**Opinion**
**Request No 2016-SA-0117**

The Director General

Maisons-Alfort, 17 July 2018

# OPINION
## of the French Agency for Food, Environmental and Occupational Health & Safety

**on the development of a TRV by the respiratory route for perchloroethylene**

**(CAS No. 127-18-4)**

*ANSES undertakes independent and pluralistic scientific expert assessments.*
*ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.*
*It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.*

*It provides the competent authorities with the necessary information concerning these risks as well as the requisite expertise and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).*

*Its opinions are made public.*
*This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 17 July 2018 shall prevail.*

On 18 March 2016, ANSES received a formal request from the Directorate General for Health (DGS) to propose acute, subchronic and chronic TRVs by inhalation (with and without a threshold) for trichloroethylene, perchloroethylene, ammonia and four chloroanilines. This opinion relates only to the proposed TRVs for perchloroethylene.

## 1. BACKGROUND AND PURPOSE OF THE REQUEST

As part of the risk assessments carried out when examining dossiers concerning classified installations for environmental protection (ICPE) or the management of polluted sites and soils, the Regional Health Agencies (ARSs) or consultancies send questions to the DGS about the choice of TRVs for certain substances. This choice is made with regard to information note No. DGS/EA1/DGPR/2014/307 of 31 October 2014 on the methods for selecting chemical substances and choosing TRVs in order to conduct health risk assessments in the framework of impact and

management studies for polluted sites and soils. In this note, ANSES is designated as the expert agency for selecting and establishing TRVs. For certain substances, such as perchloroethylene (PCE), ANSES's recommendation was to adopt the excess risk by inhalation developed by the US EPA (corresponding to a non-threshold TRV) (ANSES, 2013). ANSES thus received a formal request to propose TRVs (threshold and non-threshold) for these substances by inhalation corresponding to the acute, subchronic and chronic durations of exposure.

A toxicity reference value, or TRV, is a toxicological indicator for qualifying or quantifying a risk to human health. It establishes the link between exposure to a toxic substance and the risk of occurrence of an adverse health effect. TRVs are specific to a duration (acute, subchronic or chronic) and route (oral or respiratory) of exposure. The way TRVs are established differs depending on the knowledge or assumptions made about the substances' mechanisms of action. Currently, the default assumption is to consider that the relationship between exposure (dose) and effect (response) is monotonic. In the current state of knowledge and by default, it is generally considered that for non-carcinogenic effects, toxicity is only expressed above a threshold dose (ANSES, 2015a).

In practice, establishing a TRV involves the following steps:

- identifying and analysing the available toxicity data, based on epidemiological and/or experimental studies;
- identifying the target organ(s) and critical effect;
- identifying the assumption according to which it is established: with or without a threshold dose, depending on the substance's mode of action;
- choosing a good quality scientific study generally enabling establishment of a dose-response relationship;
- defining a critical dose for humans or animals from this study, and if required, in the case of a critical dose obtained in animals, adjusting this dose to humans;
- for a threshold TRV, applying uncertainty factors to this critical dose so as to derive a TRV that is applicable to the entire population in question;
- for a non-threshold TRV, conducting a linear extrapolation to the origin in order to determine an excess risk per unit.

TRVs are established according to a highly structured and rigorous approach involving collective assessments by groups of specialists.

## 2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French Standard NF X 50-110 "Quality in Expert Appraisals – General Requirements of Competence for Expert Appraisals (May 2003)".

The expert appraisal falls within the sphere of competence of the Expert Committee (CES) on "Characterisation of substance hazards and toxicity reference values" (hereinafter referred to as the CES "Substances"). The methodological and scientific aspects of the work were presented to the CES between May and November 2016. It was adopted by the CES "Substances" at its meeting on 23 February 2017.

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals.

The experts' declarations of interests are made public *via* the ANSES website (www.anses.fr).

## 3. ANALYSIS AND CONCLUSIONS OF THE CES

### 3.1. Summary of the health effects

#### 3.1.1. Acute effects

Several studies of controlled exposure to PCE in humans have shown that the main effects observed were eye and respiratory irritation, loss of coordination, and other effects on the central nervous system (headache and drowsiness). In both humans and animals, among the neurological effects studied**,** colour vision disorders are the effects that occur at the lowest levels of exposure to PCE.

#### 3.1.2. Chronic non-carcinogenic effects

Human exposure to PCE induces renal, hepatic and central nervous system effects. After repeated inhalation exposure, moderate tubular lesions in the kidney have been reported. The observed liver effects are enzymatic induction with increased gamma-glutamyl transferase or structural abnormalities revealed by ultrasound (mild to moderate structural abnormalities of the hepatic parenchyma). Lastly, damage to the central nervous system includes memory disorders, increased response time, and loss of colour vision. The effects occurring at the lowest levels of exposure to PCE are the neurological effects.

#### 3.1.3. Carcinogenic-genotoxic effects

In 1994, the International Agency for Research on Cancer (IARC) had classified PCE in Group 2B ("The agent is possibly carcinogenic to humans") based on limited evidence in humans and sufficient evidence in animals:

- Carcinogenicity studies in animals were positive in two rodent species (rats and mice) and in both sexes. Hepatocarcinomas have been observed in mice, while neoplasms of the haematopoietic system and kidneys, and brain gliomas, have been observed in rats.
- Epidemiological studies (mainly five cohort studies) have shown a positive association between exposure to PCE and the risk of developing oesophageal or cervical cancer, or non-Hodgkin lymphoma, although confounding factors such as smoking, alcohol and socio-economic status could not be ruled out.

During its re-assessment of chlorinated agents in October 2012, the IARC classified PCE as "probably carcinogenic to humans" (Group 2A). Thus, based on new studies (including three cohort studies and 11 case-control studies), the IARC experts came out in favour of a positive association between PCE and bladder cancer. For other organs, namely the oesophagus, kidneys and cervix, and for non-Hodgkin lymphoma, the epidemiological evidence was considered insufficient.

The ATSDR (1997), DECOS (2003) and EU-DRAR (2008) conducted extensive critical reviews of the literature on genotoxic effects *in vitro* and *in vivo:* the majority of *in vivo* and *in vitro* studies on the genotoxicity of PCE were negative.

In the ANSES report entitled "Analysis of the US EPA's 2012 toxicity reference values by inhalation for perchloroethylene", the CES experts concluded that the data were insufficient to rule on whether or not there was a threshold for cancer induction. Based on current knowledge and considering the methodology for establishing TRVs for carcinogenic effects, the working group suggested that PCE should be considered by default as a **potentially carcinogenic substance with a non-threshold mechanism of action** (ANSES 2013a). Since then, no new data have led to these conclusions being reversed.

### 3.2. Development/choice of the TRVs by inhalation

#### 3.2.1. Acute TRV by inhalation

- Choice of the critical effect

Among PCE's acute effects, the CES regards **neurotoxicity** to be the most sensitive health effect. Among the neurological effects studied**,** colour vision disorders in particular are described as being the most sensitive effects, occurring at the lowest levels of exposure to PCE.

- Analysis of the existing TRVs

Among the existing acute TRVs (OEHHA, 2008 and ATSDR, 1997), in 2009 the Agency had selected the value of the ATSDR (2 ppm, or 1.38 $mg \cdot m^{-3}$) for establishing an IAQG. The critical effect selected was neurotoxicity (AFSSET, 2009). This ATSDR value is currently being replaced by a new ATSDR TRV, but as it is still in the form of a preliminary report it cannot be used.

The OEHHA (2008) selected neurotoxicity and irritations of the upper respiratory tract and eyes as critical effects, based on the study by Stewart *et al.* (1970). In 2009, the experts of the IAQG WG had decided that the source study by Stewart *et al.* (1970) had a less robust methodology and results than the study by Altmann *et al.* (1992) used by the ATSDR (AFSSET, 2009). The time adjustment proposed by the OEHHA had also not been considered relevant by the experts of the IAQG WG.

**The CES experts therefore decided not to select any of the existing TRVs and to establish a new acute TRV by inhalation.**

- Choice of the key study

The CES experts selected the study by Altmann *et al.* (1992) as the key study. Male volunteers were subjected to a battery of neurobehavioural tests before and after exposure to PCE to assess motor performance and coordination, concentration, pattern recognition, learning and mood.

- Choice of the critical concentration

In the study by Altmann *et al.* (1992), 12 male volunteers were exposed to 10 ppm and 16 volunteers to 50 ppm of PCE for 4 days, for 4 hours/day. At 50 ppm, a significant increase was noted in the latency time of visual evoked potentials (VEPs) compared to baseline pre-exposure levels ($p<0.05$), as well as significant performance deficiencies in vigilance ($p=0.04$) and hand-eye coordination ($p=0.05$), compared to subjects exposed to 10 ppm of PCE for whom no effect was observed.

The CES experts selected a **NOAEC of 10 ppm, or 69 $mg \cdot m^{-3}$** as the critical concentration.

- Temporal adjustment

To take account of the discontinuity of the exposure, a time adjustment was made:

$NOAEC_{ADJ}$ = 10 x 4/24 = 1.7 ppm, rounded to 2 ppm, or 13.8 $mg \cdot m^{-3}$

- Choice of uncertainty factors

The TRV was calculated using the following uncertainty factors (ANSES, 2017):

- Inter-species variability ($UF_A$): 1. Key study performed in humans.
- Inter-individual variability ($UF_H$): 10. There were no scientific data available to reduce the default value.
- Use of a NOAEC ($UF_{B/L}$): use of a NOAEC, therefore the value of 1 was selected,

- Inadequacy of the data ($UF_D$): 1 because the literature review revealed that there were many studies on PCE.

An overall uncertainty factor of **10** was thus used to establish the TRV.

- Proposed acute TRV by inhalation

**TRV = 1.38 mg·m$^{-3}$ (0.2 ppm)**

- Confidence level

The overall confidence level **high** was assigned to this TRV, based on four criteria: nature and quality of the data (high confidence level), choice of the critical effect and the mode of action (high confidence level), choice of the key study (high confidence level) and choice of the critical dose (moderate confidence level).

### 3.3. Chronic TRV by inhalation

- Choice of the critical effect

Among the non-carcinogenic effects of PCE, the CES considers that **neurotoxicity** is the adverse effect regarded as the most sensitive. Among the neurological effects observed**,** colour vision disorders are described as being the most sensitive effects, occurring at the lowest levels of exposure.

- Analysis of the existing TRVs

Regarding the existing chronic TRVs (Health Canada, 2015; US EPA, 2012; WHO, 2010; RIVM 2001; ATSDR, 1997 and OEHHA, 1991), the CES considers that none of these values can be used due to the choice of critical effect (pulmonary effects considered irrelevant) and/or the application of uncertainty factors not consistent with the ANSES methodology (ANSES, 2017). **The CES experts therefore decided to establish a new chronic TRV by inhalation.**

- Choice of the key study

The experts selected the study by Cavalleri *et al.* (1994) as the key study. This study included 35 employees of dry-cleaning companies and a group of 35 unexposed control subjects. The Lanthony colour discrimination test was used.

- Choice of the critical concentration

In the study by Cavalleri *et al.* (1994), the average overall exposure was 6.2 ppm, or 41 mg·m$^{-3}$ (7.3 ppm (50 mg·m$^{-3}$) for the 22 operators and 4.8 ppm (33 mg·m$^{-3}$) for the 13 people working on ironing). The average exposure duration was 8.8 years. The results on the 35 people showed a significant increase in the Colour Confusion Index (CCI)[1]. This increase was not significant for the ironing sub-group.

The CES experts selected a **LOAEC of 50 mg·m$^{-3}$ (7.3 ppm)**.

[1] The CCI is an index that quantifies errors in the Lanthony test. It is the ratio between the patient's Total Colour Distance Score and the optimal value of the score based on the sum of the distances measured between the points of the colour vision test. Impaired colour vision results in a CCI of more than 1.

- Temporal adjustment

To take account of the discontinuity of the exposure, a time adjustment was made:
$LOAEC_{ADJ}$ = 50 x [(8h/24h) x (5d/7d)] = 11.9 mg·m$^{-3}$, rounded to 12 mg·m$^{-3}$ (1.8 ppm)

- Choice of uncertainty factors

The TRV was calculated using the following uncertainty factors (ANSES, 2017):

- Inter-species variability ($UF_A$): 1. Key study performed in humans.
- Inter-individual variability ($UF_H$): 10. There were no scientific data available to reduce the default value.
- Use of a LOAEC ($UF_{B/L}$): 3. Value selected when using a LOAEL (ANSES 2017)
- Inadequacy of the data ($UF_D$): 1 because the literature review revealed that there were many studies on PCE.

An overall uncertainty factor of **30** was thus used to establish the TRV.

- Proposed chronic TRV by inhalation

**TRV = 0.4 mg·m$^{-3}$, or 0.06 ppm**

- Confidence level

The overall confidence level **high** was assigned to this TRV, based on the following four criteria: nature and quality of the data (high confidence level)**,** choice of the critical effect and the mode of action (high confidence level), choice of the key study (high confidence level) and choice of the critical dose (moderate confidence level).

### 3.4. Subchronic TRV by inhalation

- Choice of the critical effect

Among the non-carcinogenic effects of PCE, the CES considers that **neurotoxicity** is the health effect regarded as the most sensitive. Among the neurological effects studied**,** colour vision disorders in particular are described as being the most sensitive effects, occurring at the lowest levels of exposure.

- Analysis of the existing TRVs

There are no subchronic TRVs by inhalation. The CES experts therefore decided to establish one.

- Proposed subchronic TRVs

The CES experts selected the chronic TRV as the subchronic TRV, based on the study by Cavalleri *et al.* (1994), with the critical effect being the decline in colour vision. The blood PCE concentration reaches an equilibrium state after around two weeks of continuous exposure, and therefore a longer exposure time does not *a priori* generate a higher blood PCE concentration.

**TRV = 0.4 mg·m$^{-3}$, or 0.06 ppm**

### 3.5. Non-threshold TRV (carcinogenic effects)

In 2013, ANSES had adopted the non-threshold TRV proposed by the US EPA for carcinogenic effects by inhalation (ANSES, 2013b). Since the knowledge available was insufficient for precisely identifying PCE's mechanism of action in the development of liver tumours, ANSES had considered a non-threshold carcinogenic mechanism of action by default (ANSES, 2012).

This TRV of $2.6 \cdot 10^{-7}$ $(\mu g \cdot m^{-3})^{-1}$ was based on an animal study (JISA, 2013) where the critical effect was the concentration-dependent increase in hepatocellular adenomas/carcinomas.
**No new TRV or new study calls into question the choice made by ANSES in 2013.**

## 4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The French Agency for Food, Environmental and Occupational Health & Safety endorses the conclusions and recommendations of the CES "Substances" on the formulation and choice of toxicity reference values for inhalation for perchloroethylene.

**Table 1: Threshold TRVs proposed by ANSES for perchloroethylene**

| Critical effect (key study) | Critical concentration | UF | Value of the TRV |
|---|---|---|---|
| **Acute TRV** | | | |
| Decreased performance in coordination and vigilance tests<br>Altmann *et al.* (1992) | NOAEC = 69 mg·m$^{-3}$ (10 ppm)<br>Temporal adjustment<br>NOAEC$_{ADJ}$ = 13.8 mg·m$^{-3}$ (2 ppm) | 10<br>UF$_H$ = 10 | **TRV = 1.38 mg·m$^{-3}$** or 0.2 ppm<br>**Confidence level: high** |
| **Subchronic TRV** | | | |
| Decline in colour vision<br>Cavalleri *et al.* (1994) | LOAEC = 50 mg·m$^{-3}$ (7.3 ppm)<br>Temporal adjustment<br>LOAEC$_{ADJ}$ = 12 mg·m$^{-3}$ (1.8 ppm) | 30<br>UF$_H$ = 10<br>UF$_L$ = 3 | **TRV = 0.4 mg·m$^{-3}$ or 0.06 ppm**<br>**Confidence level: high** |
| **Chronic TRV** | | | |
| Decline in colour vision<br>Cavalleri *et al.* (1994) | LOAEC = 50 mg·m$^{-3}$ (7.3 ppm)<br>Temporal adjustment<br>LOAEC$_{ADJ}$ = 12 mg·m$^{-3}$ (1.8 ppm) | 30<br>UF$_H$ = 10<br>UF$_L$ = 3 | **TRV = 0.4 mg·m$^{-3}$ or 0.06 ppm**<br>**Confidence level: high** |

**Table 2: Non-threshold TRV proposed by ANSES for perchloroethylene (US EPA, 2012)**

| Critical effect and source study | Establishment method | Value of the TRV |
|---|---|---|
| Hepatocellular adenomas and carcinomas in male mice<br>JISA, 1993 | Calculation of a BMC$_{10\%}$L$_{95\%}$ = 3.9·10$^5$ µg·m$^{-3}$<br>PBPK model (Chiu and Ginsberg, 2011) | **2.6·10$^{-7}$ (µg·m$^{-3}$)$^{-1}$**<br>**1.8·10$^{-3}$ (ppm)$^{-1}$**<br>Concentrations associated with several levels of risk:<br>**10$^{-4}$: 400 µg·m$^{-3}$**<br>**10$^{-5}$: 40 µg·m$^{-3}$**<br>**10$^{-6}$: 4 µg·m$^{-3}$**<br>**Confidence level: moderate** |

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**KEYWORDS**

toxicity reference value, inhalation, perchloroethylene, tetrachloroethylene, acute, subchronic, chronic, carcinogenic, threshold, no threshold