Social Europe

Recommendation from the Scientific Committee on Occupational Exposure Limits for tetrachloroethylene (perchloroethylene)

SCOEL/SUM/133

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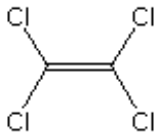
8 hour TWA	20 ppm [138 mg/m^3]
STEL (15 min)	40 ppm [275 mg/m^3]
BLV	0.4 mg tetrachloroethylene per liter blood [sampling time: prior to the last shift of a work-week] 3 ppm [0.435 mg/m^3] tetrachloroethylene in end-exhaled air [sampling time: prior to the last shift of a work-week]
SCOEL carcinogen group:	D (non-genotoxic carcinogen with threshold)
Notation:	'skin'

Substance identification

Tetrachloroethylene

Synonyms	tetrachloroethene, perchloroethylene, PCE, PER, 1,1,2,2,-tetrachloroethylene, ethylene tetrachloride, 1,1,2,2,-tetrachloroethene, perchloroethene
EINECS No.	204-825-9
CAS No.	127-18-4
Molecular formula	C_2Cl_4
Structural formula	
Molecular Weight	168.85
Conversion factors	At 25°C, 1 atm, 1 ppm= 6.89 mg/m^3; 1 mg/m^3 = 0.145 ppm
EU Classification	carcinogen cat. 3: R40 and N; R51-53

This document is based on documents published by the joint Nordic Expert Group and Dutch Expert Committee on Occupational Standards (NEG-DECOS, 2003), with amendments by DECOS (2003, 2004), the references based therein and other studies identified using the on-line PubMed database. The human health component of the EU RAR was made available to SCOEL and was

also incorporated. A draft document had been prepared by a contractor, which was subsequently revised by SCOEL.

Physico-chemical properties

Tetrachloroethylene is a colourless liquid. The melting point is between -22 and -22.7°C and the boiling point is 121.2°C. The specific gravity is 1.623 at 20°C. The vapour pressure is 1.9kPa at 20°C. The vapour density is 5.8 and it may therefore have a tendency to accumulate at ground level. Tetrachloroethylene is sparingly soluble in water (149 mg/L) and miscible with alcohol, ether, chloroform and benzene.

1. Occurrence/Use

Tetrachloroethylene is produced by oxychlorination, chlorination and/or dehydrochlorination reactions of hydrocarbons or chlorinated hydrocarbons in closed systems. The most common methods are chlorination of propylene and oxychlorination of 1,2-dichlorethane.

The main uses of tetrachloroethylene are as a dry cleaning agent and as a chemical intermediate. Other uses include metal cleaning and extraction processes. Minor uses include as a textile scouring solvent, fumigant, stain remover, paint remover and heat transfer media ingredient. The EU RAR indicates that about 164,000 tonnes were produced in the EU in 1994, although Eurochlor's estimate of sales of tetrachloroethylene was only about 100,000 tonnes during the early 1990s, falling to about 80,000 tonnes in 2004 (http://www.eurochlor.org/consumption). The reduction in consumption reflects improved use management, such as better emission control and increased use of solvent recycling systems and waste management. The quantity of tetrachloroethylene used to dry clean a given mass of gloves is now less than 10% of that used 20 years ago.

Methods of exposure monitoring and analysis

A number of methods are available for the sampling and analysis of tetrachloroethylene in workplace air. Samples may be collected on pumped sorbent tubes or diffusive samplers and analysis is normally by gas chromatography, followed by thermal desorption (UK Health And Safety Executive 1988, 1993, 1995, 2000; NIOSH 2003; OSHA, 1999). The limits of detection for four-hour samples have quoted as 98 and 705 µg x m^{-3} for pumped tubes and diffusive samplers respectively (OSHA Method 1001).

Biological monitoring methods include analysis of tetrachloroethylene in exhaled air or in body fluids, including blood and urine. NIOSH Method 3704 (NIOSH, 1998) has been established for the measurement of tetrachloroethylene in exhaled breath using a portable gas chromatograph.

2. Health Effects

2.1. Toxicokinetics

Studies in humans and animals have demonstrated that tetrachloroethylene is readily absorbed following exposure by inhalation, skin contact or ingestion (NEG-DECOS, 2003). In humans, about 90% of inhaled tetrachloroethylene is initially retained falling to about 50% after an 8 hour exposure. Uptake is increased by exercise. Uptake through the skin is usually much less than through the respiratory tract.

Tsuruta (1975) reports an in vivo transdermal flux of 0.24 mg/cm^2 per h for tetrachloroethylene in mice. ECETOC (1993) has suggested that a skin notation should be assigned when the amount of chemical absorbed upon exposure of both hands and lower arms (2000 cm^2) for one hour is expected to contribute more than 10% to the systemic dose, compared to the amount absorbed via inhalation exposure at the OEL during a full work day (assuming that 10 m^3 air is inhaled during an 8-h workday and that 50% is absorbed). Applying this calculation to tetrachloroethylene, the systemic dose from such skin exposure would be 70% of that from inhalation exposure at an OEL of 20 ppm.

By contrast, Kezic et al. (2000) and Riihimäki & Pfäffli (1978) estimated a dermal uptake of only 0.3% and 1%, respectively, of the respiratory uptake. Poet et al. (2002), in a comparative study, concluded that the perpeability cefficient (K_P) for humans is much lower than for rats. However, these figures do not consider the de-greasing properties of tetrachloroethylene, when brought as

a liquid to the skin. After de-greasing, the skin is rendered much more permeable for tetrachloroethylene (see Recommendation).

Tetrachloroethylene is only slowly metabolised and accumulates in fatty tissue as the unchanged compound. Rates of absorption by and removal from fatty tissue are slow. Regardless of the route of exposure, the main route of elimination of absorbed tetrachloroethylene is via exhalation as the unchanged compound (about 95%). In consequence, determination of (unmetabolised) tetrachloroethylene in blood, 16 h after end of shift (DFG 2005) or prior to the last shift of a workweek (ACGIH 2001) is a possibility of biological monitoring that has proved reliable in practice (see chapter 5.1.1).

The main metabolic pathway is thought to be epoxidation by cytochrome P450. There is clear animal and human evidence that this oxidative metabolism of tetrachloroethylene is a saturable process. The major urinary metabolite identified in humans is trichloroacetic acid, representing about 1-3% of the inhaled dose. Oxalic acid and ethylene glycol have been detected in the urine of exposed animals (IPCS, 1984). Several studies have detected trichloroethanol in the blood and urine of exposed humans and trichloroethanol has also been found in some, but not all, animal experiments. There is some uncertainty as to whether trichloroethanol is a metabolite of tetrachloroethylene or whether it is related to the presence of trichloroethylene as an impurity in the tetrachloroethylene (ATSDR, 1997).

To a much lesser extent direct conjugation of tetrachloroethylene with glutathione may also occur (NEG-DECOS, 2003). The presence in rat and mouse urine of small quantities of a mercapturate metabolite indicates the existence of a further metabolic pathway, involving hepatic conjugation of tetrachloroethylene with glutathione to give S-(1,2,2-trichlorovinyl)glutathione. The conjugate is then converted by the enzymes of mercapturic acid formation to S-(1,2,2-trichlorovinyl)cysteine and ultimately to N-acetyl-S-(1,2,2-trichlorovinyl)cysteine which is excreted in the urine. S-(1,2,2-trichlorovinyl)cysteine is also a substrate for renal β-lyase, producing the reactive intermediate dichlorothioketene. This intermediate is subsequently hydrolysed to yield dichloroacetic acid. One study indicates that the glutathione conjugation step of this pathway occurs in rats following exposure to relatively high concentrations (approx. 1000 ppm, 6900 mg/m^3) of tetrachloroethylene at which the P450 oxidation pathway tends to become saturated. However, more recent evidence using a more sensitive technique shows that this pathway occurs with linear kinetics. Dose-dependent increases in the levels of N^{ε}-(dichloroacetyl)-L-lysine (the protein adduct deriving from interaction with dichlorodithioketone) were found in the kidney, serum and liver of rats exposed from 10 ppm (69 mg/m^3) up to 400 ppm (2760 mg/m^3) tetrachloroethylene for 6-hours. A similar pathway in the case of trichloroethylene, which is metabolised to a much higher extent than tetrachloroethylene, has been linked with the occurrence of renal cancers (Brüning and Bolt 2000, Harth et al. 2005).

Evidence that the first step of the glutathione-dependent metabolic pathway also occurs in humans comes from the detection of N-acetyl-S-(1,2,2-trichlorovinyl)-L-cysteine in the urine of occupationally-exposed workers (8h-TWA of 50 ppm) and human volunteers (from 10 up to 40 ppm, 69 to 276 mg/m^3 for 6 hours). Dose-dependent increases in the urinary excretion of N-acetyl-S-(1,2,2-trichlorovinyl)-L-cysteine in human volunteers further indicate that in humans, like rats, the glutathione conjugation of tetrachloroethylene is not an high dose phenomenon, but occurs with linear kinetics. The data also suggest that there are very large quantitative differences in the activity of the glutathione conjugation step between sexes and species. Studies in vivo have shown that in rats the urinary excretion of the mercapturic acid, N-acetyl-S-(1,2,2-trichlorovinyl)-L-cysteine, is 2-3 fold greater in males compared to females and is 10-fold greater in rats compared to mice. Exposure of rats and human volunteers to 40 ppm (276 mg/m^3) tetrachloroethylene for 6 hours has shown that glutathione conjugation is also 10-fold more active in rats compared to humans. Overall, these data indicate that the first step of this

pathway with the production of N-acetyl-S-(1,2,2-trichlorovinyl)-L-cysteine is more active in male rats compared to females and is roughly an order of magnitude lower in mice and humans.

There are also in vitro studies that inform on the rates of glutathione conjugation of tetrachloroethylene in human, rat and mouse microsomal and cytosolic fractions of liver and kidney. The rate of S-(1,2,2-trichlorovinyl)glutathione formation was found to be 4-5 times greater in male rats than in female rats and in mice of either sex. The formation of S-(1,2,2-trichlorovinyl)glutathione in humans was below the limit of detection although glutathione S-transferase activity was confirmed. These in vitro data reinforce the picture obtained in vivo as they confirm that the first step of the glutathione pathway is more active in rats compared to mice, and that humans are likely to be even less active in this pathway than mice.

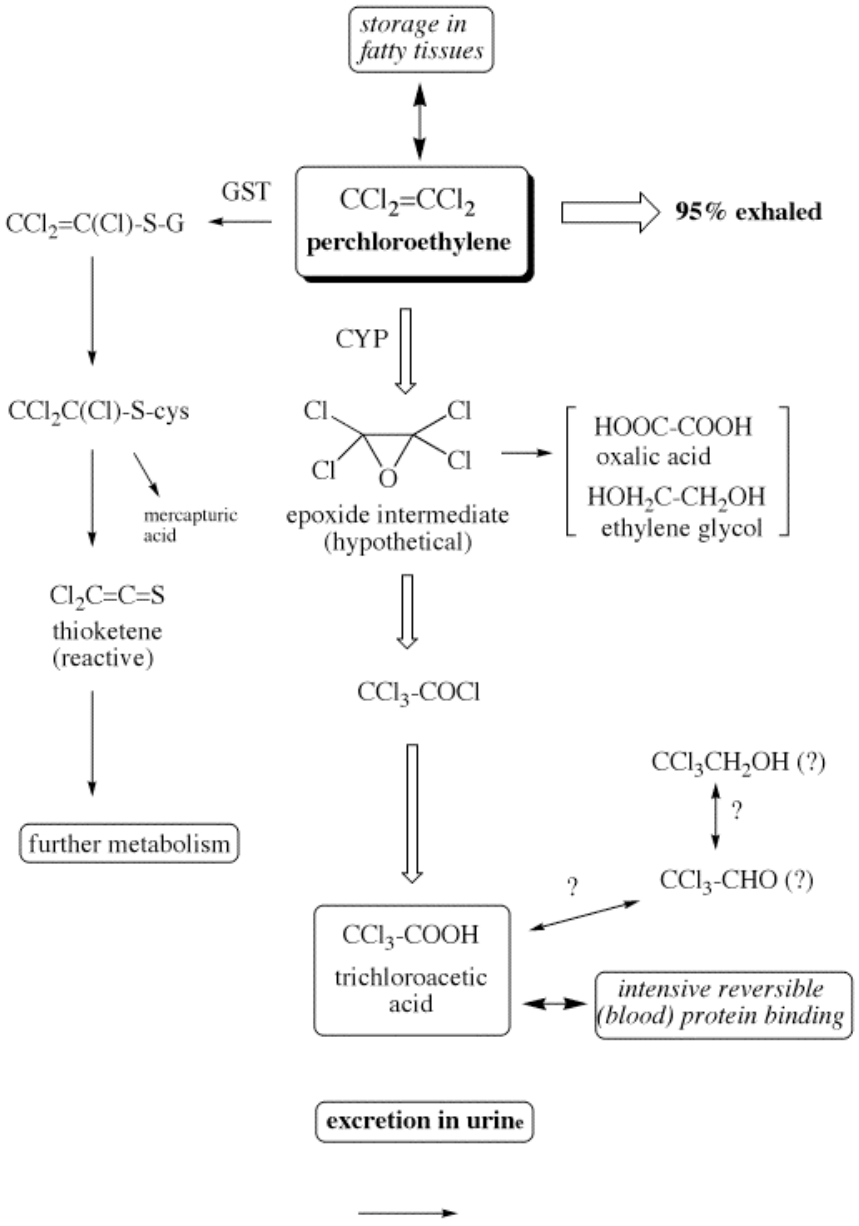


Figure 1: Disposition of tetrachloroethylene (perchloroethylene) in the mammalian organism
[CYP: cytochrome P-450; GST: glutathione-S-transferase(s); G: gltathionyl; cys: cysteinyl]; for known species differences, see text (chapter 5.1)

As noted above, the conjugate S-(1,2,2-trichlorovinyl)cysteine is also a substrate for renal β-lyase, producing the reactive intermediate, dichlorodithioketene. Its hydrolysis yields the urinary metabolite dichloroacetic acid. This urinary metabolite has been detected in vivo in rats, but not in humans indicating that there was no β-lyase activity or it was below the limit of detection in 6 volunteers exposed up to 40 ppm (276 mg/m^3) tetrachloroethylene for 6 hours. There is a lack of evidence concerning whether or not dichloroacetic acid is produced in mice. The finding of no apparent β-lyase activity in humans in vivo was confirmed in a second study in which no N^{ε}-(dichloroacetyl)-L-lysine (the protein adduct deriving from interaction with dichlorodithioketene) formation was detected in the serum of 6 volunteers exposed up to 40 ppm (276 mg/m^3) tetrachloroethylene for 6 hours. This is considered a reliable finding in that a very sensitive analytical technique was used (limit of detection of 0.01 pmol/mg protein). In this study exposure of rats to 40 ppm (276 mg/m^3) tetrachloroethylene resulted in the formation of 0.4 pmol of serum N^{ε}-(dichloroacetyl)-L-lysine/mg protein which indicates that the activity of this overall pathway is at least 40 fold (0.4 pmol/limit of detection) lower in humans compared to rats. The only evidence of some limited β-lyase activity in humans comes from in vitro data showing that in kidney cytosol fractions the activity of the β-lyase was 14-30 fold (around one order of magnitude) lower in humans and mice compared to rats and 2-fold greater in male rats compared to female rats. Overall, it can be concluded that there is likely to be little, if any, β-lyase activity in humans and that the conjugation/β-lyase pathway is likely to be at least 40-fold less active in humans (and probably mice) compared to rats (EU RAR, 2004).

The pathways discussed here are compiled in *Figure 1*.

Biological monitoring

As described above, most of tetrachloroethylene taken up by the body is not metabolised, but finally exhaled unchanged. There is storage of the lipophilic tetrachloroethylene in the adipose tissue compartments of the body. This has led to the recommendation to use tetrachloroethylene in blood as a parameter of biological monitoring, and a sampling time prior to a workshift, after preceding shifts (16h after the last preceding shift), has been recommended. Based on the toxikokinetics of tetrachloroethylene, an 8h TWA exposure of 20 ppm would result in a tetrachloroethylene blood concentration of 0.4 mg/l after 16 hours (ACGIH 2001, DFG 2005). Tetrachloroethylene blood concentrations of persons not occupationally exposed range below 1 ppb (ACGIH 2001).

Gobba et al (2003) reviewed the correlation between concentrations of tetrachloroethylene in alveolar air, blood and urine as biological indices of exposure in dry cleaning workers exposed to relatively low levels of tetrachloroethylene. Correlation coefficients between environmental concentrations and concentrations in blood, alveolar air and urine were 0.94, 0.81 and 0.67 respectively.

As a screening method, the determination of the urinary metabolite trichloroacetic acid (TCA) has been proposed. An 8h TWA exposure to 20 ppm tetrachloroethylene would result in a urinary excretion of 3 mg TCA/liter (ACGIH 2001). However, as other chlorinated solvents (trichloroethylene and, to a lesser extent, 1,1,1-trichloroethane) are converted to the same metabolite, this parameter is non-specific. Especially a co-exposure to trichloroethylene will dominate the TCA excretion, as the rate of metabolism to TCA of trichloroethylene is much higher than that of tetrachloroethylene.

The different strategies for biological monitoring (measuring tetrachloroethylene in blood and in end-exhaled air, and trichloroacetic acid excretion) were compared by McKernan et al. (2008) in a field study on 18 female employees of dry-cleaning shops. The authors concluded that,

under practical field conditions, tetrachloroethylene in blood was the preferred biological index to monitor exposure. Post-shift tetrachloroethylene concentrations in exhaled breath increased gradually throughout the workweek. The pre-shift blood levels of tetrachloroethylene were found in general accordance with the evaluations of ACGIH (2001) and DFG (2005). According to this field study, the expected pre-shift concentration of tetrachloroethylene in end-exhaled air, corresponding to a TWA exposure of 20 ppm, is 3.17 ppm.

2.2. Acute toxicity

2.2.1. Human data

Cases of accidental exposure to tetrachloroethylene were reviewed by NEG-DECOS (2003). For instance, firemen exposed to tetrachloroethylene fume for three minutes became light-headed and lost co-ordination. Changes in liver function persisted for two months following the incident. Other case reports have also described reversible liver changes of varying severity, kidney effects, depression of the central nervous system and loss of consciousness. In one case where a dry cleaning worker was found unconscious, breath concentrations of tetrachloroethylene were over 4,000 mg/m^3 a few hours after exposure. There is little other data to allow linkage of acute effects to levels of exposure in industrial accidents.

Two volunteer studies are cited in the EU RAR concerning the effects of single exposure. The main effects observed were irritation of the eyes and respiratory system, loss of co-ordination and other central nervous system(CNS) effects (Table 1). In the first study (Rowe et al, 1952), groups of 2-6 men were exposed to mean concentrations of tetrachloroethylene of 1060 ppm (7314 mg/m^3) for a period of 1 or 2 minutes, 600 ppm (4140 mg/m^3) for 10 minutes, 280 or 216 ppm (1932 or 1490 mg/m^3) for up to 2 hours or 106 ppm (731 mg/m^3) for 1 hour. Irritation was noted at 216 ppm and above (see section 4.1.2.3). Dizziness occurred in at least some of the subjects at 216 ppm and above, along with drowsiness (216 ppm), a sensation of congestion of the frontal sinuses (216 and 280 ppm), impaired motor co-ordination and tightness about the mouth (280 and 600 ppm) and some loss of inhibitions (600 ppm). No significant effects were apparent at 106 ppm. In nearly all cases recovery was complete within 1 hour. Although there were no controls, the dose-response trend seen lends credence to the findings as reliable representations of tetrachloroethylene effects [section 4.1.2.3 of EU RAR (2007)].

In the second volunteer study (Stewart et al, 1970), 16 men and 1 woman were exposed to 100 ppm (690 mg/m^3) tetrachloroethylene for 7 hours. When they were asked, subjective effects including headache, sleepiness, difficulty with speech and light-headedness were each affirmed in 25-40% of the subjects. There were also complaints of irritation (see section 4.1.2.3). The only objective response was a decreased balancing ability (modified Romberg test) obtained in 4 subjects, and 3 of these gave a normal test when it was repeated. Although there were no control exposures in this study, only one concentration was tested and the reported symptoms are rather unspecific, an incidence of 40% for subjective CNS effects is too high to be considered a chance finding. Furthermore, these effects observed at 100 ppm (690 mg/m^3) for a 7-hour exposure are consistent with those reported at 216 ppm (1490 mg/m^3) for a 2-hour exposure in the other volunteer study available [section 4.1.2.3 of EU RAR (2007)].

Table 1: Human volunteer studies reviewed by NEG-DECOS (2003) and/or ATSDR (1997)

Subjects	Exposure Regime	Effects	Study
4 males	3,253 mg/m^3 (472 ppm) for 130 minutes	Eye irritation, secretion from mucous membranes, sensory changes, slight feeling of elation	Carpenter (1937)
	6,277 mg/m^3 (911 ppm) for 95 minutes	Lassitude, mental fogginess, exhilaration	
	Increase to 9991 mg/m^3 (9991 mg/m^3) after 95 minutes	Inebriation	
	Increase to 13367 mg/m^3 (1,940 ppm)	"ringing in the ears", subjects left the exposure room after 7.5 minutes	
4 subjects	6,408-8,165 mg/m^3 (930-1,185 ppm) 1-2 minutes	Marked irritation of the eyes and the upper respiratory tract, considerable dizziness in one person after 2 minutes exposure, complete recovery	Rowe *et al* (1952)
2 males	3,535-4,745 mg/m^3 (513-690 ppm) 10 minutes	Irritation of eyes and nose, dizziness, tightness and numbness about the mouth, some loss of inhibition, difficulty in co-ordination, complete recovery within an hour	
4 males	1,419-2,453 mg/m^3 (206-356 ppm) for up to 2 hours	Lightheadedness, burning sensation in the eyes, congestion of the frontal sinuses, thickening of the tongue, irresponsibility, nausea, impaired motor co-ordination. One subject felt unwell for several hours, others recovered within one hour	
4 subjects	1,419-1,619 mg/m^3 (206-235 ppm), 45-120 minutes	Eye irritation and congestion of nasal sinuses with discharge within 20-30 minutes, dizziness (inebriation), sleepiness	
6 subjects	572-896 mg/m^3 (83-130 ppm), 1 hour	Eye irritation at times of peak concentration	
6 males	517-551 mg/m^3 (75-80 ppm), 1-4 minutes	Very slight eye irritation that ceased after a few minutes of exposure	Stewart *et al* (1961)
6 males	689-827 mg/m^3 (100-120ppm), 4-6 minutes	Slight soft palate irritation and dryness	
6 males	1378 mg/m^3 (200 ppm), 6-30 minutes	Romberg test normal	
6 males	1,447-1,681 mg/m^3 (210-244 ppm), 30+ minutes	Slight light headedness, difficulty in maintaining a normal Romberg test	
16 subjects	690 mg/m^3 (100 ppm), 7 hours,	Most subjects reported one or more of: mild eye, nose or throat	Stewart *et al*

	single exposure (11 volunteers), exposure on 5 successive days (5 volunteers)	irritation, frontal headache, flushing, sleepiness, difficulty in sleeping, Effects diminished on reported exposure. 3/16 subjects showed an abnormal Romberg test within 3 hours of exposure	(1970)
2 to 4 males or females	0, 138, 689 and 1,034 mg/m^3 (0, 20, 100 or 150 ppm) for 1, 3 or 7.5 hours/day, 5 days	EEG scanning suggested altered patterns indicative of cortical depression, effects on co-ordination in 100 and 150 ppm groups, no effects on other neurological or physiological parameters, some unspecified subjective symptoms that disappeared with continued exposure. NOEL identified as 20 ppm (138 mg/m^3).	Hake and Stewart (1977)
6 males and 6 females	0, 172 or 690 mg/m^3 (0, 25 or 100 ppm) for 5.5 hours/day for 11 weeks	No effects on blood count; no effects on urine analysis; no evidence that tetrachloroethylene changed the response to diazepam or ethanol	Stewart *et al* (1977)
10 male and 10 female	0, 138, 689 and 1,034 mg/m^3 (0, 20, 100 or 150 ppm) tetrachlorethylene vapour for 1 hour, 3 hours or 7.5 hours/day, 5 days/week for 1 month	No effects on urine composition or liver enzyme activity; altered EEG pattern similar to that seen during drowsiness, light sleep or the first stages of anaesthesia; no effects on pulmonary function	Stewart *et al* (1981)
Groups of 11 males	68.9 or 345 mg/m^3 (10 or 50 ppm) for 4 hours/day for 4 days	Increased visual evoked potential peak latencies during exposure at 50 ppm, no effects at 10 ppm	Altmann *et al* (1990)

2.2.2. Animal data

A large number of acute inhalation experiments have been performed. Reported LC_{50} values (*i.e.* concentration lethal to 50% of experimental animals) in mice range from 2,975 ppm [20,500 mg/m^3] for a 6 hour exposure period to 5,800 ppm [40,000 mg/m^3] for a 2 hour exposure. In rats, the reported 6-hour LC_{50} is 4100 ppm [28,250 mg/m^3] (NEG-DECOS, 2003). Four-hour LC_{50} values of 36,600 and 27,600 mg/m^3 (5,300 ppm and 4,000 ppm) have been reported for mice and rats respectively (ACGIH, 2005).

The main reported effects of acute exposure to tetrachloroethylene are neurotoxicity. In 4-hour experiments in rats, the NOEL for reaction to a light stimulus was 67 ppm [462 mg/m^3]. In mice, 4 hours exposure to 713 [4,900 mg/m^3] caused a 50% reduction in mobility in a swimming test. Exposure to 90 ppm [620 mg/m^3] for 1 hour, caused a dose-related increase in activity at the start of exposure (NEG-DECOS, 2003). Other effects include liver toxicity and effects on immune function (NEG-DECOS, 2003). Effects on liver enzyme activity were reported following 1 hour exposure to 3450 mg/m^3 (500 ppm) and degeneration of the liver has been reported in mice exposed to 2760 mg/m^3 (400 ppm) for 4 hours. Exposure to 172 and 345 mg/m^3 (25 or 50 ppm) for 3 hours significantly increased the mortality of mice following exposure to Streptococcal pneumonia and reduced pulmonary bactericidal activity. Effects on the kidney have been reported in mice exposed for 6 hours to 2975 ppm [20,500 mg/m^3] and cardiac arrhythmias have been reported in rabbits exposed for 1 hour to 5196 ppm [35,800 mg/m^3] (NEG-DECOS, 2003).

NEG-DECOS (2003) provide a comprehensive review of the acute toxicity of tetrachloroethylene, including toxicity following other routes of administration.

2.3. Irritation

In human volunteer experiments, exposure to 1,490 mg/m^3 (216 ppm) for 45 minutes to 2 hours caused respiratory irritation (Rowe *et al*, 1952) and respiratory irritation has been reported in workers exposed to concentrations of 1,600 to 2,656 mg/m^3 (232 to 385 ppm) during a degreasing operation. Dry cleaning workers exposed to 138 mg/m^3 (20 ppm; 8 hour average) complained of irritation (Cai *et al*, 1991).

In animals, dogs exposed for 10 minutes to 68,900 mg/m^3 (10,000 ppm) showed upper respiratory irritation (Reinhardt *et al*, 1973) but no effects were observed at 34,450 mg/m^3 (5,000 ppm). Mice exposed to 2,069 mg/m^3 (300 ppm) for 6 hours/day for 5 days showed epithelial degeneration of the olfactory mucosa (Aoki et al, 1994). Such epithelial lesions were more severe in the olfactory mucosa and appeared earlier than in the respiratory mucosa.

Tetrachloroethylene is a skin irritant in humans, causing reddening and blistering. Symptoms may persist for several months following severe skin contact.

2.4. Sensitisation

Tetrachloroethylene has not been widely reported to be a sensitiser. As a respiratory irritant, tetrachloroethylene would be expected to exacerbate pre-existing asthma and high levels of exposure might give rise to Reactive Airways Dysfunction Syndrome (RADS). One case reported describes tetrachloroethylene induced asthma following high levels of exposure in a drying cleaning establishment (Palacek, 1970). NEG-DECOS describe two case reports of tetrachloroethylene skin sensitisation in humans.

2.5. Repeated dose toxicity

2.5.1 Human data

Case reports were reviewed by NEG-DECOS (2003) indicate that exposure to high levels of tetrachloroethylene (more than 200 ppm; 1,380 mg/m^3) is associated with neurotoxicity and liver damage. Reported effects include fatigue, inebriation, dizziness, headache, nausea, vomiting, lack of appetite, sleeplessness, irritability, irritation of the eyes and impaired liver function.

Neurological effects

NEG-DECOS (2003) and the EU RAR reviewed a number of studies on neurotoxic effects among exposed workers (relevant data in Table 2).

A behavioural study of 65 tetrachloroethylene-exposed dry-cleaners was carried out to follow up findings obtained in 4 patients referred for investigation of possible "solvent encephalopathy" (Echeverria *et al*, 1995). For these patients, no tetrachloroethylene exposure levels were available, although tetrachloroethylene was considered by the authors to be the major occupational exposure of concern for three of them. For the fourth, exposure was at home after tetrachloroethylene was apparently applied in error to interior woodwork. All four underwent detailed interviews and extensive batteries of neuropsychological tests. Long-term deficits in visuospatial function and memory, and disturbances in mood, were clinically identified. However, considering the cases in isolation, any attempt to relate these effects to previous exposure to tetrachloroethylene must be regarded with caution as exposure to other potential neurotoxicants cannot be excluded.

In the subsequent behavioural study, the dry-cleaners were categorised into low (24 counter clerks), moderate (18 pressers) and high (23 operators) cumulative exposure groups. The mean 15-minute personal breathing zone tetrachloroethylene concentrations for these groups were respectively 11.2, 23.2 and 40.8 ppm (77.3, 160 and 282 mg/m^3) for the 17 dry-cleaning shops using the wet transfer process. The mean periods in the current job for the 3 groups were respectively 2.1, 3.9 and 14.6 years.

Relatively small but statistically significantly lower mean scores were found in tests for visual reproduction (14% lower), the number correct (7%) and the response time (10%) for pattern memory and the number correct for pattern recognition (4%) in the high tetrachloroethylene group compared with the low tetrachloroethylene group after adjustment for other factors considered to affect performance in these behavioural tests (age, education, vocabulary and alcohol consumption). No statistically significant differences were detected for response time for pattern recognition, nor for the digit span, symbol digit matching and trailmaking tests. It has been suggested by the study authors that this pattern of results indicates a potential effect of tetrachloroethylene exposure on visually mediated functions. There was no association between tetrachloroethylene exposure and the profile of mood states, such as tension, depression, anger, fatigue and confusion. The only symptom that apparently increased with tetrachloroethylene exposure was dizziness.

There are a number of deficiencies associated with this study, including a low participation rate (only 23 out of the 125 dry-cleaning shops approached), failure in taking into account prior neurotoxicant exposures and the lack of an unexposed control

group. In view of this and considering the relatively low magnitude of the changes observed in some of the administered tests, the toxicological significance of the decrements observed is difficult to assess.

An Italian study examined the neurobehavioural effects of occupational exposure to tetrachloroethylene in 60 female dry-cleaning workers (with an average of 10 years service) by comparing them with 30 age-, vocabulary test score- and sex-matched controls recruited from an industrial cleaning plant where solvents were not in use (Ferroni *et al*, 1992). Selection criteria included: (i) absence of metabolic diseases; (ii) absence of neuropsychiatric disorders; (iii) alcohol intake of less than 80 ml ethanol a day. Tetrachloroethylene airborne concentration measured through static sampling during four-hour random periods varied from 1 to 67 ppm, 6.9 to 462 mg/m^3 (median 15 ppm, 104 mg/m^3). A set of five neurobehavioural tests (finger tapping with both dominant and non-dominant hands, simple reaction times, digit symbol, and shape comparison in two different versions constructed to test vigilance and the response to moderate stress, respectively) from a computer-based performance evaluation system was administered. In addition, blood samples were taken just before performance evaluation to measure serum prolactin and tetrachloroethylene levels. These measurements were performed to test the hypothesis that long-term exposure to tetrachloroethylene may impair the dopaminergic control of prolactin secretion and negatively affect neurobehavioural performance.

Although the simple reaction times were statistically significantly increased in all tests in dry-cleaners compared with the matched controls, significant correlations between performance and either duration of exposure or air and blood concentrations of tetrachloroethylene were not found. Furthermore, at present, there are no clear criteria to establish what the normal ranges for neurobehavioural perfomance are. In the tetrachloroethylene-exposed females, who were in the proliferative phase of the menstrual cycle (n=41), there were statistically significantly higher basal levels of serum prolactin (12.1±6.7μg/l) as compared to their matched controls (n=23) (7.4±3.1μg/l). However, again, no significant correlations between the increased prolactin levels and the exposure variables were found, and no normal reference ranges for this hormone level were provided. Therefore, overall, there was no clear evidence for an effect of repeated exposure to tetrachloroethylene (up to 67 ppm, 462 mg/m^3) on prolactin secretion and on neurobehavioural performance in this study.

A German study evaluated 101 employees of dry-cleaning shops, including ironers and touch-up workers as well as actual cleaners, all of whom were employed for 'several years' and a control group of 84 sales staff from department stores and hotel receptionists (Seeber, 1989). Of the 101 dry-cleaning shop employees, 57 were assigned to a low tetrachloroethylene exposure group (shift TWA = 12 ppm, 83 mg/m^3) and 44 to a high exposure group (shift TWA = 54 ppm, 373 mg/m^3). Tetrachlororethylene exposure was determined by room air sampling and individual passive sampling using badge dosimetry. A neurological symptoms questionnaire and a series of psychological tests were carried out. Regression analysis was used to control for the confounding factors of sex, age and intelligence between the control and exposed groups. Analysis also indicated that alcohol consumption did not influence the results obtained. The test battery included perceptual speed, finger tapping, aiming, digit span memory, digit symbol, choice reaction time, cancellation task (measuring attention), logical thinking, Mira and Santa Ana tests.

The means of all tests in all groups did not extend into the abnormal reference range. Statistically significant, small decreases in performance in perceptual speed, choice reaction time, digit span memory, cancellation task and digit symbol tests were seen in exposed groups relative to the controls. However, since these decreases were still within the normal reference ranges, they are not considered of toxicological significance. No significant differences between scores in the low and high tetrachloroethylene groups were seen. The frequency of neurological symptoms was significantly higher than in controls in the low tetrachloroethylene exposure group but not in the high exposure group. Overall, given the lack of any exposure-response relationship, the study does not establish a clear association between tetrachloroethylene exposure (up to 54 ppm, 373 mg/m^3) and neurological symptoms. Also no significant neurobehavioural deficits were detected.

An earlier American study looked at 9 male and 9 female dry-cleaners (mean 8-hour TWA for tetrachloroethylene of 18 and 32 ppm (124 and 221 mg/m^3) in females and males respectively, range = 1-37 ppm (6.9 – 255 mg/m^3), peak = 215 ppm (1484 mg/m^3) determined by analysing breath samples and through static sampling), and compared them with 9 female laundry workers as controls (Tuttle *et al*, 1977). The mean tetrachloroethylene exposure period was 6.7 years for females and 9.8 years for the men, 4 of whom had previous exposure to petroleum solvents for a mean period of 16.5 years. Other individuals had been exposed to carbon tetrachloride for 5 years and to carbon disulphide for 10 years. No differences were found for light-headedness and headache, but the dry-cleaners seemed to have a greater tendency for drowsiness during their shifts. Neurological examinations revealed a statistically significant decrease in the overall neurological rating (total of the scores for symptoms, for the neurological assessment by the neurologist and for the electro-diagnostic evaluation obtained from ratings by the electromyographer) for the tetrachloroethylene-exposed workers compared with laundry workers, but multiple regression analysis indicated that the neurological deficits correlated with previous exposure to hydrocarbon solvents, not with tetrachloroethylene.

A large battery of behavioural tests (feeling tone checklist, Wechsler digit span, Wechsler digit symbol, Neisser letter search, critical Flicker fusion, Santa Ana dexterity test, choice reaction time and simple reaction time) was administered before and after a shift over a 5-day period. The scores obtained on different days were averaged, thus ignoring day effects. Different comparisons were performed. When the pre-shift and post-shift averaged scores obtained in the dry-cleaners were compared to those of the controls, small, statistically significant decrements in performance of the digit scan, critical flicker and critical fusion tests, but significant improvements in performance of the Santa Ana dexterity, digit symbol, reaction time, Neisser letter search and feeling tone tests were found in dry-cleaners compared to controls. In view of the pattern of results obtained, with decrements in some tests and improvements in others, the deficits reported in the performance of the digit span, critical flicker and critical fusion tests are likely to be of no toxicological significance. When the pre-shift and post-shift scores obtained for the different tests in dry-cleaners were compared, significant improvements in performance of the Santa Ana, Neisser letter search and digit symbol tests were noted post-shift compared to the pre-shift performance, i.e. dry-cleaners performed better following work than before they started their workshift. Only the post-shift score for the critical flicker frequency was statistically significantly lower than the correspondent pre-shift score, indicating a decrement in performance after work. However, multiple regression analysis showed that this decrement was an acute effect due to fatigue rather than to short-term exposure to tetrachloroethylene. Overall, no clear evidence for an adverse

effect of repeated exposure to tetrachloroethylene (up to 37 ppm, 255 mg/m^3) on neurobehavioural performance and neurological health was found in this study.

A comprehensive study of the behavioural and neurological effects of exposure to tetrachloroethylene (TWAs 25 and 100 ppm, 173 and 690 mg/m^3 for 5.5 hours), on its own and in combination with low doses of diazepam or alcohol, was carried out in 6 male and 6 female healthy volunteers (Stewart *et al*, 1977). The exposures were performed during 10 weeks of an 11-week period, with the subjects generally being exposed to tetrachloroethylene on 3 days and to air on 2 days of each week. Only one volunteer was present throughout the whole study, receiving 20, 10 and 17 exposures to respectively 0, 25 and 100 ppm tetrachloroethylene. During the exposure sessions the subjects completed a battery of neurological and behavioural tests, comprising eye-hand co-ordination, rotary pursuit, Flanagan co-ordination, saccade eye velocity, dual attention tasks and electroencephalogram. The only detrimental effect observed with tetrachloroethylene alone was a small statistically significant reduction in the scores of the Flanagan co-ordination test obtained at 100 ppm on a limited number of days. However, this effect was considered inconsistent by the authors. Overall, the results of this study provide no evidence for any toxicologically significant effect due to single periods of tetrachloroethylene exposure at up to 100 ppm (690 mg/m^3).

In further tests carried out by the same group, 10 healthy male volunteers were exposed to a sequence of tetrachloroethylene concentrations (TWAs of 0, 100, 20, 100 and 150 ppm, 0, 690, 138, 690 and 1035 mg/m^3) in a controlled environment chamber. Exposure at each concentration involved 5 sessions (each lasting 1 hour for subgroup I of 4 volunteers, 3 hours for subgroup II of 3 volunteers or 7.5 hours for group III of 3 volunteers) on 5 consecutive days of the week (Monday to Friday) for a total of 5 weeks (Stewart *et al*, 1981). Eight healthy females were also treated according to the same exposure schedule but at concentrations of tetrachloroethylene of 0 and 100 ppm (0 and 690 mg/m^3) only, and hence for a total of two weeks only. There were no significant differences between the groups regarding the subjective symptoms looked for, which included headache, nausea, dizziness, chest pain and irritation of the eyes, nose and throat. No statistically significant effects were found in cardiac or pulmonary functions. Objective tests of alertness, time estimation, reaction time, co-ordination and balance were carried out, and electroencephalograms and visually evoked potentials were recorded.

Preliminary signs were detected in electroencephalograms from 3/4 males and 4/5 females during exposure at 100 ppm for 7.5 hours, and a statistically significant impairment in co-ordination was obtained in the males exposed at 150 ppm for 7.5 hours. This group of males had been exposed to 150 ppm for 5 consecutive days and the co-ordination test had been performed at the end of the exposure period (7.5 hours) on days 1, 3 and 5. The scores obtained on the different days were combined and compared with those obtained in the same manner by the same male subjects exposed to 0 ppm tetrachloroethylene for 5 consecutive days. Since the scores obtained on different days were combined and no information is available in the report regarding the individual scores on days 1, 3 and 5, it is not possible to assess whether or not this co-ordination impairment was significant starting from day 1 or if it became significant or worse towards the last day of exposure. In the absence of this information, it cannot be established whether this finding is likely to be an acute effect arising from single periods of exposure or the consequence of repeated exposure. Some other statistically significant effects were not considered to be toxicologically important, due to their random occurrence. Overall, no conclusions for an adverse effect of repeated exposure

to tetrachloroethylene (up to 150 ppm, 1035 mg/m^3) on neurobehavioural performance can be drawn from this study.

In another volunteer study, two groups of 12 and 10 healthy men were exposed in an inhalation chamber to respectively 10 ppm or 50 ppm (69 or 345 mg/m^3) tetrachloroethylene, for 4 hours/day on 4 consecutive days (Altmann *et al*, 1990). After the first 2 hours of exposure on each of the 4 days, measurements of visually-evoked potentials (VEP) and brainstem auditory-evoked potentials (BAEP) were made. Control readings were taken the day before the first exposure session (day 0) and for a smaller group of volunteers on day 6 after completing the exposure sessions. In a sub-sample of 5 subjects visual contrast sensitivity was also assessed at the end of each exposure day.

At 50 ppm, 3 of the 6 VEP peak latencies monitored increased significantly compared to those recorded on the control day. The average latency increase was highest on the last exposure day. In one subject two of these latency values returned to normal on control day 6, while the N150 latency remained elevated after 24 hours from the end of the exposure. At 10 ppm, the VEP latency values did not differ from those recorded on the control day, although some insignificant decreases were observed on all exposure days. Statistically significantly higher VEP latency values were found in the 50 ppm group compared to the 10 ppm group on the third and fourth exposure day. In contrast, neither the BAEP peak latencies for the two groups, nor the amplitudes of the event related potentials differed significantly in comparison to the control readings. Data on visual contrast sensitivity was obtained from 2 subjects of the 50 ppm group and 3 subjects from the 10 ppm. The group comparison indicated a tendency (not statistically significant) for contrast sensitivity loss during exposure to 50 ppm tetrachloroethylene. Overall, the evaluation of the results is difficult. The statistical analysis is not described in details. No factorial analysis of variance was performed and only a multitude of unadjusted group comparisons were reported. The observed VEP latency changes observed during the two investigated tetrachloroethylene concentrations were not dose-dependent. While the 50 ppm group showed prolonged VEP peak latencies (i.e. a likely deficit) the 10 ppm group showed reduced latencies (i.e. improvement of visual information processing). The magnitude of the observed effect is very weak. The significant VEP latency prolongations were in a range between 1 and 2.5 ms. Moreover, only 3 of the 6 patterns used to elicit VEPs were affected, the amplitudes of all VEPs were not changed and the BAEP were not affected at all. Thus, changes in VEP latencies recorded in this study are a highly selective results and the toxicological significance of this finding is not clear.

Subsequently, the same authors (Altmann *et al*, 1992) published the results of neurobehavioural investigations conducted on the same volunteers exposed to tetrachloroethylene according to the same exposure schedule as in Altmann *et al* (1990). At the end of the exposure session on each of the 4 days, the volunteers were administered a large test battery which included finger tapping, eye-hand coordination, simple reaction time (SRT), continuous performance (CPT to assess vigilance), symbol-digit, visual memory, pattern recognition, digit learning, paired associates learning and retention, vocabulary and profile of mood scales tests. Pre-exposure baseline assessment was conducted the day before the first exposure session. Statistically significant performance deficits for CPT and eye-hand coordination, as well as borderline prolongation of SRT were found in the 50 ppm group compared to the 10 ppm group over the 4 days. In both groups, the performance in these tests did not worsen over the 4 days; on the contrary, in the 10 ppm group, a slight improvement was seen on days 3 and 4 which is likely to be due to the increased familiarity with the tests.

Once again, the evaluation of this study is difficult due to the same methodological limitations reported for the other Altmann et al. (1990) study. At a first glance, the results of this study seem to provide some evidence for a psychomotor deficit at tetrachloroethylene exposure levels of 50 ppm. However, due to the large number of tests conducted and to the large number of comparisons performed, it is likely that the statistically significant findings reported in this study at 50 ppm have arisen by chance. Furthermore, since the psychomotor deficit observed at 50 ppm did not worsen over the 4 days, it is likely it represents an acute effect arising from single periods of exposure rather than the consequence of repeated exposure. Therefore, no evidence for an adverse effect of repeated exposure to tetrachloroethylene (up to 50 ppm, 345 mg/m^3) on neurobehavioural performance can be derived from this study.

Summary of studies investigating potential neurological effects

The potential effects of repeated exposure to tetrachloroethylene on the nervous system have been investigated by 4 studies in dry-cleaners, 1 study in people living in close proximity to dry-cleaning shops and 4 studies in volunteers. The majority of these studies have examined neurobehavioural performance and neurological symptoms. Two studies have also examined electroencephalograms (EEG) and 3 studies have examined visual-evoked potentials (VEP). Small decrements in performance were obtained in a proportion of the neurobehavioural tests carried out in dry-cleaners. In one study a higher frequency of neurological symptoms was also observed. However, due to a number of methodological shortcomings, including no or inappropriate control groups, lack of exposure-response relationships, inconsistency of results between tests and between studies and the small sample sizes, no toxicological significance can be attributed to these findings. Overall, a clear association between a neurobehavioural/neurological deficit and repeated exposure to tetrachloroethylene at exposure levels up to 67 ppm (462 mg/m^3) has not been established.

Similarly, in the volunteer studies, small deficits in performance were obtained in a very small proportion of the neurobehavioural tests administered at exposure levels ranging from 50 ppm (339 mg/m^3) up to 150 ppm (1035 mg/m^3) for variable periods of time. One study also reported an increase in VEP peak latencies in volunteers exposed at 50 ppm (345 mg/m^3) but not 10 ppm (69 mg/m^3) for 4 hours/day on 4 consecutive days. However, due to a number of inconsistencies between the direction of the changes observed (decrements and improvements), between tests and between studies, and given that in some studies false positive results may have arisen as a result of multiple comparisons, the evidence in support of a neurobehavioural/neurological deficit caused by tetrachloroethylene exposure is not convincing. Furthermore, it is important to consider that in these volunteer studies, the exposure schedule included a limited number of repeated single exposures rather than long-term repeated exposure sessions. Therefore, even if some of the findings were real treatment-related effects, they would be likely to be acute CNS effects arising from repeated single exposures rather than the consequence of long-term repeated exposure. Overall, there is no clear evidence for an effect of repeated exposure to tetrachloroethylene up to 150 ppm (1035 mg/m^3 7.5 hours/day for 5 days) on neurobehavioural performance in these volunteer studies.

Taking all of these points into consideration, a crucial issue in relation to the impact of tetrachloroethylene on the nervous system is the need to avoid acute CNS depressant effects and associated symptomatology. At 50 ppm some authors describe marginal effects, which appear not to be adverse.

Studies investigating potential effects on colour vision

There are very few studies that have specifically investigated the effects of tetrachloroethylene on colour discrimination. These are revieved in detail in the EU RAR. A large-scale study in Japanese workers showed no effects of long-term exposure to tetrachloroethylene concentrations in the region of 12 to 13 ppm (83 to 90 mg/m^3) relative to a control group. However, the test methodology used was relatively insensitive to changes in colour discrimination and hence the results do not provide reassurance for an absence of subtle effects. A study in Italian dry-cleaners suggested a slight impairment of colour discrimination relative to controls, associated with relatively low exposures to tetrachloroethylene (mean 8 h TWA exposure ~6 ppm [~41.4 mg/m^3]). Overall, there is so little information on the effects of tetrachloroethylene on colour discrimination that no reliable conclusions can be drawn.

Table 2: Epidemiological studies of the neurotoxic effects of tetrachloroethylene reviewed by NEG-DECOS (2003)

Study description	Exposure	Effects	Study
Comparison of 18 dry cleaners with 9 laundry workers	124 mg/m^3 (8 hour TWA)	Effects found 2 out of 11 workers neurological tests	Tuttle *et al* (1977)
Cross sectional study comparing 60 female dry cleaning workers with 30 females from a cleaning plant not using solvents	Range 6.9-462 mg/m^3; Median 103 mg/m3	Exposed group showed poorer performance in neurobehavioural tests, but no evidence of a dose-related response.	Ferroni *et al* (1992)
65 dry cleaners	Low: 77 mg/m^3 Medium: 161 mg/m^3 High: 281 mg/m^3	Decreased performances for visual reproduction, pattern memory and pattern recognition in high exposure group	Echeverri a *et al* (1995)
106 workers exposed while cleaning machine and engine parts in railway repair shop, 101 controls	Some measured concentrations >2800 mg/m^3 (400 ppm) but 75% of measurements between 1.4-344 mg/m^3 (0.2 and 50 ppm)	Dizziness but no objective evidence of neurological effects (abnormal reflexes, sensory disturbances, motor disturbances)	Essing *et al* (1975)
56 dry cleaning workers	138 mg/m^3 (20 ppm; 8 hour TWA)	Subjective evidence of neurotoxicity	Cai *et al* (1991)
Dry cleaning workers	83 or 372 mg/m^3 (12 or 54 ppm; duration of exposure not specified)	Significant impairment of perceptual function, attention and intellectual function compared to a control group; no significant difference between low and high exposure groups or correlation with biological measures of exposure	Seeber (1989)

Studies investigating liver, kidney and respiratory toxicity

In epidemiological studies reviewed by NEG-DECOS (2003; see Table 5), possible effects on kidney function were found in workers with exposure to a mean concentration of 10 ppm (69 mg/m^3; 8 hour TWA), although other studies failed to find an effect at much higher concentrations (Table 3; also Solet and Robins, 1991; Vyskocil *et al* 1990). More recently Verplanke *et al* (1999), in a study of 101 dry cleaning workers in the Netherlands, reported effects on kidney function associated with a mean level of exposure of 400 mg/m^3.months (range 12-4,900 mg/m^3.months). Measured shift mean concentrations ranged from 1 to 221 mg/m^3 with a mean of 8.4 mg/m^3. Brodkin *et al* (1995) found evidence of changes in liver structure, as detected using ultrasonography, in dry cleaning workers exposed to mean concentrations of 16 ppm (110 mg/m^3; 8 hour TWA), although the effect on liver enzyme activity was small. More recently, Blair *et al* (2003) reported excess risks of mortality from emphysema in dry cleaners (SMR 1.7; 95% CI 1.0-2.5) but no overall increased risk of mortality and no relationship between emphysema risk and solvent exposure.

Table 3: Epidemiological investigations of liver and kidney toxicity reviewed by NEG-DECOS (2003)

Study description	Exposure	Effects	Study
Comparison of 26 dry cleaning workers with 33 unexposed workers	61.4-259 mg/m^3 (8.9-37.5 ppm)	No effects on liver function, no clear evidence of effects on kidney function	Lauwerys *et al* (1983)
Comparison of 141 workers from 47 small laundries and dry cleaning shops, controls of 130 university staff and students	8 hour TWA < 345 mg/m^3 (50 ppm)	No clear effects on liver enzymes	Gennari *et al* (1992)
Case control study involving 50 dry cleaning workers	Air concentrations ranged up to 586 mg/m^3 (85 ppm) with a median of 102 mg/m^3 (14.8 ppm)	Some evidence of glomerular and tubular kidney damage related to exposure, but no dose response relationship	Mutti *et al* (1992)
57 dry cleaning workers, 80 controls	Estimated as 68.9 mg/m^3 (10 ppm)	Some evidence of minor effects on the tubules of the kidney	Franchini *et al* (1983)
106 workers exposed while cleaning machine and engine parts in railway repair shop, 101 controls	Concentrations often exceeded 2759 mg/m^3 (400 ppm) but 75% of measurements between 1.4-345 mg/m^3 (0.2 and 50 ppm)	No evidence of effects on liver or kidney function	Essing *et al* (1975)
56 dry cleaning workers	138 mg/m^3 (20 ppm; 8 hour TWA)	No evidence of effects on liver or kidney function or of effects on blood	Cai *et al* (1991)

Animal data

The major target organs for tetrachloroethylene toxicity, studied in inhalation experiments, are the liver and central nervous system. Mice appear to be more susceptible to liver damage arising from tetrachloroethylene exposure than rats. The LOEL for effects on the liver in mice following continuous exposure was 9 ppm (62 mg/m^3; Table 4) although no effects in were observed in rats exposed for 7 months to 70 ppm (483 mg/m^3) for 8 hours/day, 5 days/week. A LOEL of 60 ppm (414 mg/m^3 continuous exposure) was identified for neurotoxic effects in gerbils. Longer term experiments in rats and mice have reported adverse effects on the kidney associated with two years exposure to 689 to 2,759 mg/m^3 (100 to 400 ppm) for 6 hours per day, 5 days per week (NTP, 1986). In the same experiments, thrombosis and squamous metaplasia of the nasal epithelium was reported in rats and congestion of the lung was reported in mice. The results of experiments by Rowe *et al* (1952) in a range of species suggest some interspecies variability in susceptibility, although the group sizes were small.

NEG-DECOS (2003) reviewed a number of investigations of the toxicology of tetrachloroethylene following oral administration. Drinking water studies in mice have reported effects on the haemopoietic system (i.e. effects on the spleen) in the absence of liver or kidney toxicity at doses equivalent to 0.05 mg/kg body weight per day for 7 weeks. Liver toxicity has been reported in mice exposed to 100 mg/kg body weight on 5 days per week for 6 weeks with a NOEL of 20 mg/kg. Kidney effects have been reported in rats at 500 mg/kg body weight per day and effects on kidney weight have been reported at 400 mg/kg/day.

Conclusions from studies investigating hepatotoxic / nephrotoxic effects

Hepatotoxic and nephrotoxic effects have been described in experimental animals upon repeated exposure to tetrachloroethylene. In general, such effects appeared at inhalation exposures higher than 100 ppm. There are indications that mice are more susceptible to liver damage caused by tetrachloroethylene, which may be explained by a higher extent of metabolism to reactive intermediates. In humans, the overall metabolism of tetrachloroethylene is only low (about 5% of an inhaled dose, see 5.1).

In interpreting the available data from humans (Table 3) the impact of high peak concentrations occurring in the dry cleaning process must be considered. In general, no clear effects on liver and kidney were seen, if the mean concentration of tetrachloroethylene remained under 50 ppm. This is again compatible with the experimental data in animals. As further explained in the Recommendation section, an NOAEL of 25 ppm for humans appears to be a conservative figure.

Table 4: Summary of repeated dose experiments demonstrating adverse effects on the liver (from NEG-DECOS, 2003)

Species	Duration	Exposure regime	Outcome	Study
Rat	18 days	17,245 mg/m^3 (2,500 ppm) Up to 13x7 hours	4/5 animals died in each group, , cloudy swelling in liver with few diffusely distributed small fat vacuoles	Rowe *et al* 1952
Rabbit	39 days	28x7 hours	parenchymatous degeneration of the liver	
Guinea Pig	24 days	18x7 hours	increased liver and kidney weight, central fatty degeneration in liver, cloudy swelling in renal tubuli	
Rat	25 days	11,036mg/m^3 (1600 ppm) 18x7 hours	Decreased body weight, enlarged liver and kidneys	Rowe *et al* 1952
Guinea Pig	8 days	8 x 7 hours	Decreased body weight; increased liver weight, moderate central fatty degeneration of the liver, slight degenerative changes in germinal epithelium	
Rat	183 days	2759 mg/m^3 (400 ppm) 130x7 hours	No adverse effects	Rowe *et al* 1952
Guinea Pig	236 days	169x7 hour s	Depressed growth, increased liver weight, increased neutral fat and esterfied cholesterol in liver, central fatty degeneration in liver with slight cirrhosis	
Rabbits	222 days	159x7 hour s	No adverse effects found	
Rhesus monkey	250 days	179x7 hour s	No adverse effects found	
Guinea Pig	220 days	1,380 mg/m^3 (200 ppm) 158x7 hour s	Depressed growth; increased liver weight; increased total lipid and esterfied cholesterol in liver; central fatty degeneration in liver	Rowe *et al* 1952
	18 days	14x7hours	Depressed growth; increased liver weight; very slight fatty degeneration of the central area of the liver	
Guinea Pig	185 days	689 mg/m^3 (100 ppm) 132 x 7 hours	Females: increased liver weight Males: few small fat vacuoles in liver	Rowe *et al* 1952
	17 days	13x 7 hours	No adverse effects	
Mouse	Up to 8	1,380 mg/m^3 (200	Severity of liver damage increased with increasing number of exposure. After	Kylin *et al*

	weeks	ppm), 4 hours/day, 6 days week	8 weeks, massive, central infiltration of about 80% of the liver with fat was observed	(1965)
Rabbit	9 weeks	12,347 mg/m^3 (1,790 ppm) 4 hours/day, 5 days/week	Increase in Serum Glutamic Oxaloacetic Transaminase (SGOT), Serum Glutamic Pyruvic Transaminase (SGPT) and glutamic dehydrogenase (GDH) in serum, damage to cytoplasmic and mitochondrial structures of the liver parenchyma	Mazza (1972)

Table continued overleaf

Species	Duration	Exposure regime	Outcome	Study
Mouse and rat	28 days	1380 or 2,759 mg/m^3 (200 or 400 ppm), 6 hours day	Significant but small increases in liver weight in mice accompanied by increased peroxisomal cyanide insensitive CoA oxidation, much smaller effects in rats	Odum (1988)
mouse	30 days	62 mg/m^3 (9 ppm), continuous 75 ppm (517 mg/m^3), continuous	Significant increase in liver weight Doubling in liver weight with cell hypertrophy and vacuolisation	Kjellstrand (1984, 1985)
Mouse	2 years	689 or 1380 mg/m^3 (100 or 200 ppm), 6 hours/day, 5 days/week	Liver degeneration and necrosis, significant increase in tumours	NTP (1986)
Rat	2 years	1380 or 2759 mg/m^3 (200 or 400 ppm), 6 hours/day, 5 days/week	No effects on the liver	NTP (1986)
Rat	12 months	2069 & 4139 mg/m^3 (300 or 600 ppm) 6 hours/day, 5 days/week	No effects on the liver	Rampy *et al* 1985

Table 5: Summary of repeated dose experiments demonstrating adverse effects on the CNS (from NEG-DECOS, 2003)

Species	Duration	Exposure regime	Outcome	Study
Rat Rabbit Guinea pig	18 days 39 days 24 days	2,500 ppm (17,250 mg/m^3) Up to 13x7 hours 28x7 hours 18x7 hours	4/5 animals died in each group, severe CNS depression, loss of consciousness Severe CNS depression Severe CNS depression, weight loss	Rowe *et al* (1982)
Rat Guinea pig	25 days 8 days	1,600 ppm (11,037 mg/m^3) 18x7 hours 8 x 7 hours	Various marked effects on behaviour that could be prevented by intraperitoneal administration of atropine, decreased body weight Decreased body weight	Rowe *et al* (1982)
Rat Guinea pig Rabbits Rhesus monkey	183 days 236 days 222 days 250 days	400 ppm (2,759 mg/m^3) 130x7 hours 169x7 hour s 159x7 hour s 179x7 hour s	No CNS effects	Rowe *et al* (1982)
Rat	1 month	200, 400 and 800 ppm (1380, 2,759, 5,518 mg/m^3), continuous	Dose-related decrease of acetylcholine in the striatum combined with slight changes in dopamine in the striatum, norepinephrine in the hypothalamus and serotonin in the cortex and hippocampus	Honma *et al* (1980a)
Rat	1 month	200, 400 and 800 ppm (1380, 2,759, 5,518 mg/m^3), continuous	Marked dose-related increase of glutamine, threonine and serine while gamma-butyroamino acid decreased	Honma *et al* (1980b)
Gerbil	12 months	120 ppm (828 mg/m^3) continuous	Small change of fatty acid pattern of phospholipids; decrease of long-chain linolenic acid-derived 22-carbon fatty acids; no changes in content/concentrations of protein, lipid phosphorus and cholesterol in	Kyrklund *et al* (1987)

			hippocampus and cerebral cortex - concluded that small changes in membrane fatty acids occurred at doses well below those causing anaesthesia	
Gerbil	3 months	60 and 320 ppm (414 and 828 mg/m^3) continuous	Slightly increased concentrations of the astroglial protein S100 in hippocampus, cerebral occipital cortex and cerebellum. S100 as well as DNA concentrations were decreased in the fontal cerebral cortex. Effects on DNA concentrations at 60 ppm	Rosengren *et al* (1986)
Gerbil	3 months	60 ppm (414 mg/m^3) continuous	Slight decrease in DNA concentration in frontal cerebral cortex	Karlsson *et al* (1987)
gerbil	3 months	320 ppm (828 mg/m^3) continuous	Minor decrease of brain weight, shift in fatty acids of ethanolamine phospholipids towards less saturated forms	Kyrklund *et al* (1987)
Rat	30 days	320 ppm (828 mg/m^3) continuous	Slight reduction of cholesterol and phospholipids in the brain; shift in fatty-acid composition of the brain	Kyrklund *et al* (1990a)
Rat, guinea pig and gerbil	30 days	320 and 160 ppm (414 and 828 mg/m^3) (guinea pigs) continuous	Tendency towards decreased brain weight, exposure of guinea pigs during second half of gestation revealed no increased sensitivity	Kyrklund *et al* (1988)
Rat	90 days	320 ppm (2,207 mg/m^3) continuous	Slight changes in fatty acid composition of brain phosphoipids that largely normalised subsequent to exposure; slight persistent changes in brain cholesterol content	Kyrklund *et al* (1990b)
rat	4 or 12 weeks	300 and 600 ppm (2,069 and 4,139 mg/m^3) continuous	Slower increase in brain weight at 600 ppm. At highest dose, after 12 weeks decrease in DNA total protein and brain region weights in frontal cerebral cortex and brain stem but not in hippocampus. Glial and neuronal cytoskeletal proteins decreased in frontal cortex at highest dose. Glial proteins were decreased in frontal cortex, brain stem and hippocampus at the highest dose. No effects on neuronal enolase. Changes interpreted to reflect a reduction in the number of brain cells.	Wang *et al* (1993)
mice	2 weeks	100-1,750 ppm (689 – 12071 mg/m^3) 6 hours/day, 5 days/week	Dyspnoea, hypactivity, hyperactivity, anaesthesia and ataxia at highest dose	NTP 1986
rats	4 days	200 ppm (1,380 mg/m^3), 6 hours/day	Behavioural alteration	Savolainen *et al* (1977)

2.6. Genotoxicity

NEG-DECOS (2003) provide a summary of the genotoxicity data that was then available.

Most *in vitro* assays in bacteria, yeasts, mammalian cells and insects have yielded negative results. Some positive results reported in tests with bacteria could have resulted from the presence of impurities in the tetrachloroethylene used. Most *in vivo* studies with mammals have also yielded negative results (*i.e.* host-mediated assay, cytogenetic studies, sperm-head abnormalities, dominant lethality, unscheduled DNA synthesis). Where positive results have been obtained in these assays, the tetrachloroethylene test substance was of relatively low purity. Evidence of DNA damage, single strand breaks, were however found in the liver and kidneys, but not lungs of mice treated with a high purity preparation of tetrachloroethylene.

NEG-DECOS (2003) concluded that tetrachloroethylene is virtually devoid of genotoxic properties in mammals.

2.7. Carcinogenicity

2.7.1. Human data

A large number of studies have investigated the possible association between employment in the dry cleaning industry and excess cancer risk (Table 6). In most of these studies, workers were exposed to a number of solvents and only a few studies specifically investigated tetrachloroethylene. Many studies did not differentiate between laundry workers with very low solvent exposures and dry cleaners which weakened their power to detect effects due to solvent exposure. Most studies did not take account of smoking or alcohol consumption. Some of the observed excess cancer risks could be due to smoking, although the general absence of evidence of a lung cancer risk suggests that smoking is unlikely to explain all of the observed cancer risk. Overall the results of the various studies are suggestive of an association between exposure to dry cleaning fluids and an excess risk of some respiratory tract cancers and/or bladder cancer. They do not provide clear evidence of an association between tetrachloroethylene exposure and cancer.

Several studies of tetrachloroethylene contamination of drinking water have pointed to a possible small excess of cancers of the breast (Aschengrau *et al*, 1998), lung, possibly colon (Paulu *et al*, 1999), bladder and leukaemia (Aschengrau *et al*, 1993). However, it is unclear what other contaminants may have been present and whether the absence of similar reports from elsewhere is due to an absence of investigation, a comparative rarity of this particular form of contamination or an absence of effect.

Table 6: Epidemiological investigations of tetrachloroethylene carcinogenicity

Study description	Effects	Study
Retrospective cohort mortality study of 1,597 workers employed in dry cleaning shops for at last one year before 1960	Significant excess of urinary tract and colon cancers	Kaplan (1980)
Expansion of cohort to 1,690 (493 deaths, 42,467 person-years at risk)	Significant excess of bladder cancers, no liver cancers, significantly fewer cancers of the lympathatic and haemopoietic systems No excess of urinary tract cancers	Brown *et al* (1987)
Subcohort of 615 (137 deaths) of workers exposed almost exclusively to tetrachloroethylene	No account taken of smoking history	
Study update	Significant excess of oesophagus cancer in both main cohort and subcohort	Ruder *et al* (1994)
1,708 dry cleaning workers exposed to tetrachloroethylene for at least one year before 1960. Most of these workers were also exposed to a petroleum based dry cleaning agent.	An excess cancer risk was detected with elevated mortality from tongue, bladder, oesophagus, intestine, lung and cervical cancers.	Ruder *et al* (2001)
11,062 dry cleaners employed between 1945 and 1977	Increased incidences of laryngeal cancer, bladder cancer and lymphoma in workers employed before 1963 (exposure dominated by solvents other than tetrachloroethylene); significant increase in oesophagus cancer in black males with medium or high tetrachloroethylene exposure No enhanced liver cancer risk No account taken of smoking history	Blair *et al* (1985)
Follow up of 5369 dry cleaners from the 1985 study	Increased mortality rates for Hodgkin's disease, cancers of the oesophagus, larynx, lung and cervix (SMRs 95% CIs respectively: 2.0; 0.6-4.6; 2.2; 1.5-3.3; 1.7; 0.6-3.7; 1.4; 1.1-1.6; 1.6; 1.0-2.3); no clear relationship between solvent exposure and cancer risk	Blair *et al* (2003)
Proportional mortality study of 279 dry cleaners dying between 1957 and 1977	Elevated proportional mortality rates for lung cancer, cervix uteri, skin cancer, leukaemia, and liver cancer; deficit for breast cancer	Blair *et al* (1979)

	No account taken of smoking history or exposure to other solvents	
Proportional mortality study of 671 female laundry and dry-cleaning workers who died between 1963 and 1977	Elevated PMRs found for cancers of the genitalia and kidney, nonsignificant excesses of bladder and skin cancer No account taken of smoking history or exposure to other solvents. Inclusion of laundry workers with little solvent exposure will have limited power of study to detect effects	Katz and Jowett (1981)
440 laundry and dry-cleaning workers who died between 1975 and 1981	No excess deaths for all cancers, significant excess for respiratory tract cancer, lung cancer and kidney cancer; lower than expected incidence of breast, bladder and liver cancer; Smoking history not considered; petroleum solvents accounted for >50% of dry cleaning fluids used	Duh *et al* (1984)
1711 laundry and dry cleaning workers who died between 1971 and 1980 Smoking and drinking habits known for 294 workers	No excess for all cancers, excess of cancers of the small intestine; Only 30% of Japanese dry cleaning shops used tetrachloroethylene, study included laundry workers with no solvent exposure	Nakamura (1985)
Case-referent study - 103 workers employed for at least 6 months in dry cleaning or laundry shops and 5,776 subjects in other occupations with possible exposure to similar chemicals, 1,869 subjects with no chemical exposure	Relative risk of 1.31 (not significant) was found for bladder cancer in nonsmokers employed in dry cleaning shops. Inclusion of laundry workers limited power of study to detect effects	Smith *et al* (1985)
Case-referent study – 7,405 cases of renal cancer	No association between employment in laundry or dry cleaning shops and renal cancer	McLaughlin *et al* (1987)
Retrospective cohort study of 14,457 aircraft maintenance workers exposed to over 20 different solvents	Tetrachloroethylene for more than one year associated with an excess of multiple myeloma/ non-Hodgkin's lymphoma in female workers (no account taken of smoking or alcohol, or exposure to other solvents)	Spirtas *et al* (1991)
77,965 workers employed for at least 1 year at a large aircraft manufacturing facility on or after 1960, mortality experience determined until the end of 1996.	No overall excess risk of cancer was detected. A non-significant excess of non-Hodgkin's lymphoma was found in workers exposed to trichloro-or tetrachloroethylene.	Boice *et al* (1999)
Cohort of 2,050 men and 1,924 women exposed to	No excess of specific cancers could be linked with tetrachloroethylene	Anttila *et al* (1995)

tetrachloroethylene, trichloroethylene and trichloroethane followed from 1967-1992	exposure (tetrachloroethylene monitoring data was available for 1974-1983)	
Proportional mortality study in 8,163 former laundry and dry cleaning workers	Black men had elevated PMRs for all cancers and oesophagus cancer, white men had an elevated PMR for cancer of the larynx; no separate analysis made of laundry and dry cleaning workers	Walker *et al* (1997)
Case control study, 404 cases	Possible excess risk of oesophageal cancer in dry cleaners based on two cases; study had low power to reliably detect an effect	Vaughan *et al* (1997)
Case control study with 59 cases of renal cell cancer and 84 controls	No association with tetrachloroethylene was found	Vamvakas *et al* (1998)
Case control study, 741 cases, 741 controls	Nonsignificant association between tetrachloroethylene and astrocytic brain cancer. Study was subsequently criticised for poor exposure classification	Heineman *et al* (1994)

2.7.2 Animals

A statistically significant increase of hepatocellular carcinoma was observed in mice following inhalation exposure to 690 or 1,378 mg/m^3 (100 or 200 ppm) for 6 hours each day, 5 days per week for 2 years (NTP, 1986). Similar effects were observed following oral administration of 386-1,072 mg/kg body weight for 5 days per week over 78 weeks (NCI, 1977). The major metabolite of tetrachloroethylene, trichloroacetic acid, induces hepatocellular carcinomas and adenoma in mice following oral administration. It appears very plausible that the liver tumours observed in mice exposed to tetrachloroethylene are the result of carcinogenicity of trichloroacetic acid based on a non-genotoxic mechanism. This is supported by data of Odum et al. (1988) showing that trichloroacetic acid induces peroxisome proliferation in the liver of B6C3F1 mice and F-344 rats. In rats, a non-significant increase of tubular cell adenoma and adenocarcinoma was observed in males but not females following inhalation exposure to 689 or 1,378 mg/m^3 (200 or 400 ppm) for 6 hours/day, 5 days/week for 2 years (NTP, 1986). Effects may have been related to the male-specific formation of protein droplets in cells, again pointing to a non-genotoxic mode of action. Rats also showed a significant increase in mononuclear cell leukaemia, but this cancer had a high background incidence in the rat strain tested so that the significance in the assessment of human cancer risks is uncertain.

In experiments where tetrachloroethylene was applied to the skin of mice, no increase in tumours was observed (Van Duuren *et al*, 1979).

Conclusion

The limited evidence linking exposure to tetrachloroethylene to cancers in humans is not convincing, whereas results of animal experiments demonstrate a clear association with cancers of the liver in mice. Mice may have an enhanced susceptibility to liver tumours arising from tetrachloroethylene exposure arising from a higher rate of production of the metabolite trichloroacetic acid than found in other species. The link between hepatic peroxisome proliferation and trichloroacetic acid suggests that the liver tumours found in mice after exposure to tetrachloroethylene are not relevant for human carcinogenesis at levels of occupational exposure. The cancers reported in humans are mostly of the bladder or respiratory tract; so far no excess risk of cancers of the liver in humans could be identified.

IARC (1995) classified tetrachloroethylene as a probable human carcinogen (Group 2A) on the basis of limited evidence of carcinogenicity in humans combined with sufficient evidence of carcinogenicity in animals. The EU classification (carcinogenicity) is of category 3 (R40).

In view of the SCOEL strategy to derive OELs for carcinogens (Bolt and Huici-Montagud 2008), the following arguments are important:

- Characterisation of tetrachloroethylene as non-genotoxic in vivo (see 5.6)
- Identification of a mode of action for mouse liver tumours, associated with the peroxisome-proliferating potency of the metabolite trichloroacetic acid

- Clear quantitative species differences in the oxidative (CYP-dependent) and reductive (GSH-dependent) pathways (see 5.1), leading in humans to exhalation of 95% of tetrachloroethylene unchanged.

In essence, this justifies a categorisation of tetrachloroethylene in the SCOEL carcinogen group D, as a non-genotoxic carcinogen, the carcinogenic effect of which is subject to a threshold.

2.8. Reproductive and developmental toxicity

Experiments in mice have demonstrated that tetrachloroethylene can cross the placenta and accumulate in amniotic fluid and the foetus (Ghantous *et al*, 1986). Tetrachloroethylene has also been detected in human milk.

2.8.1 Human data

The studies reviewed by NEG-DECOS (2003) show some evidence for an association between maternal occupation of dry cleaning and increased risk of spontaneous abortion and more limited information to suggest an association more specifically with tetrachloroethylene (Table 7). There is also very limited evidence of an association between tetrachloroethylene and disruption of the menstrual cycle. There is no evidence of an association between tetrachloroethylene and congenital malformations or between paternal exposure to tetrachloroethylene and increased risk of spontaneous abortion. There is no clear evidence of an effect on male fertility, although the available data do not exclude the possibility of a small effect. There have been no epidemiological investigations of the effects of infant exposure to tetrachloroethylene in breast milk but obstructive jaundice and hepatomegaly have been described in the breast fed child of a mother exposed to tetrachloroethylene (Bagnell *et al*, 1977). No new studies appear to have been published since the NEG-DECOS review in 2003.

Table 7: Summary of studies of reproductive effects in humans reviewed by NEG-DECOS (2003)

Study description	Effects	Study
Nested case-control study with 120 cases of spontaneous abortion and 251 controls based on a file of 6,000 male workers monitored for exposure to six solvents	Incidence of spontaneous abortion in wives of men occupational exposed to organic solvents was significantly raised but no effects seen in wives of men exposed to tetrachloroethylene or other halogenated solvents; no association between paternal exposure to solvents and congenital malformations or between maternal exposure and spontaneous abortion in women exposed to solvents	Taskinen *et al* (1989)
Questionnaire study of 68 dry cleaning and 76 laundry workers	Incidences of dysmenorrhoea, unusual cycle length, menorrhagia and premenstrual syndrome were higher in dry-cleaning workers than among laundry workers, no difference in the mean cycle length between the 2 groups	Zielhuis and Van der Gulden (1989)

Study description	Effects	Study
Examination of semen quality of 34 men exposed tetrachlorethylene (dry cleaning workers) and 48 laundry workers with no exposure	No differences in average number of sperm cells between the two groups but incidence of low sperm counts in both groups relatively high	Eskenazi *et al* (1991a)
Examination of pregnancy outcome in partners of 17 dry cleaners and 32 laundry workers from study above	Number of pregnancies and standardised fertility ratios similar in both groups, no difference in spontaneous abortions, wives of dry cleaning workers more than twice as likely to have taken more than 12 months to become pregnant or sought care for an infertility problem	Eskenazi *et al* (1991b)
197 women exposed to organic solvents	Daily or high levels of exposure to solvents was associated with significantly reduced fecundity whereas exposure to tetrachloroethylene had a non-significant effect	Sallmen *et al* (1995)
9,000 chemical workers	Incidence of spontaneous abortions in laundry workers significantly increased compared with "all women" in Finland	Hemminki *et al* (1980)
Male and female workers exposed to a wide range of chemicals and other substances at work	No effects on spontaneous abortions in women exposed to solvents (730 pregnancies) or among the wives of men exposed to solvents. Significant increase in spontaneous abortions in female laundry workers (416 pregnancies)	Lindbohm *et al* (1984)
67 females in dry cleaning shops	The incidence of spontaneous abortions among women working in dry cleaning shops was 4 times higher than among housewives but no statistically significant differences observed in the incidences of low birth weights, spontaneous abortions, still births and congenital birth defects between the two groups.	Bosco *et al* (1987)
Cross sectional study among 56,067 women who delivered or were treated for a spontaneous abortion	No association between employment in a dry cleaning shop and spontaneous abortion, stillbirth, congenital defects and low birth weight	McDonald *et al* (1987)
Cohort of 5,700 female dry-cleaning and laundry workers	Statistically significant association between spontaneous abortion and exposure to tetrachloroethylene, no effects on congenital malformations	Kyyronen *et al* (1989)
Two cohorts of women employed in laundry or dry cleaning work – 1) 48 cases and 110 referents; 2) 68 cases and	No association between tetrachloroethylene and adverse birth outcomes (spontaneous abortion, perinatal death, congenital	Ahlborg (1990)

131 referents	malformations and low birth weight)	
Women monitored for exposure to organic solvents – 73 cases and 167 controls	Statistically non-significant small increased risk of spontaneous abortion in women exposed to tetrachloroethylene	Lindbohm *et al* (1990)
Case control study in women experiencing a spontaneous abortion before 20 weeks gestation	Significant association between the incidence of spontaneous abortion and exposure to tetrachloroethylene but based on only 5 cases and in 4 cases women had also been exposed to trichloroethylene	Windham *et al* (1991)
7,305 women employed in dry cleaning	Increased risk of spontaneous abortion in women employed in dry cleaning than in laundry or women not employed in dry cleaning or laundry	Doyle *et al* (1997)

Two studies of the effects of tetrachloroethylene contamination of drinking water on birth outcome have been published, but in both studies exposures were to a mixture of chlorinated hydrocarbons. Sonnenfeld *et al* (2001) reported possible weak associations between tetrachloroethylene and reduced birth weight, small-for-gestational-age infants and preterm birth. They found more evidence for associations in older mothers and mothers with histories of foetal loss and suggested that some foetuses may be at greater risk than others. Bove *et al* (1995) found possible evidence of an association between tetrachloroethylene in drinking water and cleft palate.

2.8.2. Animal data

The results of animal experiments suggest that inhalation exposure to high levels of tetrachloroethylene may be associated with adverse effects on male fertility. There is limited evidence that tetrachloroethylene may be toxic to the foetus, but only at levels of exposure that are associated with maternal toxicity. There is no evidence for teratogenic effects. The lowest exposure concentration associated with possible foetal toxicity is 300 ppm [2,067 mg/m^3] and the lowest concentration associated with effects on male reproductive organs 300 ppm [2,067 mg/m^3]. The data, as compiled by DECOS (2003), are presented in Table 8. In addition, a recent study by Carney et al (2006) found no developmental effects at 65 ppm. The EU RAR has quoted this study as the "Huntingdon Life Sciences Study 2005", providing additional information in the rat at concentrations of 65, 250 and 600 ppm. This is supported by a 2-generation inhalation study in rats (Tinston 1995), also cited in the EU RAR.

Thus, an NOAEL for reproductive effects of 65 ppm appears compatible with all experimental studies reported so far.

Table 8: Investigations of reproductive toxicity reviewed by NEG-DECOS (2003)

Species	Exposure regime	Concentration	Outcome	Study
Rats	7 hours/day for 5 days	0, 689, 3,445 mg/m^3	No effects on sperm head morphology	Beliles *et al* (1980)
Mice			Increased anomalies in sperm head morphology at 3,445 mg/m^3	
Rats	Two generation study 6 hours/day, 5 days/week 11 weeks prior to mating, males of F0 and F1 generation exposed for 19 and 35 weeks respectively	0, 689, 2,067 or 6890 mg/m^3	At highest dose, decreased body weight in F0 and F1 generation, increased kidney and liver weights; reduced testis weight in F1 males at two highest doses, no effects on fertility	Tinston (1995)
Mice	7 hours/day, days 6-15 of gestation	0 and 2,067 mg/m^3	Relative liver weight increased in dams, decreased foetal weight, delayed ossification of skull bones and sternebrae	Schwetz *et al* (1975)
Rats			Decreased maternal body weight, increased number of absorptions	
Rats	Gestational day 0-18 or 6-18 with or without 3 week exposure prior to mating	0 and 3,445 mg/m^3	No maternal toxicity except for increased kidney weight in group exposed for 3 weeks prior to mating; no foetal toxicity or teratogenicity	Beliles *et al* (1980)
Rabbits	Gestational day 0-21 or 7-21 with or without 3 week exposure prior to mating		No maternal or foetal toxicity, no teratogenicity	

*industry studies

Recommendation

Tetrachloroethylene is readily absorbed following exposure by inhalation, ingestion or through the skin. By far the major route of elimination is exhalation of the unchanged compound. There is a relatively large amount of information on the potential repeated dose effects of tetrachloroethylene from studies both in humans and in animals.

In relation to the studies in humans, there are general worker health surveys and studies specifically investigating potential effects on the liver, kidney, nervous system and colour vision. Variable results and interpretational difficulties have arisen in surveys of workers exposed to lower (below 100 ppm, 690 mg/m^3) concentrations of tetrachloroethylene, with a study finding no effects on the frequency of subjective symptoms, psychomotor test results and markers of liver and kidney toxicity in dry-cleaners with a mean 8-hour TWA exposure of 21 ppm (145 mg/m^3 for 6 years) compared with an unexposed control group. Two specific hepatotoxicity studies together with the hepatotoxicological investigations of several worker health surveys have provided no clear evidence for tetrachloroethylene-induced liver toxicity at exposure concentrations below 50 ppm (339 mg/m^3; mean 8h TWA). Similarly, the specific six nephrotoxicity studies together with the nephrotoxicological investigations of several worker health surveys have provided no convincing evidence for tetrachloroethylene-induced kidney toxicity at mean exposure levels in the range 1.2 – 23 ppm (8.3 – 156 mg/m^3). From the studies that have specifically investigated the potential effects of tetrachloroethylene on the nervous system, a clear association between neurobehavioural/neurological deficits and repeated exposure to tetrachloroethylene in the workplace (dry-cleaners) at exposure levels up to 67 ppm (462 mg/m^3 for 10 years) or in volunteers at concentrations up to 150 ppm (1035 mg/m^3 for 7.5 hours/day for 5 days) has not been established. There are very few studies that have specifically investigated the effects of tetrachloroethylene on colour discrimination, such that no reliable conclusions can be drawn. Overall, there is no clear evidence from studies in humans for repeated dose effects of tetrachloroethylene at exposure levels up to 25 ppm (173 mg/m^3). This value is taken forward to the risk characterisation as a human NOAEL (see also 5.5.2.1).

In relation to the animal studies, the liver, kidneys and lungs have been shown to be the main target organs of tetrachloroethylene-induced toxicity. Liver damage seen in mice following either inhalation exposure or oral administration has been shown to involve peroxisomal proliferation, an effect to which humans are not responsive. No liver toxicity was observed in rats. For kidney damage, which was observed in both rats and mice following either inhalation or oral exposure, an inhalation LOAEL of 100 ppm, 690 mg/m^3 (equivalent to an internal dose of 345 mg/kg/day) and an oral LOAEL of 390 mg/kg/day have been identified from the mouse inhalation and oral cancer bioassays respectively. Evidence of hyaline droplet nephropathy was found in male rats following either inhalation or oral exposure, but the data indicate that this phenomenon, which is male rat-specific and hence not relevant to humans, only occurs at relatively high levels of exposure (1000 ppm, 6900 mg/m^3 and 1000 -1500 mg/kg/day) when relatively short exposure durations are employed. Congestion of the lungs was seen in mice following inhalation exposure at ≥ 100 ppm (690 mg/m^3) for 2 years. One hundred ppm (690 mg/m^3) is therefore also the LOAEC for this effect in the lungs.

Overall, taking the human and the animal evidence together, an NOAEL of 25 ppm, as discussed above, appears to be sufficiently conservative.

The joint DECOS/Nordic Expert Group (2003) has concluded that central nervous system effects can be expected in humans at short-term exposure to 100 ppm [689 mg/m³] tetrachloroethylene. Reported effects include headache, dizziness, light-headedness, flushing, difficulty in speaking, sleepiness, loss of inhibitions, exhilaration, feelings of elation, and impaired motor coordination. It was also concluded that some inadequately performed studies suggest neurological effects below 100 ppm (15 ppm median level).

Another key effect for setting an OEL is on the central nervous system. According to the documentation of NEG-DECOS (2003) a level of 20 ppm [138 mg/m³] can be regarded to be a NOAEL in humans.

Tetrachloroethylene has induced liver cancer in mice and renal tubular tumours in male rats. Some studies suggest that it may cause cancer in humans, but these are not conclusive. Interpretation is hampered by concomitant exposure to other solvents and limited by lack of control for lifetime-related factors. The results from genotoxicity testing warrant the conclusion that exposure to tetrachloroethylene does not present a genotoxic risk to humans. It can be concluded that the experimental tumours produced by tetrachloroethylene in rodents are based on non-genotoxic modes of action. This is likely to be mediated via the metabolite trichloroacetic acid. This allows to categorise tetrachloroethylene as a group D carcinogen (non-genotoxic, associated with a threshold) and to establish a health-based OEL. The arguments are further outlined in chapter 5.7.3. This OEL must be set at a level that avoids damage of the parenchymal organs liver and kidney.

There is very limited evidence that suggests that human exposure to tetrachloroethylene is associated with an increased risk of spontaneous abortion. There is no evidence of associations with congenital malformations or a substantial effect on male fertility. Tetrachloroethylene is secreted in breast milk and liver toxicity has been reported in the breast fed child of a mother exposed to tetrachloroethylene. In animal experiments, foetal toxicity has only been reported at maternally toxic levels of exposure. Minor effects on male reproductive organs have been reported at 300 ppm [2,067 mg/m³]. There are insufficient multiple-dose data to determine no-effect levels. A recent documentation has been presented by DECOS (2003).

For establishing a STEL, DECOS (2004) has evaluated a short-term LOAEL of 1500 mg/m³ (218 ppm) and a NOAEL of 750 mg/m³ (109 ppm) based on the studies of Stewart et al. (1961) and Rowe et al. (1952). In consideration of the limited database, a recommendation of a STEL of 40 ppm [275 mg/m³] appears sufficiently conservative.

Under these provisions, SCOEL recommends for tetrachloroethylene an OEL (8h TWA) of 20 ppm and a STEL (15 min) of 40 ppm.

Based on the derivations outlines in chapter 5.1.1, SCOEL recommends for biological monitoring a BLV of 0.4 mg tetrachloroethylene per liter whole blood, at a sampling time prior to the last shift of a workweek (16h after the last preceding shift). As a non-invasive alternative, a BLV of 3 ppm tetrachloroethylene in end-exhaled air is recommended (sampling time: prior to the last shift of a work-week, i.e. 16 h after the last preceding shift)

As specified in chapter 5.1, skin absorption of tetrachloroethylene can be relevant under practical workplace conditions. In consequence, a 'skin' notation is recommended.

References

ACGIH (2001) Tetrachloroethylene BEI. In: Documentation of BLVs and BEIs. American Conference of Governmental Industrial Hygienists, Cincinnati, OH: ACGIH.

ACGIH. (2005). Guide to Occupational Exposure Values 2005; TLVs and BEIs. Threshold Limit Values and Biological Exposure Indices. Cincinnati, OH: ACGIH.

ASTDR. (1997). Toxicological profile for tetrachloroethylene (update) ATSDR/TP-97/18. Atlanta, Georgia: US Department of Health human Services, Public Health Service, Agency for Toxic Substances and Disease Registry (www.atsdr.cdc.gov)

Ahlborg G Jr. (1990). Pregnancy outcome among women working in laundries and dry-cleaning shops using tetrachloroethylene. American Journal of Industrial Medicine; 17:567-575.

Altmann L, Bottger A, Wiegand H. (1990). Neurophysiological and psychophysical measurements reveal effects of acute low-level organic solvent exposure in humans. International Archives of Occupational and Environmental Health; 62:493-499.

Altmann L, Wiegand, H, Bottger A, Elstermeier F, Winneke G (1992): Neurobehavioural and neurophysiological outcomes of acute repeated perchloroethylene exposure. Appl. Psychol: An International Review 41: 269-279.

Altmann L, Neuhann HF, Kramer U, Witten J, Jermann E. (1995). Neurobehavioral and neurophysiological outcome of chronic low-level tetrachloroethene exposure measured in neighbourhoods of dry cleaning shops. Environmental Research; 69: 83-89.

Anttila A, Pukkala E, Sallmen M, Hernberg S, Hemminki K. (1995). Cancer incidence among Finnish workers exposed to halogenated hydrocarbons. Journal of Occupational and Environmental Medicine; 37: 797-806.

Aoki A, Suzaki H, Kawabata Y, Nomura Y (1994) Effect of perchloroethylene inhalation on nasal mucosa in mice. Eur Arch Otorrhinolaryngol 251: 361-365.

Aschengrau A, Paulu C, Ozonoff D (1998) Tetrachloroethylene-contaminated drinking water and the risk of breast cancer. Environmental Health Perspectives; 106 (Suppl 4): 947-953.

Aschengrau A, Ozonoff D, Paulu C, Coogan P, Vezina R, Heeren T, Zhang Y. (1993). Cancer risk and tetrachloroethylene-contaminated drinking water in Massachusetts. Archives of Environmental Health; 48:284-292.

Bagnell PC, Ellenberger HA. (1977). Obstructive jaundice due to a chlorinated hydrocarbon in breast milk. Canadian Medical Association Journal; 117:1047-1048.

Beliles RP, Bruisck DJ, Mecler FJ. (1982). Teratogenic-mutagenic risk of workplace contaminants: trichloroethylene, perchloroethylene and carbon disulfide. US DHEW-NIOSH PB 82-185075. (cited by NEG-DECOS).

Blair A, Petralia SA, Stewart PA (2003) Extended mortality follow-up of a cohort of dry cleaners. Annals of Epidemiology; 13: 50-56.

Blair A. Tolbert P, Thomas T, Grauman D (1985) Mortality among dry cleaners. Proceedings of the 4th International Symposium of Epidemiology (cited by NEG-DECOS)

Blair A, Decoufle P, Grauman D. (1979). Causes of death among laundry and dry cleaning workers. American Journal of Public Health; 69: 508-511.

Bolt HM, Huici-Montagud A (2008) Strategy of the Scientific Committee on Occupational Exposure Limits (SCOEL) in the derivation of occupational exposure limits for carcinogens and mutagens. Arch Toxicol 82: 56-69.

Boice JD Jr, Marano DE, Fryzek JP, Sadler CJ, McLaughlin JK. (1999). Mortality among aircraft manufacturing workers. Occupational and Environmental Medicine; 56: 581-597.

Bosco MG, Figa-Talamanca I, Salerno S. (1987). Health and reproductive status of female workers in dry cleaning shops. International Archives of Occupational and Environmental Health; 59:295-301.

Bove FJ, Fulcomer MC, Klotz JB, Esmart J, Dufficy EM, Savrin JE. (1995). Public drinking water contamination and birth outcomes. American Journal of Epidemiology; 141: 850-862.

Brodkin CA, Daniell W, Checkoway H, Echeverria D, Johnson J, Wang K, Sohaey R, Green D, Redlich C, Gretch D, et al. (1995). Hepatic ultrasonic changes in workers exposed to perchloroethylene. Occupational and Environmental Medicine; 52: 679-85.

Brown DP, Kaplan SD. (1987). Retrospective cohort mortality study of dry cleaner workers using perchloroethylene. Journal of Occupational Medicine; 29: 535-541.

Brüning T, Bolt HM (2000) Renal toxicity and carcinogenicity of trichloroethylene: key results, mechanisms and controversies. Crit. Rev. Toxicol. 30: 253-285.

Cai SX, Huang MY, Chen Z, Liu YT, Jin C, Watanabe T, Nakatsuka H, Seiji K, Inoue O, Ikeda M. (1991). Subjective symptom increase among dry-cleaning workers exposed to tetrachloroethylene vapor. Industrial Health; 29:111-21.

Carney EW, Thorsrud BA, Dugard PH, Zablotny CL (2006) Developmental toxicity studies in Crl:CD (SD) rats following inhalation exposure to trichloroethylene and perchloroethylene. Birth Defects Res B 77: 405-412.

Carpenter CP. (1937). The chronic toxicity of tetrachloroethylene. Journal of Industrial Hygiene and Toxicology; 19: 323-336

DECOS (2003) Tetrachloroethylene (PER). Evaluation of the effects on reproduction, recommendation for classification. The Hague: Health Council of the Netherlands, publication no. 2003/04OSH

DECOS (2004) Tetrachloroethylene (PER) - 2. Health-based occupational exposure limit for short-term exposure. The Hague: Health Council of the Netherlands, publication no. 2004/03OSH

DFG (2005) Tetrachloroethylene, Addendum. In: The MAK-Collection Part II: BAT Value Documentations, Vol.4, pp.127-129. DFG, Deutsche Forschungsgemeinschaft. WILEY-VCH Verlag, Weinheim.

Doyle P, Roman E, Beral V, Brookes M. (1997).Spontaneous abortion in dry cleaning workers potentially exposed to perchloroethylene. Occupational and Environmental Medicine; 54: 848-53.

Duh RW, Asal NR. (1984). Mortality among laundry and dry cleaning workers in Oklahoma.
American Journal of Public Health; 74:1278-1280.

ECETOC (1993) Strategy for assigning a skin notation. Document No. 31. ECETOC, Brussels.

Echeverria D, White RF, Sampaio (1995). A behavioral evaluation of PCE exposure in patients and dry cleaners: a possible relationship between clinical and preclinical effects.
Journal of Occupational and Environmental Medicine; 37: 667-680.

Essing, HG. (1975). [Field study on the hepato- and nephrotoxicity of perchloroethylene after long-term occupational exposure]. Stuttgart: Gentner Verlag. (in German). (cited by DECOS-NEG).

Eskenazi B, Fenster L, Hudes M, Wyrobek AJ, Katz DF, Gerson J, Rempel DM. (1991). A study of the effect of perchloroethylene exposure on the reproductive outcomes of wives of dry-cleaning workers. American Journal of Industrial Medicine; 20: 593-600.

Eskenazi B, Wyrobek AJ, Fenster L, Katz DF, Sadler M, Lee J, Hudes M, Rempel DM. (1991). A study of the effect of perchloroethylene exposure on semen quality in dry cleaning workers. American Journal of Industrial Medicine; 20: 575-591.

EU RAR (2007/2008) EU Draft Risk Assessment Report for Tetrachloroethylene [chapter "Health Effects"].

Ferroni C, Selis L, Mutti A, Folli D, Bergamaschi E, Franchini I. (1992). Neurobehavioral and neuroendocrine effects of occupational exposure to perchloroethylene. Neurotoxicology; 13:243-7.

Franchini I, Caratorta A, Falzoi M, Lucertini S, Mutti A. (1983). Early indicators of renal damage in workers exposed to organic solvents. International Archives of Occupational and Environmental Health; 52: 1-9.

Gennari P, Naldi M, Motta R, Nucci MC, Giacomini C, Violante FS, Raffi GB. (1992). gamma-Glutamyltransferase isoenzyme pattern in workers exposed to tetrachloroethylene. American Journal of Industrial Medicine; 21:661-671.

Gobba F. (2000). Color vision: a sensitive indicator of exposure to neurotoxins. Neurotoxicology; 21:857-862.

Gobba F, Righi E, Fantuzzi G, Roccatto L, Predieri G, Aggazzotti G. (2003). Perchloroethylene in alveolar air, blood, and urine as biologic indices of low-level exposure. Journal of Occupational and Environmental Medicine; 45:1152-7.

Hake, C.L. & Stewart, R.D. (1977). Human exposure to tetrachloroethylene: Inhalation and skin contact. Environmental Health Perspectives; 21: 231-238.

Harth V, Brüning T, Bolt HM (2005) Renal carcinogenicity of trichloroethylene: update, mode of action, and fundamentals for occupational standard setting. Rev. Environ. Health 20: 103-118.

Heineman EF, Cocco P, Gomez MR, Dosemeci M, Stewart PA, Hayes RB, Zahm SH, Thomas TL, Blair A. (1994). Occupational exposure to chlorinated aliphatic hydrocarbons and risk of astrocytic brain cancer. American Journal of Industrial Medicine; 26:155-69.

Hemminki K, Niemi ML, Saloniemi I, Vainio H, Hemminki E. (1980). Spontaneous abortions by occupation and social class in Finland. International Journal of Epidemiology; 9:149-53.

Honma T, Hasegawa H, Sato M, Sudo A (1980) Changes of free amino acid content in rat brain after exposure to trichloroethylene and tetrachloroethylene. Industrial Health; 18: 1-8

Honma T, Sudo A, Miyagawa M, Sato M, Hasegawa H. (1980.) Effects of exposure to trichloroethylene and tetrachloroethylene on the contents of acetylcholine, dopamine, norepinephrine and serotonin in rat brain. Industrial Health 18: 171-178.

IARC (1995). Tetrachloroethylene. Lyon: WHO. (IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans 20).

IPCS (1984). Tetrachloroethylene. Geneva: WHO. (International Programme on Chemical Safety, Environmental Health Criteria 31).

Kaplan SD (1980). Dry-cleaner worker exposed to perchloroethylene; a retrospective cohort mortality study. Contract NO 210-77-0094 Cincinnati, OH: US Department of Health, Education and Welfare. (cited by NEG-DECOS).

Karlsson JE, Rosengren LE, Kjellstrand P, Haglid KG (1987) Effects of low-dose inhalation of three chlorinated aliphatic organic solvents on deoxyribonucleic acid in gerbil brain. Scandinavian Journal of Work, Environment & Health;13:453-458.

Katz RM, Jowett D. (1981). Female laundry and dry cleaning workers in Wisconsin: a mortality analysis. American Journal of Public Health; 71: 305-307.

Kezic S, Monster AC, Kruse J, Verberk MM (2000) Skin absorption of some vaporous solvents in volunteers. Int Arch Occup Environ Health 73: 415-422

Kjellstrand P, Holmquist B, Jonsson I, Romare S, Mansson L. (1985). Effects of organic solvents on motor activity in mice. Toxicology; 35: 35-46.

Kjellstrand P, Holmquist B, Kanje M, Alm P, Romare S, Jonsson I, Mansson L, Bjerkemo M (1984) Perchloroethylene: effects on body and organ weights and plasma

butyrylcholinesterase activity in mice. Acta Pharmacologica et Toxicologica; 54: 414-424.

Kjellstrand P, Mansson L, Holmquist B, Jonsson I (1990). Tolerance during inhalation of organic solvents. Pharmacological Toxicology; 66: 409-414.

Kylin, B., Suemegi, I., & Yllner, S. (1965) Hepatotoxicity of inhaled trichloroethylene and tetrachloroethylene, long-term exposure. Acta Pharmacolica et Toxicologica; 22: 379-385

Kyrklund T, Kjellstrand P, Haglid KG (1987). Lipid composition and fatty acid pattern of the gerbil brain after exposure to perchloroethylene. Archives of Toxicology; 60: 397-400.

Kyrklund T, Kjellstrand P, Haglid KG (1988). Effects of exposure to Freon 11, 1,1,1-trichloroethane or perchloroethylene on the lipid and fatty-acid composition of rat cerebral cortex. Scandinavian Journal of Work, Environment & Health; 14: 91-94.

Kyrklund T, Kjellstrand P, Haglid KG. (1990). Long-term exposure of rats to perchloroethylene, with and without a post-exposure solvent-free recovery period: effects on brain lipids. Toxicology Letters; 52: 279-85.

Kyyronen P, Taskinen H, Lindbohm ML, Hemminki K, Heinonen OP (1989) Spontaneous abortions and congenital malformations among women exposed to tetrachloroethylene in dry cleaning. Journal of Epidemiology and Community Health.; 43:346-51.

Lauwerys R, Herbrand J, Buchet JP, Bernard A, Gaussin J. (1983). Health surveillance of workers exposed to tetrachloroethylene in dry-cleaning shops. International Archives of Occupational and Environmental Health; 52: 69-77.

Lindbohm ML, Taskinen H, Sallmen M, Hemminki K (1990) Spontaneous abortions among women exposed to organic solvents. American Journal of Industrial Medicine; 17: 449-463.

Mazza, A. (1972). (Enzyme modifications following experimental tetrachloroethylene intoxication.) Folia Medica, (Naples, Italy), 55: 373-381 (in Italian). (cited by NEG-DECOS).

McLaughlin JK, Malker HS, Stone BJ, Weiner JA, Malker BK, Ericsson JL, Blot WJ, Fraumeni JF Jr. (1987). Occupational risks for renal cancer in Sweden. British Journal of Industrial Medicine; 44:119-123.

McKernan LT, Ruder AM, Petersen MR, Hein MJ, Forrester CL, Sanderson WT, Ashley DL, Butler MA (2008) Biological exposure assessment to tetrachloroethylene for workers in the dry cleaning industry. Environ Health 7: 12

Mutti A, Alinovi R, Bergamaschi E, Biagini C, Cavazzini S, Franchini I, Lauwerys RR, Bernard AM, Roels H, Gelpi E, et al. (1992). Nephropathies and exposure to perchloroethylene in dry-cleaners. Lancet; 340:189-193.

NCI. (1977). Bioassay of tetrachloroethylene for possible carcinogenicity. (NCI-CG-TR-13, DHEW Publ. No. (NIH) 77-813). Washington, DC: US Govt. Printing Office. (cited by NEG-DECOS).

NTP. (1986). Toxicology and carcinogenesis studies of tetrachloroethylene (perchloroethylene) (CAS No 127-18-4) in F344/N rats and B6C3F1 mice (inhalation studies). National Toxicology Program – Technical Report series no 311. Research Triangle Park, North Carolina

NEG-DECOS. (2003). Tetrachloroethylene (PER). The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and The Dutch Expert Committee on Occupational Standards. Stockholm: National Institute for Working Life.

Odum J, Green T, Foster JR, Hext PM. (1988). The role of trichloroacetic acid and peroxisome proliferation in the differences in carcinogenicity of perchloroethylene in the mouse and rat. Toxicology and Applied Pharmacology; 92:103-112

Palacek I (1970) So-called chemical asthma. Arhiv Za Higijenu Rada I Toksikologiju; 21: 161-166 (cited by NEG-DECOS).

Paulu C, Aschengrau A, Ozonoff D. (1999). Tetrachloroethylene-contaminated drinking water in Massachusetts and the risk of colon-rectum, lung, and other cancers. Environ Health Perspectives; 107: 265-271.

Poet TS, Weitz KK, Gies RA, Edwards JA, Thrall KD, Corley RA, Tanojo H, Hui X, Maibach HI, Wester RC (2002) PBPK modelling of the percutaneous absorption of perchloroethylene from a soil matrix in rats and humans. Toxicol Sci 67: 17-31.

Rampy, LW, Quast, JF, Balmer, MF, Leong, BKJ., Gehring, PJ. (1978). Results of a long-term inhalation toxocity study on rats of a perchloroethylene (tetrachloroethylene) formulation. Midland, Michigan: Toxicology Research Laboratory, Health and Environmental Research, Dow Chemical Company. (cited by NEG-DECOS).

Riikimäki V, Pfäffli P (1978) Percutaneous absorption of solvent vapours in man. Sand J Work Environ Health 4: 73-85

Rosengren LE, Kjellstrand P, Haglid KG. (1986). Tetrachloroethylene: levels of DNA and S-100 in the gerbil CNS after chronic exposure. Neurobehavioural Toxicology and Teratology; 8: 201-6.

Rowe, VK, Mccollister, DD, Spencer HC., Adams, EM, Irish, DD; (1952). Vapor toxicity of tetrachloroethylene for laboratory animals and human subjects. Archives of Industrial. Hygiene and Occupational Medicine; 5: 560-579 .

Ruder AM, Ward EM, Brown DP. (1994). Cancer mortality in female and male dry-cleaning workers. Journal of Occupational Medicine.; 36: 867-874.

Ruder AM, Ward EM, Brown DP. (2001). Mortality in dry-cleaning workers: an update. American Journal of Industrial Medicine; 39: 121-132.

Sallmen M, Lindbohm ML, Kyyronen P, Nykyri E, Anttila A, Taskinen H, Hemminki K (1995) Reduced fertility among women exposed to organic solvents. American Journal of Industrial Medicine; 27: 699-713.

Savolainen H, Pfaffli P, Tengen M, Vainio H. (1977). Biochemical and behavioural effects of inhalation exposure to tetrachloroethylene and dichloromethane. Journal of Neuropathology and Experimental Neurology; 36: 941-949.

Schreiber JS, Hudnell HK, Geller AM, House DE, Aldous KM, Force MS, Langguth K, Prohonic EJ, Parker JC (2002) Apartment residents' and day care workers' exposures to tetrachloroethylene and deficits in visual contrast sensitivity. Environmental Health Perspective 110:655-64.

Schwetz BA, Leong BKJ., Gehring, PJ (1975). The effect of maternally inhaled trichloroethylene, perchloroethylene, methyl chloroform, and methylene chloride on embryonal and fetal development in mice and rats. Toxicology and Applied Pharmacology; 32: 84-96

Seeber A (1989). Neurobehavioral toxicity of long-term exposure to tetrachloroethylene. Neurotoxicology and Teratology; 11: 579-583.

Solet D, Robins TG. (1991). Renal function in dry cleaning workers exposed to perchloroethylene.
American Journal of Industrial Medicine.;20: 601-614.

Sonnenfeld N, Hertz-Picciotto I, Kaye WE. (2001). Tetrachloroethylene in drinking water and birth outcomes at the US Marine Corps Base at Camp Lejeune, North Carolina. American Journal of Epidemiology;154: 902-908.

Spirtas R, Stewart PA, Lee JS, Marano DE, Forbes CD, Grauman DJ, Pettigrew HM, Blair A, Hoover RN, Cohen JL (1991) Retrospective cohort mortality study of workers at an aircraft maintenance facility. I. Epidemiological results. British Journal of Industrial Medicine; 48: 515-530.

Stewart, R.D., Arbor, A., Gay, H.H., Erley, D.S., Hake, C.L., & Schaffer, A.W. (1961) Human exposure to tetrachloroethylene vapor. Archives of Environmental Health; 2: 516-522.

Stewart, R.D., Baretta, E.D., Dodd, H.C., & Torkelson, T.R.(1970) Experimental human exposure to tetrachloroethylene. Archives of Environmental Health; 20: 224-229.

Stewart RD, Hake CL, Wu A, Kalbfleisch J, Newton PE. (1977). Effects of perchloroethylene/drug interaction on behaviour and neurological function. Cont No CDC 201-75-0059 Cincinatti: US Department of Health, Education and Welfare, Public Health Services, NIOSH. (cited by NEG-DECOS).

Stewart RD, Hake CL, Forster HV et al (1981) Tetrachloroethylene: development of a biological standard for the industrial worker by breath analysis. Cincinnati OH: NIOSH Contract HSM 99-72-84 – NIOSH-MCOW-ENVM-PCE-74-6 NTIS No PB82-152166. (cited by ATSDR).

Taskinen H, Anttila A, Lindbohm ML, Sallmen M, Hemminki K. (1989). Spontaneous abortions and congenital malformations among the wives of men occupationally

exposed to organic solvents. Scandinavian Journal of Work, Environment and Health; 15: 345-352.

Tinston DJ (1995) Perchloroethylene: multigeneration inhalation study in the rat. Zeneca Central Toxicology Laboratory, Report CTL/P/4097; cited by EU RAR

Trense, E. Von, & Zimmermann, H. (1969) (Fatal poisoning by inhalation resulting from the long-term action of perchloroethylene vapours.) Zentralblatt fur Arbeitsmedizin, Arbeitsschutz und Ergonomie; 19: 131-137 (in German). (cited by NEG-DECOS).

Tsuruta H (1975) Percutaneous absorption of organic solvents. I) Comparative study of the in vivo percutaneous absorption of chlorinated solvents in mice. Industrial Health 13:227-236.

Tsuruta H (1977) Percutaneous absorption of organic solvents. II) A method for measuring the penetration rate of chlorinated solvents through excised rat skin. Industrial Health 15:131-139.

Tuttle TC, Wood GD, Crether CB, et al (1977): A behavioural and neurological evaluation of dry cleaners exposed to perchloroethylene, US DHEW / NIOSH Report No. 77-214

UK Health and Safety Executive. (1993). Volatile organic compounds in air. Laboratory method using pumped solid sorbent tubes, thermal desorption and liquid chromatography. Sudbury: HSE Books. (Methods for the Determination of Hazardous Substances 72). (www.hse.gov.uk)

UK Health and Safety Executive. (2000). Volatile organic compounds in air. Laboratory method using pumped solid sorbent tubes, thermal desorption and gas chromatography. Sudbury: HSE Books. (Methods for the Determination of Hazardous Substances 96). (www.hse.gov.uk)

UK Health and Safety Executive. (1995). Volatile organic compounds in air. Laboratory method using diffuse solid sorbent tubes, thermal desorption and gas chromatography. Sudbury: HSE Books. (Methods for the Determination of Hazardous Substances 80). (www.hse.gov.uk)

UK Health and Safety Executive. (1998). Volatile organic compounds in air. Laboratory method using diffuse samplers, solvent desorption and gas chromatography. Sudbury: HSE Books. (Methods for the Determination of Hazardous Substances 88). (www.hse.gov.uk).

Ursin C, Hansen CM, Van Dyk JW, Jensen PO, Christensen IJ, Ebbehoej J (1995) Permeability of commercial solvents through living human skin. American Industrial Hygiene Association Journal 56(7):651-660.

US NIOSH. (2003). NIOSH method 1003, issue 3. National Institute for Occupational Health and Safety. (www.cdc.gov/niosh).

US NIOSH. (1998).NIOSH Method 3704. National Institute for Occupational Health and Safety (www.cdc.gov/niosh).

US OSHA. (1999) OSH Method 1001. Occupational Safety and Health Administration. (www.osha.gov).

Vaughan TL, Stewart PA, Davis S, Thomas DB. (1997). Work in dry cleaning and the incidence of cancer of the oral cavity, larynx, and oesophagus. Occupational and Environmental Medicine; 54: 692-695.

Verplanke AJ, Leummens MH, Herber RF. (1999). Occupational exposure to tetrachloroethene and its effects on the kidneys. Journal of Occupational and Environmental Medicine; 41:11-16.

Vyskocil A, Emminger S, Tejral J, Fiala Z, Ettlerova E, Cermanova A. (1990). Study on kidney function in female workers exposed to perchlorethylene. Human and Experimental Toxicology; 9:377-80.

Wang S, Karlsson JE, Kyrklund T, Haglid K. (1993). Perchloroethylene-induced reduction in glial and neuronal cell marker proteins in rat brain. Pharmacology and Toxicology; 72: 273-8.

Windham GC, Shusterman D, Swan SH, Fenster L, Eskenazi B. (1991). Exposure to organic solvents and adverse pregnancy outcome. American Journal of Industrial Medicine; 20: 241-259.

Zielhuis GA, Gijsen R, van der Gulden JW. (1989). Menstrual disorders among dry-cleaning workers. Scandinavian Journal of Work, Environment & Health; 15: 238.