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Environmental Health Criteria 10

CARBON DISULFIDE

Published under the joint sponsorship of
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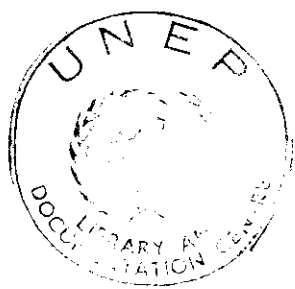
and the World Health Organization



World Health Organization
Geneva, 1979

ISBN 92 4 154070 2

PRINTED IN THE UNITED KINGDOM

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NOTE TO READERS OF THE CRITERIA DOCUMENTS

While every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication, mistakes might have occurred and are likely to occur in the future. In the interest of all users of the environmental health criteria documents, readers are kindly requested to communicate any errors found to the Division of Environmental Health, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda which will appear in subsequent volumes.

In addition, experts in any particular field dealt with in the criteria documents are kindly requested to make available to the WHO Secretariat any important published information that may have inadvertently been omitted and which may change the evaluation of health risks from exposure to the environmental agent under examination, so that the information may be considered in the event of updating and re-evaluation of the conclusions contained in the criteria documents.

WHO TASK GROUP ON ENVIRONMENTAL HEALTH CRITERIA FOR CARBON DISULFIDE

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ENVIRONMENTAL HEALTH CRITERIA FOR CARBON DISULFIDE

A WHO Task Group on Environmental Health Criteria for Carbon Disulfide met in Prague from 13 to 20 June 1977. Dr M. El Batawi, Chief Medical Officer, Office of Occupational Health, opened the meeting on behalf of the Director-General and expressed the appreciation of the Organization to the Government of Czechoslovakia for kindly acting as host to the meeting. In reply, the Group was welcomed by Professor J. Teisinger, Institute of Hygiene and Epidemiology, Prague. The Task Group reviewed and revised the second draft criteria document and made an evaluation of the health risks from exposure to carbon disulfide.

The first draft of the criteria document was prepared by Dr Djurić, Institute of Occupational and Radiological Health, Belgrade, Yugoslavia, in consultation with Professor Teisinger, Dr E. Lukáš, Institute of Hygiene and Epidemiology, Prague, Czechoslovakia, and several research workers in Belgrade and Prague. The second draft was prepared by Dr S. Hernberg, Institute of Occupational Health, Helsinki, Finland taking into consideration comments by Professor K. Freundt, Institute of Toxicology and Pharmacology, Mannheim, Federal Republic of Germany, Professor Sh. Goto, Osaka University, Japan, Dr I. Lancranjan, Institute of Hygiene and Public Health, Clinic of Occupational Diseases, Bucharest, Romania, Dr J. Lieben of the American Viscose Division, PM Corporation, Philadelphia, USA, Dr A. Massoud, National Research Centre, Cairo University, Egypt, Dr A. M. Seppäläinen, Institute of Occupational Health, Helsinki, Finland, and Dr P. G. Vertin, Institute of Social Medicine, Catholic University of Nijmegen, Netherlands.

The Secretariat wishes to acknowledge the collaboration of these experts and, in particular, to thank Dr Djurić and Dr Hernberg for their valuable help in all phases of the preparation of the document, and Dr H. Nordman, Institute of Occupational Health, Helsinki, Finland, for his assistance in the scientific editing.

This document is based primarily on original publications listed in the reference section but much valuable information has also been obtained from various publications reviewing the toxicity and health aspects of carbon disulfide including those of the US National Institute of Occupational Safety and Health (NIOSH, 1977) and Brieger & Teisinger, ed. (1966). In addition, much useful data has been drawn from reports of several international symposia and meetings including: Zbornik radova o toksikologiji CS_2, Yugoslavia, Loznica, 3–5 June 1965; the II International Symposium on the Toxicology of Carbon Disulfide, Yugoslavia, Banja

Kovilijaca, 25–28 May 1971; the III International Symposium on the Toxicology of Carbon Disulfide, Egypt, Cairo and Alexandria, 4–9 May 1974; and the IV International Symposium on Occupational Health in the Production of Artificial Fibres, Finland, Helsinki and Valkeakoski, 6–10 June 1977.

Details of the WHO Environmental Health Criteria Programme including some terms frequently used in the documents may be found in the general introduction to the Environmental Health Criteria Programme published together with the environmental health criteria document on mercury (Environmental Health Criteria 1, Mercury, Geneva, World Health Organization, 1976), now also available as a reprint.

The following conversion factor has been used in this document:

carbon disulfide 1 ppm = 3.12 mg/m^3

When converting values expressed in ppm to mg/m^3, the numbers have been rounded up to 2 or, exceptionally, 3 significant figures. Where concentrations were expressed as ppm in the original publication, this value has been given in parentheses together with the converted value.

1. SUMMARY AND RECOMMENDATIONS FOR FURTHER RESEARCH

1.1 Summary

1.1.1 Uses and sources of exposure

By far the most important use of carbon disulfide in industry is in the production of viscose rayon fibres. It is also used, to some extent, as a solvent in various industrial processes including the refining of paraffin and petroleum, and more recently in the production of flotation agents and herbicides. However, the risk of being exposed to high concentrations[a] of carbon disulfide during these processes is small compared with that in the viscose industry. Viscose rayon fibres are used in the production of rayon filament textile yarn, rayon tire yarn, rayon stable fibre and Cellophane film. In these processes, carbon disulfide exposure occurs concomitantly with exposure to hydrogen sulfide. The amounts of carbon disulfide and hydrogen sulfide vapour liberated depend on the process. For every kilogram of viscose used, about 20–30 g of carbon disulfide and 4–6 g of hydrogen sulfide will be emitted. About 0.6–1.0 kg of viscose is used per hour in the different processes involved in the production of textile yarn. However, exposure to carbon disulfide is usually highest in connection with the production of staple fibre and Cellophane, where the equivalent amounts of viscose used are approximately 70–100 kg and 1800–2000 kg per hour, respectively.

1.1.2 Populations at risk

Carbon disulfide is a typical industrial toxic chemical and exposure is almost exclusively confined to occupational situations. In theory, any worker engaged in processes using carbon disulfide may be exposed to some degree. However, in practice, only workers in the viscose rayon industry are exposed to concentrations high enough to have deleterious effects on health. The exposure of the general population living in the vicinity of carbon disulfide-emitting industries cannot be assessed at present, because information is inadequate.

1.1.3 Estimation of exposure

Exposure to carbon disulfide can be estimated either by direct measurement of air concentrations or by the determination of carbon

[a] Throughout the document the word concentration refers to mass concentration unless otherwise stated.

disulfide metabolites in the urine of exposed individuals. Air samples can be taken either at fixed sites, or from the breathing zone of the workers. Sampling at fixed sites is recommended for engineering purposes, while sampling from the breathing zone is indicated for the assessment of personal exposure.

Monitoring at fixed sites is best done by continuous measurement with gas analysers based on electrical conductivity or light absorption in the infrared region. Gas detector tubes may be used for preliminary screening, since the procedure is rapid and simple, but their usefulness is limited because of lack of accuracy and a high detection limit; thus, this procedure should always be complemented by more accurate methods.

Personal exposure is best monitored by samples collected from the breathing zone of the workers, using portable samplers. The carbon disulfide is adsorbed on activated charcoal and later determined by gas chromatography. Absorption in liquids is not possible, when using portable samplers. Depending on desorption efficiency and the type of gas chromatograph used, determination of carbon disulfide concentrations below 1 mg/m^3 is possible. Furthermore, hydrogen sulfide does not cause interference.

The method most extensively used for the indirect assessment of personal exposure is the iodine-azide test in which the concentration of carbon disulfide metabolites present in the urine is measured. The "chronometric" iodine-azide test, based on the time elapsing from adding the iodine-azide reagent to the urine until decolorization of the iodine solution takes place, offers a simple method to be used at the plant level, but its rather high detection limit restricts its use to exposure levels in excess of 50 mg/m^3. Titrimetric modification of the same test increases sensitivity and allows assessment of exposure at levels down to 10 mg/m^3.

Because of the poor correlation with carbon disulfide concentrations in air as well as for analytical reasons, the concentration of carbon disulfide in blood is not a useful test of exposure.

1.1.4 Metabolism

Inhalation is the principal route of absorption of carbon disulfide in man, equilibrium between the carbon disulfide contents of inhaled and exhaled air being reached in about 1–2 h. At this point, retention is about 40–50%. Absorption through the skin is a much less important route than inhalation and other routes are negligible. Carbon disulfide is distributed in the organism by the blood stream. It is taken up by the erythrocytes and plasma in the blood in the ratio of 2:1. It is readily soluble in fats and lipids and binds to amino acids and proteins; hence, it disappears rapidly from the blood stream and has a high affinity for all tissues and organs. Because

of the rapid elimination of carbon disulfide, the distribution pattern in the human organism has not been fully elucidated. Ten to 30% of absorbed carbon disulfide is exhaled, less than 1% is excreted in the urine, and the remaining 70–90% undergoes biotransformation before excretion in the urine in the form of metabolites.

1.1.5 Mechanisms of toxic action

The biochemical mechanisms of the adverse effects of carbon disulfide are largely unknown. However, a number of possible mechanisms have been suggested including:

(*a*) A chelating effect of the metabolites on various essential trace metals;

(*b*) Inhibition of some enzymes (this may be explained, to some extent, by chelation, but the nature of other mechanisms is not yet known);

(*c*) Disturbance of the vitamin metabolism (experimental evidence in animals has shown an impairment of vitamin B_6 and nicotinic acid metabolism);

(*d*) Disturbance of the catecholamine metabolism;

(*e*) Disturbance of the lipid metabolism;

(*f*) Interaction with the microsomal drug metabolizing system (the liver toxicity may be, at least, partly explained by the destruction of cytochrome P-450 via the oxidative desulfuration of carbon disulfide).

1.1.6 Carbon disulfide poisoning; evaluation of the health risk to man

Carbon disulfide can cause both acute and chronic forms of poisoning. Massive, short-term exposure to concentrations of about 10 000 mg/m^3 or more can cause "hyperacute" poisoning, characterized by rapid falling into coma and, eventually, death. Acute and subacute poisoning is associated with short-term exposure to concentrations of 3000–5000 mg/m^3 accompanied by predominantly psychiatric and neurological symptoms such as extreme irritability, uncontrolled anger, rapid mood changes, euphoria, hallucinations, paranoic and suicidal tendencies, and manic delirium. Exposure over many years may produce the syndrome of chronic poisoning manifested by a variety of symptoms and signs arising from manifold adverse effects on different organ systems. Because of the lack of reliable retrospective data on exposure levels, dose-effect and dose-response relationships are extremely difficult to establish, and the no-observed-effect-level is unknown for most effects.

Psychiatric signs and symptoms indicative of adverse effects on the central nervous system following prolonged exposure to high concentrations of carbon disulfide include restlessness, excitation, and loss of temper with gradual development of anxiety, depression, and paranoic tendencies. The

development of chronic encephalopathy has been associated with exposure to levels of 150 mg/m^3 or more over a period of several years. Psychological and behavioural changes have been recorded following exposure to levels ranging from 30–120 mg/m^3, for more than 6 years, and increases in the frequency and severity of such symptoms as headache, impairment of memory, rapid mood changes, paraesthesia, and fatigue have been noted at concentrations ranging from 20–90 mg/m^3. As poisoning progresses further, neurological symptoms become more predominant. Both pyramidal and extrapyramidal symptoms may develop indicating impairment of the central nervous system.

Symmetric polyneuropathy primarily affecting the nerves of the lower extremities and characterized by paraesthesia, dysaesthesia, fatiguability, and diffuse pain, sometimes with hyperaesthesia or hypersensitivity of the muscles, constitutes a well known syndrome. Recent studies indicate that peripheral neurological dysfunction such as the reduced conduction velocity of peripheral nerves may follow prolonged exposure to carbon disulfide concentrations in the range of 30–90 mg/m^3. Sensory polyneuropathy with increased pain threshold has been reported following 10–15 years of exposure to concentrations as low as 10 mg/m^3.

Vascular atherosclerotic changes are also caused by long-term exposure. Studies in Finland, Norway, and the United Kingdom have shown that carbon disulfide promotes the development of coronary heart disease and that exposure to levels ranging from 30 to 120 mg/m^3, for more than 10 years, appears to increase coronary mortality.

Ophthalmological changes of various types, such as increased pressure, retrobulbar neuritis, etc. were formerly connected with severe forms of poisoning but, under present conditions of exposure, such findings are uncommon. However, an increased frequency of retinal microaneurysms, related to the duration and intensity of exposure, has been found in Japanese workers. No such abnormalities have been diagnosed, with certainty, in European workers, in spite of well-controlled comparative studies.

Effects on the endocrine system include a reduction in adrenal activity attributable to reduced secretion of corticotrophine, impairment of spermatogenesis, and disturbance of the hormonal balance in women, evidenced by menstrual irregularities, spontaneous abortions, and premature deliveries. Moreover, the thyroid function may be altered, probably due to impairment of the hypothalamic-hypophyseal system. The most sensitive endocrine changes, i.e., depression of blood progesterone, increase of estriol, and irregular menstruation may occur at concentrations as low as 10 mg/m^3, whereas increases in spontaneous abortions and premature births have been reported in association with an exposure level of 30 mg/m^3.

Gastrointestinal symptoms including dyspeptic complaints, gastritis, and ulcerative changes have been found in workers, heavily exposed to carbon disulfide.

1.1.7 Diagnosis of carbon disulfide poisoning

The effects of carbon disulfide are nonspecific, making individual diagnosis a matter of probability based on the confirmation of exposure, the presence of symptoms and signs compatible with carbon disulfide exposure, and the exclusion of other diseases. In workers with ascertained exposure, carbon disulfide poisoning should be suspected whenever subjective and neurasthenic symptoms, signs of peripheral neuropathy, psychological disturbances, or vascular changes are present. The diagnosis in acute forms of poisoning is straightforward, whereas the insidious development of adverse effects in chronic carbon disulfide poisoning makes early detection difficult. The probability of an accurate diagnosis increases as the number of abnormalities present increases. One recent study suggests that a positive diagnosis can be made only if changes in the choroidal circulation are found and provided that these occur in conjunction with polyneuropathy, or behavioural changes, or both.

1.1.8 Surveillance of exposed workers

For the early detection of adverse effects and for the continuous surveillance of exposed workers, medical examinations should be carried out once or twice yearly. The following examinations are recommended for a pre-employment check: (*a*) thorough medical history; (*b*) clinical and neurological examination; (*c*) electromyogram (EMG) examination; especially conduction velocity measurements; (*d*) psychological tests; (*e*) measurement of the blood pressure; (*f*) electrocardiography; and (*g*) serum cholesterol determinations.

All or some of these examinations should be repeated regularly during the supervision of exposed workers, whenever exposure exceeds half the maximum permissible concentration. It is recommended that personal exposure rather than background exposure should be measured. For this purpose, either personal samplers, or the iodine-azide test should be employed. The iodine-azide test should be carried out from 2 to 12 times a year depending on the level of exposure. Recommendations for early detection and prevention of adverse effects should, of course, be combined with technical and administrative measures for the protection of the health of exposed workers. The adoption of a maximum permissible concentration

of carbon disulfide in the air is considered indispensable, and it is equally important to take all measures needed for achieving and maintaining conditions that will keep exposure below this level.

1.2 Recommendations for Further Research

1.2.1 Analytical aspects

In the field of occupational hygiene technology there is a need to:

(*a*) Improve and harmonize the methods of assessment of carbon disulfide in the work environment with a view to facilitating the comparability of data;

(*b*) to improve, use, and harmonize personal sampling techniques in epidemiological studies; and

(*c*) to further investigate the relationship, if any, between exposure as measured by personal sampling, and the iodine-azide test.

1.2.2 Studies on health effects

There is a need for internationally co-ordinated research on exposure-response relationships using, as far as possible, harmonized, experimental and epidemiological methods.

It is advisable to undertake comparative studies on the relationships between carbon disulfide concentrations and coronary artery disease both in countries with a high, and countries with a low prevalence of the disease to find out whether or not the present information from some industrialized countries, such as Finland, is applicable to countries with a low prevalence of coronary artery disease.

The possible carcinogenicity, teratogenicity, and mutagenicity of carbon disulfide should be studied.

The effects of continuous exposure to low levels of carbon disulfide, such as may be found in the neighbourhood of factories, are unknown. Studies are recommended to elucidate exposure levels and any health risks associated with such exposure, and to introduce control measures.

1.2.3 Mechanisms of toxic action

The mechanisms of the toxic action of carbon disulfide are still hypothetical and further studies concerning the biochemical basis of these effects deserve high priority.

2. PROPERTIES AND ANALYTICAL METHODS

2.1 Chemical and Physical Properties

Carbon disulfide (CS_2) when pure, is a colourless, mobile, refractive solution of sweetish aromatic odour, similar to that of chloroform. However, the crude technical product is a yellowish liquid with a disagreeable odour of decaying radishes.

Carbon disulfide evaporates at room temperature and the vapour is 2.62 times heavier than air (one litre of vapour weighs 3.017 g). Carbon disulfide vapour forms a highly explosive mixture with air. Furthermore, liquid carbon disulfide may produce a static electric charge that can initiate an explosion. Thus, it must be handled with the greatest caution, and should never come into contact with an electric charge or spark, a flame, or even high temperatures. Carbon disulfide is spontaneously flammable at 130–140°C, and fire extinguishers of the foam type must always be available, when it is handled.

Because of its solubility in fats and lipids, carbon disulfide is widely used as a solvent for fats, lipids, resins, rubber, sulfur monochloride, white phosphorus, and some other substances.

Some basic physical and chemical properties of carbon disulfide are summarized in Table 1.

Table 1. Physicochemical data on carbon disulfide.[a]

Synonym	carbon disulphide, carbon bisulphide
Formula	CS_2
Relative molecular mass	76.14
Melting point	111.53° C
Boiling point	46.3° C
Density	1.263 g/cm³ at 20° C
Water solubility	0.2 g/100 ml at 20° C
Vapour density (air = 1)	2.64
Flash point	below −30° C (closed cup)
Explosive limits (% by volume in air)	lower 1.0% upper 50.0%
Vapour pressure at (28° C)	53.3 kPa (400 mmHg)

[a] From: Weast, R. C. (1970); Faith et al. (1965).

2.2 Analytical Procedures

2.2.1 Measurement of carbon disulfide in air

Control of exposure depends, to a great extent, on the measurement of carbon disulfide concentrations in air.

Samples of carbon disulfide may be extracted either by the activated charcoal tube method or by the liquid absorption method.

The following methods are recommended for the measurement of carbon disulfide:

(*a*) direct measurement using gas detector tubes;

(*b*) photometric determination of carbon disulfide samples taken by the liquid absorption method;

(*c*) gas–liquid chromatography of carbon disulfide samples taken by the activated charcoal tube method;

(*d*) continuous measurement by gas analyser.

2.2.2 Sampling methods

2.2.2.1 *The activated charcoal tube method*

This method of sampling is preferable because the sample can be taken from the breathing zone of the worker (see for example Truhaut et al., 1972) and because, when combined with the biological iodine-azide test (section 2.2.3.5), it offers the best measure of personal exposure to carbon disulfide. The sampling device, which consists of a charcoal tube fastened to the worker's shoulder and a pump fastened to the belt, is small enough to be worn for the whole working period without discomfort.

The carbon disulfide, which is absorbed by activated carbon in the tube, is later desorbed by a solvent and determined by gas chromatography (section 2.2.3). To determine the time-weighted average concentration of carbon disulfide, the volume of air sampled should be large enough to allow the determination of concentrations below the threshold limit value (TLV). A sampling period of 15 minutes should be used for the determination of maximum or ceiling concentrations. An advantage of this sampling method is that the presence of hydrogen sulfide does not impair sampling efficiency (McCammon et al., 1975). Further information concerning possible interference with sampling efficiency can be found in reports by McCammon et al. (1975) and NIOSH (1977).

2.2.2.2 *The liquid absorption method*

The liquid absorption method can only be used for the determination of carbon disulfide concentrations at fixed sites. The principle of the method is that air is drawn through the absorption liquid using two fritted bubblers in series. The carbon disulfide in the air reacts with the liquid, which is an ethanolic solution of copper salt and diethylamine. Hydrogen sulfide, present in the air, must be trapped on cotton-wool treated with lead acetate before the air enters the absorption solution (Bagon et al., 1973).

2.2.3 Methods for the determination of carbon disulfide

2.2.3.1 *Direct measurement using gas detector tubes*

This method of measurement is based on a reaction between the tested gas and a specific reagent mixture. For carbon disulfide, the indicating layer in the detector tube contains a combination of a copper salt and an alkylamine that yields a copper-dialkyldithiocarbamate complex with carbon disulfide. A known volume of air is drawn through the tube. The length of the coloured zone is a measure of the concentration. Detector tube systems provide a rapid, inexpensive, and simple method for evaluating the level of a contaminant in the industrial environment, the relative standard deviation of which is about 20–30%. However, the results of this method are only approximate and, if measurements indicate that air contaminant levels are excessive, additional measurements should be made by more accurate methods.

2.2.3.2 *Photometric determination*

The principle of this colorimetric method is that carbon disulfide reacts in an ethanolic solution with diethylamine and a copper salt to give a yellow-brown metallic complex of diethyldithiocarbamate. The colour of the solution is directly proportional to the concentration of carbon disulfide (Department of Employment and Productivity, 1968).

The carbon disulfide concentration in the sample can be determined using a spectrophotometer at 420 nm. Five mg of carbon disulfide per m^3 of air may be determined by this method. Hydrogen sulfide causes interference and should be removed by the method described in section 2.2.2.2 (Cullen, 1964).

2.2.3.3 *Gas–liquid chromatographic determination*

Gas chromatography in combination with the activated charcoal sampling method (section 2.2.2.1) is widely used for the determination of personal exposure to carbon disulfide. A method using a gas chromatograph equipped with a flame photometric detector and a sulfur filter has recently been described in detail (NIOSH, 1977). The assay was validated over a range of 45.6–182.3 mg of carbon disulfide per m^3 of air, at an atmospheric temperature and pressure of 22° C and 102.1 kPa (766 mmHg), respectively, using a 6 litre sample. With this concentration range, the coefficient of variation was 0.059 corresponding to a standard deviation of 5.6 mg/m^3, at a carbon disulfide concentration of 93 mg/m^3. However, the detection of much smaller amounts is possible using this method, if the desorption efficiency is adequate (NIOSH, 1977). It must be emphasized

that any compound having the same retention time as the analyte may cause interference and that, if this possibility exists, separation conditions (column packing, temperature, etc.) should be adjusted accordingly.

2.2.3.4 *Continuous measurement using gas analysers*

Some types of gas analysers are convenient for the continuous monitoring of carbon disulfide in workroom air. The measurements can be carried out at one or several fixed sampling sites depending on the construction of the equipment.

Analysers suitable for continuous monitoring include:

(*a*) Analysers based on electrical conductivity in which an air flow is conducted through a suitable absorbing solution. The gas to be measured reacts with the solution and changes its electrical conductivity according to the concentration of the gas.

In the case of carbon disulfide, the gas must first be oxidized in a combustion oven, the determination is then based on the reaction of carbon dioxide or sulfur dioxide with the absorbing solution.

(*b*) Analysers based on light absorption in the infrared region in which the measuring effect is based on the specific radiation absorption of heteroatomic gases in the infrared spectral range between 2.5 and 12 μm wavelength. Absorption occurs at strictly separated frequencies that are associated with the natural vibrations of the molecules.

When measuring low concentrations of carbon disulfide using infrared analysers, some other gases, especially water vapour, can cause interference. The interference can be eliminated and the sensitivity improved, if the carbon disulfide is first oxidized in a combustion oven to sulfur dioxide and the latter measured by infrared-analyser.

Numerous systems for continuous gas monitoring have been developed; detailed information concerning the measurement of carbon disulfide by this method can be found in Schütz (1970), Leithe (1971), Verdin (1973), Weigman (1973).

2.2.3.5 *Determination of metabolites in urine*

Since there is only a poor, if any, correlation between carbon disulfide concentrations in blood and air, and only 1% or less of absorbed carbon disulfide is excreted unmetabolized into the urine, there is no basis for using the determination of carbon disulfide in either blood or urine as an exposure test (section 4.2.3 and 4.3.2). In contrast, good results have been obtained using the concentration of metabolites of carbon disulfide in the urine as a measure of exposure.

(*a*) The iodine-azide test is based on the finding of Yoshida (1955) that

the iodine-azide reaction:

$$2NaN_3 + I_2 \longrightarrow 3N_2 + 2NaI$$

is catalysed by a metabolite present in the urine of animals exposed to carbon disulfide. Subsequently, it was found that the C—SH and C—S groups act as catalysts in the reaction, and a quantitative test was developed based on the time interval between adding the iodine-azide reagent to urine and the decolorization of the iodine solution, as measured by a stop watch (Vašák, 1963; Vašák et al., 1963). In order to simplify the test, the time was corrected according to the creatinine concentration to avoid the collection of 24-h urine samples. This time served as a basis for the calculation of the exposure coefficient, which was indirectly proportional to the concentration of carbon disulfide metabolites excreted in the urine. Vašák et al. (1967) later elaborated a diagram for the evaluation of the average concentration of carbon disulfide during the shift. Provided that the urine is not too dilute, i.e., the creatinine concentration is not much below 2.25 mg/ml, exposure may be considered negligible if decolorization of the iodine-azide reagent does not take place within 3 h. The "chronometric" iodine-azide test may be successfully used on workers, when the average exposure is above 50 mg/m^3 (Djurić et al., 1965). However, recent data from Sweden indicate that a short decolorization time in the iodine-azide test may occur in some workers exposed to 30–40 mg/m^3, suggesting individual differences in the reaction to carbon disulfide (Kolmodin-Hedman, 1976).

A modification of the "chronometric" test was developed by Jakubowski (1968, 1971). The modified procedure was not based on the time of reaction, but on measurements of the amount of iodine used for titration of carbon disulfide metabolites catalysing the iodine-azide reaction in 1 ml of urine and calculated for a standard creatinine concentration of 1.5 mg/kg. With this method, it was possible to assess exposure to levels as low as 10 mg of carbon disulfide per m^3 of air with a precision of ±20%.

(*b*) A method for the determination of thiourea was developed by Pergal et al. (1977a), based on the colorimetric determination of a complex produced in a reaction between thiourea present in the urine and potassium ferrocyanide (K_4FeCN_6) present as a reagent in an acid media. Levels of thiourea excretion between 0.001 and 0.1 mg/ml could be determined by this method. Preliminary results showed that the amount of thiourea in the urine sampled at the end of the working shift was not strongly correlated with the results of the iodine-azide test. It is necessary to study the excretion dynamics of this metabolite to establish if this method can be used as an exposure test. So far, the results suggest that the excretion of this metabolite reflects the rate of carbon disulfide metabolism rather than recent exposure (Pergal et al., 1977a).

3. EXPOSURE TO CARBON DISULFIDE

3.1 Occupational Exposure

Carbon disulfide was first used as a solvent in 1851 as a phosphorus solvent in the manufacture of matches. During the 19th century, it was used as a solvent for fats, lacquers, and camphor, for the refining of jelly, paraffin, and petroleum, and in the extraction of oil from olives, palmstones, bones, and rags. In the latter half of the century, it was used extensively in the vulcanization of rubber. These applications still prevail to some extent and, today, it is also used in the production of flotation agents, herbicides, rubber accelerators, and neoprene cement, and in the fumigation of grain. However, by far the most important use of carbon disulfide is in the production of viscose rayon fibres.

The industrial production of viscose, which began in 1906, quickly expanded all over the world, particularly during and after World War I. The synthesis of other artificial fibres after World War II slowed down this expansion, but rayon fibres are still of considerable industrial importance. As viscose rayon production is the most important source of exposure to carbon disulfide, a more detailed description of the technological process and the exposure hazards that may be associated with various stages of production has been given in Annex I. The brief account given here highlights the processes associated with the highest risk of exposure.

Carbon disulfide is introduced into viscose production during the so-called process of xanthation, where it is added to shredded and oxidized alkali cellulose to form sodium cellulose xanthate. Although exposure to carbon disulfide at this stage is mechanically controlled, exposure to high concentrations may still occur. The sodium cellulose xanthate is dissolved in caustic soda to produce viscose that can be further processed either by spinning to form textile yarn, tire yarn, or staple fibre, or by casting to form Cellophane. Carbon disulfide, and to a lesser extent hydrogen sulfide, are evolved during spinning and casting, and exposure to high concentrations of carbon disulfide can occur during doffing and when filaments break. Carbon disulfide is further emitted in the cutting of rayon filaments for staple fibre, and in the washing and drying processes. Because of the high input of viscose, carbon disulfide emissions are highest in the production of staple fibre and Cellophane.

3.2 Community Exposure

At the present time, very little information is available concerning exposure to carbon disulfide outside the workplace or the effects on the

general population. Although concentrations outside the workplace are expected to be much lower than those found inside, special consideration must be given to the possibility that individuals in poor health or the very young may be exposed and also that workers, who are exposed to carbon disulfide at work may also be exposed during non-working hours if they live close to their place of work.

In 1976, Peyton et al. reviewed the literature concerning environmental studies of carbon disulfide and carbonyl sulfide. Both compounds are emitted by man-made, as well as natural sources. Although carbon disulfide appears to be relatively stable in the atmosphere, oxidation leads to the formation of sulfur dioxide, carbon monoxide, and carbonyl sulfide. It has been suggested that carbonyl sulfide itself elicits a toxic response in man because of partial decomposition to hydrogen sulfide in the lungs and bloodstream.

From the limited data available, it appears that individuals living close to workplaces where carbon disulfide is used can be exposed to high enough concentrations to result in measurable uptake. When 70 children living 400 m from a factory discharging carbon disulfide into the atmosphere were compared with a control group of 30 children living 15 km from the factory, physical and psychological examinations did not show any health disorders in the exposed group even though urine concentrations of carbon disulfide indicated increased uptake compared with the controls (Helasova, 1969). Environmental measurements were taken for both hydrogen sulfide and carbon disulfide. Ninety-two out of 127 measurements of carbon disulfide concentrations in air were higher than 0.01 mg/m^3.

By applying data on workplace exposure to conditions in the general environment, Peyton et al. (1976) recommended that limiting long-term average concentrations to 0.3 mg of carbon disulfide per m^3 of air should be sufficient to protect the general population against long-term health effects. In the USSR, the maximum allowable concentration for carbon disulfide in the ambient air is 0.03 mg/m^3 with an allowable 24-h average of 0.005 mg/m^3 (Bajkov, 1963). In addition, the USSR has also established an allowable level of carbon disulfide in waterways (prior to treatment) of 1.0 mg per litre (Vinogradov, 1966).

4. METABOLISM

4.1 Absorption

Inhalation and skin contact are the only significant routes of absorption of carbon disulfide. The only way carbon disulfide may enter the human organism through ingestion is by accidental (or intentional) intake.

4.1.1 Inhalation

Inhalation represents the main route of carbon disulfide absorption in occupational exposure. Data reported earlier by Teisinger & Souček (1952), namely that, in spite of considerable variation between individuals, absorption seemed to be proportional to the concentration of carbon disulfide in inhaled air, were confirmed by Demus (1967).

Toyama & Kusano (1953) studied the absorption of carbon disulfide through the lungs of rabbits. They found that equilibrium in the carbon disulfide contents of inhaled and exhaled air was reached after 90–150 min of exposure, and that 70–80% was retained at equilibrium. Inhalation studies have also been performed on human volunteers, but the data obtained have been diverse, even controversial (Teisinger & Souček, 1949; Teisinger, 1954; Brieger, 1961, 1967; Djurić, 1963, 1967; Davidson & Feinleib, 1972). It was reported by Mádlo & Souček (1953) that equilibrium in man was reached during the first 90–120 min of exposure and that, at this stage, the retention of carbon disulfide was about 30% of the amount present in the inhaled air. However, in a number of Japanese studies, Tazuka (1955) found that equilibrium was reached 30–60 min after the beginning of exposure, Toyama & Harashima (1962), after about 180 min, and Tahara (1961), at the end of a working shift of 8 h (480 min). The discrepancies can probably be explained by differences in exposure conditions.

In studies by Teisinger & Souček (1949), higher retention was observed in volunteers exposed for the first time to carbon disulfide than in continuously exposed workers. In volunteers, equilibrium was reached after 120 min of exposure. An initial retention of 80% fell to 45%, when equilibrium was reached. Equilibrium in industrial workers was already reached after 45–60 min. Harashima & Masuda (1962) obtained similar results with exposed workers but found a retention of 65% at equilibrium. Average retentions of 41% after the first 60 min and 48% after 240 min of exposure were reported by Petrović & Djurić (1966).

Thus, the majority of authors agree that, in man, an equilibrium between

the carbon disulfide concentrations in inhaled and exhaled air is reached during the first 60 min of exposure. The percentage retained at equilibrium appears to be about 40–50% of the amount of carbon disulfide in the inhaled air and depends on both the concentration of carbon disulfide in the air and the partition coefficient between blood and tissues. This percentage is lower in continuously exposed workers than in volunteers exposed for the first time to carbon disulfide. This difference should be taken into account in the planning of inhalation studies as well as in the interpretation of the results.

4.1.2 Skin absorption

As an organic solvent, carbon disulfide can be expected to pass through the skin and this has been confirmed in a number of studies.

Dutkiewicz & Baranowska (1967) studied absorption from an aqueous solution through the skin of immersed hands. The solution contained 0.33–1.67 g of carbon disulfide per litre and, after 1 h, the quantity absorbed ranged from 0.23 to 0.78 mg/cm^2 of skin. The authors calculated that immersion of a hand for 1 h in a washing bath in a viscose rayon plant could result in the absorption of 17.5 mg of carbon disulfide into the organism.

It is obvious that workers exposed to carbon disulfide solution and vapour will absorb some through the skin and that, though these amounts will be less than the quantities inhaled, they will still be important and should be considered in the evaluation of total exposure.

4.2 Distribution and Biotransformation

4.2.1 Balance of absorbed carbon disulfide

In animal experiments, where carbon disulfide was administered into the gastrointestinal tract, most of it was eliminated in the faeces and only a small part was excreted by exhalation (Souček, 1957). However, after intraperitoneal injection, rats and guineapigs exhaled about 55% and 70%, respectively, of the amounts administered (Souček, 1959, 1960a,b).

Studies in man, as summarized by Souček (1957), show that 10–30% of the carbon disulfide absorbed into the body is exhaled and that less than 1% is excreted unchanged in the urine; thus, 70–90% undergoes biotransformation and is excreted in the form of metabolites. Demus (1964) reached similar conclusions. About 10% of the absorbed carbon disulfide represents a body burden that is excreted slowly in the urine,

mainly in the form of metabolites. In contrast to these studies, Dutkiewicz & Baranowska (1967) reported that, when carbon disulfide was absorbed through the skin, only 3% was exhaled.

4.2.2 Transport by the bloodstream

There are differences among animal species with regard to the affinity between carbon disulfide and blood. The affinity is higher in rats than in guineapigs (Souček, 1959, 1960a) and this is quite in accordance with the differences in exhalation rates after intraperitoneal injection, referred to in section 4.2.1. The disappearance of carbon disulfide from the circulation can be accelerated by the administration of a mixture of fresh air and 5% carbon dioxide; this results in a more rapid disappearance of narcotic effects (Souček, 1959).

In man, the carbon disulfide that is not exhaled is distributed in the body by the bloodstream, twice as much being taken up by erythrocytes as by the plasma (Souček & Pavelkova, 1953). Carbon disulfide disappears quickly from the blood because of its affinity for lipid-rich tissues and organs. However, traces of carbon disulfide have still been found in the blood of exposed workers 80 h after termination of exposure (Souček & Pavelkova, 1953).

4.2.3 Determination of carbon disulfide in blood

Bartoniček (1957, 1958, 1959) showed that the determination of carbon disulfide in blood did not give reproducible results and that the correlation between carbon disulfide concentrations in blood and air was very weak or non-existent. Thus, determination of the concentration of carbon disulfide in the blood is not a useful test of exposure. The reasons for these discrepancies are explained by the results of studies by Bartoniček (1957, 1958, 1959) on "free" and "bound" carbon disulfide (section 4.2.4).

4.2.4 Distribution in the organism

Souček (1960a) established that the partition coefficients for carbon disulfide from air to blood and from blood to organs were 2.8 and about 100, respectively. This explains the rapid disappearance of carbon disulfide from the blood (section 4.2.2).

The solubility in lipids and fats, and binding to amino acids and proteins,

explains the affinity of carbon disulfide for all tissues and organs. However, at the beginning of absorption, some initial preference for some organs seems to exist. Animal experiments have given various results concerning the order of affinity for different organs, but these may be explained by interspecies differences, by differences in the mode of administration or both. These aspects have been studied in animals only, since even postmortem studies in man are impracticable because of the rapid elimination of carbon disulfide. McKee (1941) first performed such experiments and results obtained up to 1954 have been reviewed by Teisinger (1954). In studies on guineapigs by Strittmatter et al. (1950) using labelled carbon disulfide, initial accumulation occurred in the liver followed by uniform distribution in the organism after some days. The following order of initial prevalence of carbon disulfide in rats was established by Merlevede (1951): liver, bile, kidneys, heart, adrenals, brain. Teisinger (1954) found the largest amount of carbon disulfide in the brain of guineapigs and Mádlo & Souček (1953) demonstrated its presence in the peripheral nerves of rats.

In studies on the distribution of carbon disulfide labelled with ^{35}S, radioactivity was retained in the brain for 2 days (Büssing et al., 1953; Büssing & Sonnenschein, 1954).

Bartoníček (1957) found that "total" carbon disulfide accumulated initially in the adrenals, blood, and brain of exposed rats. At the same time, he observed the existence of both "free" and "bound" forms in the body. "Free" carbon disulfide denotes the fraction of carbon disulfide dissolved in body fluids and "bound" carbon disulfide, the fraction that has reacted with amino acids to give thiocarbamates, a reaction that is reversible. This form is acid labile. It has been shown by De Matteis & Seawright (1973) that the sulfur released during the process of desulfuration of carbon disulfide can form covalent bonds with other sulfur radicals. By determining "free" and "bound" carbon disulfide separately, Bartoníček (1957) obtained another order of initial accumulation. "Free" carbon disulfide disappeared quite quickly from the organs following an exponential curve and reached very low values, 10–16 h after the termination of exposure, while the "bound" form decreased irregularly. Thus, according to Bartoníček (1958, 1959), "free" carbon disulfide accumulates in the liver, muscles, spleen, blood, lungs, brain, kidneys, and heart while "bound" carbon disulfide accumulates in the blood, spleen, liver, lungs, heart, muscles, kidneys, and brain. Gradually more uniform distribution takes place. The existence of 2 forms with quite different initial affinities for blood and organs, could explain the controversial results obtained earlier and the poor correlation between carbon disulfide concentrations in the blood and air (section 4.2.3).

4.2.5 Binding in blood and tissues

According to Teisinger (1954), in 1910, Siegfried & Weidenhaupt proved by *in vitro* experiments that carbon disulfide was bound to glycine in blood in alkaline medium, producing glycine-dithiocarbamic acid characterized by free –SH groups. These authors stated that similar reactions took place with phenylalanine, sarcosine, and asparagine. Chromatographic and spectrophotometric studies have shown that amino acids of the blood plasma react with carbon disulfide to form dithiocarbamic acid and a cyclic compound of the thiazolinone type (Souček & Mádlo, 1953; Mádlo, 1953; Yoshida, 1955; Cohen et al., 1959). Bobsien (1954) demonstrated the binding of carbon disulfide to euglobulin and albumin through –SH groups; he found that binding to pseudoglobulin was negligible. The binding of carbon disulfide to cysteine, methionine, and glutathione in the blood was established by Büsing (1952), but the nature of the binding was not stated.

Using human blood, Souček & Mádlo (1953) established *in vitro*, that carbon disulfide was bound to amino acids in the blood by a first-order reaction, the half-time of which was 6.5 h. Various acids and formaldehyde blocked this reaction, producing dithiocarbamic acid and thiazolinone. In further *in vitro* studies, the same authors (Souček & Mádlo, 1954, 1955, 1956) found that, at pH 7.3–8.3 and at a temperature of 37° C, carbon disulfide was quantitatively bound to albumin but not to gammaglobulin. The product formed possessed free-SH groups that could be determined by titration with iodine chloride. The product was very stable, not hydrolysing even at 100° C. On the other hand, the product formed after the binding of carbon disulfide to amino acid did not show such stability. Souček (1957) showed that the same processes took place *in vivo*.

The binding of carbon disulfide to proteolytic enzymes (trypsin, pepsin, chymotrypsin) forming a labile compound similar to dithiocarbamic acid was also reported by Souček et al. (1957) and Souček (1959). Souček & Mádlo (1955) assumed that the formation of dithiocarbamic acid took place in the blood and the liver, and that the compound formed then appeared in the liver, adipose tissues, blood, and, in small quantities, in the brain and muscles.

4.3 Elimination of Carbon Disulfide and Metabolites

4.3.1 Elimination by breath, saliva, sweat, and faeces

Some basic data on the exhalation of absorbed carbon disulfide have already been discussed (section 4.2.1). The process takes place in 3 phases.

In the first phase, there is rapid elimination of the carbon disulfide absorbed on the mucosa of the lungs and upper part of the tract. In a second slower phase, exhalation of carbon disulfide released from the blood occurs. In the third, very slow phase, carbon disulfide released from tissues and organs is exhaled. Each phase can be presented as a separate curve with a different angle (Souček & Pavelkova, 1953). In experiments on animals, De Matteis & Seawright (1973) established that a significant part of the carbon, released from the carbon disulfide by a desulfuration process, was exhaled as carbon dioxide.

It was reported by Merlevede (1951) that small quantities of carbon disulfide were excreted in the saliva and sweat. Harashima & Masuda (1962) demonstrated the excretion of "free" carbon disulfide through the skin of exposed workers, stating that, sometimes, the amounts excreted by this route were as much as 3 times higher than the amounts of unmetabolized carbon disulfide excreted in the urine.

It is generally accepted that the elimination of inhaled carbon disulfide in the faeces is negligible.

4.3.2 Excretion of carbon disulfide and metabolites in urine

Less than 1% of absorbed carbon disulfide is excreted unchanged in the urine but about 70–90% of retained carbon disulfide is metabolized and excreted in the urine in the form of various metabolites (Souček, 1957).

A number of experimental studies on rats, dogs, and guineapigs have shown that carbon disulfide is excreted in the form of inorganic sulfates into the urine (Binet & Bourlier, 1944; Strittmatter et al., 1950). Using labelled carbon disulfide, Strittmatter et al. (1950) showed that, in guinea-pigs, 30% of intravenously injected carbon disulfide was metabolized to form such end-products. Jakubowski (1968, 1971) isolated 3 metabolites, and Kopecký (1973) identified 2-mercapto-thiazoline-4-carbonyl acid in the urine of exposed rats.

In contrast with the results obtained in animal studies, Merlevede (1951) did not observe any increase in the total sulfate concentration in the urine of exposed workers and registered only a relative increase in the ethereal fraction. This was corroborated by Delić et al. (1966) and Djerassi & Lambroso (1968). Delić et al. (1966) studied the urinary excretion of sulfates in 111 workers, 52 of whom were exposed to high concentrations of carbon disulfide, i.e., 100–1000 mg/m^3, 36 to concentrations below 150 mg/m^3 and 23 to concentrations below 30 mg/m^3. In the most heavily exposed group, 15.5% of the workers showed an increased excretion of total sulfates (3.8–6 g/litre). On the other hand, an equally high percentage (15%) of workers exposed to levels below 30 mg/m^3 displayed a similar

increase (3–3.2 g/litre); 5.6% of the workers exposed to concentrations below 150 mg/m^3 also showed an increased excretion. Thus, there was no correlation between excretion of total sulfates and exposure. A relative increase in the ethereal (organic) fraction of sulfates that was evident in 60% of all the workers was also unrelated to exposure level. The results appeared to suggest that a conjugation process of some carbon disulfide metabolites took place rather than an oxidation to inorganic sulfates.

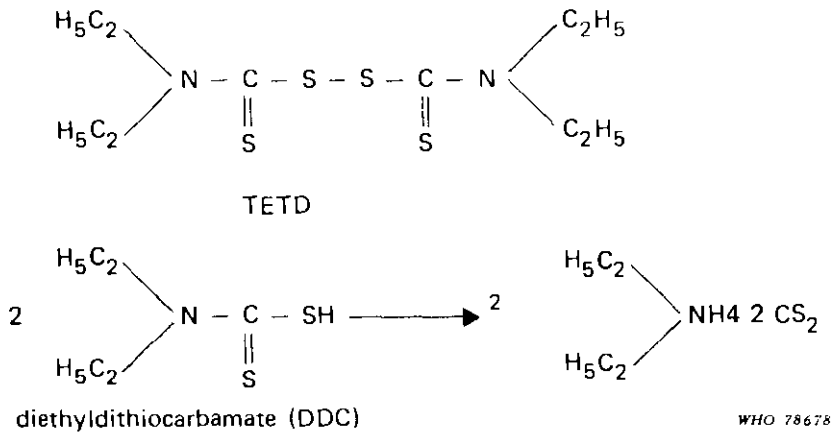

Fig. 1. Metabolism of tetraethylthiuramdisulfide (TETD) (From: Djurić et al., 1973).

The responsibility of metabolites for the discoloration of iodine azide remained hypothetical until Pergal et al. (1972a,b) isolated 3 metabolites from human urine and identified 2 of them as thiourea and mercapto-thiazolinone; thiourea is by far the most important of these metabolites. Later, Pergal et al. (1977a) developed a quantitative method for the micro-determination of thiourea in the urine of exposed workers or of alcoholics treated with tetraethylthiuramdisulfide (TETD, Disulfiram, Antabuse). The authors suggested that the third metabolite was 2-mercapto-thiazoline-4-carbamic acid (Pergal et al., 1977b). Tetraethylthiuramdisulfide is metabolized in a way that liberates carbon disulfide (Fig. 1). Consequently, alcoholics treated with this agent are exposed to carbon disulfide and its metabolites. Skalicka (1967) and Novak et al. (1968) measured the iodine-azide reaction and determined diethyldithiocarbamates (DDC) in the urine of alcoholics treated with TETD. These results led Djurić et al. (1973) to use TETD as a test for the evaluation of the metabolic rate of sulfur compounds in the organism of workers, the so-called "antabuse test".

Studies on the microsomal metabolism of carbon disulfide in the liver of

rats revealed that it was desulfurated to form carbonylsulfide and that this was further oxidized, yielding carbon dioxide which was exhaled (De Matteis & Seawright, 1973; De Matteis, 1974; Dalvi et al., 1974).

Data from human and animal studies on ethereal sulfate excretion (Magos, 1973) have shown that bivalent sulfur represents a small part of retained carbon disulfide, probably less than 5%. The major pathway leads to the formation of sulfates that are excreted in urine.

5. BIOCHEMICAL EFFECTS OF CARBON DISULFIDE

From the chemical point of view, carbon disulfide is highly reactive with nucleophilic reagents characterized by the presence of a group with a free pair of electrons in the molecule. The most important nucleophilic groups are mercapto (—SH), amino ($—NH_2$) and hydroxy (—OH) groups (Vašák & Kopecký, 1967). However, physiological pH values do not favour these reactions (Kopecký, 1977, private communication).

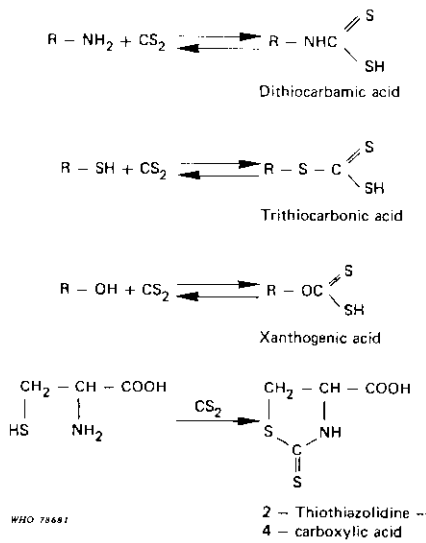

Fig. 2. Reaction of carbon disulfide with nucleophilic groups (From: Vašák & Kopecký, 1967).

According to the chemical structure of compounds participating in the reactions, carbon disulfide will produce dithiocarbamic, trithiocarbonic, or xanthogenic acid. If carbon disulfide reacts with an organic compound with 2 nucleophilic groups, a cyclic compound of the thiazolinone type is formed (see Fig. 2).

The majority of biochemically important compounds, such as amino acids, biogenic amines, and sugars, contain these nucleophilic groups and, thus, may react with carbon disulfide. This is true of a large number of substances existing in the organism.

A number of possible mechanisms of the effects of carbon disulfide on the organism have been postulated including:

(*a*) the chelating effect of carbon disulfide metabolites on various metals, essential for the functioning of enzymes;

The hypothesis of a chelating effect has been supported by the results of other studies including those of Andreeva (1970), who reported an increase in zinc and copper excretion in exposed rats, and Lukáš et al. (1974), who found increased copper levels in the peripheral nervous tissue of exposed rats. A decreased level of ceruloplasmin in rats with experimental carbon disulfide polyneuropathy was reported by Lukáš et al. (1975). This decrease was related to the intensity and extent of the electromyographic signs of polyneuropathy. Gadaskina & Andreeva (1969) and Cimbarevič (1970) noticed a decrease in ceruloplasmin activity in workers exposed to carbon disulfide for more than 10 years. However, in other studies, the ceruloplasmin levels in exposed workers were in the normal range (Andruszczak, 1967; Kujalová, 1973). Andruszczak (1967) found increased ceruloplasmin levels in patients suffering from chronic carbon disulfide poisoning.

Increased excretion of trace metals in the urine of workers exposed to carbon disulfide was not observed in studies by Djurić et al. (1967). Hernberg & Nordman (1969), and Hernberg et al. (1969). However, these negative results do not necessarily exclude a chelating effect, since exposure may have been too low. Thus, the more recent results of El Gazzar et al. (1973) showing a temporary increase in the zinc contents of all serum protein fractions as well as in urinary excretion may reflect the effects of a higher exposure level than in the previous studies.

It is known that copper and zinc ions are essential for the prosthetic groups of many enzymes. The neurotoxic action of carbon disulfide and its interference with the activity of many enzymes could easily be explained by chelating effects. Zinc is required for the activity of enzymes such as lactic acid dehydrogenase (EC 1.1.1.27)[a], carbonic anhydrase (EC 4.2.1.1), glutamate dehydrogenase (EC 1.4.1.2), and alcohol dehydrogenase (EC 1.1.1.1). Copper, on the other hand, represents a cofactor of pyridoxol, a form of vitamin B_6.

Copper is required for the proper functioning of enzymes such as cytochrome *c* oxidase (EC 1.9.3.1), the coenzyme A dehydrogenase system, and dopamine β hydroxylase (EC 1.14.17.1). The loss of copper from the spinal cord is accompanied by cellular damage, producing tissue degeneration. Disturbances of the central and peripheral nervous systems, resulting from carbon disulfide exposure, could be connected with the loss of copper due to chelation and consequent inhibitory effects on enzyme systems (Scheel, 1967).

[a] The numbers within parentheses following the names of enzymes are those assigned by the Enzyme Commission of the Joint IUPAC-IUB Commission on Biochemical Nomenclature.

(*b*) the effect of carbon disulfide on enzymatic systems;
(*c*) disturbances of vitamin metabolism;
(*d*) impairment of catecholamine metabolism;
(*e*) changes in lipid metabolism;
(*f*) interaction with microsomal drug-metabolizing enzyme systems.

5.1 Chelating Effects of Carbon Disulfide Metabolites

The hypothesis of the chelating effect of carbon disulfide metabolites was advanced by Cohen and coworkers and was based on experiments on rabbits (Cohen et al., 1958; Paulus et al., 1957; Scheel et al., 1960; Scheel, 1965, 1967). Considerable shifts were found in the copper and zinc contents of various tissues, especially in the nervous tissue, in rabbits poisoned by carbon disulfide. The concentration of copper in the brain and spinal cord of animals killed 2 weeks after final exposure was less than half of that in the controls. On the other hand, the zinc level in exposed rabbits was 20% higher than that in the control animals. In general, pathological examination of the tissues did not indicate any changes, except in the kidneys and in the spinal cord, which showed marked degeneration of the axis of the cylinder. The Purkinje cells of the cerebrum also showed signs of degeneration.

The following hypothesis, based on an observation that the levels of metal ions in tissues were altered by exposure to carbon disulfide, was formulated by Scheel (1967):

—carbon disulfide reacts with the amino groups of amino acids and proteins to form thiocarbamate in blood and tissues, as was stated by Souček & Mádlo (1956);

—thiocarbamates, possessing sulfhydryl groups, may chelate polyvalent inorganic ions. Because of the low dissociation of the product, they would, thus, interfere with cellular metabolism.

—when such interference becomes sufficiently limiting, the body would respond by oxidizing fat and general loss in body-weight would occur;

—ultimately, as the metabolic limitation increases, cellular death and loss of associated function would occur, producing signs of tissue injury.

Since the entire hypothesis rests on chelation of metal ions, it should be possible to prevent the occurrence of such an effect by supplying an excess of metal ions in the diet of animals exposed to carbon disulfide (Scheel et al., 1960; Scheel, 1967). Such a protective effect is claimed to have been achieved by Scheel (1967).

5.2 Effects on Enzyme Systems

Inhibition of monoamine-oxidase (EC 1.4.3.4) (MAO) activity occurs as soon as exposure of an animal to carbon disulfide begins, but it is reversible (Magistretti & Peirone, 1961; Lazarev et al., 1965). The mechanism of inhibition is not yet clear, but it is known that MAO contains a copper pyridoxal complex. Vašák & Kopecký (1967) found a decrease in catecholamine in the urine of exposed rats. This result suggests the possibility that carbon disulfide forms a compound with catecholamine which cannot be split by MAO. However, Magos & Jarvis (1970b), who also exposed rats to carbon disulfide, did not find any inhibition of MAO. They suggest that Vašák & Kopecký's (1967) finding could be explained by the inhibition of dopamine β hydroxylase.

Alkaline phosphatase (EC 3.1.3.1) activity was inhibited in the tissues and serum of rabbits exposed for more than 22 weeks to high concentrations of carbon disulfide, i.e., concentrations up to about 2350 mg/m^3 (750 ppm) (Cohen et al., 1959). Chervenka & Wilcox (1956) did not find any influence of carbon disulfide on derivatives of chymotrypsinogen or on succinate dehydrogenase (EC 1.3.99.1) activity and Minden et al. (1967) did not register any effects on glycolytic enzymes, Kreb's cycle enzymes, and transaminases in experimental animals.

No changes in glycolysis were found in the brain tissue of rats after either acute or chronic exposure to carbon disulfide (Tarkowski & Cremer, 1972; Tarkowski, 1973). Changes in the brain free amino acid metabolism observed in rats exposed to a carbon disulfide concentration of 2400 mg/m^3 for 15 h included reductions in the levels of glutamic δ-amino butyric acids. These effects were accompanied by decreased activity of brain glutamate decarboxylase (EC 4.1.1.15) (Tarkowski, 1974).

Both, acute and chronic exposures of animals to carbon disulfide result in changes in mitochondrial respiration and oxidative phosphorylation. Respiration of the brain mitochondria was partly inhibited in rats exposed to carbon disulfide (Tarkowski & Sobczak, 1971); cytochrome oxidase activity was also inhibited (Tarkowski, Wrońska-Nofer, 1966). Oxidative phosphorylation in the mitochondria was partly inhibited and partly uncoupled, and was accompanied by a reduction in the activity of adenosinetriphosphatase (EC 3.6.1.3) (Tarkowski & Sobczak, 1971).

Gregorczyk et al. (1975a,b) did not find any changes in liver enzymes, proteins, and free amino acids in rats exposed to a carbon disulfide concentration of 1300 mg/m^3 for 12–26 weeks, and 5 and 10 h daily. The authors concluded that carbon disulfide was not hepatotoxic under such exposure conditions; this seems to be supported by the fact that they did

not find any changes in the blood serum enzymes (Gregorczyk et al. 1975a,b).

Decreased activity of triosephosphate dehydrogenase (EC 1.2.1.9), lactate dehydrogenase, and glycerophosphate dehydrogenase found in the muscles of rats with developed neuropathy was accompanied by an increase in hexokinase (EC 2.7.1.1) activity (Lukáš et al., 1977).

Further studies should establish which enzymes are inhibited by exposure of the organism to carbon disulfide, at what levels of exposure, and the inhibition of which enzyme systems would present a significant health hazard.

5.3 Effects on Vitamin Metabolism

5.3.1 Vitamin B_6

There are 3 forms of vitamin B_6, i.e., pyridoxol, pyridoxal, and pyridoxamine, that play the role of coenzymes in various enzyme systems. These 3 forms are in equilibrium because they are enzymatically converted into each other (Fig. 3). The binding of one form of vitamin B_6 will block the reactions of the enzymes containing the remaining forms. Vašák & Kopecký (1967) reported that carbon disulfide reacted *in vitro* with pyridoxamine to form a salt of pyridoxamine dithiocarbamic acid. Some authors think that this process could also occur *in vivo*, causing inhibition

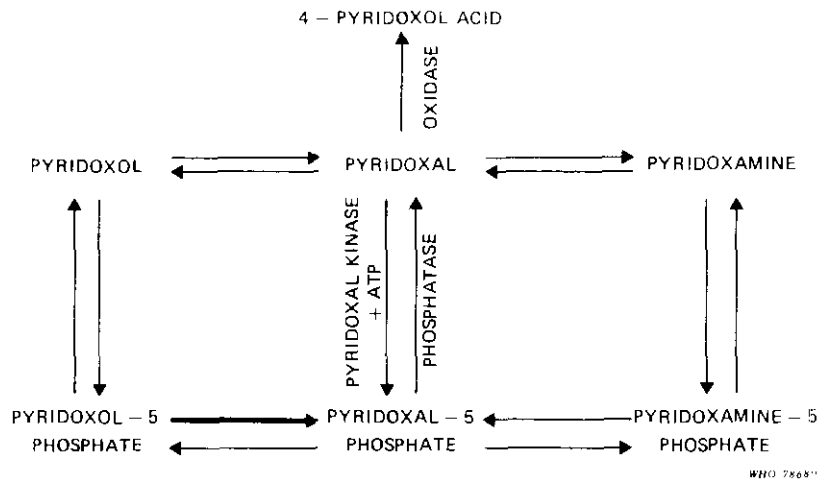

Fig. 3. Active forms of pyridoxine in the organism (Adopted from: Vašák & Kopecký, 1967).

of the enzyme systems in which vitamin B_6 is involved as a coenzyme. Disturbance of pyridoxol metabolism during chronic intoxication was shown in experiments on rats by Kujalová (1971). After the tryptophan load test, excretion of xanthurenic acid increased in exposed animals while excretion of pyridoxol acid decreased.

The temporal development and the severity of this disturbance depended on the diet given to the animals in question (Kujalová, 1971; Górny, 1974). Pyridoxol deficiency due to carbon disulfide intoxication could be eliminated in the animals by giving a diet rich in pyridoxol (10 times the normal dietary level). However, this diet did not prevent the development of neuropathy (Lukáš, 1970) or influence the deterioration in motor activity in rats (Frantik, 1970; Teisinger, 1971).

That pyridoxol deficiency might result from carbon disulfide intoxication was proved by Górny (1971), who showed that the pyridoxal phosphate concentration decreased in the serum of acutely intoxicated rats. Furthermore, increases have been reported in nicotinamides, the metabolites of nicotinic acid (Nofer & Wrońska-Nofer, 1966) and in hydroxyindolacetic acid (a metabolite of serotonine) (Abuczewicz et al., 1971) in the urine of rats exposed to carbon disulfide. All these substances are derived from tryptophan.

In a review on the mechanisms of chronic carbon disulfide poisoning, Teisinger (1971) concluded that disturbance of vitamin B_6 metabolism was obvious but that it did not play a major role in the pathogenesis of nervous tissue lesions.

Transaminases are sensitive to vitamin B_6 deficiency. Thus, metabolic pathways in which transaminases are involved may be inhibited. This is the case in tryptophan metabolism, where it is manifested by increased excretion of xanthurenic acid in both man (Tintera et al., 1972) and rat (Fig. 4) (Abramova, 1967).

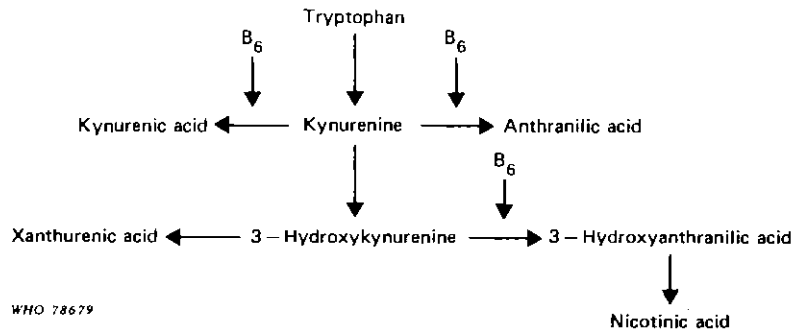

Fig. 4. The pathway of tryptophan metabolism (From: Vašák & Kopecký, 1967).

5.3.2 Nicotinic acid

Exposure to carbon disulfide resulted in increased excretion of methyl nicotinamide, a nicotinic acid metabolite, in the urine of rats (Liniecki, 1960; Wrońska-Nofer et al., 1965). An increase in serum lipids during the exposure of rabbits and rats to carbon disulfide was prevented by administration of nicotinic acid (Nofer & Wrońska-Nofer, 1966; Wrońska-Nofer, 1970). The biochemical background of this phenomenon is still obscure, but a hypothesis based on the interference of carbon disulfide with pyridine nucleotide and nicotinamide metabolism has been advanced (Nofer & Wrońska-Nofer, 1966). However, feeding nicotinic acid to the exposed animals did not prevent the development of neuropathies in these experiments.

As the increase in urinary excretion of nicotinamide metabolites did not occur at the cost of the systematic pool of nicotinamide-adenine dinucleotides, Wrońska-Nofer et al. (1970) suggested that it reflected an increase in the whole turnover rate. The mechanism of the process was not clarified but it may be assumed that an increase in the synthesis via tryptophan occurs.

5.4 Effects on Catecholamine Metabolism

Disturbance of the catecholamine metabolism can play a part in many pathological processes. In studies on rats acutely intoxicated with carbon disulfide, significant changes were found in the brain catecholamine metabolism (Magos & Jarvis, 1970b; Magos, 1975). There was a decrease in the level of noradrenaline accompanied by an increased concentration of dopamine. Inhibition of dopamine β-hydroxylase, an essential enzyme in catecholamine metabolism, was demonstrated *in vivo* in studies on rats by Magos (1975), and *in vitro* by McKenna & Di Stefano (1975). Magos (1975) advanced a theory concerning the central role played by catecholamine disturbances in carbon disulfide pathology, especially where central nervous system changes were involved, and in cardiovascular pathology. Cavalleri et al. (1977) suggested that this could also explain the involvement of the endocrine system.

5.5 Effects on Lipid Metabolism

Disturbance in the lipid metabolism has long since been linked with carbon disulfide exposure. Increased levels of serum lipids, free and total

cholesterol, and β-lipoproteins have been reported in rabbits exposed to carbon disulfide (Paterni et al., 1958; Cohen et al., 1959; Přerovská et al., 1961). Harashima et al. (1960) reported elevated total and esterified cholesterol levels in the serum of heavily exposed workers, whereas workers exposed to levels of about 15–60 mg/m^3 (5–19 ppm) displayed normal serum cholesterol concentrations. Elevated cholesterol levels were also found in exposed workers by Manu et al. (1971) and in patients with previous exposure to carbon disulfide (the patients had not been exposed for several years) by Graovac-Leposavić et al. (1977). Higher levels of serum lipids and especially cholesterol may be due to an increased rate of synthesis in the liver and to the inhibition of the degradation of lipids (Wrońska-Nofer, 1969; Laurman & Wrońska-Nofer, 1977). The fact that elevated cholesterol levels have not been found consistently may be explained by the different exposure levels in different studies (Toyoma & Sakurai, 1967). Bittersohl & Thiele (1977) found that a higher frequency of cholesterol values exceeding 6.72 mmol/litre (260 mg/dl) in workers exposed to carbon disulfide was strongly correlated with the duration of exposure.

A decreased clearing factor activity was found by Ruikka (1959) in workers exposed to carbon disulfide and Martino et al. (1963, 1964) reported an elevated β-lipoprotein fraction in the serum of exposed workers.

Changes in the lipid metabolism found in the aorta tissue may contribute to the development of atheromatic changes in blood vessels (Wrońska-Nofer, 1976).

An increase in serum lipids during the exposure of rabbits to carbon disulfide was prevented by administration of nicotinic acid (Nofer & Wrońska-Nofer, 1966) and in rats (Wrońska-Nofer, 1970) (section 5.3.2).

5.6 Interaction with Microsomal Drug Metabolism

An important feature of the liver toxicity caused by carbon disulfide seems to be the destruction of cytochrome P-450 (Bond & De Matteis, 1969). There is evidence that this effect is due to the oxidative desulfuration of carbon disulfide by mixed-function oxidases (De Matteis & Seawright, 1973). The resulting, highly reactive, sulfur becomes covalently bound to the microsomal protein (Dalvi et al., 1974; De Matteis, 1974; Jarvisalo et al., 1977), mainly to the apoprotein of cytochrome P-450 (Neal et al., 1976; Jarvisalo & De Matteis, 1977; Savolainen et al., 1977a). It is possible that the liberated sulfur is the real toxic agent in liver toxicity arising from carbon disulfide exposure.

Experiments on rats have shown that exposure to carbon disulfide in

concentrations up to 1250 mg/m^3 (400 ppm) for 8 h is followed by an increase in microsomal RNA content and in total protein in the hepatic microsomal fraction and also increased incorporation of 2,4-^{3}H-L-phenylalanine in liver microsomes (Freundt et al., 1974b). Such changes follow the action of inducing agents, such as phenobarbital, in the microsomal enzyme system. It has, therefore, been suggested that carbon disulfide may have an inducing as well as an inhibiting effect on mixed-function oxygenases. However, there is no real evidence of such an effect at present (Freundt, 1977).

6. CARBON DISULFIDE POISONING

6.1 Historical Review

At the end of 1850, several physicians observed cases of strange nervous and mental diseases, the origin of which remained obscure. In 1856, Delpech, reported 24 cases of carbon disulfide poisoning and confirmed the diagnosis by animal experiments (Delpech, 1856a,b). In 1863, he reported 80 more cases of "carbon disulfide neurosis" (Delpech, 1863). Cases of chronic poisoning were also reported in England by Bruce (1884) and Foreman (1886). Laudenheimer (1899) described carbon disulfide poisoning in German vulcanization shops, stirring public opinion by drawing attention to about 50 cases of "insanity". As further cases were reported in the USA (Jump & Cruice, 1904; Francine, 1905), the need for hygienic improvement in work places was recognized. The first epidemic of carbon disulfide poisoning due to the vulcanization process ended at the beginning of the 20th century. At the same time, the viscose rayon industry started to develop and expanded rapidly. Sporadic cases of carbon disulfide poisoning in the viscose industry were reported between 1900 and 1930 (Quarelli, 1928) but the problem became serious in the 1930s. Raneletti (1933), Quarelli (1934) and others described cases of psychotic and polyneurotic disorders and extrapyramidal disturbances (Audio-Gianotti, 1932; Teisinger, 1934).

In Japan, the viscose rayon industry was established in 1916 and, in 1929, the first cases of carbon disulfide poisoning were reported by Tokuhara, followed by other authors (review by Kubota, 1967). Many cases of poisoning were also described in the USA (Hamilton, 1925, 1940; Bashore et al., 1938). The so-called Pennsylvania study by Gordy & Trumper (1938) resulted in the establishment of the first TLV of 20 ppm adopted by the American Standards Association (1941). As the hygienic standard in this industry improved, the incidence of severe poisoning decreased. However, during World War II, the hygienic situation in the expanding viscose industry deteriorated and severe poisoning again became common.

During and after World War II, many cases of carbon disulfide poisoning were reported, mainly from Italy (e.g., Vigliani et al., 1944; Vigliani, 1946) but also from Belgium (Langelez, 1946; Merlevde, 1951) and Finland (Noro, 1944). After World War II, the viscose rayon industry spread to many developing countries, where the whole sequence of degrees of exposure was repeated. In the developed countries, attention is now

focused on slowly developing symptoms due to long-standing exposure to relatively low concentrations.

6.2 Clinical Picture of Carbon Disulfide Poisoning

Carbon disulfide intoxication has been classified as hyperacute, acute, subacute, and chronic.

Hyperacute poisoning occurs in extreme cases of massive exposure for a short time to concentrations of about 10 000 mg/m^3 or more. The victim quickly falls into a coma and eventually dies. Acute and subacute poisoning occurs with short exposure to carbon disulfide concentrations ranging from 3000–5000 mg/m^3 with predominantly psychiatric and neurological signs and symptoms such as extreme irritability, uncontrolled anger, rapid mood changes including maniac delirium and hallucinations, paranoic ideas, and suicidal tendencies. Other symptoms include memory defects, severe insomnia, nightmares, fatigue, loss of appetite, gastrointestinal troubles, asthenia, and interference with sexual functions, such as impotency.

The symptoms and signs of chronic carbon disulfide poisoning were described by Vigliani (1946, 1961) and the following classification of the different syndromes was suggested by Nesswetha & Nesswetha (1967):

—psychoses characterized by manic and depressive symptomatology and disorientation;

—polyneuropathy of the lower extremities, with diminished or completely absent Achilles and patellar tendon reflexes, sensory disturbances in a glove-stocking distribution, diminished faradic and galvanic excitability, and decrease of the motor and sensory conduction velocity in the peripheral nerves;

—disturbances of the gastrointestinal tract in the form of chronic, hyper- and hypoacidic gastritis and duodenal ulceration;

—myopathy of the calf muscles;

—neurasthenic syndrome with disturbances in the autonomous nervous system;

—optic neuritis;

—atherosclerotic vasculoencephalopathy; the principal forms being bulbar-paralytic, hemiplegic, or extrapyramidal.

The typical mental deterioration has been called an organic psycho-syndrome, which may be due to general cerebral atherosclerosis, to direct toxic action upon the brain cells, or to both.

The pattern of carbon disulfide poisoning has changed with improvements in hygienic standards in industry. However, when the viscose

industry is established in a country with no former experience, there is always the risk of severe poisoning; this has occurred many times.

6.3 Effects on Organ Systems

6.3.1 Dermatological effects

Liquid carbon disulfide represents a severe irritant for both the skin and mucosa. Hueper (1936) found blisters in viscose rayon workers and also in experimental animals that often resembled second and third degree burns.

6.3.2 Ophthalmological effects

Studies on the ophthalmological effects of carbon disulfide in animals have mostly been of a histological nature. In 1899, Koester observed changes in the retinal ganglia. Seto (1958) found vacuolar degeneration and tigrolysis in the retina, and atrophy of the optic nerve in rabbits exposed to a carbon disulfide concentration of about 3700 mg/m^3 for 1–3 h.

Ophthalmological examinations in man are informative because it is possible to observe the visual capacity and to study the changes in the vessels of the ocular fundus directly. According to the literature (e.g., Nunziante-Cesaro et al., 1952; Savić, 1967) the following effects have been observed:

—changes in the motility of the eyelids;

—changes in the sensitivity of the cornea and conjunctiva;

—changes in the motility of the ocular bulbus;

—changes in convergency and accommodation;

—morphological changes in the fundus such as focal haemorrhage, exudative changes, atrophy of the optic nerve, retrobulbar neuritis, microaneurysms, and sclerotic changes of the blood vessels;

—functional changes, e.g., disturbances of colour vision, adaptation to the dark, reaction of the pupil to light, accommodation, and decrease in visual accuracy.

Most of the effects mentioned above have resulted from heavy exposure. Many that were observed decades ago, when the observations often lacked comparison materials, are open to criticism. Nowadays, under prevailing working conditions such grave changes are rarely, if ever, seen.

Increased systolic and diastolic blood pressure in the retinal arteries and damage to the arterial walls have been reported (Maugeri et al., 1966d; Goto et al., 1971). Maugeri et al. (1966d, 1967) studied the arterial pressure in 107 workers who had been exposed to carbon disulfide at concentrations

ranging from 200–500 mg/m^3, with peak concentrations of up to 900 mg/m^3, for 1–9 years. Using an ophthalmodynamographic method, the authors found an average increase in both systolic and diastolic pressures in exposed workers of about 18.4/14.7 kPa (138/110 mmHg) compared with controls which averaged 15.3/11.6 kPa (115/87 mmHg). The increase was more marked for the diastolic pressure than for the systolic. Measurement of the pressure of the ophthalmic arteries may be a test that needs further evaluation in the light of the demonstrated disturbance of the brain catecholamine metabolism induced by carbon disulfide.

Savić (1967) studied changes in the nervous system of the eyes of young workers exposed to carbon disulfide levels of 100–400 mg/m^3. Changes were observed but only after a long period of exposure (>5 years) (Hotta & Savić, 1972). Retinal microaneurysms have been reported in a high proportion of Japanese viscose rayon workers (Goto & Hotta, 1967; Goto et al., 1971; Sugimoto et al., 1976). In one study, the prevalences of microaneurysms as judged by fundus photography, were 8% and 2% among exposed and unexposed male workers, respectively (Goto & Hotta, 1967). In a subsequent study (Hotta & Goto, 1971; Goto et al., 1971), a prevalence of 56% of microaneurysms was found in the exposed group (241 subjects) and 15% in a control group (30 subjects). The extremely high prevalence in the exposed groups in these studies was due to biased selection of the subjects; one-half of them were selected for examination because of known microaneurysms revealed by ophthalmoscopy. Later studies by the same team did not show such a high prevalence (Sugimoto et al., 1976), but a statistically significant difference between exposed and unexposed subjects still persisted. Retinopathy was found in 89 out of 289 carbon disulfide workers (31%), but only in 2 out of 49 controls (4%). The frequency of retinopathy was correlated with both the duration and the intensity of exposure (Sugimoto et al., 1976). It has been suggested that the retinal microaneurysms found in Japanese workers were related to the diabetogenic action of carbon disulfide (Goto et al., 1971). However, microaneurysms are generally associated with hypoxia and, though they may occur in advanced cases of diabetes, they are not, by any means, specific for the disease. Thus, to ascribe the excess of aneurysms found in Japanese studies to subclinical diabetes caused by carbon disulfide is not justified. It is more likely that they were caused by a direct effect on the retinal vessels, possibly in association with local hypoxia coacting with ethnic or environmental factors.

The results of recent Finnish studies do not tally with the Japanese findings. Out of 100 exposed men and 97 controls, only 3 exposed and 2 control subjects showed 1–5 microaneurysms, and one exposed subject showed more than 5 (Raitta et al., 1974). Furthermore, general narrowing

of the arteries and calibre irregularity were so common in the fundus of both the exposed and control subjects that plain ophthalmoscopy did not have any discriminatory value in this study. A subsequent Japanese–Finnish study showed that the differences in values obtained in the 2 studies were true differences and were not caused by inter-observer variation (Sugimoto et al., 1977).

The most interesting finding in a study by Raitta et al. (1974) was the high frequency of delayed peripapillary filling that occurred in 68 exposed and 38 unexposed men. The findings of Raitta & Tolonen (1975), suggest that studying the microcirculation of the ocular fundus by fluorescein-angiography and oculosphygmography would help in the early detection of carbon disulfide effects, especially since the vessels can be observed directly in their natural state. Ophthalmoscopy is indicated for the examination of patients suspected to be suffering from carbon disulfide poisoning and for following-up such patients, but it is too prone to inter- and intra-observer variation to be used routinely by plant physicians for regular health checks. Fundus photography eliminates some of this variation, but its evaluation should be standardized. The diagnosis of retinal microaneurysms requires a fundus angioscreenography, but this method is recommended for research purposes only.

It should be added that a mixture of carbon disulfide, hydrogen sulfide and sulfuric acid mist from an acid bath caused keratoconjunctivitis in exposed workers (Savić & Jovičić, 1965). This phenomenon is called "spinner's eye".

6.3.3 Otological effects

Sulkowski & Latkowski (1969) observed that exposure to carbon disulfide impaired hearing ability. The authors examined 60 workers occupationally exposed to carbon disulfide for between one year and more than 10 years. The workers were below 50 years of age. Audiometric examinations showed impairment of hearing of the receptory type in more than 50 workers and also a decreased ability to distinguish sound intensity within the range 1.5–3.0 dB. This suggested a central and supracochlear localization of the impairment. Electronystagmographic examinations performed by these authors disclosed reduced excitability of the vestibular apparatus, suggesting an extralabyrinthine localization of the lesion. Loss of sensitivity to high frequency tones has also been attributed to carbon disulfide exposure (Zenk, 1970). Since noise levels are often very high in viscose rayon plants, it is possible that the lesions found may be at least partly due to this cause. Vestibular symptoms, as manifested by vertigo and nystagmus may also be present in carbon disulfide intoxication (Zenk, 1967, 1970).

6.3.4 Respiratory effects

Carbon disulfide is a known irritant, but few data exist about its effects on the respiratory system (Zenk, 1967). Ranelletti (1933) described chronic cough as a consequence of the irritant effect of carbon disulfide, but it is necessary to take into consideration the irritative effects of hydrogen sulfide and sulfuric acid mist and of other irritants present in the air of viscose rayon plants. The findings of Massoud et al. (1971) i.e., cough, phlegm, wheezing, dyspnoea, precordial pain and palpitations, may also have been due to such mixed exposure rather than to carbon disulfide alone.

6.3.5 Gastrointestinal effects

Gastrointestinal symptoms are common among heavily exposed workers and patients with carbon disulfide poisoning. Bashore et al. (1938) found a prevalence of such symptoms of 25%, Vigliani (1954), 28%, Karajović et al. (1964), 66%, Lysina (1967), 27%, and Hass et al. (1967), 27%. Since such symptoms occur among unexposed people too, especially in shift work, the figures listed cannot be attributed exclusively to carbon disulfide exposure (Knave et al., 1974). A higher prevalence of gastrointestinal disorders and liver and bile duct dysfunction was observed in 2 groups of workers (800 and 492 subjects, respectively) exposed to very low carbon disulfide concentrations (4–12 mg/m^3) than in a control group of 453 unexposed workers. The prevalence in the 2 exposed groups was 4.7 and 5.6%, respectively, and that in the control group, 2.2% (Murashko, 1975). Later, Bittersohl & Thiele (1977) found a prevalence of 22.7% of gastrointestinal changes in 309 exposed shift workers as opposed to 5.9% in 345 unexposed shift workers.

Based on histological studies of the gastric mucosa of 75 workers exposed to carbon disulfide, Hassman et al. (1967) suggested classification into 5 groups: normal gastric mucosa, superficial gastritis, chronic gastritis with incipient atrophy, chronic atrophic gastritis, and gastritis of undetermined type. Duodenal ulceration was only found in 2 out of 75 subjects in this study. Of the workers examined, 11% had dyspeptic complaints and gastritis was verified in 60% of the cases. A similar figure (66%) was found by Karajović et al. (1964).

6.3.6 Hepatic effects

Exposure to carbon disulfide has caused fatty degeneration and haemorrhages of the liver in animals (Bashore et al., 1938). Experimental studies on rats have shown that pretreatment with a drug that stimulates

liver microsome enzyme activity alters the degree of liver damage on exposure to carbon disulfide. Thus, Bond et al. (1969) reported necrosis in the livers of rats that had been pretreated with phenobarbital and subsequently received a single oral dose of carbon disulfide (1 ml/kg body weight) but not in rats treated only with carbon disulfide. Moreover, only pretreated rats displayed hydropic degeneration of the liver. Magos & Butler (1972) found that starvation potentiated the effect of phenobarbital in rats subsequently treated with carbon disulfide, and that the resulting hydropic degeneration was reversible. Similar results were obtained by Freundt et al. (1974a), when they administered a single oral dose of 1 ml of carbon disulfide per kg body weight to rats pretreated with phenobarbital. However, no degenerative changes in the liver were observed in pretreated rats following exposure by inhalation to carbon disulfide at about 60 mg/m^3 (20 ppm) and 620 mg/m^3 (200 ppm) for up to 7 days. In experiments performed on rats with short-term (8-h) exposure to carbon disulfide at concentrations ranging from 62–1250 mg/m^3 (20–400 ppm), the energy potential of the organism was damaged mainly because of a reversible augmentation of hepatic glycolysis (Kürzinger & Freundt, 1969; Freundt & Kürzinger, 1975).

The possible effects of carbon disulfide on the liver have been discussed in numerous reports of clinical observations. Some authors deny that exposure to carbon disulfide results in toxic effects in the liver, some claim degenerative changes of the hepatocytes, and others state that sclerotic changes are produced under conditions of chronic exposure. Such controversial observations can be explained by nonuniformity in approach to the method of examination. Vidaković et al. (1965a) examined workers hospitalized because of chronic carbon disulfide poisoning. The exposure of these workers had been extremely high, ranging from 1400–2200 mg/m^3 (Petrović & Djurić, 1965). Functional disturbances of the liver and fatty degeneration of hepatocytes were found but no necrotic changes were observed.

Pirotskaja (1972) examined the protein-forming function of the liver in workers (40 women and 6 men) who had been exposed to carbon disulfide for 5 years. At first, the workers were exposed to a carbon disulfide concentration of 90 mg/m^3 but later, concentrations ranged from 8–14 mg/m^3. All exposed subjects were between 30 and 40 years of age. The mean concentrations on cystine, thyroxine, methionine, valine, leucine, and tryptophan in serum showed statistically significant increases in comparison with a control group. Statistically valid decreases occurred in the levels of glutamic acid, aspartic acid, olanine, and lysine. The levels of histidine, arginine, and serine did not differ from those in the control group. There was a correlation between these changes and the

clinical signs of carbon disulfide intoxication. There was no difference in the serum contents of total protein in the exposed and control groups.

6.3.7 Renal effects

Some authors have drawn attention to nephrosclerosis in autopsies of patients with carbon disulfide poisoning (Uehlinger, 1952; Yamagata et al., 1966; Sbertoli et al., 1969), but this could be ascribed to a general atherosclerotic process induced by carbon disulfide. For example, in the cases studied by Uehlinger (1952), typical glomerulosclerosis of the Kimmelstiel-Wilson type was established in 4 patients, while the fifth showed arteriosclerotic injury of the kidney. Obviously renal involvement represents a very late consequence of heavy, protracted carbon disulfide exposure, since Graovac-Leposavić & Jovičić (1971) reported that only one patient with persistent kidney insufficiency had ever been diagnosed in a large viscose rayon plant employing several thousands of workers. In another study of viscose rayon workers, Hernberg et al. (1971) found a slight but statistically significant rise in the mean plasma creatinine concentration compared with a control group. All values were within "normal" limits, however.

6.3.8 Haematological effects

Brieger (1949) studied the bone marrow of exposed rats and found retarded maturation of the erythrocytes. Mild anaemia, a slight decrease in the haemoglobin concentration, slight reticulocytosis, eosinophilia, and hypercoagulability of the blood have also been recorded in exposed rats (Vidaković et al., 1965b).

Ivanova (1967) found a moderate decrease in the haemoglobin concentration and erythrocyte count in men with only slight exposure to carbon disulfide. Such results cannot be attributed to carbon disulfide effects, but rather to poor standardization of the study conditions, since significant haematological changes in the peripheral blood were not observed, even in highly-exposed workers (Vidaković & Andjelkovski, 1965; Fahim et al., 1973). Thus, it has not been confirmed that carbon disulfide causes anaemia or polyglobulia. It is probable that the anaemia mentioned in some clinical reports reflects malnutrition or some other nonoccupational cause, perhaps even defective study design, rather than an effect of carbon disulfide.

The effects of carbon disulfide on blood coagulation mechanisms are discussed in section 6.3.14.

6.3.9 The endocrine system

Damage to the endocrine structures with functional alterations was described in animals by Ranelletti as early as 1931, and by Audio-Gianotti in 1932. Impaired sexual function in patients with carbon disulfide poisoning was reported by Gordy & Trumper (1938), Langelez (1946), and Vigliani (1946). Vesce et al. (1953) observed a decrease in 17-ketosteroids excretion in the urine of exposed rabbits. This phenomenon was confirmed in studies on exposed workers by Fruscella (1962) and Olienacz et al. (1964). Most of these observations were made on workers belonging to older age-groups and the confounding effect of age was not controlled. Cavalleri & Zuccato (1965), however, obtained the same results taking the age factor into account.

In 1965, a joint Italian–Yugoslav group began an investigation on young workers in a Yugoslav viscose rayon plant. The workers were classified according to duration of exposure to carbon disulfide. The average ages of various groups ranged from 26 to 33 years and they were exposed to average carbon disulfide concentrations of about 200–500 mg/m^3 with peak concentrations of up to 900 mg/m^3. The excretion of 17-ketosteroids in the urine showed a linear decrease with the duration of exposure (Cavalleri et al., 1966a,b, 1967). The decrease in excretion of 17-hydroxycorticosteroids was most marked in workers with short exposure and did not decrease any more as exposure continued. The excretion of androsterone appeared to decrease progressively with duration of exposure, probably in a linear fashion; that of etiocholanolone did not show any uniform pattern (Cavalleri et al., 1966c,d). Urinary excretion of testosterone and gonadotropin luteinizing hormone was also reduced in workers exposed to concentrations of 100–400 mg/m^3 for 2–12 years[a]. Lancranjan et al. (1971) reported a decrease in 17-ketosteroid and 17-hydroxycorticosteroid excretion in the urine of exposed workers.

The thyroid function has been studied in exposed workers by determination of serum thyroxine (Cavalleri et al., 1971; Cavalleri, 1975; Massoud et al., in press). Decreases reported in thyroxine levels suggest a reduction of thyroid activity.

Mild hypothyroidism was reported in 8% of exposed workers in studies by Lancranjan (1972). This effect may be primary or may be due to inhibition of the hypothalamus–hypophysis axis. A decrease in thyrotropin-stimulating hormone, observed in human subjects given tetraethylthiuram, favours the hypothesis of an impairment of the hypothalamic–hypophyseal system (Cavalleri et al., 1977).

[a] Exposure data submitted by Professor Cavalleri as private communciation to the Task Group.

When the thyroid function is inhibited, disturbances in the lipid metabolism will appear. A well-known manifestation of subclinical hypothyreosis is elevation of the serum cholesterol level, which in turn may contribute to the vascular changes typical of carbon disulfide poisoning. The isolation and identification of two metabolites, thiourea and mercaptothiazoline, may help to explain the mechanism (Pergal et al., 1972a,b). Neither of these metabolites is directly toxic, but both may have some influence on thyroid activity. In fact, drugs containing substances of the thiourea and mercaptothiazolinone type are used in the treatment of hyperthyroidism.

Lancranjan et al. (1969, 1972), reported hypospermia, asthenospermia, and tetratospermia in the spermatic liquid of young exposed workers, confirming the gonadal injury reported by Cavalleri et al. (1965).

Disturbances were found in the ovarian function of 500 young females, exposed to concentrations of carbon disulfide of around 20 mg/m^3, and of 209 women exposed to a concentration of less than 10 mg/m^3 (Vasiljeva, 1973). In a comparison with a group of 429 unexposed women, menstrual flow durations of more than 5 days occurred in 18% of the first group and in 11% of the second compared with 5% in the control group. Irregular menstruation occurred in 8% of those exposed to 20 mg/m^3 as opposed to 2% in the comparison group. Other menstrual disorders followed a similar pattern, and were correlated with the length of exposure. When vaginal smears were examined from subsamples, cellular disturbances were most frequent in the group with highest exposure. A biochemical study of the sex hormones in the urine confirmed the vaginal-smear findings. Hence, even rather low exposure to carbon disulfide appeared to induce hormonal and functional disturbances in young women. Other studies corroborate these findings (Petrun, 1967, Finkova et al., 1973).

In a study of 380 women exposed to around 30 mg/m^3, Petrov (1969) found more pregnancy complications than in a control group of 191 women. Spontaneous abortions occurred in 14% of the exposed, and 7% of the unexposed women. "Threatened pregnancy terminations" also occurred more frequently in the exposed women than in the controls (26% and 13% respectively). Exposed women gave birth prematurely significantly more frequently than controls (9% and 3%, respectively).

It has been reported in several studies that carbon disulfide produces primary damage at the hypothalamic–hypophyseal level (Cavalleri et al., 1965; Lancranjan et al., 1971; Maugeri et al., 1971; Cavalleri, 1972). The hypothalamus produces the releasing factors that stimulate the hypophysis to synthesize and release polypeptide hormones, which in turn stimulate the target glands in question. The impairments found would, therefore, represent a secondary consequence.

Thus, carbon disulfide causes several disturbances of the endocrine systems that can be summarized as follows:

—a reduction of adrenal activity that can be repaired by ACTH administration and can therefore be ascribed to reduced secretion of corticotrophin;

—a reduction of the endocrine activity of the testis and impairment in spermatogenesis possibly due to direct gonadal damage; this finding could explain the decrease in "libido" and "potentiae" often found in exposed workers;

—disturbances in the hormonal balance in women, resulting in menstrual irregularities, spontaneous abortions, and premature births;

—impairment of thyroid function, which could be primary or due to a deficiency in the thyrotropin-stimulating hormone (TSH) or the TSH releasing factor or both.

6.3.10 Effects on the nervous system

6.3.10.1 *Central nervous system*

In experimental animals, carbon disulfide causes destruction of the myelin sheet and axonal changes in both the central and peripheral neurons. Degenerative changes have been observed in the cortex, basal ganglia, the thalamus, the brain stem, and the spinal cord (Wiley et al., 1936; Ferraro et al., 1941; Lewey et al., 1941; Fischer & Michalova, 1956; Drogičina, 1968).

The mechanism by which carbon disulfide causes these changes has not been elucidated, however. Mitochondrial enzymes may be inhibited (Tarkowski & Wrońska-Nofer, 1966; Tarkowski & Sobczak, 1971), and the tyrosine and catecholamine metabolism may be disturbed (Magos et al., 1974). The content of free glutamine increases as a result of carbon disulfide exposure (Efremova & Uzbekov, 1968; Tarkowski & Cremer, 1972). Such changes were observed with acute experimental poisoning, but chronic, repeated exposure did not produce gross changes (Tarkowski, 1973).

Horvath & Mikiška (1957) followed the electroencephalographic changes in rabbits exposed to carbon disulfide and found a transitory decrease in the amplitude of basic and superimposed beta rhythms.

The results of animal experiments have to be extrapolated to man with extreme caution; however, many data obtained from animal studies are in good agreement with clinical observations in man. Like other narcotic agents, carbon disulfide produces a clinical symptomatology of irritation and excitation on one hand, and inhibited psychomotor activity, psycho-

logical alterations, insomnia, hypersomnia, loss of consciousness and death, on the other.

In acute poisoning, the first typical signs from the central nervous system (CNS) are excitation, euphoria, and aggressive behaviour. Subacute and chronic cases are first characterized by neurotic signs of unrest, excitation, and loss of temper. Gradually the patient becomes depressive, anxious, paranoiac and sometimes there is a suicidal tendency. Nightmares, apathy, loss of initiative, vegetative disturbances, and headache are common symptoms (Melissinos & Jacobides, 1967; Mihail et al., 1968). In the further course of chronic intoxication, neurological signs become prominent. Both diffuse cortical and focal symptoms from the subcortical grey matter and extrapyramidal system are typical (Teisinger, 1934). Typical Parkinson symptomatology with bradykinesia, bradylalia, muscle rigidity, tremor, and increased elementary postural reflexes is similar to that in arteriosclerotic or postencephalitic parkinsonism (Nakamura et al., 1974). Psychic, pyramidal and extrapyramidal symptomatology, including signs from other parts of the brain (vestibular, cerebellar) give a picture compatible with diffuse effects, described under the term of "toxic encephalopathy". Furthermore, nervous involvement in general may be reflected as changes in the sensitive branch of the trigeminal nerve, in the function of the III, IV, and VI cranial nerves, and in the sympathetic and parasympathic nerves of the eye.

Disturbances in cerebral circulation probably explain some of the manifestations of neurotoxicity. Vigliani et al. (1944) demonstrated hyalinosis of the arterioles and precapillaries histologically, a finding that fits into the picture of general atherosclerosis caused by carbon disulfide. Thus, the vascular changes described by Vigliani (1961) as "encephalovasculopathia sulfocarbonica", are probably responsible for many of the manifestations of central nervous system pathology.

On the other hand, authors of some recent publications have tried to explain some mechanisms by direct interference of carbon disulfide and its metabolites in the system of enzymatic processes in the brain. Morphological studies indicate that long axons in the spinal cord are preferentially destroyed in chronic carbon disulfide poisoning (Szendzikowski et al., 1973).

The typical neuropathological picture includes an increase in neurofilaments, and secondary effects on the myeline sheath (Juntunen et al., 1974). Biochemical studies have shown that oxidative desulfuration also take place in the brain (Savolainen et al., 1977b), and that the highest specific binding of the liberated sulfur is detected in spinal cord axons (Savolainen & Vainio, 1976). It appears that most of the liberated sulfur binds to neurofilaments that are essential to normal axon functions

(Savolainen et al., 1977c). Thus, there is evidence of a direct toxic action upon the nervous system.

The results reported by Abramova (1967), Vašák & Kopecký (1967), and others (section 5.3.1) regarding inhibition of the vitamin B_6 metabolism, might explain some changes in the peripheral myelin sheet and even some effects on the central nervous system. The consequences of vitamin B_6 inhibition, or interference with the transamination of glutamic acid and inactivation of pyridoxamine could, perhaps, produce irritative cortical symptomatology, including epileptiform cramps. Furthermore, studies showing interactions between carbon disulfide and, tissue respiration; depression of cytochrome oxidase, succinic dehydrogenase, alkaline phosphatase, and dopamine-β-hydroxylase; and influence of inhibitors of serum elastase (EC 3.4.21.11), suggest that besides a purely vascular etiology, it is plausible to consider a direct toxic interference of carbon disulfide with tissue metabolism (section 5.2). In fact, direct toxic effects of carbon disulfide on peripheral nerve cells (Szendzikowski et al., 1973), and on the myoneural junctions (Juntunen et al., 1977) have been shown in animals. The central nervous system may react in the same manner.

From all these considerations, it can be concluded that the effects of carbon disulfide on the nervous system may be influenced by many factors. The method most often used for the study of cerebral involvement in man is electroencephalography (EEG). However, studies on carbon disulfide poisoning are rare. Early studies emphasize the frequent occurrence of very flat records among subjects chronically exposed to carbon disulfide (Królikowská & Rucinska, 1959). More recently, Seppäläinen & Tolonen (1974) found 21 abnormal EEGs in an exposed group comprising 54 viscose workers compared with only 6 in a control group of 50 paper-mill workers. Thiele & Wolf (1976) found EEG changes in 52% of a group of 139 spinning workers. The abnormalities consisted of slight, diffuse slow-wave abnormalities, slight to moderately severe focal slow-wave abnormalities and even spike and wave discharges in 3 exposed men. Thus, mild brain dysfunctions were clearly more prevalent in the exposed group than in the control. EEG findings among 250 workers with longstanding occupational exposure to carbon disulfide (mean exposure 11.2 years) were recently described by Stýblvá (1977) and compared with the EEGs of 61 healthy controls and 47 patients suffering from cerebral arteriosclerosis. Increased frequency of abnormal EEGs was found in 33.2% of the exposed workers, compared with 6.6% in the control group ($P < 0.01$). The most frequent abnormalities among the exposed workers were episodic theta activity (33%) and diffuse abnormality (30%) (it was not, however, indicated or even deducible from the data presented, how these percentages had been calculated, i.e., from which population they were

taken). Local abnormalities were rare. Local EEG abnormalities predominated in patients with cerebrovascular disease. The episodic activity in the EEG was considered to reflect the direct toxic effects of carbon disulfide on mesodiencephalic structures. The author proposed that diffuse abnormality could be a manifestation of vasculoencephalopathy resulting from toxic changes in the small diameter vessels. The frequency of alpha activity tended to be lower among exposed workers and this was considered to indicate a cerebral metabolic disorder due to carbon disulfide exposure.

Studies on the behavioural and psychological effects of carbon disulfide exposure have indicated disturbances in deep subcortical structures, namely vegetative centres, and more diffuse cortical involvement. The methods used have included diagnostic interviews, behavioural observations (mainly on experimental animals), and psychological test batteries.

Both structured and unstructured interviews of human subjects showed differences in the clinical pictures of carbon disulfide poisoning at rather high concentrations i.e., about 950–2400 mg/m^3 (300–760 ppm) and at much lower concentrations i.e., around 20–50 mg/m^3 (7–30 ppm) over a long period of exposure. At high concentrations, symptoms of headache, muscle pain, fatigue, paraesthesia, and general weakness were consistently reported (Gordy & Trumper, 1940; Manu et al., 1970). At lower levels of exposure, fewer complaints of muscular pain and overall weakness were noted, the main symptoms being headache, memory impairment, rapid mood changes, insomnia, paraesthesia, and fatigue (Seppäläinen et al., 1972; Lilis, 1974).

Standardized batteries of tests yield results that are directly quantifiable and comparisons can be made between groups at different exposure levels and control groups. Using this method, Hänninen (1971) presented 3 groups of workers with different exposures and clinical profiles (unexposed, exposed without clinical symptoms, and poisoned). The results suggested that syndromes of latent and manifest carbon disulfide poisoning differ in quality as well as in intensity, i.e., "clinically manifested poisoning is characterized by lowered vigilance, diminished intellectual activity, diminished rational control, retarded speed, and motor disturbances, whereas traits indicative of depressive mood, slight motor disturbances, and intellectual impairment are characteristic of latent poisoning" (Hänninen, 1971). Analysis of intercorrelations among test sources for each of the 3 groups resulted in substantially different factor structures across the 3 groups. This supports the contention that behavioural differences between groups exposed to different concentrations are qualitative as well as quantitative (Hänninen, 1974). Naturally, the extent to which such distinctions are, in fact, true, depends on the number of false-positive diagnoses in the poisoned group (i.e., how many

patients with other diseases had been classified as cases of carbon disulfide poisoning), and, since this aspect could not be evaluated, it may be premature to accept the qualitative changes found as real facts. As to the quantitative changes, it is self-evident that their severity must be correlated with the degree of poisoning, at least on a group basis. The specificity of the psychological and behavioural examination increases when other subclinical signs of carbon disulfide exposure, such as EEG and EMG findings are present.

Hänninen & Mäenpää, as reviewed by Tolonen (1974), applied the same type of tests to 97 exposed male viscose rayon workers (mean exposure time 15 years) and 96 age-and-sex matched controls from a paper mill with no history of exposure to carbon disulfide. The most distinct difference was in the retardation of psychomotor speed, where the relative risk was 2.2 ($P = 0.02$). As a whole, 40% of the exposed and 25% of the control group showed "poor" performance, as defined according to criteria published by Tolonen (1974). These results show a clear group difference; however, the test battery has a low specificity for carbon disulfide, as could be seen from the high number of "false positive" results.

Recently, Hänninen and her co-workers increased the specificity of the test battery, reducing the number of tests on the basis of information gathered from new analytical approaches applied to results of 206 exposed and 152 unexposed men, examined in 1972. According to a multiple discriminant analysis, the most specific variables for carbon disulfide effects were those indicating retarded speed, retarded emotionality and energy, and psychomotor disturbances (Hänninen et al., 1978). Another approach, starting from test results classified as abnormal, resulted in similar conclusions (Tolonen et al., 1976). Now, the test battery can be restricted to a few rather specific tests applicable to suspected cases of poisoning that can also be used at periodic health examinations.

Analogous results concerning the depressing effects of carbon disulfide on psychological performance and behaviour have been reported by Foá et al. (1976), Gherase (1976), Schneider (1976), Tuttle et al. (1976)[a] and Hakky (1977).

Foá et al. (1976) demonstrated an exposure–effect relationship by comparing workers from 2 plants with different degrees of exposure. A relationship between exposure time and performance was demonstrated by Schneider (1976), but the role of age as a confounding factor could be excluded for 2 test variables only.

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[a] Tuttle, T. C., Wood, G. D., & Grether, C. B. (1976) Behavioral and neurological evaluation of workers exposed to carbon disulfide (CS_2). Unpublished report submitted to NIOSH (National Institute for Occupational Safety and Health) by Westinghouse Electric Corporation. Behavioral Services Center, Columbia, MD, USA, 156 pp.

From these data, it can be concluded that, at rather low exposure levels, psychological test results are almost the only way of assessing involvement of the central nervous system. Relationships may exist between psychological impairment and EEG abnormalities, but further studies are needed to clarify this point.

6.3.10.2 *Peripheral nervous system*

Many authors have studied the neuropathy and myelopathy of animals exposed to carbon disulfide (Fischer & Michalova, 1956; Higashida et al., 1959; Scheel, 1967; Frantik, 1970; Lukáš, 1973; Szendzikowski et al., 1973; Wrońska-Nofer et al., 1973; Seppäläinen & Linnoila, 1975, 1976). Destruction of the myelin sheet has been the most prominent finding, but axonal changes have also been observed. In the muscle fibres, atrophy of the denervation type occurred secondary to the polyneuropathy. Some species differences in susceptibility to carbon disulfide have been found. Cats and rabbits tolerated only low concentrations of carbon disulfide. On the other hand, polyneuropathy in rats was produced only with exposure to extremely high concentrations (1200–2400 mg/m^3). The slowing of nerve conduction velocity in the sciatic nerve in rabbits and rats preceded clinical symptoms such as clumsiness and later on, paresis. In rabbits, electromyographic abnormalities suggested the presence of myelopathy together with peripheral neuropathy (Seppäläinen & Linnoila, 1975, 1976). Neuropathological studies (Linnoila et al., 1975) showed severe morphological alterations in the lateral and anterior funiculi of the spinal cord in addition to pronounced axonal alterations in the peripheral nerves of rabbits.

Lukáš (1970, 1973) established by electromyography (EMG) that the development of neuropathy in the rat was influenced by dose, duration of exposure, physical conditions, and the nutritional state of the animal. This confirms the long-standing clinical belief that the individual constitution bears some relationship to the quantity and quality of the effects of carbon disulfide (Djurić, 1967, 1971; Djurić et al., 1973; Goto et al., 1971).

The protective effects of some substances have also been studied in animals. The addition of zinc and copper salts (Scheel, 1967; Lukáš, 1970), and of pyridoxine to the diet (Frantik, 1970; Lukáš, 1970) did not change the toxic effects of carbon disulfide but improved the biochemical consequences of the intoxication, for example by decreasing the excretion of xanthurenic acid with urine (Kujalová & Tintera, 1970). Addition of nicotinic acid (Wrońska-Nofer, 1970) provided some protection against the effects of carbon disulfide lipid metabolism. The clinical picture of carbon disulfide intoxication in man is mainly based on toxic polyneuropathy (Bashore et al., 1938; Vigiliana, 1954, 1961; Lukáš, 1969; Lukáš &

Hromadka, 1977; Milkov et al., 1970; Seppäläinen et al., 1972; Seppäläinen & Tolonen, 1974; Seppäläinen, 1977; Gilioli et al., 1977). The subjective complaints include paraesthesia, dysaesthesia, and fatiguability and diffuse pains of the lower extremities. Sometimes irritative signs are prevalent and sometimes the patients have a feeling of local hyperaesthesia, or hypersensitivity on palpation in the muscles of the lower limbs.

Distribution of the complaints is mostly symmetrical, and, objectively, there is hyporeflexia. Klimková-Deutschová (1965) pointed out the characteristic dissociation of the patellar reflex response, which is normal or increased, with a decreased or absent Achilles tendon reflex. As the neuropathy develops, changes first appear in the sensitive fibres of the lower extremities, later reaching the upper extremities. (Lukáš, 1969; Lukáš & Hromadka, 1977). Hyperaesthesia is mostly of a "sock" character, but sometimes it is also diffuse. Palpation of the nerve roots and sometimes of the whole muscle groups is painful. Today, the development of symptoms seldom reaches the stage of motor paresis and, consequently, atrophic changes (amyotrophy) are rare. The same is true of vasomotoric changes. Amyotrophy has been described in the earlier literature in the area of the triceps surae and quadriceps muscles of the legs, as well as in the small muscles of the hand, the thenar, the hypothenar, and in the interosseal muscles.

It has also been suggested that cells in the spinal cord are injured (Manu et al., 1970; Seppäläinen et al., 1972). On the other hand, disturbances in myoneural function have resulted in myastheniform signs (Seppäläinen et al., 1972).

Needle electromyography and measurement of the motor conduction velocities of peripheral nerves have proved to be sensitive methods for detecting early nerve damage, even in neurologically normal, exposed workers (Lukáš, 1969; Manu et al., 1970; Seppäläinen et al., 1972; Lilis, 1974; Seppäläinen & Tolonen, 1974; Knave et al., 1974; Thiele & Wolf 1976; Lukáš et al., 1977). The EMG abnormality most often found consists of a reduced number of motor units at maximal contraction and an increase in the duration of motor unit potentials and fibrillation. The maximum motor conduction velocities (MCV) are lower, especially in the leg nerves, and the distal latencies are prolonged. However, the most sensitive test for peripheral nervous involvement appears to be the conduction velocity of the slower fibres of the ulnar and deep peroneal nerves, and that of the H-reflex in the region of tibial nerve (Lukáš, 1969, 1977; Seppäläinen & Tolonen, 1974; Gilioli et al., 1977). In a recent epidemiological study (Seppäläinen & Tolonen, 1974) comprising 118 male viscose rayon workers and 100 control subjects from a paper mill, the most important findings were as follows: the conduction velocities in the nerves of the

exposed men were generally slower than those of the controls. The most distinct differences (all P values smaller than 0.01) were obtained for the conduction velocity of the slower fibres of the ulnar and deep peroneal nerves, the MCV of the deep peroneal and posterior tibial nerves, and the motor distal latency of both the median and ulnar nerves. The exposed group in this study was predominantly composed of clinically "well" men, exposed for a number of years (median 15) to carbon disulfide plus hydrogen sulfide concentrations[a] of about 60–190 mg/m^3 (20–60 ppm) in the 1950s, about 30–95 mg/m^3 (10–30 ppm) in the 1960s, and mainly below 60 mg/m^3 (20 ppm) during the last years. A little more than half of the men were still exposed at the time of examination, the rest were working in "clean" departments.

Different types of nervous system symptoms and findings among 51 Swedish viscose factory workers were evaluated by Knave et al. (1974). The iodine-azide test was used as a measure of exposure intensity. The comparison group consisted of 51 subjects matched for sex and age. Symptoms of peripheral nervous dysfunction (e.g., restless legs, cramps, pain, and numbness) were over-represented among workers, especially the combination of these symptoms. Only one neurological sign—namely tremor—showed a higher prevalence in the exposed than in the control group. The authors measured only the maximal MCV of the median nerve and found minor slowing in this MCV when the duration of employment was between 5 and 30 years, but not after shorter exposure.

The prognosis of carbon disulfide polyneuropathy has not been considered to be too poor. According to one follow-up study of exposed workers, electroneuromyographic abnormalities tend to ameliorate if the exposure level decreases or exposure is stopped (Seppäläinen, 1977). A tendency for repair and restitution of lost functions has also been demonstrated experimentally in animals (Lukáš, 1970; Seppäläinen & Linnoila, 1975, 1976).

However, it has been shown that, even after periods of 10–15 years without exposure, abnormal conduction velocity values may be found in workers with previous carbon disulfide poisoning or previous long-term exposure to carbon disulfide (Seppäläinen et al., 1972). This corresponds with the experience of Gilioli et al. (1977), who found the reduction in conduction velocity to be irreversible. In another study, Seppäläinen (1977) described an amelioration in the EMG findings when carbon disulfide exposure was reduced or stopped.

[a] Exposure levels in studies by Hernberg et al. (1970, 1973, 1976), Raitta et al. (1974), Tolonen (1974), Tolonen & Seppäläinen (1974), and Tolonen et al. (1975) refer to combined concentrations of carbon disulfide and hydrogen sulfide. Hydrogen sulfide concentrations were about 10% of the carbon disulfide concentrations (Hernberg et al., 1970).

6.3.11 Cardiovascular effects

A number of studies have shown that carbon disulfide causes vascular changes in various organs of experimentally exposed animals (Lewey, 1941; Guarino & Arcello, 1954; Paterni et al., 1958). In man, evidence of vascular changes caused by long-term exposure, has been accumulating since World War II. Attinger (1948) was the first to describe such changes in 5 autopsy cases. Further clinical and autopsy studies showed clearly that carbon disulfide was a vasotropic poison (Uehlinger, 1952; Attinger, 1954; Vigliani & Pernis, 1955; Crepet et al., 1956; Rechenberg, 1957; Maugeri et al., 1966a,b; Prerovska & Roth, 1968; Maugeri et al., 1971; Prerovska & Zvolsky, 1973).

According to Vigliani & Pernis (1955) the "vasculopathia sulfocarbonica" appears in 2 forms, namely in cerebral arteries causing encephalopathy, and in the renal arteries causing nephropathy and hypertension. The syndromes that follow these types of vascular damage have already been described in sections 6.2, 6.3.7, and 6.3.10.1. Autopsy studies have revealed that sclerosis is prevalent in large and middle-size arteries and hyalinization in arterioles and capillaries. These changes appear in the blood vessels of all organs but they are particularly prominent in the central nervous system and kidneys.

Vascular changes due to carbon disulfide exposure are similar to those produced with atherosclerosis due to age. Thus, the picture in older persons is confused by the influence of age. The carbon disulfide induced vasculopathy is therefore best studied in young persons with a sufficiently long exposure time. With this in mind, a joint Italian/Yugoslav team selected 104 young workers (age around 30–35 years) with more than 10 years' exposure for closer study (Maugeri, et al.., 1966a,b; Maugeri et al., 1971; Taccola et al., 1971). Of these, 28 were invalids due to carbon disulfide poisoning. Organic changes in blood vessels were discovered, mostly in the invalids, by means of cerebral rheography. The results obtained suggested progression of such changes even after the termination of exposure. Using peripheral rheography, plethysmography, and oscillography, the authors established functional vasoconstriction in the arteries of the upper and lower extremities. Organic alterations of the sclerotic type were rare and mainly appeared after prolonged exposure and in the lower extremities.

During the last 10 years or so, it has become increasingly evident that long-standing exposure to carbon disulfide promotes coronary heart disease, even under circumstances where clinical poisoning is uncommon. Of the several attempts made to connect carbon disulfide exposure with coronary heart disease, only a few have complied with necessary methodological requirements. The first such investigation was a careful

mortality study in Britain published by Tiller et al. (1968). They found a 2.5-fold excess mortality in viscose rayon workers exposed to carbon disulfide for 10 years or more, compared with that of other workers. The same study demonstrated that, in the 3 plants studied, coronary mortality was proportionally higher among workers engaged in the viscose spinning process than in other workers, men living in the locality, and the national statistics derived from the Registrar General's tables. Similar results have been obtained from Norway, where a 3-fold excess mortality from coronary heart disease was found among workers, aged 35–54 years, compared with unexposed workers in other departments (Mowé, 1971).

A prospective study that was initiated in 1967 in Finland, showed that the 5-year mortality in a cohort of 343 male viscose rayon workers exposed to about 30–95 mg/m^3 (10–30 ppm) was almost 5-fold (14 deaths compared with 3) that of an unexposed comparison cohort from a nearby paper mill. Other causes of death were evenly distributed (Hernberg et al., 1970, 1973). The incidence of nonfatal first myocardial infarctions was almost 3 times that in the comparison cohort (11 compared with 4) (Tolonen et al., 1975). In a continuation of the follow-up extending to 8 years, the cumulative incidence rate for mortality from coronary heart disease was 5.8% in the exposed group and 2.6% in the comparison group, giving a rate difference of 3.2% (Hernberg et al., 1976; Nurminen, 1976). Between the sixth and ninth years of follow-up, no further excessive mortality was observed, probably because most (81%) of the originally exposed workers were no longer exposed to carbon disulfide and also overall concentrations of carbon disulfide had decreased to less than 30 mg/m^3 (10 ppm). This positive trend was promising with regard to coronary heart disease: the prognosis of exposed workers improved with improved occupational hygienic measures and with a reduction in the length of exposure over a lifetime.

Anamnestic angina was more prevalent both in 1967–68, and at re-examination in 1972, whereas there were no great differences in coronary electrocardiographic findings (Hernberg et al., 1970; Tolonen et al., 1975) as coded by the "Minnesota Code" (Blackburn et al., 1960). These results showed that the greatest effect of carbon disulfide on coronary arteries was on the production of fatal infarctions (relative risk 4.8) followed in reducing order by all infarctions, fatal and nonfatal (relative risk 3.7), nonfatal infarctions (relative risk 2.8), angina (relative risk 2.2), and coronary ECGs (relative risk 1.4). In other words, the more serious the outcome, the greater the relative risk. The interpretations may be that exposure to carbon disulfide not only worsens the prognosis of existing coronary heart disease but increases the incidence of new cases. However, it is not certain that this mode of action operates in countries where coronary heart disease is less

common than in Finland. Coronary heart disease has a multifactorial etiology, and the pattern described above may be noticeable only when a sufficient number of other coronary risk factors are present at the same time. In fact, some other studies have shown a more distinct excess of coronary ECGs (Goto & Hotta, 1967; Cirla et al., 1972). It is possible that both dose-dependent, methodological, and even geographical factors may be responsible for the discrepancies reported so far. For example, it may be that the pattern of excess coronary heart disease differs in different populations, depending on the concomitant prevalence of other coronary risk factors such as elevated blood lipids and hypertension.

A joint analysis of the prevalence of angina pectoris, exercise ECGs, and blood pressure measurements in Finnish and Japanese workers exposed to carbon disulfide and in 2 unexposed control groups supported this view (Tolonen et al., 1976). Angina was rare and evidence of past infarction nonexistent in both exposed and unexposed Japanese men; in the Finnish exposed and unexposed groups the prevalence of angina was 15 and 10%, respectively. The prevalence of coronary ECGs was almost equal among the exposed and unexposed men in both the Japanese and the Finnish groups. Angina plus coronary ECGs as evidence for coronary heart disease occurred with a prevalence of nil for both exposed and unexposed Japanese, and 5 and 2% for the exposed and unexposed Finnish groups, respectively. The study did not yield any evidence of an excess in any of the variables examined among the exposed Japanese workers. However, a follow-up study of this group is necessary to shed more light on the possibility of excess morbidity and mortality from coronary heart disease. Vertin (1977) did not find any significant differences in coronary heart diseases, ECG changes, serum cholesterol concentrations, and arterial pressure in workers exposed to carbon disulfide concentrations of about 30–95 mg/m^3 (10–30 ppm) compared with a control group.

Carbon disulfide vasculopathy may be due to the combined action of several biochemical and physiological disturbances, namely:

(*a*) changes in lipid metabolism (section 6.3.9);

(*b*) disturbances in the coagulation mechanism (section 6.3.14);

(*c*) elevation of blood pressure (Hernberg et al., 1970; Sakurai, 1972; Tolonen et al., 1975);

(*d*) subclinical hypothyroidism (Cavalleri et al., 1971);

(*e*) a toxic effect on the myocardium, either direct or through interference with the catecholamine metabolism (Magos, 1972).

However, much work remains to elucidate the mechanism of carbon disulfide-induced atherosclerosis. In particular, coronary heart disease has a multicausal origin and is closely related to the saturated fat intake of the population. Furthermore, its incidence is influenced by a large number of

other risk factors, such as smoking, diabetes, and physical inactivity. A combination of 2 or more risk factors greatly increases the incidence. Thus, it may be postulated that carbon disulfide will only become evident as a coronary risk factor in the presence of other risk factors.

6.3.12 Carcinogenicity and mutagenicity

No reports are available that indicate any carcinogenic or mutagenic effects of carbon disulfide.

6.3.13 Teratogenic effects

Only a weak teratogenic effect appeared in rats following low-level exposure to a combination of hydrogen sulfide and carbon disulfide (Bariljak et al., 1975).

A marked impairment (increase in early embreonal mortality, reduction in fetal weight, malformations in the brain and limbs, behavioural deviation) in the prenatal development of 2 successive generations was produced in rats exposed to carbon disulfide concentrations of 100 and 200 mg/m^3 throughout the period of gestation (Tabacova et al., 1977).

6.3.14 Other effects

The literature is contradictory concerning the effects of carbon disulfide on blood coagulation. Saita & Gattoni (1957) found a slight decrease in factor VII and prothrombin in exposed workers. On the other hand, Moreo & Candura (1960) and De Nicola et al. (1962) reported hypercoagulability in the blood of experimental animals, a finding that was later confirmed in studies of exposed workers by Candura et al. (1962), Saita et al. (1964), and Danilova (1968). An increase in fibrinolysis was found by De Nicola et al. (1962) in animals suffering from acute poisoning. In contrast, Candura et al. (1962) found decreased fibrinolysis in workers exposed to carbon disulfide.

The coagulation mechanism in highly-exposed young workers in a viscose factory was studied by Visconti et al. (1966a,b,c, 1967). They found protracted coagulation, retarded production of active thromboplastin, decreases in plasminogen and in the activity of plasmin, and a decrease in antiheparinic activity in workers exposed for up to 9 years. These disturbances were most pronounced during the first years of exposure.

Visconti et al. (1966a) supposed that carbon disulfide could affect blood coagulation either directly by interfering with the system itself, or indirectly, by liver injury. Different routes of entry, differences in the level and duration of exposure and in the distribution of carbon disulfide in the organism, and also interspecies differences are probably responsible for the confusing results.

It has been reported that the glucose metabolism is disturbed by carbon disulfide both in experimental animals (rabbits) (Hara, 1958) and in exposed workers (Goto et al., 1971). There are also a few clinical studies reporting an increased occurrence of diabetes in patients suffering from severe carbon disulfide poisoning (Austoni & d'Agnolo, 1957; Finulli & Ghislandi, 1959; Ferrero, 1969). Lack of proper control groups renders the interpretation of these results difficult.

6.3.15 Interactions with other chemical compounds

The combined effects of carbon disulfide with other chemical compounds were first reported by Lazarev et al. (1965) who indicated that repeated exposure to a concentration of carbon disulfide of 3900 mg/m^3, for 2 h per day, over a period of 20–30 days considerably prolonged both the hexobarbital sleeping time and alcohol retention time in rats and mice (see also section 6.3.6).

Carbon disulfide caused reversible inhibition of the oxidative drug metabolism in rat liver endoplasmic reticulum (Bond et al., 1969; Freundt & Dreher, 1969; Freundt & Kuttner, 1969; Freundt & Henschler, 1971; Freundt, 1973; Sokal, 1973; Freundt et al., 1974b, 1975, 1976). This effect was also produced in man after exposure to a carbon disulfide concentration of about 30 mg/m^3 (10 ppm) over a 6-h period (Mack et al., 1974); the treatment led to a rapidly reversible but significant decrease in the oxidative *N*-demethylation of the analgesic, aminopyrine.

Simultaneous exposure to carbon disulfide and ethanol resulted in an increase in blood acetaldehyde in rats and man that was considered to be a consequence of the inhibition of aldehyde dehydrogenase by carbon disulfide (Freundt & Netz, 1973; Freundt & Lieberwirth, 1974; Freundt, 1974; Freundt et al., 1976). In 12 healthy male volunteers, a 50% increase in blood acetaldehyde was noted following exposure to a carbon disulfide concentration of about 60 mg/m^3 (20 ppm) for 8 h with simultaneous ingestion of ethanol in orange juice at a concentration that maintained the blood ethanol level at about 0.8%. However, no signs of an "antabuse syndrome" were observed under these experimental conditions (Freundt et al., 1976).

6.4 Diagnosis

Since all isolated effects are nonspecific, individual diagnosis becomes a matter of probability based on: (*a*) the ascertainment of exposure; (*b*) the demonstration of signs and symptoms of poisoning and the combination in which they occur; and (*c*) the exclusion of other diseases.

The changes due to carbon disulfide exposure described in sections 6.2–6.3.15 affect so many different organ-systems that, in considering the etiology of a single case, the probability of it being caused by carbon disulfide increases in proportion to the number of these signs and symptoms present. Although, in 1941, Lewey drew attention to the importance of the concomitant occurrence of different neuropsychiatric and vascular effects, as well as to their connection with the severity of the disease, there have been few, if any, studies systematically analysing the knowledge that has emerged since then. For this reason it is difficult to find quantitative data. However, carbon disulfide poisoning should always be suspected when a viscose worker presents with subjective, neurasthenic symptoms, signs of peripheral neuropathy, psychological disturbances, and vascular changes in the cerebral, coronary, renal, or peripheral systems. When exposure to toxic levels of carbon disulfide occurs, the following chronological effects can usually be expected: the appearance of neurasthenic symptoms accompanied by psychological behavioural changes; signs of peripheral nervous system involvement as shown by electromyographic changes, initially mainly in the afferent fibres but later in the motor fibres; simultaneous disturbances in the central nervous system may appear but may be more difficult to detect objectively than the lesions of the peripheral nervous system. Another early finding is a decrease in the level of serum thyroxine that is probably due to damage of the hypothalamic–hypophyseal axis (section 6.3.9). Cardiovascular damage appears after longer periods of exposure. The appearance and severity of the above-mentioned signs and symptoms are related to the level of the uptake and to the duration of exposure to carbon disulfide. The changes are also dependent on the individual constitution and health status of exposed workers.

In the differential diagnosis of true cases, atherosclerosis due to other causes should be considered including, postencephalitic or atherosclerotic Parkinsonism, brain tumours, syphilis, multiple sclerosis, and psychiatric diseases of other origins such as endogenic depression, schizophrenia, and alcoholism. Peripheral polyneuropathy should be distinguished from that due to alcoholism, diabetes, and other toxic agents.

The subclinical stage is, by definition, more difficult to identify. First, the presence of pathological symptoms and signs must be established, which

requires sensitive techniques. Second, the causal connection between an established symptom or sign and carbon disulfide exposure should be shown. Both aspects pose great difficulties because of the nonspecificity of the manifestations and their vagueness in the initial stages. So far, the only attempt to approach this problem in a systematic way has been made by Tolonen (1974).

He studied 97 men exposed to carbon disulfide in a viscose factory and 96 controls of the same age from a paper mill. The mean age was 48 years (range 33–67 years), and the mean exposure time was 15 years (range 1–27 years). The intensity of background exposure ranged from about 60 to 125 mg/m^3 (20 to 40 ppm) in the 1950s and then from about 30–95 mg/m^3 (10–30 ppm). Personal exposure data were not available. The group comprised both completely "healthy" workers as well as some partly incapacitated patients with past poisoning. About half of the men were still exposed to carbon disulfide, the rest being employed in "clean" departments. The groups underwent many examinations including: (*a*) examination of the heart (positive = history of verified myocardial infarction, and/or "Minnesota Codes" I_{1-3}, IV_{1-3}, V_{1-3}, VII_1, $VIII_3$, $XI_{1-3,5-7}$, and/or typical angina): (*b*) psychological testing (section 6.3.10.I); (*c*) measurement of the conduction velocities of 8 peripheral nerves (polyneuropathy was considered to exist when 2 or more nerves

Table 2. Prevalence (%) of coronary heart disease (CHD), delayed peripapillary circulation (EYE), polyneuropathy (PN) and behavioural symptoms (BS), their combinations in subjects in the exposed and control groups, and the differences between the groups.[a]

	Exposed ($N = 97$)	Group control ($N = 96$)	Difference = excess morbidity
Free of disease	5	31	
CHD only	4	9	−5
EYE only	19	19	0
PN only	6	6	0
BS only	7	6	1
CHD + EYE	4	4	0
CHD + PN	1	1	0
CHD + BS	1	2	−1
EYE + PN	12	5	7
EYE + BS	7	4	3
PN + BS	4	5	−1
CHD + EYE + PN	9	0	9
EYE + PN + BS	11	5	6
CHD + PN + BS	2	1	1
CHD + EYE + BS	2	2	0
CHD + EYE + PN + PS	6	0	6
Total	100	100	26

[a] From: Tolonen (1974).

showed reduced conduction velocities) and (*d*) examination of the circulation of the ocular fundus (the criterion for disturbed circulation was delayed peripapillary filling—circumferential, segmental, or both). The occurrence of isolated and combined signs is shown in Table 2.

As many as 59% of the exposed and 29% of the unexposed men were affected by more than one disorder under study but most combinations of disorders occurred more frequently in the exposed group; a combination of 3 abnormalities was 3 times more common in the exposed group than in the controls and a combination of all 4 abnormalities occurred only in the exposed group. Only 5% of the exposed subjects compared with 31% of the controls were without any abnormalities. Since disturbances in the choroidal circulation were present in all cases of excess "morbidity" (68% of the exposed, Raitta et al., 1974), it seems that this abnormality represents the earliest manifestation of carbon disulfide toxicity, at least, of those considered here.

Thus, it can be postulated that a positive diagnosis of carbon disulfide poisoning can only be made if changes in the choroidal circulation have been observed and providing that exposure has extended over 10 years or more, with an intensity of the magnitude of about 30–90 mg/m^3 (10–30 ppm). The estimated probability that a combination of findings is of occupational origin is the excess morbidity over total morbidity. The results also showed that the etiological role of carbon disulfide could be demonstrated with greater probability, the greater the number of abnormalities present at the same time.

The necessity to ascertain exposure is so obvious that it should not need to be mentioned. It should be stressed that recent experience has shown the importance of evaluating personal, as opposed to background exposure, since the former may be only weakly correlated with the latter. Personal exposure can be measured using personal samplers, or by the iodine-azide test. The latter has been claimed to discriminate particularly sensitive workers (whose test does not return to normal after 16 h away from exposure) (Graovac-Leposavić et al., 1967).

6.5 Surveillance of the Health of Exposed Workers

Considering the early manifestations of chronic carbon disulfide effects and the factors that may influence the appearance and the severity of such effects (section 6.4), the following examinations are recommended for health surveillance:

(*a*) Clinical neurological investigation;

(*b*) Electroneuromyographic (ENMG) examination wherever possible (especially the conduction velocity test, which should be carried out on several nerves);

Additional tests that may give valuable information include:

(*a*) Psychological and behavioural testing with a narrow battery of well validated tests;

(*b*) Serum thyroxine measurement repeated at least once a year;

(*c*) Blood pressure measurements;

(*d*) Electrocardiography (preferably an exercise ECG);

(*e*) Fundus photography (in some countries);

(*f*) Blood lipid pattern estimation, if the exposure level is high;

(*g*) Electroencephalography (EEG), if there are special indications;

These tests should be performed at the pre-employment examination and subsequently at regular intervals to detect early deviation from baseline values. Changes observed in the same individual over a period of time may suggest a relationship with carbon disulfide uptake.

Depending on the intensity of exposure, the iodine-azide test should be carried out from 2–12 times a year, both immediately after the work shift and the next morning. Those with positive tests should be seen by the plant physician, since a pathological test in the morning is a warning of incipient poisoning (Graovac-Leposavić et al., 1967). In addition to this, medical examinations should be made once or twice a year. They should comprise a thorough history and a neurological examination.

When suspect signs of early carbon disulfide effects appear, the worker should be removed from exposure to a "clean" job. In the light of the new findings concerning coronary heart disease, the removal of workers who develop coronary risk factors, such as hypertension, hypercholesterolaemia, and ECG changes may be indicated, irrespective of their etiology. In some plants, there is the practice of regular periods of work in a clean atmosphere, e.g., every sixth month, or of extra vacations in the winter.

Some authors believe in the importance of the diet of exposed workers. However, the protective effect of various diets and supplements for man remains unclear. Scheel (1965) claimed that addition of zinc and copper salts to the diet of exposed rats had a protective effect against carbon disulfide exposures. A diet poor in proteins, especially amino acids containing sulfur, but enriched in vitamin B_6 and glutaminic acid was suggested by Agronovskij & Goloscapov (1972). Lukáš (1973) established that rats on an "optimal" diet were more resistant to the effects of carbon disulfide than rats on a normal diet. In the first group, the signs of intoxication appeared after a longer time and the effects were less marked than in the second group.

At the present time, the only recommendation that can be given in the case of man is that workers should be provided with a diet containing sufficient amounts of energy foods to provide the required joules, proteins, vitamins, and trace elements. This recommendation is of particular importance in countries where such dietary requirements are not necessarily fulfilled normally. However, basing the preventive programme mainly on diets or drugs should be condemned, since the fundamental question is that of technical improvements.

6.6 Contraindications for Exposure to Carbon Disulfide

An inborn error of metabolism manifesting itself as an abnormal iodine-azide reaction in subjects working under conditions of high or moderate carbon disulfide exposure (less than 50 mg/m^3) should be considered an absolute contraindication for exposure.

Other contraindications for working in an environment containing carbon disulfide include those common to all other toxic exposures such as youth (below 18 years), pregnancy, concomitant chronic disease such as psychiatric neurological, cardiac, renal, and pulmonary diseases, and any condition that prevents the use of respirators, etc.

In addition, contraindications based on the specific toxicity of carbon disulfide include diseases of the metabolic system, such as liver disease and endocrine disorders. Any neurological or psychiatric disorder is also a contraindication, including vegetative dystony and psychic lability. A history of gastritis and peptic ulcer is a relative contraindication, depending, for instance, on whether or not there will be shift work and on the intensity of exposure. Recently, attention has been focused on to what extent the presence of coronary risk factors should be regarded as a contraindication; no strict recommendations can be given, but as a general rule the presence of several of these in an individual, or alternatively strongly abnormal values for one risk factor, should be regarded as contraindications (the strongest coronary risk factors apart from age itself are elevated serum cholesterol or triglycerides, heavy cigarette smoking, hypertension, and diabetes). In the evaluation of these and other contraindications, the exposure intensity and hygienic conditions should, of course, be taken into consideration.

The employment of women in work places with carbon disulfide exposure is a special problem.

Considering the studies referred to in section 6.3.9, it is advisable to exclude pregnant women from carbon disulfide exposure. The same is true for lactating women and for those with expressed disturbances of menstruation and habitual abortion.

7. EXPOSURE–EFFECT AND EXPOSURE–RESPONSE RELATIONSHIPS

7.1 Validity of Exposure Data

In general, valid exposure data are available only from experimental studies on animals. Almost all epidemiological studies have failed to document the exposure levels pertinent to the effects studied. There is a universal lack of retrospective exposure data that usually renders the assessment of the relationship between chronic effects and the exposure levels responsible for their occurrence impracticable. Furthermore, even when exposure data are available, they often consist of occasional short-time measurements from fixed sites that are not necessarily representative of the workers' exposure. It is, therefore, extremely difficult, if not impossible, to establish exposure–effect or exposure–response curves for carbon disulfide, based on epidemiological evidence. Even the relation of isolated findings reported in the literature, to given exposure levels is difficult. Thus, the attempts in this document, to relate the intensity of exposure to the intensity and frequency of effects must be regarded with caution.

7.2 Experimental Data

7.2.1 Acute animal exposure

Acute exposure to carbon disulfide in animal experiments by inhalation or by intramuscular or intraperitoneal injection has provided information regarding the mechanism of carbon disulfide toxicity, but it is difficult to apply this information to the industrial exposure of man.

7.2.2 Long-term animal exposure

Several experiments on the inhalation of carbon disulfide have been performed on different types of animals. In most of these studies, exposure was to carbon disulfide only, but in a few, a combination of carbon disulfide and hydrogen sulfide was used.

The concentrations of carbon disulfide ranged from 0.1–2330 mg/m^3 and those of hydrogen sulfide, from 0.1–140 mg/m^3; the exposure periods ranged from 30 min per day to 6 h per day for up to 15 months.

The reactions to such exposures included increased mortality, teratogenic changes, testicular lesions, aspermatogenesis, engorged blood vessels, weakness, paralysis, lethargy, weight changes, metabolic changes, behavioural changes; sometimes there were no observed effects. Some of the effects resembled lesions found in exposed workers; others did not bear any relationship to those arising from human exposure (Wakatsuki & Higashikawa, 1959; Goldberg et al., 1964; Minden et al., 1967; Yaroslavski, 1969; Frantik, 1970; Gondzik, 1971; Misiakiewicz et al., 1972; Szendzikowski et al., 1973; Bariljak et al., 1975; Seppäläinen & Linnoila, 1976; Tabacova et al., 1977). The considerable differences in ranges of concentrations and periods of exposure used in these experiments make conclusions regarding exposure–effect and exposure–response curves impossible. This regrettable situation emphasizes the need for international coordination of toxicological experiments to make comprehensive scientific evaluation possible.

7.3 Epidemiological Data

All studies so far reported have been from the viscose rayon industry, where exposure to carbon disulfide occurs together with exposure to hydrogen sulfide. However, generally, the levels of carbon disulfide are at least one order of magnitude higher than those of hydrogen sulfide, and most authors have attributed the health effects found to carbon disulfide rather than to hydrogen sulfide exposure.

Only some of the various effects reviewed in section 6 can be related to exposure levels. The following section contains a brief review of exposure–effect and exposure–response data for neurological, cardiovascular, ocular, and gonadal effects.

7.3.1 Neurological and behavioural effects

Severe acute neurological effects such as psychosis and paralysis occur when exposure exceeds 1500–3000 mg/m^3 (500–1000 ppm) (Vigliani, 1954). Chronic encephalopathy may develop with long-standing exposure to 150 mg/m^3 (50 ppm) or more (Vigliani, 1954). More subtle neurological changes, detectable by neurophysiological examination or psychological testing, have been reported at lower concentrations. For example, slowing of nerve conduction velocities and prolonged distal latencies of several nerves have been found among viscose rayon workers with a median exposure time of 15 years to combined concentrations of carbon disulfide and hydrogen sulfide of 60–190 mg/m^3 (20–60 ppm) in the 1950s, 30–95

mg/m³ (10–30 ppm) in the 1960s, and mainly below 60 mg/m³ (20 ppm) during the years preceding the examination (Seppäläinen & Tolonen, 1974). The same workers were also studied for psychological performance (Tolonen, 1974). The most distinct difference compared with a control group was found in the retardation of psychomotor speed. As a whole, "poor" performance, as defined by Tolonen (1974), occurred 1.6 times more frequently among the exposed workers. These results suggest that concentrations around 60–90 mg/m³ (20–30 ppm) can produce psychological disturbances. In an indirect way, Tuttle et al.[a] corroborated this view by being able to relate behavioural test scores to other indices of neurological health, thought to occur under similar exposure conditions, but because no exposure data were available, their findings are not directly applicable in the exposure–effect sense.

According to Martynova et al. (1976), an excess of functional nervous disorders was found among 108 workers exposed to carbon disulfide concentrations about 8–11 mg/m³ (maximum approximately 20–25 mg/m³), for 10–15 years, compared with 390 control subjects. For example, sensory polyneuritis was much more frequent and the threshold for pain was significantly higher in the exposed group.

These studies indicate that background concentrations below about 60 mg/m³ (20 ppm) may cause neurological dysfunction.

7.3.2 Cardiovascular effects

Severe vascular effects manifesting themselves as vasculoencephalopathy and renal atherosclerosis developed with long-term exposure to carbon disulfide concentrations exceeding 150–300 mg/m³ (50–100 ppm) (Vigliani, 1954; Nofer et al., 1961). Excess incidence of coronary heart disease has been reported with longstanding exposure to concentrations averaging 30–125 mg/m³ (10–40 ppm) (Hernberg et al., 1970, 1973, Tolonen et al., 1975). The mortality rate from coronary heart disease appeared to be most affected while the incidence of milder manifestations such as angina and ECG-changes was less influenced. In fact, most studies, published so far, have failed to reveal any difference in the prevalence of ECG-findings between exposed and unexposed workers (Tolonen et al., 1976).

Quite recently, Vertin (1977) reported no difference between the incidence of coronary heart disease found in control subjects and that in workers exposed to about 30–95 mg/m³ (10–30 ppm) suggesting a no-observed effect level for coronary heart disease in this range. This finding

[a] Tuttle et al., 1976. Unpublished report. (See footnote to section 6.3.10.1.)

does not necessarily contradict those referred to above; possibly, the true exposure levels responsible for the excess coronary heart disease in the Finnish studies were higher than those in Vertin's study. It is probable that, in general, differences in actual personal exposure levels in the studies— not necessarily those levels measured and reported— account for seeming discrepancies in results and that exposure data are inadequate in most published studies.

Differences in blood pressure have been reported by Hernberg et al. (1970) and Tolonen et al. (1975) between workers exposed to a carbon disulfide concentration of about 60 mg/m^3 (20 ppm) and unexposed subjects, and by Martynova et al. (1976) in workers exposed for 10–15 years to concentrations of about 10 mg/m^3. These findings indicate that effects upon the vascular system begin at low exposure levels.

7.3.3 Ophthalmological effects

Among Japanese workers, the occurrence of retinal microaneurysms was related to the duration of exposure (Sugimoto et al., 1976). The

Table 3. Some exposure–effect and exposure–response relationships for long-term exposure of man to carbon disulfide.

Concentration (mg/m^3)	Exposure time (years)	Symptoms & signs	Reference
10	5–10	Blood progesterone depressed, estriol increased, irregular menstruation;	Vasiljeva (1973)
10	10–15	Sensory polyneuritis, increased pain threshold;	Martynova et al. (1976)
30	>3	Spontaneous abortions twice as common and premature births 3 times as common as in controls;	Petrov (1969)
30–120	>10	Coronary mortality about 5 times that in controls, life expectancy decreased 0.9–2.1 years depending on age; nonfatal infarctions 2.8 times more frequent than in controls; angina pectoris about twice as prevalent as in controls; slightly higher systolic and diastolic blood pressure than in controls;	Tolonen et al. (1975) Hernberg et al. (1973) Nurminen (1976) Hernberg et al. (1970)
30–120	>6	Peripheral nervous and CNS dysfunction, conduction velocities slowed, psychological changes;	Seppäläinen & Tolonen (1974); Tolonen (1974)
100–140	2–12	Decrease of testosterone and gonadotrophin LH in urine;	Cavalleri et al. (1970)
200–500	1–9	Ophthalmic pressure 18.4/14.7 vs 15.3/11.6 kPa (138/110 vs 115/87 mmHg) in controls;	Maugeri et al. (1966, 1967)
500–2500	0.5	Polyneuritis, myopathy acute psychoses	Vigliani (1946)

exposure levels in earlier Japanese studies were not reported; in present studies they are probably of the order of 60 mg/m^3 (20 ppm). The findings of retinal microaneurysms appears to be confined to Japanese workers, since, according to a recent joint study, no such effect could be demonstrated in Finns (Sugimoto et al., 1977). In contrast, Finnish workers showed delayed peripapillary filling and wider calibre of retinal arteries compared with control subjects (Raitta et al., 1974). Exposure conditions under which these changes occurred are described in section 6.3.2 and indicate that haemodynamic changes in the ocular circulation are induced as early as coronary effects.

7.3.4 Gonadal effects

The results of Vasiljeva (1973), Petrov (1969), and Finkova et al. (1973) suggest that carbon disulfide concentrations below 10 mg/m^3 (3 ppm) may cause disturbances in the ovarian function of young females, resulting in menstrual disorders, pregnancy complications, and spontaneous abortions. Given that the exposure measurements reported are comparable with those of other studies, it would seem that these would be the earliest detectable type of effects in human beings.

A summary of the most relevant exposure–effect and exposure–response findings is given in Table 3.

8. CONTROL OF EXPOSURE IN THE VISCOSE INDUSTRY

Technical and administrative measures for the protection of the health of workers exposed to carbon disulfide in the production of viscose rayon include:

—exchange of production methods (substitution or elimination);

—enclosure and local exhaust ventilation of the technological process;

—dilution (general) ventilation of the work room;

—isolated and well-ventilated rooms for process control operators and for rest periods;

—use of personal respiratory protective equipment under certain hazardous circumstances and,

—rotation of workers periodically to areas free from carbon disulfide exposure.

New developments such as the SINI viscose process make it possible to reduce the total consumption of carbon disulfide to 70–80% of that used in conventional processes (Sihtola, 1976). Occupational health aspects must be taken into consideration at the planning stage in the construction of new plants.

Enclosure of processes and machines is the second most effective means of technical prevention. This technique should be applied in the sulfidizing process and for spinning and washing machines. Possible leakages in closed systems should be controlled by gas detectors. The air removed from the processes by the exhaust ventilation should be transported to a recovery system. The benefits of such a system are both economic, since the plant has an interest in the recovery of useful material, and hygienic, as the possibility of the pollution of both the working rooms and the environment around the factory is reduced. The air removed by exhaust ventilation is compensated with pure air, which is brought to working sites by ventilation systems.

It is not possible to protect the workers in all situations by ventilation systems alone. In certain circumstances, the workers may be exposed to very high concentrations of carbon disulfide, in which case respiratory protective devices must be used. The type of respirator may vary from a chemical cartridge (organic vapour) respirator, used for low concentrations, to supplied air or self-contained breathing devices for very high concentrations. It is also important to provide special isolated rooms with a slightly positive pressure, compared with the work area contaminated with carbon disulfide, for process control workers and for rest pauses.

Another factor of concern in the control of exposure and uptake of carbon disulfide involves skin absorption resulting from direct contact with

the liquid. Where workers may come into contact with liquid carbon disulfide, appropriate protective clothing, such as synthetic rubber gloves and goggles or face shields, should be worn.

If carbon disulfide is spilled, potential sources of ignition should be eliminated immediately, spark-proof ventilation provided, and the spill cleaned up. A small spill should generally be allowed to evaporate under conditions of good air circulation. However, large spills should be covered with water and flushed into a retention basin under a water layer. Carbon disulfide should not be drained into a sewer system because of the possibility of an explosion.

In addition to these control methods, data obtained through the biological monitoring of exposed workers can be used to determine excessive uptake situations that require additional control measures. The procedure for biological monitoring is discussed in section 6.5.

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PRODUCTION OF VISCOSE AND ITS END-PRODUCTS

The technological process of viscose rayon production, which is schematically presented in Annex I Fig. 1, can briefly be described in the following way:

(*a*) Cellulose pulp arrives at the factory in the form of sheets which are placed in a hydraulic press or pulverized and steeped in a solution of caustic soda to form alkali cellulose;

(*b*) the alkali cellulose is shredded to form crumbs to facilitate aging and xanthation;

(*c*) after storage in aging tanks until the right level of polymerization has been reached, the crumbs are placed in mechanical churns;

(*d*) in a separate operation, sulfur is melted and poured onto glowing charcoal where it reacts to give carbon disulfide. The liquid carbon disulfide is stored in special tanks that are protected against flames, static electricity, and heat;

(*e*) the liquid carbon disulfide, which is gradually metered into the mechanical churns, reacts with the alkali cellulose to form orange crumbs consisting of colourless cellulose xanthate and orange sodium trithiocarbonate (Na_2CS_3);

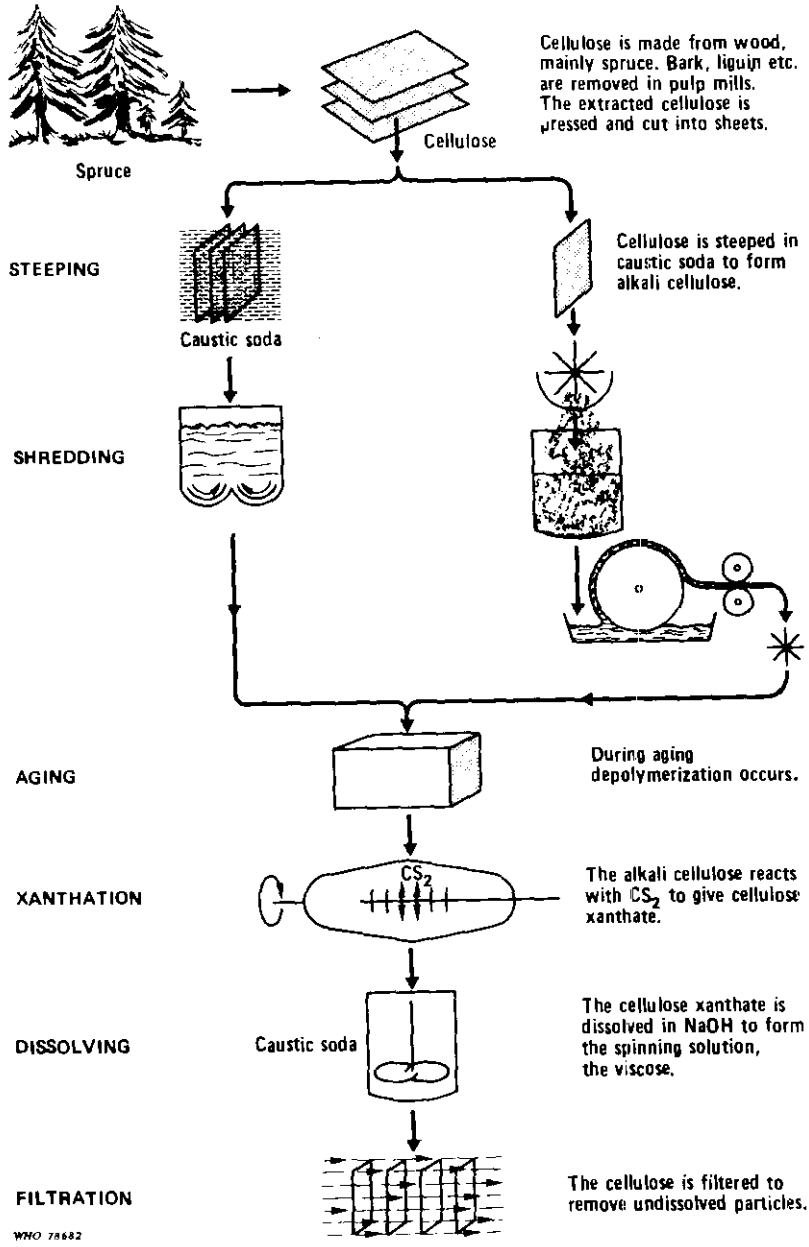
(*f*) these crumbs are dissolved in caustic soda solution to give a viscose solution;

(*g*) the viscose is stored in aging tanks, filtered, de-aerated, and then pumped into the spinning tanks where it is forced through spinnerets that are submerged in a solution of sulfuric acid (H_2SO_4) and sodium and zinc sulfates (Na_2SO_4–$ZnSO_4$). Filaments are formed by coagulation of the viscose when partial decomposition of the cellulose xanthate and the trithiocarbonate takes place, according to the reactions:

$$(1)\ ROC\overset{S}{\underset{SNa}{}} + H_2SO_4 - ROH + NaHSO_4 + CS_2$$

$$(2)\ Na_2CS_3 + H_2SO_4 - H_2S + CS_2 + Na_2SO_4$$

During this process, considerable quantities of carbon disulfide and hydrogen sulfide vapours are liberated representing a danger to the exposed workers. It is important that reaction (2) should proceed much more quickly than reaction (1) during spinning, so that practically all the hydrogen sulfide is already formed in the spinning bath or immediately over it, and the part of the carbon disulfide that is supplied by the xanthate is mainly freed outside the spinning bath in the acid yarn and/or in further treatments. The quantities of carbon disulfide and hydrogen sulfide vapours



Annex I. Fig. 1. The production of viscose rayon yarn and staple fibre.

that are liberated depend on the process and the end-use of the rayon product.

The following products may be produced from viscose: *rayon filament textile yarn* used in the textile industry in linings and furniture fabrics; *rayon filament tire yarn* used as reinforcing material in the carcass and belt of tires; *rayon staple fibre* combined in textile fabrics with natural or synthetic fibres, such as cotton or polyester; and *Cellophane film*, used for packaging.

On leaving the spinning bath, *textile rayon yarn* may be:

(*a*) wound up on acid spools on the spinning machine above the spinning bath;

(*b*) formed into a cylindrical acid cake in a centrifugal pot also incorporated in the spinning machine; or

(*c*) continuously transported through the regeneration, washing, and drying treatments and then wound up as the finished product.

During spinning, the spinning machines are more or less hermetically sealed. However, during doffing or when filament breaks occur, the worker must open the "windows" or covers. At such times, hydrogen sulfide and carbon disulfide vapours escape into the air. All hydrogen sulfide is formed in the spinning bath or immediately over it. Most of the carbon disulfide will be absorbed in the acid spool or cake and either be retained for a long time or be immediately freed in a hot acid bath. Consequently, hydrogen sulfide will mainly be found in the atmosphere of the machine and the acid baths, whereas carbon disulfide also occurs in the departments where the acid spools and cakes undergo further treatment (storage room, washing and drying departments). In spool spinning, the worker has to lean over the spinning bath to perform the doffing and spinning-in operations. In cake spinning, doffing takes place either at the front of the machine, under conditions that are roughly the same as for spool spinning, or at the rear of the machine, where the worker is not forced to breathe in the machine atmosphere.

Approximately 50% of the quantity of carbon disulfide that was originally added is present in the spool and is recovered by steaming. The cake contains less carbon disulfide because the centrifugal, motion of the pot removes a certain amount.

Tire yarn is mostly spun in glass tubes, where the viscose is in direct contact with the spinning bath. The bath acid drains to the sealed spinning tanks via return pipes and the yarn is run through a hot acid bath, where the xanthate is largely decomposed. This second hot acid bath may either be incorporated in the spinning machine or installed outside it. In both cases the concentration of carbon disulfide over this bath is high and, when a yarn breaks, the worker may be exposed to the vapours.

After leaving the hot acid bath, the yarn is either (*a*) wound on large acid spools; (*b*) made into cakes in centrifugal pots or (*c*) run through washing and drying sections.

Staple fibre, like textile filament yarn, is mostly spun in an open bath. However, hydrogen sulfide and carbon disulfide concentrations are much higher, because of the large amounts of viscose used per unit time and per spinning position. The thick tow is treated in a separate sealed hot-acid bath (as in tire yarn spinning) for further regeneration and large amounts of carbon disulfide are freed in the process. After this stage, the cable is cut and more carbon disulfide is emitted. The staple fibre is then washed and dried continuously and carbon disulfide emissions are much lower.

Cellophane casting takes place on a continuous machine. The sheet is cast in an open casting bath, like the spinning bath in textile filament spinning. The Cellophane sheet then passes through a number of baths in which decomposition, washing, bleaching, and drying take place. In Cellophane casting, large quantities of viscose are pressed into relatively small acid and second baths. As a result, hydrogen sulfide and carbon disulfide emissions are very high over a relatively small surface area.

The following data and Annex 1 Table 1 give some insight into the emissions of hydrogen sulfide and carbon disulfide in the different processes:

For every kg of yarn, staple fibre, or Cellophane, some 10–12 kg of viscose is fed into the spinning or casting bath.

1 kg of viscose will give approximately: 20–30 g CS_2

4–6 g H_2S

(i.e., about 5 times more CS_2 than H_2S)

Viscose inputs in the spinning or casting machine per hour per position are:

textile yarn	0.6–1.0 kg
tire yarn	10–12 kg
staple fibre	70/100 kg
Cellophane	1800–2000 kg

Total amounts of vapours and gases (in grams) that can be liberated per hour per position are:

	CS_2	H_2S
textile yarn	20–25	3–5
tire yarn	225–250	40–50
staple fibre	1000–1500	200–300
Cellophane	38 000–42 000	9000–10 000

Annex 1. Table 1. Percentage emissions of carbon disulfide and hydrogen sulfide during the formation of viscose products.

	Acid bath tanks	Spinning machine over first and second baths	In the spool, cake, tow, or Cellophane after the baths	
textile yarn	35	55	10	H_2S
		25	65	CS_2
tire yarn	15	5–55	15	H_2S
			25	CS_2
staple fibre	45	40	15	H_2S
	8	12–45	35	CS_2
Cellophane	15	70	15	H_2S
	25	55	20	CS_2

Annex II

MAXIMUM PERMISSIBLE CONCENTRATIONS FOR CARBON DISULFIDE IN DIFFERENT COUNTRIES

Chronic manifest poisoning can be prevented in the viscose rayon industry by maintaining the carbon disulfide concentrations below 60 mg/m^3 (20 ppm). However, recent studies have shown that gynaecological cardiovascular, neurological, and neurophysiological effects can still be detected under such conditions (sections 6.3.9, 6.3.10, 6.3.11, 7.3). It appears that a time-weighted average (TWA) of 30 mg/m^3 (10 ppm) is the lowest level at which most of these effects can be found. However, it has been reported in some studies from the USSR that gynaecological, cardiovascular, and neurological disorders may occur at even lower levels. It seems possible that most toxic effects could be prevented by keeping carbon disulfide levels, expressed as background TWAs, below 30 mg/m^3 (10 ppm). The levels for personal exposure may prove to be different but too few data are available, at present, to make any definite statements.

If the effect is severe, as in the case of coronary deaths, it is prudent to apply a safety margin for that effect. The need for such a safety margin must be considered separately in each case. Both, the new NIOSH recommendation (NIOSH, 1977) and the USSR maximum allowable concentration (MAC) value include safety margins. Most other countries have not yet considered it necessary or practically feasible to adapt safety margins. Table 1 in this annex presents permissible exposure levels for a number of countries.

Based on results of studies on man and animals, the USSR has adopted

Annex II. Table 1 Maximum permissible concentrations in various countries. If not otherw stated, the figures represent TWAs.

Country	ppm	mg/^{3}
Czechoslovakia (1963)		30
Egypt (1974)		30
Finland (1972)		30
German Democratic Republic (1971)		50
Germany, Federal Republic of (1975)	10	30
Hungary		20
Japan (1974)	10	30
Poland (1976)		25
Sweden (1975)	10	30
Switzerland (1971)	10	30
United Kingdom	10	30
USA (1973)	20	60
	100 (MAC)	300 (MAC)
USSR (1976)		1 (MAC)
Yugoslavia (1971)	15	50 (MAC)

an MAC value of 1 mg/m^3. Measurements of carbon disulfide conce trations were made during the last 5 years of exposure on workers expo to 10 mg/m^3 for 10–15 years. No significant changes in the wo environment had reportedly occurred during the entire exposure period. The workers showed neurological, cardiovascular and gynaecologic disorders. (Petrov, 1969; Vasiljeva, 1973; Martynova et al., 1976). Anim exposed to 100 and 10 mg/m^3, respectively, showed several adverse effe while only those exposed to 1 mg/m^3 were free from symptoms.

The Federal Republic of Germany has adopted a level of 30 mg/m "because at 60 mg/m^3 level the liver oxygenesis was inhibited an between 30–60 mg/m^3 of longstanding exposure, coronary heart disease hypertension, psychological and neurophysiological disturbances can occur" (Freundt, 1975).

In the USA, NIOSH (1977) has recommended a standard of 3 mg/m (1 ppm) as a 10-h TWA concentration during a 40-h working week. A lev of 30 mg/m^3 (10 ppm) for a 15-minute sampling period is recommended t avoid acute toxicity. NIOSH based its choice of levels on the probabilit of excess coronary deaths, and applied a safety factor of 10 to the lowe concentration thought to be associated with such cardiovascular disorders.

It should be stressed that the background concentration does not reflec personal exposure, which may be considerably higher. Therefore, the use a personal sampler is recommended for the assessment of actual uptake carbon disulfide by individual workers, accompanied by the use of t iodine-azide test. As already suggested, it may well be that such experienc will create a need for expressing maximum permissible concentrations in terms of personal exposure instead of background exposure.