SCOEL/SUM/82

March 2008

Recommendation from the Scientific Committee on Occupational Exposure Limits for Carbon Disulphide

8-hour TWA	:	5ppm (15 mg/m^3)
STEL (15 mins)	:	none
Further notation	:	Skin
BLV	:	1.5 mg TTCA/g creatinine

Substance

Carbon Disulphide CS_2 S=C=S

Synonyms : carbon bisulphide
carbon bisulfide
carbon sulphide
dithiocarbonic anhydride
sulphocarbonic anhydride

CAS N^o : 75-15-0

EINECS N^o : 2008436

EEC N^o : 006-003-3

EU classification F; 11
Repr.Cat.3; R62-63
T; R48/23
Xi; R36/38

Mwt : 76.14g/mol

Conversion factor (25^{o}C, 1 bar): 1mg/m^3 = 0.317ppm
1ppm = 3.16mg/m^3

Occurrence/uses:

Carbon disulphide (CS_2) is a dense, highly volatile and refractive clear liquid which yellows on exposure to air and light and usually has an offensive odour due to minor impurities such as mercaptans. CS_2 is highly flammable and its vapours can auto-ignite at temperatures above 102^{o}C. It is slightly soluble in water, miscible in many organic solvents and a good solvent for a wide range of organic substances, sulphur and phosphorus. CS_2 can be found in natural sources such as salt marshes (Aneja *et al*., 1982) and volcanic plume and ash (Beauchamp, 1983). Traces also occur in crude oil and coal tars. Until the 1950s, it was manufactured from charcoal and sulphur vapour by the retort process and the electro-thermal process, but it is now mostly manufactured by the catalytic reaction of sulphur vapour and methane (in natural gas) (DECOS, 1994). It is principally used in making viscose rayon fibre, cellulose film and other viscose products. It is also used in the production of carbon tetrachloride and for the manufacture of other chemicals, pesticides, dyes, drugs, and in rubber curing. Its use as a laboratory agent is becoming more restricted due to its high reactivity, flammability and toxicity (DECOS, 1994).

Health significance

There is extensive literature on the toxic effects of CS_2 in humans and animals, including a number of comprehensive reviews (BUA, 1993; DFG, 1999, 2003 and DECOS, 1994).

Toxicokinetic and Metabolism

CS_2 is rapidly taken up into the blood following all routes of exposure in both humans and experimental animals. In all animal species a steady-state concentration of free CS_2 in the blood is reached within 30-120 minutes. For acid-labile CS_2, which is probably covalently bound to proteins, a steady state might take several days to reach, depending on the exposure concentration or dose (BUA, 1993). In humans it has been calculated that up to 90% of inhaled CS_2 is retained in tissues (BUA, 1993). The metabolism of CS_2 is reasonably well documented and in general involves an oxidation by the mixed-function oxidase and then decomposition of the reactive intermediate. One of the known pathways via dithiocarbamates and trithiocarbamates leads to the production of urinary 2-thiothiazolidine and 2-thiothiazolidine-4-carboxylic acid (TTCA). This latter metabolite is used for biological monitoring because its levels correlate well with exposure (Drexler *et al*., 1995a). For many experimental animal species, some unaltered CS_2 is eliminated via the lungs following all routes of exposure. Metabolites are excreted via the urine and faeces.

Local effects

Following local application, severe effects of CS_2 on skin and mucous membranes, including blistering, ulceration and degeneration of sweat glands and local nerve endings, have been described in animal studies, but the potential for such effects in humans has not been investigated thoroughly. There are no available studies on the allergenic potential of CS_2.

Acute effects

Acute toxic effects of CS_2 in humans have been reported only rarely, except from accident situations. Effects such as headache, nausea (Spyker *et al*., 1993) and cerebral damage were noted in one individual exposed for about 20 minutes to a poorly characterised but potentially very high concentration (Kruse *et al*., 1982) Animal studies support the rather low acute toxicity of CS_2 (BUA, 1993).

Effects of repeated exposure

In relation to repeated exposure, many of the most serious toxic effects of CS_2, such as neurotoxicity, cardiotoxicity and reproductive toxicity, have been reported in investigations using experimental animals and also in humans in the occupational setting, and are well established. This toxicity is probably due to CS_2 reacting with biological macromolecules (DeCaprio *et al*., 1992). Such reactions can result in the formation of thiocarbamates, isocyanates, thiourea and urea, which can also then go on to participate further in a range of specific reactions with biological systems.

Neurological effects

The ability of CS_2 to produce chronic neurological damage to both the central (CNS) and peripheral nervous systems (PNS) is well established.

Chronic exposure of all species of experimental animals can lead to pronounced changes in the CNS with degeneration of neurons in various parts of the brain. Morphological changes observed in the spinal cord and the peripheral nervous system result from swelling of axons caused by an increase in neurofilaments (CS_2 can bind to neurofilaments resulting in the formation of cross links and subsequent axonal swelling (Graham *et al*., 1995)). This results in functional changes such as reduced velocity of stimuli transfer. Secondary myelin alterations also occur. Ataxia and paresis are frequently observed as marked manifestations of peripheral neuropathy (BUA, 1993).

Neurobehavioral changes have also been reported in a number of occupational studies (Herborn, 1992 and Cassitto *et al*., 1993), but there was uncertainty regarding the actual exposure concentrations involved. 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 12mg/m^3 (4ppm) over 40 years (8-hour day and 5-day week) (Chu *et al*., 1995 and Ruijten *et al.*, 1990). Effects on the autonomic nervous system were also reported (Ruijten *et al.*, 1993). However, a more recent occupational study (Reinhardt *et al.*, 1997) found no such neurotoxic effects at a median exposure of 12mg/m^3 (4ppm) 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) with current average air concentrations of 12.5mg/m^3 with peaks up to 120mg/m^3. In a follow-up study, cerebrovascular effects of CS_2 exposures were studied by brain magnetic resonance imaging to determine hyperintense spots (HIS, “silent cerebral infarctions”) in Japanese viscose rayon factory workers (Nishiwaki *et al.,* 2004). 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 4.9 ppm (15 mg/m^3) and 1.6 mg/g creatinine, respectively. In the follow up period, the CS_2 exposure level was 2.5 ppm (8 mg/m^3) in the lowest quartile and 8.1 ppm (26 mg/m^3) 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 HIS 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, 95% CL) was significantly increased in exposed (2.27 (1.37-3.76)), but not in the ex-exposed workers (1.33 (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 HIS cases 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**.** The conclusion of the authors is supported. Even if the formation of hyperintense spots may be partially attributable to CS_2 exposure, the absence of a dose-response relationship, the limitations of the study and the relative newness of application of MRI scans in the identification of toxic responses with the lack of criteria for the definition of adverse effects indicate that the results of this study are not suitable for setting an OEL.

An increased prevalence of colour discrimination disturbances in CS_2-exposed workers was observed at 10-15mg/m^3 (3-8 ppm) (Valic *et al.*, 2001) and at 14-20mg/m^3 (4-6 ppm) (Wang *et al.*, 2002); however the relevance of such findings is not clear due to methodological shortcomings.

Effects on hearing

In humans, adverse effects on hearing, such as a reduction in auditory threshold and loss of hearing have been reported for 8h TWA exposure to CS_2 above 30mg/m^3 (9.5ppm; Hirata *et al*., 1992a) whereas in rats, slight but detectable changes in auditory brainstem responses were recorded after exposure to CS_2 concentrations of 600mg/m^3 (190ppm) for 15 weeks (Hirata, 1992b). In workers exposed to CS_2 at concentrations of 10-35mg/m^3 (3-11 ppm) and high noise levels, hearing impairment was reported (Kowalska *et al.*, 2000).

Cardiovascular effects

In experimental animals, functional and morphological changes of the heart including necrosis of the myocardium, have been observed at relatively high dosages or exposure concentrations of CS_2 and have been attributed to both a direct effect of CS_2 on the heart and to increased incorporation of cholesterol and lipoproteins into heart vessels leading to arteriosclerosis (BUA, 1993).

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 8h TWA levels of approximately 30mg/m^3 (9.5ppm) for periods of up to 10 years caused electrocardiogram changes (Kamal *et al*., 1991 and Vanhoorne *et al*., 1992). It is probable that the cardiotoxic effects are associated with reported increases in cholesterol, serum triglycerides, low density lipoprotein and apolipoprotein A1 and B (Egeland *et al*., 1992; Stanosz *et al*., 1994 and Vanhoorne *et al*., 1992). However, such results have not been consistent; although Stanosz *et al.*, (1994) reported elevation of blood lipids at 15 to 20mg/m^3 (5-6ppm), 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 12mg/m^3 (4ppm) over a median duration of 66 months (Drexler *et al*., 1995b). In a large cohort of Dutch viscose workers (1,434 workers) exposed for 6 months or longer, the standard mortality ratio for death from cardiac infarction was 126 (statistically significant) (Swaen *et al*., 1994). The authors estimated an average 8h TWA exposure of 22mg/m^3 (7ppm), but the data appeared to show an inverse dose-response relationship (Swaen *et al*., 1994). 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 8h TWA concentration of 12mg/m^3 (4ppm) for a median duration of 66 months (Drexler *et al*., 1995b). However, in the same study a non-clinical haemodynamic increase (1-2mm) in the diameter of the left heart chamber was noted in exposed versus control workers. The role of CS_2 and the clinical significance of this finding are uncertain; examination of subjects during exercise did not reveal any apparent ill-health

consequences. 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 and it is altogether unclear what the contribution of CS_2 to these effects is (Vanhoorne *et al*., 1995).

In a study in which workers were exposed to current concentrations of 10-18mg/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).
Earlier suspicions that CS_2 had a negative inotropic effect on heart muscle were not confirmed (Korinth *et al.,* 2003).
Changes in resting or 24 hours ECG were demonstrated in workers with CS_2 exposure for more than 20 years (Bortkiewicz *et al.,* 2001) and increased cholesterol levels were reported in workers with current CS_2 exposures less than 30mg/m^3 (10 ppm) but cumulative exposure indices of more than 100mg/m^3 (30 ppm) (Kotseva, 2001). Workers with cumulative exposure indices of more than 150mg/m^3 (50 ppm) showed increased risk of coronary heart disease, ischaemic ECG and ischaemia (Kotseva *et al.,* 2001a). The same workers also demonstrated reduced arterial wall dispensability and increased heart rate (Braeckman *et al.,* 2001; Kotseva *et al.,* 2001b).
In women exposed "chronically" to CS_2 concentrations between 9.36 and 23.4mg/m^3 (3 and 8ppm), there were reported significant effects on the plasma lipid fraction and in the coagulation system (Stanosz *et al., 1*998). In a recent critical evaluation of studies on cardiovascular effects (Sulsky *et al.,* 2002), 37 investigations of sufficient quality were appraised and the authors 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 (>20ppm), the associations with coronary heart diseases or other clinical indications were inconsistent and often contradictory. The authors of this review have noted the difficulties and complexity (of deriving a clear no effect level for CVD or early markers of disease in these studies and have not attempted to derive one in their review.
In viscose fibre-production workers, sub-clinical effects on the retinal artery (microaneurysm) were reported (Omae *et al*., 1998) with current average air concentrations of 12.5mg/m^3 (4.1ppm) with peaks up to 120mg/m^3 (30ppm). A follow-up study on cardiovascular effects of CS_2 exposures (Takebayashi *et al.,* 2004) was performed. The exposed, ex-exposed 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, IV_{1-3}, V_{1-3} (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 significantly increased in the exposed group (2.0 (1.1-3.6)). Exposures were divided into quartiles. The odds ratio of the ischaemic findings was significantly increased in the highest quartile (4.2 (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. However, with more severe electrocardiographic signs for defining ischaemia both incidence and prevalence were 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 (2.3 (1.0-5.4)) among exposed workers, but not in the ex-exposed group (1.4 (0.3-4.9)). If the cases in the exposed and ex-exposed groups are combined and compared with the referent group in an univariate analysis,

it can be calculated that the CS_2 exposure accounts for 32% of the new onset ischaemic signs and 39% of the retinal micro- aneurysm cases in the combined group CS_2 group. Exposure data on CS_2 concentrations prior to 1992 was unavailable. The ECG changes were only evident using the Minnesota electrocardiographic codes I, IV_{1-3}, V_{1-3} (tested at rest and after step test). The value of exposure-related findings with the "Minnesota code" is disputed. When (generally accepted) "rigorous" ECG criteria were applied on the findings, e.g. ST depression $\geq$ 2 mm, no significant effects of CS_2 exposure were found any more. The ECG findings in this study using the "Minnesota code" are therefore not of clinical relevance. The incidence of retinal micro-aneurysm was increased with marginal significance in the high exposure group (8.7ppm) and has been reduced over time. In 1998 peak exposure was up to 30ppm and may be responsible for the effects observed. The clinical relevance of this marginal statistical significant effect seems to be low. The study indicates therefore no clinically relevant cardiovascular effects at mean exposure levels of 5ppm CS_2.

A recent study describes the effects on Chinese viscose rayon workers of CS_2 exposure at concentrations well below the ACGIH TLV of 31 mg/m^3 (10 ppm), but above the Chinese MAC of 10 mg/m^3 (3,3 ppm) (Tan *et al.*, 2004). This is an important study because although the design is cross-sectional, the reliability of the exposure assessment is good. In this case, as the main production process had remained unchanged an inference was made that the current exposure levels observed are representative of those from past exposure. 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 the MAC of 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 (4.6 ppm) (staple workers) and 20.05 mg/m^3 (6.7 ppm) (filament workers); the BEI was less than the ACGIH standard (5 mg/g creatinine) in the majority of cases. 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. This study also indicates no clinically relevant cardiovascular effects at mean exposure levels of up to 6.7ppm CS_2.

Genotoxicity and Carcinogenicity

CS_2 has been shown to be negative in a range of tests for genotoxicity (BUA, 1993). A number of studies have considered the carcinogenic potential of CS_2 (Nurminen & Hernberg, 1984, 1985; Wilcosky *et al.*, 1984 and Swaen *et al.*, 1991), but no effect has been shown. A study with strain A/J mice with 6 months exposure (6-hour day, 5-day week) at 936mg/m^3 (296ppm) did show an increase in lung adenomas in exposed animals compared to controls (Adkins *et al.*, 1986). However, the animal model used, the nature of the results and the study design are not considered appropriate for interpretation for the identification of carcinogenic potential for humans.

Reproductive Toxicity

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 8h TWA exposures of around 30mg/m^3 (10ppm; BUA, 1993). This has not been confirmed in other studies (Vanhoorne *et al.*, 1993 and 1994), although a reduction in workers' libido and

potency was noted at 30mg/m^3 (10ppm) and above (Vanhoorne *et al*., 1994). In female workers, inconsistent findings of menstrual disorders have been reported with 8h TWA exposures of 40-60mg/m^3 (13-20ppm) for 1-6 years (Cai & Bao, 1981) and 3-15mg/m^3 (1-5ppm) for 1->10 years (Zhou *et al*., 1988). In this latter study, no effect was found on other reproductive functions, or outcomes such as toxaemia, emesis, spontaneous abortion, stillbirth, premature and overdue delivery, or congenital malformation. Exposure was estimated by the use of fixed-point monitoring and time activity matrix, and thus will have some uncertainty in terms of true personal exposure. In addition, an increased incidence of abortion in female workers exposed to CS_2 over a wide range of concentrations has been reported (DFG, 1995). In rats, CS_2 can impair male fertility by affecting the sperm count and mating behaviour (NOAEL of >1000mg/m^3, 300 ppm) (BUA, 1993). In experimental animal studies there are suggestions that CS_2 is embryotoxic at doses that are not maternally toxic (25-150mg/m^3 (8-48ppm). Sensitivity varies between species. Teratogenic effects have only been observed in experimental animals at maternally toxic doses (≥150mg/m^3, 50 ppm), BUA, 1993).

Biological monitoring

CS_2 readily penetrates the skin and is accumulating in the body. Therefore, biological monitoring of CS_2 exposure is widely used and reliable methods are available. The method most frequently used is the determination of the metabolite 2-thiothiazolidine-4-carboxylic acid (TTCA) in urine. Recent studies have shown that a 8-h TWA inhalation exposure of 5 ppm (15 mg/m^3) of CS2 will correspond to a mean biological value of about 1.0 to 1.6 mg TTCA/g creatinine (see table 1). Higher values may be indicative of excessive inhalation and/or dermal exposure. The study by Shih *et al.* (2003) will not be taken into consideration due to higher TTCA-concentration in urine of a low number of workers compared to the other studies.

Table 1. Correlation between concentration of CS_2 in the air and the concentration of its metabolite 2-thiothiazolidine-4-carboxylic acid (TTCA) in urine

Exposed group	CS_2 in the air (ppm)	TTCA in urine (mg/g creatinine) post-shift	Reference
61	5	1.7	Unpublished study (UK) 2006
184 workers	4.8; 1.8 (GM; GSD)	1.5; 1.9 (GM; GSD)	Takebayashi et al., 2004
254 workers	5.0; 1.8 (GM; GSD)	1.6; 1.9 (GM; GSD)	
367 workers	[6.36; 0.42 (GM; GSD)]	1.07; 0.38 (GM; GSD) 0.08-1.56 (95% CI)	Tan et al., 2004
	[4.35; 0.35 (GM; GSD)]	1.18; 0.43 (GM; GSD) 0.06-2.13 (95% CI)	
325 workers	6.04 (mean) 0.03-91.08 (range)	1.14 (mean) 0.02-11.50 (range)	Korinth et al., 2003
5 workers (8-h shift)	6.3±0.64 (AM±SD)	3.24±0.63 (AM±SD)	Shih et al., 2003
7 workers (12-h shift)	11.3±1.47 (AM±SD)	5.73±2.79 (AM±SD)	
10 workers	10.1	3.0	Chang et al., 2002
279	5	2.085	Drexler *et al.*1995
{109}	5	{1.91}	Drexler *et al.*1995
{93}	5	{2.65}	Drexler et al., 1995
{37}	5	{2.71}	Drexler et al., 1995
{95}	5	{1.915}	Drexler et al., 1995
{16}	5	{1.37}	Drexler et al., 1995
51	5	2.16	Drexler et al., 1994
39	5	5.98	Krstev et al;,1993
20	5	2.34	Riihimäki et al,1992
29	5	1.10	Meuling et al., 1990
30	5	1.8	Campbell1 et al.,1985
15	5	2.2	Freudlspergel et al; 1982

Abbreviations: AM: arithmetic mean; GM: geometric mean, GSD: geometric standard deviation; SD: standard deviation

Recommendation

There is an extensive database on the health and toxicological effects of CS2 in humans and in experimental animasl. For experimental animals, a NOAEL for long-term exposure appears to be in the range 150 to 800mg/m^3 (48-254ppm; BUA, 1993). However, effects in humans are seen at much lower exposure concentrations, therefore the quantitative aspect of the experimental animal data is not suitable for establishing a reliable basis for an OEL.

Although there has been a long history of the known toxic effects of CS_2, particularly on the nervous system and the cardiovascular system, SCOEL noted in their deliberations that there has been considerable difficulty for other OEL-setting committees and reviews in establishing clear dose-response for these effects for a number of reasons:

1. Past exposures relevant to many of the chronic cardiovascular effects may have been at levels considerably higher than those currently prevailing. They may have been inadequately measured and based on static samples, and thus may have underestimated true exposure (Göen *et al*, 1995).

2. The often poorly reported co-exposure to hydrogen sulphide in the most important industry, the production of viscose rayon fibre, may complicate the interpretation of some study effects.

Thus, to evaluate the dose-response effects observed in earlier epidemiological studies on exposed workers, the cumulative effect of CS_2 and underestimation of exposure due to inadequate analysis (Göen *et al.*, 1995) have to be considered but, the degree of underestimation cannot be easily quantified. Thus, SCOEL have endeavoured to take these factors into account when arriving at a recommendation for a health-based IOELV.

The critical health effects in humans are neurotoxicity and cardiotoxicity. The CNS effects range from overt psychosis to subtle neurobehavioral changes, and it is likely that the threshold of such subtle neurological changes may be around or above 30mg/m^3 (10 ppm). Similarly, it appears that the NOAEL for the PNS effects is around 24mg/m^3 (8ppm). Taking into account a 40 year working life, a NOAEL of 12 mg/m^3 (4ppm) was estimated for neurotoxicity based on estimated past exposure (Ruijten *et al.*, 1990). The occurrence of hyperintense spots in T2 weighted brain images in workers exposed to 4.9ppm CS_2 (Nishiwaki *et al.*, 2004) cannot be used for OEL setting due to a lack of dose-response relation and due to limitations of the study.
Of particular importance is ischaemic heart disease, in regard to which 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) have analysed data from 15 studies in 11 countries and suggest a threshold for ischaemic heart disease of around 63mg/m^3 (20ppm). This must be set against other studies which have shown changes in blood lipids, cardiac infarction and neurotoxicity at around 20mg/m^3 (6ppm), whilst other studies have found no such effects at estimated median exposures of 12mg/m^3 (4ppm) while earlier concentrations in the 1980s were of around 60mg/m^3 (19ppm) (Ruijten *et al*., 1990; Drexler *et al*., 1995b and 1996; Reinhardt *et al.*, 1997). Minor cardiovascular effects of little clinical relevance have been reported in a follow-up study in workers exposed to 5ppm CS_2 (Takebayashi *et al.*, 2004). In a recent study with reliable exposure estimation, no cardiovascular effects were observed in workers exposed up to 20 mg CS_2/m^3 (6.7ppm) for about 10 years (Tan *et al.*, 2004).

Overall, taking the strength and weaknesses of the above studies into account, the threshold/NOAEL for the earliest non-clinical changes appear to be in the range of 10-30 mg/m^3 (3-10 ppm), with the more reliable human studies relating to the upper end of this range. SCOEL considered that, taking into account the extensive human database, using a point of departure at a presumed threshold of 30 mg/m^3(10ppm), and the serious nature of the effects, an uncertainty factor of 2 would be appropriate. This would lead to the recommendation of an 8-h TWA of 15mg/m^3 (5ppm).This exposure concentration, which is based on the most subtle neurological and cardiovascular effects, is considered to be protective against the other reported effects, including those on reproductive function.

The data are insufficient to set a short-term exposure limit.

In view of its ability to readily penetrate the skin, a skin notation is appropriate and a biological limit value is most reliable for monitoring internal exposure. Corresponding to an 8-h TWA of 5 ppm (15 mg/m^3) a mean biological value of 1.5 mg TTCA/g creatinine to be measured at the end of the shift is proposed.

At the levels recommended no measurement difficulties are foreseen.

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