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Evaluation of health hazards by exposure to Tetrachloroethylene and proposal of a health-based quality criterion for ambient air

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Title:

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Content

Preface

Tetrachlorethylene was evaluated in 1995 and a health-based air quality criterion of 0.00017 mg/m^3 was set based on the carcinogenic potential (liver tumours in mice) of tetrachloroethylene with the assumption of a non-threshold mechanism (genotoxicity) for the critical effect (Larsen 1995). The C-value was set at 0.01 mg/m^3, and tetrachloroethylene was placed in Main Group 1.

In 2001, the documentation for tetrachloroethylene was updated and revised (Larsen 2001) and the health-based air quality criterion was changed to 0.006 mg/m^3 and based on the toxicity to the liver, an endpoint for which a threshold mechanism is assumed. The C-value was still set at 0.01 mg/m^3, and tetrachloroethylene was still placed in Main Group 1.

New assessments and evaluations of tetrachloroethylene as well as new data have been published since the 2001 revision of the documentation for the health-based air quality criterion for tetrachloroethylene:

Tetrachloroethylene is a high production volume (HPV) chemical, which has been prioritised for risk assessment within the former EU Existing Substances Regulation. The UK has prepared a comprehensive risk assessment report (RAR) for tetrachloroethylene (EU-RAR 2001, 2007), which has been discussed in the EU former 'Technical Committee on New and Existing Substances' (TC NES). The final version of the draft risk assessment report, human health part (EU-RAR 2007) was send to the EU Scientific Committee on Health and Environmental Risks (SCHER) for commenting and SCHER has published its opinion in 2008 (SCHER 2008).

In June 2008, the US-EPA released its draft 'Toxicological Review of tetrachloroethylene' (US-EPA 2008). At the request of the US-EPA, the National Research Council (NRC) convened a committee to conduct an independent scientific review of the draft assessment. The NRC review was published in 2010 in form of a book as well as a free summary; the free summary (NAS 2010) has been used in this document. The US-EPA has recently published the final version of the 'Toxicological Review of tetrachloroethylene' (US-EPA 2012).

In addition to the EU and US-EPA assessments, a Concise International Chemical Assessment Document (CICAD) was published in 2006 (CICAD 2006). The CICAD is published under the joint sponsorship of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO), and the World Health Organization (WHO), and produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals. The CICAD contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the United Nations Environment Programme, the International Labour Organization, or the World Health Organization.

The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG) and The Dutch Expert Committee on Occupational Standards (DECOS) published a criteria document in 2003 (NEG/DECOS 2003).

Finally, a new genotoxicity study on tetrachloroethylene was published in 2010 (Cederberg et al. 2010a).

The purpose of this document is to consider whether the current health-based air quality criterion should be revised with a primary focus on the new data, assessments and evaluations regarding the genotoxic and carcinogenic effects of tetrachloroethylene as these effects have given rise to an intensive debate nationally as well as internationally, and no consensus has been arrived at yet. In addition, focus will also be on effects following repeated inhalation exposure, which also are essential for a possibly revision of the current health-based air quality criterion. Other endpoints such as acute toxicity, irritation, sensitisation and toxicity to reproduction are only addressed briefly.

This document has been prepared based on the final version of the draft EU risk assessment report, human health part (EU-RAR 2007) as the Danish EPA has taken part in the EU TC NES discussions and therefore has acknowledged the conclusions in the draft EU RAR. It should be noted that the draft EU-RAR, human health part (EU-RAR 2007) can only be cited, quoted or copied if permission of the Member State rapporteur (UK) has been obtained beforehand. As the Danish EPA has taken part in the EU TC NES discussions and acknowledged the conclusions in the draft EU-RAR, and as the draft EU-RAR is publicly available, it has been decided by the Danish EPA that the draft EU-RAR can be cited, quoted and copied for use in this document. Thus, all the information in Chapters 2, 3, 4 and 6 in this document has been extracted from the EU-RAR (2007) unless otherwise stated.

The assessments and evaluations from the SCHER Opinion (SCHER 2008), the US-EPA Toxicological Review (US-EPA 2012), the NRC review (NAS 2010), the Concise International Chemical Assessment Document (CICAD 2006), and the NEG/DECOS criteria document (NEG/DECOS 2003) in relation to the genotoxic and carcinogenic effects of tetrachloroethylene have been cited in Section 6.7 as the purpose of this document is primarily to focus on the new data, assessments and evaluations regarding these effects. Attention has also been given to the genotoxicity study published in 2010 (Cederberg et al. 2010a).
In addition, the assessments and evaluations from the US-EPA Toxicological Review (US-EPA 2012) in relation to the toxic effects following repeated inhalation exposure have also been cited in Section 6.7 as these effects also are a focus in this document.
No further references were consulted specifically in the preparation of this document.

This document has been prepared by the Division of Toxicology and Risk Assessment, National Food Institute, Technical University of Denmark.

The document has been elaborated according to the overall practice laid down in the Danish EPA guideline document for the setting of health based quality criteria for chemical substances in relation to soil, ambient air and drinking water (MST 2006).

Furthermore, the document has been subjected to review and discussion and has been adopted in a steering committee with representatives from the following Danish authorities/ institutions:

- The National Board of Health
- The Danish Working Environment Authority
- The Danish Veterinary and Food Administration
- Danish Environmental Protection Agency

1 General description

1.1 Identity

Molecular formula:	C_2Cl_4
Structural formula:	$Cl_2C=CCl_2$
Molecular weight:	165.85
CAS-no.:	127-18-4
Synonyms:	Perchlor Perchloroethylene Tetrachlorethene 1,1,2,2-Tetrachloroethylene

1.2 Physical / chemical properties

Description:	Colourless liquid with an ethereal odour
Purity:	99-100% May contain stabilizers
Melting point:	-22 to -22.7ºC
Boiling point:	121.2ºC
Density:	1.623 (at 20ºC)
Vapour pressure:	14.3 mmHg (1.9 kPa) (at 20ºC)
Saturated vapour concentration:	25,000 ppm (169,500 mg/m^3) (at 20ºC)
Vapour density:	5.8
Conversion factor:	1 ppm = 6.78 mg/m^3 1 mg/m^3 = 0.147 ppm
Flash point:	Not flammable
Solubility:	149 mg/l (water) Miscible with alcohol, ether, chloroform and benzene
Log $K_{o/w}$:	2.53
Incompatibilities:	When exposed to light and air, tetrachloroethylene will slowly oxidise to trichloroacetyl chloride and phosgene at

ambient temperatures. This auto-oxidation is suppressed by the addition of stabilisers (usually amines or phenols).

Odour threshold, air: ~180 mg/m^3 (recognition)

Reference: EU-RAR (2001)

1.3 Production and use

Tetrachloroethylene is a high production volume chemical.

The major uses of tetrachloroethylene are as a chemical intermediate and a dry cleaning solvent. Other uses include in metal cleaning and extraction processes. Some minor uses have been reported and these include use as a textile scouring solvent, fumigant, stain remover, paint remover and heat transfer media ingredient. (EU-RAR 2001).

1.4 Environmental occurrence and fate

The information in this section is extracted from the EU-RAR (2001) unless otherwise stated.

Tetrachloroethylene is released to the environment during production and use.

1.4.1 Environmental distribution

Tetrachloroethylene is distributed between environmental compartments by volatilisation, precipitation and adsorption. Tetrachloroethylene is predominantly released and transported to the atmosphere. Based upon its environmental chemistry, computer models predict that the atmosphere will be the major sink for tetrachloroethylene.
Tetrachloroethylene has the potential to dissolve in atmospheric water droplets and be deposited by rainout.

Tetrachloroethylene released to surface waters is rapidly lost through volatilisation to the atmosphere. The evaporation half-life of
tetrachloroethylene from field measurements and theoretical considerations is of the order of 1-10 days in rivers and 10 days to one month in lakes and ponds.

Tetrachloroethylene can be adsorbed onto soils of varying organic carbon contents. The amounts adsorbed are negligible hence tetrachloroethylene is relatively mobile in groundwater in the absence of any removal processes.

1.4.2 Degradation in the environment

Once released to the environment tetrachloroethylene may undergo a number of degradation and removal processes. The processes that can occur are dependent upon the systems into which the release occurs.

1.4.2.1 Atmospheric degradation

Tetrachloroethylene will react in the atmosphere with a number of photochemically produced species. The major reaction that occurs is with hydroxyl radicals, and this is the major removal process for tetrachloroethylene from the atmosphere. The reaction with atmospheric chlorine atoms is thought to be the next most important atmospheric degradation mechanism for tetrachloroethylene. The overall lifetime for the two processes combined is thought to be around 3 months, although the exact contribution of the reaction with chlorine atoms to the overall degradation of tetrachloroethylene is uncertain.

The main products formed during the photochemical degradation of tetrachloroethylene in air are phosgene, trichloroacetyl chloride, hydrogen chloride, carbon dioxide and carbon monoxide, but other products such as carbon tetrachloride, dichloroacetyl chloride and chloroform have also been detected

The lifetime for removal of tetrachloroethylene by gas phase photolysis has been calculated to be about 3 years in the troposphere. Direct photolysis is therefore thought to be of negligible importance compared to other tropospheric removal mechanisms.

1.4.2.2 Aquatic degradation

A number of studies have been reported on the biodegradation of tetrachloroethylene.
Based upon the data reported tetrachloroethylene undergoes anaerobic biodegradation by a process of reductive dechlorination. The degradation products reported are trichloroethylene, dichloroethylene, vinyl chloride, ethene and ethane. The degradation products found vary and are dependent upon the experimental conditions used.
Tetrachloroethylene does not appear to undergo aerobic biodegradation.

Degradation of tetrachloroethylene in water by hydrolysis is very slow, with half lives in the order of years reported.

Tetrachloroethylene may be removed from aquatic systems by photochemical reactions, involving free radicals or electronically excited molecular species. These reactions are only likely to compete with volatilisation in still, sunlit waters where volatilisation is limited by the available surface area for evaporation.

Reductive pathways involving transition metals or their organic complexes may be significant in the presence of soils or sediments.

1.4.3 Accumulation

Bioconcentration factors (BCFs) of approximately 40-50 have been reported for aquatic species with tetrachloroethylene. Based on these data, no significant bioaccumulation of tetrachloroethylene is expected.

The log $K_{o/w}$ value for tetrachloroethylene is below 3, indicating a low potential for bioaccumulation.

1.4.4 Environmental concentrations

The majority of measured atmospheric levels are below 10 μg/m^3, with most levels below 1 μg/m^3.

Tetrachloroethylene levels have been measured in a number of water systems. Measured concentrations in the majority of drinking water samples are below 0.5 μg/l.
In 1999 tetrachloroethylene was found in approximately 2% of samples taken in the general groundwater monitoring part of the general Danish Monitoring Programme NOVA (n ≈ 1000), whereas the detection frequency in drinking water wells was 5% (n ≈ 1700) (Personal Communication (Danish EPA), 2001).

No measured soil levels are reported.

1.5 Human exposure

The information in this section is extracted from the EU-RAR (2007) unless otherwise stated.

The most significant human exposure via the environment is likely to occur in flats above dry-cleaning establishments. Exposure to a person living above a dry-cleaning establishment and eating food that has been stored in the vicinity is regarded as a foreseeable worst-case scenario for exposure via the environment. This gives a predicted exposure of approximately 1429 μg/kg bw/day from air + 15.7 μg/kg bw/day from food which is equivalent to a total predicted exposure of 1445 μg/kg bw/day (1.45 mg/kg bw/day).

For combined exposure, consideration is given to a consumer who may also be exposed indirectly via the environment. A worst-case scenario would be a consumer exposed daily from wearing freshly dry-cleaned clothes (46 mg/day equivalent to 0.66 mg/kg bw/day for a 70 kg individual), and who also lives in the vicinity of a dry-cleaning establishment and consuming food stored in the vicinity (1.45 mg/kg bw/day), which is equivalent to a total of 2.11 mg/kg bw/day.

2 Toxicokinetics

2.1 Absorption, distribution, and excretion

The information in this section is extracted from the EU-RAR (2007) section 4.1.2.1 'Toxicokinetics'.

A substantial amount of human information and animal studies are available on the toxicokinetics of tetrachloroethylene.

In both humans and animals, tetrachloroethylene is rapidly and extensively absorbed by the inhalation and oral routes of exposure. In the EU-RAR (2007), values of 100% have been taken forward to the risk characterisation.

Skin absorption of liquid tetrachloroethylene has been detected in studies in humans, animals and *in vitro*. In the EU-RAR (2007), a worst-case absorption value of 50% has been considered appropriate for risk characterisation purposes.

Human evidence indicates that dermal absorption of vapour would contribute only a minimal amount (~0.3-1%) of that which would be absorbed by inhalation under normal conditions.

Following absorption, tetrachloroethylene is subject to widespread systemic distribution to all organs and tissues, with selective partitioning into fat. Tetrachloroethylene penetrates the blood-brain barrier, crosses the placenta and enters the foetus, and also enters breast milk.

Human and animal evidence indicates that relatively little of the absorbed tetrachloroethylene is metabolised; the fraction of the absorbed dose, which is metabolised decreases with increasing dose in a manner consistent with saturable metabolism.
Maximum rates of metabolism have been measured in mice in which 25% of a low dose (20 mg/kg bw/day) was metabolised, compared with only 5% of a high dose (2000 mg/kg bw/day).
In humans, less than 2% of the retained amount of tetrachloroethylene was metabolised and excreted in the urine within 67 hours following a 3-hour exposure to 87 ppm (600 mg/m^3). Since a mean half-life of about144 hours for the elimination of urinary metabolites following inhalation exposure has been calculated in humans, it can, according to the EU-RAR (2007), be estimated that, in total about 8% of an inhaled dose is eliminated as urinary metabolites.

The majority of absorbed tetrachloroethylene is exhaled unchanged in the breath (approximately 80% in humans; up to 91% in rats).
The metabolites of tetrachloroethylene are excreted in the urine (approx. 8% of an inhaled dose), with very low percentages of the absorbed amount exhaled as carbon dioxide (1%) or eliminated in the faeces (2%).

Precise values for the half-life of elimination of tetrachloroethylene in humans cannot be identified from the available data, but rough estimates indicate values of

6-10 days. Furthermore, there is some evidence that with repeated exposure tetrachloroethylene accumulates in fat stores.

The metabolism of tetrachloroethylene shows inter-species variability, with some differences in dose-response trends.

The major route of metabolism in humans and animals involves cytochrome P450 oxidation (Figure 1); this proceeds more rapidly in mice than in rats, and more rapidly in rats than in dogs. The pathway leads to the formation of an epoxide (1,1,2,2-tetrachlorooxirane) and ultimately to trichloroacetic acid, which in turn may be reduced to trichloroethanol. There is, according to the EU-RAR (2007), clear animal and human evidence that the oxidative metabolism of tetrachloroethylene is a saturable process.

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-trichlorovinylglutathione. The conjugate is then converted by the enzymes of mercapturic acid formation to S-1,2,2-trichlorovinylcysteine and ultimately to N-acetyl-S-1,2,2-trichlorovinylcysteine which is excreted in the urine. S-1,2,2-trichlorovinylcysteine is also a substrate for renal β-lyase, producing the reactive intermediate dichlorodithioketene. This intermediate is subsequently hydrolysed to yield dichloroacetic acid.
Although one study indicates that the glutathione conjugation step of this pathway may occur 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, more recent evidence using a more sensitive technique, shows that this pathway occurs with linear kinetics. Dose-dependant 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 (69 mg/m^3) up to 400 ppm (2760 mg/m^3) tetrachloroethylene for 6-hours.

Evidence that the first step of this 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, 345 mg/m^3) 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 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, which have investigated the rates of glutathione conjugation of tetrachloroethylene in human, rat and mouse microsomal and

cytosolic fractions of liver and kidney. The rate of the S-(1,2,2-trichlorovinyl) glutathione formation was seen 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 even though glutathione S-transferase activity had been confirmed, which indicates that human liver samples exhibit the potential to conjugate tetrachloroethylene, but at a much lower extent than male rats (at least 80-fold lower).

It is important to note, according to the EU-RAR (2007), that these *in vitro* data reinforce the picture obtained *in vivo* as they confirm that the first step of this pathway is more active in male rats compared to female rats and mice, and that humans are likely to be even less active in this pathway than mice.

The conjugate S-1,2,2-trichlorovinylcysteine 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 (cumulative levels of 0.72 μmol/kg bw at an exposure of 40 ppm for 6 hours), but not in humans indicating that there was no β-lyase activity or it was below the limit of detection (< 50 ng dichloroacetic acid/ml urine) in 6 volunteers exposed up to 40 ppm (276 mg/m^3) tetrachloroethylene for 6 hours.
In relation to mice, it is unclear from the data whether or not dichloroacetic acid was investigated and not detected or whether it was not measured at all.

The result of no apparent β-lyase activity in humans *in vivo* has also been confirmed in a second study where no N^{ε}-(dichloroacetyl)-L-lysine (the protein adduct deriving from interaction with dichlorodithioketene, the final reactive metabolite of the glutathione conjugation/β-lyase pathway) formation was detected in the serum of 6 volunteers exposed up to 40 ppm (276 mg/m^3) tetrachloroethylene for 6 hours, in spite of using a very sensitive technique (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 pathway is at least 40-fold (0.4 pmol/limit of dectection) 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 lower in humans and mice compared to rats and 2-fold greater in male rats compared to female rats.

Overall, it was concluded (EU-RAR 2007), 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.

3 Human toxicity

3.1 Single dose toxicity

The information in this section is extracted from the EU-RAR (2007) section 4.1.2.2.3 'Summary of acute toxicity'.

Accidental inhalation by humans of tetrachloroethylene has led to death. Signs of CNS depression, such as unconsciousness and narcosis, have commonly been reported. There may also be transient and relatively minor effects in the liver.

Information from volunteers is limited.
A NOAEC of 106 ppm (731 mg/m^3) was identified in one study for subjective CNS effects, following a 1-hour exposure. Dizziness and drowsiness occurred at 216 ppm (1490 mg/m^3) following a 2-hour exposure.
Subjective CNS effects were also reported at 100 ppm (690 mg/m^3), the only concentration tested, following a 7-hour exposure in another volunteer study. A LOAEC of 100 ppm (690 mg/m^3) for a 7-hour exposure can be identified from this study.
Although both these human volunteer studies were considered in the EU-RAR (2007) as being limited in their study design, the NOAEC and LOAEC were considered to be sufficiently robust to be taken forward to the risk characterisation.

3.2 Irritation

The information in this section is extracted from the EU-RAR (2007) section 4.1.2.3.3 'Summary of irritation'.

There is evidence from observations in humans that tetrachloroethylene is irritating (but not corrosive) to the skin.

Slight and transient eye irritation which developed within the first two hours of exposure and subsided before the end of the 7-hour exposure has been reported by human volunteers at about 100 ppm (690 mg/m^3).

Mild nasal irritation was reported by volunteers exposed at 216 ppm (1490 mg/m^3) for 2 hours but not at 106 ppm (731 mg/m^3) for 1 hour, and at 100 ppm (690 mg/m^3) for 7 hours.
According to the EU-RAR (2007), the nasal irritation reported in the two human volunteer studies available is very mild and of transient nature.

3.3 Sensitisation

The information in this section is extracted from the EU-RAR (2007) section 4.1.2.5.2 'Sensitisation, Studies in humans'.

Published information is limited to a letter reporting a positive closed patch test with tetrachloroethylene in a metal-worker complaining of acute dermatitis of the hands and wrists. An allergic reaction to tetrachloroethylene was claimed.

There are two reports of dry-cleaning workers who developed symptoms of asthma following exposure to unquantified but clearly high concentrations of tetrachloroethylene.
Although both of these reports implicate tetrachloroethylene in the production of symptoms of asthma, it is unlikely, according to the EU-RAR (2007) that the underlying mechanism is immunologically-mediated. Rather, the limited information available suggests that irritation of the airways was a significant factor in the development of the asthmatic symptoms observed.

3.4 Repeated dose toxicity

The information in this section is extracted from the EU-RAR (2007) section 4.1.2.6.2 'Repeated dose toxicity, Studies in humans, Inhalation'.

Although there are a considerable number of studies on the health of workers repeatedly exposed to tetrachloroethylene, the EU-RAR (2007) considered that deficiencies in the conduct and/or reporting of most of them make interpretation of their findings difficult.

In general health surveys, variable results and interpretational difficulties have arisen in those surveys in which workers were exposed to concentrations below 100 ppm (690 mg/m^3) 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.
The subjective symptoms of CNS depression have also been described in several studies with exposure concentrations as high as 300-400 ppm (2034-2712 mg/m^3) tetrachloroethylene.
Since this symptomatology is associated with the acute CNS depressant effects of tetrachloroethylene, these latter effects are, according to EU-RAR (2007), very much likely to be acute CNS effects arising from single peak exposures rather than the consequence of repeated exposure.

Two specific hepatotoxicity studies together with the hepatotoxicological investigations of several worker health surveys have, according to the EU-RAR (2007), provided no clear evidence for tetrachloroethylene-induced liver toxicity at exposure concentrations below 50 ppm (339 mg/m^3; 8-hour TWA).

The potential for workplace exposure to tetrachloroethylene to produce kidney toxicity has been investigated in six studies focusing specifically on nephrotoxicity, and also in a number of general health surveys. These studies have, according to the EU-RAR (2007), provided no convincing evidence of kidney toxicity at mean exposure levels in the range 1.2-23 ppm (8.3-159 mg/m^3).

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, according to EU-RAR (2007), 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, according to EU-RAR (2007), 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, according to EU-RAR (2007), 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, according to EU-RAR (2007), be likely to be acute CNS effects arising from repeated single exposures rather than the consequence of long-term repeated exposure.
Overall, there is, according to EU-RAR (2007), 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, the rapporteur (United Kingdom) proposes that the 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.

There are very few studies that have specifically investigated the effects of tetrachloroethylene on colour discrimination.
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, according to EU-RAR (2007), so little information on the effects of tetrachloroethylene on colour discrimination that no reliable conclusions can be drawn.

3.5 Toxicity to reproduction

The information in this section is extracted from the EU-RAR (2007) section 4.1.2.9.2 ‘Human reproduction’.

3.5.1 Fertility and general reproductive performance

The effects of tetrachloroethylene on fertility and reproductive performance have not been well-investigated in humans; the two studies available relating to fertility and tetrachloroethylene were, according to the EU-RAR (2007), of insufficient power to allow firm conclusions to be drawn.
Other reports provide some information on menstrual disorders and on semen quality among dry-cleaners exposed to tetrachloroethylene. However, due to a number of limitations (size of the studies, lack of information on exposure, marginal significance of the effects reported), no firm conclusions can, according to the EU-RAR (2007), be drawn.

3.5.2 Developmental toxicity

A recent UK retrospective cohort study of dry-cleaners has shown no significant difference in the risk of spontaneous abortion between laundry workers and dry-cleaners. Although in this study small, but statistically significant, increases were observed in the so-called dry-cleaning ‘operators’ compared with ‘non-operators’, it was impossible, according to the EU-RAR (2007), to conclude with any confidence that this increase was due to exposure to tetrachloroethylene. Although the study authors claim that exposure to tetrachloroethylene was higher for the operators compared to the non-operators, no actual data/measurements were provided to substantiate this claim. Moreover, no consideration was given to any different distribution between operators and non-operators of many important confounding factors such as bending down and heavy lifting.

Previous evidence for a positive association with tetrachloroethylene exposure derives mainly from two case-control studies, both of which involve small numbers and may be subject to various criticisms, including the fact that they failed to take into account known work-related risk factors for spontaneous abortion such as strenuous work, prolonged standing, bending down, shift-work and high work. Both studies have a number of limitations: for example, telephone interviewing, as used in the Windham study, often raises suspicions, and the study did not have any objective measure of exposure. The Kyyronen study was conducted in an industry where concern, due to the findings of earlier studies, might have been high resulting in a degree of reporting bias. The Windham study was conducted across a broad industrial base, involved some mixed exposures and included only one dry-cleaning worker.

Overall, the results of these studies in humans can, according to the EU-RAR (2007), not be taken as convincing evidence that exposure to tetrachloroethylene results in an increased risk of developmental toxicity including spontaneous abortion, but they raise a concern among some experts.

The available developmental toxicity data in humans were discussed by the Commission Group of Specialised Experts in the fields of Carcinogenicity, Mutagenicity and Reprotoxicity in September 2000. No clear agreement on the interpretation of these data was reached. Some epidemiologists and several other

experts stressed the consistency of the observations at high tetrachloroethylene exposure between the Kyyronen and Doyle studies (using different methodologies), as convincing evidence for an increased risk of spontaneous abortions. While for some individual Experts these data led to an unambiguous Category 1, the majority of the Specialised Experts did not regard the data quite sufficient for this Category and favoured classification of tetrachloroethylene in category 2 for effects upon development. Other Experts indicated that the Kyyronen and Doyle studies, both with borderline results, could not be considered as sufficient evidence for an increased risk of spontaneous abortions in humans. For these Experts the overall interpretation of the human evidence was inconclusive. Assertive corroboration or at least non-contradiction by animal toxicology, respectively the type and strength of the animal evidence, was important in reaching the final conclusion.

3.6 Mutagenic and genotoxic effects

The information in this section is extracted from the EU-RAR (2007) section 4.1.2.7.3 ‘Human genotoxicity’.

A study has been conducted in Japan involving cytogenetic investigations of phytohaemagglutinin-stimulated peripheral lymphocytes from 10 (7 male and 3 female) workers. No exposure-related effects were observed in the frequency of chromosomal aberrations or sister chromatid exchanges in the lymphocyte cultures, compared with those from an ill-defined group of 11 unexposed controls. Similarly, negative results for sister chromatid exchanges in phytohaemagglutinin-stimulated lymphocytes were obtained in a study of 27 Japanese dry-cleaning workers. Overall, however, no firm conclusions can, according to the EU-RAR (2007), be made, due to limitations regarding the small numbers of subjects, lack of normal reference data and/or poor matching of the controls.

A recent study has investigated the effect of tetrachloroethylene on oxidative DNA damage in female dry cleaners. Tetrachloroethylene levels in blood were two orders of magnitude higher in dry cleaners compared to launderers. A significant correlation was noted between airborne concentrations of tetrachloroethylene compared to laundry workers. In contrast, urinary levels of 8-epi-PGF or 8-OHdG did not differ between launderers and dry cleaners. While the leukocyte 8-OHdG assessment suggests that tetrachloroethylene exposure resulted in reduced damage from oxidative stress or increased repair of oxidative DNA damage, the other measures of oxidative stress do not support this conclusion. The assessment of urinary 8-epi-PGF is consistent with the conclusion that there is no association between tetrachloroethylene exposure in the study population and oxidative stress. If increased repair was responsible for decreased leukocyte 8-OHdG, a corresponding increase in urinary 8-OHdG would have been expected. This, however, was not the case.

3.7 Carcinogenic effects

The information in this section is extracted from the EU-RAR (2007) section 4.1.2.8.2 ‘Human carcinogenicity’.

Several large-scale studies of cancer mortality and cancer incidence among workers exposed to tetrachloroethylene in dry-cleaning and laundering have been reported.

The occupational mortality studies have generally been, according to the EU-RAR (2007), limited by the lack of clear information on the levels of exposure to tetrachloroethylene, and by possible confounding due to exposure to other solvents among the subjects studied. In this regard, the widespread use of tetrachloroethylene in the dry cleaning industry did not begin until the 1960s, and assuming a latency for tumour development of 15-20 years, the cancer deaths observed in some of the studies for periods up to 1980-82, if occupationally related, would be attributable to exposure conditions prior to the widespread use of tetrachloroethylene.
In those studies where cancer mortality could be distinguished among workers employed in establishments using tetrachloroethylene only, no increases in the risks for liver and renal cancers were observed.
In this sub-cohort of tetrachloroethylene-exposed dry-cleaners, elevated mortality was seen only in relation to cancer of the oesophagus, buccal cavity and pharynx, and tongue. The anatomical location of these tumours suggests, according to the EU-RAR (2007), a role for a locally acting carcinogen, which is not supported by the available genotoxicity and animal carcinogenicity database. Latency considerations for this study also argue, according to the EU-RAR (2007), against a possible role for tetrachloroethylene.

In cancer incidence studies, no increases in risks from exposure to tetrachloroethylene for any specific type of cancer, including risks for liver and renal cancers, have, according to the EU-RAR (2007), been observed.

According to the EU-RAR (2007), a recent critical review of the epidemiological literature on occupational exposure to tetrachloroethylene and cancer has considered that the current evidence does not support a conclusion that occupational exposure to tetrachloroethylene is a risk factor for cancer of any specific site, although a firm conclusion cannot be drawn based on the available data.

4 Animal toxicity

4.1 Single dose toxicity

The information in this section is extracted from the EU-RAR (2007) section 4.1.2.2.3 ‘Summary of acute toxicity’.

In animals, as in humans, the main signs of acute inhalation toxicity are indicative of CNS depression. Acute lethality is low, with LC_{50} values for rat and mouse mostly being greater than 3000 ppm (20 mg/l).

4.2 Irritation

The information in this section is predominantly extracted from the EU-RAR (2007) section 4.1.2.3.1 ‘Irritation, Studies in animals’ and section 4.1.2.3.3 ‘Summary of irritation’.

There is evidence from a good-quality animal study that tetrachloroethylene is a pronounced skin irritant, but not corrosive.

In a rabbit eye irritation study instillation of liquid tetrachloroethylene produced only minimal effects.

A study of the respiratory irritant potential of tetrachloroethylene in male rats indicates that exposures of about 10000 ppm (69000 mg/m^3) for 25 minutes did not cause respiratory irritation.

4.3 Sensitisation

The information in this section is predominantly extracted from the EU-RAR (2007) section 4.1.2.5.1 ‘Sensitisation, Studies in animals’.

Information is limited to the findings of a split adjuvant-type assay conducted in 9 test guinea pigs; no skin sensitisation was apparently observed in any of the test animals, but the specific conditions (e.g. induction and challenge concentrations) and results are so briefly reported that it is impossible to properly assess the stringency of the test as an evaluation of the skin sensitising potential of tetrachloroethylene. Clearly, the test does not comply with modern regulatory requirements, and no firm conclusions can, according to the EU-RAR (2007) be reached.

No information is available on respiratory tract sensitisation.

4.4 Repeated dose toxicity

The information in this section is extracted from the EU-RAR (2007) section 4.1.2.6.1 'Repeated dose toxicity, Studies in animals, Inhalation'.

4.4.1 Studies in rats

There is a substantial amount of information available from repeated inhalation toxicity studies in rats.

Mortality, CNS depression, body weight effects and lung congestion occur at very high exposure concentrations (1600-2500 ppm; 11040-17250 mg/m^3).
At lower exposure concentrations, the data indicate that the kidney is the main target organ of toxicity.

An increased incidence of tubular cell karyomegaly and cytomegaly was observed in both sexes (with a higher incidence in males compared to females) of F344 rats exposed to ≥ 200 ppm (1380 mg/m^3) in a 2-year cancer bioassay.
It has been postulated that a plausible mechanism for this kidney toxicity in rats is via a genotoxic/cytotoxic metabolite formed in the kidney via the glutathione conjugation/β-lyase pathway. The toxicokinetic data show that this pathway is more active in male F344 rats (for which the incidence of karyomegaly/ cytomegaly was higher) compared to female F344 rats (for which the incidence of karyomegaly/cytomegaly was lower) and is approximately 40-fold less active in humans compared to F344 rats.
Based on this effect, an inhalation LOAEC of 200 ppm (1380 mg/m^3) can, according to the EU-RAR (2007), be set for kidney toxicity in the rat, although humans are considered to be approximately 40-fold less sensitive to this effect than rats.

Renal tubule hyaline droplet formation was also seen in male F344 rats but only at the very high exposure concentration of 1000 ppm (6900 mg/m^3) for 10 days and not at 800 ppm (5520 mg/m^3) for 28 days, indicating, according to the EU-RAR (2007), that this phenomenon, which is male rat-specific and hence, not relevant to humans, only occurs at very high levels of exposure which were administered for relatively short periods of time.
In addition, a slightly increased incidence of minimal chronic progressive glomerulonephropathy and of nuclear pleomorphism within the proximal tubule was reported at the relatively high exposure concentration of 1000 ppm (6900 mg/m^3) in the parental generation of a 2-generation study.

In relation to the liver, hepatic congestion was seen at ≥ 200 ppm (1380 mg/m^3) in a 13-week study. Also, hepatic centrilobular hypertrophy was seen at 400 ppm (2760 mg/m^3) in both sexes and at 200 ppm (1380 mg/m3) in males only in a 28-day study, and slight centrilobular eosinophilia was seen at 800 ppm (5520 mg/m^3) but not at 400 ppm (2760 mg/m^3) in another 28-day study.
The reliability of these findings is, according to the EU-RAR (2007), rather doubtful as no liver lesions were seen in a 2-year cancer bioassay at exposure concentrations up to 400 ppm (2760 mg/m^3) and in a 2-generation study at exposure concentrations up to 1000 ppm (6900 mg/m^3) for 14-17 weeks.

Alterations of the visual evoked potentials were observed in a good-quality study at 800 ppm (5520 mg/m^3) for 13 weeks, but no other neurotoxic effects were

observed in the same study at exposure concentrations of up to 200 ppm (1380 mg/m^3).
A number of other studies have reported small changes in the fatty-acid composition of the cerebral cortex, in brain amino acids content, in neurotransmitter levels and in some glial and neuronal cell marker proteins.
It is noted that, in the absence of normal reference ranges, the toxicological significance of these small changes in these non-standard parameters cannot be determined. However, as these changes were small, were not accompanied by any histopathology, behavioural or functional impairment or related electrophysiological changes, and did not show any consistent pattern across different studies, it is, according to the EU-RAR (2007), reasonable to conclude that they are of no toxicological significance.

4.4.2 Studies in mice

As with rats, mortality, CNS depression and body weight effects occur only at very high exposure concentrations (1600-1750 ppm; 11040-12075 mg/m^3).
At lower exposure concentrations, the data indicate that the liver, kidneys and lungs are the main target organs of toxicity.

In relation to the liver, fatty vacuolation was seen at 875 and 1750 ppm (6038 and 12075 mg/m^3) in a 2-week study. Also, leucocyte infiltration, centrilobular necrosis and bile stasis were observed at ≥ 400 ppm (2760 mg/m^3), but not at 200 ppm (1380 mg/m^3) in a 13-week study, and fatty degeneration was seen at 200 ppm (1380 mg/m^3) for 1 week up to 8-week exposure. In the 2-year cancer bioassay degeneration, necrosis, vacuolation, inflammatory infiltration and regenerative foci were reported at ≥ 100 ppm (690 mg/m^3). Mechanistic studies have, according to the EU-RAR (2007), shown evidence of peroxisomal proliferation at exposure levels of 200 and 400 ppm (1380 and 2760 mg/m^3) for up to 28 days and formation of trichloroacylated protein adducts following single or repeated (up to 6 weeks) exposure to 120 ppm (828 mg/m^3). Based on these toxicokinetic studies, it is, according to the EU-RAR (2007), considered that the underlying mechanism leading to liver toxicity in mice involves peroxisomal proliferation, an effect to which humans are not responsive. The oxidative metabolic pathway to trichloroacetic acid, an established peroxisomal proliferator in rodents, is particularly active in mouse liver.
In view of this mechanism, the liver toxicity observed in mice is, according to the EU-RAR (2007), considered to be of no relevance to human health.

In relation to the kidney, an increased incidence of tubular cell karyomegaly was seen at ≥ 200 ppm (1380 mg/m^3) but not at 100 ppm (690 mg/m^3) in a 13-week study. An increased incidence of tubular cell karyomegaly, nephrosis and casts was also reported at ≥ 100 ppm (690 mg/m^3) in the 2-year cancer bioassay. No hyaline droplet formation was reported.
As with rats, a plausible mechanism for this kidney toxicity in mice is, according to the EU-RAR (2007), via the reactive metabolite formed in the kidney via the glutathione conjugation/β-lyase pathway, which is approximately 1 order of magnitude less active in mice compared to rats. However, given that the kidney toxicity observed in mice occurs at approximately the same dose (100 ppm ≈ 345 mg/kg bw/day) at which nephrotoxicity is seen in rats (200 ppm ≈ 331 mg/kg bw/day), it is, according to the EU-RAR (2007), considered that the underlying mechanism leading to renal toxicity in mice is unlikely to be via the reactive metabolite of the glutathione conjugation/β-lyase pathway. This also, according to the EU-RAR (2007), casts doubts on the glutathione conjugation/β-lyase pathway metabolite being the toxic product responsible for the renal damage seen in rats.

Based on the available studies, an inhalation LOAEC of 100 ppm (690 mg/m^3) is, according to the EU-RAR (2007), set for kidney toxicity in mice.

In relation to the lung, congestion was seen in the 2-year cancer bioassay in B6C3F1 mice at ≥ 100 ppm (690 mg/m^3), which is, according to the EU-RAR (2007), also the LOAEC for this effect in the lungs.

No specific neurotoxicity investigations were conducted in mice.

4.5 Toxicity to reproduction

The information in this section is extracted from the EU-RAR (2007) section 4.1.2.9.1 'Toxicity to reproduction, Studies in animals'.

4.5.1 Fertility and general reproductive performance

The effects of tetrachloroethylene on fertility and general reproductive performance have been thoroughly investigated in a well-conducted two-generation study in rats exposed to 0, 100, 300 and 1000 ppm (0, 690, 2070 and 6900 mg/m^3). Observed effects on reproduction (reductions in litter size and pup survival at 1000 ppm, and pup body weight at 1000 and 300 ppm) are, according to the EU-RAR (2007), considered likely to be the non-specific consequences of maternal toxicity. No adverse effects on fertility or mating parameters were, according to the EU-RAR (2007), apparent, even at 1000 ppm.

Supporting evidence is also available from several more limited investigations.

There is no evidence, according to the EU-RAR (2007), that tetrachloroethylene possesses hazardous properties with respect to fertility and mating performance.

4.5.2 Developmental toxicity

Several studies designed specifically to investigate the developmental toxicity of tetrachloroethylene by the inhalation route have been conducted in rats, mice and rabbits at concentrations ranging from 65 to 1000 ppm. Individually, each of these studies has, according to the EU-RAR (2007), weaknesses, notably the use of a single exposure level. Additional information on developmental toxicity is provided by a modern standard inhalation developmental toxicity study in the rat, using concentrations of 65, 250 and 600 ppm (509, 1695 and 4068 mg/m^3) and by a modern inhalation 2-generation study also in rats, using concentrations of 100, 300 and 1000 ppm (described above). Collectively, these studies provide, according to the EU-RAR (2007), a basis of an assessment of the developmental toxicity of tetrachloroethylene that is sufficient for risk assessment purposes.

There was, according to the EU-RAR (2007), no evidence that inhalation exposure to tetrachloroethylene can cause foetal malformations. At 100 ppm no developmental toxicity was reported in the rat 2-generation study in the offspring (F1 and F2a) exposed *in utero*, providing, according to the EU-RAR (2007), a reliable estimate of the NOAEC for developmental toxicity.
However, at exposure levels above 100 ppm the toxicity profile is, according to the EU-RAR (2007), unclear with respect to development because of inconsistencies in the results of studies and limitations in the design of the majority of them.

At 250 ppm, one study reported slight developmental retardation in the absence of any maternal toxicity in the rat.
In a further study, at 300 ppm a marginal increase in the numbers of resorptions associated with slight maternal toxicity in rats and a slight developmental retardation in the absence of convincing evidence of maternal toxicity in mice were observed.
In contrast, there was no evidence of developmental toxicity in the presence of maternal toxicity at about 500 ppm in rats or rabbits or at 900 ppm in rats in other studies. At 1000 ppm, slight developmental retardation was seen in the absence of reported evidence of maternal toxicity in one study and reduced litter size, pup weights and survival was seen in association with significant maternal toxicity in the 2-generation study.

To conclude, an inhalation NOAEC of 100 ppm for developmental toxicity can, according to the EU-RAR (2007), be identified. At higher exposure levels there is some limited evidence that tetrachloroethylene can cause developmental toxicity, manifested as developmental delays and post-implantation loss of the conceptus. It is, according to the EU-RAR (2007), possible that the developmental effects may be a secondary non-specific consequence of maternal toxicity, but because of the weaknesses in the available data no firm conclusion regarding the role of maternal toxicity can be drawn.

4.6 Mutagenic and genotoxic effects

4.6.1 *In vitro* studies

The information in this section is extracted from the EU-RAR (2007) section 4.1.2.7.1 ‘Mutagenicity, In vitro studies’.

In extensive testing there is, according to the EU-RAR (2007), convincing evidence that tetrachloroethylene of high purity is not mutagenic in bacteria. In relation to its metabolites, evidence from Ames tests has shown that trichloroacetyl chloride, trichloroacetic acid, trichloroethanol and oxalic acid are not mutagenic in bacteria. However, metabolites of tetrachloroethylene associated to both the cytochrom P450 oxidation pathway (tetrachloroethylene oxide) as well as to the gluthathion-S-transferase conjugation pathway (S-1,2,2-trichlorovinylglutathione, S-1,2,2-trichlorovinylcystein and N-acetyl-S-1,2,2-trichlorovinylcysteine) have been identified as genotoxic in bacterial test systems.

Investigations with yeast systems have not been thorough, and although all findings have been negative, no firm conclusion can, according to the EU-RAR (2007), be reached.

The single test available for mammalian cell gene mutation (a mouse lymphoma assay) was, according to the EU-RAR (2007), convincingly negative.

The positive result obtained in the novel *in vitro* mouse micronucleus test is, according to the EU-RAR (2007), unreliable as the test method and the cell system employed appear to be oversensitive and unspecific. It should be noted, however, that there are some Member States who are of the opinion that these results are valid, especially because they have been generated in a study of high quality performed in a very reputable laboratory.

The available assays examining chromosomal aberrations and sister chromatid exchange were negative, but the test protocols were, according to the EU-RAR

(2007), not sufficiently stringent to provide complete reassurance regarding these endpoints.

There is, according to the EU-RAR (2007), no evidence that tetrachloroethylene of high purity can induce UDS, although complete confidence in the negative findings of several studies is not possible, due to their poor conduct and/or reporting.

Overall, there is, according to the EU-RAR (2007), evidence from a number of studies to suggest that in *in vitro* test systems tetrachloroethylene does not cause gene mutations in bacterial and mammalian cells or have clastogenic activity, but the quality of some of the available studies is unsatisfactory. A positive result for clastogenicity and aneugenicity was obtained in a novel *in vitro* micronucleus test, but this is considered to be unreliable as the test method and the cell system employed appear to be oversensitive and unspecific. Metabolites associated to both the cytochrom P450 oxidation pathway (tetrachloroethylene oxide) as well as to the gluthathion-S-transferase conjugation pathway (S-1,2,2-trichlorovinylglutathione, S-1,2,2-trichlorovinylcystein and N-acetyl-S-1,2,2-trichlorovinylcysteine) have been identified as genotoxic in bacterial test systems.

4.6.2 *In vivo* studies

The information in this section is extracted from the EU-RAR (2007) section 4.1.2.7.1 'Mutagenicity, In vivo studies' unless otherwise stated.

Tetrachloroethylene has been tested in three bone marrow cytogenetics (one by i.p. and two by inhalation), one i.p. liver and erythrocyte micronucleus, one oral kidney UDS, two liver and kidney SSB (one by i.p. and one by gavage) and one inhalation dominant lethal assay. Although there are, according to the EU-RAR (2007), deficiencies in the conduct and/or reporting of all of these studies, generally the pattern of results is negative.

Tetrachloroethylene of high purity gave a negative response in the bone marrow cytogenetics studies, in the i.p. erythrocyte micronucleus assay, in the oral kidney UDS test, in the gavage kidney SSB study and in the dominant lethal assay. Although in the majority of these studies exposure was up to doses causing systemic toxicity (or presumed to cause systemic toxicity), cytotoxicity was not observed, which demonstrates, according to the EU-RAR (2007), that sufficient exposure of target cells did not occur.

A positive result was observed in the i.p. liver micronucleus test; however, this was, according to the EU-RAR (2007), likely to be an unspecific effect (due to cytotoxicity) from direct exposure to tetrachloroethylene under unphysiological conditions (hepatectomy). This interpretation of the study is shared by 7 other Member States.
There is however a significant number (9) of Member States who are of the opinion that the two negative experiments (the one in erythrocytes and the one in the liver exposed to tetrachloroethylene before partial hepatectomy) are inadequate and should not contribute to the weight of evidence. These Member States are also of the opinion that the positive result obtained in the liver exposed to tetrachloroethylene after partial hepatectomy raises concern for a possible mutagenic potential of tetrachloroethylene *in vivo*. A positive result (only at 1 hour but not at 23 hours after dosing) was also seen in the i.p. liver and kidney SSB study; however, again, this was, according to the EU-RAR (2007), likely to be the consequence of direct exposure to tetrachloroethylene in the i.p. cavity.

Overall, 8 Member States (including the rapporteur) are of the opinion that the pattern of response is negative, but not entirely convincing, while 9 Member States are of the opinion that the results on induction of micronuclei raise concern for a possible mutagenic potential of tetrachloroethylene.

Since the EU-RAR (2007) was finalised in the former EU TC NES, a new *in vivo* study has been published by Cederberg et al. (2010a).
Induction of DNA damage in the liver and kidney of male CD1 mice was studied by means of the alkaline comet assay after oral administration of tetrachloroethylene at the doses of 1000 and 2000 mg/kg bw/day. A statistically significant dose-related increase in tail intensity was established in hepatocytes, indicating that tetrachloroethylene induced DNA damage in the liver. No effect on DNA damage was observed in the kidney. The results are, according to the authors, in agreement with carcinogenicity data in mice, in which tetrachloroethylene induced tumours in the liver but not in the kidney, and support that a genotoxic mode of action might be involved in liver carcinogenicity in mice.

4.7 Carcinogenic effects

The information in this section is extracted from the EU-RAR (2007) section 4.1.2.8.1 'Carcinogenicity, Studies in animals, Inhalation'.

Inhalation carcinogenicity studies conducted to modern regulatory standards are available in rats and mice.

For the rat study, evidence of carcinogenicity was, according to the EU-RAR (2007), shown by an increased incidence of renal tubular cell carcinomas. This increase, comprising two tumours in high dose (400 ppm, 2760 mg/m^3) males, with none seen in the other two male or the three female groups, was not statistically significant. However, this type of tumour had not occurred among nearly 2000 historical control animals, so that the effect was, according to the EU-RAR (2007), considered toxicologically significant.

For the mouse study, clear evidence for carcinogenicity was, according to the EU-RAR (2007), provided by the increased incidence of hepatocellular carcinoma obtained in both males (7/49 at 0 ppm; 25/49 at 100 ppm, 690 mg/m^3; 26/50 at 200 ppm, 2760 mg/m^3) and females (1/48; 13/50; 36/50).

5 Regulations and evaluations

5.1 Ambient air

Denmark (C-value): 0.01 mg/m^3, Main Group 1 (MST 2002).

5.2 Drinking water

Denmark: 1 µg/l (for volatile organic chlorinated compounds such as e.g., tetrachloroethylene (MM 2011).

5.3 Soil

Denmark: 5 mg/kg (MST 1995).

5.4 Occupational Exposure Limits

Denmark: 10 ppm, 70 mg/m^3, notation for carcinogenic effect and notation for dermal penetration (At 2007).

5.5 Classification

Tetrachloroethylene is classified Carc. 2 H 351 (Suspected of causing cancer), and Aquatic Chronic 2 H 411 (Toxic to aquatic life with long lasting effects) (ESIS 2012).

5.6 IARC

There is limited evidence in humans for the carcinogenicity of tetrachloroethylene. There is sufficient evidence in experimental animals for the carcinogenicity of tetrachloroethylene. (IARC 1995).

Overall evaluation: Tetrachloroethylene is probably carcinogenic to humans (Group 2A).

In making the overall evaluation, the Working Group considered the following evidence (IARC 1995):

(i) Although tetrachloroethylene is known to induce peroxisome proliferation in mouse liver, a poor quantitative correlation was seen between peroxisome proliferation and tumour formation in the liver after administration of tetrachloroethylene by inhalation. The spectrum of mutations in proto-oncogenes in liver tumours from mice treated with tetrachloroethylene is different from that in liver tumours from mice treated with trichloroethylene.

(ii) The compound induced leukaemia in rats.

(iii) Several epidemiological studies showed elevated risks for oesophageal cancer, non-Hodgkin's lymphoma and cervical cancer.

5.7 EU-RAR / SCHER

In the risk characterisation, the NOAEC/LOAEC is compared with the estimated exposure levels. The ratio (effect/exposure), Margin of Safety (MOS), is used to evaluate 'concern' / 'no concern' for a given exposure scenario. The estimated MOS is evaluated against a reference MOS, which is equivalent to a total uncertainty factor.

The risk characterisation for repeated dose toxicity, carcinogenicity and toxicity to reproduction is based on the following NOAEC / LOAEC (EU-RAR 2007):

Repeated dose toxicity:

The risk characterisation for repeated dose toxicity in workers, consumers and indirect exposure via the environment was performed based on the inhalation LOAEC of 690 mg/m^3 for nephrotoxicity and lung damage in the 2-year mouse study, as well as based on the human NOAEC of 173 mg/m^3 for no clear evidence from studies in humans for repeated dose effects of tetrachloroethylene .
SCHER (2008) agreed with these NOAEC / LOAEC.

Workers:
The risk characterisation was based both on animal LOAEC and human NOAEC:
"*MOSs of ≥ 30 has been obtained. The calculated MOS values have been derived through a comparison with a LOAEL … derived from animal studies and therefore, variability between and within species is a consideration. In the animal studies adverse effects on the kidney (tubular cell cytomegaly, karyomegaly, nephrosis and casts) and lung (congestion) have been seen. However, there is no evidence of any adverse effect on either the kidney or lung from the extensive human data, which indicate that below 25 ppm* (173 mg/m^3, MOS 2.2) *there are no repeated dose toxicity effects. Taking into account that humans may not be as susceptible as animals, the default interspecies factor seems excessive. Therefore, an MOS of 30 to account for both the inter- and intraspecies differences and for the use of a LOAEL rather than a NOAEL is considered to provide adequate reassurance that repeated dose toxicity effects will not occur in these scenarios.*"

Consumers:
The lowest MOS derived was 523 (based on the animal LOAEC).
"*Even though this MOS has been derived through a comparison with a LOAEC, it is considered that such a large MOS provides sufficient reassurance that exposure to tetrachloroethylene will not result in repeated dose toxicity.*"

Indirect exposure via the environment:
A MOS of 238 (based on the animal LOAEC) was "*considered to provide sufficient reassurance that adverse effects due to repeated exposure to tetrachloroethylene will not occur especially given the lack of adverse effects on the kidney and lung in the extensive number of human studies in workers exposed up to 25 ppm* (173 mg/m^3) *(8h-TWA; human NOAEC).*
A MOS of 17 (based on the human NOAEC) was "*considered to provide sufficient reassurance (after allowing for additional intraspecies susceptibility of the general population compared to workers) that adverse effects due to repeated exposure to tetrachloroethylene will not occur.*"

Carcinogenicity:

The risk characterisation was based on a LOAEC of 1380 mg/m^3 for kidney damage (including hyperplasia) in a 2-year rat study.

Workers:
" MOS value of 154 is considered to provide sufficient reassurance that carcinogenic effects will not occur after allowing for variability between and within species and for use of a LOAEL rather than a NOAEL."
"MOS values below 34 are considered to be too low for taking into account variability between and within species and for use of a LOAEL rather than a NOAEL."

Consumers:
"MOS (585) is considered to provide sufficient reassurance that carcinogenic effects will not occur after allowing for variability between and within species and for use of a LOAEL rather than a NOAEL."

Toxicity to reproduction:

The risk characterisation was based on a NOAEC of 690 mg/m^3 for developmental toxicity in a 2-generation rat study.

Workers:
"MOS value of 66 is considered to provide sufficient reassurance that adverse effects on development will not occur after allowing for variability between and within species."
"MOS values below 14.4 are considered to be too low for taking into account variability between and within species."

Consumers:
"An MOS value of 66 is considered acceptable as this MOS resulted from a comparison of an exposure estimate from an infrequent event (properly used coin-operated dry-cleaning machines) with a NOAEL from repeated exposure."
"MOS value of 17 is not considered to provide adequate reassurance that an adverse developmental effect will not occur."

5.8 US-EPA / NRC

US-EPA (2012) has estimated an 'inhalation reference concentration ' for non-cancer toxicity and an 'inhalation unit risk' for carcinogenicity.

Inhalation reference concentration (RfC):

RfC = 0.04 mg/m^3 (the midpoint of a range from 0.015-0.056 mg/m^3 rounded to one significant figure):

The RfC was derived based on the following endpoints from two principal neurotoxicological studies: colour vision changes (Cavalleri et al. 1994) with a LOAEC of 15 mg/m^3; and cognitive and reaction time changes (Echeverria et al. 1995) with a LOAEC of 56 mg/m^3.
A total uncertainty factor (UF) of 1000 (10 for intraspecies variation, 10 for a LOAEC instead of a NOAEC, 10 for database uncertainty, i.e. to address the lack

of data to adequately characterise the hazard and dose response in the human population with critical data gaps in relation to neurological, developmental and immunological effects) was applied.

Based on19 relevant studies, the NRC Committee estimated an RfC interval of 0.0002-2.6 mg/m^3, which could be narrowed to 0.04-0.34 mg/m^3 if the 5 most robust studies were selected (NAS 2010).

Inhalation unit risk:

Inhalation unit risk = $2x10^{-3}$ per ppm ($3x10^{-7}$ per µg/m^3), based on the male mouse hepatocellular tumour data from a Japanese study (Japanese Industrial Safety Association, 1993. Carcinogenicity Study of Tetrachloroethylene by Inhalation in Rats and Mice), a study which is not included in the EU-RAR 2007).
It is noted that the unit risk should not be used with exposures exceeding 60 ppm (400 mg/m^3) because above this exposure level, the dose-response relationship is not linear, and the unit risk would tend to overestimate risk.

The NRC Committee noted that it internationally has been discussed and still is discussed how animal tumour data can be interpreted and used in relation to an evaluation of the carcinogenic risk for humans. It was noted that the NRC Committee was unable to reach consensus on the selection of the critical cancer endpoint. The majority of the members judged that the uncertainties associated with mononuclear-cell leukaemia (MCL) were too great to support using MCL data rather than data on hepatic or renal cancer for determining quantitative estimates of risk and suggested to use the liver cancer data.
The NRC Committee did not come up with a specific value for the unit risk.

5.9 CICAD

Tolerable concentration (TC) for non-cancer toxicity:

The TC of 0.2 mg/m^3 is based on neurotoxicity "*disruption of visual spatial function and CNS (cognitive) processing of visual information*" (occupational cohort study of Seeber 1989), in which "*a mean LOAEC of 83 mg/m^3*" was identified and adjusted to a LOAEC of 20 mg/m^3 for continuous exposure (83 × 8/24 × 5/7). An uncertainty factor of 100 (10 for intraspecies variation and 10 for LOAEC-to-NOAEC) was applied.
It was noted that "*Setting a TC using the study TWA exposure is a precautionary approach, as effects might be the result of occasional high exposures.*"

Risk estimates for carcinogenicity:

Based on the following considerations "*There is clear evidence that tetrachloroethene is carcinogenic in rodents and limited evidence of carcinogenicity in humans exposed occupationally. Although tetrachloroethene is not mutagenic in standard bacterial tests and shows little evidence of genotoxicity in other assays, there is some evidence to support the involvement of genotoxic metabolites in the induction of tumours in laboratory animals.*" it was "*decided to calculate BMC and BMCL for each animal tumour and use these figures as a point of departure for linear low-dose extrapolation*".
BMC_{10} and $BMCL_{10}$ of 56 and 20 mg/m^3 and unit risks of 1.8×10^{-3} and 5.2×10^{-3} per mg/m^3, respectively, were calculated based on liver tumours in male mice

(Nagano et al. 1998 – this reference is a short summary of the Japanese 2-year inhalation studies, which were available for the US-EPA (see above) but not included in the EU-RAR 2007) and by using the multistage model as this procedure gave the "*Highest risk estimates*".

It is noted that the TC of 0.2 mg/m^3 corresponds to a cumulative lifetime risk of 0.4×10^{-3} by linear extrapolation based on the BMC_{10}.

Note: Unit risk of 5.2×10^{-3} per mg/m^3 corresponds to 0.0002 mg/m^3 for a 10^{-6} lifetime risk ($5.2x10^{-3}$ per mg/m^3 ~ $1x10^{-3}$ per 1/5.2 mg/m^3 = $1x10^{-3}$ per 0.19 mg/m^3 = $1x10^{-6}$ per 0.00019 mg/m^3 ~ $1x10^{-6}$ per 0.0002 mg/m^3).

5.10 NEC/DECOS:

These committess considered the neurotoxicity as the critical effect of tetrachloroethylene following inhalation exposure and that neurotoxic effects could be expected to occur from around 690 mg/m^3 (100 ppm) and thus, considered as a LOAEL.

A specific value for an OEL was not provided.

6 Summary and evaluation

6.1 Description

The information in this section is from the EU-RAR (2001).

Tetrachloroethylene is a colourless liquid with an ethereal odour. It is slightly soluble in water (139 mg/l) and volatile with a vapour pressure of 14.3 mmHg (1.9 kPa).

6.2 Environment

The information in this section is from the EU-RAR (2001).

Tetrachloroethylene is released to the environment during production and use, predominantly to the atmosphere. When released to surface waters, tetrachloroethylene is rapidly lost through volatilisation to the atmosphere.

In the atmosphere, tetrachloroethylene will primarily react with a number of photochemically produced species. The major reaction is with hydroxyl radicals, the major removal process for tetrachloroethylene from the atmosphere. The reaction with atmospheric chlorine atoms is thought to be the next most important atmospheric degradation mechanism for tetrachloroethylene. The overall lifetime for the two processes combined is thought to be around 3 months.
The main products formed during the photochemical degradation of tetrachloroethylene in air are phosgene, trichloroacetyl chloride, hydrogen chloride, carbon dioxide and carbon monoxide, but other products such as carbon tetrachloride, dichloroacetyl chloride and chloroform have also been detected

The majority of measured atmospheric levels are below 10 $\mu g/m^3$, with most levels below 1 $\mu g/m^3$.

6.3 Human exposure

The information in this section is from the EU-RAR (2007).

The general population is exposed to tetrachloroethylene via environmental sources as well as consumer products.

The most significant human exposure via the environment is likely to occur in flats above dry-cleaning establishments. According to the EU-RAR (2007), the predicted exposure is approximately 1.4 mg/kg bw/day from air and 15.7 µg/kg bw/day from food, equivalent to a total predicted exposure of 1.45 mg/kg bw/day) for a person living above a dry-cleaning establishment and eating food that has been stored in the vicinity.

For a consumer exposed daily from wearing freshly dry-cleaned clothes (0.66 mg/kg bw/day), and who also lives in the vicinity of a dry-cleaning establishment

and consuming food stored in the vicinity (1.45 mg/kg bw/day), the total predicted exposure is 2.11 mg/kg bw/day.

6.4 Toxicokinetics

The information in this section is from the EU-RAR (2007).

In both humans and animals, tetrachloroethylene is rapidly and extensively absorbed by the inhalation and oral routes of exposure. In the EU-RAR (2007), values of 100% have been taken forward to the risk characterisation.
Dermal absorption of vapour would contribute only a minimal amount (~0.3-1%) of that which would be absorbed by inhalation under normal conditions.

Following absorption, tetrachloroethylene is distributed to all organs and tissues, with selective partitioning into fat. Tetrachloroethylene crosses the blood-brain barrier and the placenta and enters the foetus, and also enters breast milk.

The majority of absorbed tetrachloroethylene is exhaled unchanged in the breath (approximately 80% in humans; up to 91% in rats).
The fraction of the absorbed dose, which is metabolised, decreases with increasing dose in a manner consistent with saturable metabolism.
The metabolites of tetrachloroethylene are excreted in the urine (approx. 8% of an inhaled dose), with very low percentages of the absorbed amount exhaled as carbon dioxide (1%) or eliminated in the faeces (2%).
Precise values for the half-life of elimination of tetrachloroethylene in humans cannot be identified from the available data, but rough estimates indicate values of 6-10 days. Furthermore, there is some evidence that with repeated exposure tetrachloroethylene accumulates in fat stores.

The metabolism of tetrachloroethylene shows inter-species variability, with some differences in dose-response trends.

The major route of metabolism in humans and animals involves cytochrome P450 oxidation; this proceeds more rapidly in mice than in rats, and more rapidly in rats than in dogs. The pathway leads to the formation of trichloroacetic acid, which in turn may be reduced to trichloroethanol. This oxidative metabolism is a saturable process.

Another metabolic pathway, involving hepatic conjugation of tetrachloroethylene with glutathione to give S-1,2,2-trichlorovinylglutathione has been identified in the rat and mouse. The conjugate is converted to S-1,2,2-trichlorovinylcysteine and ultimately to N-acetyl-S-1,2,2-trichlorovinylcysteine, which is excreted in the urine.
There is evidence that the first step of this metabolic pathway also occurs in humans as N-acetyl-S-(1,2,2-trichlorovinyl)-L-cysteine has been detected in the urine of occupationally-exposed workers and in human volunteers.
In humans, like rats, the glutathione conjugation of tetrachloroethylene is not a high dose phenomenon, but occurs with linear kinetics.
The data also suggest that there are large quantitative differences in the activity of the glutathione conjugation step between sexes and species. Overall, *in vivo* 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.

The conjugate S-1,2,2-trichlorovinylcysteine is also a substrate for renal β-lyase, producing the reactive intermediate dichlorodithioketene, which is subsequently hydrolysed to the urinary metabolite dichloroacetic acid.
Overall, the data indicate 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.

6.5 Human toxicity

6.5.1 Single dose toxicity

The information in this section is from the EU-RAR (2007).

Accidental inhalation by humans of tetrachloroethylene has led to death. Signs of CNS depression, such as unconsciousness and narcosis, have commonly been reported. There may also be transient and relatively minor effects in the liver. Subjective CNS effects have been reported at 690 mg/m^3 in two human volunteer studies and this concentration can be considered as a LOAEC for acute toxicity.

6.5.2 Irritation

The information in this section is from the EU-RAR (2007).

Tetrachloroethylene is irritating (but not corrosive) to the skin.
Slight and transient eye irritation has been reported by human volunteers at about 690 mg/m^3.
Mild nasal irritation has been reported by human volunteers at 216 ppm (1490 mg/m^3).

6.5.3 Sensitisation

The information in this section is from the EU-RAR (2007).

Given the widespread and extensive nature of exposure to tetrachloroethylene via work activities and consumer products, the lack of reports of skin and respiratory sensitisation indicates, according to the EU-RAR, that the potential of tetrachloroethylene to cause these conditions is negligible.

6.5.4 Repeated dose toxicity

The information in this section is from the EU-RAR (2007).

There is a relatively large amount of information from studies in humans including 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, according to the EU-RAR (2007), arisen in surveys of workers exposed to lower (below 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 145 mg/m^3 for 6 years.

Two specific hepatotoxicity studies together with the hepatotoxicological investigations of several worker health surveys have, according to the EU-RAR (2007), provided no clear evidence for tetrachloroethylene-induced liver toxicity at exposure concentrations below 339 mg/m^3 (mean 8-hour TWA).

Six specific nephrotoxicity studies together with the nephrotoxicological investigations of several worker health surveys have, according to the EU-RAR (2007), provided no convincing evidence for tetrachloroethylene-induced kidney toxicity at mean exposure levels in the range 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 462 mg/m^3 for 10 years, or in volunteers at concentrations up to 1035 mg/m^3 for 7.5 hours/day for 5 days has, according to the EU-RAR (2007), not been established.

There are very few studies that have specifically investigated the effects of tetrachloroethylene on colour discrimination. Overall, there is, according to the EU-RAR (2007), so little information on the effects of tetrachloroethylene on colour discrimination that no reliable conclusions can be drawn.

6.5.5 Toxicity to reproduction

The information in this section is from the EU-RAR (2007).

The effects of tetrachloroethylene on fertility and reproductive performance have not been well-investigated in humans. No firm conclusions can, according to the EU-RAR (2007), be made from these data.

There is, according to the EU-RAR (2007), no convincing evidence that tetrachloroethylene causes developmental toxicity in humans due to a number of limitations in the studies conducted. However, concern has been raised regarding the risk of spontaneous abortion, particularly, in dry-cleaning workers. The available evidence does, according to the EU-RAR (2007), not confirm a consistent elevation of risk of spontaneous abortion in the dry-cleaning industry in general. Nevertheless, the evidence may not be sufficiently robust to entirely negate the hypothesis that tetrachloroethylene may be a risk factor for this endpoint.

6.5.6 Mutagenic and genotoxic effects

The information in this section is from the EU-RAR (2007).

No exposure-related effects were observed in the frequency of chromosomal aberrations or sister chromatid exchanges in peripheral lymphocyte cultures from 10 Japanese workers. Similarly, negative results for sister chromatid exchanges in lymphocytes were obtained in a study of 27 Japanese dry-cleaning workers. Overall, no firm conclusions can, according to the EU-RAR (2007), be made, due to limitations of these studies.

A recent study has investigated the effect of tetrachloroethylene on oxidative DNA damage in female dry cleaners indicated no association between exposure in the study population and oxidative stress.

6.5.7 Carcinogenic effects

The information in this section is from the EU-RAR (2007).

Several large-scale studies of cancer mortality and cancer incidence among workers exposed to tetrachloroethylene in dry-cleaning and laundering have been reported.

In the occupational mortality studies where exposure was to tetrachloroethylene only, no increases in the risks for liver and renal cancers were observed. In these mortality studies, specifically conducted in dry-cleaners, elevated mortality was seen in relation to cancer of the oesophagus, buccal cavity and pharynx, and tongue.

In cancer incidence studies no increases in risks from exposure to tetrachloroethylene have been observed for any specific type of cancer, including risks for liver and renal cancers.

6.6 Animal toxicity

6.6.1 Single dose toxicity

The information in this section is from the EU-RAR (2007).

In animals, as in humans, the main signs of acute inhalation toxicity are indicative of CNS depression. Acute lethality is low, with LC_{50} values for rat and mouse mostly being greater than 20 mg/l.

6.6.2 Irritation

The information in this section is from the EU-RAR (2007).

Tetrachloroethylene is a pronounced skin irritant, but not corrosive. It produced only minimal eye irritation and did not cause respiratory irritation in male rats exposed to about 69000 mg/m^3 for 25 minutes.

6.6.3 Sensitisation

The information in this section is from the EU-RAR (2007).

No adequate information on skin sensitisation and o information on respiratory tract sensitisation is available. Tetrachloroethylene does, according to the EU-RAR (2007), not possess any structural alerts for sensitisation.

6.6.4 Repeated dose toxicity

The information in this section is from the EU-RAR (2007).

There is a substantial amount of information available for tetrachloroethylene from repeated inhalation toxicity studies in rats and mice.

The results of these studies indicate that the liver, kidneys and lungs are the main target organs of toxicity.

Liver damage (degeneration, necrosis, vacuolation, inflammatory infiltration and regenerative foci) was seen in mice following inhalation exposure at ≥ 690 mg/m^3. No liver damage was seen in rats at exposure concentrations up to 2760 mg/m^3 for 2 years or up to 6900 mg/m^3 for 14-17 weeks.

Kidney damage was observed in both rats (tubular cell karyomegaly and cytomegaly) at ≥ 1380 mg/m^3 and mice (tubular cell karyomegaly, nephrosis and casts) at ≥ 690 mg/m^3. Renal tubule hyaline droplet formation was also seen in male rats at 6900 mg/m^3 for 10 days, but not at 5520 mg/m^3 for 28 days.

Congestion of the lungs was seen in mice following inhalation exposure at ≥ 690 mg/m^3 for 2 years.

Alterations of the visual evoked potentials were observed in rats at 5520 mg/m^3 for 13 weeks; no other neurotoxic effects were observed in the same study at exposure concentrations of up to 1380 mg/m^3. No specific neurotoxicity studies were conducted in mice.

6.6.5 Toxicity to reproduction

The information in this section is from the EU-RAR (2007).

The effects of tetrachloroethylene on fertility and general reproductive performance have been thoroughly investigated in a well-conducted two-generation study in rats. Observed effects on reproduction (reductions in litter size and pup survival at 6900 mg/m^3, and pup body weight at from 1695 mg/m^3) are, according to the EU-RAR (2007), considered likely to be the non-specific consequences of maternal toxicity. No adverse effects on fertility or mating parameters were, according to the EU-RAR (2007), apparent, up to 6900 mg/m^3.
There is no evidence, according to the EU-RAR (2007), that tetrachloroethylene possesses hazardous properties with respect to fertility and mating performance.

Several studies designed specifically to investigate the developmental toxicity of tetrachloroethylene by the inhalation route have been conducted in rats, mice and rabbits at concentrations ranging from 509 to 6900 mg/m^3. Individually, each of these studies has, according to the EU-RAR (2007), weaknesses. Additional information on developmental toxicity is provided by a modern standard inhalation 2-generation study in rats, and collectively these studies provide, according to the EU-RAR (2007), a basis of an assessment of the developmental toxicity of tetrachloroethylene that is sufficient for risk assessment purposes.

There was, according to the EU-RAR (2007), no evidence that inhalation exposure to tetrachloroethylene can cause foetal malformations.
At 690 mg/m^3 no developmental toxicity was reported in the rat 2-generation study in the offspring (F1 and F2a) exposed *in utero*.

An inhalation NOAEC of 690 mg/m^3 for developmental toxicity can, according to the EU-RAR (2007), be identified. At higher exposure levels there is some limited evidence that tetrachloroethylene can cause developmental toxicity, manifested as developmental delays and post-implantation loss of the conceptus. It is, according to the EU-RAR (2007), possible that the developmental effects may be a secondary non-specific consequence of maternal toxicity, but because of the weaknesses in the available data no firm conclusion regarding the role of maternal toxicity can be drawn.

6.6.6 Mutagenic and genotoxic effects

The information in this section is from the EU-RAR (2007).

The genotoxicity of tetrachloroethylene has been investigated in several experimental *in vitro* and *in vivo* test systems.

Convincing negative results have, according to the EU-RAR (2007), been obtained in an extensive series of bacterial (Ames) tests and in a mouse lymphoma gene mutation assay.
Metabolites of tetrachloroethylene associated to both the cytochrom P450 oxidation pathway (tetrachloroethylene oxide) as well as to the gluthathion-S-transferase conjugation pathway (S-1,2,2-trichlorovinylglutathione, S-1,2,2-trichlorovinylcystein and N-acetyl-S-1,2,2-trichlorovinylcysteine) have been identified as genotoxic in bacterial test systems.

A positive result for clastogenicity and aneugenicity was obtained in a novel *in vitro* micronuleus test, but this is, according to the EU-RAR (2007), considered to be unreliable as the test method and the cell system employed appear to be oversensitive and unspecific. However, there are some Member States who are of the opinion that these results are valid.

Other *in vitro* tests have also produced negative findings, but deficiencies in the conduct and/or reporting of these studies prevent, according to the EU-RAR (2007), conclusions being drawn with full confidence.

In *in vivo* studies, tetrachloroethylene of high purity gave a negative response in two bone marrow cytogenetics studies, in an i.p. erythrocyte micronucleus assay, in an oral kidney UDS test, in a gavage kidney SSB (single-strand breaks) study, and in a dominant lethal assay. A positive result was observed in an i.p. liver micronucleus test. A positive result (only at 1 hour but not at 23 hours after dosing) was also seen in an i.p. liver and kidney SSB study.

In a recent *in vivo* study (Cederberg et al. 2010a), Induction of DNA damage in the liver and kidney of male CD1 mice was studied by means of the alkaline comet assay after oral administration of tetrachloroethylene. A statistically significant dose-related increase in tail intensity was established in hepatocytes, indicating that tetrachloroethylene induced DNA damage in the liver. No effect on DNA damage was observed in the kidney.

6.6.7 Carcinogenic effects

The information in this section is from the EU-RAR (2007).

Inhalation carcinogenicity studies are available in rats and mice.

In the rat study, an increased incidence of renal tubular cell carcinomas was observed comprising two tumours in high dose (2760 mg/m^3) males, with none seen in the other two male or the three female groups.

In the mouse study, increased incidence of hepatocellular carcinoma was obtained in both males (7/49; 25/49; 26/50) and females (1/48; 13/50; 36/50) at 0, 690 and 2760 mg/m^3, respectively.

6.7 Evaluation

The purpose of the evaluation in this document is to consider whether the current health-based air quality criterion should be revised with a primary focus on the new data, assessments and evaluations regarding the genotoxic and carcinogenic effects of tetrachloroethylene as these effects have given rise to an intensive debate nationally as well as internationally, and no consensus has been arrived at yet. Therefore, only these endpoints are addressed in detail in this section.

As effects following repeated inhalation exposure also are considered essential for a possibly revision of the current health-based air quality criterion these effects are also addressed in this section.

Information on other endpoints such as acute toxicity, irritation, sensitisation and toxicity to reproduction are only addressed in the respective summary sections.

6.7.1 Genotoxicity

An intensive debate nationally as well as internationally regarding the genotoxic potential of tetrachloroethylene is on-going, and no consensus has been arrived at yet. Therefore, this section will present the summaries and conclusions of different institutions, bodies and committees.

6.7.1.1 EU-RAR (2007)

"The genotoxicity of tetrachloroethylene has been fairly well-investigated in experimental in vitro and in vivo test systems. However, limitations and deficiencies in the conduct and/or reporting of the studies prevent an overall conclusion being drawn with full confidence."

"Convincing negative results have been obtained in an extensive series of bacterial (Ames) tests and in a mouse lymphoma gene mutation assay. However, metabolites of tetrachloroethylene associated to both the cytochrom P450 oxidation pathway … as well as to the gluthathion-S-transferase conjugation pathway … have been identified as genotoxic in bacterial test systems. A positive result for clastogenicity and aneugenicity was obtained in a novel in vitro micronuleus test, but this is considered to be unreliable as the test method and the cell system employed appear to be oversensitive and unspecific. Other in vitro and several in vivo tests have also produced negative findings, but deficiencies in the conduct and/or reporting of these studies prevent conclusions being drawn with full confidence."

"Generally, the pattern of the in vivo results is negative. Tetrachloroethylene of high purity gave a negative response in two bone marrow cytogenetics studies, in an i.p. erythrocyte micronucleus assay, in an oral kidney UDS test, in a gavage kidney SSB (single-strand breaks) study, and in a dominant lethal assay. Although

in the majority of these studies exposure was up to doses causing systemic toxicity (or presumed to cause systemic toxicity), cytotoxicity was not observed, which demonstrates that sufficient exposure of target cells did not occur. A positive result was observed in an i.p. liver micronucleus test; however, this was likely to be an unspecific effect (due to cytotoxicity) from direct exposure to tetrachloroethylene under unphysiological conditions (hepatectomy). This interpretation of the study is shared by 7 other Member States. There is however a significant number (9) of Member States who are of the opinion that the two negative experiments (the one in erythrocytes and the one in the liver exposed to tetrachloroethylene before partial hepatectomy) are inadequate and should not contribute to the weight of evidence. These Member States are also of the opinion that the positive result obtained in the liver exposed to tetrachloroethylene after partial hepatectomy raises concern for a possible mutagenic potential of tetrachloroethylene in vivo. A positive result (only at 1 hour but not at 23 hours after dosing) was also seen in an i.p. liver and kidney SSB study; however, again, this was likely to be the consequence of direct exposure to tetrachloroethylene in the i.p. cavity."

"In humans, three studies have looked for evidence of genotoxicity in relation to occupational exposure to tetrachloroethylene. These studies proved negative, but limitations in the design of two of them (the older ones) mean that no firm conclusions can be drawn."

"Overall, 8 Member States (including the rapporteur) are of the opinion that, considering the negative pattern of results obtained in the available in vitro and in vivo studies, it can be concluded that tetracholoroethylene does not possess genotoxic activity, while 9 Member States are of the opinion that the results on induction of micronuclei raise concern for a possible mutagenic potential of tetrachloroethylene and that further testing is necessary in order to obtain a better basis for a conclusion."

6.7.1.2 SCHER Opinion (2008)

"In the RAR, the available mutagenicity studies on tetrachloroethylene are evaluated. In summary, most of the studies using oxidative activation by cytochrome P450 gave negative results suggesting that this pathway in tetrachloroethylene biotransformation does not result in formation of genotoxic metabolites. As indicated in the RAE, the glutathione S-conjugate of tetrachlorethylene and downstream products (cysteine S-conjugate, mercapturic acid) are mutagenic in bacteria and tetrachloroethylene itself has also been shown to be mutagenic in bacteria under conditions favouring the formation of these conjugates."

"One in vivo mutagenicity study in mice using specific conditions (intraperitoneal administration of a high dose after partial hepatectomy) showed a marginal increase in the frequency of micronuclei in hepatocytes."

"SCHER does not conclude that these results indicate a need for further mutagenicity testing. The small increase in micronucleus frequency may be due to secondary effects such as cytotoxicity or related to the mode-of-action of tetrachloroethylene for liver tumour induction in mice, which is peroxisome proliferation (not considered relevant for humans). Even a positive response in a repeat of this test will not affect the overall weight-of-evidence conclusion that tetrachloroethylene, under conditions of oxidative biotransformation as occurring in the liver, is not mutagenic."

"However, the RAR will need to consider the relevance of the observed mutagenicity of tetrachloroethylene under conditions favouring glutathione S-conjugates for conclusions on mutagenicity. These experiments gave a positive response, and the mutagenicity of metabolites formed by further metabolism of glutathione S-conjugates was also demonstrated. However, this pathway becomes relevant only after application of high doses in animals."

6.7.1.3 US-EPA (2012)

"In conclusion, uncertainties with regard to the characterisation of tetrachloroethylene genotoxicity remain. This is primarily because in vivo tests of tetrachloroethylene have been equivocal, with at most, modest evidence of genotoxic effects in rodent tumour tissues examined (including mouse liver and rat kidney) following exposure at tumourigenic doses. However, no evidence is available regarding the potential contribution of tetrachloroethylene genotoxicity to other rodent tumour types (particularly, MCL, testes, and brain). Ames assays of tetrachloroethylene have yielded largely negative results. The tetrachloroethylene metabolites S-(1,2,2-trichlorovinyl) glutathione, S-(1,2,2,-trichlorovinyl)-L-cysteine, N-acetyl trichlorovinyl cysteine, tetrachloroethylene oxide, and dichloroacetic acid are genotoxic, but not all such metabolites have been sufficiently tested in the standard screening battery to support clear conclusions about their genotoxic potential. However, the predominance of positive data for these metabolites supports their potential genotoxicity following in situ production and/or bioactivation. This, in turn, supports the view that contribution of genotoxicity to tetrachloroethylene carcinogenesis cannot be ruled out for one or more target organs. Additional testing of the genotoxicity of tetrachloroethylene and its metabolites (particularly those from the GSH conjugation pathway) using state-of-the-art methods and in a more comprehensive panel of tumour tissues is warranted."

6.7.1.4 NAS (2010)

"In conclusion, there is no convincing evidence that tetrachloroethylene has important genotoxic or mutagenic activity in intact organisms. The committee agrees … that several metabolites of tetrachloroethylene are clearly … . However, it is still questionable whether the metabolites of tetrachloroethylene play an important role in the mode of action of tetrachloroethylene carcinogenesis … in view of the absence of convincing evidence of mutagenic and tumor-initiating activity of tetrachloroethylene in vivo. Additional studies of genotoxicity in vivo with state-of-the-art methods would be valuable."

6.7.1.5 Cederberg et al. (2010a)

"From the results of this study, we conclude that oral administration (single dose of 1000 or 2000 mg/kg) of tetrachloroethylene to mice results in a weak, but dose-related and statistically significant induction of DNA damage in the liver of the animals, as detected by the alkaline comet assay. … No effect on DNA damage was observed in the kidney. The results are in agreement with carcinogenicity data in mice, in which tetrachloroethylene induced tumours in the liver but not in the kidney, and support that a genotoxic mode of action might be involved in liver carcinogenicity in mice."

An alternative interpretation of the results of the Cederberg et al. (2010) study has been conveyed by the Study Director at the test facility (Covance), who concluded that tetrachloroethylene did not induce DNA damage in the liver and kidney of mice under the experimental conditions used (Lillford et al. 2010).

Lovell (2010) discussed the statistical approaches used and commented on the different conclusions reached by Cederberg et al. (2010a) and Lillford et al. (2010). He concluded *"It is not possible from this single experiment to say whether the finding represents a small but real genotoxic effect or is a false-positive result as a consequence of a Type 1 statistical error. The result, however, illustrates the problems that arise from trying to dichotomise a result using a decision criteria based upon a statistical reaching a certain level of statistical significance. Not surprisingly, there may be disagreement over the interpretation. … Statistical input into both the design and assessment of the results is critical for the biological interpretation of a study. However, statistical significance should not be the sole determinant of the interpretation of a result. Statistical analysis and biological interpretation should be complementary not contradictory."*

The NRC review (NAS 2010) evaluated the Cederberg et al. (2010) study and concluded *"Overall, the paper by Cederberg et al. does not present convincing evidence for a genotoxic activity of tetrachloroethylene."*

The US-EPA review (US-EPA 2012) also evaluated the Cederberg et al. (2010) study:
"A recently published report on DNA strand breaks showed a marginal increase in only one parameter from the Comet assay (tail length) following oral exposure to tetrachloroethylene in mice, but the statistical and biological significance of this result has been disputed."
"… tetrachloroethylene at higher concentrations induces at most modest increases in DNA damage in liver tissue."
"Limited in vivo studies of tetrachloroethylene are inconsistent, with only negative … or equivocal (Cederberg et al., 2010a …) genotoxicity assay results demonstrated following inhalation or oral exposure to tetrachloroethylene in animals."

6.7.1.6 CICAD (2006)

"Although a few assays have produced positive results, a weight-of-evidence approach suggests that tetrachloroethene itself does not have significant in vivo genotoxic potential. Mammalian metabolites of tetrachloroethene have induced mutations in Ames assays."

6.7.1.7 NEG/DECOS (2003)

"In view of the great number, as well as the types of negative tests, the committees conclude that PER is virtually devoid of genotoxic properties in mammals."

6.7.1.8 The evaluation by the author of this document

Tetrachloroethylene induced DNA damage in the liver of mice, as detected by the alkaline comet assay in the study by Cederberg et al. (2010a); no effect on DNA damage was observed in the kidney. On this basis, Cederberg et al. concluded that tetrachloroethylene is weakly genotoxic in the liver of mice.

It should be noted that:

- The DNA damage was only seen at very high oral doses (1000-2000 mg/kg);
- The magnitude of the effect compared to the vehicle control value was very slight, 1.3- and 1.4-fold at 1000 and 2000 mg/kg, respectively;
- The effect is probably caused by mutagenic metabolites of tetrachloroethylene, not by tetrachloroethylene itself;
- An alternative interpretation of the results has been conveyed by the Study Director at the test facility (Covance), who concluded that tetrachloroethylene did not induce DNA damage in the liver and kidney of mice under the experimental conditions used;
- The conclusion of Cederberg et al. has been questioned and debated intensely since the study was published;
- The comet assay provides no indications regarding the type(s) of DNA damage and thus, precludes a conclusion whether there is a threshold for the DNA damage observed in comet assay.

Overall, there is no convincing evidence that tetrachloroethylene itself possesses a significant genotoxic activity *in vivo*. Several metabolites of tetrachloroethylene are clearly genotoxic. The DNA damage in the liver of mice, as detected by the alkaline comet assay (Cederberg et al. 2010a), was only seen at very high oral doses (1000 and 2000 mg/kg), the increase was very slight (1.3- and 1.4-fold the vehicle control value at 1000 and 2000 mg/kg, respectively) and was not dose-related, and probably caused by mutagenic metabolites of tetrachloroethylene, not by tetrachloroethylene itself.
The weight-of-evidence suggests that tetrachloroethylene does not have a significant *in vivo* genotoxic potential, if any, at the exposure levels generally measured in ambient air (majority of measured levels below 10 µg/m^3, with most levels below 1 µg/m^3).

6.7.2 Carcinogenicity

An intensive debate nationally as well as internationally regarding the carcinogenic potential of tetrachloroethylene is on-going, and no consensus has been arrived at yet. Therefore, this section will present the views of different institutions, bodies and committees.

6.7.2.1 EU-RAR (2007)

"Overall, although there are many epidemiological studies examining cancer mortality and incidence among dry-cleaners and certain other groups of workers, those that provide any useful information relating specifically to tetrachloroethylene are considerably fewer. When factors such as latency, confounding exposures and biological plausibility are taken into account, it becomes apparent that the evidence shows no increased risk of cancer in humans resulting from exposure to tetrachloroethylene. However, there is an indication for an increased risk of cervical and oesophageal cancers in some studies from the US, not confirmed in Denmark, Finland, Norway and Sweden, that cannot be completely disregarded.
This conclusion is consistent with the evaluation performed by IARC in 1995, which states that there is evidence for consistently positive associations between

exposure to tetrachloroethylene and the risks for oesophageal and cervical cancer and non-Hodgkin's lymphoma. These associations appear unlikely to be due to chance, although confounding cannot be excluded and the total numbers in the cohort studies combined are relatively small."

"In relation to animal data, tetrachloroethylene has been tested in two species (mice and rats) producing clearly different patterns of results. In the mouse, tetrachloroethylene induced liver tumours by the inhalation (from 100 ppm – 690 mg/m^3) and oral (from 540 mg/kg/day) routes of exposure, but not kidney tumours; in the rat, no liver tumours were found but a non-statistically significant, low incidence (2/50) of kidney tumours (tubular cell adenocarcinomas) was observed in males only exposed by inhalation to 400 ppm (2760 mg/m^3) tetrachloroethylene for 2 years."

"For the mouse liver tumours, the mechanism has been shown to involve peroxisomal proliferation (binding to the nuclear receptor PPARα, peroxisome proliferation, oxidative stress, cytotoxicity/necrosis, regenerative cell proliferation, hyperplasia and tumours), an effect to which humans are not responsive. The oxidative metabolic pathway to trichloroacetic acid, an established peroxisomal proliferator in rodents, is particularly active in mouse liver, where effects indicative of such proliferation have been reported in repeated dose studies of tetrachloroethylene. Overall, the evidence demonstrates that the liver tumours obtained in mice are of no significance in relation to human health."

"For the rat kidney tumours seen in F344 males but not in females or in mice of either sex following inhalation exposure to 400 ppm (2760 mg/m3) tetrachloroethylene, there are still some uncertainties about the underlying mechanism. … Overall, it can be concluded that, although the mechanism leading to the formation of these kidney tumours in male rats has not been fully elucidated, on balance, the available evidence supports a threshold approach to risk characterisation ...".

6.7.2.2 SCHER Opinion (2008)

SCHER did not have any specific comments regarding the evaluation of the carcinogenicity of tetrachloroethylene as described in the EU-RAR (2007).

6.7.2.3 US-EPA (2012)

"Following EPA (2005a) Guidelines for Carcinogen Risk Assessment, tetrachloroethylene is "likely to be carcinogenic in humans by all routes of exposure." This characterization is based on suggestive evidence of carcinogenicity in epidemiologic studies and conclusive evidence that the administration of tetrachloroethylene, either by ingestion or by inhalation to sexually mature rats and mice, increases tumor incidence."

"Tetrachloroethylene increased the incidence of liver tumors (hepatocellular adenomas and carcinomas) in male and female mice and of mononuclear cell leukemia (MCL) in both sexes of rats. These findings were reproducible in multiple lifetime bioassays employing different rodent strains and, in the case of mouse liver tumors, by inhalation and oral exposure routes. Additional tumor findings in rats included significant increases … of testicular interstitial cell tumors and kidney tumors in males, and brain gliomas in males and females. In mice,

hemangiosarcomas in liver, spleen, fat, and subcutaneous skin were reported in males in the JISA study."

"The available epidemiologic studies provide a pattern of evidence associating tetrachloroethylene exposure and several types of cancer, specifically bladder cancer, non-Hodgkin lymphoma, and multiple myeloma. Associations and exposure-response relationships for these cancers were reported in studies using higher quality (more precise) exposure-assessment methodologies for tetrachloroethylene. Confounding by common lifestyle factors such as smoking are unlikely explanations for the observed results. For other sites, including esophageal, kidney, lung, liver, cervical, and breast cancer, more limited data are available."

"The specific active moiety(ies) and mode(s) of action involved in the carcinogenicity of tetrachloroethylene and its metabolites are not fully characterized.
For rat kidney tumors, it is generally believed that metabolites resulting from GSH conjugation of tetrachloroethylene are involved. The hypothesized modes of action for this endpoint include mutagenicity, peroxisome proliferation, α2μ-globulin nephropathy, and cytotoxicity not associated with α2uμ-globulin accumulation.
For mouse liver tumors, it is generally believed that metabolites resulting from P450-mediated oxidation of tetrachloroethylene are involved. The mode of action (MOA) hypotheses for this endpoint concern mutagenicity, epigenetic effects (especially DNA hypomethylation), oxidative stress, and receptor activation (focusing on a hypothesized PPARα activation MOA). However, the available evidence is insufficient to support the conclusion that either rat kidney or mouse liver tumors are mediated solely by one of these hypothesized modes of action.
In addition, no data are available concerning the metabolites or the mechanisms that may contribute to the induction of other rodent tumors (including mononuclear cell leukemia, brain gliomas, or testicular interstitial cell tumors in exposed rats and hemangiosarcomas in exposed mice).
Furthermore, no mechanistic hypotheses have been advanced for the human cancers suggested to be increased with tetrachloroethylene exposure in epidemiologic studies, including bladder cancer, non-Hodgkin lymphoma and multiple myeloma.
Although tetrachloroethylene is largely negative in genotoxicity assays - including in the Ames mutagenicity test - tetrachloroethylene has been shown to induce modest genotoxic effects (e.g., micronuclei induction following in vitro or in vivo exposure, and DNA binding and single strand breaks in tumor tissue) and mutagenic effects under certain metabolic activation conditions. In addition, some tetrachloroethylene metabolites have been shown to be mutagenic. Thus, the hypothesis that mutagenicity contributes to the tetrachloroethylene carcinogenesis cannot be ruled out for one or more target organs, although the specific metabolic species or mechanistic effects are not known."

6.7.2.4 NAS (2010)

"Two rodent bioassays have demonstrated that high doses of tetrachloroethylene produced liver tumors in mice. While there is clear evidence that this occurs, the basis for their occurrence is not clear and may actually involve more than one MOA. This makes the determination of the relevance to humans more difficult. This is particularly true with respect to the importance of PPARα as the predominant or sole MOA, which led to a split opinion among committee members and a dissenting statement.

Further studies are needed to define the MOAs for tetrachloroethylene-induced liver tumors, which particular emphasis on the importance of PPARα and whether species difference might exist. In addition, further study is needed to determine the relative roles of metabolites of tetrachloroethylene in tumor development. "

"The EPA concluded there is limited evidence that perchloroethylene causes cancer (kidney) in humans and the Committee agrees with this assessment.
The EPA evaluated bioassay studies to provide evidence suggestive of an effect. The Committee considers this and the similarity to trichloroethylene to support the conclusion that tetrachloroethylene induces kidney tumors in rodents. While the mode of action of perchloroethylene tumorigenesis is not understood, the α2μ-globulin nephropathy and peroxisome proliferator modes of action are not consistent with experimental results. A mutagenic mode of action cannot be ruled out.
Further studies are needed to determine whether tetrachloroethylene and its metabolites formed from TCVG are mutagenic in other mammalian cell assays."

6.7.2.5 CICAD (2006)

"There is limited evidence that tetrachloroethene is a carcinogen in humans exposed occupationally."

"Tetrachloroethene was clearly carcinogenic in laboratory animals. On repeated inhalation, it induced leukaemia in both sexes of F344 rats (in two studies) and malignant kidney tumours in male F344 rats in one study (of two). In inhalation studies, it induced malignant liver tumours in both sexes of B6C3F1 and BDF1 mice and benign Harderian gland tumours in BDF1 male mice."

"Currently, no mechanisms have been proposed for the leukaemias and benign Harderian gland tumours induced in rats and male mice, respectively. Non-genotoxic mechanisms have been recognized for the formation of kidney tumours in male rats and liver tumours in mice for some chemicals. The available data on mode of action for tetrachloroethene are limited and the dose-response data related to these recognized mechanisms are not consistent with the dose-response relationships for cancr induction by tetrachloroethene. In the absence of suitable supporting evidence to the contrary, it is concluded that the cancers produced by tetrachloroethene in rodents are of potential relevance to humans."

6.7.2.6 NEG/DECOS (2003)

"Several epidemiological studies were focused on the cancer mortality of drycleaners and other workers exposed to PER. On the whole, these studies do not lead to definitive conclusions about the carcinogenicity of PER exposure.
In most studies a substantial exposure of the exposed group to other solvents in addition to PER could not be excluded. Furthermore, the value of most studies is affected by the fact that life-style-related factors, in particular smoking, were not or not adequately accounted for.
In view of the outcome of animal experimental studies, it is reassuring that no consistent increases of liver or kidney cancer were found.
The committees conclude that the results warrant further investigation of the incidence of certain cancers, in particular oesophagus and bladder cancer, but that they do not allow the conclusion that working with PER leads to an enhanced cancer risk."

"Mice showed a statistically significant increase of hepatocellular carcinoma upon respiratory and oral exposure. TCA, the major metabolite of PER, induces hepatocellular carcinomas and adenomas in mice upon oral administration, which strongly suggests that the hepatocarcinogenicity of PER is actually caused by TCA. The sensitivity of the mouse for the hepatocarcinogenic effects of PER can most probably be attributed to the higher rate of the oxidative biotransformation in this organism resulting in the peroxisome proliferator and carcinogen TCA."

"A not significant increase of tubular cell adenoma and adenocarcinoma was found for male rats upon respiratory exposure. The sex-specificity of nephrotoxicity and the induction of kidney tumours can most probably be attributed to the male-specific formation of protein droplets in tubular cells. Moreover both sexes of this species showed a significant increase of mononuclear cell leukaemia, a type of cancer with a high background incidence in the applied strain."

6.7.2.7 The evaluation by the author of this document

The epidemiological studies (workers) are inconclusive and thus, no clear conclusion on the carcinogenicity of tetracholoroethylene exposure can be drawn based on these data.

Tumours have been observed in various organs and tissues in experimental animals. The specific active moiety(ies) and mode(s) of action involved in the carcinogenicity of tetrachloroethylene and its metabolites are not fully characterised.

<u>Liver tumours:</u>
Liver tumours have been observed in mice following inhalation exposure to tetrachloroethylene (from 690 mg/m^3), but not in rats.
The mode of action is not clearly understood, but peroxisome proliferation seems to play a role, an effect to which humans are much less responsive compared to mice. DNA damage (observed at high oral doses in the comet assay) might also play a role. Other modes of action may also play a role and possibly more than one mode of action is involved.
There is probably a threshold for the hepatocarcinogenicity of tetrachloroethylene and/or its metabolites in mice.

<u>Kidney tumours:</u>
A non-statistically significant, low incidence (2/50) of kidney tumours was observed in male rats exposed by inhalation to tetrachloroethylene (2760 mg/m^3).
The mode of action has not been fully elucidated, but the male rat specific $\alpha 2\mu$-globulin nephropathy, cytotoxicity, one or more toxic intermediates, genotoxicity, or a combination of more than one mode of action might be involved in the tumour formation. It should be noted that toxic effects are observed in the kidneys of both rats and mice at lower concentrations (from 1380 and 690 mg/m^3, respectively) than those resulting in tumour formation in male rats (2760 mg/m^3).
There is probably a threshold for the nephrocarcinogenicity of tetrachloroethylene and/or its metabolites in male rats.

<u>Mononuclear cell leukaemia (MCL):</u>
MCL has only been observed in F344 rats, a rat strain which has a very high spontaneous rate of this tumour form. It is therefore, generally accepted that this tumour form is of no relevance to humans.
There is probably a threshold for MCL formation in F344 rats.

Other tumours:
Additional tumour findings in rats include significant increases of testicular interstitial cell tumours in male rats, and brain gliomas in male and female rats. Haemangiosarcomas in liver, spleen, fat, and subcutaneous skin were reported in male mice.
No data are available concerning the metabolites or the mechanisms that may contribute to the induction of these tumour forms.

Overall, the tumours observed in experimental animals (rats and mice) may be of relevance to humans, but a clear conclusion cannot be drawn as the mode of action(s) leading to the tumour formations have not been fully elucidated and understood.
Tetrachloroethylene is not considered to have a significant *in vivo* genotoxic potential, if any, at the exposure levels generally measured in ambient air (majority of measured levels below10 µg/m^3, with most levels below 1 µg/m^3).
The weight-of-evidence therefore suggests that there probably is a threshold for the tumour formation.
For the purpose of proposing a health-based air quality criterion, a threshold approach is considered.

6.7.3 Repeated dose toxicity

In 2001, the documentation for tetrachloroethylene was updated and revised (Larsen 2001) and the health-based air quality criterion (0.006 µg/m^3) was based on a LOAEC (61 mg/m^3) for toxicity to the liver of mice observed in the study by Kjellstrand et al. (1984).
The repeated dose toxicity of tetrachloroethylene has been extensively reviewed in the EU-RAR (2007) and in the recent US-EPA Review (US-EPA 2012). Other studies than the Kjellstrand et al. (1984) study have formed the basis for the risk characterisation for repeated dose toxicity in the EU-RAR (kidney an lung damage in a 2-year mouse study) and for the setting of the inhalation RfC (Reference concentration) by the US-EPA (neurotoxicity, human data). Therefore, this section will briefly present the views in these two evaluations.

6.7.3.1 EU-RAR (2007)

"There is a relatively large amount of information on the potential repeated dose effects of tetrachloroethylene from studies in humans and from inhalation studies in animals."

"In relation to the studies in humans, there are general worker health surveys and studies investigating specifically 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 (below100 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) compared with an unexposed control group."
"No clear evidence for tetrachloroethylene-induced liver toxicity at exposure concentrations below 50 ppm (339 mg/m^3; mean 8h TWA)" has been provided.
"No convincing evidence for tetrachloroethylene-induced kidney toxicity at mean exposure levels in the range 1.2-107 ppm (8.3-738 mg/m^3)" has been provided.
"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) or in volunteers at concentrations up to 150 ppm (1035 mg/m^3) 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 NOAEC."

"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 administrations 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 LOAEC of 100 ppm, 690 mg/m^3 … been identified from the mouse inhalation … cancer bioassays … Evidence of hyaline droplet nephropathy was found in male rats following … inhalation … 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 … when relatively short exposure durations are employed."
"Congestion of the lungs was seen in mice following inhalation 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, the relevance to human health of the kidney damage seen in mice and rats … and of the lung congestion seen in mice … cannot be excluded. The inhalation mouse LOAEC of 100 ppm (690 mg/m^3) set for nephrotoxicity and lung damage … hence taken forward to the risk characterisation of this endpoint."

6.7.3.2 US-EPA (2012)

"The database of human and animal studies on inhalation toxicity of tetrachloroethylene is adequate to support derivation of inhalation and oral reference values. A number of targets of toxicity from chronic exposure to tetrachloroethylene have been identified in published animal and human studies. These targets include the central nervous system, kidney, liver, immune and hematologic system, and development and reproduction. In general, neurological effects were judged to be associated with lower tetrachloroethylene exposures."

"Neurotoxic effects have been characterized in human controlled exposure, occupational and residential studies, as well as in experimental animal studies, providing evidence of an association between tetrachloroethylene exposure and neurological deficits.
In conclusion, the weight of evidence across the available studies of humans and animals exposed to tetrachloroethylene indicates that chronic exposure to tetrachloroethylene can result in decrements in color vision, visuospatial memory, and possibly other aspects of cognition and neuropsychological function, including reaction time."
"… two studies - Cavalleri et al. (1994) and Echeverria et al. (1995) - are considered principal studies by EPA for the RfC. Endpoints selected for the candidate RfCs were reaction time measures (Echeverria et al., 1995), cognitive changes (Echeverria et al., 1995), and visual function changes (Cavalleri et al., 1994)."

"Each of the candidate studies provided lowest-observed-adverse-effect levels (LOAELs) that were selected as PODs. The adjusted LOAELs are as follows: 56 mg/m^3 [for either visual reproduction, pattern memory, and pattern recognition, or reaction time in pattern memory in Echeverria et al. (1995)] and 15 mg/m^3 [for color confusion in Cavalleri et al. (1994)]."

"The human evidence for kidney effects is limited." … *"Although human studies have not systematically investigated nephrotoxicity, an association between tetrachloroethylene exposure via inhalation and chronic kidney disease, as measured by urinary excretion of renal proteins and end-stage renal disease, is supported."*
"Adverse effects on the kidney have been observed in studies of animals exposed to high concentrations of tetrachloroethylene by inhalation …". … "Overall, multiple lines of evidence support the conclusion that tetrachloroethylene causes nephrotoxicity in the form of tubular toxicity, mediated potentially through GSH conjugation products."

"Evidence of liver toxicity is primarily from several well-conducted rodent studies, including chronic bioassays."

"The few published reports of experimental studies examining immune or hematologic system toxicity are consistent with the limited findings in the human occupational studies. These include evidence of an effect of tetrachloroethylene exposure on red blood cells …". "… and increases in total white cell counts and lymphocyte counts …". "In addition, increases in several other immunological parameters … were observed in tetrachloroethylene-exposed dry-cleaning workers."

"No human studies identified adverse effects on the respiratory tract, and no lung toxicities in rodents were reported in chronic bioassays … or other published reports."

6.7.3.3 The evaluation by the author of this document

Different views and conclusions regarding various endpoints and critical effects following repeated inhalation exposure to tetrachloroethylene as well as on the (no) effect level(s) for repeated dose toxicity have been expressed in the EU-RAR (2007) and in the US-EPA Review (US-EPA 2012). The major discrepancies in the views and conclusions are sumarised below.

Neurotoxicity, human data:
The EU-RAR (2007) concluded that a clear association between neurobehavioural /neurological deficits and repeated exposure (up to 462 mg/m^3) has not been established, and that no reliable conclusions regarding the effects on colour discrimination can be drawn.
In contrast, US-EPA (2012) considered the neurotoxic effects observed in the human studies as the critical effects for the setting of the inhalation RfC. LOAECs of 56 mg/m^3 (for either visual reproduction, pattern memory, and pattern recognition, or reaction time in pattern memory) and 15 mg/m^3 (for colour confusion) were identified and used as point of departure for the setting of the RfC.

Nephrotoxicity, human data:
The EU-RAR (2007) concluded that no convincing evidence for kidney toxicity has been provided at mean exposure levels in the range 8.3-738 mg/m^3.

In contrast, US-EPA (2012) concluded that the human evidence for kidney effects is limited, but an association between tetrachloroethylene exposure via inhalation and chronic kidney disease is supported.

Nephrotoxicity, studies in animals:
The EU-RAR (2007) concluded that kidney damage has been observed in both rats and mice. An inhalation LOAEC of 690 mg/m^3 was identified from the 2-year mouse inhalation study.
The US-EPA (2012) concluded that adverse effects on the kidney have been observed in studies of animals exposed to high concentrations (not further specified) of tetrachloroethylene by inhalation and that the evidence supports that the nephrotoxicity is mediated potentially through GSH conjugation products.

Lung toxicity, studies in animals:
The EU-RAR (2007) concluded that effects in the lungs (congestion) have been seen in mice. An inhalation LOAEC of 690 mg/m^3 was identified from the 2-year mouse inhalation study.
In contrast, US-EPA (2012) concluded that no lung toxicities in rodents were reported in chronic bioassays.

Risk characterisation (EU) / standard setting (US-EPA):
In the EU-RAR (2007) the risk characterisation for repeated dose toxicity in workers, consumers and indirect exposure via the environment was performed based on the inhalation LOAEC of 690 mg/m^3 for nephrotoxicity and lung damage in the 2-year mouse study, and for workers and indirect exposure via the environment also on the human NOAEC of 173 mg/m^3 for no clear evidence from studies in humans for repeated dose effects of tetrachloroethylene. The potential risk was discussed for the various populations and for the selected exposure scenarios (see section 5.7), but a specific reference MOS (equivalent to a total uncertainty factor) for comparison with the estimated MOS values was not established.
US-EPA has based the setting of the inhalation reference concentration (RfC, 0.04 mg/m^3, the midpoint of the range from 0.015-0.056 mg/m^3 rounded to one significant figure) on the LOAECs for neurotoxic effects (15 mg/m^3 for colour vision changes; 56 mg/m^3 for cognitive and reaction time changes) observed in the two human principal studies. A total uncertainty factor of 1000 (10 for intraspecies variation, 10 for a LOAEC instead of a NOAEC, 10 for database uncertainty) was applied.

In general, well-performed and valid human studies are preferred to animal studies for the setting of health-based air quality criteria.
The US-EPA view regarding the validity of the human studies expressed in the final Review (US-EPA 2012) was previously brought forward in the peer review of the US-EPA draft Review (US-EPA 2008) performed by NRC (NAS 2010). On this basis, the human data are considered as being valid for the purpose of proposing a health-based air quality criterion for tetrachloroethylene and the neurotoxic effects observed in the human studies are considered as the critical effects for the setting of the health-based air quality criterion. It is noted that the EU-RAR (2007) has expressed the view that humans may not be as susceptible as animals to the toxicity of tetrachloroethylene. This is considered as a further support to the selection of the human studies as the basis for the setting of the health-based air quality criterion for tetrachloroethylene.
LOAECs of 56 mg/m^3 (for cognitive and reaction time changes) and 15 mg/m^3 (for colour vision changes) were identified by the US-EPA from the two human principal studies (Echeverria et al. (1995) and Cavalleri et al. (1994), respectively).

For the setting of the health-based air quality criterion for tetrachloroethylene the LOAEC of 15 mg/m^3 (for colour vision changes) is selected as colour vision changes are considered as an adverse effect. It should be noted that the consideration of colour vision changes as an adverse effect is in concordance with the position taken in relation to the classification and labelling of styrene for specific target organ toxicity.

6.7.4 Critical effect(s) and NOAEC

Overall, the critical effects for the purpose of proposing a health-based air quality criterion for tetrachloroethylene are the repeated dose toxicity, carcinogenicity and reproductive toxicity.

In relation to repeated dose toxicity in humans, neurotoxic effects (cognitive and reaction time changes, and colour vision changes) have been observed in two well-performed and valid human studies (workers). A LOAEC of 56 mg/m^3 can be identified for cognitive and reaction time changes in the study Echeverria et al. (1995) and a LOAEC of 15 mg/m^3 can be identified for colour vision changes in the study by Cavalleri et al. (1994).
In relation to repeated dose toxicity in experimental animals, damage to the kidney (rats, mice), liver (mice) and lung (mice) has been seen following inhalation exposure to tetrachloroethylene. A LOAEC of 690 mg/m^3 can be identified for these effects from the 2-year mouse inhalation study.

In relation to carcinogenicity, the relevance to human health of the kidney tumours seen in male rats and the liver tumours seen in mice cannot be excluded. Tetrachloroethylene is not considered to have a significant *in vivo* genotoxic potential, if any, at the exposure levels generally measured in ambient air (majority of measured levels below10 µg/m^3, with most levels below 1 µg/m^3).
Although the mode of action(s) leading to the tumour formations in the experimental animals have not been fully elucidated and understood, the weight-of-evidence suggests that there probably is a threshold for the tumour formation in the kidney and liver.
For the purpose of proposing a health-based air quality criterion, a threshold approach is considered. The LOAEC of 690 mg/m^3 identified for repeated dose toxicity in the 2-year mouse inhalation study is considered for tumour formations as well.

In relation to reproductive toxicity, developmental effects were observed in mice and rats following inhalation exposure to tetrachloroethylene (from 1695 mg/m^3). A NOAEC of 690 mg/m^3 can be identified from a good-quality 2-generation study in rats.

Overall, the critical effects for the purpose of proposing a health-based air quality criterion for tetrachloroethylene are considered to be the neurotoxic effects observed in the two well-performed and valid human studies (workers). The LOAEC of 15 mg/m^3 (for colour vision changes) is selected for the estimation of the health-based air quality criterion as colour vision changes are considered as an adverse effect. This LOAEC is considered also to protect against tumour formation in the kidney and liver as well as for developmental effects. The LOAEC of 15 mg/m^3 is the adjusted LOAEC for continuous exposure (6 ppm mean 8-hour time weighted average, 41 mg/m^3 x 10/20 (breathing rate) x 5/7 corresponding to 15 mg/m^3).

It should be noted that this LOAEC is different from the LOAEC of 61 mg/m^3 (continuous exposure) for liver effects in mice (30 days of exposure) (Kjellstrand et al. 1984) which is the basis for the C-value of 0.01 mg/m^3 in the 2001 documentation (Larsen 2001).

7 Quality criterion in ambient air

The health-based quality criterion in air QC_{air} is estimated based on a LOAEC of 15 mg/m^3 identified for repeated dose toxicity (colour vision changes) from a well-performed and valid human study (workers). This LOAEC is considered also to protect against tumour formation in the kidney and liver as well as for developmental effects. The LOAEC is the adjusted LOAEC for continuous exposure.

$$QC_{air} = \frac{LOAEC}{UF_I * UF_{II} * UF_{III}} = \frac{15\ mg/m^3}{1 * 10 * 30}$$

$$= 0.05\ mg/m^3$$

The UF_I accounting for interspecies variability is set to 1 as human data are used. The UF_{II} accounting for intraspecies variability is set to 10 reflecting the range in biological sensitivity within the human population. The UF_{III} is set to 30 with a factor of 3 to account for the LOAEC-to-NOAEC extrapolation and a factor of 10 for database uncertain, e.g. the relevance to human health of the kidney tumours seen in male rats and the liver tumours seen in mice cannot be excluded and the mode of action(s) leading to the tumour formation in the experimental animals have not been fully elucidated and understood.

A QC_{air} of 0.05 mg/m^3 has been calculated. The C-value at present for tetrachloroethylene is 0.01 mg/m^3 and tetrachloroethylene is placed in Main Group 1 (MST 2002). A C-value of 0.05 mg/m^3 and placing in Main Group 2 is proposed.

7.1 C-value

0.05 mg/m^3, Main Group 2.

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Evaluation of health hazards by exposure to Tetrachloroethylene and proposal of a health-based quality criterion for ambient air.

This report is an update of the evaluation from 2001 regarding health hazards by exposure to Tetrachloroethylene and is requested by the Danish Environmental Protection Agency as a result of the publication of new data for the substance. The report is a contribution to the foundation upon which the quality criterion and the C-value are determined.

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