Health Council of the Netherlands

Carbon disulphide

Health-based recommended occupational exposure limit

Gezondheidsraad
Health Council of the Netherlands

Aan de staatssecretaris van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies over *Carbon disulphide*
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Geachte staatssecretaris,

Graag bied ik u hierbij aan het advies over de gevolgen van beroepsmatige blootstelling aan zwavelkoolstof.

Dit advies maakt deel uit van een uitgebreide reeks, waarin gezondheidskundige adieswaarden worden afgeleid voor concentraties van stoffen op de werkplek. Het genoemde advies is opgesteld door de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS) van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en omgeving.

Ik heb dit advies vandaag ter kennisname toegezonden aan de staatssecretaris van Infrastructuur en Milieu en aan de minister van Volksgezondheid, Welzijn en Sport.

Met vriendelijke groet,

prof. dr. L.J. Gunning-Schepers,
voorzitter

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Dutch Expert Committee on Occupational Safety
A Committee of the Health Council of the Netherlands

to:

the State Secretary of Social Affairs and Employment

No. 2011/26, The Hague, October 28, 2011

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Contents

Samenvatting *9*

Summary *15*

Part I Health-based recommended occupational exposure limit for carbon disulphide *21*

1 Scope *23*
1.1 Background *23*
1.2 Committee and method of work *24*
1.3 Data *24*

2 Hazard assessment *25*
2.1 Hazard identification *25*
2.2 Quantitative assessment of the health risk *29*
2.3 Skin notation *31*
2.4 Groups at extra risk *32*
2.5 Health-based recommended occupational exposure limit *32*
2.6 HBROEL DECOS versus SCOEL *32*

References *33*

Annexex *37*
A Request for advice *39*
B The Committee *41*
C Comments on the public review draft *45*

Part II Data on carbon disulphide *47*

1 Identity, properties and monitoring *49*
1.1 Identity *49*
1.2 Physical and chemical properties *50*
1.3 EU Classification and labelling *50*
1.4 Analytical methods *51*

2 Sources of exposure *55*
2.1 Natural occurrence *55*
2.2 Man-made sources *55*

3 Kinetics *57*
3.1 Absorption *57*
3.2 Distribution *58*
3.3 Biotransformation *60*
3.4 Elimination *60*
3.5 Biological monitoring *61*
3.6 Summary *63*

4 Effects *65*
4.1 Observations in man *65*
4.2 Animal experiments *84*
4.3 Summary *95*

5 Existing occupational exposure limits *99*

1 References *101*

Health Council 1994/08WGD Annex F Tables 2-21 *115*

Samenvatting

Vraagstelling

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid leidt de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS) van de Gezondheidsraad gezondheidskundige advieswaarden af voor stoffen in lucht waaraan mensen beroepsmatig blootgesteld kunnen worden. Deze aanbevelingen vormen de basis voor wettelijke grenswaarden, vast te stellen door de minister, waarmee de gezondheid van werknemers beschermd kan worden.

In 1994 heeft de Gezondheidsraad een advies uitgebracht met een evaluatie van de gezondheidsrisico's als gevolg van beroepsmatige blootstelling aan zwavelkoolstof. Enkele jaren later heeft ook de Europese 'Scientific Committee on Occupational Exposure Limits' (SCOEL) een advies uitgebracht over deze stof. In het voorliggende rapport, actualiseert de commissie haar advies uit 1994 door gebruik te maken van het SCOEL advies uit 2008 en latere gepubliceerde gegevens.

De conclusies van de commissie berusten op de wetenschappelijke publicaties die vóór januari 2010 zijn verschenen.

Fysische en chemische eigenschappen

Zwavelkoolstof is bij kamertemperatuur een kleurloze, nagenoeg reukloze, vluchtige en uiterst brandbare vloeistof. De fysische en chemisch eigenschappen zijn vermeld in Part II, hoofdstuk 1.

Monitoring

Voor het meten van zwavelkoolstof in de lucht op de werkplek hebben het Nederlands Normalisatie-instituut, het Amerikaanse 'National Institute for Occupational Safety and Health' (NIOSH), het Duitse *Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung* (IFA) en een werkgroep van de Duitse 'Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe' methoden beschreven die zijn gebaseerd op actieve monsterneming met een koolbuis, vloeistofdesorptie en gaschromatografie. IFA heeft daarnaast een methode beschreven die gebruik maakt van monsterneming door middel van diffusie en thermodesorptie.

Biologische monitoring kan het best worden uitgevoerd door met een HPLC-methode de concentratie van 4-thiothiazolidine-4-carbonzuur (TTCA) te meten in urine.

Huidige grenswaarden

Nederland kent geen wettelijke grenswaarde voor zwavelkoolstof. In de Europese Unie geldt een indicatieve grenswaarde voor beroepsmatige blootstelling van 15 mg/m^3 (5 ppm), als tijdgewogen gemiddelde over 8 uur.

In Duitsland heeft de *Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe* ook een waarde voorgesteld van 15 mg/m^3 (5 ppm), maar een commissie van de Bondsminister van sociale zaken en werkgelegenheid heeft een grenswaarde vastgesteld van 30 mg/m^3 (10 ppm).

In Denemarken en Zweden geldt een norm of aanbeveling van 15 mg/m^3 (5 ppm), in Engeland van 32 mg/m^3 (10 ppm) en in de Verenigde Staten van 1 ppm.

Duitsland en Zweden hebben bovendien een grenswaarde voor een kortdurende blootstelling van ten hoogste 15 minuten.

In alle gevallen is een huidnotatie (H) voor zwavelkoolstof van kracht, die aangeeft dat zwavelkoolstof gemakkelijk door de huid in het lichaam wordt opgenomen.

Kinetiek

Bij inhalatoire blootstelling blijft gedurende de eerste twee uur 70 tot 80 procent van de ingeademde hoeveelheid 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/uur.

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 hoeveelheid wordt omgezet in de lever of reageert met aminozuren, glutathion of cysteïne tot een verscheidenheid aan verbindingen, waaronder TTCA.

Effecten

Zowel bij mensen als bij proefdieren kan blootstelling aan zwavelkoolstof resulteren in een breed scala aan effecten: neurologische, cardiovasculaire, endocrinologische, reproductietoxische en effecten op de ogen en de ademhalingsorganen.

Proefdieronderzoek laat geen effecten zien op hart en bloedvaten of op het zenuwstelsel na inhalatoire blootstelling aan concentraties van 160 mg/m^3 (50 ppm) gedurende respectievelijk 20 en 13 weken.

Uit epidemiologisch onderzoek gericht op de effecten op hart en bloedvaten als gevolg van beroepsmatige blootstelling aan zwavelkoolstof kan worden vastgesteld dat cardiovasculaire effecten, zoals bij voorbeeld (verhoogde kans op sterfte door) een ischemische hartaandoening, optreden bij concentraties hoger dan 62 mg/m^3 (20 ppm). In een prospectief cohortonderzoek werden echter in werknemers van een aantal Japanse kunstzijdefabrieken effecten waargenomen in het rust- en inspanningselectrocardiogram (ECG) bij gebruik van de Minnesota codering (1982), maar geen veranderingen in ‘harde’ ECG-

eindpunten, zoals bij voorbeeld een ST depressie ≥2 mm. De gemiddelde blootstelling van de onderzochte groep bedroeg 15 mg/m^3 (5 ppm).

Onderzoek gericht op het zenuwstelsel geeft aan dat blootstelling aan gemiddelde concentraties van 31 mg/m^3 (10 ppm) en hoger schadelijke effecten veroorzaakt. Geen effecten op het zenuwstelsel werden gezien bij werknemers van Italiaanse en Duitse kunstzijdefabrieken, waarbij de gemiddelde blootstelling respectievelijk ≥20 mg/m^3 (7 ppm) en 12 mg/m^3 (4 ppm) bedroeg. Onderzoek in een Nederlandse fabriek leverde daarentegen wel bewijs voor schade aan het zenuwstelsel als gevolg van blootstelling aan gemiddeld 22 mg/m^3 (7 ppm). Een studie met methodologische beperkingen bij werknemers in een Belgische fabriek lijkt aan te geven dat een dergelijke schade zich zou kunnen ontwikkelen bij blootstelling aan 9 mg/m^3 (3 ppm).

Onder werknemers bij één Nederlandse en twee Finse fabrieken werd geen verhoogd risico gevonden op het krijgen van kanker als gevolg van blootstelling aan zwavelkoolstof. Er is geen onderzoek uitgevoerd met proefdieren naar de kankerverwekkende eigenschappen van zwavelkoolstof. De resultaten van tests op genotoxiciteit laten geen definitieve conclusies toe.

Onderzoek bij vrouwen wijst op mogelijke effecten op menstruatie en zwangerschap. De tegenstrijdige resultaten, gebrekkige verslaglegging en onvoldoende gegevens met betrekking tot controlegroepen en blootstellings-niveaus bemoeilijken een beoordeling. De uitkomsten van proefdieronderzoek zijn ook niet eensluidend. Bij konijnen die waren blootgesteld aan concentraties tot 930 mg/m^3 (300 ppm), zijn geen reproductietoxische effecten gevonden. De uitkomsten van onderzoekingen met ratten naar effecten op de voortplanting en ontwikkeling lijken strijdig; als gevolg van gebrekkige rapportage, bij voorbeeld met betrekking tot het genereren en controleren blootstellingsconcentraties, en methodologische verschillen zijn deze experimenten echter moeilijk onderling te vergelijken en is een definitief oordeel niet mogelijk.

Evaluatie en advies

De commissie is op de hoogte van een kritische evaluatie door Gelbke *et al*. (2009) van de epidemiologische gegevens over zwavelkoolstof die leidde tot de conclusie dat 31 mg/m^3 (10 ppm) een ‘algemeen ondersteunde’ limietwaarde voor beroepsmatige blootstelling is. De commissie wijst echter op publicaties waarin sprake is van effecten bij blootstelling aan concentraties lager dan 31 mg/m^3 (10 ppm). Hoewel er op deze studies het een en ander valt aan te merken,

vindt de commissie dat de tekortkomingen niet van dien aard zijn dat de studies daardoor terzijde zouden moeten worden geschoven. In een goed uitgevoerd prospectief cohortonderzoek werden in werknemers van een aantal Japanse kunstzijdefabrieken effecten waargenomen in het rust en inspannings ECG bij gebruik van de Minnesota codering (1982) bij een gemiddelde blootstelling van 15 mg/m^3 (5 ppm). Uit een systematisch review is gebleken dat personen met dit soort veranderingen in het ECG een verhoogde kans hebben op toekomstige cardiovasculaire mortaliteit. De commissie is daarom van mening dat deze effecten klinische betekenis hebben. De commissie beschouwt deze effecten als het kritische effect en 15 mg/m^3 (5 ppm) als het laagst waargenomen nadelig effect niveau (LOAEL).

Gebaseerd op het totaal aan epidemiologische gegevens en de als kritisch effect beschouwde cardiovasculaire bevindingen met een LOAEL van 15 mg/m^3 (5 ppm) gerapporteeerd in het goed uitgevoerde prospectief cohortonderzoek van Takebayashi *et al*. (2004), beveelt de commissie voor zwavelkoolstof een gezondheidskundige blootstellingslimiet aan van 5 mg/m^3 (2 ppm). De commissie gebruikt daarbij een onzekerheidsfactor van 3 omdat uitgegaan wordt van een LOAEL in plaats van een concentratie waarbij geen effecten zijn waargenomen (NOAEL). De commissie merkt op dat deze gezondheidskundige advieswaarde van 5 mg/m^3 (2 ppm) lager is dan de concentratie van 9 mg/m^3 (3 ppm) waarbij zich effecten op het zenuwstelsel zouden kunnen gaan ontwikkelen (zie Godderis e.a. 2006).

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.

Gezondheidskundige advieswaarde

De Commissie Gezondheid en beroepsmatige blootstelling aan stoffen stelt een gezondheidskundige advieswaarde voor beroepsmatige blootstelling aan zwavelkoolstof voor van 5 mg/m^3 (2 ppm), gemiddeld over een achturige werkdag (t.g.g. 8 uur).

De commissie beveelt tevens een huidnotatie aan voor zwavelkoolstof.

Summary

Scope

At request of the Minister of Social Affairs and Employment, the Dutch Expert Committee on Occupational Safety (DECOS), a committee of the Health Council of the Netherlands, recommends health-based occupational exposure limits for airborne substances to which people can be exposed in the air at the workplace. These recommendations serve as a basis in setting legally binding limit values by the Minister.

In 1994, the Health Council published an advice on the toxicity of carbon disulphide. In 2008, the Scientific Committee on Occupational Exposure Limits (SCOEL), an advisory committee of the European Commission, published an evaluation on the toxicity of carbon disulphide as well. In the present advice, the Committee reconsidered the former health-based occupational exposure limits for carbon disulphide based on the report of SCOEL and additional studies published since 2006.

The Committee's conclusions are based on scientific publications from prior to January 2010.

Physical and chemical properties

Carbon disulphide is at room temperature a colourless, almost odourless, volatile and extremely inflammable liquid. The physical and chemical properties are described in Part II, Chapter 1.

Monitoring

The Standardisation (Normalisatie) Institute of the Netherlands, the US National Institute for Occupational Safety and Health, the German Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA), and a working group of the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area have described methods for the measurement of carbon disulphide in the air of the workplace. These methods are based on sampling and adsorption on activated charcoal using a suitable pump, solvent desorption, and gas chromatography. IFA has presented a method using diffusive sampling and thermodesorption.

Biological monitoring can best be performed by HPLC measurement of the urinary concentration of 4-thiothiazolidine-4-carbonic acid (TTCA).

Current limit values

In the Netherlands, there is currently no legally-binding occupational exposure limit (OEL) for carbon disulphide. In the European Union, there is an indicative occupational exposure limit value (IOELV) for carbon disulphide of 15 mg/m^3 (5 ppm; eight-hour time-weighted average).

In Germany, the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area proposed a value of 15 mg/m^3 (5 ppm) but the Committee on Hazardous Substances (*Ausschuß für Gefahrstoffe* (AGS)) of the Federal Minister of Labour and Social Affairs recommended an OEL of 30 mg/m^3 (10 ppm).

Denmark and Sweden have set or recommended an OEL of 15 mg/m^3 (5 ppm), the Health and Safety Executive (HSE; UK) of 32 mg/m^3 (10 ppm), and the US American Conference of Industrial Governmental Hygienists (ACGIH) of 1 ppm).

In addition, 15-minute short-term-exposure-limits (STEL) are set or recommended in Germany and Sweden.

In all cases, a skin notation (H) has been designated.

Kinetics

Upon exposure by inhalation, 70 to 80 percent of the amount inhaled 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 were calculated for volunteers who had immersed their hands in dilute carbon disulphide. In laboratory 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 laboratory animals, but particularly in adipose tissue, liver, and kidney. Carbon disulphide can be taken up by the embryo and the fetus 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 is metabolized in the liver or reacts with amino acids, glutathione, or cysteine to form a variety of compounds, among them TTCA.

Effects

Exposure of humans and laboratory animals to carbon disulphide can lead to a wide variety of neurological, cardiovascular and endocrine effects, reproduction toxicity, and effects on eyes and the respiratory system.

In laboratory animals, no effects were seen on the cardiovascular or nervous system following exposure by inhalation to concentrations of 160 mg/m^3 (50 ppm), for 20 and 13 weeks, respectively.

Epidemiological studies on the effects of occupational exposure on the cardiovasculair system indicated that 62 mg/m^3 (20 ppm) would be a threshold for cardiovascular effects such as *e.g.* (increased mortality from) ischaemic heart disease. However, in a prospective cohort study, an increase in incidence of ischaemic findings as judged by Minnesota code 1982 in workers of Japanese viscose rayon factories exposed to mean concentrations of 15 mg/m^3 (5 ppm) was observed; however, there was no increase in ECG abnormalities applying more ‘rigorous’ criteria, *e.g.* ST depression $\geq$2 mm.

Studies investigating the nervous system showed that exposure to mean concentrations $\geq$31 mg/m^3 (10 ppm) affected the nervous system. At mean

concentrations of ≥20 mg/m^3 (7 ppm) and 12 mg/m^3 (4 ppm), no effects were reported in workers of Italian and German viscose rayon factories, respectively. On the other hand, in workers of a Dutch factory exposed to 22 mg/m^3 (7 ppm), there was evidence for adverse nervous system effects while a study with methodological deficiencies in a Belgian factory suggests that effects may start to develop at exposure to concentrations of 9 mg/m^3 (3 ppm). No evidence of carcinogenic effects were found in a study among viscose rayon plant and paper mill workers in Finland and in viscose rayon plant workers in the Netherlands. There were no relevant carcinogenicity studies in laboratory animals. Muta-genotoxicity tests did not yield results that permitted definite conclusions.

Studies in humans suggest that occupational exposure to carbon disulphide may cause menstrual disorders and affect pregnancy outcome. However, inconsistent results, poor reporting, and lack of valid information on control groups and actual exposure levels hamper a proper evaluation. Results from reproduction toxicity studies in laboratory animals were inconsistent as well. No reproduction toxicity was found in rabbits exposed to concentrations up to 930 mg/m^3 (300 ppm). Results of investigations with rats on fertility and developmental effects are contradictory; due to poor reporting, ***e.g.*** with respect to generating and controlling exposure levels, and methodological differences, these experiments are difficult to compare and do not allow definitive conclusions.

Hazard Assessment and recommended occupational exposure limit.

The Committee is aware of a critical evaluation of the total epidemiological data on carbon disulphide by Gelbke ***et al.*** (2009) that led to the conclusion that 10 ppm (31 mg/m^3) is a 'generally supported' occupational exposure limit. However, the Committee evaluated the publications that suggested effects below that level. Clearly, these studies show deficiencies, but these are not so serious that the Committee could discard the findings. Since a systematic review showed that the presence of minor ECG abnormalities such as evaluated by the Minnesota code predicts an increased risk for cardiovascular mortality, the Committee is of the opinion that the increase in incidence of ischaemic symptoms reported in the well-performed prospective cohort study of Takebayashi ***et al.*** (2004) are clinically relevant. Therefore, based on the total database of epidemiological findings and the critical findings on the cardiovascular system from the Takebayashi study together, the Committee

recommends 5 mg/m^3 (2 ppm) as a health-based occupational exposure limit applying a factor of 3 to the LOAEL of 15 mg/m^3 (5 ppm) from the Takebayashi study. The Committee notes that this recommended health-based occupational exposure limit of 5 mg/m^3 (2 ppm) is below the concentration of 9 mg/m^3 (3 ppm) at which neurotoxic effects may begin to develop (see Godderis *et al.*, 2006).

Considering that carbon disulphide, as a liquid, by penetrating the skin can contribute to a great extent to the internal dose, the Committee recommends a 'Skin-notation'.

Health based recommended occupational exposure limit

The Dutch Expert Committee on Occupational Safety recommends a health-based occupational exposure limit for carbon disulphide of 5 mg/m^3 (2 ppm), as an 8-hour time-weighted average (TWA).

The Committee also recommends a skin notation for carbon disulphide.

Part I

Health-based recommended occupational exposure limit for carbon disulphide

Chapter 1

Scope

1.1 Background

At the request of the Minister of Social Affairs and Employment (Annex A), the Dutch Expert Committee on Occupational Safety (DECOS), a committee of the Health Council of the Netherlands, performs scientific evaluations of the toxicity of substances to which man can be exposed at the workplace. The purpose of these evaluations is to recommend a health-based recommended occupational exposure limit (HBROEL) for the concentration of the substance in air, provided the database allows the derivation of such value.

In 1994, the Health Council published an advice on the toxicity of carbon disulphide and recommended a health based occupational exposure limit. Several years later, in 2008, the European Scientific Committee on Occupational Exposure Limits (SCOEL) published an evaluation on the toxicity of carbon disulphide as well.

In the present advice, the Committee reconsiders the former health-based occupational exposure limit for carbon disulphide based on the previous report of the Committee, the advice of the SCOEL, and additional published studies from 2006 until January 2010.

1.2 Committee and method of work

The present document contains the reassessment of the toxicity of carbon disulphide by DECOS. The members of DECOS are listed in Annex B.

In 2011, 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 finalizing its report.

1.3 Data

In Part I of the present document, the Committee evaluates the toxicity of carbon disulphide and recommends a health-based occupational exposure limit. This evaluation is based on the data described in Part II of the present report.

Part II of the present document presents an update of the Health Council's report on carbon disulphide, published in 1994.[5] It consists of an almost full copy of the 1994 Health Council report and additional data extracted from the 2008 SCOEL report on carbon disulphide[17], and is supplemented with data retrieved from a literature search in the on-line databases Toxline, Medline, and Chemical Abstracts (CAPlus), covering the period January 2004 to January 2010 and using the key words 'carbon disulph(f)ide', CS_2, and the CAS registry number 75-15-0.

Chapter 2

Hazard assessment

This Chapter contains an evaluation of the data on the effects of exposure to carbon disulphide based on the data summarized in Part II of the present report, and a recommendation of a health-based occupational exposure limit for carbon disulphide.

2.1 Hazard identification

2.1.1 Effects following acute exposure

No human data were available.

Carbon disulphide was markedly irritating to the skin of rabbits. The compound has low acute lethal toxicity in laboratory animals. Overall, there were no data to evaluate the need of a short-term exposure limit.

The Committee notes that in the EU, carbon disulphide is classified as '*causes skin irritation*' and '*causes serious eye irritation*'.

2.1.2 Effects following repeated exposure

There is an extensive database on toxic effects in humans and laboratory animals following long-term exposure to carbon disulphide. Gelbke *et al.* (2009)[3] reviewed this extensive epidemiological data base in detail, and discussed the various effects observed in relation to exposure. However, for reasons explained

below, the Committee does not support their conclusion that 'the data generally support an occupational exposure limit of 10 ppm (31 mg/m^3)'.

Occupational exposure to carbon disulphide results in a range of effects; especially those on the cardiovascular and nervous system are relevant for the current evaluation because they occur at the lowest exposure levels. There may have been co-exposure to hydrogen sulphide in most of the epidemiological studies but most reports do not indicate the presence of such co-exposure, and its impact is questionable. Furthermore, the Committee noted that reliable exposure assessment apparently is a problem in many studies, certainly 'past exposures' which may or may not influence the dose-response curves for the occurrence of chronic effects

Cardiovascular effects

Human data

After analysing data from 15 studies in 11 countries, Price *et al.* (1997) concluded that a threshold for ischaemic heart disease would be around 63 mg/m^3 (20 ppm).[12] Results from a more recent, cross-sectional study in Chinese workers did not show clinically relevant cardiovascular effects at mean exposure levels of about 20 mg/m^3 (7 ppm).[23] However, in a prospective cohort study, Takebayashi *et al.* (2004) reported an increase in incidence of ischaemic findings, *i.e.* minor ECG abnormalities as judged by the Minnesota code 1982, in Japanese workers exposed to mean concentrations of 15 mg/m^3 (5 ppm); however, there was no increase in ECG abnormalities applying more rigorous criteria, *e.g.* ST depression ≥2 mm.[22]

Animal data

Studies in mice did not show an enhanced rate of fatty deposit formation in the heart following exposure to 160 mg/m^3 (50 ppm), six hours/day, five days/week, for 20 weeks while this effect was seen at exposure to 1600 mg/m^3 (500 ppm).[8] In rats, no increases in serum lipid levels were observed following exposure to 230 mg/m^3 (74 ppm), six hours/day, five days/week, for eight months; exposure to 500 mg/m^3 (160 ppm) caused increases in these levels starting at exposure month 2.[25] No effect on heart or aorta morphology was seen in rats exposed to 2400 mg/m^3 (800 ppm), for 13 weeks.[18]

Nervous system effects

Effects on the nervous system range from overt psychosis to subtle, subclinical changes such as reduced nerve conduction velocities.

Human data

Gelbke *et al.* (2009) concluded that 31 mg/m^3 (10 ppm) was a 'generally supported' occupational exposure limit.[3] The Committee noted that there are a few studies below this low level of exposure that indeed were negative. Thus, Cirla and Graziano (1981) did not find changes in neurophysiological end points comparing 50 workers in an Italian viscose rayon plant exposed to mean carbon disulphide levels ≤20 mg/m^3 (7 ppm) (stationary sampling) for 3 to 12 years (mainly between 6 and 9 years) with 50 non-exposed controls.[2] Also, Reinhardt *et al.* (1997a,b) did not find clinical neurological, neuropsychological, and neurophysiological changes in 222 workers in a German plant exposed to a median concentration of 12 mg/m^3 (4 ppm; range: <0.6-205 mg/m^3 (<0.2-66 ppm); personal air sampling) for a mean of 66 months (range: 4-220 months).[13,14]

However, in five studies effects were reported at levels lower than 31 mg/m^3 (10 ppm). Ruijten *et al.* (1990) found a small decrease in the conduction velocity of the slow motor fibers of 1.1 m/s and a prolongation of the refractory period of 0.1 m/s in 45 workers in a Dutch viscose rayon plant, exposed for a mean of 20 years to a mean concentration of 22 mg/m^3 (7 ppm), with a range of 3-53 mg/m^3 (1-17 ppm) as determined by spot (1948-1983) or personal air sampling (≥1983).[15] The findings in this study were largely reproduced in a follow-up study in which 28 workers were re-examined four years later.[16]

Vanhoorne *et al.* (1995) observed neurological abnormalities (increased positional tremor, abnormalities in electromyogram and indications for peripheral polyneuropathy) in 111 workers of a Belgian viscose rayon factory, where carbon disulphide concentrations had ranged between 4 and 112 mg/m^3 (1 and 36 ppm) (eight-hour time-weighted average) until 1992 and had decreased to below 31 mg/m^3 (10 ppm) since then.[24] In a more recent additional study in this factory with a limited overlap of workers in the Vanhoorne study, Godderis *et al.* (2006) found an excess of psychomotor slowing, tremor, and peripheral polyneuropathy in a group consisting of workers with individual mean yearly exposures below 31 mg/m^3 (10 ppm) (mean of the group: 9 mg/m^3 (3 ppm)). In a further analysis, Godderis *et al.* divided the exposed workers into 3 subgroups, consisting of workers with individual mean yearly exposures of >30 mg/m^3

(10 ppm), >10–≤30 mg/m^3 (3-10 ppm), and ≤10 mg/m^3 (3 ppm), respectively.[4] This analysis suggested the presence of some effects in the lowest exposed group but did not reveal clear dose-response relations. However, the Committee noted several weaknesses concerning the characteristics of the groups (workers selected themselves for the study; composition of the groups such as the considerable number of newcomers, mostly non-Caucasians, in the group exposed <31 mg/m^3; small numbers of the subgroups), in the construction and determination of the average exposure levels, and in the data analyses.

Takebayashi *et al.* (1998) reported reduced nerve conduction velocities in 419 workers of 11 Japanese viscose fibre-production facilities exposed for a mean of 13.4 years to median breathing-zone air concentrations, measured at two occasions at the time of the study, of 12.5 mg/m^3 (4 ppm) (range: from not detectable to 124 mg/m^3 (40 ppm)). When dividing the workers into a high-exposure group involved in spinning and refining (n=301) and a low-exposure group with other activities (n=121), a significant difference with the control group was only apparent for the high-exposure group. The high-exposure group had (geometric) mean urinary 2-thiothiazolidine-4-carboxylic acid (TTCA) concentrations of 3.13±2.27 mg/g creatinine (35% exceeded 5 mg/g creatinine, corresponding to a CS_2 exposure of 31 mg/m^3 (10 ppm)), whereas the low-exposure group had a mean urinary TTCA level of 1.28 ± 2.01 mg/g creatinine (with 1.7% exceeding 5 mg/g)[21] (for exposure assessment data see Omae *et al.*, 1998[11]).

Animal data

Studies in rats showed no histological damage in the nervous system[5,18], or neurobehavioural[9], or neurophysiological[6] effects following exposure to 160 mg/m^3 (50 ppm), six hours/day, five days/week, for 13 weeks. Exposure to 500 mg/m^3 (160 ppm) for eight months produced small degenerative changes in a small number of ganglion cells while exposure to 900 mg/m^3 for six months or to 936 mg/m^3 for three months affected peripheral nerve conduction velocity and spinal cord fiber axons, respectively.[5]

Carcinogenicity/genotoxicity

No evidence of carcinogenic effects was found in a study among viscose rayon plant and paper mill workers in Finland[10] and in viscose rayon plant workers in the Netherlands[19,20]. There were no relevant carcinogenity studies in laboratory animals.

Although genotoxicity tests using bacteria, fruit flies, and mammalian cells, were negative, no definite conclusions on genotoxicity can be drawn because of several technical problems in the tests.

Reproduction toxicity

Studies in humans suggest that occupational exposure to carbon disulphide may cause menstrual disorders and affect pregnancy outcome. However, inconsistent results, poor reporting, and lack of valid information on control groups and actual exposure levels hamper a proper evaluation.

Results from reproduction toxicity studies in laboratory animals were inconsistent as well. Effects on female fertility and on development were observed but poor reporting, *e.g.* with respect to generating and controlling exposure levels, and methodological differences between studies hamper a proper comparison and evaluation.

The Committee notes that in the EU, carbon disulphide is classified as '*may damage fertility or the unborn child*'.

2.2 Quantitative assessment of the health risk

In evaluating the human data, the Committee is aware that the investigated subjects may have been exposed earlier to levels considerably higher than those at the time of investigation. These levels may also have been under-estimated because of unreliable analytical procedures and/or because of the use of stationary instead of personal monitoring. Further, for the viscose rayon industry, specific processes led to widely fluctuating levels with high peaks which is not reflected in (annual) mean or median concentrations presented in many studies or in current exposure concentrations. It is therefore difficult to assess whether changes were due to the present lower levels or to past higher exposures, considering that these alterations may not or only to a limited extent be reversible[16] (see also Gelbke *et al.*[3]).

Overall, the Committee is of the opinion that the available human studies clearly show that exposure to mean concentrations of carbon disulphide of approximately 31 mg/m^3 (10 ppm) and higher cause effects on the cardiovascular and nervous system.

As to the cardiovascular system, Takebayashi *et al.* (2004) found an increase in incidence of ischaemic findings, *i.e.* minor ECG abnormalities as judged by the Minnesota code 1982 in a prospective cohort study in Japanese workers exposed

to mean concentrations of 15 mg/m^3 (5 ppm), but not in the increase of major ECG abnormalities applying more rigorous criteria.[22] SCOEL, in its recent assessment of CS_2, considered these changes not to be of clinical relevance.[17] However, in a systematic review, Kumar *et al.* (2007) concluded that the presence of minor ECG abnormalities such as evaluated by Minnesota codes predicts an increased risk for cardiovascular mortality, independent of traditional risk factors.[7] The Committee noted that the ischaemia-related ECG abnormalities included in the Takebayashi and Kumar study partially corresponded. However, the Committee is of the opinion the overlap was sufficient to conclude from the Kumar study that the findings of Takebayashi *et al.* suggest an increased risk for cardiovascular mortality. The Committee concludes that 15 mg/m^3 (5 ppm) is a LOAEL for cardiovascular effects.

Whether or not exposure to mean levels below approximately 31 mg/m^3 (10 ppm) induces neurotoxicity is more difficult to ascertain. Cirla and Graziano (1983)[2] and Reinhardt *et al.* (1997a,b)[13,14] did not observe neurotoxic effects in workers exposed to mean levels below 20 mg/m^3 (7 ppm) and 12 mg/m^3 (4 ppm), respectively, although for relatively short periods. Ruijten *et al.* (1990, 1993)[15,16] found changes in neurophysiological end points in workers exposed to mean concentrations of 22 mg/m^3 (7 ppm) for a mean of 22 years. The study of Godderis *et al.* (2006)[4] suggested the presence of some neurotoxic effects in a group of workers exposed to mean yearly concentrations of 9 mg/m^3 (3 ppm) for a mean of approximately nine years. Although the Godderis study has several weaknesses as explained above, the Committee considers 9 mg/m^3 (3 ppm) as the LOAEL for minimal neurotoxic effects which is judged to be very close to the NOAEL.

The critical evaluation of the total epidemiological data on CS_2 led Gelbke *et al.* (2009)[3] to the conclusion that 10 ppm (31 mg/m^3) was a 'generally supported' occupational exposure limit. However, the Committee evaluated the publications that suggested effects below that level. Clearly, these studies show deficiencies, but these are not so serious that the Committee could discount the findings. Therefore, taking the total database of epidemiological findings and the critical findings on the cardiovascular system from the well-performed prospective cohort study of Takebayashi *et al.* (2004)[22], the Committee recommends 5 mg/m^3 (2 ppm) as a health-based occupational exposure limit applying a factor of 3 to the LOAEL of 15 mg/m^3 (5 ppm) from the Takebayashi study. The Committee notes that the recommended health-based occupational exposure limit of 5 mg/m^3 (2 ppm) is below the concentration of 9 mg/m^3 (3 ppm) at which neurotoxic effects may begin to develop (see Godderis study[4]).

The animal data support this value: taking the NOAELs for cardiovascular and nervous system effects of 160 mg/m^3 (50 ppm) (six hours/day, five days/ week, for 13 weeks) as starting points would lead to a health-based occupational exposure limit of 9 mg/m^3 (3 ppm)*.

The Committee notes that the currently proposed health-based occupational exposure limit of 5 mg/m^3 (2 ppm) is a factor of 2 higher than the limit value recommended in 1994. Since then, new studies on the effects of occupational exposure to carbon disulphide on the cardiovascular and nervous system have been published. This extension of the toxicological database has resulted in a different weighing of the data including different choices of key studies and assessment factors.

2.3 Skin notation

According to the Committee, a 'skin notation' is warranted if the amount absorbed by both hands and underarms (total surface area: 2000 cm^2) during a 1-hour contact with the liquid could amount to more than 10% of the amount absorbed via the lungs following exposure to the occupational exposure limit for eight hours (assuming that this limit is based on systemic effects rather than on local effects).

In a human volunteer study, an average dermal penetration rate ranging from 0.23 and 0.79 mg/cm^2/ h has been calculated[1] (see Part II, Section 3.1.1).

Using a mean rate of 0.51 mg/cm^2/ h, it can be calculated that an amount of 1020 mg CS_2 (0.51 mg/cm^2/h x 2000 cm^2 x1 h) can be taken up by dermal contact, which is far more than 10% of the amount absorbed via the lungs at an eight-hour exposure to the proposed health-based occupational exposure limit of 5 mg/m^3 (2 ppm).

Therefore, the Committee considers a 'skin notation' for CS_2 warranted.

* Using uncertainty factors of 3 for intra-individual variations, of 3 for interindividual variation, and of 2 for the differences between the experimental conditions (13 weeks) and the exposure pattern of the worker (working life time).

2.4 Groups at extra risk

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

2.5 Health-based recommended occupational exposure limit

The Dutch Expert Committee on Occupational Safety recommends a health-based recommended occupational exposure limit for carbon disulphide of 5 mg/m^3 (2 ppm) as an 8-hour time-weighted average. DECOS also recommends a skin notation.

2.6 HBROEL DECOS versus SCOEL

In 2008, the SCOEL recommended an occupational exposure limit of 15 mg/m^3 (5 ppm) based on the extensive epidemiological database

In DECOS' recommendation of the health-based occupational exposure limit of 5 mg/m^3 (2 ppm), the study of Takebayashi *et al.* (2004) that indicated effects at this exposure level has led to a lower HBROEL. DECOS notes that SCOEL considered the minor cardiovascular findings in the Takebayashi study of little clinical relevance. However, based on the conclusions in the systematic review by Kumar *et al.* (2007) presented above, DECOS takes the position that these cardiovascular findings are relevant for an HBROEL. Furthermore, DECOS also took the Godderis study (2006), in spite of its weaknesses, into account as supporting the lower HBROEL value, while SCOEL did not consider this study.

References

1 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 HWL van der Donk, PML-TNO, translation no. 664), 97-100.

2 Cirla AM, Graziano C. Health impairment in viscose-rayon workers with carbon disulphide risk below 30 mg/m^3. An exposed-controls study. G Ital Med Lav 1981; 3: 69-73.

3 Gelbke HP, Goen T, Maurer M, Sulsky SI. A review of health effects of carbon disulfide in viscose industry and a proposal for an occupational exposure limit. Crit Rev Toxicol 2009; 39 Suppl 2: 1-126.

4 Godderis L, Braeckman L, Vanhoorne M, Viaene M. Neurobehavioral and clinical effects in workers exposed to CS_2. Int J Hyg Environ Health 2006; 209(2): 139-150.

5 Health Council of the Netherlands. Carbon Disulphide. Health-based recommended occupational exposure limit. Health Council of the Netherlands, Dutch Expert Committee on Occupational Standards (DECOS); 1994: No 1994/08E.

6 Herr DW, Vo KT, Morgan DL, Sills RC. Carbon disulfide neurotoxicity in rats: VI. Electrophysiological examination of caudal tail nerve compound action potentials and nerve conduction velocity. Neurotoxicology 1998; 19: 129-146.

7 Kumar A, Lloyd-Jones DM. Clinical significance of minor nonspecific ST-segment and T-wave abnormalities in asymptomatic subjects: a systematic review. Cardiol Rev 2007; 15: 133-142.

8 Lewis JG, Graham DG, Valentine WM, Morris RW, Morgan DL, Sills RC. Exposure of C57BL/6 mice to carbon disulfide induces early lesions of atherosclerosis and enhances arterial fatty deposits induced by a high fat diet. Toxicol Sci 1999; 49: 124-132.

9 Moser VC, Phillips PM, Morgan DL, Sills RC. Carbon disulfide neurotoxicity in rats: VII. Behavioral evaluations using a functional observational battery. Neurotoxicology 1998; 19: 147-157.

10 Nurminen M, Hemberg S. Cancer mortality among carbon disulphide-exposed workers. J Occup Med 1984; 26: 341.

11 Omae K, Takebayashi T, Nomiyama T, Ishizuka C, Nakashima H, Uemura T, *et al.* Cross sectional observation of the effects of carbon disulphide on arteriosclerosis in rayon manufacturing workers. Occup Environ Med 1998; 55: 468-472.

12 Price B, Bergman TS, Rodriguez M, Henrich RT, Moran EJ. A review of carbon disulfide exposure data and the association between carbon disulfide exposure and ischaemic heart disease mortality. Regul Toxicol Pharmacol 1997; 26: 119-128.

13 Reinhardt F, Drexler H, Bickel A, Claus D, Angerer J, Ulm K, *et al*. Neurotoxicity of long-term low-level exposure to carbon disulphide: results of a questionnaire, clinical, neurological examination and neuropsychological testing. Int Arch Occup Environ Health 1997a, 69, 332-338.

14 Reinhardt F, Drexler H, Bickel A, Claus D, Ulm K, Angerer J, *et al.* Electrophysiological investigation of central, peripheral and autonomic nerve function in workers with long-term low-level exposure to carbon disulphide in the viscose industry. Int Arch Occup Environ Health 1997b; 70: 249-256.

15 Ruijten MWMM, Sallé HJA, Verberk MM, Muijser H. 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.

16 Ruijten MWMM, Sallé HJA, Verberk MM. Verification of effects on the nervous system of low level occupational exposure to CS_2. Br J Ind Med 1993; 50: 301-307.

17 Scientific Committee on Occupational Exposure Limits (SCOEL). Recommendation from the Scientific Committee on Occupational Exposure Limits for Carbon Disulphide. SCOEL; 2008: SCOEL/SUM/82.

18 Sills RC, Harry GJ, Morgan DL, Valentine WM, Graham DG. Carbon disulfide neurotoxicity in rats: V. Morphology of axonal swelling in the muscular branch of the posterior tibial nerve and spinal cord. Neurotoxicology 1998; 19: 117-127.

19 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.

20 Swaen GMH, Braun C, Slangen JJM. Mortality of Dutch workers exposed to carbon disulphide. Int Arch Occup Environ Health 1994; 66: 103-110.

21 Takebayashi T, Omae K, Ishizuka C, Nomiyama T, Sakurai H. Cross sectional observation of the effects of carbon disulphide on the nervous system, endocrine system, and subjective symptoms in rayon manufacturing workers. Occup Environ Med 1998; 55: 473-479.

22 Takebayashi T, Nishiwaki Y, Uemura T, Nakashima H, Nomiyama T, Sakurai H, *et al.* A six year follow up study of the subclinical effects of carbon disulphide exposure on the cardiovascular system. Occup Environ Med 2004; 61: 127-134.

23 Tan X, Chen G, Peng X, Wang F, Bi Y, Tao N, *et al.* Cross-sectional study of cardiovascular effects of carbon disulfide among Chinese workers of a viscose factory. Int J Hyg Environ Health 2004; 207: 217-225.

24 Vanhoorne MH, Ceulemans L, De Bacquer DA, De Smet FP. An epidemiological study of the effects of carbon disulphide on the peripheral nerves. Int J Occup Environ Health 1995; 1: 295-302.

25 Wronska-Nofer T. Disturbances of lipids metabolism in rats in dependence upon carbon disulphide concentrations in the air. Med Lav 1973; 64: 8-12.

A Request for advice

B The Committee

C Comments on the public review draft

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 occupation 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 review 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**

The Committee

- G.J. Mulder, *chairman*
  Emeritus Professor of Toxicology, Leiden University, Leiden
- P.J. Boogaard
  Toxicologist, Shell International BV, The Hague
- D.J.J. Heederik
  Professor of Risk Assessment in Occupational Epidemiology, Institute for Risk Assessment Sciences, Utrecht University, Utrecht
- B.P.F.D. Hendrikx, *observer*
  Social and Economic Council, The Hague
- R. Houba
  Occupational Hygienist, The Netherlands Expertise Centre for Occupational Respiratory Disorders, Utrecht
- H. van Loveren
  Professor of Immunotoxicology, Maastricht University, Maastricht, and National Institute for Public Health and the Environment, Bilthoven
- T.M. Pal
  Occupational Physician, Netherlands Center for Occupational Diseases, Amsterdam
- A.H. Piersma
  Professor of Reproductive Toxicology, Utrecht University, Utrecht and National Institute for Public Health and the Environment, Bilthoven

- H.P.J. te Riele
  Professor of Molecular Biology, VU University Amsterdam, Amsterdam
- I.M.C.M. Rietjens
  Professor of Toxicology, Wageningen University and Research Centre, Wageningen
- G.M.H. Swaen
  Epidemiologist, Dow Benelux N.V., Terneuzen
- R.C.H. Vermeulen
  Epidemiologist/Environmental Hygienist, Institute for Risk Assessment Sciences, Utrecht University, Utrecht
- R.A. Woutersen
  Professor of Translational Toxicology, Wageningen University, Wageningen, and TNO Quality of Life, Zeist
- P.B. Wulp
  Occupational Physician, Labour Inspectorate, Groningen
- J.T.J. Stouten, *scientific secretary*
  The Health Council, The Hague

Part II of this advice is based on the 1994 report of the Health Council and the 2008 report of the Scientific Committee on Occupational Exposure Limits (SCOEL), and was updated in 2009 by P.J.M. Weterings, Weterings Consultancy BV, Rosmalen, the Netherlands.

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the President and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are

discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

Comments on the public review draft

A draft of this report was released in 2011 for public review. The following organization and persons have commented on the draft.

- V. Gálvez-Pérez, Ministerio de Trabajo e Inmigración, Madrid, Spain
- T.J. Lenz, J. O'Callahan, R.P. Streicher, National Institute for Occupational Safety and Health (NIOSH), Cincinnati OH, USA
- C.L.J. Braun, Chris Braun Consultancy, Velp, the Netherlands

Part II

Data on carbon disulphide

Chapter 1

Identity, properties and monitoring

If not stated otherwise, information in this chapter is retrieved from the previous report of the Health Council on carbon disulphide.*

1.1 Identity**

1.1.1 Structure

S=C=S

1.1.2 Chemical name and synonyms/registry number

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

* For references see: References Part I References from Health Council 1994/08WGD.
** Data from: Amoore and Hautala, 1983; Patty, 1962; Weast,1988-1989; Windholz, 1983

1.2 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; 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

1.3 EU Classification and labelling

Additional information

The classification of carbon disulphide based on Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures (CLP) entered into force on the 20 January 2009, implementing the Globally Harmonised System (GHS), and repealing Directives 67/548/EEC and 1999/45/EC[9] is presented in Table 1-1.

Table 1-1 EU classification and labelling of carbon disulphide[9]

classification		labelling		specific concentration limits, m-factors
hazard class and category code	hazard statement code	pictogram, signal word code	hazard statement code	
Flam. Liq. 2	H225	GHS02	H225	
Repr. 2	H361f-d	GHS08	H361fd	Repr. 2; H361fd: C≥1%
STOT RE 1	H372**	GHS07	H372**	STOT RE 1; H372: C≥1% STOT RE 2; H373: 0.2%≤C≥1%
Eye irrit. 2	H319	Dgr	H319	
Skin irrit. 2	H315		H315	

H225: highly flammable liquid and vapour
H315: causes skin irritation
H319: causes serious eye irritation
H361fd: may damage fertility or the unborn child
H372: causes damage to organs through prolonged or repeated exposure
H373: may cause damage to organs through prolonged or repeated exposure

1.4 Analytical methods

1.4.1 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 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 path length of 20.25 m (Foxboro 1985). This method is only suitable when no other compounds which absorb in the same spectral region are present.

Additional information

The abovementioned NIOSH and NVN method were updated in 1994 and replaced in 1999, respectively.[19,25] In addition, similar methods were published by the German Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA[16]) and the Working Group on Analytical Chemistry of the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area.[23] The IFA methods use both active and diffusive sampling.[16]

1.4.2 *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 [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).

Additional information in SCOEL (2008)

Recent studies have shown that an eight-hour TWA inhalation exposure of 5 ppm (15 mg/m^3) of CS_2 will correspond to biological values between about 1.0 and 1.6 mg TTCA/g creatinine (Takebayashi *et al.*, 2004[SCOEL1]; Tan *et al.*, 2004[SCOEL2]; Korinth *et al.*, 2003[SCOEL3]; Shih *et al.*, 2003[SCOEL4]; Chang *et al.*, 2002[SCOEL5]; Drexler *et al.*, 1995a[SCOEL6] ; Krstev *et al.*, 1993[SCOEL7]; Riihimäki *et al.*, 1992[SCOEL8]). Higher values may be indicative of excessive inhalation and/or dermal exposure.

Chapter 2

Sources of exposure

If not stated otherwise, information in this chapter is retrieved from the previous report of the Health Council on CS_2*.

2.1 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).

2.2 Man-made sources**

2.2.1 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.

* For references see: References Part I: Health Council of the Netherlands 1994/08 WGD.
** Data from: Grothaus *et al.*, 1982 and Timmerman, 1978.

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 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.

2.2.2 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 3

Kinetics*

If not stated otherwise, information in this chapter is retrieved from the previous report of the Health Council on CS_2**.

3.1 Absorption

3.1.1 Studies in humans

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

* Data from: Beauchamp *et al.*, 1983, unless otherwise noted.
** For references see: References Part I: Health Council of the Netherlands 1994/08 WGD.

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 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 losses from 74 to 268.5 mg. The calculated absorption velocity ranged from 0.23 to 0.79 $mg.cm^{-2}.h^{-1}$.*

3.1.2 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).

3.2 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.

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

* 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.

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. $ALCS_2$ 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 CS_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 $^{14}CS_2$ 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).

3.3 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).

3.4 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 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).

3.5 Biological monitoring

3.5.1 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 chromatography.

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:

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

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.

3.5.2 *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 detect $ALCS_2$ 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.

3.6 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 4

Effects

If not stated otherwise, information in this Chapter is retrieved from the previous report of the Health Council on CS_2*.

4.1 Observations in man

4.1.1 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

* For references see: References Part I: Health Council of the Netherlands 1994/08 WGD. Tables 2-21 of this report ('Annex F') are presented on page 115.

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 SO2 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.

4.1.2 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.

4.1.3 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 18 (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 clinically 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, 1990a,b) 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 (before and after 1983, respectively), exposure levels were estimated to range from 3-53 mg/m^3 (1-17 ppm), with

a mean level of ca 25 mg/m³ (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 fibres (- 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 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 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, Ruijten et al 1993)[SCOEL12].

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/m³ (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 NOAEL cannot be derived from these data. However, exposure to concentrations less than 30 mg/m³ (10 ppm) results in minimal changes in peroneal nerve conduction velocity.

Additional neurotoxicity data in SCOEL (2008)

Neurobehavioural changes have also been reported in a number of occupational studies (Herborn 1992[SCOEL9]; Cassitto *et al.* 1993[SCOEL10]), but there was uncertainty regarding the actual exposure concentrations involved (SCOEL

2008). A polyneuropathy with irreversible reduction in motor velocity of both motor and sensory nerves has been reported by some authors with an estimated NOAEL of 12 mg/m³ (4 ppm) over 40 years (eight-hour day and five-day week) (Chu *et al.* 1995[SCOEL11]; Ruijten *et al.* 1990 (see page 15, ref 15))*. Effects on the autonomic nervous system were also reported (Ruijten *et al.* 1993)[SCOEL12]. However, a more recent occupational study (Reinhardt *et al.* 1997a)[SCOEL13] found no such neurotoxic effects at a median exposure of 12 mg/m³ (4 ppm) over a median period of 66 months. In viscose fibre-production workers, sub-clinical effects on the nervous system (reduced nerve conduction velocities) were reported (Takebayashi *et al.* 1998)[SCOEL14] with current average air concentrations of 12.5 mg/m³ (4 ppm) with peaks up to 120 mg/m³ (38 ppm).**

In a follow-up study, cerebrovascular effects of CS_2 exposures were studied by brain magnetic resonance imaging to detect hyperintense spots ('silent cerebral infarctions') in Japanese viscose rayon factory workers (Nishiwaki *et al.* 2004)[SCOEL15]. The six-year follow up study comprised 217 exposed workers, 125 workers who were transferred to other duties due to cessation of production ('ex-exposed') and 324 referent individuals. Mean duration of exposure was 19.6 years. The CS_2 concentration in the breathing zone and the urinary metabolite TTCA concentration were determined twice a year in the follow up period. The geometric mean exposure of CS_2 and TTCA in all exposed workers were 15 mg/m³ (4.9 ppm) and 1.6 mg/g creatinine, respectively. In the follow-up period, the CS_2 exposure level was 8 mg/m³ (2.5 ppm) in the lowest quartile and 26 mg/m³ (8.1 ppm) in the highest quartile. No difference was apparent from prevalence of these lesions in the exposed, ex-exposed, and reference workers. Nevertheless, the increase in hyperintense spots in the follow-up period was 24, 15, and 12% in the exposed, ex-exposed, and referent workers, respectively. The multivariate adjusted odds ratio (OR) was statistically significantly increased in exposed (OR 2.27; 95% CI 1.37-3.76), but not in the ex-exposed workers (OR

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* The Committee notes that SCOEL's conclusion on the NOAEL in these two studies is not supported by the data. Chu *et al.* (1995) found that the lowest exposure level associated with neurological effects was 47-312 mg/m³ (15-100 ppm). Ruijten *et al.* (1990a) calculated individual cumulative exposure to CS_2 on the basis of exposure in the past and individual job history. These authors concluded that a lifetime exposure below 12 mg/m³ (4 ppm) might be required to prevent the small effects observed (slightly decreased conduction velocity of the slow fibres and prolonged refractory period in peroneal nerves of workers with a mean cumulative exposure of 165 ppm-years).

** Takebayashi *et al.* (1998)[SCOEL14] divided workers in two groups, a high-exposure group involved in spinning and refining, and a low-exposure group with other activities. In the high-exposure group, average urinary TTCA amounted 3.13 ± 2.27 mg/g creatinine (35% exceeded 5 mg/g, corresponding to a CS_2 exposure of 31 mg/m³ (10 ppm)), whereas in the low-exposre group average urinary TTCA was 1.28 ± 2.01 mg/g (1.7% exceeded 5 mg/g). A statistically significant difference with the control group was only apparent for the high-exposure group.

1.33; 95% CI 0.70-2.54). In general, no exposure-response relationship was observed with mean TTCA concentrations. If the cases in the exposed and ex-exposed groups are combined and compared with the referent group in a univariate analysis, it can be calculated that the CS_2 exposure accounts for 40% of the new cases of hyperintense spots in the combined group CS_2 group. The authors of the study conclude that the results should be interpreted cautiously due to lack of an exposure-response relation and due to several potential limitations of the study.

Additional information

In a cross-sectional study in a Belgian viscose rayon factory, personal monitoring of CS_2 exposure was performed in 17 jobs. Because according to the authors the working conditions in the factory had not changed since 1932, a cumulative CS_2 exposure index was calculated for each individual. Examination of the exposed subjects (n=111), who were virtually obliged to participate, included a self-administered questionnaire, a clinical neurologic examination, and electro-neuromyography. The average CS_2 exposures of the study group ranged from 4 to 112 mg/m^3 (1.3-36 ppm). Two subgroups were identified, one of workers who had been exposed to concentrations below 31 mg/m^3 (10 ppm) (n=36) and one who had always been exposed to higher CS_2 concentrations (n=75). Seventy-four workers from three other plants (46% of the eligible subjects), not exposed to CS_2 or to any other neurotoxic agent, participated voluntarily as referents. The data were analysed with multiple regression methods, adjusting the effect of exposure for a number of possible confounders (not defined in detail). Some complaints consistent with polyneuropathy were statistically significantly more frequent in the exposed employees, but differences were not statistically significant for any subgroup in comparison to controls. There were no abnormal neurological findings by physical examination. Significant associations were found between the cumulative CS_2 indices (low, high, and total exposure groups) and symptoms consistent with polyneuropathy in the legs and with abnormal recruitment pattern and decrease of motor conduction velocities of the peroneal nerves (Vanhoorne *et al.*, 1995).[26]

The Committee challenges the claim of Vanhoorne *et al.* that the exposure conditions had not changed since 1932.

In order to examine neurophysiological effects in workers exposed to concentrations below 31 mg/m^3 (10 ppm), a second cross-sectional study was conducted in the same viscose rayon plant as described above (Vanhoorne *et al.*,1995). In this factory, CS_2 concentrations ranged from 4 to 112 mg/m^3 (1.3-36

ppm) (eight-hour time-weighted average) from 1983 to 1992. Since 1992, exposure dropped to levels below 31 mg/m^3(10 ppm) (maximum 32.4 mg/m^3 (10.4 ppm)). For each of the voluntarily participating workers (57% of the eligible subjects), a cumulative exposure index was calculated based on number of years helding a particular job and previous and recent exposure concentrations related to that job, and subsequently an average yearly exposure by dividing the cumulative exposure index by the number of working years. Thereafter, workers were divided into groups consisting of workers with individual average yearly exposures >31 mg/m^3(10 ppm) (n=25) and of workers with individual average yearly exposures <31 mg/m^3(10 ppm) (n=60), respectively. The means of the groups were 59.2±5.2 mg/m^3 (18.9±1.7 ppm) and 8.9±1.1 mg/m^3(2.8±0.4 ppm), respectively. In the high-exposure group, 52% participated in the previous study and 76% were Caucasians while in the low-exposure group, these figures were 21 and 50%, respectively. The control group, recruited among the same factories as in the Vanhoorne study, comprised 66 unexposed individuals (participation rate: 46%), of which 50% participated in the previous study and 80% were Caucasians. Employment duration range was 0.5 to 30 years. Exposure since 1995 was determined by personal monitoring (169 samples were collected on 16 days). Subjects completed questionnaires, and clinical neurological examination, computer-assisted neurobehavioral tests, and neurophysiological examinations (nerve conduction velocities and electromyography) were performed. Statistically significant differences were found between exposed (low and high) and control workers for sensorimotor complaints, finger tapping in the dominant and non-dominant hand. Statistically significant decreases in sural nerve conduction velocity, in sural nerve response amplitude, and in sympathic skin response amplitude, a statistically significant increase in sural nerve response duration, and higher prevalence of electromyography abnormalities and of peripheral polyneuropathy were also found in both exposed groups. Increased position tremor was only noticed in the low-exposure group (not related to exposure level). All effects remained significant after controlling for possible confounding factors (not specified).

Effects in the low-exposure group (<31 mg/m^3(10 ppm)) were further analyzed by stratification into two low-exposure subgroups according to exposure concentrations of ≤10 mg/m^3 (3 ppm) (n=34) and >10-≤30 mg/m^3 (3-10 ppm) (n=25). In the multiple logistic regression analysis, sensorimotor complaints were not statistically significantly more prevalent in either of the low-exposure groups. Positional tremor was statistically significantly more common in both low-exposure groups in comparison to the control group. Abnormalities in the electromyogram were statistically significantly elevated in

both low-exposure subgroups compared to controls. Similarly, sensory nerve amplitude and duration as well as conduction velocity were statistically significantly worse in both low-exposure subgroups. A statistically significant increase of sensory peripheral neuropathy and a decrease of finger tapping were also found for all both low-exposure subgroups (Godderis *et al.*, 2006).[11]

The Committee noted several weaknesses concerning the characteristics of the groups (workers selected themselves for the study; composition of the groups such as the considerable number of newcomers, mostly non-Caucasians, in the group exposed <31 mg/m^3; small numbers of the subgroups), in the construction and determination of the average exposure levels, and in the data analyses.

Cardiovascular 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 paper mill 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 work histories: 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).

Additional cardiovascular data in SCOEL (2008)

Serious cardiovascular effects of CS_2 in humans have been observed following long-term exposure in viscose workers. The effects included elevated blood pressure, angina pectoris, the more rapid development of arteriosclerosis, and excess mortality from cardiac infarction. It appears that exposure to mean levels of approximately 30 mg/m^3 (10 ppm) for periods of up to ten years caused electrocardiogram changes (Kamal *et al.*, 1991[SCOEL16] and Vanhoorne *et al.*, 1992)[SCOEL17].

SCOEL (2008) concluded that the cardiotoxic effects reported are probably associated with reported increases in cholesterol, serum triglycerides, low density lipoprotein, and apolipoprotein A1 and B (Egeland *et al.*, 1992[SCOEL18]; Stanosz *et al.*, 1994[SCOEL19]; Vanhoorne *et al.*, 1992[SCOEL17]). However, such results have not been consistent; although Stanosz *et al.* (1994) reported elevation of blood lipids at 15 to 20 mg/m^3 (5-6 ppm), another study found no changes in blood pressure, lipoproteins or blood clotting in a large well-conducted cross-sectional study (247 male workers) at a median exposure of 12 mg/m^3 (4 ppm) over a median duration of 66 months (Drexler *et al.*, 1995b)[SCOEL20].

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

In a study in which workers were exposed to current concentrations of 10-18 mg/m^3 (3-6 ppm) there were changes in several parameters of heart rate variability but this could not be attributed to CS_2 exposure alone (Bortkiewicz *et al.*, 1997)[SCOEL21].

Changes in resting or 24 hours ECG were demonstrated in workers with CS_2 exposure for more than 20 years (Bortkiewicz *et al.*, 2001)[SCOEL22] and increased cholesterol levels were reported in workers with current CS_2 exposures less than 30 mg/m^3 (10 ppm) but cumulative exposure indices of more than 100 mg/m^3 (30 ppm) (Kotseva, 2001)[SCOEL23]. Workers with cumulative exposure indices of more than 150 mg/m^3 (50 ppm) showed increased risk of coronary heart disease, ischaemic ECG and ischaemia (Kotseva *et al.*, 2001a)[SCOEL24]. The same workers also demonstrated reduced arterial wall dispensability and increased heart rate (Braeckman *et al.*, 2001[SCOEL25]; Kotseva *et al.*, 2001b[SCOEL26]).

In women exposed 'chronically' to CS_2 concentrations between 9.4 and 23.4 mg/m^3 (3-7 ppm), there were reported significant effects on the plasma lipid fraction and in the coagulation system (Stanosz *et al.*, 1998)[SCOEL27].

In a large cohort of Dutch viscose workers (1,434 workers) exposed for six months or longer, the standard mortality ratio for death from cardiac infarction was 126 (statistically significant) (Swaen *et al.*, 1994)[SCOEL29]. The authors estimated an average eight-hour exposure of 22 mg/m^3 (7 ppm), but the data appeared to show an inverse dose-response relationship. The greatest risk appeared to be 20 to 30 years after the start of exposure. In contrast, there was no increase in coronary artery disease or arteriosclerosis in a study of 247 workers exposed to a measured median concentration of 12 mg/m^3 (4 ppm) for a median duration of 66 months (Drexler *et al.*, 1995b)[SCOEL20]. However, in the same study a non-clinical haemodynamic increase (1-2 mm) in the diameter of the left heart chamber was noted in exposed versus control workers. Examination of subjects during exercise did not reveal any apparent ill-health consequences. However, in a later study, this negative inotropic effect on heart muscle was not confirmed (Korinth *et al.*, 2003)[SCOEL3]

In workers in Japanese viscose fibre-production facilities, sub-clinical effects on the retinal artery (microaneurysm) were reported (Omae *et al.*, 1998)[SCOEL30] with current average air concentrations of 12.5 mg/m^3 (4.1 ppm) with peaks up to 120 mg/m^3 (30 ppm). Exposure data on CS_2 concentrations prior to 1992 were unavailable. A six-year prospective study on cardiovascular effects of CS_2 exposures (Takebayashi *et al.*, 2004)[SCOEL1] was performed among workers of these facilities. The exposed (mean exposure concentration during the study: 15

mg/m^3 (5.0 ppm)), ex-exposed (average exposure duration during the study: 2.0 years; mean exposure concentration: 9 mg/m^3 (2.9 ppm), and non-exposed workers were 251, 140, and 359 in the respective groups. The incidence of coronary artery ischaemia, defined as Minnesota electrocardiographic codes I, IV1-3, V1-3 (tested at rest and after step test) or receiving treatment for ischaemia, was 6.4, 4.7, and 11% in the non-exposed, ex-exposed, and exposed workers, respectively. The odds ratio was statistically significantly increased in the exposed group (OR 2.0; 95% CI 1.1-3.6). Exposures were divided into quartiles. The odds ratio of the ischaemic findings was statistically significantly increased in the highest quartile (OR 4.2; 95% CI 1.8-9.7) with an exposure level of 8.7 ppm (28 mg/m^3). In the age-restricted groups (<35 years), the incidence of ischaemic findings was 3.8% in the non-exposed group and 12.4% in the exposed group, which was statistically significant. This indicates that recent exposure contributed to the development of the ischaemic findings. When 'rigorous' ECG criteria were applied for defining ischaemia, *e.g.* ST depression ≥2 mm, the incidence was comparable among the three groups.

The incidence of retinal microaneurysm was 5.0, 5.0, and 9.2%, respectively, in the three groups. The incidence in the exposed group was marginally increased (OR 2.3; 95% CI 1.0-5.4) among exposed workers, but not in the ex-exposed group (OR 1.4; 95% CI 0.3-4.9).

Another study describes the effects on Chinese viscose rayon workers of CS_2 exposure at concentrations between 10 and 31 mg/m^3 (3 and 10 ppm) (Tan *et al.*, 2004)[SCOEL2]. Cardiovascular symptoms, blood pressure, blood lipid, and ECG measurements were made in a cohort of 367 male and female CS_2-exposed workers (with a minimum of 4 years' exposure to CS_2) and 125 unexposed referents. The CS_2-exposed group was then subdivided into two groups on the basis of cumulative exposure index (CEI), with a CEI of 100 (10 years' exposure to 10 mg/m^3) used as the cut-off between low and moderate exposure. Personal monitoring revealed geometric mean values CS_2 concentration of 13.7 mg/m^3 (4.4 ppm) (staple workers) and 20 mg/m^3 (6.4 ppm) (filament workers). Since the main production process had remained unchanged, an inference was made that the current exposure levels observed are representative of those in the past. No effect on reported cardiovascular symptoms, blood pressure, blood lipid levels, or major/minor ECG abnormalities could be attributed to CS_2 exposure after adjustment for confounding factors.

In two reviews, many of the studies presented and discussed above were included. Price *et al.* (1997)[SCOEL40] specifically analysed data on ischaemic heart

disease mortality from 15 studies in 11 countries and suggest a threshold of around 50 mg/m^3 (15-20 ppm). Sulsky *et al.* (2002)[SCOEL28] evaluated 37 studies on cardiovascular effects in general and concluded that there are no strong or consistent associations between CS_2 exposure and coronary heart disease or relevant risk factors in 15 studies below 20 ppm. The only finding, but not consistently found, below this level was an increase in total or LDL cholesterol. Even at higher concentrations (>20 ppm), the associations with coronary heart diseases or other clinical indications were inconsistent and often contradictory. Sulsky *et al.* have noted the difficulties and complexity of deriving a clear no-effect level for cardiovascular disease or early markers of disease in these studies and have not attempted to derive one in their review.

Additional information

In a recent review, Gelbke *et al.* (2009)[10] commented that the high participation rate is a specific strength of the Tan *et al.* (2004)[SCOEL2] study (98% in non-exposed, 96% in exposed). A major limitation stems from the different gender distribution (a strong determinant of serum cholesterol) across exposure levels: the control group was 62% male, the low-exposure group was 49% male, and the moderate-exposure group was 89% male. It is unlikely that such disparities were adequately controlled in the adjusted analyses, and the authors' presentation of unadjusted results, only, suggests that control for confounding by gender may have attenuated any differences they did observe between groups (Gelbke *et al.*, 2009)[10].

Male workers (n=251, response rate 91%) in two plants of a viscose rayon factory in Taiwan were categorized in four exposure groups according to their work task: CS_2 manufacturing, viscose manufacturing, filament spinning, and foremen for the supervision of mechanical operation. The reference group (n=226) were male administrative staff, not exposed to CS_2. Physical examinations included blood pressure, electrocardiography, and a hearing test. Additionally, plasma triglyceride and high- and low-density lipoprotein cholesterol were determined. CS_2 exposure was measured by 24-hour on-site measurement. The CS_2 exposure level ranged from 5±1.9 mg/m^3 (1.6±0.9 ppm) for foremen to 63±71 mg/m^3 (20.1±22.8 ppm) for spinning workers. There were no differences for clinical chemical parameters between viscose rayon workers and the reference group. Prevalence rate for hypertension (defined as systolic pressure >140 mm Hg and/or diastolic pressure ≥90 mm Hg) in rayon workers was 43% against 7% in the reference group (OR 7.6; 95% CI 4.0-14.1). Among

viscose rayon workers, the prevalence for hypertension was exposure related. In the subgroup with the highest exposure to CS_2 (manufacturing), the prevalence was 53.5% (OR 14.1; 95% CI 5.9-33.5). In the group of workers with the least exposure to CS_2 (foremen), hypertension prevalence was higher than in the reference group (OR 5.1; 95% CI 1.8-14.9). The group of workers with the lowest exposure to CS_2 (foremen) worked in multiple areas and were likely exposed to higher concentrations on a regular basis. Considering cumulative exposure by multiplying the measured exposure levels and the years of employment showed that the prevalence of abnormal blood pressure was greater from systolic than from diastolic pressure. The authors conclude that they were unable to precisely measure the effect of low CS_2 exposure on blood pressure but that the data show that there is an elevated risk for acquiring hypertension at the prevailing permissible CS_2 exposure level of 31 mg/m^3 (10 ppm) (Chang *et al.*, 2007).[5]

In the same worker population, the prevalence of ECG abnormalities was 26% in the CS_2 exposure group compared to 3% in the reference group (OR 12.8; 95% CI 5.4-30.2). Foremen were at the highest risk of abnormal ECG (OR 20.6; 95% CI 6.5-65.2), followed by filament-spinning workers (OR 14.2; 95% CI 5.7-35.3), viscose manufacturing workers (OR 11.3; 95% CI 4.3-30.1), and CS_2-manufacturing workers (OR 8.1; 95% CI 2.7-25.6). Therefore, a relation with exposure is not apparent on a job category basis. Multivariate logistic regression analysis of the total workers population based on cumulative exposure index (average annual exposure times years of employment) revealed a dose-response relationship. The authors estimated the LOEL for ECG abnormalities being an exposure history of 31 to 57 ppm-year with an OR of 7.2 (95% CI 1.5-36.7) (Chang *et al.*, 2006).[4]

Chang *et al.* did not adjust for age (rayon workers were on average four years older and had been employed seven years longer than administrative staff) or shift work. Furthermore, calculating cumulative exposure ignores the fact that in the past, exposure levels have been higher (as stated by the authors).

The most highly exposed workers in viscose industry, especially spinners, work nearly exclusively under shift conditions and over many years. Shift work, per se, may lead to an increased risk for cardiovascular diseases, and there also is a correlation between duration of shift work and prevalence of cardiovascular risk factors, including alterations in triglyceride metabolism, the pattern of apolipoproteins, and decreased serum high-density lipoprotein (HDL) concentrations. Thus, studies assessing the effect of CS_2 exposure on coronary heart

disease and cardiac risk factors must account for shift work and years spent at service when defining the exposure and control groups (Gelbke *et al.*, 2009)[10].

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/m³ (1.5 ppm; range: 0.7-16 mg/m³ or 0.2-5 ppm) as measured by personal air sampling (from 1975-1981: 3-42 mg/m³ 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/m³ (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/m³ (60 ppm), although most values were less than 62 mg/m³ (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/m³ (1.5 ppm) at the time of study (exposure during the preceding 6 years ranged from 3-42 mg/m³ or 0.9-13 ppm; no further data reported). In an US study, workers exposed to 3-48 mg/m³ (1-16 ppm) at the time of study (during the preceding 22 y concentrations were usually less than 62 mg/m³ or 20 ppm) had significantly more microaneurysms and haemorrhages when compared with controls.

Additional data in SCOEL (2008)

A number of studies have reported damage to the blood vessels of the retina of the eye, such as microaneurysms and haemorrhage, in viscose workers, but co-exposure to hydrogen sulphide has also been suggested as a causative agent. It is unclear what the contribution of CS_2 to these effects is (Vanhoorne *et al.*, 1995)[SCOEL31].

An increased prevalence of colour discrimination disturbances in CS_2-exposed workers was observed at 10-15 mg/m³ (3-8 ppm) (Valic *et al.*, 2001)[SCOEL32] and at 14-20 mg/m³ (4-6 ppm) (Wang *et al.*, 2002)[SCOEL33]. However, the studies have been criticized due to methodological shortcomings (see Gelbke *et al.*, 2009[10]).*

Effects on other organs or systems

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

Additional data in SCOEL (2008)

Effects on hearing

Adverse effects on hearing, such as a reduction in auditory threshold and loss of hearing have been reported for eight-hour time-weighted average exposure to CS_2 above 30 mg/m³ (10 ppm; Hirata *et al.*, 1992[SCOEL34]). In workers exposed to CS_2 at concentrations of 10-35 mg/m³ (3-11 ppm) and high noise levels, hearing impairment was reported (Kowalska *et al.*, 2000)[SCOEL35].

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 from 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/m³ or 5-10 ppm or, 1960-1970: 31-93 mg/m³ or 10-30 ppm, 1950-1960: 62-186 mg/m³ 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 coexposure (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).

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* In the publication of Valic *et al.*, details of exposure measurements are missing. Furthermore, the poor language skills of the selected workers probably influenced the colour discrimination test. In the Wang 2002 study, an important potential confounder, age, was not controlled.

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 globulin (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 pituitarygonadal 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 nonexposed workers with respect to menstrual disturbances (suppression 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).

Additional data in SCOEL (2008)

There are reported reproductive effects in both male and female workers. In males, there are reports, not always consistent, of reduced sperm counts and changes in sperm morphology at eight-hour time-weighted average exposures of around 30 mg/m^3 (10 ppm; BUA 1993).[SCOEL36] This has not been confirmed in

other studies (Vanhoorne *et al.*, 1993[SCOEL37] and 1994[SCOEL38]), although a reduction in workers' libido and potency was noted at 30 mg/m³ (10 ppm) and above (Vanhoorne *et al.*, 1994).[SCOEL38]

Additional information

An increased incidence of miscarriages was reported for women married to men exposed to an average CS_2 concentration of 39 mg/m³ (12 ppm) in comparison to women married to workers with low CS_2 exposure (5.4 mg/m³ (1.7 ppm)). The exposed workers (n=100, low and high exposure) had been employed ten years prior to study. Workers history records were build up on number of children, miscarriages and general weakness, mental fatigue etc. The incidences of miscarriages were 5.7% in the low-exposure group and 18.9% in the high-exposure group. The findings were not statistically analysed and an unexposed control group was not included (Patel *et al.*, 2004).[20]

4.2 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.

4.2.1 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 cm³) 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.

Additional data in SCOEL (2008)

There are no available studies on the allergenic potential of CS_2.

4.2.2 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 noradrenalin 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-bhydroxylase. 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.

4.2.3 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 days 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.

Additional information

Male and female F344 rats were exposed to 0, 160, 1600, or 2400 mg/m^3 (0, 50, 500, 800 ppm) CS_2, six hours/day, five days/week, for two, four, eight (n=9/sex/group), or 13 weeks (n=18/sex/group) and neurobehavioural, neurophysiological, neurohistological, and biochemical endpoints were examined. Body weight recordings and clinical observations were made once weekly. Functional observational battery and electrophysiological examinations were conducted on all rats just prior to the start of the study and again on the morning after the last exposure of the two-, four-, eight-, and 13-week exposure groups. Thereafter, tissues were collected for morphological examinations (Sills *et al.*, 1998)[22].

There was no treatment-related mortality. In male rats exposed to 1600 mg/m^3 (500 ppm) or 2400 mg/m^3 (800 ppm), mean group body weights were affected from week 4 and 2 onwards, respectively, resulting in decreases by 14 and 23%, respectively, at week 13. In females exposed to 2400 mg/m^3 (800 ppm), body weights were decreased by 6% at week 13. Apart from postural abnormalities observed at all exposure, mostly at 2400 mg/m^3 (800 ppm), there were no consisting findings at the weekly clinical observations (Moser *et al.*, 1998)[18].

Evaluations using the functional observational battery showed that exposure to CS_2 concentrations of 1600 and 2400 mg/m^3 (500 and 800 ppm) induced a profile of neuromotor dysfunction, manifest primarily in the hind limbs. They were evident as early as two weeks of exposure and became more progressive with longer exposure duration. Other lesser effects such as tremors, ataxia, and changes in reactivity and a visual test were seen as well. At 160 mg/m^3 (50 ppm), the lowest concentration, a fairly minor but statistically significant impaired gait

was observed in male rats with scores of 'slight' in 5/18 and of 'somewhat' in 3/18 animals (on a scale of 1 to 5: 'normal' to 'severe') (Moser *et al.*, 1998).[18]

Electrophysiological examination of the nerve compound action potentials and nerve conduction velocity showed that exposure to 1600 and 2400 mg/m^3 (500 and 800 ppm) for 13 weeks produced some minor changes in the nerve conduction velocities and nerve compound action potentials of the ventral caudal tail nerves while no effects were seen in animals exposed to 160 mg/m^3 (50 ppm) (Herr *et al.*, 1998)[14].

The study also included an examination of the morphological progression and dose response of the CS_2-induced distal axonopathy in the muscular branch of the posterial tibial nerve and spinal cord at week 2, 4, or 8 in four animals/sex/group, or in week 13 in eight animals/sex/group. At the terminal sacrifice at week 13, tissues were processed for routine histopathological examination including, amongst others, whole brain (cerebrum, cerebellum, midbrain). Axonal swelling was observed in the muscular branch of the posterial tibial nerve in the animals exposed to 2400 mg/m^3 (800 ppm) for eight or 13 weeks and in the spinal cord in the animals exposed to 1600 and 2400 mg/m^3 (500 and 800 ppm) for eight or 13 weeks. These axonal swellings were not present in any of the groups exposed for two or four weeks or in the animals exposed to 160 mg/m^3 (50 ppm) for eight or thirteen weeks. CS_2-related lesions were not detected in the brain (Sills *et al.* 1998).[21]

The Committee notes that the test values for impaired gait in males at 160 mg/m^3 (50 ppm) are all within the control values and is of the opinion that the statistically significant difference at week 13 can be explained by the low score in the controls at that time point. Therefore, the Committee concludes that in this study, 160 mg/m^3 (50 ppm) is the NOAEL for neurobehavioural as well as neurophysiological, and neurohistological effects.

Groups of male and female Wistar rats (n=20/group) were exposed to 0, 50, 250, or 1250 mg/m^3 (0, 16, 80, 400 ppm) CS_2 for four hours/day, five days/week, for two months. At termination, nitric oxide synthase iso-enzymes (calcium-dependent cNOS and calcium-independent iNOS) and the respective mRNAs were determined in the hippocampus.* A dose-related decrease of cNOS activity was measured at all CS_2 treatment levels, whereas there were no significant differences in the activity of iNOS. Expression of neuronal NOS mRNA was also

* Nitric oxide synthase is the only enzyme that can synthesize endogenous nitrogen monoxide, which plays a major role in regulating releasing of neurotransmitter, modulating development of synaptic plasticity, and participating in learning and memory.

lower in the exposed groups, in a dose-related manner. mRNA for iNOS mRNA showed a dose-related increase that was statistically significant at CS_2 concentrations ≥250 mg/m^3 (80 ppm). This study presents a likely mechanism of the learning and memory impairment induced by CS_2 (Guo *et al.*, 2008).[12]

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.

Additional information

No CS_2-related lesions were seen in the heart and aorta of male and female rats exposed to 160, 1600, or 2400 mg/m^3 (50, 500, 800 ppm) CS_2, six hours/day, five days/week, for 13 weeks (see above page 87) (Sills *et al.*, 1998).[21]

Groups of 20 female C57BL/6 mice were exposed to 0, 160, 1600, or 2400 mg/m^3 (50, 500, 800 ppm) CS_2, six hours/day, five days/week, for up to 20 weeks. Half of the animals in each group were placed on a control diet and half on a high fat atherogenic diet. Animals were sacrificed after 1, 4, 8, 16, or 20 weeks of exposure, and the rates of fatty deposit formation under the aortic valve leaflets were evaluated. In mice placed on a control diet, a small but statistically significant increase in the rate of fatty deposit formation over controls was seen at 1600 and 2400 mg/m^3 (500 and 800 ppm), but not at 160 mg/m^3 (50 ppm). In the presence of the atherogenic diet, these effects were marked when compared with animals receiving the atherogenic diet alone, and also in the animals exposed to 160 mg/m^3 (50 ppm,) a small, statistically significant enhancement was observed (Lewis *et al.*, 1999).[15]

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.

Additional information

No CS_2-related lesions were seen in the liver of male and female rats exposed to 160, 1600, or 2400 mg/m³ (50, 500, 800 ppm) CS_2, six hours/day, five days/week, for 13 weeks (see above page 87) (Sills *et al.*, 1998).[21]

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/m³ 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/m³ (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.

Additional information

No CS_2-related lesions were seen in the nasal cavity, trachea, lung, and kidney of male and female rats exposed to 160, 1600, or 2400 mg/m³ (50, 500, 800 ppm) CS_2, six hours/day, five days/week, for 13 weeks (see above page 82) (Sills *et al.*, 1998).[21]

Additional data in SCOEL (2008)

Effects on hearing

In rats, slight but detectable changes in auditory brainstem responses were recorded after exposure to CS_2 concentrations of 600 mg/m³ (190 ppm) for 15 weeks (Hirata *et al.*, 1992).[SCOEL39]

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/m³ (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/m³ (3000 ppm). At 600 mg/m³ (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/m³ (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/m³) 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/m³ (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/m³ (480 ppm) for 9 months (5 h per day, 6 days per week) or to 2184 mg/m³ (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/m³ (480 ppm) for 7 months (5 h per day, 6 days per week)) and to 1600 mg/m³ (513 ppm) for 4-6 months (5 h per day, 6 days per week).

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

Continuous exposure of rats for 4 months up to 112 mg/m³ (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/m³ (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/m³ (74 ppm) for 8 months slightly increased serum cholesterol levels, while exposure to 550 mg/m³ (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/m³,

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.

Additional information

The Committee took a closer look at the above-mentioned study in which exposure of rats to 230 mg/m^3 (74 ppm) for 8 months induced slightly increased serum cholesterol level. In this study, Wronska-Nofer (1973)[27] exposed groups of eight Wistar rats (sex not indicated) to 0, 230, 500, 1000, or 1700 mg/m^3, six hours/day, five days/week, for eight months. At month 2, 4, 6, and 8, blood was taken from the tail vein and serum cholesterol, phospholipids, and triglycerids were determined. As stated above, levels of these serum lipids were clearly increased in the rats exposed to 500 mg/m^3 and higher. Generally, the changes in these end points did not show clear dose-reponse or time-response relations. The Committee notes that the test values for these lipids in the group exposed to 230 mg/m^3 were within control values and is of the opinion that the statistically significant difference at month eight can be explained by the low control values at that time point. Therefore, the Committee concludes that in this study, the NOAEL and LOAEL for cardiovascular biochemical effects are 230 mg/m^3 and 500 mg/m^3, respectively.

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 locally 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.

4.2.4 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.

4.2.5 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 threshold 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.

Additional information

No CS_2-related lesions were seen in the reproductive organs of male and female rats exposed to 160, 1600, or 2400 mg/m^3 (50, 500, 800 ppm) CS_2, six hours/day, five days/week, for 13 weeks (see above page 87) (Sills *et al.*, 1998).[21]

4.2.6 Other studies

CS_2 and H_2S mixtures

Human observations

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.

Additional information

An increased risk of hand dermatitis from CS_2 alone or from combined exposure to CS_2 and H_2S was examined in a study in 110 workers of a viscose rayon factory in Taiwan. Significant elevated odds ratios (ORs) for hand dermatitis were found in workers exposed to CS_2 exclusively (OR 44.8, $p<0.01$, n=13) and

for workers with combined exposure (OR 49.0, p<0.001, n=66), compared with the control group (n=29) (Chou *et al.*, 2004).[6]

Animal studies

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).

4.3 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.

Additional data

Regarding ischaemic heart disease, epidemiological studies in the viscose rayon spinning industry have shown the highest risk to be to those with between 15-25 years exposure. Price *et al.* (1997) analysed data from 15 studies in 11 countries and suggest a threshold for ischaemic heart disease mortality of around 50 mg/m^3 (15-20 ppm) while Sulsky *et al.* (2002) concluded from 37 studies on cardiovascular effects in general that there are no strong or consistent associations between CS_2 exposure and coronary heart disease or relevant risk factors in 15 studies below 20 ppm. The only finding, but not consistently found, below this level was an increase in total or LDL cholesterol. Even at higher concentrations (>20 ppm), the associations with coronary heart diseases or other clinical indications were inconsistent and often contradictory. In a six-year prospective cohort study, Takebayashi *et al.* (2004) found an increase in incidence of ischaemic findings as judged by Minnesota code 1982 in Japanese workers exposed to 15 mg/m^3 (5 ppm); the observed increase diminished when applying more rigorous criteria. Tan *et al.* (2004) did not report cardiovascular effects in Chinese workers at exposure levels of about 20 mg/m^3 (7 ppm).

As to neurotoxic effects, Reinhardt *et al.* (1997) did not find clinical neurological, neuropsychological, and neurophysiological changes either in 222 workers in a German plant exposed to a median concentration of 12 mg/m^3 (4 ppm; range: <0.6-205 mg/m^3 (<0.2-66 ppm); personal air sampling) for a mean of 66 months (range: 4-220 months). Ruijten *et al.* (1990) reported a small decrease in the conduction velocity of the slow motor fibers of 1.1 m/s and a prolongation of the refractory period of 0.1 m/s in 45 workers in a Dutch viscose rayon plant, exposed for a mean of 20 years to a mean concentration of 22 mg/m^3 (7 ppm), with a range of 3-53 mg/m^3 (1-17 ppm) as determined by spot (1948-1983) or personal air sampling (≥1983) (Ruijten *et al.*, 1990). The findings in this study were largely reproduced in a follow-up study in which 28 workers were re-examined four years later (Ruijten *et al.*, 1993). Vanhoorne *et al.* (1995) observed neurological abnormalities (increased positional tremor, abnormalities in electromyogram, and indications for peripheral polyneuropathy) in 111

workers of a Belgian viscose rayon factory, where CS_2 concentrations had ranged between 4 and 112 mg/m^3 (1 and 36 ppm) (eight-hour time-weighted average) until 1992 and had decreased to below 31 mg/m^3 (10 ppm) since then. In a second cross-sectional study in the same factory, Godderis *et al.* (2006) found an excess of impaired psychomotor performance, tremor, and peripheral polyneuropathy in a group of workers with average yearly CS_2 exposure levels <31 mg/m^3 (<10 ppm), and suggested that exposure to concentrations ≤10 mg/m^3 (3 ppm) could cause effects. Takebayashi *et al.* (1998) reported reduced nerve conduction velocities in 419 workers of 11 Japanese viscose fibre-production facilities exposed for a mean of 13.4 years to median breathing-zone air concentrations of 12.5 mg/m^3 (4 ppm) (range: from not detectable to 124 mg/m^3 (40 ppm)). When dividing the workers into a high-exposure group involved in spinning and refining (n=301) and a low-exposure group with other activities (n=121), a significant difference with the control group was only apparent for the high-exposure group (no exposure levels presented).

In male and female rats exposed to concentrations of 0, 160, 1600, or 2400 mg/m^3 (0, 50, 500, 800 ppm), six hours/day, five days/week, for two, four, eight, or 13 weeks, neurobehavioural, most manifest in the hind limbs and neurophysiological effects were observed at 1600 and 2400 mg/m^3. Some of the effects were evident as early as two weeks of exposure and became more progressive with longer exposure duration. No effects were observed in the animals exposed to 160 mg/m^3 (50 ppm). No CS_2-related gross or histopathological lesions were seen in the brain, heart, aorta, nasal cavity, trachea, lung, kidney, and reproductive organs in any of exposed groups.

Chapter 5

Existing occupational exposure limits

Occupational exposure limits for carbon disulphide in some European countries and the USA, listed in the most recent publications available to the Committee, are presented in Table 5.1.

Table 5.1 Occupational exposure limits for carbon disulphide in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	mg/m^3	ppm				
the Netherlands						
- Ministry of Social Affairs and Employment	-	-				17
Germany						
- DFG MAK-Kommission	16	5	8 h		S, [d]	7
	32	10	15 min[c]			
- AGS	30	10	8 h		S	1
	60	20	15 min			
Sweden	16	5	8 h		S, [e]	24
	25	8	15 min			
Denmark	15	5	8 h		S	3
United Kingdom						
- HSE	32	10	8 h	WEL	S	13
USA						
- ACGIH		1	8 h	TLV	S, [f]	2
- OSHA		20	8 h	PEL	S	
		30	ceiling			2
		100	30-min peak/8-h			2
- NIOSH	3	1	shift	REL	S	
	30	10	8 h			
			15 min			
European Union	15	5	8 h	IOELV	S	8

a S = skin notation; which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

b Reference to the most recent official publication of occupational exposure limits.

c Maximum per shift: 4, with a minimum interval between peaks of 1 hour.

d Classified in pregnancy group B: *i.e.* according to the currently available information damage to the embryo or foetus must be expected even when MAK and BAT values are observed.

e the substance causes reproduction disturbances

f classified into carcinogenicity category A4, *i.e.* not classifiable as a human carcinogen: agents which cause concern that they could be carcinogenic to humans but which cannot be assessed conclusively because of lack of data. *In vitro* or animal studies do not provide indications of carcinogenicity which are sufficient to classify the agent into one of the other categories.

References

References from Health Council 1994/08WGD

Aaserud O, Gjerstad L, Nakstad P, *et al*. 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, *et al.* 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. Cincinnati OH: ACGIH, 1991; 15.

ACGIH. Threshold limit values for chemical substances and physical agents and biological exposure indices for 1991-1992. Cincinnati OH: ACGIH, 1991; 63.

Adkins B Jr, van Stee EW, Simmons JE, *et al.* Oncogenic response of strain A/J mice to inhaled chemicals. J Toxicol Environ Health 1986; 17: 311-22.

Albright BE, Burg JR, Fagen J, *et al.* 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, *et al.* 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, *et al.* 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 pollutants 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.
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, Craven A, *et al.* A study on blood coagulation factors, fibrinolysis and platelet function in workers exposed to carbon disulphide. G Ital Med Lay 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/m^3. An exposed-controls study. G Ital Med Lav 1981; 3: 69-73.
Colombi A, Maroni M, Picchi D, *et al.* 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, *et al.* 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 and biologische Arbeitsstofftoleranzwerte 1989. Weinheim FRG: VCH Verlagsgesellschaft mbH, 1991; 106.
DFG. Maximale Arbeitsplatzkoncentrationen and biologische Arbeitsstofftoleranzwerte 1989. Weinheim FRG: VCH Verlagsgesellschaft mbH, 1991; 49.
Donner M, Falck K, Hemminki K, *et al.* 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, *et al.* Assessment of coronary heart disease risk among viscose rayon workers exposed to carbon disulphide at concentrations of about 30 mg/m^3. Scand J Work Environ Health 1982; 8: 113-20.
Gagnaire F, Simon P, Bonnet P, *et al.* 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, *et al.* 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 35S-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 druk. 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, *et al.* Salmonella mutagenicity test results for 250 chemicals. Environ Mutagen 1983; 5(suppl 1), 3-142.
Hedenstedt A, Rannug U, Ramel C, *et al.* 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 CS_2-Aufnahme bei dosierter dynamischer Belastung. Z Gesamte Hyg 1983; 29: 444-8.

Hirata M, K.Sugimoto, Misumi J, *et al.* A neurophysiological study among Chinese CS_2-exposed workers. G Ital Med Lay 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, *et al.* 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, *et al.* 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, *et al.* 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, *et al.* 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, *et al.* Langzeitwirkungen von Schwefelkohlenstoff and 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, *et al.* 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 Lay 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 (CS_2). 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 Normalisatieinstituut, 1989

Nurminen M, Hemberg S. Cancer mortality among carbon disulphide-exposed workers. J Occup Med 1984; 26: 341.

Nurminen M, Hemberg 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, *et al.* 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, *et al.* 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, *et al.* 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, Ma ryland: 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, *et al.* A behavioral examination of workers exposed to carbon disulphide. Neurotoxicology 1983; 4(1): 67-78.
Raitta C, Teir H, Tolonen M, *et al.* 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, v an Peteghem C, *et al.* 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, *et al.* 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, *et al.* 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 (CS_2). Adv Exp Med Biol 1986; 197: 237-42.
Ruijten M, Sallé H, Verberk M, *et al.* 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, *et al.* Special nerve functions and colour discrimination in workers with long term low level exposure to carbon disulphide. Br J Ind Med 1990a; 47: 589-95.
Ruijten M, Sallé H, Verberk M. (1990b). Zenuwfuncties bij werknemers met langdurige lage blootstelling aan CS_2, 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 development in rats. Toxicol Lett 1989; 48: 57-66.
Sandrini GA, Bosso A, Biscaldi G, *et al.* Electromyographic investigation in early diagnosis of carbon disulphide neuropathy: a study on 216 workers with different degrees of exposure. G Ital Med Lay 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, *et al.* An epidemiological study on CS_2 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, *et al.* Hazards for the progency after maternal exposure to low carbon disulphide concentrations. G Ital Med Lay 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, *et al.* Identification and determination 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, *et al.* 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).

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 pl ant. 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, *et al.* 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, *et al.* Combined effect of ethanol and carbon disulphide on cytochrome 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, *et al.* Serum gonadotropins and testosterone in men occupationally exposed to carbon disulphide. J Toxicol Environ Health 1983; 11: 691-701.

Zenick H, Blackburn K, Hope E, *et al.* 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, *et al.* Effects of occupational exposure to low-level carbon disulphide (CS_2) on menstruation and pregnancy. Ind Health 1988; 26: 203-14.

Zielhuis RL, Stijkel A, Verberk MM, *et al.* Health risks to female workers in occupational exposure to chemical agents. Berlijn FRG: Springer Verlag, 1984; 16-28.
Zielhuis RL, Stijkel A, Verberk MM, *et al.* Health risks to female workers in occupational exposure to chemical agents. Berlijn FRG: Springer Verlag, 1984; 16-28.

References from SCOEL (2008)

SCOEL1 Takebayashi, T., Y. Nishiwaki, T. Uemura, H. Nakashima, T. Nomiyama, H. Sakurai & K. Omae (2004). A six year follow up study of the subclinical effects of carbon disulphide exposure on the cardiovascular system. Occup. Environ. Med. 61, 127-134.

SCOEL2 Tan, X., Chen, G., Peng, X., Wang, F., Bi, Y., Tao, N., Wang, C., Yan, J., Ma, S., Cao, Z., He, J., Yi, P., Braeckman, L., Vanhoorne, M. (2004). Cross-sectional study of cardiovascular effects of carbon disulfide among Chinese workers of a viscose factory. Int. J. Hyg. Environ. Health 207, 217-225.

SCOEL3 Korinth, G., Göen, T., Ulm, K., Hardt, R., Hubmann, M., Drexler, H. (2003). Cardiovascular function of workers exposed to carbon disulphide. Int. Arch. Occup. Environ. Health 76, 81-85.

SCOEL4 Shih, T.S., Chou, T.C., Chang, H.Y., Wu, C.C., Wang, P.Y. (2003). Accumulation of urinary 2-thiothiazolidine-4-carboxylic acid (TTCA) among workers occupationally exposed to carbon disulfide for 1 week. Sci. Total. Environ. 308, 37-47.

SCOEL5 Chang, H.Y., Chou, T.C., Wang, P.Y., Shih, T.S. (2002). Biological monitoring of carbon disulphide: kinetics of urinary 2-thiothiazolidine-4-carboxylic acid (TTCA) in exposed workers. Toxicol. Ind. Health 18, 1-14.

SCOEL6 Drexler, H., Göen, T., Angerer, J (1995a). Carbon disulphide II. Investigations on the uptake of CS_2 and the excretion of its metabolite 2-thiothiazolidine-4-carboxylic acid after occupational exposure. Int. Arch. Occup. Environ. Health. 67, 5-10.

SCOEL7 Krstev S, Perunicic B, Farkic B, Varagic M (1993). Environmental and biological monitoring in carbon disulfide exposure assessment. Medicina del Lavoro, 84(6), 473–481.

SCOEL8 Riihimaki, V., Kivisto, H., Peltonen, K., Helpio, E., Aitio, A. (1992). Assessment of exposure to carbon disulfide in viscose production workers from urinary 2-thiothiazolidine-4-carboxylic acid determinations. Am J Ind Med 22, 85-97.

SCOEL9 Herborn, H. (1992). Gesundheitsgefährdung durch Schwefelkohlenstoff (CS_2) - Ergebnisse einer epidemiologischen Studie. In: Schäcke, G., Ruppe, K., Vogel-Sührig, C. (eds).

SCOEL10 Cassitto, M.G., Camerino, D., Imbriani, M., Contardi, T., Masera, L., Gilioli, R. (1993). Carbon disulphide and the central nervous system: a 15-year neurobehavioural surveillance of an exposed population. Environ. Res. 63, 252-263.

SCOEL11 Chu, C.-C., Huan, C.-C., Chen, R.-S., Shih, T.-S. (1995). Polyneuropathy induced by carbon disulphide in viscose rayon workers. Occup. Environ. Med. 52, 404-407.

SCOEL12 Ruijten, M.W.M.M., Sallé, H.J.A., Verberk, M.M. (1993). Verification of effects on the nervous system of low level occupational exposure to CS_2. Br. J. Ind. Med. 50, 301-307.

SCOEL13 Reinhardt, F., Drexler, H., Bickel, A., Claus, D., Angerer, J., Ulm, K., Lehnert, G., Neundörfer, B. (1997). Neurotoxicity of long-term low-level exposure to carbon disulphide: results of a questionnaire, clinical, neurological examination and neuropsychological testing. Int. Arch. Occup. Environ. Health, 69, 332-338.

SCOEL14 Takebayashi, T., Omae, K., Ishizuka, C., Nomiyama, T., Sakurai, H. (1998). Cross sectional observation of the effects of carbon disulphide on the nervous system, endocrine system, and subjective symptoms in rayon manufacturing workers. Occup. Environ. Med. 55, 473-479.

SCOEL15 Nishiwaki, Y., Takebayashi, T., O'Uchi, T., Nomiyama, T., Uemura, T., Sakurai, H., Omae, K. (2004). Six year observational cohort study of the effect of carbon disulphide on brain MRI in rayon manufacturing workers. Occup. Environ. Med. 61, 225-232.

SCOEL16 Kamal, A-A., Ahmed, A., Saied, K., Metwally, M. (1991). Quantitative evaluation of ECG components of workers exposed to carbon disulphide. Environ. Health Perspect. 90, 301-304.

SCOEL17 Vanhoorne, M., De Bacquer, D., De Backer, G. (1992). Epidemiological study of the cardiovascular effects of carbon disulphide. Int. J. Epidemiol. 21, 745-752.

SCOEL18 Egeland, G.M., Burkhart, G.A., Schnorr, T.M., Hornung, R.W., Fajen, J.M., Lee, S.T. (1992). Effects of exposure to carbon disulphide on low-density lipoprotein in cholesterol concentrations and diastolic blood pressure. Br. J. Ind. Med. 49, 287-293.

SCOEL19 Stanosz, S., Kuligowski, D., Zuk, E., Rzechula, D., Kosciuszkiewicz, B., Chlubek, D. (1994). The pattern of some lipid fractions in the serum of women chronically exposed to carbon disulphide. Ind. Health. 32, 183-186.

SCOEL20 Drexler, H., Ulm, K., Hubmann, M., Hardt, R., Göen, T., Mondorf, W., Lang, E., Angerer, J. and Lehnert, G. (1995b). Carbon disulphide III. Risk factors for coronary heart diseases in workers in the viscose industry. Int. Arch. Occup. Environ. Health, 67, 243-252.

SCOEL21 Bortkiewicz, A., Gadzicka, E., Szymczak, W. (1997). Heart rate variability in workers exposed to carbon disulfide. J. Auton. Nerv. Syst. 66, 62-68.

SCOEL22 Bortkiewicz, A., Gadzicka, E., Szymczak, W. (2001). Cardiovascular disturbances in workers exposed to carbon disulfide. Appl. Occup. Environ. Hyg. 16, 455-463.

SCOEL23 Kotseva, K. (2001). Occupational exposure to low concentrations of carbon disulfide as a risk factor for hypercholesterolaemia. Int. Arch. Occup. Environ. Health 74, 38-42.

SCOEL24 Kotseva, K., Braeckman, L., De Bacquer, D., Bulat, P., Vanhoorne, M. (2001a). Cardiovascular effects in viscose rayon workers exposed to carbon disulfide. Int. J. Occup. Environ. Health 7, 7-13.

SCOEL25 Braeckman, L., Kotseva, K., Duprez, D., De Bacquer, D., De Buyzere, M., Van De Veire, N., Vanhoorne, M. (2001). Vascular changes in workers exposed to carbon disulfide. Ann. Acad. Med. Singapore 30, 475-480.

SCOEL26 Kotseva, K., Braeckman, L., Duprez, D., De Bacquer, D., De Buyzere, M., Van De Veire, N., Vanhoorne, M. (2001b). Decreased carotid artery distensibility as a sign of early atherosclerosis in viscose rayon workers. Occup. Med. 51, 223-229.

SCOEL27 Stanosz S, Kuligowska E, Kuligowski D (1998). Coefficient of linear correlation between levels of fibrinogen, antithrombin III, thrombin-antithrombin complex and lipid fractions in women exposed chronically to carbon disulfide (Polish). Med Pra 49, 51-57

SCOEL28 Sulsky, S.I., Hooven, F.H., Burch, M.T., Mundt, K.A. (2002). Critical review of the epidemiological literature on the potential cardiovascular effects of occupational carbon disulfide exposure. Int. Arch. Occup. Environ. Health 75, 365-380.

SCOEL29 Swaen, G.M.H., Braun, C, Slangen, J.J.M. (1994). Mortality of Dutch workers exposed to carbon disulphide. Int. Arch. Occup. Environ. Health. 66, 103-110.

SCOEL30 Omae, K., Takebayashi, T., Nomiyama, T., Ishizuka, C., Nakashima, H., Uemura, T., Tanaka, S., Yamauchi, T., O'Uchi, T., Horichi, Y., Sakurai, H. (1998). Cross sectional observation of the effects of carbon disulphide on arteriosclerosis in rayon manufacturing workers. Occup. Environ. Med. 55, 468-472.

SCOEL31 Vanhoorne, M., De Rouck, A., De Bacquer. (1995a). Epidemiological study of eye irritation by hydrogen sulphide and/or carbon disulphide exposure in viscose rayon workers. Ann. Occup. Hyg. 39, 307-315.

SCOEL32 Valic, E., Pilger, A., Pirsch, P., Pospischil, E., Waldhör, T., Rüdiger, H.W., Wolf, C. (2001). Nachweis erworbener Farbsinnstörungen bei CS_2 exponierten Arbeitern in der Viskoseproduktion. Arbeitsmed. Sozialmed. Umweltmed. 36, 59-63.

SCOEL33 Wang, C., Tan, X., Bi, Y., Su, Y., Yan, J., Ma, S., He, J., Braeckman, L., De Bacquer, D., Wang, F., Vanhoorne, M. (2002). Cross-sectional study of the ophthalmological effects of carbon disulfide in Chinese viscose workers. Int. J. Hyg. Environ. Health 205, 367-372.

SCOEL34 Hirata, M., Ogawa, Y., Okayama, A., Goto, S. (1992a). A cross-sectional study of the brainstem auditory evoked potential among workers exposed to carbon disulphide. Int. Arch. Occup. Environ. Health. 64, 321-324.

SCOEL35 Kowalska, S., Sulkowski, W., Sinczuk-Walczak, H. (2000). Assessment of the hearing system in workers chronically exposed to carbon disulfide and noise (Polish). Med. Pra. 51, 123-138.

SCOEL36 BUA (GDCh-Advisory Committee on Existing Chemicals) (1993). Carbon disulphide: BUA Report 83 (August 1991). S Hirzel, Wissenschaftliche Verlagsgesellschaft, Stuttgart.

SCOEL37 Vanhoorne, M., Vermoeulen, A., De Bacquer, D. (1993). Epidemiological study of endocrinological effects of carbon disulphide. Arch. Environ. Health. 48, 370-375.

SCOEL38 Vanhoorne, M., Comhare, F., De Bacquer, D. (1994). Epidemiological study of the effects of carbon disulphide on male sexuality and reproduction. Arch. Envron. Health. 49, 273-278.

SCOEL39 Hirata, M., Ogawa, Y., Okayama, A., Goto, S. (1992b). Changes in auditory brainstem response in rats chronically exposed to carbon disulfide. Arch. Toxicol. 66, 334-338.

SCOEL40 Price, B., Bergman, T.S., Rodriguez, M., Henrich, R.T., Moran, E.J. (1997). A review of carbon disulfide exposure data and the association between carbon disulfide exposure and ischaemic heart disease mortality. Reg. Tox. Pharm. 26, 119-128.

SCOEL41 Drexler, H., Ulm, K., Hardt, R., Hubmann, M., Göen, T., Lang, E., Angerer, J. and Lehnert, G. (1996). Carbon disulphide IV. Cardiovascular function in workers in the viscose industry. Int. Arch. Occup. Environ. Health. 69, 27-32.

Additional references

1 TRGS 900. Grenzwerte in der Luft am Arbeitsplatz; Technische Regeln für Gefahrstoffe. July 2009. http://www.baua.de/nn_16806/de/Themen-von-A-Z/Gefahrstoffe/TRGS/pdf/TRGS-900.pdf consulted: 8-12-2009.

2 American Conference of governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values - 2009. Cincinnati OH, USA: ACGIH; 2009.

3 Arbejdstilsynet. Grænseværdier for stoffer og materialer. http://www.arbejdstilsynet.dk/REGLER/At-vejledninger-mv/Stoffer-og-materialer/At-vejledninger-om-stoffer-og-materialer/C0-Generelt-og-diverse/PDF-C01-Graensevaerdi-for-stoffer-og-mat.aspx?sc_lang=da consulted: 8-12-2009.

4 Chang SJ, Chang HY, Shih TS, Chou TC, Chen CJ, Chen PC *et al.* Electrocardiographic abnormality for workers exposed to carbon disulfide at a viscose rayon plant. J Occup Environ Med 2006; 48(4): 394-399.

5 Chang SJ, Chen CJ, Shih TS, Chou TC, Sung FC. Risk for hypertension in workers exposed to carbon disulfide in the viscose rayon industry. Am J Ind Med 2007; 50(1): 22-27.

6 Chou TC, Sheu HM, Chiu JE, Wu JD, Shih TS, Chang HY. Combined exposure to carbon disulfide and sulfuric acid simultaneously increases the risk of hand dermatitis in rayon industry. J Expo Anal Environ Epidemiol 2004; 14(7): 551-557.

7 Deutsche Forschungsgemeinschaft (DFG). List of MAK and BAT values 2009. Maximum concentrations and biological tolerance values at the workplace (rep no 45). Weinheim, FRG: Wiley:VCH Verlag; 2009.

8 European Commission: Directorate General of Employment and Social Affairs. Consolidated Indicative Occupational Exposure Limits Values (IOELVs). http://ec.europa.eu/social/main.jsp?catId=153&langId=en&intPageId=684 consulted: 8-12-2009.

9 European Parliament and the Council of the European Union. Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. Official Journal of the European Union 2008 , (L353) 1-1355. 31-12-2008. Internet: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:353:0001:1355:EN:PDF consulted 2009.

10 Gelbke HP, Goen T, Maurer M, Sulsky SI. A review of health effects of carbon disulfide in viscose industry and a proposal for an occupational exposure limit. Crit Rev Toxicol 2009; 39 Suppl 2: 1-126.

11 Godderis L, Braeckman L, Vanhoorne M, Viaene M. Neurobehavioral and clinical effects in workers exposed to CS(2). Int J Hyg Environ Health 2006; 209(2): 139-150.

12 Guo XM, Tang RH, Qin XY, Yang J, Chen GY. Effects of carbon disulfide on the expression and activity of nitric oxide synthase in rat hippocampus. Chin Med J (Engl) 2008; 121(24): 2553-2556.

13 Health and Safety Executive (HSE). EH40/2005. Workplace exposure limits: Containing the list of workplace exposure limits for use with the Control of Substances Hazardous to Health Regulations 2002 (as amended). Sudbury (Suffolk), England: HSE Books; 2007.

14 Herr DW, Vo KT, Morgan DL, Sills RC. Carbon disulfide neurotoxicity in rats: VI. Electrophysiological examination of caudal tail nerve compound action potentials and nerve conduction velocity. Neurotoxicology 1998; 19: 129-146.

15 Lewis JG, Graham DG, Valentine WM, Morris RW, Morgan DL, Sills RC. Exposure of C57BL/6 mice to carbon disulfide induces early lesions of atherosclerosis and enhances arterial fatty deposits induced by a high fat diet. Toxicol Sci 1999; 49: 124-132

16 Lichtenstein N. Kohlendisulfid 7725. In: Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (IFA), editor.BIA-Arbeitsmappe 26th ed.III/01 . 2001. Berlin, FRG Erich Schmidt Verlag.

17 Ministry of Social Affairs and Employment (SZW). Wijziging arbeidsomstandighedenregeling. Staatscourant 2006; 252: 23-7.

18 Moser VC, Phillips PM, Morgan DL, Sills RC. Carbon disulfide neurotoxicity in rats: VII. Behavioral evaluations using a functional observational battery. Neurotoxicology 1998; 19: 147-157.

19 Nederlands Normalisatie-instituut. NEN 2946:1999 Ontw. nl Luchtkwaliteit - Werkplekatmosfeer - Bepaling van de concentratie aan koolstofdisulfide door middel van actieve monsterneming met een koolbuis, vloeistofdesorptie en gaschormatografie. 1999. Delft, the Netherlands: NEN Uitgeverij.

20 Patel KG, Yadav PC, Pandya CB, Saiyed HN. Male exposure mediated adverse reproductive outcomes in carbon disulphide exposed rayon workers. J Environ Biol 2004; 25(4): 413-418.

21 Sills RC, Harry GJ, Morgan DL, Valentine WM, Graham DG. Carbon disulfide neurotoxicity in rats: V. Morphology of axonal swelling in the muscular branch of the posterior tibial nerve and spinal cord. Neurotoxicology 1998; 19: 117-128.

22 Sills RC, Morgan DL, Harry GJ. Carbon disulfide neurotoxicity in rats: I. Introduction and study design. Neurotoxicology 1998; 19: 83-88.

23 Stevenz D. Carbon disulfide, method No. 2. In: H Parlan, H Greim, editors.The MAK-collection for occupational safety and health.Part III: Air monitoring methods, Vol.11 , 59-70. 2009. Weinheim, FRG: Wiley-VCH.

24 Swedish National Board of Occupational Safety and Health. Occupational exposure limit values and measures against air contaminants. http://www.av.se/dokument/inenglish/legislations/eng0517.pdf consulted: 8-12-2009.

25 US National Institute for Occupational Safety and Health (NIOSH). Carbon disulfide: method 1600, Issue 2, dated 15 August 1994. In: NIOSH manual of analytic methods. 1994. Internet: http://www.cdc.gov/niosh/docs/2003-154/pdfs/1600.pdf.

26 Vanhoorne MH, Ceulemans L, De Bacquer DA, De Smet FP. An epidemiological study of the effects of carbon disulphide on the peripheral nerves. Int J Occup Environ Health 1995; 1(4): 295-302.

27 Wronska-Nofer T. Disturbances of lipids metabolism in rats in dependance upon carbon disulphide concentration in the air. Med Lav 1973; 64: 8-12.

Health Council 1994/08WGD 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/m³/8.25 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	intraperitoneal	1890 mg/kg	LD_{50}	Beauchamp et al, 1983.
rat	intraperitoneal	563-1545 mg/kg*	LD_{50}	Green and Hunter, 1985.
guinea pig	intraperitoneal	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[a]
rat	63 ppm (197 mg/m³)	6 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.[3] 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)	4-6 h	No signs of toxicity were noted during exposure time. A marked decrease in brain noradrenaline levels (22% after 4 h, 36% after 6 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.[3] 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.[4] 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*
<u>behaviour</u>				
rat	640 ppm (2000 mg/m³)	8 h	spontaneous motor activity decreased by 50%.	Horvath, Frantik, 1979.[3] 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.	Laing 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 Fiddler and Shideler, 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.[7] 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 16-20 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/m³) 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/m³) 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/m³) 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/m³) 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.' 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 DOT. 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	Intraperitoneal	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	intraperitoneal	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	Intraperitoneal	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, 1976.[1] Mol. Pharmacol. 14, 1099.

Table 4b. Continued.

SPECIES	ROUTE	DOSE	EFFECT	REFERENCE*
rat (1- to 40- day-old)	Intraperitoneal	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	Intraperitoneal	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	Intraperitoneal	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, 481.
kidney				
rat	inhal-ation	0.74, 4.35 ppm (2.3, 13.6 mg/m³) 4 h	Urinary output decreased; protein increased.	Sakhkova, 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, 61.
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.	Carotti et al, 1984. Arch. Toxicol. 55, 265.

* see note Table 3.

Table 8. Neurotoxic (including behavioural) effects of CS_2 due to short-term exposure by inhalation in various animal species.

SPECIES	CONC	CONDITIONS	EFFECT	REFERENCE[a]
rat	194 ppm (605 mg/m³)	4 h/d, 5 d/w, 3 w	Significant weight loss (ca 8%), 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	286 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.[3] Br. J. Ind. Med. 36, 135.
rat	481 ppm (1500 mg/m³)	5 h/d, 6 d/w, 4 - 66 w	No deterioration 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.[4] 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.[5] 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.[3] Br. J. Ind. Med. 36, 146.
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.[1] Proc. Eur. Soc. Study Drug Toxic. 15, 80.

Table 6. Continued.

SPECIES	CONC	CONDITIONS	EFFECT	REFERENCE[a]
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 posterposure.	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.[7] 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.	Hattla, Linnoila, 1976.[2] Acta Neurol. Scand. (Suppl.) 57, 255 Hattla, Linnoila, 1976.[3] 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 sleepiness 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[3] Neuropathol. Appl.Neurobiol. 2, 209

Table 8. Continued.

SPECIES	CONC	CONDITIONS	EFFECT	REFERENCE*
rat	750 ppm (2340 mg/m³)	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 6 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/m³)	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.	Sokina et al, 1979.[1] Environ. Health Perspect. 30, 31.
rabbit	0.06 ppm (0.2 mg/m³)	24 h/d, 1½ mo	Aldolase activity on neuraminic acid was reduced in exposed animals. Altered EEG after 6 week exposure.	Sokina et al, 1976.[1] Environ. Health Perspect. 13, 37.
rabbit	750 ppm (2340 mg/m³)	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. Electrophysiological 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 18 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, 1976.[2] Scand. J. Work. Environ. Health 1, 178. Linnoila et al, 1975.[3] Proc. 7th Int. Congres Neuropathol. Budapest, 383.

Table 6. Continued.

SPECIES	CONC	CONDITIONS	EFFECT	REFERENCE*
monkey	258 ppm (500 mg/m³)	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), 61.

* 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. Immunol. 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, of 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.[3] 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.[f] Biochem. Pharmacol. 26, 1521.
rat	intrape-ritoneal	12 mg/kg	daily for > 60 d	Hepatic cells damaged, including necrosis. Regeneration of cells observed.	Woyke, 1969.[1] Patol. Pol. 20, 103.
rat	intramus-cular	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.[f] In: Adverse effects of environmental chemicals and psychotropic drugs vol II, ed. Horvath, Elsevier, Amsterdam 257.
rabbit	intramus-cular	6 mg/d	once/day, for 30 and 60 d	Fatty degeneration.	Nicosini 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.	Khlshova, Khlshov, 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, 1971.[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, 995, 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.	Gothlied et al, 1985. Neurotoxicology 6 ,(4), 89.
rat	160-256 ppm (500-800 mg/m³)	8 h/d, 5 d/w, 6 mo	Degenerative changes in a small number of ganglion cells.	Milivojevic, 1961. Acta Vet. (Belgrade) 31, 129.
	256-480 ppm (800-1500 mg/m³)	8 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)	6 h/d, 6 d/w, 8 mo	Increase of activity of β-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)	6 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 β-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[a]
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.[4] 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, 5 d/w, 4-55 w	No deterioration 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 change were detected after 1-2 months. The histological lesions noted were however generally mild.	Szendzikowski et al, 1973.[1] Int. Arch. Arbeitsmed. 31, 135.

Table 10a. Continued

SPECIES	CONC	CONDITIONS	EFFECT	REFERENCE*
rat	480 ppm (1500 mg/m³)	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 myopathy. 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.[f] Int. Arch. Arbeitsmed. 31, 123.
rat	480 ppm (1500 mg/m³)	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 β-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/m³)	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 (1800 mg/m³)	5 h/d, 5 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.[3] Br. J. Ind. Med. 36, 148.
rat	576 ppm (1800 mg/m³)	5 h/d, 5 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)	5 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.	Milhojevic, 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 16.	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 tjacts 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[a]
rat	750 ppm (2340 mg/m³)	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 axoplasmic 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.[1] Scand. J. Work Environ. Health 3, 36.
rat	750 ppm (2340 mg/m³)	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, Linnoila, 1976.[2] Neuropathol. Appl. Neurobiol. 2, 209.
rat	770 ppm (2400 mg/m³)	6 h/d, 5 d/w, 22 w	No changes in EEG.	Formanek et al, 1976.[3] 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/m³)	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. 53, 255.
rat	770-1150 ppm (2400-3600 mg/m³	6 h/d, 5 d/w, 3 and 5 mo	Electromyography demonstrated reduced conduction Copper levels were elevated in affected nerves.	Lukas et al, 1980.[1] Adv. Neurotoxicol. Proc. Int. Congr., 161.
rabbit	3 ppm (10 mg/m³)	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/m³)	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, Lasse, 1977.[1] 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.	Reban et al, 1986. Neurobehav. Toxicol. Teratol. 8, 543.

* see note Table 2.

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 and of exposure or 9 months later. Examination of hearts revealed slight changes in size and composition of aorta.	Sanotskii, Grodetskaya, 1980.[1] Gig. Tr. Prof. Zabol. 1980 (7) 3.
rat	16-64 ppm (50-200 mg/m³)	8 h/d, 6 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 activities, 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, 8 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.[1] 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 cholesterol 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[a]
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.[7] 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.[8] 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.[8] Br. J. Ind. Med. 37, 387.

Table 11a. Continued.

SPECIES	CONC	CONDITIONS	EFFECT	REFERENCE*
rabbit	141, 282 ppm (440, 880 mg/m³)	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/m³ but no significant increase at 880 mg/m³. 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.	Wasolowska, Gregorczyk 1978.[3] Med. Pr. 29, 471.
rabbit	300 ppm (940 mg/m³)	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 significantly 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.	Petrini et al, 1958.[7] 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	180-256 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.	Milivojevic, 1961. Acta Vet. (Belgrade) 31, 129.
	256-480 ppm (800-1500mg/m³)	6 h/d, 5 d/w, 11 mo	Dystrophic necrobiotic changes without reactions of mesenchymal elements.	
rat	425 ppm (1300 mg/m³)	5 h/d, 4 d/w, 12 w; 5 h/d, 4 d/w, 28 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-2H 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 concomitant depression of cyt. P450 content, accompanied by stimulation of microsomal lipid peroxidation.	Wronska-Nofar 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, 1961. Acta Vet. (Belgrade) 31, 129.
rabbit	200 ppm (625 mg/m³)	3 h/d, 6 mo	Vacuolation of hepatocytic cytoplasm.	Cucurullo et al, 1976.[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] Roczn. 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.	Sajnikova, Chirkova, 1974.[3] Gig. Tr. Prof. Zabol. 1974 (12), 34.
rat	313 ppm (980 mg/m³)	2.5 h/d, 6 d/w, 6 mo or 5 h/d, 3 d/w, 8 mo	Increased urinary excretion rate of N-methylnicotinamide.	Wronska-Nofer, Knobloch, 1972.[4] 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.[5] 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.[6] Pathologica 70, 419.
rabbit	250 ppm (780 mg/m³)	6 h/d, 5 d/w, 18 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.[7] Am. Ind. Hyg. Assoc. J. 20, 300.
Lung				
rat	0.32 ppm (1 mg/m³)	continuously, 6 mo	Signs of chronic bronchitis and isolated foci of lobular pneumonia (not stated in how many animals these effects occured, 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 cinerin (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 65, reaching a maximum at day 153.	Miastkiewicz 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.[3] Med. Pr. 29, 481.

Table 13. Continued

SPECIES	CONC	CONDITIONS	EFFECT	REFERENCE*
rabbit	300 ppm (940 mg/m³)	1/2 h/d, 4 mo	Slight effect on some haematological and blood biochemistry parameters noted (increased reticulocytes, increased β and γ globulins, decreased albumin) but these returned to normal after exposure ceased.	Wakatsuki, 1959.[4] Shikoku Igaku Zasshi 15, 671.
rabbit	250 ppm (780 mg/m³)	6 h/d, 5 d/w, 6 mo; then 500 ppm (1560 mg/m³) for 5 w; then 750 ppm (2340 mg/m³) 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/m³)	6 h/d, 5 d/w, 20 w	increase of xanthurenic acid; reduced excretion of 4-pyridoxic acid.	Spertingova 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, 183.
Idem with E. Coli WP2uvrA	negative	Donner et al., 1981. Mutat. Res. 91, 183.
Sex-linked recessive lethal assay in Drosophila	negative	Donner et al., 1981. Mutat. Res. 91, 183.
Idem	negative	Belles et al., 1980. NIOSH PB82-185075.
Host mediated assay Salmonella typhimurium strain TA98 employing male and female CD-1 mice	negative	Belles et al., 1980. NIOSH PB82-185075.
Unscheduled DNA synthesis in W1-38 human fibroblasts.	negative	Belles et al., 1980. NIOSH PB82-185075.
Spermhead abnormality in mice and rats	negative	Belles et al., 1980. NIOSH PB82-185075.
Chromosomal aberrations in rat bone marrow	negative	Belles et al., 1980. NIOSH PB82-185075.
rat dominant lethal test	negative	Belles et al., 1980. NIOSH PB82-185075.
Chromosome aberrations in rat bone marrow cells	positive	Vasilova, 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)	Saknikova, Chirkova, 1974.[f] 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.	Gondek, 1976.[f] 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.	Gondek, 1971.[f] Pol. Med. J. 10, 133

* see note Table 3

Table 18. 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 pituitary.	Acadzhanova, 1976.[3] Gig. Trud. Prof. Zabol. 1976 (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.	Belilles et al, 1969. 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)	6 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 hydroxylase, 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 (8.9 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 52.3% 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.[a] Khig. Zdrav. 21 257. Tabacova et al. 1978.[a] Toxicol. Lett. 2 129. Tabacova et al, 1979.[a] Arh. Hig. Rada 30 497.

Table 17. Continued.

SPECIES	ROUTE	CONC/DOSE	CONDITIONS	EFFECT	REFERENCE*
rat	inhalation	20, 40 ppm (62.5, 125 mg/m³)	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.	Belles et al, 1980. NIOSH PB82-185075
rat	inhalation	100, 200, 400, 800 ppm (310, 620, 1250, 2500 mg/m³)	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/m³)	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/m³)	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/m³)	6 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 (5-185 mg/m³); mostly <20 ppm (62 mg/m³)	12.1 ± 6.9 y	Controls: 239 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 amplitude 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.e. pain and paraesthesia of extremities; no data on controls and former exposure levels.	Martynova et al, 1976.[3] Gig. Sanit. 1976 (6), 26.
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, Graziano, 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, 1968. 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 16. Continued

NUMBER OF SUBJECTS	EXPOSURE LEVELS	EXPOSURE DURATION	EFFECT	REFERENCE*
21	removed from exposure at least 5 y before study <19 ppm (<60 mg/m³)			
51	just employed, not-exposed			
38	at time of study: 5-10 ppm (16-31 mg/m³), 1960-1970; 10-30 ppm (31-94 mg/m³), 1950-1960; 20-60 ppm (172-187 mg/m³), <1950; >60 ppm (187 mg/m³)		Paraesthesia/cramps noted in 74% of workers. Other symptoms: muscle pain and muscle weakness. Furthermore, encephalopathic symptoms, like headache (74%), sleep disturbances (74%), fatigue (58%), 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 8 of 50).	Seppalainen, Tolonen, 1974.[1,2] Work Environ. Health 11, 145.
30	at time of study 6 ppm (15 mg/m³), earlier up to 220 ppm (688 mg/m³).	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.[1] Med. Lav. 61, 102.

Table 16. Continued

NUMBER OF SUBJECTS	EXPOSURE LEVELS	EXPOSURE DURATION	EFFECT	REFERENCE*
84	up to 72-86 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 (58%), digestive troubles (56%), sleepness (55%), depression (36%), memory loss (35%), insomnia (34%), nightmares (26%).	Manu et al, 1972.[a] 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 (5-185 mg/m³; <62 mg/m³)	1-31 y (mean: 12 y)	Controls: 187, 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 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. Cardiovascular effects due to CS_2 in exposed workers.

NUMBER OF SUBJECTS	EXPOSURE LEVELS	EXPOSURE DURATION	EFFECT	REFERENCE
60	3-8 ppm (10-25 mg/m³), mean values registered during 12 y	3-12 y	Controls: 60, 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	1.5-11 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 Environ 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. Heal 54, 127.

Table 19. Continued.

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 (5-188 mg/m³), mostly <20 ppm (62 mg/m³)	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 18 ppm (50 mg/m³)	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/4.6 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. Envir. 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
82	<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 100-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 (62-186 mg/m³)	1-27 y (mean: 15 y)	Controls: 98 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 Arch. Klin. Exp. Ophthalmol. 1: 149.

Table 20. Continued

NUMBER OF SUBJECTS	EXPOSURE LEVELS	EXPOSURE DURATION	EFFECT	REFERENCE
124	>20 ppm (62 mg/m³)	average 10.6 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, 1978.* 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 controls), 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 (91-93 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: 69 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).	1-38 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; significalty 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.