 2, 5), while the remaining authors did not mention cadmium at all (3, 4, 7—9, 12). In those articles in which the topic is discussed, it is concluded that the question is not sufficiently clarified and that further research is necessary.

In the special reviews on the associations between trace metals or cadmium and CVD, the possible relationship between cadmium and blood pressure is treated exhaustively by all the authors. In the older reviews from the 1960s and the first half of the 1970s, there is generally a belief in the hypothesis of a cadmium-blood pressure relationship (16—19, 108—110). Among these reviews, Schroeder's experiments on rats in the early 1960s play an important role. From 1976 on, skeptical articles and reviews (20, 23, 111—116) alternate with more positive ones (117—119). Considerable agreement exists regarding the relationship between cadmium exposure and increased blood pressure shown in animal experiments with rats, dogs, and rabbits, but there is no consensus on the interpretation of research on humans. After more than a quarter of a century of research comprising hundreds of experiments and investigations, Spieker et al (116) concluded in one of the most recent reviews: "The data available up to now [about the connection between human hypertension and cadmium pollution] can only be considered as a first step to clarify this problem [p 35]". This is, indeed, a modest profit from such great efforts.

In the present review, 33 investigations of cadmium and CVD (mainly blood pressure/hypertension) have been evaluated. In 11 of the studies, cadmium in blood,

urine, hair, or kidneys has been compared for live hypertensive and normotensive persons. In nine studies persons who died from hypertensive heart disease or related causes have been compared with persons who died of other causes. In these studies, the cadmium content was generally measured from the kidneys or liver. Five studies are cross-sectional investigations of representative population groups for which the blood pressure has been related to cadmium in blood or urine. Four studies have related cadmium pollution in various city areas to morbidity and mortality, and the last four are occupational medical studies. Table 2 contains a survey of the results and quality of these studies. The table indicates the following: (i) the studies examined have, in general, a low epidemiologic quality, and none of the studies have been rated "xxxx" or "xxxxx"; (ii) 13 of the studies (39 %) show (a tendency towards) a positive relationship [+ or (+)] between cadmium exposure and CVD; and (iii) there is a negative relationship between study quality and "positivity." Of the studies with a rating of "x," 46 % were positive; of the studies with a rating of "xx," 44 % were positive; and of the studies with a rating of "xxx," 27 % were positive.

Both the low share of positive studies and the negative trend in the table speak against the cadmium-CVD hypothesis. The conclusion therefore is that the null hypothesis is best supported by the investigations examined.

The methodological level of the research on cadmium and CVD (especially blood pressure/hypertension) is so low that an identification of the most common errors and flaws is important to facilitate their avoidance in future research. One of the worst problems concerns the measurement of cadmium exposure. Many studies estimated the exposure by measuring cadmium in blood (77, 80, 124, 137, 138, 140, 141, 148—151, 153). The blood cadmium level is, however, not a very reliable measure of the cadmium body burden. As early as 1976, Morgan (155) wrote: "Blood and urine may be convenient fluids to measure, but neither is well correlated with kidney or liver content, which together comprise about one half of the body burden [p 1361]." In contrast, the blood contains only 0.1 % of the body burden. Morgan recommended measuring cadmium in hair, kidneys, or liver. This view is strongly supported by other experts, including Lauwerys (112) and Perry & Kopp (119). Several studies have employed cadmium in urine as a measure of past exposure, but this measure must be regarded as being even poorer than cadmium in blood (77, 95, 107, 138, 144, 153). Seven of the 13 positive studies in table 2 have employed cadmium in blood or urine as the measure of exposure.

Table 2. Results of 33 epidemiologic studies of cardiovascular diseases (CVD) and cadmium exposure according to the methodological quality of the studies. The table is based on references 55, 77, 80, 95—97, 107, 120—154.

Degree of relationship*	Methodological quality							
	x		xx		xxx		x—xxx	
	N	%	N	%	N	%	N	%
−	—	0	1	11.1	—	0	1	3.0
(−)	—	0	1	11.1	3	27.3	4	12.1
0	3	23.1	3	33.3	5	45.5	11	33.3
(+)	2	15.4	—	0	3	27.3	5	15.2
+	4	30.8	4	44.4	—	0	8	24.2
?	4	30.8	—	0	—	0	4	12.1
Total	13	100	9	100	11	100	33	100

* See table 1 for an explanation of the symbols.

Two of the remaining six positive studies employed the cadmium content in air in a number of American cities as a measure of exposure. The results were then correlated to CVD mortality, and a positive relationship was found (131, 132). This method is problematical for many reasons. For example, the influence of cadmium in air on body burden is very slight. The significant factors are food, smoking, water, and occupational exposure.

Another major methodological problem concerns the study design employed. Many of the investigations employed a "quasi case-referent" design in which sick persons (with hypertension or IHD) were compared to healthy referents (77, 123, 124, 128, 130, 133, 140—142, 144—154). These studies are called "quasi case-referent" because in reality they are cross-sectional studies in which "disease" (hypertension, for example) is measured simultaneously with "exposure" (for example, cadmium in blood). This design is problematical for several reasons. First, because blood pressure and the blood cadmium level are measured simultaneously, it is not possible to exclude the possibility that the direction of causation is reversed, ie, that persons with hypertension have an increased content of cadmium in their blood due to metabolic changes. This possibility has, in fact, been mentioned by several authors, and one study directly concluded that hypertension increases the blood cadmium level (141). Second, in most studies the selection of both cases and referents has been described very superficially or not at all. Since selection is of paramount importance in case-referent studies, this is an important potential flaw. Third, in many studies, the researchers had matched for smoking habits, and this is an error as tobacco smoking is not a risk factor for hypertension. In reality, it is overmatching because an important source of cadmium in the body is being blocked. Conversely, relative weight and education/social status have not been matched, and such matching should be done since both are risk factors for hypertension. Fourth, comparing normotensive and hypertensive persons leads to dichotomy. Instead, one should rather have operated with the whole spectrum of values on the blood pressure scale. This problem is especially important because many authors have hypothesized that the relationship between cadmium exposure and blood pressure has a reversed U shape with the largest effect at medium-high cadmium exposure levels.

Following this critique of methodology, and turning back to the empirical studies, I found only three positive studies which measured the cadmium content of the kidneys (128, 145, 147). These three studies are of the "quasi case-referent" type just described and have so many methodological errors that they only scored "X" or "XX" for methodological quality. Thus they can be considered to be of only very little significance.

Only three investigations have been found which are not "quasi case-referent" and which do not measure cadmium in blood, urine, or air, ie, the historical prospective mortality study of 7000 workers by Kazantzis et al (120—122), the historical prospective mortality study of 525 workers by Andersson et al (134, 135), and the various projects concerning the Shipham inhabitants (125—127). These three studies scored "XXX" for methodological quality, and one of them — the Shipham study — showed a weak positive relationship between cadmium and CVD, while the two occupational studies showed a weak negative relationship.

Thus the conclusion seems clear, ie, the epidemiologic research can in no way be considered to support the hypothesis of a causal relationship between cadmium exposure and hypertension or CVD in general. At this point it seems reasonable to conclude that such a relationship does not exist. Over the past 25 years, although the number of studies in this field has grown annually, the body of knowledge has not. Despite the last three studies mentioned, there is still a great need for epidemiologically sound studies on this topic.

Finally, tobacco smokers are moderately exposed to cadmium and should therefore have increased blood pressure. But the cardiovascular epidemiology shows very clearly that tobacco smoking is not a risk factor for hypertension. This lack of relationship, which has been epidemiologically very thoroughly investigated, is a further argument against the cadmium-blood pressure hypothesis.

Cobalt

In the mid-1960s, an epidemic of cardiomyopathies was registered in Belgium, Canada, and the United States among heavy beer drinkers. The cause of the epidemic was relatively quickly established. Several beer manufacturers had begun to add cobalt sulfate to the beer in order to stabilize the foam (156—161). Nearly half the patients examined in the various studies died from their cardiomyopathy. It is paradoxic that the consumption of 6—8 mg of cobalt sulfate per day could have this dramatic effect, as cobalt has been used in medicine in much higher doses without adverse effects. There seems to be agreement that the genesis of this unexpected adverse effect was a combination of cobalt exposure, long-standing high alcohol consumption, and poor nutritional condition.

In the general reviews on CVD and environmental exposures, the cobalt-related cardiomyopathies among beer drinkers has been mentioned by several authors (2, 6, 9—11), while the remaining reviews do not mention cobalt as a risk factor for CVD at all. In addition, two case reports have been mentioned in a few of the reviews, ie, those by Barborik & Dusek (162) and Kennedy et al (163). These case reports describe two cobalt-exposed men (41 and 48 years of age) who both died from cardiomyopathy. The authors suggested that cardiomyopathy caused by cobalt exposure might often be neglected and misdiagnosed.

In addition, three epidemiologic investigations of cobalt-exposed workers were found. In 1980 and 1983, Alexandersson & Atterhog (164, 165) published a study of workers in the hard metal industry who were occupationally exposed to cobalt (exposure level 0.01—0.06 mg/m^3). The 146 exposed workers were compared to an unexposed reference group with regard to electrocardiography, pulse rate, and blood pressure. For the cobalt-exposed workers, Alexandersson & Atterhog (164) found a higher prevalence of hypertension, a higher average blood pressure, and more abnormal electrocardiographic changes. The electrocardiographic changes proved to a large extent to be reversible (165).

In an abstract from 1985, Horowitz et al (166) described cardiac manifestations of cobalt exposure in a group of 35 self-referred hard metal workers. Electrocardiographic abnormalities were found in 16 of the 35 workers.

The third study is a Danish investigation of female porcelain workers exposed to cobalt blue dye in their work (167). The median cobalt concentration in the air was 0.80 mg/m^3. When the exposed women were compared with an unexposed reference group, no differences were found with regard to electrocardiographic changes or blood pressure, but a higher average pulse rate was found in the exposed group. The authors had no explanation for this finding.

Despite these empirical studies from the 1980s, a need still remains for more and better investigations of the relationship between occupational exposure to cobalt and heart diseases. In light of the widespread use of cobalt in industry and medicine (160), it is surprising that most of the literature deals with a brief epidemic of cardiomyopathy among beer drinkers.

Arsenic

In the general reviews on cardiovascular diseases and environmental exposures, arsenic and arsenic compounds are mentioned in seven (1, 2, 6, 9—11, 13) but not in six (3—5, 7, 8, 12). The seven reviews which deal with the topic include two to nine references to empirical studies. In Landrigan's special review on health effects from arsenic exposure (168), the cardiovascular effects were treated very briefly.

Three epidemiologic studies of arsenic exposure and CVD have been found. Pinto et al (169) investigated mortality among 527 retired workers from a copper smeltery during the period 1949—1973, while Lee-Feldstein (170, 171) studied a cohort of more than

8000 men during the period 1938—1977. Axelson et al (172) conducted a case-referent study in which the exposed persons were also copper smeltery workers. In all three studies, the exposure was arsenic trioxide. In the two historical prospective studies, slightly elevated SMR values were found for CVD. Pinto et al found a value of 109 for IHD and 113 for stroke, while Lee-Feldstein found SMR values of about 130 for IHD and about 120 for stroke. In both studies, a comparison was made with the mortality experience of the rest of the population in the area. In the study by Axelson et al, which is the best of the three ("xxxx" for methodological quality), an increasing relative risk for heart disease with increasing arsenic exposure was found (risk ratio 0.7, 3.0, and 5.8 for three exposure groups). The study by Pinto et al scored "xx" for methodological quality, while the Lee-Feldstein study scored "xxx." Thus in these three investigations, clearer evidence for a relationship between arsenic exposure and CVD was found as the quality of the studies increased.

Furthermore, arsenic was part of the mixed exposure in Wingren & Axelson's case-referent studies on mortality in the Swedish glassworks industry (52, 53). In these investigations a slight increase in CVD mortality was found.

In addition to these studies of exposed workers, there have been reports of a relationship between high levels of arsenic in drinking water and the development of both heart disease in children of northern Chile and peripheral vascular disease in adults from Taiwan (1). A special "arsenic beer scandal" took place in Manchester in 1900, when beer was accidentally contaminated with arsenic. More than 6000 persons became ill and 70 died, almost all from CVD (2, 156).

The relationship between another arsenic compound, arsine, and heart disease has been described by Pinto et al (173). This study dealt with 13 poisoned men, of whom four died from acute myocardial infarction (AMI), while electrocardiographic changes were observed in the remainder. As far as is known, no epidemiologic studies have been conducted on the relationship between arsine exposure and CVD.

Even if the total epidemiologic research concerning the relationship between exposure to arsenic compounds and CVD is limited, a causal relationship is still likely. Further research is needed to clarify the relationship between the level and duration of the exposure and the risk for CVD.

Carbon monoxide

The relationship between carbon monoxide (CO) and CVD is dealt with in all the general reviews on CVD and environmental exposures (1—7, 9—13) except one (8). In a few of these reviews (1, 6, 10), the topic has been thoroughly treated, and many references have been discussed. Naturally, no disagreement exists on the potentially very serious consequences of acute high exposure to carbon monoxide, especially among persons with existing atherosclerosis. But there is considerable uncertainty and conflicting views about the possible significance of carbon monoxide exposure in the development of atherosclerosis. A few reviews concluded, without any further documentation, that carbon monoxide increases the risk of IHD (7, 12). Others presented a more cautious point of view, which can be illustrated by way of the following three quotations: "(CO) may precipitate AMI or serious arrhythmias in persons with pre-existing coronary atherosclerosis [p 17]" (5), "the question of whether CO is atherogenic remains unanswered even at the basic science level [p 1219]" (3), and "there is surprisingly little evidence for a chronic atherosclerotic effect of CO [p 219]" (11).

In addition to these general reviews, there are many special reviews on the negative health effects of carbon monoxide exposure (174—189). They contain detailed descriptions of the physiological mechanisms which result from the formation of carboxyhemoglobin in blood and present the results of many animal experiments. I will not discuss these topics in the present review; rather it should simply be stressed that the decrease in the oxygen-carrying capacity of the blood is greater than suggested by the percentage of carboxyhemoglobin because of the reduced release to the tissue of the oxygen carried by the remaining hemoglobin.

The specific reviews on carbon monoxide and health do not agree on the role of carbon monoxide in the etiology of CVD. The most "positive" reviews are probably the ones by Aronow (174, 175), Goldsmith & Aronow (177), and Atkins & Baker (176), while others are skeptical (179, 182, 188). In the remaining reviews no clear position is taken. Among the most skeptical reviews, Weir & Fabiano's critical reevaluation from 1982 (188) should be emphasized. The authors carry out an explicit and thorough discussion of the evidence for a causal relation between carbon monoxide and CVD. They specify the "...three questions that best define the current areas of controversy: (i) Does chronic exposure to CO influence the development of atherosclerosis? (ii) By what mechanism does acute exposure to CO reduce maximal exercise ability in healthy persons and in persons with pre-existing CVD? (iii) Does acute CO exposure predispose individuals to cardiac arrhythmias? [p 520]." In the evaluation of the empirical evidence for a causal relationship between carbon monoxide and CVD, it is important to keep these three questions separate, and I have attempted to do so in the following discussion.

For the present review, 22 empirical studies have been selected. Of them, most deal with persons who have been exposed to carbon monoxide occupationally, such as firemen, policemen, toll booth operators, garage personnel, motor vehicle examiners, bridge and tunnel officers, foundry workers, and blast furnace workers (190—210). (Reference 205 has been classified as two studies.)

Four of the empirical studies are not epidemiologic in the strict sense, but rather experimental (190—193).

In these four studies, which are very similar, 10 men with angina pectoris were exposed to different concentrations of carbon monoxide, and the duration of exercise before the onset of pain was registered. All four investigations found that the time before the onset of pain was significantly shorter after exposure to carbon monoxide even when the carboxyhemoglobin level was only about 1 % higher in the exposed situation than in the control situation (193).

These results could have been expected because the angina patients already had IHD. Nevertheless, these experiments stress how dangerous an increased carboxyhemoglobin level can be for this group of patients. As the prevalence of IHD is high in the population, and as exposure to carbon monoxide is common — predominantly through smoking and exposure to the exhaust fumes from cars — this is a frequently occurring risk situation.

Two studies comparing the daily incidence of death from IHD with the level of carbon monoxide in the air can be said to elucidate the same complex of problems (195, 205). In one, the expected relationship was found between carbon monoxide levels and fatality from IHD, while the same relationship could not be shown in the other. Both studies had a low methodological quality.

While the aforementioned studies provide evidence of the influence of acute exposure to carbon monoxide on persons with ischemic heart disease, the remaining studies have tried to elucidate the role of carbon monoxide for the development of atherosclerosis. Table 3 contains a survey of these 16 studies. Table 3 illustrates the following two points: (i) most empirical studies on this topic have a low methodological quality ("x" or "xx"), and (ii) there is no relationship between study quality and study outcome, since half of the poor studies ("x" or "xx") and half of the better studies ("xxx" or "xxxx") have a positive study outcome [+ or (+)].

The best support for the hypothesis of a relation between chronic carbon monoxide exposure and the development of atherosclerosis comes from three positive studies with "xxx" or "xxxx" for quality (201, 208, 209). A closer examination shows, however, that not even these studies support the hypothesis very clearly. The cross-sectional study by Hernberg et al (201) on angina pectoris, electrocardiographic findings, and blood pressure among foundry workers found a relationship between carbon monoxide exposure and angina pectoris but not between carbon monoxide and electrocardiographic findings indicating IHD. Furthermore, slightly higher blood pressure was found among the persons exposed to carbon monoxide, but this finding could have possibly resulted from exposure to heat radiation. Altogether only the relationship between carbon monoxide and the prevalence of angina pectoris was convincing, and this relationship does not necessarily support the hypothesis of a lasting effect of carbon monoxide.

The older of the two studies by Stern et al (208) found an SMR of 105 for CVD among motor vehicle examiners. Closer analyses showed that the excess deaths occurred among examiners with zero to nine years of exposure (SMR for CVD 123). There was no increase in mortality among the examiners with longer exposure.

The more recent of the investigations by Stern et al (209), which concerned bridge and tunnel officers in New York City, is probably the best epidemiologic study of carbon monoxide and CVD ever published. The study showed significantly higher IHD mortality among the heavily exposed tunnel officers than among the bridge officers, who had a low level of exposure. However, there was no relationship to the duration of the exposure, and the excess mortality among the tunnel officers disappeared in the course of a few years after the cessation of exposure. This pattern closely resembles that seen in studies of tobacco smokers, in which the increased risk for IHD disappears relatively quickly after the cessation of exposure. This pattern does not fit the hypothesis of a lasting atherosclerotic effect of carbon monoxide exposure.

In light of the many studies on tobacco smoking and CVD, it is surprising that it is still not known why smoking increases the risk for CVD. A cross-sectional study by Wald et al (210) is often quoted to show that carbon monoxide increases the risk for atherosclerosis, but a later — and methodologically better — case-referent study by Kaufman et al (203) shows that the carbon monoxide content of cigarette smoke is unrelated to the risk of IHD among smokers.

All things considered, there is thus very little — if anything — in the empirical studies referred to which supports the carbon monoxide-atherosclerosis hypothesis. In the literature, the animal experiments by the Astrup-Kjeldsen group have played a large role, as these experiments apparently showed increased atherosclerosis in rabbits exposed to carbon monoxide. However, the group published a reevaluation in 1978. In these new investigations (211), they were not able to confirm the original findings, probably due to the fact that the original studies were carried out with small sample sizes and were not blinded. Several

Table 3. Results of 16 epidemiologic studies of cardiovascular diseases (CVD) and carbon monoxide exposure according to the methodological quality of the studies. The table is based on references 194, 196—210.

Degree of relationship[a]	Methodological quality				
	x	xx	xxx	xxxx	Total
−	—	—	—	—	—
(−)	—	1	1	—	2
0	2	—	1	1	4
(+)	—	1	1	—	2
+	1	3	1	1	6
?	2	—	—	—	2
Total	5	5	4	2	16

[a] See table 1 for an explanation of the symbols.

reviews, unfortunately, appear not to have been aware of this reevaluation.

Regarding the first of Weir & Fabiano's three questions, quoted on page 250, the following conclusions can be drawn: (i) there is no relationship between study quality and support for the hypothesis; (ii) very few studies are of high methodological quality, and these studies give almost no support for the hypothesis; and (iii) the research group behind the animal experiments most often quoted in support of the hypothesis has withdrawn its results in view of established flaws in study design. Therefore, one can only concur with the conclusion of Weir & Fabiano "that there is no evidence to support the suggestion that exposure to low to moderate levels of CO increases the rate of the development of atherosclerotic disease in man. We believe that sufficient evidence is available to support the conclusion that, in fact, CO is not of pathogenic consequence in atherosclerotic disease [p 523]" (188).

Concerning the second of the three questions mentioned, Weir & Fabiano's conclusion also seems well-founded: "Acute exposure to low levels of CO does result in reversible, nonprogressive, exercise performance decrements in healthy and diseased individuals [p 523]" (188).

In the present review, I have not examined studies on carbon monoxide exposure and cardiac rhythm. Therefore, I refer the reader again to Weir & Fabiano, who concluded: "In summary, exposure to CO at acutely toxic levels results in alterations of cardiac rhythm, probably as a result of the induced hypoxia. There is no convincing evidence available to suggest that exposure to low to moderate levels of CO affects cardiac rhythm [p 523]" (188).

Even if these conclusions on carbon monoxide and CVD seem well-founded, there is still a need for further — and better — research in this field. In the epidemiologic area, there is specifically a need for the following: (i) prospective studies in which both the exposure and the development of the disease can be followed (none of the existing studies have been prospective), and (ii) studies in which carbon monoxide is not an integrated part of a mixed exposure, which is the case with cigarette smoke, exhaust fumes, etc.

Passive smoking

Passive smoking has not been mentioned in a any of the general reviews on CVD and environmental exposures, partly due to the fact that almost all research on passive smoking and chronic diseases — including lung cancer and CVD — has been conducted during the 1980s.

Most of the literature on passive smoking and CVD has, on the other hand, been reviewed in three thorough reviews on the health effects of passive smoking, ie, the Surgeon General's report (212), the report from the National Research Council (231) — both from 1986 — and Fielding & Phenow's review from 1988 (214). These reviews all conclude that further research on CVD and passive smoking is needed.

The most important information concerning the studies which have been published currently on IHD and passive smoking is shown in table 4. These studies have all been published during the period 1983—1988 and are all based on a comparison of the incidence of IHD in nonsmokers married to smokers and nonsmokers married to nonsmokers. Five of the studies (215—220) are prospective cohort studies, while the last one (221) is a case-referent study.

As shown in table 4, the studies yielded nine estimates of relative risk. These estimates varied from 0.93 to 3.25 with an accumulation of values in the area of 1.24 to 1.31. The median relative risk for all the studies was about 1.3, and it is also approximately 1.3 when only the better studies ("xxx" or "xxxx" for quality) are considered separately. Only few of these relative risk values are significantly different from 1.0 when they are regarded individually. However, I am, in this paper, more interested in the total pattern that appears when the studies are viewed as a whole.

A relative risk of 1.3 for passive smoking seems high in relation to the relative risk of about 2.0 often mentioned for active smoking. When comparing the two

Table 4. Review of the epidemiologic studies on ischemic heart disease (IHD) and passive smoking.

Study	Study design	Population	Study quality[a]	RR for IHD[b]
Hirayama (215, 216)	16-year follow-up	91 450 women	xx	1.24
Gillis et al (217)	6- to 11-year follow-up	827 men	xx	1.29
		1 917 women		3.25
Garland et al (218)	10-year follow-up	695 women	xxxx	2.7
Svendsen et al (219)	10-year follow-up	1 245 men	xxxx	1.61
Helsing et al (220)	12-year follow-up	4 162 men	xxx	1.31
		14 873 women		1.24
Lee et al (221)	Case-referent study of patients	41 male IHD patients and 133 referents	xxx	1.24
		77 female IHD patients and 318 referents		0.93

[a] The criteria for methodological quality are explained in the text.
[b] Relative risk for IHD among nonsmokers married to smokers compared to nonsmokers married to nonsmokers.

values, one should keep in mind the following three facts: (i) the relative risk for active smokers is usually calculated with nonsmokers as the reference group; since nonsmokers are almost always passive smokers, and not really unexposed, too low a relative risk is yielded for active smoking; (ii) several studies indicate that the marginal effect per cigarette on the risk for IHD is highest at a low level of consumption and is thus not linear (222); and (iii) mainstream and sidestream smoke contain almost the same components, but not in the same proportions. One does not know why cigarette smoking increases the risk for IHD; therefore, it is difficult to extrapolate directly from active to passive smoking.

In evaluating today whether there is an increased risk for IHD among passive smokers, the biggest problem is not the statistical uncertainty or other methodological difficulties. In fact, the studies in table 4 are of rather high quality compared with the other research referred to in this article. The greatest problem must be assumed to be a possible publication bias, as it can, with some justification, be claimed that negative studies were of no interest until a number of positive studies were recently published. Therefore, more methodologically good studies of IHD and passive smoking need to be carried out and to be published regardless of the result.

In addition to the aforementioned studies of IHD and passive smoking, there are several investigations addressing the time lag before the onset of pain in angina pectoris patients exposed to passive smoking or carbon monoxide. These investigations have been referred to in the section on carbon monoxide since the increased level of carboxyhemoglobin is very probably the factor which provokes the earlier onset of angina. Finally, an abstract was published in 1987 by Moskowitz et al (223). It claims that passive smoking increases the risk of IHD among pubertal boys.

Even if more studies on passive smoking and IHD are still needed, it is now reasonable to conclude that the studies published have a high methodological quality, that the results are relatively consistent (relative risk for IHD about 1.3), and that a small, but increased risk for IHD is biologically plausible.

Organic solvents

A few of the general reviews treat organic solvents thoroughly (1, 2, 6, 10). Others treat the topic more superficially (3, 7, 9, 11, 13), and some do not mention it at all (4, 5, 8, 12). In those reviews in which the topic is dealt with, most of the emphasis is placed on the halogenated hydrocarbons (perchloroethylene, trichloroethane, trichloroethylene, fluorocarbons, methylene chloride, and other solvents containing chlorine, fluorine, bromine or iodine). Most of the studies mentioned have covered acute heavy exposures resulting in arrhythmia or sudden death.

Cardiovascular effects of exposure to organic solvents have also been treated in several special reviews (224—227). Reinhardt et al (225) concluded that the sudden deaths in connection with acute heavy exposure to solvents were due to ventricular fibrillation due to sensitization of the heart to epinephrine. The review by Reinhardt et al also included a survey in which the solvents were evaluated according to cardiac sensitization properties. The most active group contained benzene, heptane, chloroform, and trichloroethylene. Steffey's review (226) of the cardiovascular effects of inhaling anesthetics is very thorough, listing 201 references. In addition, the review by Zakhari & Aviado (227) on the cardiovascular toxicology of halogenated hydrocarbons is both thorough and comprehensive (218 references and a very useful appendix with chemical formulas and properties).

The empirical basis for the aforementioned reviews consists primarily of animal experiments, which I have not discussed in this review, several case reports, and a few epidemiologic studies.

There are two types of case reports. They deal with exposure to very high levels of solvents either in connection with glue sniffing or in connection with occupational exposure. Glue sniffing has primarily been practiced by teenagers (224, 228—232), and many sudden deaths have been reported in both the United States and the United Kingdom, although a clear underreporting is likely since no anatomical changes can be observed in deceased persons. In some of the cases described, the strongly affected young "sniffer" stood up, started running, and then dropped dead (228).

The occupational case reports deal with workers who, in most instances, have been exposed to very high levels of solvents (231, 233—237). Most of the case reports concern the sudden death of healthy men 20—50 years of age after exposure to chlorinated solvents, but also after exposure to benzene (234) and methyl-cellulose paint (233). These case reports have many features in common, and several of the authors suggest that underreporting probably takes place with respect to this type of exposure also.

In addition to the case reports mentioned, five epidemiologic studies have been found (238—242). They were published during the period 1975—1988, and there is no indication of increasing research activity in this area despite the increased interest in organic solvents. The methodological quality score for these studies is medium ("xx" to "xxxx").

Speizer et al (238) studied the residents in a hospital pathology department who were exposed to fluorocarbon aerosols during the processing of cryostat sections and used radiology department employees as the reference group. They found a much higher prevalence of palpitation among the pathology residents and also a dose-response relationship between exposure to fluorocarbon 22 and the prevalence of palpitation. Moreover, resting electrocardiograms and 24-h electrocardiographic monitoring indicated premature atrial contractions, paroxysmal atrial fibrillation, and an in-

crease in premature ventricular beats. These results were unexpected in a group of young, healthy adults.

Kramer et al (239) examined 151 industrial workers who had been exposed to 1,1,1-trichloroethane and 151 matched referents. There was no difference with regard to electrocardiography, blood pressure, or serum cholesterol. Most of the persons examined were women, and most were below 35 years of age.

Blair et al (240) examined the distribution of causes of death among 330 deceased dry cleaning workers exposed to tetrachloroethylene. For CVD, a proportionate mortality ratio of 79 was found, significantly less than the "expected" value of 100. The proportionate mortality ratio has well known limitations, and this negative study only scored "xx" for study quality.

In the historical prospective study by Wilcosky & Tyroler (241), the mortality of 1284 workers exposed to several different solvents was analyzed. An excess frequency of deaths from IHD was found among workers who had been exposed to carbon disulfide, ethanol, and phenol.

Finally, Eskenazi et al (242) studied the prevalence of adverse pregnancy complications among 90 women exposed to organic solvents and 180 unexposed matched referents. They found a significantly higher proportion of women with preeclampsia (a disorder of pregnancy characterized by hypertension, edema, and proteinuria) and hypertension among the exposed women.

These epidemiologic studies are very different with regard to exposures, study design, and study end points. Therefore it is not possible to draw any conclusions on the basis of these investigations. No studies of occupational mortality have found increased CVD mortality among painters or other groups exposed to organic solvents. It is, therefore, not very likely that organic solvent exposure at moderate levels increases the risk for CVD.

Carbon disulfide

Carbon disulfide has been mentioned and recognized as a risk factor for IHD in virtually all reviews of CVD and environmental exposures published during the last 20 years. As will become apparent, this unique scientific consensus is primarily due to the Finnish study of viscose rayon workers, which was conducted by Hernberg, Nurminen, Tolonen, and their co-workers.

The first researchers to call attention to the relationship between carbon disulfide and IHD were Tiller et al, who in 1968 published their study of mortality among viscose rayon workers exposed to carbon disulfide (243). It actually consisted of two studies, one of the proportion of IHD deaths among workers from three factories, and the other a historical prospective mortality study of a cohort from one of the factories. Both studies showed a positive relationship between carbon disulfide exposure and IHD mortality.

The results from the study on Finnish viscose rayon workers have been published in many articles during a 15-year period (244—253). Furthermore, the study has been used as a pedagogical example in one of the few textbooks on the epidemiology of occupational medicine (254). The study was a 15-year follow-up of two cohorts with 343 men in each. The study cohort was exposed to carbon disulfide in a viscose factory, but otherwise resembled the reference cohort, which worked at another factory in the same town. After about five years of follow-up, a relative risk of 5.6 for coronary deaths was determined for the exposed group. This finding resulted in several different interventions to reduce both the carbon disulfide level and the exposure of the individual workers in the viscose factory. Eight years after this intervention the relative risk was approximately one (248).

This exemplary epidemiologic study was scored "xxxxx" for quality. It is a prospective study over 15 years with good confounder control, reasonable knowledge of past and present exposure, many relevant study end points, a good, clear and understandable analysis, and intervention (reduced exposure) that was followed by the expected reduction in the disease studied. The study demonstrates that it is possible to convince the scientific community of a causal relationship via a "small" study of 2×343 persons if one has well selected study groups, a good analysis, and a lot of patience.

The relationship between carbon disulfide and IHD has been confirmed during the 1980s in American studies (255, 256), of which the latest (256) is the largest ever undertaken, the cohort studied comprising more than 10 000 workers.

Since the causal relationship between carbon disulfide and IHD is, with good reason, generally accepted, there is no reason to go into more detail. References to additional studies on this subject can be found in the very exhaustive reviews which have been published (257—261).

Nitroglycerin and ethylene glycol dinitrate (nitroglycol)

The relationship between heart disease and aliphatic nitrates is mentioned in virtually all reviews on CVD and environmental exposures, and it is one of the few relationships which all authors regard as definitively demonstrated. Nitroglycerin has been used both in the medical industry and for the production of dynamite since the middle of the last century. Ethylene glycol dinitrate has been used together with nitroglycerin for dynamite production since the 1930s, as ethylene glycol dinitrate improves the quality of the product and is cheaper. However, ethylene glycol dinitrate is far more toxic and more volatile than nitroglycerin.

The first studies of the relationship between nitroglycerin/ethylene glycol dinitrate and heart disease were published in Germany and Italy in the 1950s (262, 263). They were case descriptions of the phenomenon which has later been called "Monday morning angi-

na" or "Monday morning death." The nonfatal cases are attacks which resemble angina pectoris, but which are not provoked by exercise or psychic arousal. The attacks occur 1-3 d after exposure to nitroglycerin/ethylene glycol dinitrate ceases, and consequently the designation "nitrate withdrawal symptoms" has been used. This expression covers various conditions, such as angina, coronary spasm, myocardial infarction, arrhythmia, and sudden death. In those instances in which autopsy was performed, normal coronary arteries were found.

Similar case reports have been published in other countries (264—266), and Morton's comprehensive review from 1977 (267) contains an excellent review of the literature concerning withdrawal hazards related to occupational habituation to aliphatic nitrates (74 references). It appears from Morton's review that, during the period 1952—1975, articles were published about Monday morning attacks in Germany, Italy, Japan, France, Sweden, Czechoslovakia, the Soviet Union, and the United States. It appears furthermore that the first American description was not Carmichael & Lieben's article from 1963 (264), as formerly believed, but an article from 1943 by Foulger (268). Foulger's article on "exposure to toxic chemicals" did not mention, however, that it concerned nitroglycerin/ethylene glycol dinitrate. (See, in addition, the correspondence between Foulger and Morton (269) and Morton's article on the ethical problems of concealing medical knowledge within occupational medicine (270)).

Half a year after Morton's review, Hogstedt & Axelson (271) introduced a new era in this research by publishing the first truly epidemiologic study. It was a case-referent study which was later supplemented with a prospective study (272) and with hygienic measurements (273), which together with two additional articles formed part of Hogstedt's thesis (274). In these works of high epidemiologic quality, it is documented in a convincing way that exposure to nitroglycerin/ethylene glycol dinitrate not only causes symptoms, diseases, and deaths due to nitrate withdrawal, but also raises the risk for CVD many years after the cessation of exposure.

Hogstedt's results have been confirmed during the 1980s by two other investigations (275, 276), both of which are historical prospective studies. In these studies, more CVD deaths were found than expected among the exposed workers despite preemployment screening and/or medical monitoring of the employees.

Thus it is now clear that nitroglycerin and, especially, ethylene glycol dinitrate increase the risk for CVD in the following two ways: partly via the specific "Monday morning attacks" due to nitrate withdrawal and partly via an increased risk for CVD which persists long after the cessation of exposure. This double effect is described in a few of the reviews, such as Fine's (1) and Kurppa et al's (6), while reviews on the topic were still being published during the 1980s which only or almost exclusively describe nitrate withdrawal and "Monday morning attacks" (2, 3, 5, 277).

Other chemical substances and compounds

This section briefly reviews various studies concerning CVD and other chemical substances — areas in which only a few studies have been conducted or in which several "competing" exposures occur in the same study.

Dinitrotoluene. In 1986, Levine et al (278) published a historical prospective study of workers in two factories in which the employees had been exposed to dinitrotoluene (278). As in so many other instances, it was a suspicion of carcinogenicity which motivated the study, but no increased incidence of cancer was found among these workers. However, an increased incidence of IHD (SMR 141) appeared when the data from both factories were combined, with a relationship between the duration and the intensity of the exposure and the incidence of IHD. According to the authors, only very few of the workers had been exposed to nitroglycerin or ethylene glycol dinitrate.

Organophosphates. Two cross-sectional studies — one Danish (279) and one Indian (280) — have shown an increased prevalence of "ischemic" electrocardiographic changes among workers exposed to organophosphates. The Indian study included 155 exposed persons and 60 referents, while the Danish investigation included 446 workers, of whom 114 were classified as heavily exposed. In the Danish study, the higher prevalence of electrocardiographic changes among the heavily exposed individuals remained after control for age and smoking.

Antimony trisulfide. In the work by Brieger et al from 1954 (281), a factory was mentioned in which 125 men were exposed to antimony trisulfide for eight months to two years. During this period, eight of the workers died suddenly. Two of the deaths were due to chronic heart disease. Four of the deceased were under 45 years of age. Because of this finding, the workers were examined, and electrocardiographic changes were found in 37 of the 75 examined. A review of the literature on animal experiments with antimony trisulfide seemed to show that the substance is cardiotoxic. At the factory studied, the use of antimony trisulfide was stopped, and no further sudden deaths were observed. In 12 of 56 reexamined workers, the observed electrocardiographic changes persisted. No other studies on antimony trisulfide were found in the literature.

Beryllium. In a historical prospective study by Wagoner et al (282), mortality was investigated in a cohort of 3055 workers who had been exposed to beryllium. Despite an assumed healthy worker effect, an SMR of 113 ($P < 0.05$) was found for heart disease in comparison with the mortality of American white

males. The highest value (SMR 129) was recorded for those exposed for at least five years.

Polycyclic aromatic compounds. In a case-referent study (283) of 6000 men employed by a primary aluminum smeltery, there were 306 new cases of IHD during the period 1975—1983. The persons concerned were compared with 575 matched referents. Among the blue-collar workers, a relative risk for IHD of 2.1 was found. The risk was particularly elevated among workers employed in the reduction divisions. These workers had a relative risk of 1.7 for IHD when compared with the remaining blue-collar workers. Unfortunately, the referents were matched for duration of employment, and this type of matching prevented the researchers from uncovering a possible relationship with the duration of the exposure.

Both a Danish (284) and a Swedish (285) mortality study of chimney sweeps found an excess frequency of IHD. The Danish study cohort consisted of 713 chimney sweeps, and the SMR for IHD was 222 when employed men were used as the reference. The Swedish study cohort consisted of more than 5000 chimney sweeps, and the SMR for IHD was found to be 135 when all Swedish men were used as the reference group. In both instances, the excess was significant at the 5 % level.

In a historical prospective study of gas workers, Gustavsson & Reuterwall (286) found excess mortality due to IHD (SMR 125) and stroke (SMR 152). In this study, occupationally active persons in Stockholm were used as the reference group. Due to the small numbers, these results were not statistically significant.

Common for aluminum reduction workers, chimney sweeps, and gas workers is that they are exposed to combustion products. According to several authors (6, 284, 286), it can be hypothesized that polycyclic aromatic hydrocarbons or other polycyclic aromatic compounds are not only carcinogenic, but also increase the risk for IHD. This assumption is in accordance with the monoclonal hypothesis of atherosclerosis proposed by Benditt & Benditt (287), according to which atherosclerotic lesions might be derived from the proliferation of a single cell and could be considered to be benign tumors. The excess frequency of both IHD and lung cancer among Danish cooks and bakers (288) in the national Danish mortality study further supports this theory, as it must be assumed that many working in these trades are exposed to polycyclic aromatic hydrocarbons.

Concluding remarks

During my collection of the material for this review of the literature, I found no additional studies that could be judged as sufficiently relevant for inclusion. Since, of course, the judgment of which studies are to be regarded as relevant is inevitably subjective, the reader may wish to supplement this review with other comprehensive ones dealing with CVD and chemical exposure (1, 2, 5, 6, 9, 10).

In a recently published article (283) concerning chemical exposures at work and the risk for IHD, the authors wrote: "Several personal risk factors are known to contribute to the development of IHD, but the effects of adverse working conditions have remained almost unexplored [p 659]" (283). This is a very widespread conception, but both the present review of the literature concerning chemical occupational factors and CVD and the previous article concerning nonchemical factors (14) have shown that the conception is not completely correct. Hundreds of studies, in fact, have been carried out in this field, and, in several areas, knowledge today is considerable.

The present review has, in some areas, confirmed other reviews of the literature, while in others the conclusions reached are contrary to the current view. For carbon disulfide and nitroglycerin/ethylene glycol dinitrate, the general opinion is confirmed. In these areas, studies have been conducted which have convinced virtually everybody about the causal relationship between these substances and CVD. It should be emphasized that what has convinced the scientific community is not the number of studies — as a matter of fact, there are very few — but the high methodological quality of the studies.

For lead and passive smoking, this review concludes more positively than others. The research concerning lead and CVD is very old, but not until recently has it been "discovered" in earnest. This phenomenon is, to a large extent, due to the remarkable results concerning low-level lead exposure and blood pressure from the National Health and Nutrition Examination Survey II, which were published in highly esteemed journals (70, 72). The research concerning passive smoking is new, and there are still relatively few studies, but they have a high quality and the results are consistent.

In other areas, the conclusions are more negative than usual, especially for cadmium and carbon monoxide. The research concerning cadmium and CVD is generally of poor quality, but the few good studies, together with the fact that tobacco smoking is not a risk factor for hypertension, makes it reasonable to conclude that cadmium is not a CVD risk factor. For carbon monoxide, the situation is more complicated, since there might be acute, short-term, and long-term effects. It is concluded that there are acute effects and possibly short-term, reversible effects, but that carbon monoxide does not increase the risk for atherosclerosis in occupationally exposed individuals.

In table 5, an attempt has been made to classify the possible cardiovascular risk factors which have been reviewed in this and the previous article. The basis for this classification is the view that empirical relationships are not "proved" once and for all. Hypotheses

are confirmed or invalidated through the collective and cumulative work which researchers carry out, and systematic critical reviews of the literature constitute an ever more important part of this process.

Several of the factors mentioned under "very definite" and "quite definite" in table 5 are widespread in industrialized countries. This is true for physical inactivity at work, noise, shift work, work strain, lead, and passive smoking. Even if the relative risk for CVD connected with each of these factors is modest (from approximately 1.1 to 2.0), the total etiologic fraction (attributable risk) will be considerable, and therefore the potential preventive benefit is great.

Now the classic question "Is enough known to use this knowledge for preventive activities?" arises. This is naturally not a scientific question but is still one with which researchers are often confronted and are expected to be able to answer. One answer could be that enough is known about the factors which have been mentioned under "very definite" and "quite definite" in table 5 to initiate prevention. There could however be a risk of making a mistake since one or more of the eight risk factors mentioned, at some point in the future, might prove not to be a risk factor for CVD. With respect to this possibility, the following two points are worth making: (i) if one chooses not to act until one has "100 % certain evidence," one is likely to make mistakes which have serious consequences for the health and mortality of many people, and (ii) the factors which have been mentioned in table 5 are all risk factors for diseases other than CVD. If one or more should prove not to be a risk factor for CVD, there would still be a positive effect from reducing or removing these factors.

It should be emphasized that table 5 only includes factors which have been mentioned in the literature as possible risk factors for CVD. The absence of evidence about a causal relationship should, of course, never be confused with evidence about an absent causal relationship. It should further be mentioned that the table deals with levels of exposure which occur "normally" at workplaces in Europe and North America.

Marmot & Theorell (289) recently claimed that psychosocial strain at work is probably part of the explanation for the negative correlation between social class and CVD incidence which is seen in industrialized countries. In their review, they emphasize Karasek's job strain model. The deliberations by Marmot & Theorell are an important supplement and corrective to the prevailing explanations which virtually always have their starting point in individual risk factors. It should be stressed, however, that not only job strain, but also several of the other factors mentioned in table 5, are more widespread in the lower social classes. Therefore changes in the work environment might contribute to the efforts to reduce the social inequities in morbidity and mortality which constitute an important target in the program "Health for All by the Year 2000" of the World Health Organization and in the health policy of many individual countries.

Finally, some remarks on the form and content of literature reviews within medical research. It is true for most reviews that the criteria for collecting the literature and for evaluating the individual studies are neither explicit nor systematic. The most common mode is that the authors of the review mention some positive and negative studies, observe the evident lack of consensus, and conclude that further research is necessary. This kind of review does not live up to elementary scientific demands and does not contribute to the development and clarification of research.

One of the consequences of the steeply rising number of scientific investigations all over the world is that researchers and other persons become ever more dependent on reliable reviews of the existing literature. Therefore reviews must try to live up to the demands for validity, reliability, precision, and reproducibility which are in force for the individual empirical studies. To the extent that reviews do live up to these scientific demands, they will be able to serve two very noble purposes: (i) the clarification of future research needs (one must not think only of stressing the ever present "need for more research," but of a sharper clarification of hypotheses, method and design problems, measurement problems, etc) and (ii) to indicate those areas in which the evidence is so "certain" that preventive activities ought not be postponed further. In this connection, it should be pointed out that some uncertainty must always be accepted, as is the case in other human and social contexts.

As is noted in this and the previous article (14), several reviews have been published in recent years in which attempts have been made to live up to the mentioned demands (5, 27, 188, 290—296). One must hope that development in the direction of more systematic reviews will continue in the years to come.

Table 5. Classification of possible risk factors for cardiovascular disease (CVD) in the work environment.

Causal relation to CVD	Risk factor	
	Nonchemical	Chemical
Very definite	Physical inactivity at work	Carbon disulfide, nitroglycerin/nitroglycol
Quite definite	Work strain (high demands and low influence), shift work, noise[a]	Lead[a], passive smoking
Possible		Cobalt, arsenic, combustion products
Somewhat possible	Heat[a], irradiation, power frequency magnetic fields, low-frequency noise	Organophosphates, dinitrotoluene, antimony, beryllium, carbon monoxide[a]
Probably no relationship	Microwaves, cold[a]	Cadmium, organic solvents[b]

[a] Increases the risk for CVD through increased blood pressure.
[b] High-level exposure may be fatal, especially when combined with other risk factors.
[c] High-level exposure may cause cardiac arrhythmia and sudden death.

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