COLLECTIVE EXPERT APPRAISAL: SUMMARY AND CONCLUSIONS

Regarding the "expert appraisal on recommending occupational exposure limits for chemical agents"

Assessment of the health effects and methods for the measurement of exposure levels in workplace atmospheres for

Trichloroethylene (CAS n° 79-01-6)

This document summarises and presents the work of the Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee).

Presentation of the issue

On 12 June 2007, ANSES was requested from the Directorate General for Labour to conduct the scientific expert appraisal work required for setting occupational exposure limit values (OELVs) for trichloroethylene.

France currently has[1] an 8-hour occupational exposure limit (8h-OELV) of 405 mg/m^3 (or 75 ppm) and a short-term exposure limit (STEL) of 1080 mg/m^3 (or 200 ppm).

The Directorate General for Labour asked ANSES to reassess this value and, if necessary, to propose new occupational exposure values based on health considerations.

Scientific background

The French system for establishing OELVs has three clearly distinct phases:

- independent scientific expertise (the only phase entrusted to ANSES);
- proposal by the Ministry of Labour of a draft regulation for the establishment of limit values, which may be binding or indicative;
- stakeholder consultation during the presentation of the draft regulation to the French Steering Committee on Working Conditions (COCT). The aim of this phase is to discuss the effectiveness of the limit values and if necessary to determine a possible implementation timetable, depending on any technical and economic feasibility problems.

[1] Indicative value, Circular of 1 December 1993

The OELs, as proposed by the Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee), are concentration levels of pollutants in workplace atmospheres that should not be exceeded over a determined reference period and below which the risk of impaired health is negligible. Although reversible physiological changes are sometimes tolerated, no organic or functional damage of an irreversible or prolonged nature is accepted at this level of exposure for the large majority of workers. These concentration levels are determined by considering that the exposed population (the workers) is one that excludes both children and the elderly.

These concentration levels are determined by the OEL Committee experts based on information available from epidemiological, clinical and animal toxicology studies. Identifying concentrations that are safe for human health generally requires correction factors to be applied to the values identified directly by the studies. These factors take into account a number of uncertainties inherent to the extrapolation process conducted as part of an assessment of the health effects of chemicals on humans.

The Committee recommends the use of three types of values:

- an 8-hour occupational exposure limit (8h-OEL): Unless otherwise indicated, this corresponds to the limit of the time-weighted average (TWA) of the concentration of a chemical, in the air in the worker's breathing zone, over the course of an 8-hour working day. In the current state of scientific knowledge (toxicology, medicine and epidemiology), the 8h-OEL is designed to protect workers exposed regularly and for the duration of their working life from the medium- and long-term health effects of the chemical in question.
- a short-term exposure limit (STEL): This is a limit corresponding to exposure measured over a 15-minute reference period (unless otherwise indicated) during the peak of exposure, irrespective of its duration. It aims to protect workers from adverse health effects (immediate or short-term toxic effects such as irritation phenomena) due to peaks of exposure.
- a ceiling value: This is an atmospheric concentration in the workplace that should not be exceeded at any time during the day. This value is recommended for substances known to be highly irritating or corrosive or likely to cause serious potentially irreversible effects after a short period of exposure.

These three types of values are expressed:

- either in $mg.m^{-3}$, i.e. in milligrams of chemical per cubic metre of air, and in ppm (parts per million), i.e. in cubic centimetres of chemical per cubic metre of air, for gases and vapours;
- or in $mg.m^{-3}$ only for liquid and solid aerosols;
- or in $f.cm^{-3}$, i.e. in fibres per cubic centimetre for fibrous materials.

The 8h-OELV may be exceeded for short periods during the working day provided that:

- the weighted average of values over the entire working day is not exceeded;
- the value of the short term limit value (STEL), when one exists, is not exceeded.

In addition to the OELs, the OEL Committee assesses the need to assign a "skin" notation, when significant penetration through the skin is possible. This notation indicates the need to consider the dermal route of exposure in the exposure assessment and, where necessary, to implement appropriate preventive measures (such as wearing protective gloves). Skin penetration of substances is not taken into account when determining the atmospheric limit levels, yet can potentially cause health effects even when the atmospheric levels are respected.

The OEL Committee also evaluates the applicable reference methods for the measurement of exposure levels in workplace atmospheres. The different protocols are classified according to the methods used. These methods are then assessed and ranked according to their compliance with the European Standard EN 482:2006: "Workplace atmospheres - General requirements for the performance of procedures for the measurement of chemical agents".

Organisation of the expert appraisal

ANSES entrusted examination of this request to the Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee). This body mandated rapporteurs to participate in the expert appraisal relating to the health effects of trichloroethylene.

Three ANSES officers contributed to this work.

The different protocols for measuring trichloroethylene in workplace atmospheres were identified and grouped together according to the methods used. This work was conducted by the Metrology working group reporting to the OEL Committee.

The methodological and scientific aspects of the work conducted by ANSES and the rapporteurs were regularly submitted to the OEL Committee. The final report takes account of all their observations.

This expert appraisal was therefore conducted by a group of experts with complementary skills. It was carried out in accordance with the French Standard NF X 50-110 “Quality in Expertise Activities - General Requirements of Competence for Expert Appraisals (May 2003)" to ensure compliance with the following points: competence, independence, transparency and traceability.

Description of the method

For the assessment of health effects:

A summary report was prepared by ANSES and submitted to the OEL Committee, which commented on and added to it.

This summary report on the health effects of trichloroethylene was based on existing reports such as the IARC monograph (1995); reports by the ATSDR (1997); the US EPA (2001); the Health Council of the Netherlands (2003) and the NRC (2006) as well as the draft report of the US EPA (2009) and the Risk Assessment Report of the European Chemicals Bureau (2004). The OEL Committee returned to the original articles for all the key publications to which it referred for establishing its recommendations. Furthermore, the literature review was supplemented by searches on Medline, Toxline HSDB, ToxNet and ScienceDirect conducted until December 2009. Throughout this document, trichloroethylene shall be referred to as TCE.

For the assessment of the methods for measuring exposure levels in workplace atmospheres:

The different protocols for measuring TCE in workplace atmospheres were identified and grouped according to the methods used. These methods were then assessed and classified according to their compliance with the European Standard EN 482:2006: "Workplace atmospheres - General requirements for the performance of procedures for the measurement of chemical agents". A list of the main sources consulted is detailed in the report.

These methods were classified into two categories:

- Category 1 for validated methods: these satisfy a majority of the validation criteria (range of measurements, uncertainties, sensitivity, storage of samples, etc.)
- Category 2 for indicative methods: here, the protocols do not specify or do not sufficiently explain the major validation criteria.

A detailed comparative study of the techniques in Category 1 was conducted with respect to the various validation data and the technical feasibility, in order to recommend the most suitable method(s) for measuring concentrations for comparison with OELs.

The Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents adopted:

- the summary report for the evaluation of the health effects, at its meeting on 14 June 2011;
- the summary report on the methods for measuring exposure levels in workplace atmospheres, at the meeting on 12 January 2012.

The summary and conclusions of the collective expert appraisal were adopted by the Committee on expert appraisal for recommending occupational exposure limits for chemical agents on 12 January 2012.

The collective expert appraisal work and the summary report were submitted to public consultation from 18/10/2012 to 20/12/2012. The people or organizations who contributed to the public consultation are listed in appendix of the report (only available in French). The comments received were reviewed by the OEL Committee who adopted this version on 4 April 2013.

Results of the collective expert appraisal of health effects of trichloroethylene

General information and summary of the SCOEL document

Trichloroethylene (formula $CHCl=CCl_2$), is an unsaturated chlorinated derivative of aliphatic hydrocarbons whose CAS number is 79-01-6.

TCE is used for degreasing and cleaning metal parts; industrial degreasing of textile fibres; and extracting oils and fats.

European classification 28th ATP	Carc. Cat. C2 / R 45: May cause cancer Muta. Cat. 3 / R 68: Possible risk of irreversible effects R 67: Vapours may cause drowsiness and dizziness Xi / R 36/38: Irritating to eyes and skin
CLP Regulation[2] in force and repealing Directive 67/548/EEC	Carcinogenicity Cat. 1B (H350) Germ cell mutagenicity Cat. 2 (H341) Eye irritation Cat. 2 (H319); dermal irritation Cat. 2 (H315)
IARC classification	2A (probably carcinogenic to humans)
Table of occupational diseases	General scheme: Table no. 12 Agricultural scheme: Table no. 21

[2] CLP Regulation: Regulation (EC) no 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC and amending Regulation (EC) no 1907/2006 (text with EEA relevance).

Denmark is the country with currently the lowest OELs, namely an 8h-OELV of 55 $mg.m^{-3}$ (10 ppm) and an STEL of 110 $mg.m^{-3}$ (20 ppm).

The 2009 SCOEL report considers that the critical effects of TCE are its carcinogenic effects, especially kidney cancer demonstrated in studies in workers. Kidney cancer seems to be strongly associated with the nephrotoxic effect, which has therefore been selected as the critical effect for the assessment. The SCOEL regards TCE as a genotoxic carcinogen for which there is a threshold; this assumption is supported by studies on the mechanism of action and on toxicokinetics.

The nephrotoxic effects observed in workers exposed on average to 32 ppm (175 $mg.m^{-3}$ = LOAEC) were used to establish the 8h-OEL (Green *et al.,* 2004). These results are confirmed by the study by Seldén *et al.* (1993) which did not observe any nephrotoxic effect in workers exposed to 6-10 ppm of TCE (NOAEC). An 8h-OEL of 10 ppm is therefore proposed.

As peaks of exposure have been described as critical in the development of kidney cancer in humans, a **15min-STEL** of **30 ppm** is proposed for additional protection against the possibility of accidental overexposure resulting in nephrotoxic effects, based on the average exposure of 32 ppm from the study by Green *et al.* (2004).

A skin notation is recommended due to the significant dermal absorption.

Toxicokinetics

In animals as in humans, TCE is rapidly absorbed irrespective of the route of exposure. By inhalation, TCE is absorbed rapidly and extensively (28-80%). Blood balance is reached after two hours of continuous exposure. Dermal absorption also seems high, but is difficult to measure due to the chemical nature of TCE (a lipophilic solvent), which damages the *stratum corneum*, resulting in higher absorption.

In humans and animals, regardless of the route of absorption, TCE is widely distributed through the body via the bloodstream. Given its high lipid solubility, it is mainly found in adipose tissue, but also in the liver, kidneys, nervous system and cardiovascular system. It is able to cross the placental barrier, the blood-brain barrier and can be found in breast milk.

In humans, 40 to 75% of inhaled TCE is metabolised. TCE is rapidly metabolised by two pathways, mainly in the liver but also locally or in Clara cells (lungs):

- via oxidative metabolism (involving cytochrome P450) which leads to the formation of the following main metabolites: trichloroethanol (free and conjugated glucuronide) and trichloroacetic acid (TCA). These metabolites are excreted primarily in urine. This mechanism can to a lesser extent induce the formation of dichloroacetic acid (DCA), monochloracetic acid, formic acid, carbon monoxide, oxalic acid and N-(hydroxyacetyl)-aminoethanol.
- to a lesser degree by conjugation with glutathione which leads to the formation of S-1,2-dichlorovinylcysteine (DCVC) which can then be transformed by different pathways into either N-acetyl-dichlorovinylcysteine, thioacyl chloride or chlorothioketene.

TCE's main metabolic pathway (via CYP 450) seems qualitatively identical in different animal species and in humans, regardless of the route of exposure. However, there are several quantitative differences between species and strains.

Routes of elimination of TCE are qualitatively identical in animals and humans regardless of the route of exposure. Unchanged TCE (10-28% of the dose) and the volatile metabolites (CO_2,

CO, trichloroethanol) are eliminated in expired air. The main metabolites, trichloroethanol and TCA, are excreted in urine (48-85%) and faeces. The minor metabolites (dichloroacetic and monochloracetic acids, N-(hydroxyacetyl)aminoethanol, N-acetyl-dichlorovinylcysteine) are excreted in urine.

General toxicity

In humans

In humans exposed by inhalation to high concentrations of TCE, the main target is the central nervous system (state of excitement, CNS depression, fatigue and drowsiness). For exposure by inhalation of 1-4h, various NOAECs from 520 to 1650 $mg.m^{-3}$ (95-300 ppm) have been proposed in humans.

TCE is a skin irritant. Repeated dermal contact causes skin defatting, leading to rashes, eczematous lesions and generalised exfoliative dermatitis.

Subchronic and chronic exposures by inhalation are mainly responsible for:

- renal effects (alterations to the proximal tubule);
- neuropsychological disorders (psychosomatic syndrome with asthenia, headaches, memory problems, *etc.* and vegetative syndrome with sweating, functional disorders, dizziness, *etc.*);
- hepatic effects (liver necrosis, fatty liver, cirrhosis, hepatitis, Stevens-Johnson syndrome, jaundice potentially leading to severe liver failure, increased concentrations of cholesterol and bile acid).

Recent publications have suggested a link between exposure to TCE and the onset of Parkinson's disease or induction/exacerbation of autoimmunity. There are strong suspicions concerning potential links between exposure to TCE and effects on the cardiac system.

Numerous epidemiological studies have demonstrated a link between exposure to TCE and the onset of various cancers. For instance, TCE may be associated with the onset of kidney and liver cancer, and non-Hodgkin lymphoma, sites where TCE also causes cancer in rats and mice. In 1995, the IARC classified TCE in Group 2A (probable carcinogen) on the basis of three cohort studies conducted in Northern Europe and the United States: Anttila *et al.*, 1995; Axelson *et al.*, 1994; Spirtas *et al.*, 1991. These studies showed excess risks of cancers of the liver, biliary tract and non-Hodgkin lymphoma (IARC, 1995). The IARC stated that the level of evidence in humans was limited. For other sites such as the kidneys, bladder, lungs, breasts, oesophagus, etc., the IARC stated that the level of evidence was insufficient. In 2001, the European Commission classified TCE in Group 2 for kidney cancer and non-Hodgkin lymphoma, on the basis of studies showing kidney cancer in rats, supported by epidemiological studies showing an association between exposure to TCE and kidney cancer (Henschler *et al.*, 1995; Vamvakas *et al.*, 1998; Blair *et al.*, 1998) and non-Hodgkin lymphoma (Axelson *et al.*, 1994; Anttila *et al.*, 1995; Blair *et al.*, 1998; Boice *et al.*, 1999 cited in the EU report, 2004).

In animals

The LC_{50} for 4 hours is 65 $g.m^{-3}$ (12,000 ppm) in rats and 46 $g.m^{-3}$ (8000 ppm) in mice. The main signs of toxicity observed were CNS depression, respiratory failure, eye and respiratory tract irritation (EU, 2004).

A dermal LD_{50} of 2900 mg/kg bw has been reported in rabbits (EU, 2004).

In animals, TCE mainly induces:

- neurological effects: reduced attention, increased non-REM sleep, increased spontaneous motor activity, reduced length of sleep, alteration of neurotransmitters, hearing loss. The results of the animal studies corroborate studies conducted in humans for the neurological effects;
- renal effects: TCE induces toxicity on renal tubules;
- hepatic effects: hepatocellular necrosis, hepatomegaly, fatty infiltration, increased liver weight, centrilobular hypertrophy, reduced plasma concentrations, reduced cholesterol and reduced albumin levels.

Only the studies by Henschler *et al.* (1980), Fukuda *et al.* (1983) and Maltoni *et al.* (1986, 1988), available in the literature, have investigated TCE's carcinogenicity. They show lung and liver tumours and lymphomas in mice, and kidney and Leydig cell tumours in Sprague-Dawley rats.

All the results from the genotoxicity tests indicate that TCE has low mutagenicity *in vitro* and *in vivo*. It does not seem to be highly genotoxic to somatic cells.

Several recent studies conducted in rodents indicate that exposure to TCE:

- disrupts spermatogenesis (sperm quality);
- reduces male fertility (mating tests);
- reduces the fertilisation capacity of sperm (*in vitro* fertilisation tests with sperm from exposed males);
- reduces the ability of oocytes to be fertilised in females (*in vitro* fertilisation tests with oocytes from exposed females).

Concerning effects on development, some animal studies suggest the possibility of an increased incidence of cardiac malformations, with differences between species and between studies in the same species.

Establishment of occupational exposure limit values

Based on the data currently available, the OEL Committee believes that TCE should be considered **as a non-threshold carcinogen,** and it is therefore not possible to propose a limit value to avoid the carcinogenic effects of this substance. The various studies proposing excess risks (from epidemiological studies for the US EPA and the German BAuA, from animal studies for the WHO, California's OEHHA and Health Canada) were analysed.

The OEL Committee considered that the existing excess risk calculations based on epidemiological or animal studies contained too many uncertainties and could not therefore be used for a quantitative health risk assessment. Moreover, careful examination of the studies in workers led the OEL Committee to conclude that no epidemiological or experimental study was adequate for establishing a cancer unit risk associated with occupational exposure to TCE by inhalation. In the absence of adequate data, therefore, the OEL Committee proposes the **establishment of a pragmatic OEL**. The aim of this OEL will not be to prevent the carcinogenic effects of TCE in the workplace, but to introduce a management tool that can be used to limit exposure.

The OEL Committee selected nephrotoxicity as the critical effect.

The studies in humans regarding renal toxicity were considered to be of insufficient quality. After analysing the animal studies, the one by Maltoni *et al.* (1988) was selected as the key study: the authors observed cytokaryomegaly of renal tubular cells at 300 and 600 ppm in male rats (results significant for both doses, $p < 0.01$). The authors indicate that this renal damage

can be regarded as a precursor effect of kidney cancer and was observed in rats with renal cell carcinoma. The NOAEC for renal effects was 100 ppm.

Safety factor	Rationale	Value applied
SF_A	Transposition from animals to humans: - Toxicokinetic component = 1 (Category 3 gas → US EPA recommendations) - Toxicodynamic component = 2.5	2.5
SF_H	Intra-species variability	5

Moreover, a time adjustment was made to take into account a workplace exposure scenario.

This leads to the recommendation of **an 8h-OEL of 40 mg.m^{-3} or 7 ppm.**

Short-term exposure to TCE by inhalation causes effects on the central nervous system, in humans as in animals. The available studies, either in animals or humans, suffer from methodological limitations that mean they cannot easily be used for establishing a STEL. Under these conditions and in accordance with its earlier work (AFSSET, 2008), the Committee recommends **not exceeding a value of five times the 8h-OEL for 15 min, i.e. 200 mg.m^{-3} or around 35 ppm,** to protect workers exposed to TCE concentration peaks from the neurological effects.

Several studies (Sato and Nakajima, 1978; Tsuruta, 1978, Kezic *et al.*, 2000) undertaken in volunteers clearly indicate the dermal absorption of TCE. Consequently, **the skin notation must be assigned.**

Results of the collective expert appraisal on the assessment of the measurement methods in workplace atmospheres

A sampling pump and activated charcoal tube, followed by solvent desorption and GC/FID analysis, can be used to measure occupational exposure to trichloroethylene in reference to the 8h-OEL and the 15min-STEL recommended by the OEL Committee. This measurement technique is classified in Category 1.

If these OELs are lowered further at some time in the future, this method should still be suitable, subject to further validation.

The protocols described involve FID detection. Detection by mass spectrometry is possible, provided that the analytical conditions guarantee the same level of performance quality.

Measurement using passive samplers, followed by solvent desorption and GC/FID analysis, has been validated in concentration ranges far higher than the 8h-OEL recommended by the OEL Committee, and therefore requires further validation. This method is classified in Category 2. The OEL Committee also draws attention to the air velocity constraints associated with passive sampling.

Active sampling using Tedlar bag is not recommended due to the fact that it cannot be applied to individual sampling.

The OEL Committee recommends the following method:

No.	Method	Similar protocols	Category
1	Sampling pump and activated charcoal tube – CS_2 desorption – GC/FID analysis	INRS MétroPol 029: 2009 NIOSH 1022: 1994 OSHA 1001: 1999 MTA/MA-013/R87: 1987 MTA/MA-045/A00: 2000 BGI 505-65: 2005 BGIA 6600: 2000 *MDHS 96(*):2000* *AFNOR NF ISO 16200 -1: 2001 (*)* *AFNOR NF X 43-267: 2004 (*)*	**1**

(*) These protocols are intended for the sampling and assaying of most volatile organic compounds, and define the general requirements to be met in order to validate the sampling and analytical method. The protocols MDHS 96: 2000, MDHS 88: 1997, MDHS 72: 1993, MDHS 80: 1995 and NF ISO 16200-1 refer to the NIOSH 1022 protocol for sampling and analysis of trichloroethylene.

Conclusions of the collective expert appraisal

Recommended limit values:

8h-OEL = 40 $mg.m^{-3}$ (7 ppm)

15min-STEL = /

Since the available data cannot be used to establish a STEL, it is recommended[3] not to exceed the value of 5 times the 8h-OEL for 15 min, i.e. **200 $mg.m^{-3}$ (35 ppm).** The OEL Committee emphasises the need to adhere to this STEL because of the many cases of neurological disorders observed in workers exposed to trichloroethylene concentration peaks.

Skin notation: Yes

Recommended sampling and measurement techniques

Sampling pump and activated charcoal tube – CS_2 desorption – GC/FID analysis

[3] For more details, refer to the collective expert report for setting occupational exposure limit values for chemical agents of December 2008, on the recommendations for occupational exposure limits in order to limit the size and number of exposure peaks over the working day (part 1)

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