Carbon disulphide

Health-based recommended occupational exposure limit

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Bij brief van 3 december 1993, nr. DGV/BMO U-932542, verzocht de toenmalige staatssecretaris van Welzijn, Volksgezondheid en Cultuur namens de minister van Sociale Zaken en Werkgelegenheid om advies uit te brengen over gezondheidskundige advieswaarden van stoffen ten behoeve van de bescherming van beroepsmatig aan die stoffen blootgestelden.

Per 1 januari 1994 heb ik daartoe een commissie ingesteld die de werkzaamheden voortzet van de Werkgroep van Deskundigen (WGD), een door de minister ingestelde adviescommissie van de Directeur-generaal van de Arbeid die voorheen deze advisering verzorgde.

De bedoelde commissie heeft inmiddels een advies over Zwavelkoolstof opgesteld. Ik bied u dat advies, gehoord de Beraadsgroep Toxicologie en Ecologie van de Gezondheidsraad, hierbij aan.

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Report of the Dutch Expert Committee on Occupational Standards, a committee of the Health Council of the Netherlands

To

The Minister for Welfare, Health and Cultural Affairs

The Minister for Social Affiars and Employment

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Samenvatting en advieswaarde

1 Vraagstelling

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid beveelt de Gezondheidsraad gezondheidskundige advieswaarden aan voor beroepsmatige blootstelling aan toxische stoffen in de lucht op de werkplek. Deze aanbevelingen worden opgesteld door de Commissie WGD van de Raad, de opvolger van de zogeheten Werkgroep van Deskundigen. Zij vormen de eerste stap in een drietrapsprocedure die moet leiden tot wettelijke grenswaarden (MAC-waarden).

In het voorliggende advies bespreekt de commissie de gevolgen van blootstelling aan zwavelkoolstof en beveelt zij een gezondheidskundige advieswaarde voor die stof aan. Haar conclusies zijn gebaseerd op wetenschappelijke publikaties die vóór 1992 zijn verschenen.

2 Fysische en chemische eigenschappen

Zwavelkoolstof is een kleurloze, nagenoeg reukloze, vluchtige en uiterst brandbare vloeistof. De fysische en chemisch eigenschappen zijn vermeld in hoofdstuk 2.

3 Monitoring

Voor het meten van zwavelkoolstof in de lucht op de werkplek hebben het Nederlands Normalisatie-instituut, het National Institute for Occupational Safety and Health in de

VS (NIOSH) en de Health and Safety Excutive in Groot-Brittanië (HSE) methoden beschreven die zijn gebaseerd op adsorptie aan actieve kool en op gaschromatografische analyse. Voor het vaststellen van de blootstelling aan zwavelkoolstof is daarnaast is persoonlijke bemonstering met passieve dosimeters mogelijk, waarbij kwantificering geschiedt door middel van een colorimetrische bepaling. Biologische monitoring kan het best worden uitgevoerd door met een HPLC-methode de concentratie van 4-thiothiazolidine-4-carbonzuur (TTCA) te meten in urine.

4 Grenswaarden

In Nederland geldt voor blootstelling aan zwavelkoolstof een grenswaarde voor de over 8 uur gemiddelde concentratie in de lucht van 60 mg/m^3 (20 ppm). In Zweden wordt een norm van 16 mg/m^3 (5 ppm) gehanteerd en in Duitsland, Groot-Brittannië en de VS (ACGIH) een limietwaarde van 30 mg/m^3 (10 ppm).

De American Conference of Governmental and Industrial Hygienists (ACGIH) heeft als biologische limietwaarde aanvaard: 5 mg TTCA per g creatinine, gemeten in urine die is verzameld aan het einde van de werktijd. In Duitsland is de overeenkomstige norm 8 mg TTCA per liter urine (verzameld aan het einde van de werktijd).

5 Toxicokinetiek

Bij inhalatoire blootstelling blijft gedurende de eerste twee uur 70 tot 80 procent in het lichaam achter. Deze retentie neemt vervolgens af tot 15 tot 45 procent, als een evenwichtssituatie is bereikt.

Zwavelkoolstof in vloeibare vorm kan via de huid in het lichaam worden opgenomen. Bij vrijwilligers die hun handen hadden gedompeld in verdunde zwavelkoolstof, werden penetratiesnelheden berekend die varieerden van 0,23 tot 0,79 mg.cm^{-2}.h^{-1}. In proefdieren blijkt zwavelkoolstof in het bloed voor het merendeel te zijn gekoppeld aan rode bloedcellen en te circuleren in een vrije en in een gebonden vorm. De vrije vorm verdwijnt snel, maar de gebonden vorm hoopt zich op. Zwavelkoolstof en zijn metabolieten zijn aangetoond in vele organen en weefsels van proefdieren, maar vooral in vetweefsel, de lever en de nieren. Via de placenta kan de verbinding worden opgenomen door embryo en foetus. Een tiende tot een derde van de in het lichaam opgenomen hoeveelheid zwavelkoolstof wordt onveranderd uitgeademd. Minder dan 10% verlaat het lichaam via de urine. De resterende 70 tot 90 procent wordt omgezet in de lever of reageert met aminozuren, glutathion of cysteïne tot een verscheidenheid aan verbindingen, waaronder TTCA.

6 Effecten

Zowel bij mensen als bij proefdieren kan blootstelling aan zwavelkoolstof resulteren in een brede scala aan effecten: neurologische, cardiovasculaire, endocrinologische, reproduktietoxische en effecten op de ogen en de ademhalingsorganen. Bij werkers in een Nederlandse fabriek die langdurig waren blootgesteld aan concentraties van ongeveer 22 mg/m^3 (7 ppm), zijn neurofysiologische afwijkingen gevonden. Een ander onderzoek in dezelfde fabriek leidde tot de conclusie, dat expositie aan zwavelkoolstof de kans om te overlijden ten gevolge van een hartaandoening vergroot. De sterfte aan kanker was niet verhoogd. Er is geen onderzoek uitgevoerd met proefdieren naar de kankerverwekkende eigenschappen van zwavelkoolstof. De resultaten van tests op mutageniteit laten geen definitieve conclusies toe. Bij konijnen die waren blootgesteld aan concentraties tot 930 mg/m^3 (300 ppm), zijn geen reproduktietoxische effecten gevonden. De uitkomsten van onderzoekingen met ratten naar dergelijke effecten lijken strijdig; als gevolg van methodologische verschillen zijn deze experimenten echter moeilijk onderling te vergelijken en is een definitief oordeel niet mogelijk. Onderzoek bij vrouwen wijst op mogelijke effecten op menstruatie en zwangerschap; de gebrekkige verslaglegging van dit onderzoek laat het vaststellen van dosis-effectrelaties en geen-effectniveaus niet toe.

7 Gezondheidskundige advieswaarde

De Commissie WGD stelt een gezondheidskundige advieswaarde voor van 3 mg/m^3 (1 ppm), in de vorm van een over 8 uur gemiddelde concentratie van zwavelkoolstof in de lucht (8-uur tgg). Zij baseert deze waarde op Nederlands onderzoek waaruit bleek dat langdurige blootstelling aan concentraties van ongeveer 22 mg/m^3 (7 ppm) leidt tot ongewenste effecten op het zenuwstelsel en een verhoogde kans om te overlijden aan hartaandoeningen. Aangezien zwavelkoolstof, als vloeistof, via de huid in belangrijke mate kan bijdragen aan de hoeveelheid van de stof in het lichaam, beveelt de commissie een 'H-notitie' aan.

Executive summary

1 The problem

Upon request by the Minister of Welfare, Health and Culture and the Minister of Social Affairs and Employment the Health Council of the Netherlands recommends health based occupational exposure limits for the concentration of toxic substances in the air at the workplace. These recommendations are made by the Dutch Expert Committee on Occupational Standards, a committee of the Health Council. It constitutes the first step in a three-stage procedure that leads to legally binding limit values (MAC-values).

In the present report the committee discusses the effects of exposure to carbon disulphide and recommends a health based occupational exposure limit for this substance. The committee's conclusions are based on scientific publications from prior to 1992.

2 Physical and chemical properties

Carbon disulphide is a colourless, almost odourless, volatile and extremely inflammable liquid. The physical and chemical properties are described in Chapter 2.

3 Monitoring

The Standardisation (Normalisatie) Institute of the Netherlands, the National Institute for Occupational Safety and Health of the US (NIOSH) and the Health and Safety Executive of Great Britain (HSE) have described methods for the measurement of carbon disulphide in the air of the workplace. These methods are based on adsorption on activated charcoal and on gas chromatography. Exposure to carbon disulphide can be evaluated by using individual sampling and passive dosimetry with calorimetric quantification. Biological monitoring can best be performed by HPLC measurement of the urinary concentration of 4-thiothiazolidine-4-carbonic acid (TTCA).

4 Limit values

In The Netherlands the exposure limit for carbon disulphide is an average concentration of 60 mg/m^3 (20 ppm) in the air over a period of 8 hours. A limit value of 16 mg/m^3 (5 ppm) is used in Sweden and one of 30 mg/m^3 (10 ppm) in Germany, Great Britain and the U.S.

The American Conference of Governmental and Industrial Hygienists (ACGIH) has accepted as biological limit value 5 mg TTCA per g creatinine measured in urine collected at the end of the work day. In Germany the equivalent norm is 8 mg TTCA per litre urine collected at the end of the work day.

5 Toxicokinetics

Upon exposure by inhalation 70 to 80 percent is retained by the body during the first two hours. This retention declines subsequently to 15 to 45 percent as equilibrium is approached.

Carbon disulphide can be absorbed as a liquid through the skin. Penetration velocities varying from 0.23 to 0.79 mg.cm^{-2}.h^{-1} were calculated for volunteers who had immersed their hands in dilute carbon disulphide. In experimental animals carbon disulphide is largely bound to erythrocytes and circulates in both free and bound form. The free form disappears rapidly, but the bound form is accumulated. Carbon disulphide and its metabolites have been demonstrated in several organs and tissues of experimental animals, but particularly in adipose tissue, liver and kidney. Carbon disulphide can be taken up by the embryo and the foetus via the placenta. One tenth to one third of the amount of carbon disulphide taken up is expired unchanged. Less than 10% is excreted via the urine. The remaining 70 to 90 percent is metabolised in the

liver or reacts with amino acids, glutathione or cysteine to form a variety of compounds, among them TTCA.

6 Effects

Exposure of humans and experimental animals to carbon disulphide can lead to a wide variety of neurological, cardiovascular and endocrine effects, reproduction toxicity, effects on eyes and the respiratory system. Workers in a Dutch factory who were exposed to a concentration of approximately 22 mg/m^3 (7 ppm) showed neurophysiological abnormalities. Another study in the same factory led to the conclusion that exposure to carbon disulphide increases mortality due to cardiovascular disease.

Mortality from cancer was not increased. Possible carcinogenic properties of carbon disulphide have not been investigated in experimental animals. Tests of mutagenesis did not yield results that permitted definite conclusions. No reproduction toxicity was found in rabbits exposed to concentrations up to 930 mg/m^3 (300 ppm). Results of investigations with rats are contradictory; due to methodological differences these experiments are difficult to compare and do not allow definitive conclusions. A study in women point to possible effects on menstruation and pregnancy; poor reporting of this study does not allow dose-effect relations or no-effect levels to be established.

7 Health-based recommended occupational exposure limit

The Dutch Expert Committee on Occupational Standards recommends a health based occupational exposure limit of 3 mg/m^3 (1 ppm), as a 8 hour time weighted average (TWA) concentration of carbon disulphide in air. This value is based on the Dutch investigation that showed that long-term exposure to a concentration of approximately 22 mg/m^3 (7 ppm) leads to undesirable effects on the nervous system and an increased risk of mortality of cardiovascular disease. Considering that carbon disulphide, as a liquid, by penetrating the skin can contribute to a great extent to the internal dose, the committee recommends an 'Skin-notation'.

Chapter 1

Scope

1.1 Background

In the Netherlands occupational exposure limits for chemical substances are set using a three-step procedure. In the first step a scientific evaluation of the data on the toxicity of the substance is made by the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, on request of the minister of Social Affairs and Employment.* This evaluation should lead to a health based recommended exposure limit for the concentration in air of the substance. Such an exposure limit cannot be derived if sufficient data are not available or if the toxic action cannot be evaluated using a threshold model.

In the next phase of the three-step procedure the Social and Economic Council advises the minister on the feasibility of using the health based value as a regulatory Maximal Accepted Concentration (MAC) or recommends a different MAC-value. In the final step of the procedure the minister of Social Affairs and Employment sets the official exposure limit.

* The DECOS was established in 1976 by a ministerial decree as an independent advisory committee of the Director-General of Labour. Since January 1, 1994, DECOS is a committee of the Health Council of the Netherlands. Health Council committees have an autonomous status.

1.2 Committee and method of work

The present document contains the assessment of DECOS of the toxicity of carbon disulphide and a recommended health based exposure limit for this substance. The members of DECOS are listed in annex B.

The first draft of this report was prepared by dr JThJ Stouten, from the Medical Biological Laboratory TNO, by contract with the Ministry of Social Affairs and Employment. In January 1993 the DECOS released a draft version of the report for public review. The individuals and organisations that commented on the draft are listed in annex C. DECOS has taken these comments into account in finalising its report.

1.3 Data

The data presented in this document are derived from the reviews on carbon disulphide published by Beauchamp et al (1983) and Fielder and Shillaker (1981). In addition, literature was retrieved from the on-line databases Chemabs (Chemical Abstracts) and Medline, encompassing the period 1979-1987 and 1981-1987, respectively. Regular updating was carried out until December 1990, including Chemical Abstracts 113/22 (1990) and Medline 12-90. Finally, some recent reports (Pathology Associates Inc 1991; Ruijten et al 1991; Swaen et al 1991) were made available to the committee and included in this document.

Chapter 2

Identity, physical and chemical properties, monitoring

2.1 Identity*

2.1.1 *Structure*

S=C=S

2.1.2 *Chemical name and synonyms/registry number*

▪ name	carbon disulphide
▪ CAS registry number	75-15-0
▪ synonyms	carbon disulphide carbon bisulfide carbon bisulphide carbon sulphide dithiocarbonic anhydridesulphocarbonic anhydride zwavelkoolstof (Dutch) Schwefelkohlenstoff (German)

* data from: Amoore and Hautala 1983; Patty 1962; Weast 1988-1989; Windholz 1983

2.2 Physical and chemical properties*

▪ molecular formula	CS_2
▪ molecular weight	76.14 g/mol
▪ melting point (1 bar)	-111.5 °C
▪ boiling point (1 bar)	46.5 °C
▪ density (20 °C, 1 bar)	1.2632 g/cm^3
▪ vapour pressure (20 °C, 1 bar)	396 mbar
▪ relative vapour density in saturated air (air=1; 20 °C, 1 bar)	1.74
▪ percentage of vapour in saturated air (25 °C, 1 bar)	47.4
▪ solubility (20 °C, 1 bar)	
in water	2.2 g/liter
in ethanol	miscible
in diethylether	miscible
▪ azeotropes	97.2% CS_2 + 2.8% H_2O; bp 42.6 °C
▪ odour detection threshold	0.34 mg/m^3 (0.11 ppm)
▪ conversion factors (25 °C, 1 bar)	1 mg/m^3 = 0.32 ppm^3 1 ppm = 3.12 mg/m^3
▪ physical state	highly refractive, mobile, very flammable liquid. Pure CS_2 has a sweet, pleasing and ethereal odour; usual commercial and reagent grades are foul smelling
▪ stability	decomposes on standing for a long time; burns with a blue flame to CO_2 and SO_2.

2.3 Analytical methods

2.3.1 *Environmental monitoring*

There are only two more or less validated methods to measure CS_2 in workplace air. Besides these, some other methods are described that can detect CS_2 at sub-ppm levels, using gas chromatography and a variety of detectors (Brazell et al 1981; Oppermann

* data from: Amoore and Hautala 1983; Patty 1962; Weast 1988-1989; Windholz 1983

and Popp 1981) or even at sub-ppb levels by trapping and concentrating at -196 °C using Tenax GC and direct transfer to the GC column (Tangerman 1986).

NIOSH method no. 1600 (Eller 1984)

A known volume of air is drawn through a charcoal tube to trap the organic vapours present. The CS_2 is desorbed with toluene. The amount of CS_2 is determined by gas chromatography, using a flame photometric detector and a sulphur filter.

The working range of the method is 10 to 200 mg/m^3 (3-64 ppm) for an air sample of 5 litre . The overall precision is 0.059.

No interference occurs from hydrogen sulphide. Water vapour is a potential sampling interferent which is removed by a drying tube connected to the charcoal tube. Alternate GC columns aid in resolution of chromatographic interferences.

NVN 2946 (Nederlands Normalisatie-instituut 1989)

This method is almost identical to that of NIOSH and the Health and Safety Executive (other charcoal tubes are used).

The working range is 10-300 mg/m^3 (3-96 ppm) for an air sample of 20 litre (sampling time: 1-8 h) and 30-1000 mg/m^3 (10-320 ppm) for an air sample of 3 litre (sampling time: 15 min). Based on the similarity with the NIOSH method, a variation coefficient of less than 10% may be expected.

MDHS 15

The Health and Safety Executive of the UK has published a method using charcoal adsorption tubes, solvent desorption and gas chromatography. It is comparable to that of NIOSH, published in the Methods for the Determination of Hazardous Substances Series (MDHS).

Personal air sampling with diffusive samplers

This method is based on active charcoal sampling using commercial available diffusive samplers, followed by solvent extraction and colorimetric determination of the analyte (A'Campo and Beltman 1985; Westberg and Linder 1987; Westberg et al 1984).

Infrared spectroscopy

CS_2 can be detected with (portable) infrared analysers with a minimum concentration of 16 mg/m^3 (5.2 ppm) at a wavelength of 4.7 mm and a pathlength of 20.25 m (Foxboro 1985). This method is only suitable, when no other compounds which absorb in the same spectral region are present.

2.3.2 *Biological monitoring*

Iodine-azide test

This method is restricted to exposure levels in excess of 50 mg/m^3 (16 ppm), and has therefore become obsolete.

2-Thiothiazolidine-4-carboxylic acid in urine (TTCA)

TTCA is a metabolite of CS_2 and can be determined by HPLC. Concentrations in the urine as low as $5x10^{-7}$ mol/liter are detectable (Van Doorn et al 1981). This method is a sensitive indicator of CS_2 exposure, as TTCA was easily detected after exposure to levels less than 5 mg/m^3 (1.6 ppm) of CS_2.

The best results were obtained by using a slightly modified method as published by Campbell et al (1985) and sampling all urine voided during the last 4 hours of a shift. The best relation found was between de concentration of TTCA in end-shift urine and exposure(r=0.95) and was described by equation:

$$\log [\text{TTCA end-shift}] = 1.10 + 0.84 \log [CS_2],$$

in which the concentration of TTCA is expressed in mmol per mol creatinine and that of CS_2 in mg/m^3 (Meuling et al 1990).

Chapter 3

Sources of exposure

3.1 Natural occurrence

Carbon disulphide in air can originate from biogenic sources. It emanates from salt marshes and to a considerably lesser degree from inland soils (Aneja et al 1982). Furthermore, CS_2 was found in the plume and ash that erupted from the Mount St Helens vulcano in Washington, USA (Beauchamp et al 1983).

3.2 Man-made sources*

3.2.1 *Production*

Until the 1950s CS_2 was manufactured from carbon (charcoal) and sulphur vapour by the retort process and the electrothermic process. In these processes the sulphur vapour is passed over a heated charcoal bed. In the retort process the bed is heated externally by fuel or electricity, in the electrothermic process by electric resistance heaters within the bed.

Later hydrocarbons, like methane, ethane, and propylene, were used and by about 1965 these gaseous compounds had replaced charcoal. Most CS_2 is produced by the catalytic reaction of sulphur vapour and methane (natural gas). These are preheated to 480-650 °C and circulated over a catalyst such as silica gel or aluminia. The reaction

* data from: Grothaus et al 1982 and Timmerman 1978

temperature is between 580 and 635 °C at a pressure between 250 and 500 kPa. Both hydrogen sulphide and CS_2 are formed; H_2S is separated off and recycled as a source of sulphur.

Other methods are hardly applied commercially.

3.2.2 *Uses*

CS_2 is principally used in the manufacture of viscose rayon. Other important applications are found in cellophane production and, as a raw material, in the manufacture of carbon tetrachloride. Furthermore, CS_2 is used in the manufacture of rubber vulcanisers, flotation chemicals, pesticides, corrosion inhibitors. Other applications range from preservation of fresh fruit, brightening agent in silver and gold plating, and as a sulphiding agent in the preparation of semiconductors.

The use of CS_2 as a solvent is being more and more restricted, because of its high flammability and toxicity. In some special cases, like the separation and extractions of lubricants and sulphur, and petroleum well cleaning, the compound will still find its use.

Chapter 4

Guidelines and standards

4.1 General population

In the former USSR the maximal allowable concentration of CS_2 in the atmospheric air in the populated areas was set at 0.03 mg/m^3 (once per day) and at 0.005 mg/m^3 (daily average). The concentration of CS_2 in water to be used for economic and domestic purposes was not to exceed 1 mg/liter (Grodetskaya 1983).

WHO (1979) refers to a report of the US Environmental Protection Agency published in 1976 in which it is recommended that limiting the long-term average concentration in air to 0.3 mg/m^3 should be sufficient to protect the general population against long-term health effects.

4.2 Occupational standards

4.2.1 *Occupational exposure limits*

The permissible occupational exposure levels in the Netherlands and in some other countries are presented in table 1.

DFG has added a note indicating that damage to the foetus cannot be excluded at the current German occupational exposure limit of 30 mg/m^3 (10 ppm) (DFG 1989a).

NIOSH (1977) has recommended a maximal TWA concentration (10 h, 40 h work week) of 1 ppm with a ceiling of 10 ppm for any 15 min period. WHO (1981) pro-

Table 1 Occupational exposure limits in the Netherlands and in some other countries.

country	year	level mg/m³	ppm	interpretation	skin notation	reference
Netherlands	1989	60	20	MAC/TWA	+	Arbeidsinspectie 1989
USA, ACGIH	1991/9231	10		TLV/TWA	+	ACGIH 1991a
USA, OSHA	1989a	4		TWA[a]	+	OSHA 1989
		12		PEL-STEL[a]		
FRG	1991	30	10	MAC-TWA[b]	+	DFG 1991a
		60	20	STEL (30 min)		
Sweden	1989	16	5	TVL-TWA	+	NBOSH 1989[c]
UK	1991	30	10	MEL-TWA[d]	+	HSE 1991
USSR	1985	1		MAC-ceiling		INRS 1986

[a] final rule PEL

[b] DFG indicatis that adverse effects to the unborn child due to exposure to this MAC cannot be excluded

[c] National Board of Occupational Safety and Health

[d] MEL: maximum exposure limit; the maximum concentration (8 h, TWA) to which employees may be exposed by inhalation under any circumstances

posed a maximal TWA concentration of 10 mg/m³ for male workers and of 3 mg/m³ for women of fertile age.

4.2.2 *Biological exposure limits*

ACGIH (1991b) has adopted a biological exposure index (BEI) for carbon disulphide of 5.0 mg TTCA per g of creatinine in urine, collected at the end of a workshift. DFG (1991b) has published a so-called BAT-value (Biologische Arbeitsstoftoleranzwerte) for carbon disulphide of 8 mg per litre l TTCA in the urine collected at the end of a workshift.

Chapter 5

Toxicokinetics*

5.1 Absorption

5.1.1 *Human studies*

Absorption by inhalation

Inhalation is the main route of carbon disulphide intake during occupational exposure. Investigations among volunteers and occupational exposed workers resulted in widely differing data on retention and on the time needed to attain equilibrium between the inhaled and the exhaled concentration. This is demonstrated by results of recent studies: Rosier et al (1987a) did not find an equilibrium after four consecutive exposure periods of 50 min each, whereas Herrmann et al (1982) postulated, based on 30 min experiments, that equilibrium is reached after approximately 45 min. Generally, equilibrium is attained during the first two hours of exposure. Retention declined from an initial 70%-80% of the inhaled CS_2 to 15%-45% at equilibrium.

Retention is influenced by several factors. A difference between the retention in not previously exposed volunteers and that in chronically occupational exposed workers was noted. Furthermore, physical workload caused a decrease in retention and at the same time an increase in the respiratory volume (Herrmann et al 1983; Rosier et al 1987a). As the respiratory volume is the most important factor, increasing workload

* data from: Beauchamp et al 1983, unless otherwise noted

results in increasing CS_2 uptake (Herrmann et al, 1983). Finally, Rosier et al (1987a) observed a positive correlation between the percentage of fatty tissue and the retention of CS_2.

Percutaneous absorption

Percutaneous absorption is the second potential source of occupational exposure to CS_2.

Skin absorption was evaluated by Baranowska and Dutkiewicz (1965) from experiments in which the hands were immersed in aqueous CS_2 solutions. The amount of CS_2 absorbed through the skin was determined by measuring the loss of CS_2 from the solution. Loss of CS_2 due to volatilisation was prevented by using polyvinyl foil sleeves and determined to be zero for at least 1 h. Using solutions with CS_2 concentrations varying from 0.42 to 1.49 g/liter resulted in mass lossen from 74 to 268.5 mg. The calculated absorption velocity ranged from 0.23 to 0.79 $mg.cm^{-2}.h^{-1}$*.

5.1.2 *Animal studies*

Absorption by inhalation

Studies in rabbits indicated retention values of 70%-80% when equilibrium was reached, 1.5-2.5 h after the beginning of exposure (Fielder and Shillaker 1981).

Percutaneous absorption

There is limited information available on skin absorption in animals. Exposure of rabbit skin to concentrations of 2500 mg/m^3 (800 ppm) and higher for 1 h resulted in detectable amounts of in the breath of animals. No CS_2 was detected in the breath of rabbits exposed to concentrations of 470 mg/m^3 (150 ppm) for 6 h (Fielder and Shillaker 1981).

5.2 Distribution

After absorption, CS_2 is distributed by the blood to the organs. CS_2 can exist in blood as free CS_2 and as acid-labile CS_2 ($ALCS_2$); the latter fraction can be recovered by acid treatment at elevated temperatures.

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* This figure may overestimate the actual uptake of CS_2 into the blood, because subdermal fats may retain the substance to a large, but unknown extent.

In rats, after exposure to CS_2, the majority of the compound (about 90%) was found in the red blood cells. These cells are thought to play an important role in the transport of CS_2 from the lung to the tissues and vice versa (Lam et al 1986). The majority of $ALCS_2$ (about 90%) was also present in the red blood cells. $ALCS_2$ was mainly bound to haemoglobin and, to a small extent, to other blood proteins (Lam and DiStefano 1986).

Lam and DiStefano (1982, 1983) showed that levels of free CS_2 and of $ALCS_2$ in blood are linearly related to the concentration in air inhaled by rats exposed to 15-120 mg/m^3 (4.8-38.4 ppm) (for 8 h or 500-4000 mg/m^3 (160-1280 ppm) for 4 h. ALCS2 in blood also increased linearly with time, when rats were exposed to 2000 mg/m^3 (640 ppm) () of CS_2 for up to 4 h (Lam and DiStefano 1982). Under these conditions concentrations of free CS_2 in red blood cells approached a plateau within 2 h, and in plasma within 15 min of exposure (Lam et al 1986).

CS_2 is readily distributed to the tissues and organs. Rosier and Van Peteghem (1987) have determined tissue/air partition coefficients for CS_2 from pig tissue homogenates to human blood. These coefficients varied from 2.4 for muscle to 4.4 for brain, while the coefficient for fatty tissue was 54.3.

Bergman et al (1984) studied distribution patterns in male mice after inhalation of 2340 mg/m^3 (750 ppm) of ^{35}S-labelled or ^{14}C-labelled CS_2 during 10 min by the use of low-temperature whole-body radiography. The distribution was followed up to 48 h. In contrast to other authors, they reported higher binding of C- than of S-metabolites, which was explained by differences in species, routes of administration and observation time. Immediately after inhalation a very high uptake of $C^{35}S_2$ or $^{14}CS_2$ was found in body fat, nasal mucosa, blood, and well-perfused organs as liver, kidney, and lung; very little was found in the brain and the endocrine tissue. ^{35}S-metabolites were initially concentrated in the liver and the kidney, but were rapidly eliminated from the body. There was evidence of an extensive metabolic incorporation of sulphur originating from CS_2 during its biotransformation. ^{14}C-metabolites were likewise concentrated in liver and kidney, but also in nasal mucosa, bronchi, bone, pancreas, thyroid, adrenal cortex, and testes. These metabolites were retained in large amounts in liver, thyroid (follicles), nasal mucosa, bronchi, and kidney.

Green Snyderwine and Hunter (1987) examined the distribution of $^{14}CS_2$ and $C^{35}S_2$ in 1- to 40-day-old rats by i.p. administration. Three hours after administration the tissue level of ^{35}S-CS_2-derived radioactivity exceeded levels of ^{14}C-CS_2-derived radioactivity indicating that sulphur metabolites free from the carbon atom of CS_2 were formed in rats as young as 1 day of age. ^{35}S covalently bound to tissue protein was significantly higher in 1-through 20-day-old rats than in 30- and 40-day-old rats. 24 h after dosing, up to 13 times more ^{35}S-labelled metabolites were covalently bound in organs from 1-day-old rats than in similar organs from 40-day-old rats.

Finally, Danielsson et al (1984) carried out inhalation studies by exposing pregnant mice to 2340 mg/m^3 (750 ppm) of ^{14}CS and $C^{35}S_2$. They examined the embryonal and foetal distribution of CS_2 and its metabolites in different stages of gestation. CS_2 and its metabolites passed the placenta at all stages of gestation. High levels of CS_2 metabolites were noted in the embryonic neuroepithelium. In mid and late gestation CS_2 accumulated in the cerebrospinal fluid. ^{14}C metabolites showed affinity for bone and were retained in the liver even at long survival time (24 h).

There is only one report containing data on distribution of CS_2 in humans. Milk from nursing mothers occupationally exposed to 29-66 mg/m^3 (9.3-21.2 ppm) for 6.5 h contained an average of 0.12 mg of CS_2. Exposure to 23-125 mg/m^3 (7.4-40 ppm) for 2-4 h resulted in a lower average milk concentration of 0.07 mg/liter. These data suggest, that the CS_2 content in mother milk is related to the product of the CS_2 exposure level and the exposure time. CS_2 was still present in preshift samples. CS_2 was also detected in the urine of 5 out of 10 nursed babies and in the umbilical blood of one newborn, indicating that CS_2 can reach the foetus through the placenta (Cai and Bao 1981).

5.3 Biotransformation

CS_2 reacts easily with amino groups of proteins and other substances resulting in the formation of dithiocarbamates and thiazolinone. Furthermore, CS_2 can react with glutathione and cysteine to 2-thiothiazolidine-4-carboxylic acid (TTCA). Less than 6% of the absorbed CS_2 is metabolized to TTCA (Campbell et al 1985; Rosier et al 1987b).

Finally, desulphuration of CS_2 takes place in the liver. The initial step in the process is catalysed by the cytochrome P450 containing mono-oxygenase system, in which two forms of cytochrome P450 are involved (Rubin and Kroll 1986; Torres et al 1981). The products of this reaction are monothiocarbamate (the hydrate form of COS) and a reactive sulphur species, which either binds to microsomal macromolecules or is oxidised to sulphate. The monothiocarbamate can either be converted to COS in an equilibrium reaction catalysed by carbonic anhydrase or to carbon dioxyde and the hydrogen sulphide ion, which is oxidised to thiosulphate and sulphate (Chengelis and Neal 1987).

5.4 Elimination

In rats exposed to 500-4000 mg/m^3 (160-1280 ppm) for 4 h free CS_2 was rapidly eliminated from the blood by a two-exponential first order process with half-lives of 8.7 and 55.2 min. $ALCS_2$ was similarly, but more slowly, eliminated with half-lives of 2.2 and 42.7 h (Lam and DiStefano 1982). $ALCS_2$ was also slowly eliminated from tissue. The expected accumulation of $ALCS_2$ in the blood was confirmed by an experiment in

which rats were daily exposed to 120 mg/m^3 (38 ppm), 8 h per day for 6 days. By the end of the exposure period the level of blood $ALCS_2$ was about 2.5 times that after the first 8 h exposure and about 3 times the level of free CS_2. In man, about 10%-30% of the amount of CS_2 absorbed after inhalation is excreted unchanged in the breath. The first phase of elimination is fast: the half-life is about 10 min. Since CS_2 was detected in breath 16 h after exposure, there is evidence for at least two pharmacokinetic compartments (Campbell et al 1985). This was confirmed by Rosier et al (1987a). They characterised the course of the respiratory elimination of CS_2 during a post-exposure period of 180 min by an initially fast decrease with a half-life of about 1 min followed by a relatively slow decrease with a half-life of about 110 min. Baranowska and Dutkiewicz (1965) found a much lesser degree of excretion of unchanged CS_2 in exhaled breath after absorption through the skin: 6% (range: 2%-11%).

Less than 1% is excreted unchanged in the urine. The remainder 70%-90% is metabolized. The metabolites are excreted in the urine and in the breath (as CO_2). No data on half-life as to excretion in the urine were found.

The fact that ^{35}S was found in the intestines of rats after exposure to $C^{35}S_2$ may indicate that some metabolites are excreted in the faeces (Bergman et al 1984).

5.5 Biological monitoring

5.5.1 *Determination of CS_2*

In breath

CS_2 is excreted unchanged in breath. This process can be described by means of a two-exponential decay, with half-lives for the first phase of 1 and 10 min (Campbell et al 1985; Rosier et al 1987a). For the second phase a half-life of 110 min has been reported (Rosier et al 1987a).

Two reports are dealing with the possibility of measuring CS_2 in expired air as a biological monitoring method. Campbell et al (1985) used a transportable mass spectrometer which could measure concentrations below 1 ppm with a fast response enabling the real-time analysis of the solvent without the use of breath collection devices. CS_2 could be measured in end-of-shift as well as in preshift samples. The CS_2 levels in the end-of-shift samples varied widely, probably due to fluctuating exposure levels toward the end of shift and may only reflect exposure in the period just before sampling. The significance of next-day preshift samples when the rates of elimination are much slower, was not evaluated. Rosier et al (1987a) also found a considerable dispersion of the individual respiratory elimination of carbon disulphide. They concluded that it was not possible to employ the total amount of CS_2 eliminated during 3 h postexposure to

estimate the respiratory uptake during exposure. In addition, as the concentration of CS_2 in exhaled air at the end of exposure falls rapidly, the moment of sampling became too critical, so this method was considered to be useless in evaluating recent exposure.

In blood

The determination of CS_2 in the blood did not give reproducible results and the correlation between CS_2 concentrations in blood and air was very weak or non-existing. This was explained by the observation of the existence of two forms of CS_2 in the blood: free and $ALCS_2$. Free CS_2 disappears very quickly. Campbell et al (1985) were not able to detect free CS_2 in blood samples from exposed workers using head-space gas chromotography.

In urine

Only 1% or less of the absorbed amount of CS_2 is excreted unmetabolised in the urine. The determination of CS_2 in urine was therefore deemed unsuitable as an exposure test (WHO 1979). However, Leuschke et al (1980) found a significant relationship between exposure and excretion of CS_2 in urine. After correction for the density of the urine and for the concentration of CS_2 in the urine at the beginning of the shift, this relation could be described by:

$U = 0.00242\ c\ t - 0.02$ ($n=6$, $s_{yx}=0.82$)

in which U is the CS_2 concentration in urine in μmol/liter, c the CS_2 concentration in air in mg/m^3 and t the exposure time. This equation resulted from studying a limited number of exposed persons (n=6) and was not further validated, so its actual value remains questionable.

5.5.2 *Determination of metabolites*

In blood

The majority of CS_2 in the blood is in bound form and can be released using acid and heat. This product, $ALCS_2$, was slowly eliminated and blood concentrations appeared to be linearly related to the inhalation concentration and time, as was shown in experiments with rats. Rats exposed to 67 mg/m^3 (21 ppm) of CS_2 for 8 h had measurable concentrations of blood $ALCS_2$ using a colorimetric method (Lam and DiStefano 1982). Campbell et al (1985) used a headspace gas chromatographic technique to de-

tect $ALCS_2$ in the blood of exposed workers. Although the technique was very selective and sensitive, some difficulties remained in terms of reproducibility and the correlation between $ALCS_2$ and exposure was not very satisfactory.

In urine

One of the metabolites of CS_2 excreted in the urine has been identified as 2-thiothiazolidine-4-carboxylic acid (TTCA). This metabolite was specific for CS_2 exposure and not found in the urine of workers exposed to other solvents (Van Doorn et al 1981). Rosier et al (1984) found a good relation between the TTCA levels in end-of-shift urine and exposure (exposure levels: 15-160 mg/m^3 or 5-51 ppm), especially when urine samples with creatinine concentrations below 1 mg/cm^{3}were disregarded (r=0.86; n=13). Campbell et al (1985) confirmed these findings (r=0.84) in a group exposed to 5-24 mg/m^3 (2-8 ppm), measured by personal air sampling with pumps. They calculated a concentration of TTCA of 4 mmol per mol creatinine to be equivalent to an exposure of 30 mg/m^3 (10 ppm; 8-h TWA). Meuling et al (1989) found even a better correlation coefficient of 0.92 in workers exposed to an average level of 13 mg/m^3 (4 ppm; range: 1-66 mg/m^3 or 0.3-21 ppm; n=28), measured using diffusion badges. Based on group observations, the relative TTCA concentration that precludes 95% confidence exposures exceeding 60 mg/m^3 (20 ppm; the current Dutch MAC-value) is 0.94 mmol per mol creatinine (1.27 mg/g creatinine) in urine sampled during the last 4 h of a shift.

5.6 Summary

Although CS_2 may be absorbed through the skin, the main route of occupational exposure is inhalation. Equilibrium is reached within the first two hours of exposure, when lung retention declines from an initial 70%-80% to 15%-45%. The retention is usually lower in those exposed for the first time. Furthermore, increased workload results in decreased retention and an increase in respiratory volume with as overall effect an increased CS_2 uptake. The red blood cells play an important role in the distribution of CS_2 to the organs and tissues: the two forms of CS_2 found in the blood of animals, i.e. free CS_2 and $ALCS_2$ (a bound fraction that can be recovered by acid treatment at elevated temperatures), were mainly bound to the erythrocytes. Free CS_2 disappeared rapidly from the blood, whereas $ALCS_2$ was eliminated much more slowly and was shown to accumulate. CS_2 and its metabolites were found in many organs and tissues of experimental animals although preference was observed towards body fat, liver, and kidney. Studies in pregnant mice show CS_2 and its metabolites to pass the placenta at all

stages of gestation. As to man, CS_2 was detected in the breast milk of exposed Chinese workers and in the umbilical blood of one newborn baby.

10-30% of the absorbed CS_2 is exhaled unchanged by an initial fast (half-life 1-10 min) and a second slower phase (half-life 110 min). Only a minor quantity (less than 1%) is excreted unchanged in the urine. The remaining 70%-90% is metabolized. Desulphuration occurs in the liver by the MFO system, resulting in a variety of products (CO_2, COS, thiosulphate, sulphate and a reactive sulphur species). Furthermore, CS_2 easily reacts with amino groups of amino acids and other substances to dithiocarbamates and thiazolinone, and with glutathione and cysteine to TTCA. TTCA is a specific metabolite of CS_2 and measurement of its concentration in the urine offers a method for biological monitoring of exposed workers.

Chapter 6

Effects

6.1 Animal experiments

The data from animal experiments are partly derived from the reviews by Beauchamp et al (1983) and Fielder and Shillaker (1981) and summarised in tables 2-17 (see annex F). In the next sections the conclusions from these data are presented.

6.1.1 *Irritation and sensitisation*

There is only one report, published in 1936, that describes the effects of CS_2 after application to the skin. Daily application of 2.58 mg (2 cm^3) CS_2 for 3-5 days in cotton earplugs to rabbits led to blisters within three days. Histopathological observations showed early epidermal and subepidermal vesicles progressing to ulcers. Degenerative changes were noted in sebaceous glands and local nerves.

6.1.2 *Acute toxicity*

Data on acute lethal effects of CS_2 are presented in table 2 (see annex F). From these data it can be concluded that the acute lethal toxicity of CS_2 is rather low.

Neurotoxic and neurobehavioural effects

Neurotoxic and neurobehavioural effects due to acute exposure to CS_2 are summarised in table 3 (see annex F).

Neurotoxic effects (ataxia, tremors, convulsions) have been noted in earlier studies in rats after exposure to about 2500 mg/m^3 (800 ppm) for 15 h, whereas 1970-2180 mg/m^3 (600-700 ppm) for 8 h or 4990 mg/m^3 (1600 ppm) for 4 h produced no overt signs of toxicity. Degenerative changes in 80% of the ganglion cells in the globus pallidus were found in mouse, exposed to 9360 and 14040 mg/m^3 (3000 and 4500 ppm) for 0.5 h. At lower levels, 1970 mg/m^3 (630 ppm; exposure time 4-8 h), a marked decrease was noted in brain noradrenaline levels in the rat. The minimum concentration at which this transient effect occurred was 197 mg/m^3 (63 ppm; exposure time 8 h).

Hepatotoxic effects

Data on hepatotoxic effects due to acute or single exposure are presented in tables 4a and 4b (see annex F). No hepatotoxicity and only transient effects on liver metabolism occurred in animals exposed up to 4780 mg/m^3 (1500 ppm) for 2 h. However, pretreatment with phenobarbital to induce the liver mixed function oxidase system resulted in more marked effects. Other exposure routes show the same tendency.

Effects on other organs or systems

Only a few experiments deal with effects on other organs or systems (see table 5, annex F). Inhalation of 2.3 mg/m^3 (0.74 ppm) and 13.6 mg/m^3 (4.35 ppm of CS_2 for 4 h by rats affected the renal function, but no correlation with renal morphology was made. Exposure to 1000-4000 mg/m^3 (320-1280 ppm) for 4 h reduced the rate of dopamine metabolism in the adrenals of rats indicating inhibition of dopamine-b-hydroxylase. Oral administration of a single dose of 10 and 100 mg/kg to mice reduced some drug metabolising enzyme activities and the cytochrome P450 content of the lung microsomal fraction.

CS_2 may interfere with the active absorption system of the small intestine as was concluded from the results of the xylose tolerance test after subcutaneous application of a single dose of 10 and 100 mg/kg to rabbits.

6.1.3 *Short-term toxicity*

Neurotoxic and neurobehavioural effects

Neurotoxic and neurobehavioural effects due to short-term exposure are summarised in table 6 (annex F). Most of the experiments was done with the rat. At about 625 mg/m^3 (200 ppm) and above reduced weight gain was observed. After exposure to 1500 mg/m^3 (481 ppm) for 5 h per day, 6 d ays per week, for 1 or 2 months axonopathy of the long nerves were seen in both CNS and PNS, characterised by axonal swelling. A significant, but transient reduction in conduction velocity in peripheral nerves occurred after exposure to 1600 mg/m^3 (513 ppm) for 5 h per day, 6 days per week, for 1,5 months. At 2340 mg/m^3 (750 ppm), 6 h per day, 5 days per week this effect was already noted after 2 weeks.

Generally, reduction of conduction velocity was preceding more severe effects like impairment of hind limbs. Furthermore, inhibition of brain catecholamine and dopamine synthesis was observed in rats exposed to 2000 mg/m^3 (640 ppm) for 4 h per day for 2 or more days. The same effects were noted in the rabbit. At very low levels (2 mg/m^3 or 0.6 ppm; 24 h per day, 1-6 weeks) changes in EEG and biochemical parameters of the brain of rabbits were found.

Effects on the cardiovascular system

Studies of the effects on the cardiovascular system are scarce (see table 7, annex F). Exposure of rats to 10 and 50 mg/m^3 (3.2 and 16 ppm) for 1 month (5 h per day, 5 days per week) was reported to intensify changes in the cardiovascular system and in serum proteins due to an atherogenic diet. Serum cholesterol levels in the rat were significantly elevated after exposure to 550 mg/m^3 (176 ppm) for 5 h per day, 6 days per week for 2 months or more. The same effect was noted in the rabbit during exposure to 1000 mg/m^3 (320 ppm) for 10 weeks (5 h per day, 6 days per week). This exposure combined with a cholesterol-enriched diet accelerated atherosclerotic changes.

Hepatotoxic effects

Effects due to short-term exposure on the liver are presented in table 8 (annex F). There is only one inhalation study, using mice. Exposure to 1500 mg/m^3 (480 ppm) for 23 d (4 h per day, 5 days per week) resulted in a significant decrease in UDP-glucuronyl transferase and an increase in lipid peroxidation at the end of exposure. Exposure by other routes for about 2 months resulted in fatty degeneration and necrosis.

Effects on other organs or systems

Effects on the endocrine system and the kidney and some haematological effects are summarised in table 9 (annex F).

Enhanced platelet aggregation was found in guinea pigs after exposure by inhalation to high levels of CS_2 (30 000 mg/m^3 or 9630 ppm, 15 min per day, 20 d).

Effects on the endocrine system include an increase in the thyroid activity, a decrease in oestrus cycle and adrenal function in rats exposed to 100 mg/m^3 (32 ppm; 3 h per day, 0.5 month). After subcutaneous injection of 200 mg/kg on alternate days for 30 days hypertrophy, followed by atrophy, of the adrenals of the exposed rats was noted.

Daily intramuscular injection of 315 mg/kg (50 d) to rats resulted in hyperaminoaciduria, suggesting kidney lesions.

Oral administration of 25 mg/kg, daily for 60 d, to rats caused anaemia, eosinopenia, and an increase in reticulocyte number.

Intramuscular injection of 440 mg/kg, daily for 50 d, affected the levels of some serum cations in rats.

Conclusions

From studies on short-term exposure no no-adverse-effect-levels can be determined. The significance of a number of findings cannot be assessed, because of the difficulty to relate them to (occupational) health or to evaluate them properly due to poor presentation. The lowest reported effect level is 550 mg/m^3 (176 ppm): exposure for 2 months (5 h per day, 6 days per week) resulted in elevated cholesterol levels in the serum of rats.

6.1.4 *Long-term toxicity and carcinogenicity*

Neurotoxic effects (table 10a and 10b, annex F)

No morphological changes were noted in the spinal cord and peripheral nerve of the rat after exposure to 160 mg/m^3 (50 ppm) for 90 days (6 h per day, 5 days per week) and only occasional swellings of axons in the lumbal spinal cord after exposure to 960 mg/m^3 (3000 ppm). At 600 mg/m^3 (192 ppm), 6 h per day, 5 days per week, for 3 or 6 months, no clinical or electromyographic evidence of neuropathy was found. Degenerative changes in a small number of ganglion cells were found in the brain of rats after exposure to 500-800 mg/m^3 (160-256 ppm) for 8 months, (6 h per day, 5 days per week), but no definite effect level was indicated. Exposure to 256 ppm (800 mg/m^3)

for 8 months (5 h per day, 6 days per week) did not result in remarkable morphological or ultrastructural changes in the CNS (hippocampus, cerebral cortex), but did evoke changes in the myelinated and unmyelinated fibers of the sciatic nerve; after 12 months axonal swellings, increased number of neurofilaments and disappearance of neurotubules were noted together with some biochemical effects. Significant reduction of peripheral nerve conduction velocity was seen after 6 months (5 h per day, 6 days per week) exposure to 900 mg/m^3 (288 ppm) () and more marked after 12 months. After a recovery period of 6 months only a partial, respectively entirely non improvement occurred.

Paralysis of hind extremities were reported after exposure to 1500 mg/m^3 (480 ppm) for 9 months (5 h per day, 6 days per week) or to 2184 mg/m^3 (700 ppm) for about 3 months (5 h per day, 5 days per week). Ataxia and muscular weakness were mentioned after exposure to 1500 mg/m^3 (480 ppm) for 7 months (5 h per day, 6 days per week)) and to 1600 mg/m^3 (513 ppm) for 4-6 months (5 h per day, 6 days per week).

Effects on the cardiovascular system (see table 11a and 11b, annex F)

Continuous exposure of rats for 4 months up to 112 mg/m^3 (36 ppm) did not cause effects on serum lipid levels nor any significant morphological changes in heart or aorta. The importance of the reported reduction in some enzyme activities due to exposures up to 200 mg/m^3 (64 ppm) for 5 months could not be assessed because insufficient data were presented on actual enzyme activities and their variability.

Exposure of rats to 230 mg/m^3 (74 ppm) for 8 months slightly increased serum cholesterol levels, while exposure to 550 mg/m^3 (176 ppm) resulted in a significant increase in cholesterol and phospholipid levels from month 2 and in triglyceride levels from month 4. At the end of the exposure period the rate of cholesterol biosynthesis was markedly increased. At higher levels (1000 mg/m^3, 321 ppm) the same effects were noted. Moreover, a greater increase in the rate of transfer of cholesterol from blood to aorta was seen. Exposure of rats maintained on an atherogenic diet to 1000 mg/m^3 (312 ppm) for 6 months resulted in an acceleration of the atherosclerotic changes induced by the diet.

Hepatotoxic effects (see table 12, annex F)

Exposure of rats up to 800 mg/m^3 (256 ppm) for 8 months did not reveal clinical signs of pathoanatomical changes nor histological changes in liver tissue; at levels up to 1500 mg/m^3 (480 ppm) for 11 months dystrophic necrobiotic changes were found. After exposure of rats to 1500 mg/m^3 (480 ppm) for 5 months giant mitochondria and lo-

cally degranulated rough endoplasmatic reticulum was demonstrated in some hepatocytes. Under these conditions changes in some biochemical parameters were also found.

Effects on other organs and systems

Effects on the gastrointestinal system, kidney, lung, and some haematological effects are presented in table 13 (annex F).

Exposure to CS_2 concentrations of 10-200 mg/m^3 (3.2-64 ppm), 4 h per day, for 6 months disrupted glucose absorption and inhibited intestinal enzymes responsible for hydrolysing saccharides in rats.

As to the kidney, chronic interstitial nephritis was found in rabbits following prolonged (longer than 6 months) CS_2 inhalation of 780-2340 mg/m^3 (200-750 ppm). In rats, only glomerular lesions were reported after exposure to 2000 mg/m^3 (640 ppm) for 44 h per week, up to 12 months. Several effects on renal functions (excretory abnormalities) were noted at very low levels (1-10 mg/m^3; 0.3-3 ppm), but no correlation with renal morphology was or could be made.

Carcinogenicity

At the time there is only one report dealing with carcinogenicity testing (Adkins et al 1986). However, this study was designed to evaluate the strain A/J mice lung tumour bioassay as a short-term in vivo model for predicting the potential carcinogenicity of chemicals following exposure by inhalation. Exposure for 6 h per day, 5 days per week, for 6 months to 936 mg/m^3 (300 ppm) caused significant ($p<0.05$) increases in frequency and incidence of pulmonary adenoma formation compared to corresponding control responses. The total number of adenomas was 23 versus 11 in controls. The percentage of animals with adenomas was 39 versus 28 in controls. However, the incidence of adenomas in control groups exposed to 6 other compounds ranged from 21% to 51% and the average total number of adenomas from 6 to 33. Therefore, in view of the design and the results of this study, no conclusions can be drawn with respect to the carcinogenicity of CS_2.

Conclusions

From long-term exposure studies a NAEL of 112 mg/m^3 (36 ppm) can be derived. Exposure to this levels for 4 months did not have effects on rat serum lipid levels and on rat heart or aorta morphology. Although effects due to exposure to lower levels were

noted, the significance of these findings could not be assessed because of lack of information or the difficulty to relate them to (occupational) health.

There is no relevant information on the carcinogenicity of CS_2 available.

6.1.5 *Mutagenicity*

Table 14 (annex F) summarises the findings from mutagenicity tests with CS_2, using bacteria, Drosophila, and mammalian cells. Results from several laboratories, employing various in vitro permutations of the standard Ames test, indicate that CS_2 lacks mutagenic potential for Salmonella typhimurium. CS_2 has also been found negative in other tests. However, technical problems in these studies (low exposure concentrations and omission or failure of positive controls) makes interpretation of the results difficult. There are indications that CS_2 may have genotoxic effects in mammalian systems (unscheduled DNA synthesis, cytogenic effects, and host mediated Salmonella typhimurium mutagenesis), but technical problems also exist in these studies. Therefore, these findings should be regarded as inconclusive, unless confirmation of these positive results is obtained from other laboratories.

6.1.6 *Reproduction toxicity*

Effects on the reproductive system of the male rat

The effects of CS_2 on the male reproductive system are only examined in the rat (see table 15, annex F).

Exposure to 1082 mg/m^3 (350 ppm) for 10 weeks did not have effects on reproductive organ weights or plasma hormone levels. At 1872 mg/m^3 (600 ppm) for 20 weeks significant alterations in copulatory behaviour (i.e. shorter times to mount and to ejaculate) were noted. Furthermore, ejaculated sperm counts were decreased but this was described not to a direct effect on the testes, but to an interference with the processes regulating sperm transport and ejaculation. There were no changes in reproductive organ weights and plasma hormone levels. However, intraperitoneal injection with 25 mg/kg every other day for 60 days caused degenerative changes in spermatogenic and interstitial tissue.

Effects on the reproductive system of the female animal

Table 16 (annex F) presents the effects on the reproductive system of the female animal after exposure to CS_2. After inhalation of 10 mg/m^3 (3 ppm) and above disturbances in the oestrus cycle of the rat were found.

Teratogenic effects (see table 17, annex F)

At exposures of 0.03 and 2.2 mg/m^3 (0.01 and 0.7 ppm) no adverse effects, i.e. malformations, changes in biochemical parameters, changes in maternal or foetal liver, mean litter size, mean foetal weight or size, were noted in the rat. Exposure to 10 and 12 mg/m^3 (3 and 4 ppm) did not cause foetotoxic and teratogenic effects, but some effects in the offspring were noted: retardation of the development of the MFO system and neurophysiological and behavioural disorders (at 10 mg/m^3), and kidney function disorders (at 12 mg/m^3). However, the lack of details hampered a proper evaluation of these findings.

Exposure to 50 mg/m^3 (16 ppm) revealed some teratogenic effects (not significant), whereas exposure to 100 and 200 mg/m^3 (32 and 64 ppm) resulted in a significant increase in abnormalities like hydrocephalus and club foot. Maternal toxicity was noted in animals exposed to 200 mg/m^3 (64 ppm): reduced weight gain (significant) and marked hepatic (distrophy of hepatocytes, reduced glycogen content) and placental (necrotic changes and an inflammatory reaction) effects at autopsy. Behavioural tests revealed some abnormalities in the development of the offspring of animals exposed to levels of 50 mg/m^3 (16 ppm) and above, but the significance of these observations cannot be assessed because of lack details (e.g. on generating and controlling exposure levels).

Neither significant, compound-related maternal toxicity, nor teratogenicity was found in rats exposed to 62.5 and 125 mg/m^3 (20 and 40 ppm) for 7 h per day, from day 0-18 or day 6-18 of gestation. In addition, exposure to up to 625 mg/m^3 (200 ppm) for 6 h per day, from day 6-20 did not cause effects in rats. Exposure to 1250 and 2500 mg/m^3 (400 and 800 ppm)) resulted in significantly reduced foetal body weights and an increase (not significant) in the incidence of club feet; maternal weight gain was affected as well. In addition, a significant increase in unossified sternebrae was noted at 2500 mg/m^3 (800 ppm). Hydrocephalia were not reported.

In rabbits no foetotoxic and teratogenic effects were seen after exposure to 930 mg/m^3 (300 ppm) for 6 h per day, from day 6-18. At 1860 mg/m^3 (600 ppm) there was an increase in postimplantation loss and a decrease in mean foetal weight. At the highest concentration tested, 3720 mg/m^3 (1200 ppm), an additional increase in the number of cumulative skeletal and visceral malformation (including hydrocephalus) was noted, accompanied by maternal toxicity. Club feet were not reported.

A multigeneration study, in which animals and their progeny were exposed to 0.03, 10, 100 and 200 mg/m^3 (0.01, 3.2, 32, and 64 ppm) revealed that, when F1 females were exposed to the same levels as the F0 females during gestation, the incidence of adverse effects on the prenatal and postnatal development of the F2 generation was increased, indicating that intrauterine exposure might lower the thresh-

old with respect to effects on the development of the successive generation. However, poor reporting, e.g. with respect to generating and controlling exposure levels, hampered a proper evaluation of this study.

From two oral studies with rat and rabbit, only abstracts were available.

Conclusions

Exposure to 1082 mg/m^3 (350 ppm) for 10 weeks did not affect the male rat reproductive system. Exposure to 10 mg/m^3 (3 ppm) did cause disturbances in the oestrus cycle of female rats.

With respect to the teratogenic effects in rats the results of the available studies are conflicting and comparison is hampered by methodological differences (strain, exposure regimen, end points). No NAEL can be assessed. Exposure to 100 mg/m^3 (32 ppm) may have teratogenic effects and intrauterine exposure may lower the threshold with respect to effects on the development of the successive generation. In rabbits exposed to up to 930 mg/m^3 (300 ppm), from day 6-18, no teratogenic or foetotoxic effects were observed.

6.1.7 *Other studies*

CS_2 and H_2S mixtures

At the workplace workers are usually exposed to both CS_2 and H_2S. Little is known about this combined exposure. Beauchamp et al (1983) found three reports suggesting either an additive or synergistic toxic effect of CS_2 and H_2S. From other studies, no conclusions could be drawn because no single exposure controls were included.

Gagnaire et al (1986) observed no influence of H_2S on the CS_2 induced peripheral nerve toxicity as measured by the sensory and motor tail nerve conduction velocity in rats exposed for 25 weeks to 1560 mg/m^3 (500 ppm) of CS_2 and 75 mg/m^3 (50 ppm) of H_2S. Saillenfait et al (1989) exposed pregnant rats to 310, 620, 1250 and 2500 mg/m^3 (100, 200, 400, and 800 ppm) of CS_2 alone or in combination with 150 mg/m^3 (100 ppm) of H_2S for 6 h per day, during day 6-20 of gestation. The combined exposure resulted in an increase of maternal (i.e. reduced weight gain of the dams) and foetal (i.e. reduced foetal body weights) toxicity in the two higher exposure groups.

Other combined exposures

Ethanol enhanced certain adverse effects of chronic CS_2 exposure to 800 mg/m^3 (256 ppm) for 8 months or more: effect on CNS and PNS as measured by biochemical and

ultrastructural changes (Opacka et al 1985, 1986), effect on liver MFO and MEOS (Wronska-Nofer et al 1986), and effect on memory and learning ability (Opacka et al 1984).

CS_2 is frequently used to protect experimental animals against liver damage by other chemicals by inhibiting their metabolism. However, it may also affect efficacy and duration of action of many therapeutics resulting into overdosage (Masuda and Nakayama 1982; Orzechowska-Juzwenko et al 1984).

6.2 Observations in man

6.2.1 *Acute toxicity*

Only few reports are available on acute poisonings due to CS_2. In their review on the toxicity of CS_2 Fielder and Shillaker (1981) have summarised its acute toxicity. Oral ingestion of amounts estimated to be about 18 g was fatal within a few hours on at least three occasions. Signs of toxicity noted prior to death due to CNS depression and respiratory paralysis, were spasmotic tremor, prostration, dyspnoea, cyanosis, peripheral vascular collaps, hypothermia, mydriasis, convulsions, and coma. At autopsy only mild gastrointestinal irritation and visceral congestion were noted. Exposure by inhalation to 1560-3120 mg/m^3 (500-1000 ppm) resulted in a wide range of psychiatric disturbances ranging from excitability, confusion, extreme irritability, uncontrolled anger, nightmare, and depression to manic delirium, hallucinations, suicide, or insanity. Higher levels, about 1560 mg/m^3 (5000 ppm), rapidly caused CNS depression, coma, respiratory paralysis, and death.

In 1982, two other reports have been published. After a railroad tank car accident 27 persons were exposed to CS_2 and subsequently examined. CNS toxicity was more frequent than the direct irritant effects. The most noted complaints were: headache (59%), dizziness (59%), nausea (52%), burning of throat, lips or skin (40%), and shortness of breath or chest pain (15%). Furthermore, transient changes were seen in arterial oxygen pressure and slow vital capacity (Spyker et al 1982). Although the effects were assigned to exposure to CS_2, it is very likely, in view of the circumstances (fire), that they are the result of exposure to SO_2 released from the burning of CS_2.

Kruse et al (1982) reported an accidental exposure of a 48-year-old man to a high concentration of CS_2, estimated to be between 1270 and 1,500,000 mg/m^3 (400 and 470,000 ppm)) for about 20 min. Serious persistent cerebral deterioration developed. Computerised tomographic scanning showed cerebral atrophy, neurophysiological examination established dementia, and measurement of cerebral flow showed reduced cortical flow in the right hemisphere. One year and nine months after the accident the

symptoms were still present and, in spite of treatment, the patient was unable to manage his previous work.

6.2.2 Cases

Aaserud et al (1988, 1990) performed a neurological examination, computerised tomography, cerebral blood flow examination, and neuropsychological examination in 16 Norwegian workers (mean age: 56 y, range: 43-65 y) exposed for at least 10 years (mean: 20 y; range: 10-35 y) to CS_2. At the time of investigation the workers had ceased for at least 4 years. In most of the workers abnormalities were found in clinical neurological examination as well as impairments in neuropsychological tests. The effects might be exclusively due to exposure to CS_2 in about half of the workers. However, no firm conclusions can be drawn from this study with respect to dose-response relations, because of limited exposure data and methodological flaws.

6.2.3 Epidemiology

In general, it is difficult to draw conclusions on exposure-effect or exposure-response relationships from epidemiological data. Effects are studied in workers exposed for several years during which exposure levels may have varied widely. Furthermore, measurement of exposure levels by personal air sampling (PAS) is a rather recent method. Previously reported levels originated from environmental monitoring (EM), which does not necessarily measure the actual levels to which the workers were exposed. Also, CS_2 exposure is accompanied with (mostly unknown) H_2S exposure and the effects observed may, at least in the past, be due to or influenced by this concomitant exposure.

Neurotoxic and neurobehavioural effects

Data on the neurotoxic and neurobehavioural effects of CS_2 are summarised in table 18a and 18b (see annex F). Earlier studies show that exposure to levels of 94 mg/m^3 (30 ppm) and higher affects both the CNS and the PNS.

Symptoms of CNS toxicity include headache, emotional effects, insomnia, and vertigo. Symptoms of PNS toxicity (paraesthesia, weakness) were noted initially in the legs and later in the hands of exposed workers (Fielder and Shillaker 1981). These effects were already seen in workers younger than 25 y of age) after relatively short exposure (less than two years) to 225-300 mg/m^3 (72-96 ppm). Fielder and Shillaker (1981) also refer to a series of studies in Japanese viscose rayon factories in the 1950s and 1960s which revealed that reducing exposure levels from 125-156 mg/m^3 (40-50

ppm) to 16-47 mg/m^3 (5-15 ppm) with occasional excursions up to 312 mg/m^3 (100 ppm) led to a decrease of the prevalence of the neurotoxic symptoms. At two factories no symptoms were reported regarding workers exposed for 1-10 years to levels of 15-59 mg/m^3 (5-19 ppm).

The most sensitive parameter of neurotoxicity is the conduction velocity in the peripheral nerves of the lower extremities. Reduction has been demonstrated without any other signs or symptoms of neurotoxicity at levels below 62 mg/m^3 (20 ppm).

A neurological examination was conducted on 145 workers exposed to mean CS_2 concentrations in air of 3-48 mg/m^3 (1-16 ppm) as determined by personal air sampling with charcoal tubes (Albright et al 1984; Johnson et al 1983). Previously, they were exposed to mean levels ranging from 5-186 mg/m^3 (1.5-60 ppm), most observations being below 60 mg/m^3 (20 ppm). They were divided into three exposure groups according to historical mean levels calculated for job titles. At the time of study, mean levels were measured to be 3.1, 12.8 and 23,7 mg/m^3 (1.0, 4.1 and 7.6 ppm), respectively. The reference group was matched as to sex, race, smoking and drinking habits, education, age, and employment duration. When there were indications of diabetes, excessive alcohol consumption, or elevated blood lead levels, workers were excluded. Reductions in nerve conduction velocities confined to the peroneal and sural nerves were demonstrated as a consequence of chronic, low level exposure. These reductions were very small in all exposure groups and were within a range of clinical normal values. They were related to the calculated cumulative exposure, but not the length of employment. No differences were found in the ulnar nerve and in PNS symptoms reported on a questionnaire.

Cirla and Graziani (1981) examined 50 workers exposed to 10-25 mg/m^3 (3-8 ppm; mean values registered during the 12 years preceding the study; sampling strategy not indicated). Workers were pair-matched as to age, physical feature, workshift, smoking and drinking history. No significant changes in neuropsychological parameters were found.

Ruijten et al (1988, 1990b) investigated the special peripheral and autonomic nerve functions of 45 workers (mean age: 49 y; mean exposure time: 20 y) of a Dutch viscose rayon plant. The workers were pair-matched as to age and nationality. From spot and personal air sampling exposure levels were estimated to range from 3-53 mg/m^3 (1-17 ppm), with a mean level of ca 25 mg/m^3 (8 ppm) and an average cumulative exposure of 515 mg.m^{-3}.y (165 ppm-years). The observed effects were dependent on the exposure measure (cumulative or not, weighted or not) and the corresponding classification into groups. Minimal, but statistically significant changes, related to cumulative exposure, were found in the peroneal nerve: decreased condition velocity of the slow fibers (- 1.1 m/s) and a prolongation of the refractory period (0.1 m/s). Several other neurophysiological parameters were not affected. An additional analysis

showed no difference between the conduction velocity of workers previously exposed to peak levels (defined as exposure to levels higher than 50 ppm, for more than 15 min a day, more than once a week, for more than one year) and that of workers who were not (Swaen, personal communication 1990).

A follow-up study was performed on 80 of the 87 participants, four years later. Since six of them were not eligible and some former controls appeared to have been exposed to some extent in the past, 43 exposed (mean age: 51.7 ± 7.5 y) and 31 controls (mean age: 51.9 ± 6.5 y) were reexamined. Exposure levels had not been changed; the average cumulative exposure was estimated to be 608 ± 509 $mg.m^{-3}.y$ (195 ± 163 ppm-years), range 34- 2760 $mg.m^{-3}.y$ (11-886 ppm-years). The neurophysiological examination was extended with parameters related to the sensory and motor nerve fibers of the fingers, hands, and arms. The preliminary reported results confirmed the previously found decrease in motor conduction velocity of the slow peroneal nerve fibers, related to cumulative exposure, but not the prolongation of the refractory period. Contrary to the previous study, the fast peroneal nerve fibers as well as the parameters related to the sural nerve were affected, probably because of improved technical facilities. There were no consistent changes in the autonomic and arm nerve parameters (Ruijten et al 1990a).

The results of a longitudinal analysis and a more comprehensive comparison between the two studies were not available.

Neuropathic damage due to CS_2 exposure represented by reduced conduction velocities of the slow fibers in the peripheral nerves was very persistent: reexamination of persons previously exposed to high levels of about 200 mg/m^3 (60 ppm)) for about 20 years demonstrated that 10 years after cessation there was still no significant electromyographic improvement (Corsi et al 1983).

Besides neurotoxic effects, neurobehavioural effects are noted (see table 18b, annex F). These effects are virtually always accompanied by symptoms, signs, and reliable diagnostic criteria, but there is an obvious need for greater application of modern behavioural techniques (Beauchamp et al 1983).

A NAEL cannot be derived from these data. However, exposure to concentrations less than 30 mg/m^3 (10 ppm) results in minimal changes in peroneal nerve conduction velocity.

Cardiovasular effects

Fielder and Shillaker (1981) concluded from studies carried out before 1970, that exposure to CS_2 concentrations of about 160 mg/m^3 (50 ppm) or above results in atherosclerotic lesions in the cerebral and peripheral arteries and that high levels have been

associated with a characteristic vascular encephalopathy. Because of the absence of adequate control groups it is difficult to establish whether the arterial lesions are due to exposure to CS_2 rather than to age-related changes. However, vasoconstriction and mild to moderate sclerotic changes have been noted in a group of relatively young workers, mostly below 35 years of age who were exposed to levels estimated to be ranging from 200-900 mg/m^3 (64-288 ppm). Increased serum cholesterol levels have been found in a small number of studies of workers exposed to mean concentrations ranging from 62-190 mg/m^3 (20-60 ppm). Below 62 mg/m^3 (20 ppm) no effects on serum cholesterol were noted.

More recent studies are summarised in table 19 (annex F). In a series of studies on Italian workers exposed for up to 37 years to concentrations below 35 mg/m^3 (11 ppm) no effects were seen on factors of atherogenesis when compared with a control group matched as to age, sex, physical feature, smoking and drinking history (Candura et al 1981; Cirla and Graziano 1981; Franco et al 1984).

In Chinese workers exposed for up to 20 years (mean: 10 y) to concentrations of 0.7-16 mg/m^3 (0.2-5 ppm; personal air sampling; levels from 1975-1981: 3-42 mg/m^3 or 0.9-13 ppm obtained by spot sampling) no changes in blood pressure, blood cholesterol levels, and ECG were found (Sugimoto et al 1984).

In a study in the US only changes in the blood pressure (i.e. little higher systolic reading) of workers exposed to concentrations of 3-48 mg/m^3 (1-16 ppm; obtained by personal air sampling; levels from 1957: 5-186 mg/m^3 or 1.5-60 ppm , mostly less than 62 mg/m^3 or 20 ppm; obtained by spot sampling) were seen (Albright et al 1984).

From these data it can be concluded that 30 mg/m^3 (10 ppm) can be considered to be a no-effect level as to atherogenic factors like serum lipid pattern and blood coagulation factors, platelet function, and fibrinolysis, although data on blood pressure, are conflicting at this level.

Incidence of heart disease

The first detailed investigation of the mortality due to coronary heart disease (CHD) in viscose rayon workers was reported in 1968. An increased incidence of deaths due to CHD was noted in workers in the spinning department of three viscose rayon factories in the UK. The excess mortality was most pronounced in the 1940s and had declined considerably by the early 1960s. A detailed study at one plant revealed that the death rate from CHD of men working in the spinning department was 2.5 times that of workers in other areas without CS_2 exposure; the mean concentrations in the spinning department frequently exceeded 62 mg/m^3 (20 ppm; Fielder and Shillaker 1981). Sweetnam et al (1987) have successfully reconstructed the above mentioned cohort and followed up to the end of 1982 (n=2848). The pattern of mortality at ages 45-64

years for the follow-up period is similar to that of the previous period (1950-1964). The spinners, the workers most heavily exposed, have a significantly higher mortality from all causes than the least exposed group. The excess mortality is largely accounted for by ischaemic heart disease (IHD) for which the spinners have a standardised mortality ratio of 172. When mortality is related to an exposure score in the same group, both all causes ($p<0.01$) and IHD ($p<0.001$) mortality increase with increasing exposure level. When this analysis is repeated covering all ages, these trends become much less strong and only that for IHD remains significant ($p<0.05$). Over the age of 65 there is a tendency for mortality to decline with increasing exposure. Furthermore, there is a strong trend ($p<0.01$) for IHD mortality to increase with increasing exposure in the previous two years. Both IHD ($p<0.001$) and total ($p<0.01$) mortality show highly significant trends with exposure among current workers but no such trends among workers who left industry.

Cardiovascular mortality of a cohort of 343 Finnish workers exposed for at least 5 years has been monitored prospectively from 1967-1982. Exposure data were from stationary measurements: after 1972 less than 31 mg/m^3 (10 ppm); from 1960-1972 31-93 mg/m^3 (10-30 ppm); from 1950-1960 62-186 mg/m^3 (20-60 ppm). Data for 1967-1972 showed a 4.7 fold excess mortality for heart diseases compared with a comparable reference group of papermill workers. After 1972 a preventive intervention program had been carried out: all workers with coronary risk factors were removed, exposure levels were reduced (standard lowered to 30 mg/m^3 or 10 ppm). These measures were reflected in a normalisation of the cardiovascular death rate: the relative risk declined from 3.2 (period 1972-1974) to 1.0 (period 1974-1982). The risk of the fatal heart attack remained at 11.6% throughout the 15 year follow-up period (95% confidence limit: 8.5-15.4%) among the exposed compared with 7.8% (5.3-11.2%) among the unexposed. The entire risk difference of 3.8% was accumulated during the first 7 years of follow-up (Nurminen and Hernberg, 1985).

Lyle (1981) studied the mortality of a 1957-1968 cohort of employees in a viscose factory up to the end of 1978. The 339 persons were divided into two groups: 115 little or occasionally exposed (employment duration 5.7 ± 4.4 y) and 224 exposed workers (mean levels 19-110 mg/m^3 or 6-35 ppm; employment duration: 8.6 ± 5.9 y). Exposure periods of one year or more to these levels increased the mortality from IHD slightly, but not significantly during the period of observation (SMR: 115); mortality from all cases decreased not significantly (31 observed versus 33.3 expected, SMR: 93).

In a cohort of 1282 white male production workers in the rubber industry a survivorship analysis was made comparing the cardiovascular disease mortality experience of exposed and non-exposed workers during a 15-year follow-up period. A significant association between CS_2 exposure and IHD was found only among exposed workers of 50-54 years of age in 1964 (Wilcosky and Tyroler 1983).

Albright et al (1984) determined the prevalences of angina pectoris and myocardial infarction, using the Rose questionnaire, and of coronary heart disease, evaluating the ECG using the Minnesota Code, in a cohort of 146 exposed US workers (compared with 233 controls). Due to the small numbers found and the small size of the group no conclusions could be drawn.

In 354 Chinese workers, exposed at the time of study to a mean level of 4.5 mg/m^3 (1.5 ppm) as determined by personal air sampling (previous spot levels: 2.8-41.5 mg/m^3 or 0.9-13 ppm) no cases with typical and probable angina were detected using the WHO questionnaire. The prevalence of possible angina was lower (0.6% versus 2.2%) and of a typical angina higher (4.2% versus 2.2%) (Sugimoto et al 1984).

MacMahon and Monson (1988) have carried out a study on the mortality of 10,418 men exposed to carbon disulphide in four US rayon plants, between 1957 and 1979. The cohort was followed through mid-1983 with respect to living or dead status, but employment histories were not updated after 1979. The workers were divided into exposure categories none, least, intermediate, heaviest, and variable, based on job titles. No actual exposure levels were published. The authors found no increase in overall mortality in the 4448 workers with the highest potential exposure when compared with the mortality in the 3311 non-exposed workers. There was a significant excess of death rate from arteriosclerotic heart disease among those with high and intermediate exposure (242 death observed versus 195.6 expected); those with low or variable exposure had a lower risk of death from this disease than expected. No clear relationship between exposure duration or latency (i.e. the number of years from the beginning of exposure to the end of follow-up) was found. However, the excess mortality from arteriosclerotic heart disease among the highest exposed workers employed in 1960 or later was small and not statistically significant (SMR: 114; 90%-confidence interval: 83-154) and lower than among workers employed in the years before 1960. Since no actual exposure levels were presented, a no-effect-level with respect to death from arteriosclerotic heart disease cannot be derived. The data suggest, that this effect only occurred among the highest exposed group (i.e. cutters and spinners) at times when levels were higher than the current ones.

A Dutch retrospective cohort study has been conducted mainly aimed to investigate whether exposure to CS_2 has led to increased mortality rates from cardiovascular diseases, and to establish a no-observed adverse effect level. The study group consisted of 3322 workers in a Dutch viscose textile plant who had been employed for at least half a year between 01-01-1947 and 01-01-1980. Only male production workers and maintenance personnel were eligible. The study population was divided into exposure groups according to their workhistories: continuously exposed (n = 672), intermittently exposed (n = 762)*, and non-exposed (n = 1888). From spot sampling (1949-1984) and personal air sampling (from 1984 onwards) data it was concluded

that exposure levels were fairly constant over the entire period, averaging ca 22 mg/m^3 (7 ppm) in the spool spinning department, in the bleaching area, and in the continuous spinnery. An apparent increase in exposure levels was noted in the period 1967-1978. It could not be established whether this increase was due to increased pressure on the maintenance requirements or a fallacy due to changing monitoring strategy (accident instead of routine monitoring). The total mortality of the total study population was lower than expected based on the Dutch mortality statistics: SMR exposed group: 90.6; SMR non-exposed controls: 86.1. The SMR for cardiovascular disease was 115.7 (95%-confidence limit: 100.5-132.7), being statistically significant different from 100, for the total exposed group and from 94.4 for the non-exposed control group. The data indicate that the exposed group had an increased risk for cardiovascular disease mortality. It was not possible to establish a dose-effect relation, a no-effect level, or the influence of peak exposure levels. Although life-style confounders were not analysed thoroughly, these were not considered to play an important role (Swaen et al 1991).

Effects on the eye

Studies of the effects of CS_2 on the eyes of exposed workers are presented in table 20 (annex F).

No retinal changes such as microaneurysms and small dot haemorrhages were found in Chinese workers exposed for up to 20 years to an average concentration at the time of study of 4.5 mg/m^3 (1.5 ppm; range: 0.7-16 mg/m^3 or 0.2-5 ppm) as measured by personal air sampling (from 1975-1981: 3-42 mg/m^3 or 0.9-13 ppm obtained by spot sampling) (Sugimoto et al 1984).

In a study on US workers such changes were found as well and, as in other studies, a relation between incidence and severity of signs and exposure was noted. Exposure concentrations up to 48 mg/m^3 (16 ppm) were measured at the time of the study by personal air sampling. Previous data from area sampling showed concentrations up to 186 mg/m^3 (60 ppm), although most values were less than 62 mg/m^3 (20 ppm) (Albright et al 1984).

The difference in signs between Finnish and Japanese workers exposed under almost the same conditions is remarkable . In the Japanese workers an increased incidence of retinopathy was seen, in the Finnish not. In the latter group circulatory effects were seen in workers exposed to an average concentration of 45 mg/m^3 (1.5 ppm) at the time of study (exposure during the preceding 6 years ranged from 3-42 mg/m^3 or 0.9-13 ppm; no further data reported). In an US study, workers exposed to 3-48 mg/m^3

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* not necessarily identical to a lower exposure; e.g. emergency repairs may have been associated with very high peak levels

(1-16 ppm) at the time of study (during the preceding 22 y concentrations were usually less than 62 mg/m^3 or 20 ppm) had significantly more microaneurysms and haemorrhages when compared with controls.

Effects on other organs or systems

There are no recent reports on effects on other organs or systems, from which conclusions can be drawn.

Carcinogenicity

Nurminen and Hernberg (1984) performed a 15-year study on two industrial cohorts: 343 viscose rayon plant workers exposed to CS_2 and 343 paper mill workers (controls). The mortality form lung cancer was lower among viscose rayon workers (4 per 4685 man-years) than among the comparable, unexposed paper mill workers (9 per 4830 man-years); the difference is not statistically significant. It was concluded that CS_2 is not carcinogenic, at least under moderate exposure conditions (concentrations for 1970: 16-31 mg/m^3 or 5-10 ppm or , 1960-1970: 31-93 mg/m^3 or 10-30 ppm, 1950-1960: 62-186 mg/m^3 or 20-60 ppm).

Wilcosky et al (1984) followed a closed cohort of 6678 active and retired male rubber workers for a 10-year period that began in 1964. Exposure was defined as the presence for more than one year of a worker in a process area where a given solvent (out of 20 solvents) was authorised for use according to company records. No association of CS_2 exposure was observed with cancer of the respiratory system, the stomach and the prostate. A strong association ($p<0.001$) with lymphatic leukaemia (odds ratio 15.3) and a weaker association ($p<0.05$) with lymphosarcoma (odds ratio 4.2) was found, although CS_2 has not been shown to cause lymphosarcoma or lymphatic leukaemia. The significance of this study is dubious: odds-ratios were calculated based on possible exposure (authorisation for use did not guarantee actual use), on possible co-exposure (24 other solvents and in addition many other, not mentioned chemicals are used in the rubber industry), and on a minimal number of cases (14 lymphosarcomas and leukaemias in a cohort of 6678 persons).

In the aforementioned Dutch retrospective cohort study, no excess of mortality from cancer (total as well as specific neoplasms) was found among exposed workers when compared with non-exposed controls (Swaen et al 1991).

Effects on the male reproductive system

Decreased libido, hypospermia, abnormal sperm morphology, reduced urinary excretion of 17-hydroxycorticosteroids and 17-ketosteriods, and changes in serum levels of sexual hormones were found in previous studies. However, lack of adequate control groups and limited information on actual exposure levels (probably larger than 93 mg/m^3 or 30 ppm) make it difficult to interpret these data (Fielder and Shillaker 1981).

Recent studies (see table 21, annex F) show that chronic exposure to concentrations less than 62 mg/m^3 (20 ppm) does not have adverse effects on libido, potency, sperm counts, and sperm morphology. Albright et al (1984) did not find significant differences in these parameters in workers exposed to levels ranging from 3-48 mg/m^3 (1-16 ppm, obtained with personal air sampling at time of study; previously exposures mostly not exceeding 62 mg/m^3 or 20 ppm as determined by spot sampling) when compared with controls.

Kolk and Braun (1986) investigated the influence on male sexual functions using an indirect approach: the number of children was hypothesised to be a measure for the libido, and potency or sperm disorders. Exposure to concentrations of 10-25 mg/m^3 (3-8 ppm, previously about 60 mg/m^3 or 19 ppm) did not, on average result in a smaller number of children than in the non-exposed controls.

Regarding endocrinologial functions, Cirla and Graziano (1981) found no differences in the serum levels of FSH, LH, and testosterone in workers exposed for 3-12 years to mean concentrations varying from 10-25 mg/m^3 (3-8 ppm, spot sampling), when compared with pair-matched controls.

In workers exposed for up to 36 years to concentrations less than 30 mg/m^3 (10ppm (, 75th percentiles from last 10 years; previously higher; spot sampling), FSH levels were increased and sex hormone binding globuline (SHBG) levels decreased, when compared with the reference group. When dividing the exposed into age and exposure duration groups, levels of FSH, LH, SHBG, and of free testosterone index in men under 39 years of age and exposed for up to 9 years differed significantly from controls of the same age, whereas exposure for 10 years or more, only resulted in elevated FSH levels in this age group. In men aged 40 years or more only changes in elevated FSH and LH levels were found in the group exposed for 10 years or more (Wägar et al 1983). The authors suggested that the changes might be of subclinical importance, since changes in levels of testosterone and the free testosterone index were not consistent. Furthermore, spermatogenesis was not investigated and, therefore, a full evaluation was not possible, although the hormonal balance in the pituitary-gonadal axis might be affected, increasing the risk of latent primary gonadal insufficiency.

In the aforementioned study by Albright et al (1984) no effect on the thyroid gland function was seen by determination of triiodothyroxine uptake (T3), serum thyroxine by RIA (T4), and T3-T4 index.

Effects on the female reproductive system

Literature on adverse effects of CS_2 exposure in women has been reviewed by Zielhuis et al (1984). Almost all reports deal with exposure of female workers in factories in Eastern Europe. The studies are generally lacking of adequate matched control groups and of information on actual exposure levels. However, studies on certain effects frequently point in the same direction. In five studies an increased incidence (2-5 fold) of menstrual irregularities was found. Three reports mentioned an increased prevalence (2-4 fold) of toxemia of pregnancy, four indicated an increased risk on miscarriage (factor 1.5-2.5), although in one separate study no increase in miscarriage was found. Finally, in two reports premature births were noted. In almost all studies exposure levels were suggested to be -sometimes far- below 62 mg/m^3 (20 ppm).

Recently, Zhou et al (1988) have published the results of a retrospective cohort study, in which 265 female workers exposed to CS_2 were compared to 291 non-exposed workers with respect to menstrual disturbances (suppresion of menses, abnormal bleeding) and the term and outcome of pregnancy (toxemia, emesis gravidarum, spontaneous abortion, stillbirth, premature and overdue delivery, congenital malformation). Since 1970, the viscose rayon plants involved have been monitored regularly by colorimetric analysis of spot samples. In the period 1970-1974 concentrations ranged from 5.9-30.6 mg/m^3 (1.9-9.8 ppm), in the period 1975-1979 from 2.1-12.2 mg/m^3 (0.7-3.9 ppm) and in the period 1980-1985 from 0.7-4.7 mg/m^3 (0.2-1.5 ppm). No data on potential exposure to other compounds were given. The exposure time varied from at least 1 year to more than 20 years. With respect to the term and outcome of pregnancy no differences were found between both groups. In the exposed group a significantly higher incidence of menstrual disturbances, especially of menstrual irregularity and abnormal bleeding, was found (39.5% versus 18.2%, relative risk: 2.0, $p<0.01$). However, the validity of these conclusions can be questioned because of some flaws concerning selection procedures of groups, differences between exposed and controls, statistical methods, and exposure data. In addition, a criterion such as 'menstrual disturbances' is open to individual interpretation, and worker (recall) and interviewer bias.

These data do not allow firm conclusions due to poor reporting and the lack of valid information on control groups and actual exposure levels. However, these studies point in the same direction indicating that exposure to CS_2 can produce adverse effects

on the menstrual cycle and the outcome of pregnancy, probably even at low levels. There were no indications that such effects occur at levels below 3 mg/m^3 (1 ppm).

6.3 Summary

CS_2 is markedly irritant to rabbit skin. It has low acute lethal toxicity in animals. Exposure to concentrations of about 1900 mg/m^3 (600 ppm) for several hours produces no overt signs of toxicity.

Short-term and long-term exposures affect all major organ systems and tissues as is demonstrated mainly by inhalation experiments with rats. Long-term exposure studies indicate a no-adverse-effect level of 112 mg/m^3 (36 ppm): exposure for 4 months did not cause changes in serum lipid levels nor morphological changes in the heart and the aorta of rats. The lowest reported effect level concerns the cardiovascular system: exposure to 230 mg/m^3 (74 ppm) for 8 months causes a slight, but significant increase in serum cholesterol levels.

Exposure to CS_2 combined with an atherogenic diet accelerates atherosclerotic changes.

There are no data from life-time carcinogenicity studies available. Although mutagenicity tests using bacteria, Drosophila, and mammalian cells, were negative, no definite conclusions can be drawn because of several technical problems in the tests.

CS_2 affects the male as well as the female reproductive system. Inhalation of CS_2 concentrations of about 110 mg/m^3 (350 ppm) did not cause lesions in the testes, whereas i.p. injections did. Inhalation of concentrations of 1870 mg/m^3 (600 ppm) did alter copulatory behaviour and caused a decrease in sperm counts. Exposure to 10 mg/m^3 (3 ppm) and above resulted in disturbances in the oestrus cycle of the female rat. Foetotoxic (reduced litter size) and teratogenic (hydrocephalus and club foot) were noted at exposure levels of 100 mg/m^3 (32 ppm) in one study, but not in other studies at exposure levels up to 625 mg/m^3 (200 ppm), although under methodologically different conditions. Intrauterine exposure may lower the threshold with respect to effects on the development of the successive generation. In rabbits, a no-observed effect level of 940 mg/m^3 (300 ppm) was found.

Although at the workplace CS_2 exposure is usually accompanied with H_2S exposure, little is known about this combined exposure. The enhancement of certain adverse effects of CS_2 by ethanol is known. Finally, because CS_2 affects the MFO system, it may inhibit the metabolism of certain drugs and in doing so, influence their efficacy and duration of action.

As to observations on man, accidental exposure to CS_2 is rare. High levels (1600-3200 mg/m^3, 500-1000 ppm) for a few hours produce severe psychiatric disturbances. Most effects observed are due to occupational exposure for several years.

Exposure to concentrations of about 95 mg/m^3 (30 ppm) and above affects both the CNS and PNS, characterised by symptoms like headache and numbness and weakness of legs and hands. At levels below 30 mg/m^3 (10 ppm) only minimal effects in the form of very small reductions in nerve conduction velocities occur.

With respect to the cardiovascular system, exposure to concentrations less than 30 mg/m^3 (10 ppm) is considered to have no effect on atherogenic factors like serum lipid pattern, blood coagulation factors, platelet function, fibrinolysis and blood pressure. However, in Dutch workers with long-term exposure to mean concentrations of ca 22 mg/m^3 (7 ppm) a significantly increased SMR from cardiovascular disease was observed.

Adverse effects in the eye like retinal microaneurysms and haemorrhages were seen in US-workers, exposed to concentrations ranging from 3-48 mg/m^3 (1 to 16 ppm). No such effects were demonstrated in Chinese workers exposed to concentrations less than 15 mg/m^3 (5 ppm); the mean exposure level was about 5 mg/m^3 (1.5 ppm). Comparison of a group of Japanese workers with a group of Finnish workers with the same exposure conditions (i.e. about same mean duration and same levels from 1960 below 60-95 mg/m^3 or 2-30 ppm, previously higher) showed remarkable differences. The Japanese had significant increase in the incidence of retinopathy. This was not seen in the Finnish, but they did show circulatory effects.

In Dutch workers with long-term exposure to mean levels of ca 22 mg/m^3 (7 ppm) no excess of mortality from total as well as specific neoplasms was found.

As to the male reproductive system decreased libido, hypospermia, abnormal sperm morphology, and changes in urinary and serum levels of certain steroids and hormones were found at concentrations presumably above 95 mg/m^3 (30 ppm). At concentrations below 62 mg/m^3 (20 ppm) no adverse effects on libido, potency, sperm counts, and sperm morphology were demonstrated. Reports on several hormone levels around this concentration level are conflicting.

Reports on effects on the female reproductive system are generally of poor quality. However, the tendency exists that exposure levels below 31 mg/m^3 (10 ppm) produce adverse effects on the menstrual cycle and the outcome of pregnancy.

Chapter 7

Previous evaluations by other national and international bodies

The current German standard has been set in 1975: 30 mg/m^3 (10 ppm), time-weighted average at work places. In this value excursions to higher levels are included. This standard is considered to be tentative and is based on the effects noted at experimental and occupational exposure to levels ranging from 31-125 mg/m^3 (10-43 ppm). These effects include significant increase in blood pressure (systolic, diastolic), increased incidence of angina pectoris and fatal heart attacks, increased plasma creatinine and decreased glucose tolerance, all noted after 5-25 years exposure to about 62 mg/m^3 (20 ppm) with a range of 31-125 mg/m^3 (10-40 ppm), as well as increased blood pressure, coronary diseases, changes in lung function, in clinical-chemical parameters in blood and urine, and in neurophysiological parameters at concentrations between 31-62 mg/m^3 (10 and 20 ppm). A 'skin' notation has been added, because CS_2 is considerably absorbed by the human skin (Henschler 1988).

NIOSH (1977), in its criteria document in CS_2, recommended a TWA exposure limit (10 h, 40 h workweek) of 1 ppm with a 10 ppm ceiling for any 15 min period. This recommendation is based on cardiovascular and neurological studies indicating that 31 mg/m^3 (10 ppm) is the lowest concentration causing demonstrated health effects. A few reports of adverse findings (e.g. as to reproductive effects) at lower concentration levels were cited, but their validity was questioned because of shortcomings in sampling, analytical or experimental methodologies. A safety factor of ten was applied to the lowest concentration shown to be associated with cardiovascular effects (i.e. 31 mg/m^3 or 10 ppm), because coronary heart disease frequently results in sudden death.

The TLV established by ACGIH is based on literature from before 1980. The 20 ppm limit was selected primarily to prevent neurological disturbances. However, it has been critized as to high even on this basis. The finding of cardiovascular effects in workers exposed to relatively low concentrations should result in a reduced A 'skin' notation has been added (ACGIH, 1986).

OSHA (1989b) has determined that an 8-h TWA limit of 4 ppm, a STEL of 12 ppm and a skin notation are necessary to reduce the risk of cardiovascular disease and reproductive effects among CS_2 exposed workers and has established these limits in its final rule. OSHA stated that a lower limit (former 8-h TWA limit: 20 ppm) was needed based on the evidence that exposure to CS_2 presents risks of cardiovascular, foetotoxic and neurological material impairment of health.

A WHO Study Group recommended a tentative health-based occupational exposure limit of 10 mg/m^3 (3 ppm) in the form of a time weighted average for the long-term exposure of male workers. This limit is based on the various adverse effects noted in the concentration range 10-30 mg/m^3 (or even lower), such as neurological disorders, including autonomic innervation of the cardiovascular system, biochemical changes, changes in the spectra of serum glycoproteins, oestrogen imbalance, diminished immunological reactivity, and pathological changes observed in experiments on pregnant rats. In view of the latter changes the Study Group recommended a tentative health-based occupational exposure limit of 3 mg/m^3 (time-weighted average) for women of fertile age, in order to avoid the risk of harming the developing foetus, should they become pregnant. The short-term exposure limit (15 min) should not exceed 60 mg/m^3 during the working day, maintaining the time-weighted average of 10 mg/m^3 (WHO, 1981).

In almost all evaluations the difficulties met in assessing the validity of the various investigations because of deficiency or lack of adequate information on exposure and control groups, sampling strategy or exposure level, are mentioned.

At the time no evaluation by the IARC is available.

Chapter 8

Evaluation of human health risk

8.1 Groups at extra risk

Workers with coronary risk factors may run a higher risk with respect to ischaemic heart disease.

8.2 Assessment of health risk

There are sufficient human data concerning the effects due to exposure to CS_2 to establish an occupational exposure limit. The evaluation will be limited to data from studies dealing with exposure levels around and below the current occupational exposure limit of 60 mg/m^3 (20 ppm).

The assessment of health risks from exposure to CS_2 is hampered by a number of factors. Usually, effects are studied in workers exposed for several years during which exposure levels may have varied widely. In addition, previous data on exposure levels are from environmental monitoring and not based on personal air sampling; such data are not necessarily equal to the concentrations to which the workers are actually exposed. Finally, in the occupational setting CS_2 exposure may be accompanied with H_2S exposure. Most reports do not indicate the presence of such co-exposure.

In deriving an occupational standard data on effects on nervous, cardiovascular, and reproductive system are of interest. Data concerning the carcinogenic potency of CS_2 in animals are lacking, but in a Dutch cohort exposed to mean levels of ca 22 mg/m^3 (7 ppm) no excess mortality from cancer was observed.

US workers, exposed to concentrations up to 50 mg/m^3 (16 ppm) at the time of study as obtained by personal air sampling (previously up to 181 mg/m^3 or 60 ppm but generally below 60 mg/m^3 or 20 ppm; spot sampling), had significantly reduced nerve conduction velocities (Albright et al 1984). However, these changes were very small and within the range of clinically normal values. The prevalence of angina pectoris, myocardial infarction, and coronary heart disease could not be evaluated due to the small numbers found and the small number of groups. The exposed workers had a little higher systolic (129.8 mmHg versus 127.1 mmHg, age and obesity adjusted; $p<0.05$) and diastolic (74.2 mmHg versus 72.5 mmHg, age and obesity adjusted, not significant) blood pressures, but these values are considered to be within the normal range.

Finally, significantly more microaneurysms and haemorrhages were found in the eyes of exposed workers. However, the significance of these findings in terms of health risk is not clear.

In Dutch workers, exposed to a mean concentration of 25 mg/m^3 (8 ppm), with a range of 3-50 mg/m^3 (1-17 ppm) as determined by spot and personal air sampling, a small decrease of the conduction velocity of the slow fibers of 1.1 m/s and a prolongation of the refractory period of 0.1 m/s was found (Ruijten et al 1988).

In the same plant, a retrospective cohort study of 1434 exposed workers revealed a significantly increased risk for cardiovascular disease mortality (Swaen et al 1991).

In another study in this plant no influence of CS_2 exposure on male sexual function or libido was found when the number of children was taken as the effect measure (Kolk and Braun 1986).

In Italian workers, exposed for 3-12 years to mean, environmental concentrations of up to 25 mg/m^3 (8 ppm), no effects were seen on the nervous system, the cardiovascular system, atherosclerotic risk factors, and endocrinological functions (Candura et al 1981; Cirla and Graziano 1981; Franco et al 1982).

Chinese workers, exposed at the time of study to a mean concentration of 4.5 mg/m^3 (1.5 ppm) as obtained by personal air sampling (previous levels from spot sampling: 2.8-41.5 mg/m^3 or 0.9-13 ppm) did not differ from controls with respect to blood pressure, cholesterol levels, and prevalence of microaneurysms and small dot haemorrhages of the eyes (Sugimoto et al 1984).

In Finnish studies it was shown that reduction of exposure levels to below 30 mg/m^3 (10 ppm) together with the removal of workers with coronary risk factors from places with CS_2 exposure lowered the relative risk of cardiovascular death to 1.0 (Nurminen and Hernberg 1985). However, a safe level as to cardiovascular death cannot be derived, since the exposure of most cohort members had ceased. Furthermore, there was a rather drastic intervention, leaving the most healthy workers at work. On the other hand, the MacMahon/Monson study (1988) among US rayon workers suggest,

that the risk on death from arteriosclerotic heart disease is only increased among workers with high exposure (cutters and spinners) and employed before 1960, i.e. at times when levels were higher than the current ones. In 1979, Albright et al (1984) carried out personal air sampling one of the four rayon plants from the MacMahon/Monson study and measured average concentrations of 28-41 mg/m^3 (9-13 ppm) for cutters and spinners, respectively. This would imply that levels around 31 mg/m^3 (10 ppm) do not increase the risk of cardiovascular death. Contrary, Swaen et al (1991) found an increased risk for cardiovascular disease mortality in workers with long-term exposure to mean levels of ca 22 mg/m^3 (7 ppm). A dose-effect relation, a no-effect level, or the influence of peak exposure levels could not be established.

CS_2 has adverse effects on the reproductive system (menstrual cycle, outcome of pregnancy) of women. Although the validity of the respective studies can be questioned, taking them together, they point in the same direction. In addition, these findings are supported by indications of teratogenic and foetotoxic effects in experimental animals. The effect level of CS_2 on the female reproduction system requires valid epidemiological studies, and the confirmation of the findings from the studies by Tabacova et al (1981, 1983) in rats.

From the aforementioned data, long-term exposure to mean concentrations of approximately 22 mg/m^3 (7 ppm) is concluded to result in adverse effects: an increased risk of cardiovascular death has been observed in Dutch workers. In addition, small, but unwanted changes in neurophysiological parameters, that may adversely influence the quality of life at an advanced age, were found.

Therefore, applying a factor of 3 for extrapolating from an adverse-effect level to a no-adverse-effect level and an additional safety (uncertainty) factor of 3, the committee proposes a health-based occupational exposure limit for CS_2 of 3 mg/m^3 (1 ppm), as an 8-h TWA concentration. This limit is considered to protect women from adverse effects on the reproductive system as well.

Skin notation

Exposing 2000 cm^2 of skin during 1 h may lead to an expected uptake of

2000 (cm^2) x 1 (h) x 0.51 (mg.cm^{-2}.h^{-1}) = 1020 mg

The absorption rate is the mean of 0.23 and 0.79 mg.cm^{-2}.h^{-1}, see section 7.1.1). Uptake D by inhalation of air with a concentration equal to the health based recommended exposure limit can be calculated from

$D = C \times AMV \times t \times R = 3\ (mg/m^3) \times 10\ (m^3) \times 0.3 = 9\ mg,$

in which C is the exposure limit, AMV x t is the volume of air inhaled during a 8 h working day and R is the pulmonary resorption. Exposure of 2000 cm^2 of the skin (i.e. hands and fore-arms) to liquid CS_2 during 1 h leads to an additional uptake of more than 10% of the maximum allowed uptake by inhalation according to the proposed occupational exposure limit. Therefore a skin notation should be added.

8.3 Recommended occupation exposure limit

The Dutch Expert Committee on Occupational Standards recommends a health-based recommended occupational exposure limit of 3 mg/m^3 (1 ppm) as an 8-h Time Weighted Average concentration. A skin notation should be added.

Chapter 9

Recommendations for research

In order to improve the knowledge on the effects of exposure to CS_2, the committee recommends that:

- The current monitoring methods should be evaluated as to their abiolity to detect concentrations of exposure of 3 mg/m^3 (1 ppm).
- Further studies on the mutagenicity should be performed in order to assess the mutagenic potential of CS_2.
- The teratogenic and foetotoxic potential in rats should be confirmed in inhalation studies.
- Valid epidemiological studies are needed with respect to (no) effect levels concerning the female reproductive system.

For the committee,
The Hague, 5 July 1994

mrs ir C Hoeksema
scientific secretary

prof dr VJ Feron
chairman

References

- Aaserud O, Gjerstad L, Nakstad P, e.a. Neurological examination, computerized tomography, cerebral blood flow and neuropsychological examination in workers with long-term exposure to carbon disulphide. Toxicology 1988; 49: 277-82.
- Aaserud O, Hommeren OJ, Tvedt B, e.a. Carbon disulphide exposure and neurotoxic sequelae among viscose rayon workers. Am J Ind Med 1990; 18: 25-37.
- A'Campo CPMG, Beltman JB. Method for the determination of carbon disulphide in work place atmospheres of rayon plants. Arnhem: AKZO, 1985; AKZO Research report CRL D 85/52.
- ACGIH. Documentation of the threshold limit values and biological exposure indices, 5e druk. Cincinnati OH: ACGIH, 1986; 157-8.
- ACGIH. Threshold limit values for chemical substances and physical agents and biological exposure indices for 1991-1992. Cincinatti OH: ACGIH, 1991; 15.
- ACGIH. Threshold limit values for chemical substances and physical agents and biological exposure indices for 1991-1992. Cincinatti OH: ACGIH, 1991; 63.
- Adkins B Jr, van Stee EW, Simmons JE, e.a. Oncogenic response of strain A/J mice to inhaled chemicals. J Toxicol Environ Health 1986; 17: 311-22.
- Albright BE, Burg JR, Fagen J, e.a. Health effects of occupational exposures to carbon disulphide. NIOSH, 1984; PB85-110229.
- Amoore JE, Hautala E. Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J Appl Toxicol 1983; 3: 272-90.
- Aneja VP, Aneja AP, Adams DF. Biogenic sulfur compounds and the global sulfur cycle. J Air Pollut Control Assoc 1982; 32: 803-7.

- Antov G, Kazakova B, Spasovski M, e.a. Effect of carbon disulphide on the cardiovascular system. J Hyg Epidemol Microbiol Immunol 1985; 29: 329-35.
- Arbeidsinspectie. De Nationale MAC-lijst 1986. Den Haag: Arbeidsinspectie, 1989; publikatie nr P145, 25.
- Baranowska D, Dutkiewicz T. The excretion of carbon disulphide by the lungs at absorption through the skin. Symp. Ind. Toxicol. Socialist Countries, 7-11 December, 1965, Lodz, Poland (translated by H.W.L. van der Donk, PML-TNO, translation no. 664), 97-100.
- Beauchamp RO Jr, Bus JS, Popp JA, e.a. A critical review of the literature on carbon disulphide toxicity. CRC Crit Rev Toxicol 1983; 11: 169-278.
- Beliles RP, Brusick DJ, Mecler FJ. Teratogenic-mutagenic risk of workplace contaminants: trichloroethylene, perchloroethylene and carbon disulphide. NIOSH, 1980; PB82-185075.
- Bergman K, Danielsson BRG, d'Argy R. Tissue disposition of carbon disulphide: I. Whole-body autoradiography of 35S- and 14C-labelled carbon disulphide in adult male mice. Acta Pharmacol Toxicol 1984; 54: 141-50.
- Brazell RS, Andrawes FF, Gibson EK. Direct determination of polluntants in air by gas chromatography helium ionization detection. J High Resolut Chromatogr Chromatogr Commun 1981; 4: 188-90.
- Cai SX, Bao YS. Placental transfer, secretion into mother milk of carbon disulphide and the effects on maternal function of female viscose rayon workers. Ind Health 1981; 19: 15-28. Cam85
  Campbell L, Jones AH, Wilson HK. Evaluation of occupational exposure to carbon disulphide by blood, exhaled air and urine analysis. Am J Ind Med 1985; 8: 143-53.
- Candura F, Mannucci PM, Craveri A, e.a. A study on blood coagulation factors, fibrinolysis and platelet function in workers exposed to carbon disulphide. G Ital Med Lav 1981; 3: 127-30.
- Caroldi S, Jarvis JAE, Magos L. In vivo inhibition of dopamine—hydroxylase in rat adrenals during exposure to carbon disulphide. Arch Toxicol 1984; 55: 265-7.
- Chengelis CP, Neal RA. Oxidative metabolism of carbon disulphide by isolated rat hepatocytes and microsomes. Biochem Pharmacol 1987; 36: 363-8.
- Cirla AM, Graziano C. Health impairment in viscose-rayon workers with carbon disulphide risk below 30 mg/m3. An exposed-controls study. G Ital Med Lav 1981; 3: 69-73.
- Colombi A, Maroni M, Picchi D, e.a. Carbon disulphide neuropathy in rats. A morphological and ultrastructural study of degeneration and regeneration. Clin Toxicol 1981; 18: 1463-74.
- Corsi G, Maestrelli P, Picotti G, e.a. Chronic peripheral neuropathy in workers with previous exposure to carbon disulphide. Br J Ind Med 1983; 40: 209-11.
- Danielsson BRG, Bergman K, d'Argy R. Tissue disposition of carbon disulphide. II Whole-body autoradiography of 35S- and 14C-labelled carbon disulphide in pregnant mice. Acta Pharmacol Toxicol 1984; 54: 233-40.
- DFG. Maximale Arbeitsplatzkoncentrationen und biologische Arbeitsstofftoleranzwerte 1989. Weinheim FRG: VCH Verlagsgesellschaft mbH, 1991; 106.
- DFG. Maximale Arbeitsplatzkoncentrationen und biologische Arbeitsstofftoleranzwerte 1989. Weinheim FRG: VCH Verlagsgesellschaft mbH, 1991; 49.

- Donner M, Falck K, Hemminki K, e.a. Carbon disulphide is not mutagenic in bacteria of Drosophila. Mutat Res 1981; 91: 163-6.
- Eller PM, red. NIOSH manual of analytical methods. Vol 2. 3e druk. Cincinnati OH: US DHHS (NIOSH), 1984; Pub. No. 84-100, 1600.
- Fielder RJ, Shillaker RO. Toxicity Review 3. Carbon disulphide. Londen: Health and Safety Executive, Her Majesty's Stationary Office, 1981.
- Foxboro. OSHA concentration limits for gases. Incorporating infrared analytical data for compliance testing and other applications. ??: Foxbory Company, 1985; PUB-522A.
- Franco G, Malamami T, Germani L, e.a. Assessment of coronary heart disease risk among viscose rayon workers exposed to carbon disulphide at concentrations of about 30 mg/m3. Scand J Work Environ Health 1982; 8: 113-20.
- Gagnaire F, Simon P, Bonnet P, e.a. The influence of simultaneous exposure to carbon disulphide and hydrogen sulfide on the peripheral nerve toxicity and metabolism of carbon disulphide in rats. Toxicol Lett 1986; 34: 175-83.
- Gottfried MR, Graham DG, Morgan M, e.a. The morphology of carbon disulphide neurotoxicity. Neurotoxicology 1985; 6(4): 89-96.
- Green EC, Hunter A. Toxicity of carbon disulphide in developing rats: LD50 values and effects on the hepatic mixed-function oxidase enzym system. Toxicol Appl Pharmacol 1985; 78: 130-8.
- Green-Snyderwine E, Hunter A. Metabolism and distribution of 14C- and 35-S labelled carbon disulphide in immature rats of different ages. Drug Metab Dispos 1987; 15: 289-94.
- Grothaus H, Theis G, Freundt KJ. Schwefelkohlenstoff. In: Bartholomé E, Biekert E, Hellman H, Ley H, Weigert WM, Weise E, red. Ullmans Encyclopädie der technischen Chemie. Vol 21. 4e dru. Weinheim FRG: Verlag-Chemie, 1982; 87-99.
- Grodestkaya NS. Carbon disulphide. In: Izmerov NF, red. Scientific reviews of Soviet literature on toxicity and hazards of chemicals, no. 41, Moskou: USSR/UNEP-IRPTC, 1983.
- Haworth S, Lawlor T, Mortelmans K, e.a. Salmonella mutagenicity test results for 250 chemicals. Environ Mutagen 1983; ?(suppl 1), 3-142.
- Hedenstedt A, Rannug U, Ramel C, e.a. Mutagenicity and metabolism studies on 12 thiuram and dithiocarbamate compounds used as accelerators in the Swedish rubber industry. Mutat Res 1979; 68: 313-25.
- Henschler D, red. Schwefelkohlenstoff. In: Gesundheitsschädliche Arbeitsstoffe. Toxicologisch-arbeitsmedizinische Begründung von MAK-Werten, 1-14th ed. Weinheim FRG: VCH Verlagsgesellschaft mbH, 1988.
- Herrmann G, Leuschke W, Viehrig J. Zur inhalativen Aufnahme von Schwefelkohlenstoff. Z Gesamte Hyg 1982; 28: 305-10.
- Hermann G, Leuschke W, Viehrig J. Zur inhalativen Aufnahme von Schwefelkohlenstoff-Untersuchungen zur CS2-Aufnahme bei dosierter dynamischer Belastung. Z Gesamte Hyg 1983; 29: 444-8.
- Hirata M, K.Sugimoto, Misumi J, e.a. A neurophysiological study among Chinese CS2-exposed workers. G Ital Med Lav 1984; 6: 107-11.
- Health and Safety Executive. Occupational exposure limits 1991. Guidance Note EH 40/91, 1991, 9.

- Hänninen H, Nurminen M, Tolonen M, e.a. Psychological tests as indicators of excessive exposure to carbon disulphide. Scand J Psychol 1978; 19: 163-74.
- INRS. Valeurs limites pour les concentrations des substances dangereuses dans l'air des lieux de travail. Cah Notes Doc 1986; 125: 249-85.
- Izmerov NF, Sanotsky IV, Sidorov KK. Toxicometric parameters of industrial toxic chemicals under single exposure. Moskou: IRPTC-UNEP, 1982, 32.
- Jirmanova I, Lukas E. Ultrastructure of carbon disulphide neuropathy. Acta Neuropathol 1984; 63: 255-63.
- Johnson BL, Boyd J, Burg JR, e.a. Effects on the peripheral nervous system of workers' exposure to carbon disulphide. Neurotoxicology 1983; 4(1): 53-66.
- Jones-Price C, Wolkowski-Tyl R, Marr MC, e.a. Teratologic evaluation of carbon disulphide (CAS.no. 75-15-0) administered to New Zealand white rabbits on gestational days 6 through 19. NTIS/PB84-192350 (cited from Chemical Abstracts 101(1984), 145754).
- Jones-Price C, Wolkowski-Tyl R, Marr MC, e.a. Teratologic evaluation of carbon disulphide (CAS.no. 75-15-0) administered to CD rats on gestational days 6 through 15. NTIS/PB84-192343 (cited from Chemical Abstracts 101 (1984), 124646).
- Klein G, Gromadies B, Bürger A, e.a. Langzeitwirkungen von Schwefelkohlenstoff und Halogenkohlenwasserstoffen, besonders Perchoräthylen, auf den Fettstoffwechsel. Z Gesamte Hyg 1981; 27: 48-51.
- Kolk JJ, Braun C. Carbon disulphide and male reproduction. Proc. 14th Int. Congr. Occup. Health Chem. Ind., 16-19 September, Ludwigshafen, FRG, 1986; 385-94.
- Krüse A, Borch-Johnsen K, Pedersen LM. Cerebral damage following a single high exposure to carbon disulphide. J Soc Occup Med 1982; 32: 44-5.
- Lam CW, DiStefano V. Behavior and characterization of blood carbon disulphide in rats after inhalation. Toxicol Appl Pharmacol 1982; 64: 327-34.
- Lam CW, DiStefano V. Blood-bound carbon disulphide: an indicator of carbon disulphide exposure, and its accumulation in repeatedly exposed rats. Toxicol Appl Pharmacol 1983; 70: 402-10.
- Lam CW, DiStefano V, Morken DA. The role of the red blood cell in the transport of carbon disulphide. J Appl Toxicol 1986; 6: 81-6.
- Lam CW, DiStefano V. Characterization of carbon disulphide binding in blood and to other biological substances. Toxicol Appl Pharmacol 1986; 86: 235-42.
- Leuschke W, Köhler R, Höhl H, e.a. Untersuchungen über die Verwendbarkeit der Schwefelkohlenstoffausscheidung im Urin zur Bestimmung des Expositionsrisikos von Schwefelkohlenstoffexponierten Arbeitskräften. Z Gesamte Hyg 1980; 26: 332-5.
- Lewis RL Sr, Sweet DV, red. Registry of toxic effects of chemical substances 1983-1984 supplement, vol. 1. Cincinnati OH: DHHS (NIOSH), 1985; Pub. No. 86-103.
- Liang YX, Glowa JR, Dews PB. Behavioral toxicology of volatile organic solvents. III. Acute and subacute effects of carbon disulphide exposure on the behavior of mice. J Am Coll Toxicol 1983; 2: 379-89.
- Lyle WH. Mortality of the 1957-68 cohort of employees in a viscose factory up to 31 December 1978. G Ital Med Lav 1981; 3: 53-5.

- MacMahon B, Monson RR. Mortality in the U.S. rayon industry. J Occup Med 1988; 30: 698-705.
- Masuda Y, , Nakayama N. Protective effect of diethyldithiocarbamate and carbon disulphide against liver injury induced by various hepatotoxic agents. Biochem Pharmacol 1982; 31: 2713-25.
- Masuda Y, Nakayama N. Prevention of butylated hydroxytoluene-induced lung damage by diethyldithiocarbamate and carbon disulphide in mice. Toxicol Appl Pharmacol 1984; 75: 81-90.
- Masuda Y, Yasoshima M, Nakayama N. Early, selective and reversible suppression of cytochrome P-450-dependent mono-oxygenase of liver microsomes following the administration of low doses of carbon disulphide in mice. Biochem Pharmacol 1986; 35: 3941-7.
- Merigan WH, Wood RW, Zehl DN. Recent observations on the neurobehavioral toxicity of carbon disulphide. Neurotoxicology 1985; 6(4): 81-8.
- Meuling WJA, Bragt PC, Braun CLJ. Biological monitoring of carbon disulphide. Am J Ind Hyg 1990; 17: 247-54.
- Milivojevic V. Investigations of pathomorphological changes in the liver and brain of rats chronically poisoned by carbon disulphide (CS2). Acta-Vet (Belgrade) 1981; 31: 129-30.
- Moore L. Carbon disulphide hepatoxicity and inhibition of liver microsome calcium pump. Biochem Pharmacol 1982; 31: 1465-7.
- National Board of Occupational Safety and Health. Hygieniska gränsvärden. AFS 1989; 4(suppl 1): 28.
- NIOWH. Criteria for a recommended standard... Occupational exposure to carbon disulphide. Cincinnati OH: DHEW (NIOSH), 1977; Pub no 77-156.
- Nederlands Normalisatie Instituut. Luchtkwaliteit-Werkplekatmosfeer. Bepaling van de concentratie aan koolstofdisulfide door middel van actieve monsterneming met een koolbuis, vloeistofdesorptie en gaschromatografie. In: Nederlandse voornorm, NVN 2946, 1e druk. Delft: Nederlands Normalisatie-instituut, 1989
- Nurminen M, Hernberg S. Cancer mortality among carbon disulphide-exposed workers. J Occup Med 1984; 26: 341.
- Nurminen M, Hernberg S. Effects of intervention on the cardiovascular mortality of workers exposed to carbon disulphide: a 15 year follow up. Br J Ind Med 1985; 42: 32-5.
- Opacka J, Wronska-Nofer T. Biochemical alterations in the peripheral nerves of rats intoxicated with carbon disulphide. Toxicol Lett 1982; 10: 139-44.
- Opacka J, Baranski B, Wronska-Nofer T. Effect of alcohol intake on some disturbances induced by chronic exposure to carbon disulphide in rats. I. Behavioural alterations. Toxicol Lett 1984; 23: 91-7.
- Opacka J, Wronska-Nofer T, Kolakowski J, e.a. Effect of alcohol intake on some disturbances induced by chronic exposure to carbon disulphide in rats II. Biochemial and ultrastructural alterations in the peripheral nerves. Toxicol Lett 1985; 24: 171-7.
- Opacka J, Opalska B, Kolakowski J, e.a. Neurotoxic effects of the combined exposure to carbon disulphide and ethanol in rats. Toxicol Lett 1986; 32: 9-18.
- Oppermann G, Popp P. Applications of the environmental gas chromatograph UGC. Z f I Mitt 1981; 43A: 109-125.

- Orzechowska-Juzwenko K, Wronska-Nofer T, Wiela A, e.a. Effect of chronic exposure to carbon disulphide on biotransformation of phenazone in rabbits. Toxicol Lett 1984; 22: 171-4.
- OSHA. Fed. Reg. 54, 2535-2538. 1989.
- OSHA. Fed. Reg. 54, 2534. 1989.
- Pathology Associates Inc. Developmental Toxicology Report. Developmental inhalation toxicity study of carbon disulphide in the New Zealand white rabbit, Project No. 2100-2-2. Frederick, Maryland: Pathology Associates, Inc., 1991.
- Patty FA. Arsenic, phosphorus, selenium, sulfur and tellurium. In:Industrial hygiene and toxicology, vol. II, toxicology. 2e druk. Fassett DW, Irish DD, red. New York: Interscience Publishers, 1962; 901-4.
- Putz-Anderson VR, Albright BE, Lee ST, e.a. A behavioral examination of workers exposed to carbon disulphide. Neurotoxicology 1983; 4(1): 67-78.
- Raitta C, Teir H, Tolonen M, e.a. Impaired color discriminations among viscose rayon workers exposed to carbon disulphide. J Occup Med 1981; 23: 189-92.
- Rebert CS, Sorenson SS, Pryor GT. Effects of intraperitoneal carbon disulphide on sensory-evoked potentials of Fisher-344 rats. Neurobehav Toxicol Teratol 1986; 8: 543-9.
- Rebert CS, Becker E. Effects of inhaled carbon disulphide on sensory-evoked potentials of Long-Evans rats. Neurobehav Toxicol Teratol 1986; 8: 533-41.
- Rosier J, Billemont G, van Peteghem C, e.a. Relation between the iodine azide test and the TTCA test for exposure to carbon disulphide. Br J Ind Med 1984; 41: 412-6.
- Rosier J, Veulemans H, Masschelein R, e.a. Experimental human exposure to carbon disulphide. II. Urinary excretion of 2-thiothiazolidine-4-carboxylic acid (TTCA) during and after exposure. Int Arch Occup Environ Health 1987; 59: 243-50.
- Rosier J, Veulemans H, Masschelein R, e.a. Experimental human exposure to carbon disulphide. I. Respiratory uptake and elimination of carbon disulphide under rest and physical exercise. Int Arch Occup Environ Health 1987; 59: 233-42.
- Rosier JA, van Peteghem CH. Determination of toxicologically important partition coefficients of carbon disulphide by means of the vial equilibration method. Br J Ind Med 1987; 44: 212-3.
- Rubin RJ, Kroll R. Further evidence for a role of isozymes of P450 in the metabolism and toxicity of carbon disulphide (CS2). Adv Exp Med Biol 1986; 197: 237-42.
- Ruijten M, Sallé H, Verberk M, e.a. Autonome zenuwfunktie, zenuwgeleiding en refractaire periode bij werknemers met langdurige lange blootstelling aan zwavelkoolstof. T Soc Gezondheidsz 1988; 66: 100-2.
- Ruijten MWMM, Sallé HJA, Verberk MM, e.a. Special nerve functions and colour discrimination in workers with long term low level exposure to carbon disulphide. Br J Ind Med 1990; 47: 589-95. Rui90b Ruijten M, Sallé H, Verberk M. Zenuwfuncties bij werknemers met langdurige lage blootstelling aan CS2, preliminary report. Amsterdam: Coronel Laboratory, Faculty of Medicine, University of Amsterdam, September 1990.
- Saillenfait AM, Bonnet P, Ceaurriz J. Effects of inhalation exposure to carbon disulphide and its combination with hydrogen sulfide on embryonal and fetal develoment in rats. Toxicol Lett 1989; 48: 57-66.

- Sandrini GA, Bosso A, Biscaldi G, e.a. Electromyographic investigation in early diagnosis of carbon disulphide neuropathy: a study on 216 workers with different degrees of exposure. G Ital Med Lav 1983; 5: 199-202.
- Sperlingova I, Kujalova V, Frantik E. Chronic carbon disulphide exposure and impaired glucose tolerance. Environ Res 1982; 29: 151-9.
- Spyker DA, Gallanosa AG, Suratt PM. Health effects of acute carbon disulphide exposure. J Toxicol Clin Toxicol 1982; 19: 87-93.
- Sugimoto K, Seki Y, Goto S, e.a. An epidemiological study on CS2 angiopathy in a Chinese viscose rayon factory. Int Arch Occup Environ Health 1984; 54: 127-34.
- Swaen GMH, Braun CLJ, Slangen JJM. Mortality of Dutch workers exposed to carbon disulphide. Maastricht: Department of Epidemiology and Biostatistics, University of Limburg, September 1991.
- Sweetnam PM, Taylor SWC, Elwood PC. Exposure to carbon disulphide and ischaemic heart disease in a viscose rayon factory. Br J Ind Med 1987; 44: 220-7.
- Tabacova S, Hinkova L, Nikiforov B, e.a. Hazards for the progency after maternal exposure to low carbon disulphide concentrations. G Ital Med Lav 1981; 3: 121-5.
- Tabacova S, Nikiforov B, Balabaeva L. Carbon disulphide intrauterine sensitization. J Appl Toxicol 1983; 3: 223-9.
- Tangerman A. Determination of volatile sulphur compounds in air at the parts per trillion level by tenax trapping and gas chromatography. J Chromatogr 1986; 336: 205-16.
- Tepe SJ, Zenick H. The effects of carbon disulphide on the reproductive system of the male rat. Toxicology 1984; 32: 47-56.
- Timmerman RW. Carbon disulphide. In: Kirk-Othmer Encyclopedia of chemical technology, vol. 4. 3e druk. Mark HF, Othmer DF, Overberger CG, Seaborg GF, red. New York: J. Wiley and Sons, 1978; 742-57.
- Torres M, Järvisalo J, Hakim J. Effects of in vivo carbon disulphide administration on the hepatic monooxygenase systems of microsomes from rats. Exp Mol Pathol 1981; 35: 36-41.
- Van-Doorn R, Delbressine LPC, Leijdekkers CM, e.a. Identification and determiantion of 2-thiothiazolidine-4-carboxylic acid in urine of workers exposed to carbon disulphide. Arch Toxicol 1981; 47: 51-8.
- Van-Stee EW, Simmons JE, Sloane RA, e.a. Failure of carbon disulphide and levothyroxine to modify the cardiovascular response to rabbits to a high-cholesterol diet. Toxicology 1986; 40: 45-58.
- Vasileva IA. Investigation of the action of carbon disulphide on the chromosome apparatus of adult and embryonic rat cells. Cytol Gen 1982; 16(2), 68-70. (translated from Tsitol Genet 1982; 16(2): 57-9).

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Weast RC, red. CRC Handbook of chemistry and physics, 67th ed. Boca Raton FL: CRC Press, Inc., 1988; C-196.

- Westberg H, Jansson L, Andersson K. A charcoal sampling method and a colorimetric analytical procedure for carbon disulphide. Measurement data from a viscose rayon manufacturing plant. G Ital Med Lav 1984; 6: 123-5.

- Westberg H, Linder B. The use of diffusion samplers in carbon disulphide sampling. Proceedings VII Int. Symp. Occup. Health in the Production of Artificial Organic Fibers, May 10-17 1987, Wolfheze, The Netherlands, Braun CLJ, red., 1987; 118-22.
- WHO. Carbon disulphide. In: Environmental Health Criteria 10. Geneve: WHO, 1979.
- World Health Organization (WHO). Recommended health-based limits in occupational exposure to selected organic solvents. In: World Health Organization Technical Report Series 664. Geneve: WHO, 1981; 38-54.
- Wilcosky TC, Tyroler HA. Mortality from heart disease among workers exposed to solvents. J Occup Med 1983; 25: 879-85.
- Wilcosky TC, Checkoway H, Marhall EG, e.a. Cancer mortality and solvent exposures in the rubber industry. Am Ind Hyg Assoc J 1984; 45: 809-11.
- Wilkie IW, Seawright AA, Hrdlicka J. The hepatotoxicity of carbon disulphide in sheep. J Appl Toxicol 1985; 5: 360-8.
- Windholz M, red. The Merck Index, An encyclopedia of chemicals and drugs 10e druk. Rahway NJ: Merck and Co., Inc., 1983; 251.
- Wronska-Nofer T, Klimczak J, J.M.Wisniewska-Knypl, e.a. Combined effect of ethanol and carbon disulphide on cytrochrome P-450 monooxygenase, lipid peroxidation and ultrastructure of the liver in chronically exposed rats. J Appl Toxicol 1986; 6: 297-302.
- Wägar G, Tolonen M, Helpiö E. Endocrinological studies of Finnish viscose rayon workers exposed to carbon disulphide. G Ital Med Lav 1981; 3: 103-5.
- Wägar G, Tolonen M, Tanner P, e.a. Serum gonadotropins and testosterone in men occupationally exposed to crbon disulphide. J Toxicol Environ Health 1983; 11: 691-701.
- Zenick H, Blackburn K, Hope E, e.a. An evaluation of the copulatory, endocrinologic, and spermatotoxic effects of carbon disulphide in the rat. Toxicol Appl Pharmacol 1984; 73: 275-83.
- Zhou SY, Liang YX, Chen ZQ, e.a. Effects of occupational exposure to low-level carbon disulphide (CS2) on menstruation and pregnancy. Ind Health 1988; 26: 203-14.
- Zielhuis RL, Stijkel A, Verberk MM, e.a. Health risks to female workers in occupational exposure to chemical agents. Berlijn FRG: Springer Verlag, 1984; 16-28.

A Request for advice

B Membership of the committee

C Comments on the public review draft

D Abbreviations

E DECOS-documents

Annexes

Annex **A**

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupational standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request for

advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in the case of genotoxic carcinogens, a 'exposure versus tumour incidence range' and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

- The evaluation of documents that form the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in annex B.

Annex **B**

Membership of the committee

The membership of the Dutch Expert Committee on Occupational Standards, a committee of the Health Council of the Netherlands, is:

- prof dr VJ Feron, toxicologist, *chairman*
  TNO-Nutrition, Zeist
- dr RB Beems, animal pathologist
  Laboratory for pathology RIVM, Bilthoven
- prof dr JSM Boleij, occupational hygienist
  director Board for the Authorisation of pesticides, Wageningen
- mr JJAM Brokamp, *advisor*
  Social and Economic Council
- prof dr PTh Henderson, toxicologist
  University of Limburg, Maastricht
- dr G de Jong, MD
  Health, Safety and Environment Division, Shell International Petroleum Maatschappij, The Hague
- dr G de Mik, toxicologist
  director Department of Substances and Risks, National Institute of Public Health and Environmental Protection, Bilthoven
- mrs J Molier-Bloot, MD
  LarRora Occupational Health Service, Amersfoort

- dr PC Noordam, *advisor*
  Ministry of Social Affairs and Employment, The Hague
- dr H Roelfzema, *advisor*
  Ministry of Welfare, Health and Cultural Affairs, Rijswijk
- dr T Smid, occupational hygienist
  KLM Medical Services, Schiphol
- dr GMH Swaen, epidemiologist
  University of Limburg, Maastricht
- dr HG Verschuuren, toxicologist
  DOW Europe, Switzerland
- dr AAE Wibowo, toxicologist
  Coronel Laboratory, University of Amsterdam, Amsterdam
- F de Wit, MD
  Labour Inspectorate, Deventer
- mrs ir C Hoeksema, *scientific secretary*
  Health Council of the Netherlands, The Hague

The first draft of the present advisory report was prepared by JTJ Stouten, from the Medical Biological Laboratory, TNO, Rijswijk by contract with the Netherlands Ministry of Social Affairs and Employment.

Secretarial assistance was provided by Mrs MC Bergsma-Lucassen.

Annex C

Comments on the public review draft

A draft of the present report was released in 1993 for public review. The following organisations and persons have commented on the draft document:

- CJL Braun, WW Brouwer, A Giessen
  AKZO Nederland BV, Arnhem (NL)

Annex **D**

Abbreviations

- *HBR-OEL*
  health based recommended occupational exposure limit
- *LOAEL*
  lowest observed adverse effect level
- *MAC*
  maximaal aanvaarde concentratie (maximal accepted concentration)
- *MAK*
  maximale arbeitplatzkonzentration
- *MOAEL*
  minimal observed adverse effect level
- *MTD*
  maximum tolerated dose
- *NOAEL*
  no observed adverse effect level
- *NEL*
  no effect level
- *OEL*
  occupational exposure limit
- *PEL*
  permissible exposure limit

- *REL*
  recommended exposure limit
- *TLV*
  threshold limit value
- EC_{50}
  concentration at which a described effect is found in 50% of the exposed animals or at which the effect is decreased up to 50% of the controlvalue
- IC_{50}
  concentration at which inhibition of a certain function is found up to 50% of the controlvalue
- LD_{50}
  lethal dose 50% kill
- LC_{50}
  lethal concentration 50% kill
- *LDlo*
  lowest lethal dose
- *LClo*
  lowest lethal concentration
- RD_{50}
  dose at which 50% of the exposed animals show respiratory disorders
- *bp*
  boiling point
- *h*
  hour
- *ppm*
  parts per million (v/v)
- *ppb*
  parts per billion (v/v)
- *STEL*
  short term exposure limit
- *TWA*
  time weighted average
- *tgg*
  tijd gewogen gemiddelde

Organisations

- *ACGIH*
  American Conference of Governmental and Industrial Hygienists

- *CEC*
  Commission of the European Communities
- *DECOS*
  Dutch Expert Committee on Occupational Standards
- *DFG*
  Deutsche Forschungsgemeinschaft
- *EPA*
  Environmental Protection Agency (USA)
- *FDA*
  Food and Drug Administration (USA)
- *HSE*
  Health and Safety Executive (UK)
- *IARC*
  International Agency for Research on Cancer (WHO)
- *INRS*
  Institut National de Recherche et de Sécurité (France)
- *NIOSH*
  National Institute for Occupational Safety and Health (USA)
- *NTP*
  National Toxicology Programme (USA)
- *OECD*
  Organisation for Economic Cooperation and Development
- *OSHA*
  Occupational Safety and Health Association (USA)
- *RTECS*
  Registry of Toxic Effects of Chemical Substances
- *SER*
  Social and Economic Council (Sociaal-Economische Raad NL)
- *WATCH*
  Working group on the assessment of toxic chemicals (UK)
- *WHO*
  World Health Organisation

Toxicological terms

- *bw*
  body weight
- *bid*
  bis in diem (two times per day)

- *CHD*
  coronary heart disease
- *CNS*
  central nervous system
- *CARA*
  chronic non-specific respiratory diseases
- *ECG*
  electrocardiogram
- *EEG*
  electro encephalogram
- *FCA*
  Freunds Complete Adjuvans
- *FSH*
  follicle stimulating hormone
- *FEV*
  forced expiratory volume
- *GD*
  gestation days
- *GPMT*
  guinea pig maximisation test
- *GSH*
  glutathion
- *HLiA*
  hamster liver activated
- *IHD*
  ischaemic heart disease
- *im*
  intramusculair
- *ip*
  intraperitoneal
- *ipl*
  intrapleural
- *it*
  intratracheal
- *iv*
  intravenous
- *LH*
  lutheinising hormone

- *MAC*
  minimal alveolair concentration
- *MFO*
  mixed function oxidase
- *NA*
  not activated
- *po*
  per os (= oral)
- *PNS*
  peripheral nervous system
- *RLIA*
  rat liver activated
- *RBC*
  red blood cells
- *sc*
  subcutane
- *SCE*
  sister chromatid exchange
  UDS
  unscheduled DNA-synthesis

Statistical terms

- *GM*
  geometric mean
- *SD*
  standard deviation
- *SEM*
  standard error of mean
- *SMR*
  standard mortality ratio
- *OR*
  Odds Ratio
- *RR*
  Relative Risk

Analytical methods

- *AAS*
  atomic absorption spectroscopy
- *BEEL*
  biological equivalent exposure limit
- *BEI*
  biological exposure index
- *BEM*
  biological effect monitoring
- *BM*
  biological monitoring
- *ECD*
  electron capture detection
- *EM*
  environmental monitoring
- *FID*
  flame ionisation detection
- *GLC*
  gas liquid chromatography
- *GC*
  gas chromatography
- *GSC*
  gas solid chromatography
- *HPLC*
  high performance liquid chromatography
- *IR*
  infrared
- *MS*
  mass spectrometry
- *NMR*
  nuclear magnetic resonance
- *PAS*
  personal air sampling
- *TLC*
  thin layer chromatography
- *UV*
  ultraviolet

Annex **E**

DECOS-documents

DECOS has produced documents on the following substances.

Acrylonitril	1994/07
Butanol (1,2- and t-)	1994/10
Carbon disulphide	1994/08
Methyl Methacrylate	1994/09
Methacrylates. Ethyl methacrylate, n-butyl methacrylate and isobutyl metacrylate	1994/11

The following documents, that were published before 1994, can be ordered at the Sdu Uitgeverij Den Haag.

Acetaldehyde	RA 6/92
Acrylaten	RA 13/87
Aflatoxine B1, B2, G1 en G2	RA 6/87
Allylglycidylether	RA 1/92
Amyl acetate	RA 4/90
Aniline	RA 2/89
Anorganisch Lood	RA 2/80
Anorganische Kwikzouten	RA 3/82

Arc welding fume particles not containing chromium and nikkel	RA 1/93
Arseenverbindingen (Anorganische)	RA 2/84
Asbest	RA 1/84
Asbest, Evaluatie van risico op kanker bij beroepshalve blootstelling aan (aanvullend op RA 1/84)	RA 9/89
Benzeen	RA 5/89
Beryllium and Beryllium compounds	RA 4/88
Blootstelling, Gezondheidskundige aspecten van het begrip en van het meten/schatten ervan	RA 8/90
Butadiene (1,3-)	RA 5/90
Cadmium	RA 5/80
Caprolactam	RA 4/84
Carbon disulphide	RA 9/92
Carbon monoxide	RA 7/92
Carbonylfluoride and PTFE Pyrolysis products	RA 3/88
Carcinogene stoffen	RA 3/80
Chloor	RA 6/80
Chloroform	RA 7/87
ß-Chloroprene	RA 4/93
Chroom en chroomverbindingen	RA 6/85
Cyclohexane	RA 15/90
Cyclohexanol	RA 3/90
Cyclohexanone	RA 9/93
Dibroomethaan	RA 5/87
Dichloorethaan (1,1-)	RA 8/87
Diisocyanates	RA 3/91
Dimethyl- en diethylsulfaat	RA 12/90
Dimethylamine	RA 10/90
Dimethylbutane (2,2- & 2,3-)	RA 7/93
Dimethylhydrazine	RA 2/87
Dinitro-ortho-cresol (4,6-)	RA 4/87

Dioxaan (1,4-)	RA 1/87
Epichloorhydrine	RA 1/86
Ethyl accrylate	RA 6/90
Ethyl acetate	RA 10/91
Ethyl Methanesulphonate (EMS)	RA 4/89
Ethyl amine	RA 7/90
Ethylbenzene	RA 9/91
Ethyleenoxide	RA 6/89
Fenylhydrazine	RA 2/87
Fluorcarbons (except FC11)	RA 15/87
Fluorine compounds (inorganic)	RA 1/89
Fluorine	RA 1/89
Formaldehyde	RA 3/87
Fosfine	RA 1/80
Fijn hinderlijk stof; gezondheidskundige aspecten van bijlage 3 bij de Nationale MAC-lijst 1989	RA 9/90
Gasoline	RA 3/92
Heptaan (n-)	RA 1/81
Heptane (n-)	RA 6/93
Hexaan (n-)	RA 11/87
Hexachlorobenzene	RA 2/88
Hexanone (2-)	RA 2/90
Hydrazine	RA 2/87
Hydrogenfluorine	RA 1/89
Hydroxyethylhydrazine	RA 12/87
Isopropylglycidylether	RA 1/92
Isopropoxyethanol (2-)	RA 2/87
Koolmonoxide (Carbon monoxide)	RA 2/79 (7/92)
Kwikalkylverbindingen - Korte keten	RA 5/82
Kwikverbindingen (Organische)	RA 4/82
Lachgas (Nitrous oxide)	RA 2/85 (2/92)

Lasrook (Arc welding fume.....nickel)	RA 1/93
Mangaan	RA 1/82
Mertallisch Kwik	RA 5/81
1-Methoxypropanol-2	RA 5/93
2-Methoxypropanol-1	RA 5/93
1-Methoxypropylacetate-2	RA 5/93
2-Methoxypropylacetate-1	RA 5/93
Methyl acrylate	RA 1/90
Methyleenchloride (Methylene chloride)	RA 1/83 (8/92)
Methyl ethyl ketone	RA 16/90
Methyl isobutyl ketone	RA 4/91
Methyl Methanesulphonate (MMS)	RA 4/89
Methylbromide	RA 13/90
Methylpentane (2- & 3-)	RA 7/93
Monochloorethaan	RA 2/82
Monoketones (7/8 Carbon chain Aliphatic)	RA 14/90
Nikkel en nikkelverbindingen	RA 3/85
Nitropropaan (2-)	RA 1/85
Nitrous oxide	RA 2/92
Ozone	RA 4/92
Para-Dichloorbenzeen	RA 1/88
Pentaan	RA 2/81
Phthalate esters	RA 8/93
Phthalic anhydride	RA 3/89
Pieperazine	RA 7/91
Polyvinyl chloride (PVC) dust	RA 2/93
Poxyethanol (2-)	RA 12/87
Propoxyethylacetate (2-)	RA 12/87
Pyridine	RA 3/93
Selenium en verbindingen	RA 7/89
Silicon dioxide, Crystalline forms of	RA 5/92

Stikstofdioxide	RA 5/85
Styreen	RA 8/89
Talc dusts	RA 6/91
Tetrahydrofuran	RA 1/91
Thiourea	RA 11/90
Tolueen Diisocyanaat	RA 4/80
Tolueen	RA 2/91
Trichloorethaan (1, 1, 1-)	RA 3/81
Trichloorethyleen	RA 3/83
Trichlorofluoromethane	RA 14/87
Triethylamine	RA 2/83
Trimethylamine	RA 9/87
Vadium en metaal anorganische verbindingen	RA 10/87
Wood dust	RA 8/91
Xylene	RA 5/91
Wood dust	RA 8/91
Xylene	RA 5/91
Zwaveldioxide	RA 4/85

Annex **F**

Tables 2-21

Table 2. Lethal effects of CS_2 in various animal species.

SPECIES	ROUTE	CONC/DOSE	EFFECT	REFERENCE
mouse	inhalation	700 mg/m³/1 h (224 ppm)	LC_{50}	Beauchamp et al, 1983.
mouse	inhalation	10,000 mg/m³/2 h (3200 ppm)	LC_{50}	Izmerov, 1982.
rabbit	inhalation	16,000 mg/m³/6.25 h (5120 ppm)	lethal	Henschler, 1988.
cat	inhalation	23,000 mg/m³/3 h (7360 ppm)	lethal	Henschler, 1988.
cat	inhalation	122,000 mg/m³/0.75 h (39040 ppm)	lethal	Henschler, 1988.
mouse	oral	3020 mg/kg	LD_{50}	Beauchamp et al, 1983.
mouse	intragastric	2780 mg/kg	LD_{50}	Izmerov, 1982.
rat	intragastric	3188 mg/kg	LD_{50}	Izmerov, 1982.
guinea pig	intragastric	2125 mg/kg	LD_{50}	Izmerov, 1982.
rabbit	intragastric	2550 mg/kg	LD_{50}	Izmerov, 1982.
mouse	intraperitioneal	1890 mg/kg	LD_{50}	Beauchamp et al, 1983.
rat	intraperitioneal	583-1545 mg/kg*	LD_{50}	Green and Hunter, 1985.
guinea pig	intraperitioneal	400 mg/kg	LD_{50}	Lewis and Sweet, 1985.
rabbit	subcutaneous	300 mg/kg	lethal	Henschler, 1988.

* depending on age of rats tested (from 1-day-old to 40-days-old).

Table 3. Neurotoxic (including behavioural) effects of CS_2 due to acute exposure in various animal species.

SPECIES	CONC	TIME	EFFECT	REFERENCE*
rat	63 ppm (197 mg/m³)	8 h	No signs of toxicity were noted during the exposure period. This was the minimum concentration at which a significant reduction in brain noradrenaline levels occured- effects were transient.	McKenna, DiStefano, 1977.[2] J. Pharmacol. Exp. Ther. 202, 253.
rat	94 ppm (293 mg/m³)	2 h	Brain protein metabolism affected; i.e. increased proteolysis and changes in protein synthesis.	Savolainen, Jarvisalo, 1977.[1] Chem. Biol. Interact. 17, 51.
rat	630 ppm (1970 mg/m³)	4-8 h	No signs of toxicity were noted during exposure time. A marked decrease in brain noradrenaline levels (22% after 4 h, 36% after 8 h). A similar reduction in noradrenaline levels in the heart and adrenal gland was also noted. An increase, of somewhat smaller magnitude was noted in brain dopamine levels. These effects were reversible, with 90% recovery after 16 h.	McKenna, DiStefano, 1977.[2] J. Pharmacol. Exp. Ther. 202, 253.
rat	800 ppm (2500 mg/m³)	18 h	Diminished P:O ratio in mitochondria, suggesting uncoupling of oxidative phosphorylation.	Tarkowski, Sobczak, 1971.[1] J. Neurochem. 18, 177.
mouse	3000-4500 ppm (9360-14040 mg/m³)	0.5 h	Degenerative changes in globus pallidus region.	Kuljak et al., 1974.[1] Med. Lav. 65, 193.

Table 3. Continued.

SPECIES	CONC	TIME	EFFECT	REFERENCE*
behaviour				
rat	640 ppm (2000 mg/m³)	8 h	spontaneous motor activity decreased by 50%.	Horvath, Frantik, 1973.[2] In: Adverse effects of environmental chemicals and psychotropic drugs vol. I, ed. Horvath, Elsevier, A'dam, 11.
mouse	120-3700 ppm (375-11545 mg/m³)	0.25 h	120 ppm: no effect 580 ppm: decreased responding in most mice as low as 0.55 of control. 2250 ppm: decreased responding in all mice as low as 0.55 of control. 3700 ppm: all responding abolished.	Liang et al, 1983. J. Am. Coll. Toxicol. 2, 379.
monkey	200-600 ppm (624-1872 mg/m³)	2 h	reduced ability in shock-avoidance test.	Weiss et al, 1979.[2] Environ. Health Perspect. 30, 39.

* [1] data from Beauchamp et al., 1983 (see Chapter 10).
* [2] data from Fielder and Shillaker, 1982 (see Chapter 10).

Table 4a. Hepatotoxic effects of CS_2 due to acute exposure by inhalation in the rat.

SPECIES	CONC/TIME	EFFECT	REFERENCE*
rat	20, 100, 200, 400 ppm (62-1250 mg/m³) 8 h	Signs of toxicity noted during the exposure period included decreased food and water intake and a decrease in body weight at 100 ppm and above. Rectal temperature decreased at 100 ppm and above (38.1 ± 0.13°C and 37.5 ± 0.1°C at 100 and 400 ppm vs 39.0 ± 0.8°C in the control group; $p<0.01$). Oxygen consumption of whole animal increased significantly, being 10.4 ± 0.5 x 10^{-4} l/h/cm² at 100 ppm and 12.3 ± 0.4 x 10^{-4} at 400 ppm (vs control value of 8.8 ± 0.08 x 10^{-4}). Animals were killed immediately post-exposure and blood samples were taken for determination of serum enzymes indicative of liver toxicity. The livers were removed and were subjected to certain biochemical tests to assess energy metabolism (glycogen content, oxygen consumption of liver slices). No effects were noted at any concentration on serum lactate dehydrogenase, glutamate pyruvate transaminase, and glutamate oxalo-acetate transaminase levels. A decrease in liver weight was noted at all dose levels, due to a marked decrease in glycogen content ($p<0.01$ at 20 ppm and above). An increase in liver lactate and inorganic phosphate levels was also noted, together with increased oxygen consumption by liver slices at 100 ppm and above. Thus adverse effects noted on energy supply of liver at 20 ppm and above. The effects were rapidly reversible, and all parameters were normal after 24 h exposure to the highest concentration. No evidence of any liver toxicity was obtained from serum GOT, GPT, and LD levels. In a separate experiment, liver function (as determined by BSP clearance in bile) was not affected by exposure to up to 400 ppm.	Freundt, Kurzinger, 1975.[2] Int. Arch. Arbeitsmed. 34, 269.
rat	480 ppm (1500 mg/m³) 5 h	Prolongation of hexobarbital sleeping time (3.5 fold): decrease activity of aniline p-hydroxylase and microsomal ethanol oxidizing system; no depressing of cyt. P450 content.	Wronska-Nofer et al, 1986. J. Appl. Toxicol. 6, 297.
rat	641 ppm (2000 mg/m³) 4 h	No histological evidence of liver damage 18-20 h postexposure. Starvation + phenobarbital pretreatment: Hepatotoxic effects noted; these consisted of hydropic degeneration in parenchymal cells of the centrilobular zone. No evidence of any flammatory reaction. More extensive lesions in starved animals.	Magos, Butler, 1972.[2] Br. J. Ind. Med. 29, 95.

Table 4a. Continued.

SPECIES	CONC/TIME	EFFECT	REFERENCE*
rat	1280 ppm (4000 mg/m^3) 4 h	Pretreatment with phenobarbital. Sacrificed 0, 1, 6, 12, 34, 36, 48 h after exposure. Dilatation of RER cisternae of centrilobular hepatocytes; mitochondria and other organelles normal in PB pretreated rats only; occasional necrotic cells.	Butler et al, 1974.[1] J. Pathol. 113, 79.
rat	1280 ppm (4000 mg/m^3) 4 h	Pretreatment with phenobarbital, sacrificed 0, 3, 6, 12, 24, 48, 74, 168 h post-exposure. Centrilobular loss of glucose 6-phosphatase activity; hydropic degeneration is maximum at 12-16 h.	Butler et al, 1974.[1] J. Pathol. 113, 79.
rat	1280 ppm (4000 mg/m^3) 4 h	Pretreatment with phenobarbital. Sacrificed 0, 3, 6, 12, 24, 48, 72, 168 h postexposure. Increased water content returning to normal in 48 h, increased Na^+, K^+ content with retention of normal concentrations.	Butler et al, 1973.[1] J. Pathol. 109 (1), XV. Butler et al, 1974.[1] J. Pathol. 113, 53.
rat	1500 ppm (4680 mg/m^3) 2 h	Groups of animals were killed at 1, 4, and 46 h post-exposure and the effects on liver mixed function oxidase (MFO) enzymes and on brain protein metabolism were investigated. The animals were somnolent during exposure but soon recovered. No overt signs of toxicity were present at 46 hours post-exposure. No effects on liver cyt. P450 levels were noted at any time, the only change in MFO enzyme levels noted being a transient decrease in ethoxycoumarin deethylase activity. Effects on brain protein metabolism were also noted at 1 and 4 hours post-exposure only (increased protease activity and increased amino acid uptake). A marked but transient inhibition in cyt. P450 levels, and in the activity of MFO enzymes was noted in animals that had been pretreated with phenobarbitone. The levels were similar to the control animals by 46 hours post-exposure.	Savolainen, Jarvisalo, 1977.[2] Chem.Biol.Interact. 17, 51. Jarvisalo et al, 1977.[2] Chem. Biol. Interact. 17, 41.

*see note Table 3.

Table 4b. Hepatotoxic effects of CS_2 due to single exposure in various animal species.

SPECIES	ROUTE	DOSE	EFFECT	REFERENCE*
rat	oral	0.5 ml/kg, 1 ml/kg (0.63 g/kg, 1.26 g/kg)	Pretreatment with phenobarbital. Sacrificed after 24 h. High dose (no PB)- liver wt. increased. Fat increased in periportal zone. High/low doses (+PB)-extensive centrilobular zone of necrosis with marked hydropic change. SKF 525 prevented severe liver cell necrosis in exposed animals (+PB).	Bond et al, 1969.[1] Br. J. Ind. Med. 26, 335.
rat	oral	1 ml/kg (1.26 g/kg)	Starvation + pretreatment with phenobarbital, sacrificed after 1 or 24 h. + PB: inhibition of liver endoplasmatic reticulum calcium pump. Extensive centrilobular necrosis. - PB: fatty infiltration, but little necrosis.	Moore, 1982. Biochem. Pharmacol. 31, 1465.
mouse	oral	0.003 - 2.0 g/kg	No signs of hepatic damage. Considerable decrease in drug metabolizing enzyme activities (such as hydroxylation of aniline, O-dealkylation of p-nitroanisole, 7-ethoxycoumarin, and 7-ethoxyresorufin, and N-demethylation of N,N-dimethylaniline), NADPH-cytochrome P450 reductase and P450 associated peroxidase activities, already at 0.003 and 0.03 g/kg. Flavin containing mono-oxygenase, UDP-glucuronyl transferase, glucose-6-phosphatase and haem oxygenase in microsomes, and glutathione S-transferases in the soluble fraction did not change significantly, when tested up to 0.3 g/kg.	Masuda et al, 1986. Biochem. Pharmacol. 35, 3941.
sheep	oral	0.05 ml/kg (0.063 g/kg)	pretreatment with DDT. 1-2 days after application: development of a transient hydropic degeneration of the hepatocytes. Decrease in microsomal cyt. P450.	Wilkie et al, 1985. J. Appl. Toxicol. 5, 360.

Table 4b. Continued.

SPECIES	ROUTE	DOSE	EFFECT	REFERENCE*
rat	intraperi-toneal	1.38 mmol/kg (0.105 g/kg)	Starvation + pretreatment with phenobarbital. Sacrificed after 24 h. Centrilobular hydropic degeneration varied greatly between strains; high incidence of focal coagulative necrosis in most susceptible strains. Liver weights, liver water content and cyt. P450 levels after carbon disulphide showed strain differences in degree of response.	Tucker et al, 1980.[1] Arch. Toxicol. 45, 287.
rat	intraperi-toneal	30 μl (38 mg; 0.190 g/kg)	Pretreatment with phenobarbital. Sacrificed within 3 h. Hydropic degeneration around hepatic centrilobular veins in exposed animals (no PB). In PB pretreated exposed animals hepatocellular necrosis was noted mainly around central veins. Ultrastructural studies demonstrated a large number of lysosomes. Cyt. P450 concentration was reduced by CS_2. Effect was greater in phenobarbital pretreated animals. Aniline hydroxylase activity was decreased by CS_2, but increased in phenobarbital pretreated animals. Microsomal peroxidase and cytosolic glutathione reductase activities were increased by CS_2 but reduced in phenobarbital pretreated animals.	Torres et al, 1980.[1] Exp. Mol. Pharmacol. 33, 333.
rat	intraperi-toneal	20, 50 μl (25, 63 mg; 0.125, 0.315 g/kg)	Starvation + pretreatment with phenobarbital. Sacrificed after 1 h. Rats pretreated with PB and exposed to CS_2 caused depressed cyt. P450 activity through damage to its apoprotein causing loss of liver haem. Formation of bile pigments increased stimulation of haem oxygenase and possible depression of 5-aminolevulinate-synthetase.	Jarvisalo et al, 1978.[1] Mol. Pharmacol. 14, 1099.

Table 4b. Continued.

SPECIES	ROUTE	DOSE	EFFECT	REFERENCE*
rat (1- to 40- day-old)	intraperi-toneal	375 mg/kg	After 24 h: no hepatic injury in terms of plasma aspartate aminotransferase elevation in 1- to 20-day-old rats. Some injury in 30- and 40-day-old rats. Decrease in cyt. P450 and aniline hydroxylation in all except 1-day-old.	Green, Hunter, 1985. Toxicol. Appl. Pharmacol. 78, 130.
mouse	intraperi-toneal	0.1, 0.3, 0.5 ml/kg (0.126, 0.378, 0.630 g/kg)	Sacrified after 4, 8, and 12 h. Inhibition of liver UDP-glucuronyl transferase.	Yoshida et al, 1976.[1] Bull. Environ. Contam. Toxicol. 15 (4) 421.
mouse	intraperi-toneal	1, 1.5, 2 g/kg	1 and 1.5 g/kg: moderate hepatic injury. 2 g/kg: all mice (5) dead within 24 h.	Masuda et al, 1986. Biochem. Pharmacol. 35, 3941.

* see note Table 3.

Table 5. Effects of CS_2 due to acute or single exposure in various animal species.

SPECIES	ROUTE	CONC/DOSE	EFFECT	REFERENCE*
gastrointestinal system				
rabbit	subcu-taneous	20 mg/kg, 100 mg/kg	Xylose tolerance test on 10th and 37th day of experiment: absorptive capacity of small intestine as measured by xylose was reduced.	Klein, Paulova, 1977.[1] Cesk. Gastroenterol. Vyz. 31, 461.
kidney				
rat	inhal-ation	0.74, 4.35 ppm (2.3, 13.6 mg/m³) 4 h	Urinary output decreased; protein increased.	Salnikova, Chirkova, 1974.[1] Gig. Tr. Prof. Zabol. 1974 (12), 34.
lung				
mouse	oral	10 mg/kg, 100 mg/kg	Dose-dependent reduction of some drug metabolizing enzyme activities of lung microsomes: aniline hydroxylase, N-methyl-p-chloroaniline N-demethylase, p-nitroanisole O-demethylase (not of biphenyl 4-hydroxylase); reduced cyt. P450 content.	Masuda, Nakayama, 1984. Toxicol. Appl. Pharmacol. 75, 81.
adrenals				
rat	inhal-ation	320-1280 ppm (1000-4000 mg/m³) 4 h	Dose-dependent inhibition of dopamine-β-hydroxylase detected as soon as 30 min. postexposure.	Caroldi et al, 1984. Arch. Toxicol. 55, 265.

* see note Table 3.

Table 6. Neurotoxic (including behavioural) effects of CS_2 due to short-term exposure by inhalation in various animal species.

SPECIES	CONC	CONDITIONS	EFFECT	REFERENCE*
rat	194 ppm (605 mg/m³)	4 h/d, 5 d/w, 3 w	Significant weight loss (ca 6%), the effect being noted after 4 exposures. Animals subjected to behaviour test (effect on training to avoid shock) during last hour of each exposure. Significant alteration in behaviour noted from day 8 (increase in number of shocks received). It was stated that no effect was noted at 100 ppm, but no details of study given.	Goldberg et al, 1964.[2] Acta Pharmacol. Toxicol. 21, 36.
rat	288 ppm (900 mg/m³)	5 h/d, 6 d/w, 1.5 - 12 mo	No signs of toxicity noted during experimental period. No effect on peripheral nerve conduction velocity during first 3 months.	Knobloch et al, 1979.[2] Br. J. Ind. Med. 36, 135.
rat	481 ppm (1500 mg/m³)	5 h/d, 6 d/w, 4 - 65 w	No deteriotation in general condition during first 7 months. Marked degeneration of the myelinated fibres of the spinal column, with axonal swelling from about month 1. No effects on blood vessels. Initial changes in myelinated fibres of PNS (sciatic nerve), characterized by axonic swelling, after 1-2 months.	Szendzikowski et al, 1973.[2] Int. Arch. Arbeitsmed. 31, 135.
rat	481 ppm (1500 mg/m³)	5 h/d, 6 d/w, 1 - 14 mo	Reduced rate of weight gain from about 1 month.	Wronska-Nofer et al, 1973.[2] Int. Arch. Arbeitsmed. 31, 123.
rat	513 ppm (1600 mg/m³)	5 h/d, 6 d/w, 1.5 - 9 mo	Transient reduction in conduction velocity after 1½ months.	Knobloch et al, 1979.[2] Br. J. Ind. Med. 36, 148.
rat	640 ppm (2000 mg/m³)	4 h/d, 2 d	Decrease of dopamine concentration by 16% after second exposure and of noradrenaline by 13%, suggesting inhibition of dopamine-β-hydroxylase	Magos, 1971.[1] Proc. Eur. Soc. Study Drug Toxic. 12, 24.
rat	640 ppm (2000 mg/m³)	4 h/d, 10 d	Inhibition brain catecholamine dopamine synthesis.	Magos, et al, 1974.[2] Proc. Eur. Soc. Study Drug Toxic. 15, 80.

Table 6. Continued.

SPECIES	CONC	CONDITIONS	EFFECT	REFERENCE*
rat	640 ppm (2000 mg/m³)	4 h/d, 5 d/w, 6 w	Decreased hind limb extensor response and impaired motor coordination. Recovery 3 weeks postexposure.	Tilson et al, 1979.[1] Neurobehav. Toxicol. 1, 57.
rat	700 ppm (2135 mg/m³)	5 h/d, 5 d/w, up to 12 w	No deaths were noted during the exposure period but test animals failed to increase in weight and some appeared drowsy during exposure. Signs of peripheral neuropathy (impairment in posterior limbs on standing and walking) noted after 9 weeks. Reduced motor nerve conduction velocity (both maximum and slow fibres) of sciatic nerve noted after 4 weeks. Biochemical studies on brain synaptosomal fractions revealed a marked decrease in Na^+K^+ ATPase levels after 4 weeks. Examination of sections of peroneal nerve at the end of the exposure period, by optical microscopy revealed axonic swelling and the presence of giant fibres and a thin myelin sheath. Electron microscopy showed a marked decrease in the number of axonal neurotubules with an increase in the number of neurofilaments and sparing of the myelin sheath.	Maroni et al, 1979.[2] Med. Lav. 70, 443.
rat	750 ppm (2340 mg/m³)	intermittently for 2 - 3 mo	Signs of peripheral neuropathy noted after 2-3 months, consisting of severe hind limb weakness. Reduction in motor nerve conduction velocity noted prior to this. Histological evidence of distal axonopathy noted in long nerves of both central and peripheral nervous system, characterized by axon swelling due to accumulation of thick bundles of neurofilaments.	Haltia, Linnoila, 1978.[2] Acta Neurol. Scand. (Suppl.) 57, 255 Haltia, Linnoila, 1978.[2] J. Neuropathol. Exp. Neurol. 37, 621.
rat	750 ppm (2340 mg/m³)	6 h/d, 5 d/w, 2 - 5 w	Reduced weight gain. Animals lethargic during first weeks, but no sign of clinical disturbance other than sleepness after daily exposure. A slight but significant decrease in MCV of sciatic nerve was noted after 2 weeks. No further change in MCV occurred. Within a month of the end of exposure, MCV's returned to pre-exposure values.	Seppalainen, Linnoila, 1976[2] Neuropathol. Appl.Neurobiol. 2, 209

Table 6. Continued.

SPECIES	CONC	CONDITIONS	EFFECT	REFERENCE*
rat	750 ppm (2340 mg/m^3)	6 h/d, 5 d/w, 10 w; then 3 d/w, 12 w	Reduced weight gain. Ataxia after 6 weeks, and a progressive weakening of hind limbs after 8 weeks, motor condition velocity of sciatic nerve decreased steadily from 4 weeks for about 12 weeks (significant after 8 weeks).	Seppalainen, Linnoila, 1976.[2] Neuropathol. Appl. Neurobiol. 2, 209.
rabbit	0.05, 0.6 ppm (0.2, 2 mg/m^3)	24 h/d, 1, 2, 6 w	Low dose intensified while high dose inhibited cortical processes as determined by EEG analysis. CS_2 inconsistently altered neuraminic acid content and the lysosomal enzyme activity in brain.	Bokina et al, 1979.[1] Environ. Health Perspect. 30, 31.
rabbit	0.06 ppm (0.2 mg/m^3)	24 h/d, 1½ mo	Aldolase activity on neuraminic acid was reduced in exposed animals. Altered EEG after 6 week exposure.	Bokina et al, 1976.[1] Environ. Health Perspect. 13, 37.
rabbit	750 ppm (2340 mg/m^3)	6 h/d, 5 d/w, 10 w	One animal refused to eat or drink for some of the exposure period and was killed after 8½ weeks. Animals were drowsy during exposure period and for 24 hours postexposure especially in the early stages. Weight loss was noted in all animals from 4 weeks. Signs of hind leg paralysis were noted from 7 weeks in two animals; all showed severe signs of paralysis after 9 weeks. Electrophysological measurements of the sciatic nerve were recorded throughout the experiment. A significant reduction in the motor conduction velocity was noted, compared to the pre-exposure value of 39.6 m/s, from the first month, and this increased throughout the test. Mean reductions during the first, second and third months were 8, 17, and 19 m/s ($p<0.05$, 0.01, 0.001 resp.). The amplitude of the motor response decreased after 6 weeks. After 9 weeks most animals showed fibrillation of the gastrocnemius muscle. The extent of recovery of two rabbits was followed after exposure ceased. The motor conduction velocity showed signs of gradual recovery, but was still much below normal 3 months post-exposure.	Seppalainen, Linnoila, 1975.[2] Scand. J. Work. Environ. Health 1, 178. Linnoila et al, 1975.[2] Proc. 7th Int. Congres Neuropathol. Budapest, 383.

Table 6. Continued.

SPECIES	CONC	CONDITIONS	EFFECT	REFERENCE*
monkey	256 ppm (500 mg/m^3)	6 h/d, 5 d/w, 7 w	Visual acuity dropped more than 5 fold during exposure. Flicker resolution only slightly and transiently impaired. Motor function briefly and partially disrupted. No evidence of retinal vascular changes.	Merigan et al., 1985. Neurotoxicology 6(4), 81.

* see note Table 3.

Table 7. Effects of CS_2 on cardiovascular system due to short-term exposure in various animal species.

SPECIES	ROUTE	CONC/DOSE	CONDITIONS	EFFECT	REFERENCE*
rat	inhalation	3, 16 ppm (10, 50 mg/m³)	5 h/d, 5 d/w, 1 mo	+ Atherogenic diet. CS_2 intensified changes in cardiovascular system and in serum proteins due to the atherogenic diet. Even combination of 3.2 ppm + diet intensified the development of sclerotic process.	Antov et al, 1985. J. Hyg. Epidemiol. Microbiol. Immnol. 29, 329.
rat	inhalation	176 ppm (550 mg/m³)	5 h/d, 6 d/w, up to 8 mo	Significant increase in cholesterol and phospholipid levels from month 2.	Wronska-Nofer, 1972.[2] Int. Arch. Arbeitsmed. 29, 285.
rat	inhalation	1280 ppm (4000 mg/m³)	4 h/d, 2-5 d	Pretreated with phenobarbital. Exposure to CS_2 enhanced noradrenaline induced myocardial damage in NaPB treated animals. Myocardial necrosis is also observed when cold-exposure is used in place of noradrenaline.	Chandra et al., 1977.[1] Exp. Mol. Pathol. 17, 249.
rabbit	inhalation	320 ppm (1000 mg/m³)	5 h/d, 6 d/w, 10 w	Animals received also 0.1 g cholesterol per day throughout the test in their diet. Average of 30% reduction in weight compared to controls. Cholesterol administration alone resulted in marked increase in serum cholesterol, phospholipids, and triglycerides, cf untreated animals. Carbon disulphide treatment resulted in somewhat enhanced cholesterol levels and decreased phospholipid and triglyceride levels, but effects not statistically significant. At autopsy examination limited to aorta and heart. CS_2 treatment produced an increase in aortic (marked) and coronary atheromatosis and also in lipid droplets. The CS_2 treatment was shown to accelerate atherosclerotic changes induced by dietary cholesterol in the rabbit.	Wronska-Nofer et al, 1978.[2] Atherosclerosis 31, 33.
rat	intramuscular	0.05 ml (315 mg/kg)	daily, 6 d/w, for 10-60 doses	Total lipid, phospholipid, and cholesterol increased in early dose period (doses 10-40) but progressively decreased later (doses 40-60). Decrease attributed to decreased synthesis of cholesterol or esterification by the body organs, e.g., liver.	El-Hawary et al. 1977.[1] Egypt. J. Occup. Med. 5 279.

* see note Table 3.

Table 8. Hepatotoxic effects of CS_2 due to short-term exposure in various animal species.

SPECIES	ROUTE	CONC/DOSE	CONDITIONS	EFFECT	REFERENCE*
mouse	inhalation	480 ppm (1500 mg/m³)	4 h/d, 5 d/w, 23 d	Tolerated well, with no sign of toxicity being noted during test. Groups of 4 animals were killed 3 hours post-exposure on various days between 2-23. Livers were removed and examined for level of enzymes of mixed function oxidase system and also for lipid content. A marked reduction in the cyt. P450 and cytochrome c-reductase content was noted after 2-3 days but level returned to normal by the end of the test period. A significant decrease in UDP-glucuronyl transferase was noted at the end of the exposure period. The only significant effect noted on hepatic lipids was an increase in lipid peroxidation (measured by extent of diene conjugation) after 9 days and through the rest of the exposure period.	Jarvisalo et al. 1977.[2] Biochem. Pharmacol. 26, 1521.
rat	intraperitoneal	12 mg/kg	daily for > 60 d	Hepatic cells damaged, including necrosis. Regeneration of cells observed.	Woyke, 1969.[1] Patol. Pol. 20, 103.
rat	intramuscular	0.35 ml/kg (442 mg/kg)	daily for 60 d	No signs of toxicity were reported during the experiment. This study was limited to investigating the effects on the liver. A significant increase in serum glutamic oxalacetic transaminase, alkaline phosphatase, and lactic dehydrogenase was noted after 30 days and in glutamic pyruvic transaminase after 40 days. At autopsy signs of liver damage were noted after 10 days (diffuse fatty infiltration). A severe inflammatory reaction with some necrosis was noted after 50-60 days.	Formanek et al, 1976.[2] In: Adverse effects of environmenta chemicals and psychotropic drugs vol II, ed. Horvath, Elsevier, A'dam 257.
rabbit	intramuscular	6 mg/d	once/day, for 30 and 60 d	Fatty degeneration.	Nicrosini et al., 1963.[1] Arch. Sci. Med. 115, 109.

* see note Table 3.

Table 9. Effects of CS_2 due to short-term exposure by different routes in various animal species.

SPECIES	ROUTE	CONC/DOSE	CONDITIONS	EFFECT	REFERENCE*
Endocrine system					
rat	inhalation	32 ppm (100 mg/m³)	3 h/d, 1.5 mo	Thyroid activity increased; decrease in oestrus cycles; adrenal function decreased; changes appeared earlier in younger animals than in older rats.	Kramarenko et al, 1969.[1] Gig. Tr. Prof. Zabol. 1969 (13), 42.
rat	subcutaneous	200 mg/kg	every 1-2 d for 30 days	Hypertrophy of adrenals followed by atrophy. Vitamin B_6 or glutamic acid partially prevented adverse effects.	Khlishova, Khlishov, 1973.[1] Mater. Povolzh. Konf. Fiziol. Uchastiem Biokhim. Farmakol. Morfol. 6th, 2, 187.
kidney					
rat	intramuscular	0.063 g (0.05 ml) (0.315 g/kg)	daily for 50 d	Hyperaminoaciduria suggestive of kidney lesion; hypoaminoacidaemia.	El-Dessoukey et al, 1977.[1] Z. Ernährungswiss. 16, 31.
haematology/clinical chemistry					
guinea pig	inhalation	9630 ppm (30000 mg/m³)	0.25 h/d, 20 d	Enhanced platelet aggregation	Malfitano et al, 1971.[1] Haematologica 56, 488.
rat	oral	25 mg/kg	daily for 60 d	Normochromic and normocytic anaemia; eosinopenia; reticulocyte cell number increased; no changes in leukocyte or platelet numbers.	Pilarska et al, 1973.[1] Acta Haematol. Pol. 4, 33.
rat	intramuscular	0.35 ml/kg (442 mg/kg)	daily for 50 d	Study limited to investigation of effect on serum cations. Significant decrease in iron, calcium, and magnesium and increase in potassium noted after 20 days; decrease in potassium noted after 20 days; decrease in zinc became significant after 30 days. Effects became more marked at later stages of the experiment. These changes were reversible if exposure ceased after 50 days.	El-Dessoukey et al, 1977.[2] Z Ernährungswiss. 16, 153.

* see note Table 3.

Table 10a. Neurotoxic (including behavioural) of CS_2 due to longterm exposure by inhalation in various animal species.

SPECIES	CONC	CONDITIONS	EFFECT	REFERENCE*
rat	50, 300, 800 ppm (166, 936, 2500 mg/m³)	6 h/d, 5 d/w, 90 d	No morphological differences between two strains tested. At 50 ppm, no changes noted. At 300 ppm only occasional swellings of axons in the dorsal corticospinal fibers of the lumbar spinal cord. At 800 ppm: extensive changes in the spinal cord and peripheral nerve, i.e., neurofilamentous axonal swellings in the distal portions of long fibers of the spinal cords and numerous paranodal and internodal swellings as well as Wallerian degeneration of the posterior tibial nerve.	Gottfried et al, 1985. Neurotoxicology 6 ,(4), 89.
rat	160-256 ppm (500-800 mg/m³)	6 h/d, 5 d/w, 8 mo	Degenerative changes in a small number of ganglion cells.	Milivojevic, 1981. Acta Vet. (Belgrade) 31, 129.
	256-480 ppm (800-1500 mg/m³)	6 h/d, 5 d/w, 11 mo	Dystrophy of ganglion cells; swelling of endothelium of some capillaries and arterioles in brain tissue; paresis of the hind extremities.	
rat	256 ppm (800 mg/m³)	5 h/d, 6 d/w, 8 mo	Increase of activity of ß-glucuronidase in the hippocampus and to lesser extent in the cerebral cortex. No remarkable morphological or ultrastructural changes. PNS: no significant biochemical effects.	Opacka et al, 1986. Toxicol. Lett. 32, 9.
rat	256 ppm (800 mg/m³)	5 h/d, 6 d/w, 12-15 mo	Biochemical effects in peripheral nerves, i.e., increase in cholesterol esters and in the ratio of cholesterol esters to free cholesterol, slight decrease in phospholipidal content and increase of ß-glucuronidase activity. These changes more pronounced after 15 months. After 12 months ultrastructural changes: axonal swellings, increased number of neurofilaments, disappearance of neurotubules.	Opacka et al, 1985. Toxicol. Lett. 24, 171.

Table 10a. Continued

SPECIES	CONC	CONDITIONS	EFFECT	REFERENCE*
rat	288 ppm (900 mg/m³)	5 h/d, 6 d/w, 1.5-12 mo	No effect on peripheral nerve conduction velocity noted during the first 3 months. A significant reduction occurred after 6 months and this was only partially reversible during the 6-months recovery period. A more marked reduction occurred after 12 months exposure and this was essentially irreversible, no improvement at all being noted 6 months after the exposure period.	Knobloch, 1979.[2] Br. J. Ind. Med. 36, 148.
rat	400-800 ppm (1250-2500 mg/m³)	7 h/d, 7 d/w, 11 w	800 ppm was detrimental to the health: decreased weight, rhinitis, rough fur, lethargy, apparent weakness. Significant changes in electrophysiological parameters occured in all modalities tested. 400 ppm: only significant changes in pattern reversal-evoked potential and in brainstem auditory-evoked response.	Rebert, Becker, 1986. Neurobeh. Toxicol. Teratol. 8, 533.
rat	480 ppm (1500 mg/m³)	5 h/d, 6 d/w, 4-65 w	No deteriotation noted in general condition during first 7 months. Weight loss, muscular weakness, and ataxia noted from that time, with development of paralysis during later stages. Examination of myelinated fibres of the brain, cerebellum, and pons showed no distal injury throughout the experiment. Marked degeneration of the myelinated fibres of the spinal column was however noted, with axonic swelling from about 1 month; this progressed until complete destruction of the axis cylinder was noted, with breakdown of the axis fibres and spongy degeneration. No effects were noted on blood vessels. A similar progressive effect was noted in myelinated fibres of the PNS (sciatic nerve) characterised by axonic swelling; the initial changs were detected after 1-2 months. The histological lesions noted were however generally mild.	Szendzikowski et al, 1973.[2] Int. Arch. Arbeitsmed. 31, 135.

Table 10a. Continued

SPECIES	CONC	CONDITIONS	EFFECT	REFERENCE*
rat	480 ppm (1500 mg/m^3)	5 h/d, 6 d/w, 1-14 mo	Reduced rate of weight gain from about 1 month, with actual loss of weight from 10 months. General deterioration of condition after 9 months with signs of paresis and paralysis of hind limbs noted from this stage. At autopsy, no compound-related effects noted on gross or microscopic examination of tissues, apart from the muscle atrophy described below and chronic nephrosis in the kidneys of animals with advanced muscular atrophy. Histological examination of muscles revealed evidence of progressive atrophy from about 4 months. These first effects were noted in the quadriceps femoris. Marked atrophy of fibres was noted in all muscles examined after 6-8 months. The muscular atrophy was of the denervation type with progressive degeneration of the myelinated fibres. There was no evidence of any inflammatory reaction or dystrophic myophathy. A significant reduction in the nucleotide level (NAD, NADP and reduced forms) of quadriceps femoris was noted only after ca. 10 months, and was secondary to muscular atrophy.	Wronska-Nofer et al, 1973.[2] Int. Arch. Arbeitsmed. 31, 123.
rat	480 ppm (1500 mg/m^3)	5 h/d, 6 d/w, 6 mo	Biochemical changes in peripheral (sciatic) nerves: total and free cholesterol slightly reduced; cholesterol esters increased; acid phosphatase and ß-glucuronidase activities increased. These changes associate with morphological symptoms of the peripheral nerve degeneration.	Opacka, Wronska-Nofer, 1982. Toxicol. Lett. 10, 139.
rat	500 ppm (1560 mg/m^3)	5 d/w, 25 w	Significant, time-dependent slowing down of sensory and motor tail nerve conduction velocity. Lacking of main structural features of neuropathy at end of exposure period.	Gagnaire et al, 1986. Toxicol. Lett. 34, 175.

Table 10a. Continued

SPECIES	CONC	CONDITIONS	EFFECT	REFERENCE*
rat	513 ppm (1600 mg/m³)	5 h/d, 6 d/w, 1.5-9 mo	Loss of body weight, ataxia and muscular weakness noted after 4-6 months. Conduction velocity in peripheral nerves (sciatic and tibial nerves) reduced. Reduction was greater after more prolonged exposure. After 1.5 months effect was reversible; after 3 months, no recovery during the first 3 months following the exposure period and only a moderate improvement over the next 3 months.	Knobloch et al, 1979.[2] Br. J. Ind. Med. 36, 148.
rat	576 ppm (1800 mg/m³)	5 h/d, 6 d/w, 10 mo	No distict changes in P:O ratio. Same type of oxidative phosphorylation disorder in brain mitochondria (acute vs chronic).	Tarkowski, Sobczak, 1971.[1] J. Neurochem. 18, 177.
rat	640 ppm (2000 mg/m³)	6 h/d, 5 d/w, 12 mo	Movements slow and non-coordinated; paresis of hind extremities. Dystrophic changes of brain ganglion cells with diffuse multiplication of the glial elements.	Milivojevic, 1981. Acta Vet. (Belgrade), 31, 129.
rat	700 ppm (2184 mg/m³)	5 h/d, 5 d/w, 12 w	Impairment of hind extremities. Decrease of maximal and slow fibres motor conduction velocity of sciatic nerve. Giant axons with increased number of neurofilaments and a decreased number of neurotubules. At the 3rd week of recovery: conduction velocity reached almost their lowest value; spontaneous movements strikingly reduced; advanced muscular atrophy evident. Pathological lesions in nerves progressed. Improvement started at week 8; recovery almost complete at week 18.	Colombi et al, 1981. Clin. Toxicol. 18, 1463.
rat	750 ppm (2340 mg/m³)	6 h/d, 5 d/w, 5 w - 5 mo	Weakness in posterior extremities; appearance of non-specific cholinesterase in intramuscular nerve tracts in adult rats with polyneuropathy. Ultrastructural studies demonstrated disappearance of neurotubules, increased neurofilaments, distended smooth-surfaced vacuoles and dense bodies.	Juntunen et al, 1974.[1] Acta Neuropathol. 29, 361.

Table 10a. Continued

SPECIES	CONC	CONDITIONS	EFFECT	REFERENCE*
rat	750 ppm (2340 mg/m^3)	6 h/d, 5 d/w, 10 w; then 3 d/w, 6 w	Marked weakness in hind limbs noted after 4 months. At end of exposure period animals were killed and the anterior tibial muscles examined by light and electron microscopy. Signs of marked degeneration were noted in terminal axons (disappearance of preterminal exaplasmic neurotubules, partial disappearance of synaptic vesicles, and appearance of dense bodies). Synaptic clefts often widened with Schwann cell interposition. Lesions limited essentially to presynaptic side, since histochemical distribution of acetylcholinesterase (postsynaptic) similar in treated animals compared to controls.	Juntunen et al, 1977.[2] Scand. J. Work Environ. Health 3, 36.
rat	750 ppm (2340 mg/m^3)	6 h/d, 5 d/w, 10 w; then 3 d/w, 12 w	Reduced weight gain. Ataxia was noted after 6 weeks, and a progressive weakening of the hind limbs after 8 weeks. During recovery period some improvement noted. Motor conduction velocity (MCV) of the sciatic nerve was measured at 2 week intervals. This decreased steadily from 4 weeks for about 12 weeks (the effect being statistically significant after 8 weeks), it then remained fairly constant. Some improvement was noted in the recovery period after 8 weeks. Electromyography (gastrocnemius muscle) revealed rather active voluntary electrical activity throughout the experimental period.	Seppalainen, Linniola, 1976.[2] Neuropathol. Appl. Neurobiol. 2, 209.
rat	770 ppm (2400 mg/m^3)	6 h/d, 5 d/w, 22 w	No changes in EEG.	Formanek et al, 1976.[2] In: Adverse effects of environmental chemicals and psychotropic drugs, Vol. II, ed Horvath, Elsevier, A'dam, Neth., 257.

Table 10a. Continued

SPECIES	CONC	CONDITIONS	EFFECT	REFERENCE*
rat	770 ppm (2400 mg/m^3)	6 h/d, 5 d/w, 6 mo	Giant axonal swelling (paranodal or internodal). At the swollen paranodes, myelin sheet was thinned; in other regions large intramyelinic vacuoles indicative of more dramatic demyelination were observed at axonal enlargements.	Jirmanova, Lukas, 1984. Acta Neuropathol. 63, 255.
rat	770-1150 ppm (2400-3600 mg/m^3	6 h/d, 5 d/w, 3 and 6 mo	Electromyography demonstrated reduced conduction Copper levels were elevated in affected nerves.	Lukas et al, 1980.[1] Adv. Neurotoxicol. Proc. Int. Congr., 181.
rabbit	3 ppm (10 mg/m^3)	12 mo	Brain acetylcholinesterase increased.	Kulinskaya, 1967.[1] Bull Eksp. Biol. Med. 63 (7), 67.
rabbit	250, 500, 750 ppm (gradually increase) (780, 1560, 2340 mg/m^3)	6 h/d, 5 d/w, 16 w; then 500 ppm for 5 w; then 750 ppm for 17 w	Reduced weight gain was noted from start of exposure, with actual loss in weight after concentration increased to 750 ppm (i.e. after 21 weeks). Signs of loss of muscular control noted after 29 weeks. Effects limited essentially to lower lumbar region and rear quarters. Marked impairment in all animals by the end of week 38 when exposure terminated. At autopsy: marked changes in the CNS, affecting the brain and spinal column. In the brain pathological changes were noted in the meninges, with swelling and lymphocyte infiltration, and degeneration of nerve cells in cerebral cortex, with spongiosis. Some pathological changes were also noted on the cerebellum, principally degeneration of Purkinje cells. In the spinal column, pronounced spongiosis of the white matter was noted in all animals at the end of the exposure period. In addition, swelling and degeneration of the nerve axis cylinders occurred. No loss of myelin was noted, nor were any vascular or meningeal changes noted. No lesions were noted in optic nerve. Two rabbits were subject to interim killing and autopsy 12 weeks after exposure to 250 ppm CS_2. Definite pathological lesions were noted in the brain (meningeal swelling and lymphocyte infiltration).	Cohen et al, 1959.[2] Am. Ind. Hyg. Assoc. J. 20, 203.

* see note Table 3.

Table 10b. Neurotoxic (including behavioral) effects of CS_2 after repeated application in the rat.

SPECIES	ROUTE	DOSE/COND	EFFECT	REFERENCE*
rat	oral	0.24 ml/kg (303 mg/kg), twice/ week for 8 w; then 0.49 ml/kg (606 mg/kg) twice/ week for 12 w	Signs of toxicity noted during exposure included transient disorientation and reeling gait immediately following exposure for the first 2 weeks only. Alopecia was from 12 weeks and paralysis of the fore and hind limbs together with increasing disorientation after 16 weeks. Groups of animals were killed at intervals between 4 and 20 weeks, and the brain and spinal cord examined. The main effects noted on histological examination of brain were as follows: destruction of ganglion cells in both cerebrum and cerebellum after 12 weeks and necrosis of cortical cells after 4 months. In addition, axonic swelling and destruction of the myelin sheaths of nerve fibres of the CNS noted after 5 months. Histochemical determinations of brain levels of monoamine oxidase and various other enzymes after 16 and 20 weeks revealed a general decrease in activity of arylsulphatases and glutamic dehydrogenase. No effect noted on monoamine oxidase level.	Dietzmann, Laass, 1977.[2] Exp. Pathol. 13, 320.
rat	intraperitoneal	172, 286, 400 mg/kg; 5 d/w, 11 w	Decrease in grip strength, interference with escape from shock, disturbance of visual and auditory evoked potentials. An effect on central auditory tract conduction was noted. Conduction velocity in the ventral caudal nerve and latencies of somatosensory evoked potential components were unaffected.	Rebert et al, 1986. Neurobehav. Toxicol. Teratol. 8, 543.

* see note Table 3.

Table 11a. Effects of CS_2 on the cardiovascular system due to long-term exposure by inhalation in various animal species.

SPECIES	CONC	CONDITIONS	EFFECT	REFERENCE*
rat	0.4, 4.2, 36 ppm (1.2, 13, 112 mg/m³)	4 mo	No effects on serum lipid levels at end of exposure or 9 months later. Examination of hearts revealed slight changes in size and composition of aorta.	Sanotskii, Grodetskaya, 1980.[2] Gig. Tr. Prof. Zabol. 1980 (7) 3.
rat	16-64 ppm (50-200 mg/m³)	8 h/d, 5 mo	Significant reduction in glucose-6-phosphatase dehydrogenase (28%) and an increase in succinate dehydrogenase (31%) and lactate dehydrogenase (23%) noted in myocardial homogenates of animals exposed to 50 mg/m³. Effects more marked at higher dose levels. Insufficient data given on actual enzyme acitivities, and their variability, to make any assessment of this work.	Antov et al, 1980.[2] Gig. Tr. Prof. Zabol. 1980 (11), 17.
rat	3.2-64 ppm (10-200 mg/m³)	5 h/d, 5 d/w, 3 mo; 8 h/d, 5 d/w, 6 mo	Changes in the metabolic and energetic processes in the myocardium and in the quantitative and qualitative characteristic of the aortal vessel wall were observed. Minimal effective conc. 50 mg/m³. The established disorders follow the dose-effect dependence.	Antov et al, 1985. J. Hyg. Epidemiol. Microbiol. Immunol. 29, 329.
rat	74-176 ppm (230-550 mg/m³)	5 h/d, 5 d/w, 8 mo	At 74 ppm: slight increase in serum cholesterol after 8 months. 176 ppm: significant increase in cholesterol and phospholipid levels (from mo 2) and in triglycerides (from mo 4). Rate of cholesterol synthesis increased.	Wronska-Nofer, 1973.[2] Med. Lav. 64, 8.
rat	256-320 ppm (900-1000 mg/m³)	4, 10, 13 mo	Increased free and esterified cholesterol in aorta and skeletal muscle.	Laurman, Wronska-Nofer, 1977.[1] Med. Pr. 28, 77.
rat	313 ppm (960 mg/m³)	2,5 h/d, 6 d/w, 8 mo and 5 h/d, 3 d/w, 8 mo	Liver chfolesterol synthesis increased. Serum cholesterol phospholipids and triglycerides increased.	Wronska-Nofer, Knobloch, 1972.[1] Bull. Acad. Pol. Sci., Ser. Sci. Biol. 20, 813.

Table 11a. Continued.

SPECIES	CONC	CONDITIONS	EFFECT	REFERENCE*
rat	321 ppm (1000 mg/m³)	5 h/d, 6 d/w, 6-8 mo	Total cholesterol content of aorta was slightly increased and the cholesterol ester level more markedly increased. Rate of cholesterol biosynthesis slightly elevated, but a greater increase was noted in the rate of transfer of cholesterol from blood to aorta.	Wronska-Nofer, Parker, 1978.[2] Int. Arch. Occup. Environ. Health 42: 63.
rat	321 ppm (1000 mg/m³)	5 h/d, 6 d/w, 6 mo	+ atherogenic diet The atherogenic diet resulted in a marked increase in serum cholesterol levels and also in aorta cholesterol (especially esterified) levels as compared to control animals on a normal diet. No gross atheroma were however noted at the end of the exposure period, but histological examination revealed increased lipid accumulation, especially near the aortic valves. Treatment with carbon disulphide produced a significant increase in serum and aortic cholesterol levels. No gross evidence for atheroma was noted at the end of the exposure period, but more advanced lipid infiltrates were observed on histological examination of the coronary arteries. These changes were less marked in animals maintained on a high cholesterol diet, but not containing thiouracil. The results suggest that carbon disulphide may have some accelerating effect on atherosclerotic changes induced by dietary hypercholesterolaemia.	Wronska-Nofer et al, 1980.[2] Br. J. Ind. Med. 37, 387.
rat	321 ppm (1000 mg/m³)	5 h/d, 6 d/w, 15 mo	No effect on serum cholesterol levels noted after 6 months, but an increase in both total cholesterol and cholesterol ester levels was observed at 15 months. An increase in cholesterol (total and esterified) levels was noted in the aorta at that time. No gross or histological lesions; lipid droplets occasionally noted in coronary arteries.	Wronska-Nofer et al, 1980.[2] Br. J. Ind. Med. 37, 387.

Table 11a. Continued.

SPECIES	CONC	CONDITIONS	EFFECT	REFERENCE*
rabbit	141, 282 ppm (440, 880 mg/m^3)	5 h/d, 6 d/w, 12 or 26 w	A significant increase in serum cholesterol levels (both esterified and total) was noted after 26 weeks at 440 mg/m^3 but no significant increase at 880 mg/m^3. However, there was much variation in the control values throughout the experiment and the significance of the result is difficult to assess. A significant increase in total cholesterol levels in the aorta was noted after 26 weeks at both dose levels.	Wesolowska, Gregorczyk 1978.[2] Med. Pr. 29, 471.
rabbit	300 ppm (940 mg/m^3)	6 h/d, 5 d/w, 12 w	With or without 2% cholesterol in diet. In both cases significant reduction in serum thyroxine level. Response of heart and aorta to the 2% cholesterol was not siginificantly affected by exposure to CS_2.	Van Stee et al, 1986. Toxicology 40, 45.

Table 11b. Effects of CS_2 on the cardiovascular system due to long-term, intraperitoneal application in various animal species.

SPECIES	DOSE	CONDITIONS	EFFECT	REFERENCE*
rabbit	6 mg/kg	daily, 180 d	No effect noted throughout the exposure period on total serum cholesterol levels, but a tendency was noted for free cholesterol levels to increase and esterified cholesterol to decrease. No evidence of any arteriosclerotic lesions were noted in animals killed and histologically examined after 80 days. When given a cholesterol enriched diet, markedly increased total and free serum cholesterol levels noted during exposure period, of similar magnitude but occuring earlier than in control animals fed a cholesterol-enriched diet. At autopsy more extensive, marked arteriosclerotic lesions when compared to controls.	Pateini et al, 1958.[2] Fol. Med. 41, 705.
rat	25 mg/kg	weekly, 3-6 mo	Myocardial lesions, no vascular lesions.	Mihalache et al, 1977.[1] Rev. Med-Chir. 81, 439.

* see note Table 3.

Table 12. Hepatotoxic effects of CS_2 due to long-term exposure by inhalation in various animal species.

SPECIES	CONC	CONDITIONS	EFFECT	REFERENCE*
rat	160-256 ppm (500-800 mg/m³)	6 h/d, 5 d/w, 8 mo	No clinical signs of patho-anatomical changes, nor histological changes in liver tissue. Dystrophic necrobiotic changes without reactions of mesenchymal elements.	Milivojevic, 1981. Acta Vet. (Belgrade) 31, 129.
	256-480 ppm (800-1500mg/m³)	6 h/d, 5 d/w, 11 mo		
rat	426 ppm (1300 mg/m³)	5 h/d, 4 d/w, 12 w; 5 h/d, 4 d/w, 26 w; 10 h/d, 4 d/w, 10 w	Liver isoenzymes of lactate dehydrogenase and malate dehydrogenase were elevated in the serum. Increase α-1 globulin fraction and decrease α-2M and α-2H globulin fraction. No change in other liver derived enzymes or in liver function tests.	Gregorczyk et al, 1975.[1] Int. Arch. Arbeitsmed. 34, 65.
rat	480 ppm (1500 mg/m³)	5 h/d, 5 d/w, 5 mo	Ultrastructural examination demonstrates, in some hepatocytes, giant mitochondria and locally degranulated rough endoplasmatic reticulum. Marked decrease in activity of aniline p-hydroxylase and microsomal ethanol oxidizing system with concomittant depression of cyt. P450 content, accompanied by stimulation of microsomal lipid peroxidation.	Wronska-Nofer et al, 1986. J. Appl. Toxicol. 6, 297.
rat	640 ppm (200 mg/m³)	6 h/d, 5 d/w, 12 mo	Dystrophic necrobiotic changes with occasional multiple necrosis, without reaction of the parenchyma.	Milivojevic, 1981. Acta Vet. (Belgrade) 31, 129.
rabbit	200 ppm (625 mg/m³)	3 h/d, 6 mo	Vacuolaction of hepatocytic cytoplasm.	Cuccurullo et al, 1978.[1] Pathologica 70, 419.

* see note Table 3.

Table 13. Effects of CS_2 due to long-term exposure by inhalation in various animal species.

SPECIES	CONC	CONDITIONS	EFFECT	REFERENCE*
gastrointestinal system				
rat	3.2-65 ppm (10-200 mg/m³)	4 h/d, 6 mo	Disrupted glucose absorption and inhibited intestinal enzymes.	Murashko, Tantsyura, 1977.[1] Vopr. Pitan 1977 (6), 32.
kidney				
rat	0.32 ppm (1 mg/m³)	continuously for 6 mo	Increased urinary coproporphyrin excretion from day 123.	Misiakiewicz et al, 1972.[2] Rocz. Panstw. Zakl. Hig. 23, 465.
rat	0.42, 3.33 ppm (1.3, 10.4 mg/m³)	4 h/d, 6 mo	Urinary output decreased, protein increased.	Salnikova, Chirkova, 1974.[1] Gig. Tr. Prof. Zabol. 1974 (12), 34.
rat	313 ppm (960 mg/m³)	2.5 h/d, 6 d/w, 8 mo or 5 h/d, 3 d/w, 8 mo	Increased urinary excretion rate of N-methylnicotinamide.	Wronska-Nofer, Knobloch, 1972.[1] Bull. Acad. Pol. Sci. Ser. Sci. Biol. 20, 813.
rat	640 ppm (2000 mg/m³)	44 h/w, up to 12 mo	Thickened glomerular basement membranes with hyalinosis, fatty degeneration and calcification Bowmans capsule lined by cuboidal epithelium.	Isler, 1957.[1] Z. Ges. Exp. Med. 128, 134.
rabbit	200 ppm (624 mg/m³)	3 h/d, 6 mo	Interstitial nephritis, tubular nephrosis; glomerulopathy.	Cuccurullo et al, 1978.[1] Pathologica 70, 419.
rabbit	250 ppm (780 mg/m³)	6 h/d, 5 d/w, 16 w; then 500 ppm (1560 mg/m³) for 5 w; then 750 ppm (2340 mg/m³) for 17 w.	Increased incidence of chronic interstitial nephritis.	Cohen et al, 1959.[2] Am. Ind. Hyg. Assoc. J. 20, 303.
Lung				
rat	0.32 ppm (1 mg/m³)	continuously, 6 mo	Signs of chronic bronchitis and isolated loci of lobular pneumonia (not stated in how many animals these effects occurred, significance cannot be assessed).	Misiakiewicz et al, 1972.[2] Roc. Panstw. Zakl. Hig. 23, 465.

Table 13. Continued

SPECIES	CONC	CONDITIONS	EFFECT	REFERENCE*
rat	170 ppm (530 mg/m³)	5 h/d, 6 d/w, 5 mo	Intense histiocytic infiltration in lung stroma; methysergide decreased such infiltration while neither cinarin (quinic acid derivative) nor serotonin inhibited infiltration.	Dominiczak et al, 1974.[1]. Med. Pr. 25, 421.
Haematology and clinical chemistry				
rat	0.32 ppm (1 mg/m³)	continuously, 6 mo	Blood cholinesterase asparagine transaminase increased from day 85, reaching a maximum at day 153.	Misiakiewicz et al, 1972.[2] Rocz. Panstw. Zakl. Hig. 23, 465.
rat	160 ppm (500 mg/m³)	5 h/d, 5 mo	Increased soluble fibrin monomer complexes in blood and decreased fibrinolytic activity.	Wojewski et al, 1972.[1] Thromb. Diath. Haemorrh. 27, 72.
rat	160 ppm (500 mg/m³)	5 h/d, 6 d/w, 5 mo	Number of erythrocytes increased, percentage reticulocytes increased.	Kiczak et al, 1972.[1] Med. Pr. 23, 265.
rabbit	141, 256 ppm (440, 800 mg/m³)	5 h/d, 6 d/w, 3 or 6 mo	At the higher dose level, a slight increase in fibrinogen level was noted after 3 months, and significant ($p<0.05$) increase after 6 months. In addition, a marked increase in fibrinolytic time (538 ± 163 min., cf 293 min. $p<0.05$) was observed at 6 months. No significant effects were noted on the other parameters measured. No effects were noted at 256 ppm on these parameters apart from an increase in immediate but not progressive antiplasmin levels after 6 months. *In vitro* test to determine platelet adhesiveness were carried out on blood samples taken from the marginal ear vein after 3 and 6 months. A significant increase in the percentage of adhesive platelets was noted at both concentrations after 6 months, values of 36 ± 12.2% and 35 ± 13.4% being obtained at 141 and 256 ppm respectively as compared to 22% in the controls ($p<0.05$). However, no data were given on the variability of the control value (no SD) nor on the actual numbers of platelets present, and it is thus difficult to assess the significance of this result.	Cwajda, Woyke, 1978.[2] Med. Pr. 29, 287. Cwajda, Woyke, 1978.[2] Med. Pr. 29, 481.

Table 13. Continued

SPECIES	CONC	CONDITIONS	EFFECT	REFERENCE*
rabbit	300 ppm (940 mg/m^3)	1/2 h/d, 4 mo	Slight effect on some haematological and blood biochemistry parameters noted (increased reticulocytes, increased ß and γ globulins, decreased albumin) but these returned to normal after exposure ceased.	Wakatsuki, 1959.[2] Shikoku Igaku Zasshi 15, 671.
rabbit	250 ppm (780 mg/m^3)	6 h/d, 5 d/w, 6 mo; then 500 ppm (1560 mg/m^3) for 5 w; then 750 ppm (2340 mg/m^3) for 17 w.	CS_2 exposure increases urinary and faecal zinc excretion. Serum zinc decreases.	Cohen et al, 1959.[1] Am. Ind. Hyg. Assoc. J. 20, 303.
Glucose tolerance				
monkey	384 ppm (1200 mg/m^3)	6 h/d, 5 d/w, 20 w	Increase of xanthurenic acid; reduced excretion of 4-pyridoxic acid.	Sperlingova et al, 1982 Environ. Res. 29, 151.

* see note Table 3.

Table 14. Summary of findings in mutagenicity test with CS_2.

TEST	RESULT	REFERENCE*
Salmonella typhimurium plate incorporation assay (with and without metabolic activation) strains TA98, TA100, TA1535, TA1537.	negative	Haworth et al., 1983.
Idem with strain TA100	negative	Hedenstedt et al., 1979.[1] Mutat. Res. 68 313.
Bacterial fluctuation test with Salmonella typhimurium strain TA98 and TA100	negative	Donner et al., 1981. Mutat. Res. 91, 163.
Idem with E. Coli WP2uvrA	negative	Donner et al., 1981. Mutat. Res. 91, 163.
Sex-linked recessive lethal assay in Drosophila	negative	Donner et al., 1981. Mutat. Res. 91, 163.
Idem	negative	Beliles et al., 1980. NIOSH BP82-185075.
Host mediated assay Salmonella typhimurium strain TA98 employing male and female CD-1 mice	negative	Beliles et al., 1980. NIOSH PB82-185075.
Unscheduled DNA synthesis in W1-38 human fibroblasts.	negative	Beliles et al., 1980. NIOSH PB82-185075.
Spermhead abnormality in mice and rats	negative	Beliles et al., 1980. NIOSH PB82-185075.
Chromosomal aberrations in rat bone marrow	negative	Beliles et al., 1980. NIOSH PB82-185075.
rat dominant lethal test	negative	Beliles et al., 1980. NIOSH PB82-185075.
Chromosome aberrations in rat bone marrow cells	positive	Vasileva, 1982. Cytol. Genet. 16 (2), 68-70.

Table 15. Effects of CS_2 on the reproductive system of the male rat.

ROUTE	CONC/DOSE	CONDITIONS	EFFECT	REFERENCE*
inhalation	0.7, 4 ppm (2.3, 13.6 mg/m³)	4 h	No effect on seminal epithelium and sperm cells in various stages of development (examined histologically).	Salnikova, Chirkova, 1974.[2] Gig. Trud. Prof. Zabol. 1974 (12), 34.
inhalation	0.4, 3 ppm (1.3, 10.4 mg/m³)	4 h/d, 6 mo	No effect (see above).	see above.
inhalation	350 ppm (1082 mg/m³)	5 h/d, 5 d/w, 10 w	No change in reproductive organ weights, nor in plasma gonadotropin levels.	Tepe, Zenick, 1984. Toxicology 32, 47.
inhalation	426 ppm (1330 mg/m³)	12-28 w	No effect on microstructure of testes.	Gondzik, 1976.[1] Med. Pr. 27, 21.
inhalation	600 ppm (1872 mg/m³)	5 h/d, 5 d/w, 10 w	No change in reproductive organ weights, no change in plasma hormone levels; decrease in ejaculated sperm counts. Shorter times to mount and to ejaculate.	Tepe, Zenick, 1984. Toxicology 32, 47.
intraperitoneal	12.5 mg/kg 25.0 mg/kg	every other day for 60 d every other day for 60 d and 120 d	Signs of degeneration and atrophy of both seminiferous epithelium and interstitial cells noted after 60 days with 25 mg/kg. Effect more pronounced after 120 days, with complete inhibition of spermatogenesis and lack of spermatogonia in many tubules.	Gondzik, 1971.[2] Pol. Med. J. 10, 133.

* see note Table 3.

Table 16. Effects due to inhalation of CS_2 on the reproductive system of the female animal.

SPECIES	CONC	CONDITIONS	EFFECT	REFERENCE*
rat	<4.0 ppm (12.7 mg/m³)	98 d	Animals in cages in viscose rayon plant concomitantly exposed to noise levels up to 90 dB. Progressive increase in the length of the oestrus cycle.	Vasileva, 1973.[2] Gig. Sanit. 1973 (7), 24.
rat	0.3, 3, 32 ppm (1, 10, 100 mg/m³)	4 mo	Prolongation of oestrus cycle at 3 ppm and above. At the end of the experiment, the animals were killed and the pituitary, ovaries, adrenals and thyroid examined histologically. No effects were noted at 0.3 ppm, but some effects on these endocrine glands were noted at 3 ppm and above. These included an increase in folliculotrophs and colloid substance in the parenchyma of the pituitary, vacuolation of the ovarian cells, and the occurence of cyst-like dilated follicles, changes in the adrenal cortex (hyperaemia and haemorrhages), signs of increased activity of the thyroid. These effects were consistent with a stimulation of the trophic hormones of the anterior lobe of the pituiray.	Acadzhanova, 1978.[2] Gig. Trud. Prof. Zabol. 1978 (4), 10.
rat/rabbit	20, 40 ppm (62, 125 mg/m³)	7 w	No changes in reproductive organ weights; no histological changes in these organs.	Beliles et al, 1980. NIOSH PB82-185075.

* see note Table 3.

Table 17. Teratogenic effects of CS_2 in various animal species.

SPECIES	ROUTE	CONC/DOSE	CONDITIONS	EFFECT	REFERENCE*
rat	inhalation	0.01, 3 ppm (0.03, 10 mg/m³)	8 h/d through-out gestation	No maternal toxicity: duration of pregnancy, maternal weight gain, and general condition normal; no changes in indices of lipid metabolism, of aniline hyroxylase, and of aminopyrine N-demethylase. 50% reduction of cyt. P450 in liver (at 3 ppm; not significant) and mild inhibition of oxygen consumption in the placenta at end of gestation (not significant). Insignificant elevation of preimplantation lethality at 3 ppm. No congenital malformations, biochemical changes or reduction of foetal body weight. No effect at birth on mean litter size, live birth index, average litter weight. Postnatal sequelae of exposure to 3 ppm, reduction of viability, retardation of morphological and sensory development, malfunction of liver MFO system, neurophysiological and behavioural disorders. Reproductive capacity of the progeny is not impaired.	Tabacova et al, 1981. G. Ital. Med. Lav. 3, 121.
rat	inhalation	0.7, 4 ppm (2.2, 13 mg/m³)	4 h/d through-out gestation	No effect on litter size, number of preimplantation or post-implantation deaths, mean foetal weight or size. No abnormalities noted on gross or microscopic examination of foetuses other than an increased incidence of blood effusion in a number of tissues at 4 ppm. Offspring: no changes in post-natal mortality, weight gain. At 4 ppm: some adverse effects in kidney function (decrease in diuresis; increase in urine albumine); increase in relative kidney weight. At both levels: increase in relative weight of heart, lung, liver, spleen.	Salnikova, Chirkova, 1974[2]. Gig. Trud. Prof. Zabol. 1974 (12), 34.

Table 17. Continued

SPECIES	ROUTE	CONC/DOSE	CONDITIONS	EFFECT	REFERENCE*
rat	inhalation	16, 32, 64 ppm (50, 100, 200 mg/m³)	8 h/d through-out gestation	At sacrifice, marked effects were noted in the liver (dystrophy of hepatocytes, reduced glycogen content) of the maternal animal at 64 ppm, and also in the placenta (necrotic changes and an inflammatory reaction). Mild hepatic effects were noted at 32 ppm but not at 16 ppm. In the teratogenicity study, significant foetotoxic effects were noted at 32 ppm and above, with a reduced number of viable foetuses per dam (8.8 at 32 ppm, 9.0 at 64 ppm, vs 10.1 in the controls) and reduced mean foetal weight (4.45 g at 32 ppm, 4.53 g at 64 ppm, vs 4.79 in the controls). Teratogenic effects were noted at all dose levels but they were not statistically significant at 16 ppm. The main abnormality noted was hydrocephalus with 5.5%, 27%, and 38.4% of litters affected at 16, 32, and 64 ppm, vs 0% of the controls. In addition, club foot was noted in 3.1%, 11.9%, and 19.2% of the litters respectively, as compared to 0% in the control group. Tail deformities were noted in the 2 higher groups only (1.2% and 6.9% of litters). Skeletal abnormalities were noted in all test groups as well as the controls, with 62.3% of foetuses affected at 64 ppm, vs 21.5% of the controls. The increase in the test group was not statistically significant at 16 ppm. The effects were mainly associated with the cranium (retarded ossification and certain structural defects) and the ribs (deformations and additions). Observation of the development of the offspring of animals allowed to come to term showed a reduction in weight gain at 32 ppm and above. Behavioural tests revealed abnormalities in the offspring from all test groups (reduced exploratory activity and increased emotional activity).	Tabacova et al 1978.[2] Khig. Zdrav. 31 257. Tabacova et al, 1978.[2] Toxicol. Lett. 2, 129. Tabacova et al, 1979.[2] Arh. Rig. Rada 30 497.

Table 17. Continued.

SPECIES	ROUTE	CONC/DOSE	CONDITIONS	EFFECT	REFERENCE*
rat	inhalation	20, 40 ppm (62.5, 125 mg/m^3)	7 h/d, d 0-18 and d 6-18 of gestation	Half of the animals pre-exposed (5 d/w, 3 w). No significant, compound related maternal toxicity, teratogenicity.	Beliles et al, 1980. NIOSH PB82-185075
rat	inhalation	100, 200, 400, 800 ppm (310, 620, 1250, 2500 mg/m^3)	6 h/d, d 6-20 of gestation	No effects at 100, 200 ppm. 400, 800 ppm: significantly reduced maternal weight gain; significantly reduced foetal body weight. 800 ppm: significant increase in unossified sternebrae.	Saillenfait et al, 1989. Toxicol. Lett. 48, 57.
rat	inhalation	641 ppm (2000 mg/m^3)	2 h/d throughout gestation	Decreased number of viable foetuses per litter; reduced litter size due to an increase in pre-implantation mortality. No decrease in weight of surviving foetuses, no other abnormalities.	Yaroslavskii, 1969.[2] Bull. Eksp. Biol. Med. 68, 88.
		641 ppm (2000 mg/m^3)	2 h/d first 19-20 d of pregnancy	Animals killed on day 19-20 of gestation. Uteri and contents examined. Marked reduction in litter size due to increase in pre-implantation mortality.	
rat	inhalation	0.01, 3.2, 32, 64 ppm (0.03, 10, 100, 200 mg/m^3)	8 h/d throughout gestation, F_1 also throughout gestation	Functional deficiencies in F_1 due to exposure to 0.01 and 3.2 ppm (i.e. retarded development of liver drug metabolizing system; deficient CNS function) diminish and tend to disappear by the end of first month of life. Exposure of F_1 to same levels during gestation induced more pronounced adverse maternal and foetal effects. At 32 and 64 ppm the increased teratogenic susceptibility is manifested by a marked increase in the incidence and severity of the malformations induced in the F_2 offspring. At 0.01 and 3 ppm morphological alterations are found in the F_2 progeny; development of hepatic drug metabolizing system is more markedly delayed, disturbed CNS-function is more apparent.	Tabacova et al, 1983. J. Appl. Toxicol. 3, 223.

Table 18. Neurotoxic effects of CS_2 in exposed workers.

NUMBER OF SUBJECTS	EXPOSURE LEVELS	EXPOSURE DURATION	EFFECT	REFERENCE*
145	PAS during study: 1-16 ppm (3-48 mg/m³), spot sampling from 1957: 1.5-60 ppm (5-186 mg/m³); mostly <20 ppm (62 mg/m³)	12.1 ± 6.9 y	Controls: 233 persons, male, white, differs as to age and employment duration; smoking/drinking habits and education similar. Low background exposure (0.2 ppm mean). Small, but significant reductions of sural sensory conduction velocity (dose-related). Significant reduction in amplitudo ratio for the peroneal nerve. No increase attributable to CS_2 in prevalence of symptoms related to PNS disorders.	Johnson et al, 1983. Neurotoxicology 4, (1), 53.
108	last 4 years usually about 3 ppm (9 mg/m³), maximum up to 8 ppm (25 mg/m³), earlier probably much higher	10-15 y	Symptoms of polyneuritis i.c. pain and paraesthesia of extremities; no data on controls and former exposure levels.	Martynova et al, 1976.[2] Gig. Sanit. 1976 (5), 25.
50	3-8 ppm (10-25 mg/m³; spot sampling) (mean values registered during 12 y)	10-15 y	Controls: 50, pair-matched as to age, physical feature, workshift, smoking/drinking history. No significant changes in neuropsychological parameters.	Cirla, Grazlano, 1981. G. Ital. Med. lav. 3, 69.
45	1-17 ppm (3-53 mg/m³), estimation based on PAS and spot samples	>10 y (mean: 20 ± 9 y)	Controls: 42 pair-matched as to age, nationality. No differences regarding length, smoking/drinking habits. Small changes in slower fiber conduction velocity and in refractory period of peroneal nerve.	Ruijten et al, 1988. T. Soc. Gezondheidsz. 66 100.
110	10-19 ppm (30-60 mg/m³)	4 y	Significant decrease in maximal motor conduction velocity of peroneal nerve in exposed groups compared to not-exposed.	Sandrini et al, 1983. G. Ital. Med. Lav. 5, 199.
34	<10 ppm (<30 mg/m³)	>4 y		

Table 18. Continued

NUMBER OF SUBJECTS	EXPOSURE LEVELS	EXPOSURE DURATION	EFFECT	REFERENCE*
21	removed from exposure at least 5 y before study <19 ppm (<60 mg/m^3)			
51	just employed, not-exposed			
36	at time of study: 5-10 ppm (16-31 mg/m^3), 1960-1970: 10-30 ppm (31-94 mg/m^3), 1950-1960: 20-60 ppm (172-187 mg/m^3), <1950: >60 ppm (187 mg/m^3)		Paraesthesia/cramps noted in 74% of workers. Other symptoms: muscle pain and muscle weakness. Furthermore, encephalopathic symptoms, like headache (74%), sleep disturbances (74%), fatique (69%), loss of libido and organopsychosyndrome. Electromyographic examinations of several muscles revealed many abnormalities including fibrillation. Decreased maximum motor conduction velocity of median ulnar and common peroneal nerves. Decreased sensory fiber conduction velocity.	Seppalainen et al, 1972.[1,2] Work Environ. Health 9, 71.
118	see above	1-27 y (mean: 25 y)	Controls: 100, age-matched paper mill workers. Significantly reduced peripheral nerve conduction velocity in CS_2 workers. No overt signs of toxicity. Polyneuropathy in 48% of exposed (vs 24% in paper mill workers). Abnormal EEG in 21 of 54 exposed (vs 6 of 50).	Seppalainen, Tolonen, 1974.[1,2] Work Environ. Health 11, 145.
30	at time of study 5 ppm (15 mg/m^3), earlier up to 220 ppm (688 mg/m^3).	10-16 y	Polyneuropathy; paraesthesia/cramps (73%), muscle pain (73%), muscle weakness (33%), distal sensory loss (27%). Motor conduction velocity normal; sensory conduction velocity lowered. Distal sensory evoked potential amplitude and muscle evoked potential lowered. Headache was found, just like fatigue, loss of libido and mild Parkinsonism (in 2 of 30).	Vasilescu, Florescu, 1980.[2] Med. lav. 61, 102.

Table 18. Continued

NUMBER OF SUBJECTS	EXPOSURE LEVELS	EXPOSURE DURATION	EFFECT	REFERENCE*
84	up to 72-96 ppm (225-300 mg/m³)	<2 y (67%)	Most workers younger than 25-years-old. Symptoms of peripheral neuropathy in 88% of workers. Physical examination revealed distal hypo-aesthesia in 66 of the workers and abolished or markedly reduced Achillean and patellar reflexes in 30%. Lower motor neurone injury (88%) at electromyographic examination. Other symptoms: headache (77%), fatigue (72%), irritability (56%), digestive troubles (56%), sleepness (56%), depression (35%), memory loss (35%), insommia (34%), nightmares (26%).	Manu et al, 1972.[2] Med. Lav. 61, 102.
25	3-8 ppm (10-25 mg/m³; spot sampling) (mean values registered during 12 y)	3-12 y	Controls: 25-pair-matched as to age, physical feature, workshift, smoking/drinking history. No differences in the Memory Scale. Exposed persons seemed to have lower results in the intelligence test and mainly in the performance tests, whose scores were widely dispersed. However, these differences were not statistically significant.	Cirla, Graziano, 1981. G. Ital. Med. Lav. 3, 69.
131	PAS during study 1-16 ppm (3-48 mg/m³) spot sampling from 1957: 15-60 ppm, mostly <20 ppm (5-186 mg/m³; <62 mg/-m³)	1-31 y (mean: 12 y)	Controls: 167, only male and white; younger less long employed; no differences regarding smoking, alcohol, and education. No significant differences between exposed and non-exposed. Tested were: mood and excitability, cognitive and psychomotor performance. Questionaire: exposed reported significantly more symptoms.	Putz-Anderson et al, 1983 Neurotoxicology 4 (1), 67.

Table 19. Cardiovascular effects due to CS_2 in exposed workers.

NUMBER OF SUBJECTS	EXPOSURE LEVELS	EXPOSURE DURATION	EFFECT	REFERENCE
50	3-8 ppm (10-25 mg/m³), mean values registered during 12 y	3-12 y	Controls: 50, matched as to age, sex, physical feature, workshift, smoking/alcohol history. No statistically significant differences in serum lipid pattern, blood coagulation system, blood pressure, ECG, ophtalmoscopy, thyroid function.	Cirla, Graziano, 1981. G. Ital. Med. lav. 3, 69.
70	1.6-11 ppm (5-35 mg/m³)	1-37 y	Controls: 70, pair-matched for age, physical feature. Prevalence of known or supposed risk factors of atherogenesis the same in exposed and controls. Atherosclerosis factors like blood coagulation factors, platelet function, and fibrinolysis are examined: no significant differences.	Candura et al, 1981. G. Ital. Med. Lav. 3, 127.
70	1972-1979: <11 ppm (35 mg/m³)	<5->21 y	Controls: 70, pair-matched (age, physical feature). No differences in total cholesterol, HDL-cholesterol, triglycerides, blood pressure, and two coronary heart disease risk indices.	Franco et al, 1982. Scand. J. Work Enviro Health 8, 113.
354	PAS at study 0.2-5 ppm (0.7-16 mg/m³), spot sampling 1975-1981: 0.9-13 ppm (3-42 mg/m³)	<4-20 y (mean: 10 y)	Controls: 177, age- and sex-matched. No effect on blood pressure, blood cholesterol levels. No effect on ECG. Questionaire: no case with typical and probable angina detected. Prevalence of possible angina higher in reference group.	Sugimoto et al, 1984. Int. Arch. Environ. Healt 54, 127.

Table 18. Continued.

NUMBER OF SUBJECTS	EXPOSURE LEVELS	EXPOSURE DURATION	EFFECT	REFERENCE*
206	at time of study <10 ppm (31 mg/m³)	6-28 y (mean: 17 y)	Controls: 152 paper mill workers, age-matched. At time of study: 58% were still exposed, 36% were removed to non-contaminated places, 3% had retired. Exposed slower in the performance of Bourdon-Wiersma vigilance and Santa Ana dexterity tests. Workstyle more careful. Scored as well as non-exposed in intelligence tests, but less in personality test and in tests for general adaptibility, emotional stability, and original intellectual activity.	Hänninen et al., 1978. Scand. J. Psychol. 19, 163

* see note Table 3.

Table 19. Continued.

NUMBER OF SUBJECTS	EXPOSURE LEVELS	EXPOSURE DURATION	EFFECT	REFERENCE
145	PAS during study: 1-16 ppm (3-48 mg/m^3), spot sampling from 1957: 1.5-60 ppm (5-186 mg/m^3), mostly <20 ppm (62 mg/m^3)	average: 12.1 ± 6.9 y	Controls: 233, male, white; differs as to age and employment duration; smoking/drinking habits and education similar; low background exposure (0.2 ppm, average). Questionaire: prevalences of angina and myocardial infarction too small to permit conclusions. Blood pressure (adjusted for age and obesity) differences in all three phases, systolic reading significantly higher in exposed. Too few ECG abnormalities to permit conclusions. No significant differences for serum cholesterol, triglycerides, HDL, LDL (elevated) and LDL/HDL ratios (elevated).	Albright et al, 1984. NIOSH PB85-110229.
111	about 16 ppm (50 mg/m^3)	2-10 y	Controls: 222 age-, sex-matched. Significant increase in the amount of hyperlipoproteinaemia and in LDL-cholesterol.	Klein et al, 1981. Z. Gesamte Hyg. 27, 48.

Table 20. Effects on the eye due to CS_2 in exposed workers.

NUMBER OF SUBJECTS	EXPOSURE LEVELS	EXPOSURE DURATION	EFFECT	REFERENCE
354	PAS at study 0.2-5 ppm (0.7-16 mg/m³) (average: 1.5 ppm/4.5 mg/m³), spot sampling 1975-1981: 09-13 ppm (3-42 mg/m³)	<4-20 y (mean: 10 y).	Controls: 177, age-, sex-matched. No retinal changes such as microaneurysms and small dot haemorrhages.	Sugimoto et al, 1984. Int. Arch. Occup. Enviro Health 54, 127.
145	PAS at study: 1-16 ppm (3-48 mg/m³), spot sampling from 1957 1.5-60 ppm (5-186 mg/m³), mostly <20ppm (62 mg/m³)	average 12.1 ± 6.9 y	Controls: 233, male, white, differ as to age and employment duration; smoking/alcohol habits and education similar; low background exposure (0.2 ppm, average). Significantly more retinal microaneurysms and retinal haemorrhages. Association between exposure and small artery disease.	Albright et al, 1984. NIOSH PB85-110229
62	<10 ppm (30 mg/m³), previously higher (see below)	6-36 y (mean: 16 y)	Controls: 40, age-matched. Effect on optic nerve by giving the Farnsworth Munsell 1100-Hue Test for color discrimination (impairment in the receptiveness of the ganglion cells or demyelination of the optic nerve fibers).	Raitta et al, 1981. J. Occup. Med. 23, 189.
100	at time of study (1972): 5-10 ppm (16-31 mg/m³), 1960-1970: 10-30 ppm (31-93 mg/m³), 1950-1960: 20-60 ppm (62-180 mg/m³)	1-27 y (mean: 15 y)	Controls: 93 paper mill workers, same age. Fluorescein angiography: disturbances in microcirculation of the ocular fundus. Delayed filling of the choroid in the peripapillary region noted in 68 workers (vs 38 in controls; $p<0.01$). Increased width of arterioles. No evidence for any CS_2-induced effects on visual acuity, visual field, eye mobility, pupillary reaction, intraocular pressure, or retinal microaneurysms. Oculospygmographic techniques: disturbances in the ocular pulse wave. These plus the above mentioned changes were suggestive of increased rigidity of the vascular bed. Alterations irreversible: no improvement after cessation.	Raitta, Tolonen, 1975.* Albrecht v. Graefes Ar Klin. Exp. Ophtalmol. 1: 149.

Table 20. Continued

NUMBER OF SUBJECTS	EXPOSURE LEVELS	EXPOSURE DURATION	EFFECT	REFERENCE
124	>20 ppm (62 mg/m³)	average 10.8 y	Controls: 49 (same mean age). Incidence and severity of retinopathy, characterized by microaneurysms, increased with increasing duration of exposure. Not age-related. Most severe signs: dot haemorrhages, retinal exudate.	Sugimoto et al, 1976.* Int. Arch. Occup. Environ. Health 37, 1.
127	<20 ppm			
419	since 1960: <20 ppm (62 mg/m³), usually 5-15 ppm (26-47 mg/m³), 1950-1960: 15-35 ppm (47-109 mg/m³)	1-31 y (mean: 17 ± 59 y)	Controls: 391 men; age, smoking habits, incidence of obesity comparable. Japanese workers: retinal red dots (microaneurysms and/or small haemorrhages in 25% of workers (vs 4% of controles), increasing with exposure duration.	Sugimoto et al, 1977.* Int. Arch. Occup. Environ Health 39, 79. Sugimoto et al, 1978.* Scand. J. Work Environ. Health 4, 151.
188	at time of study: 5-10 ppm (16-31 mg/m³), 1960-1970: 1-3 ppm (81-93 mg/m³), 1950-1960: 20-60 ppm (62-186 mg/m³)	mean: 14.2 ± 8.8 y	Controls: 76 papermill workers of roughly same age. Finnish workers: no significant increase in the incidence of retinopathy (4% vs 3%).	

* data from Fielder and Shillaker, 1981 (see chapter 10).

Table 21. Effect of CS_2 on the male reproductive system of exposed workers.

NUMBER OF SUBJECTS	EXPOSURE LEVELS	EXPOSURE DURATION	EFFECT	REFERENCE
50	3-8 ppm (10-25 mg/m³; spot sampling) (mean values registered during 12 y)	· 3-12 y	Controls: 50, matched for sex, age, physical feature, workshift, smoking/drinking history. No differences in endocrinological functions (thyroxine, FSH, LH, testosterone).	Cirla, Graziano, 1981. G. Ital. Med. Lav. 3, 69.
67	PAS at study: 1-16 ppm (3-48 mg/m³), spot sampling from 1957: 15-60 ppm (5-186 mg/m³), mostly <20 ppm (62 mg/m³)	12.1 ± 6.9 y	Controls: 89 male, white, differ as to age, duration of employment smoking/drinking habits and education similar; low background exposure (0.2 ppm average). No significant differences in sperm counts, ejaculate volume, sperm morphologic characteristics, libido, or potency. No effect on thyroid gland.	Albright et al, 1984. NIOSH PB85-110229.
231	PAS at study: 3-8 ppm (10-25 mg/m³), 1950-1960: about 19 ppm (60 mg/m³)		pair-matched as to age, nationality, employment duration, marriage, job level. No such disorders in the libido that have resulted in a smaller number of children on average that in the non-exposed employees.	Kolk, Braun, 1986. Proc. 14th Int. Congr. Occup. Health Chem. Ind. Ludwigshafen, FRG, 385.
69	<10 ppm (30 mg/m³); spot sampling) (during last 10 y, previously higher).	1-36 y (mean: 12.5 y)	Controls: 24 paper mill workers. FSH increased; sex hormone binding globulin (SHBG) decreased, LH increased in 24-31 years-old men. In men under 39-years-old exposed for 1-9 years: significally difference in FSH. In men older than 40 years, exposed for > 10 years: FSH and LH increased.	Wägar et al, 1983. J. Toxicol. Environ. Health 11, 691.