COLLECTIVE EXPERT APPRAISAL: SUMMARY AND CONCLUSIONS

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

On the evaluation of biomarkers of exposure and recommendation for biological limit values and biological reference values for trichloroethylene

(n° CAS 79-01-6)

This document summarises the work of the Expert Committee on « Health reference values » and the Working Group on biomarkers (Biomarkers WG).

Presentation of the issue

On 12 June 2007, AFSSET, which became ANSES in July 2010, was asked by the Directorate General for Labour to carry out the necessary assessment for setting occupational exposure limits for trichloroethylene (TCE).

France currently has an indicative 8-hour occupational exposure limit of 405 mg.m^{-3} (75 ppm) and an indicative short-term exposure limit of 1080 mg.m^{-3} (200 ppm) (Circular[1] of 1983).

The Directorate General for Labour requested that ANSES re-assess these values and, if necessary, propose new occupational exposure limits based on health considerations.

This request was entrusted to the Expert Committee on "expert appraisal for recommending occupational exposure limits for chemical agents" (OEL Committee) which, in April 2013, issued a report recommending for TCE:

- establishing a pragmatic 8h-OEL[2] of 40 mg.m^{-3} (7 ppm)
- that exposure over a 15-minute period should not exceed five times the value of the 8-hour OEL, i.e. a pragmatic 15 min-STEL of 200 mg.m^{-3} (35 ppm)
- assigning a "skin" notation

ANSES decided to supplement its appraisal by assessing the data on biological monitoring in the workplace for trichloroethylene in order to assess the suitability of recommending the monitoring of one or more biomarkers in addition to the atmospheric OEL and the establishment of biological limit values for the selected biomarker(s).

[1] Circular of 1st December 1983 supplementing and amending the Circular of 19 July 1982 relative to permitted values for concentrations of certain hazardous substances in the workplace atmosphere

[2] The aim of this OEL is not to set a value below which there is no carcinogenic effects but rather to provide OSH experts with a risk management tool to limit occupational exposure.

It should be noted that the European expert committee in charge of expert appraisals on occupational exposure limits for chemical agents (SCOEL[3]) recommended in April 2009 an 8h-OEL of 10 ppm (54.7 $mg.m^{-3}$) and a STEL (15 min) of 30 ppm (161.1 $mg.m^{-3}$). In addition to assigning a "skin" mention, SCOEL recommended a biological limit value of 20 $mg.L^{-1}$ for trichloroacetic acid in urine.

Scientific background

Biological monitoring of exposure in the workplace has emerged as a complementary method to atmospheric metrology for assessing exposure to chemical agents. Biological monitoring assesses a worker's exposure by including all the routes by which a chemical penetrates the body (lung, skin, digestive tract). It is particularly worthwhile when a substance has a systemic effect, and:

- when routes other than inhalation contribute significantly to absorption,
- and/or when the pollutant has a cumulative effect,
- and/or when the working conditions (personal protection equipment, inter-individual differences in respiratory ventilation, etc.) determine large differences in internal dose that are not taken into account by atmospheric metrology.

With regard to prevention of chemical risk in the workplace, the French Labour Code provides for the use of biological monitoring of exposure and biological limit values.

Committee definitions

Biomarker of exposure (BME): parent substance, or one of its metabolites, determined in a biological matrix, whose variation is associated with exposure to the targeted agent. Biomarkers of early and reversible effects are included in this definition when they can be specifically correlated to occupational exposure.

Biological limit value (BLV): This is the limit value for the relevant biomarkers.

Depending on the available data, the recommended biological limit values do not all have the same meaning:

- if the body of scientific evidence is sufficient to quantify a dose-response relationship with certainty, the BLVs will be established on the basis of health data (no effect for threshold substances or risk levels for non-threshold carcinogens);
- in the absence of such data for substances with threshold effects, BLVs are calculated on the basis of the expected concentration of the biomarker of exposure (BME) when the worker is exposed to the 8-hour OEL. For carcinogens, in the absence of sufficient quantitative data, the biological limit value is calculated on the basis of another effect (pragmatic BLV). These latter values do not guarantee the absence of health effects, but aim to limit exposure to these substances in the workplace.

Whenever possible, the Committee also recommends biological reference values (BRVs). These correspond to concentrations found in a general population whose characteristics are similar to those of the French population (preferentially for BMEs) or in a control population not occupationally exposed to the substance under study (preferentially for biomarkers of effects).

These BRVs cannot be considered to offer protection from the onset of health effects, but do allow a comparison with the concentrations of biomarkers assayed in exposed workers. These values are particularly useful in cases where it is not possible to establish a BLV (ANSES, 2017).

[3] Scientific Committee on Occupational Exposure Limits

Organisation of the expert appraisal

ANSES entrusted examination of this request to the OEL Committee then the Expert Committee on “Health reference values”. The Agency also mandated the Working Group on biomarkers (Biomarkers WG) for this expert appraisal.

Several ANSES employees contributed to the work and were responsible for scientific coordination of the different expert groups.

The methodological and scientific aspects of the work of this group were regularly submitted to the Expert Committees. The report produced by the Working Group takes account of observations and additional information provided by the Committee members.

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”.

Preventing risks of conflicts of interest

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

The experts’ declarations of interests are made public on ANSES's website (www.anses.fr).

Description of the method

Two rapporteurs of the Biomarkers WG and two ANSES employees produced a summary report on biomarkers of exposure and the recommendation of biological limit values (BLVs) and biological reference values (BRVs) for the BME(s) considered relevant.

The summary report on the BMEs for trichloroethylene was based on bibliographical information taking into account the scientific literature published on this substance until 2018. The bibliographical research was conducted in the following databases: Medline, Scopus and the Public Health Database. The rapporteur reassessed the original articles or reports cited as references whenever he considered it necessary, or whenever the Committee requested it.

The scientific articles selected to assess biomonitoring data on trichloroethylene were identified particularly using the following keywords: "trichloroethylene", "biomarker", "biomonitoring", "biological monitoring", "urine", "blood", "occupational", "analytical method" and the search was limited to human data. Queries for the complementary bibliographic search (between 2011 and 2018) are described in figure 1.

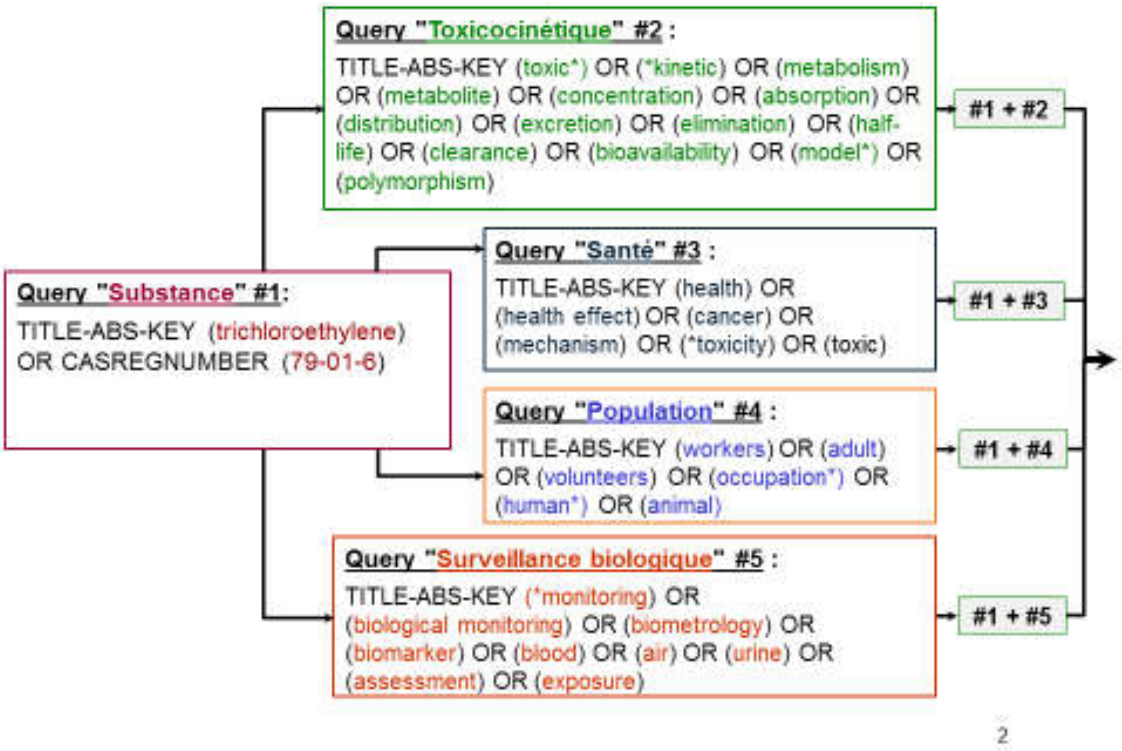

Figure 1 : queries for the bibliographic search

The report, the summary and conclusions of the collective expert appraisal work were adopted by the Expert Committee on "Health reference values" on 9 May 2019.

The collective expert appraisal work and the summary report were submitted to public consultation from 19/12/2019 to 19/02/2020. No comments were received. The Health Reference Values Committee (term of office 2017-2020) adopted this version on 15/05/2020.

Result of the collective expert appraisal

Toxicokinetics data

TCE is rapidly absorbed, regardless of the route of exposure (oral, dermal or by inhalation) (ATSDR, 2014).

By inhalation, the absorption of TCE through the alveolar epithelium is relatively rapid and extensive (blood:air partition coefficient of eight to 12 in humans) (Lash *et al.,* 2000 and IARC, 2014). ATSDR (2014) reports that 37% to 64% of inhaled TCE is absorbed in the lungs at rest. The absorbed dose is proportional to the inhaled concentration, the duration of exposure and the alveolar ventilation rate (US EPA, 2011). Total pulmonary absorption seems to be more influenced by lean body mass than by the quantity of adipose tissue (Monster *et al.*, 1979).

The dermal absorption of TCE in vapour or liquid form was assessed in several studies in volunteers (Sato and Nakajima, 1978; Tsuruta, 1978; Kezic *et al.*, 2000; Kezic *et al.,* 2001). According to Kezic *et al.* (2000), the dermal route plays a very small role in the absorption of TCE vapour. In 2001, Kezic *et al.* reported dermal flux of 430 $nmol \cdot cm^{-2} \cdot min^{-1}$ following exposure to a TCE solution on 3 cm^2 of skin for one minute.

Studies reporting cases of acute poisoning have demonstrated that oral absorption is extensive and rapid (ATSDR, 2014).

TCE is widely distributed throughout the body by the bloodstream, in humans and animals, regardless of the route of absorption. Since it is lipophilic, it is mainly found in adipose tissue, but also in the liver, kidneys, nervous system and cardiovascular system. TCE is capable of crossing the placental barrier and blood-brain barrier and is found in breast milk (ATSDR, 2014).

In humans, 40% to 75% of inhaled TCE is metabolised. Most of the adverse effects induced by TCE are thought to be attributable to its metabolites (IARC, 2014). TCE is rapidly metabolised by two pathways, mainly in the liver (figure 2):

- via oxidative metabolism, TCE is rapidly converted by cytochrome P450 (in particular CYP450 2E1) into an unstable epoxide, trichloroethylene oxide (TCE-O), which is primarily converted into trichloroacetaldehyde or chloral (CHL). This is rapidly hydrolysed into chloral hydrate (CH). Chloral hydrate then serves as a substrate for alcohol dehydrogenase and aldehyde dehydrogenase, respectively leading to the formation of free trichloroethanol (TCOH) and trichloroethanol glucuronide (TCOG) on the one hand and trichloroacetic acid (TCA) on the other hand. These are the main metabolites and are excreted primarily in urine. To a lesser extent, the unstable epoxide can also lead to the formation of dichloroacetic acid (DCA), monochloroacetic acid, formic acid, carbon monoxide, oxalic acid and N-(hydroxyacetyl)-aminoethanol.
- by conjugation with glutathione to a lesser extent, TCE is also metabolised via glutathione-S-transferase into N-acetyl-S-(1,2-dichlorovinyl)glutathione or N-acetyl-S-(2,2-dichlorovinyl)glutathione (N-acetyl-1,2-DCVG or N-acetyl-2,2-DCVG); these metabolites are activated into S-(1,2-dichlorovinyl)-L-cysteine or S-(2,2-dichlorovinyl)-L-cysteine (1,2-DCVC or 2,2-DCVC). These metabolites can then be converted, via various pathways, either into N-acetyl-S-(1,2-dichlorovinyl)-L-cysteine or N-acetyl-S-(2,2-dichlorovinyl)-L-cysteine (N-acetyl-1,2-DCVC or N-acetyl-2,2-DCVC) by an N-acetyltransferase, or into thioacyl chloride or chlorothioketene via a β-lyase. Chlorothioketene can then be hydrolysed into monochloroacetic acid.

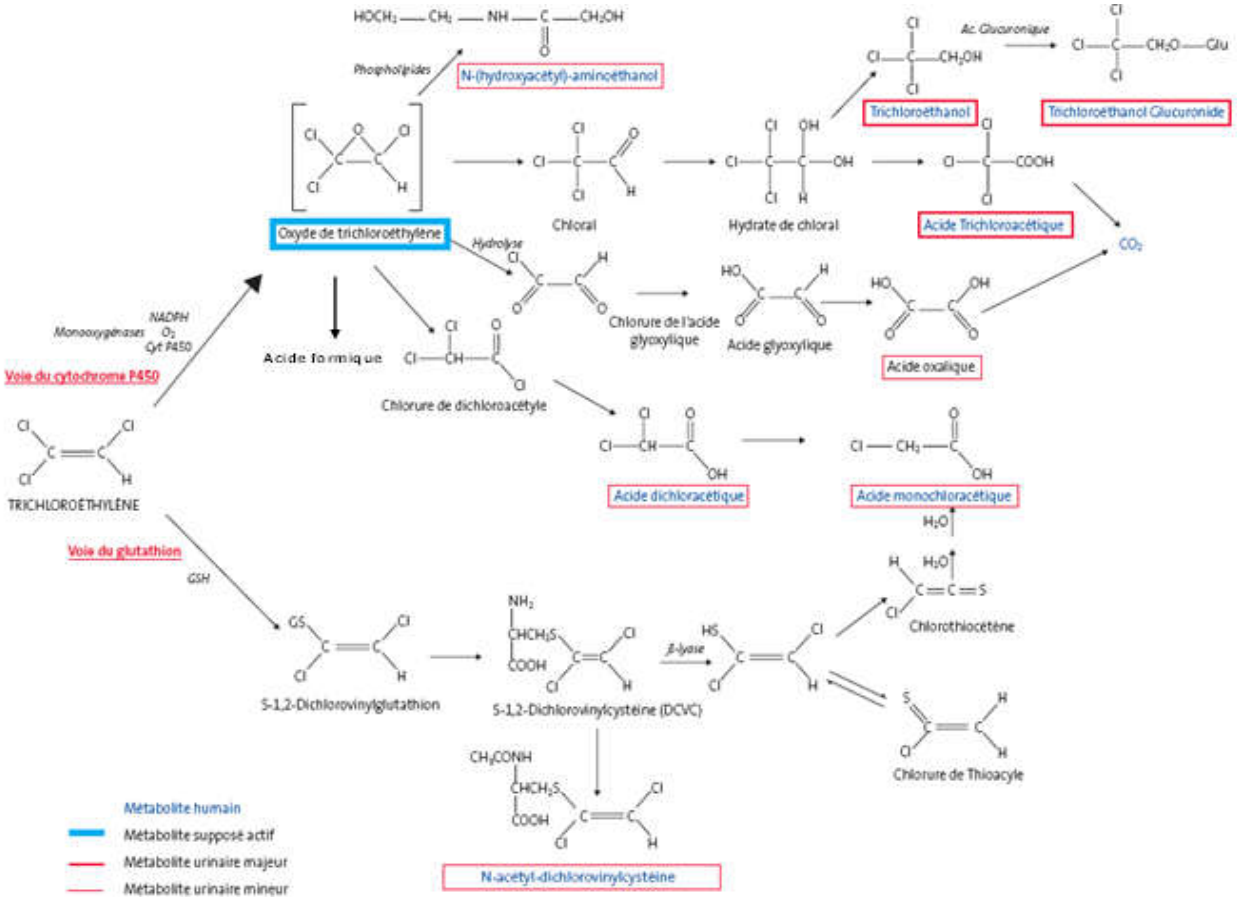

Figure 2 : Metabolism of TCE (adapted from INRS, 2011)

In humans, no saturation has been found at experimental exposure conditions of up to 300 ppm (ATSDR, 2014). According to ATSDR (2014), authors have calculated, by mathematical modelling, that the metabolism of TCE could be saturated with exposure (inhalation) to levels above 2000 ppm.

Genetic polymorphisms in several enzymes involved in the metabolism of TCE (CYP450 and GST in particular) contribute to inter-individual variability (in the production of metabolites that are useful as biomarkers of exposure (BMEs) as well as in individual susceptibility to the effects of TCE). Moreover, exposure to other substances that act by inhibiting or inducing CYP450 enzymes can also influence the metabolism of TCE.

Ethanol can modulate (by inhibiting or increasing) TCE metabolism by the CYP450 (CYP2E1)-dependent oxidative pathway according to several factors: the time between exposure to ethanol and to TCE, the exposure doses, and the usual nature of alcohol consumption (regular use induces CYP2E1 whereas concomitant use can cause the competitive inhibition of biotransformation by alcohol dehydrogenase). Other compounds are known to influence the metabolism of TCE: compounds with a short carbon chain and an alcohol function (isopropanol), and compounds inhibiting the enzymes involved in alcohol metabolism.
The elimination pathways of TCE are qualitatively identical in animals and humans and are not influenced by the route of exposure. Unchanged TCE (10-28% of the dose) and the volatile metabolites (CO_2, CO, TCOH) are eliminated in exhaled air (EC, 2004). Unchanged TCE is eliminated in exhaled air for 18 hours after a single exposure. Very few data were found in the scientific literature regarding the elimination kinetics of unchanged TCE in urine. The main metabolites, TCOH and TCA, are eliminated in urine (48-85%) and faeces. The elimination of TCOH in urine is complete five days after the end of exposure, while that of TCA is complete after 13 days (INRS, 2011; INERIS, 2005).

The main toxicokinetic parameters for TCE are summarised in Table 1.

Table 1: Summary of toxicokinetic parameters for TCE and its metabolites

	Inhalation exposure considered	**Estimated percentage of absorbed dose**	**Time of peak concentration (relative to the beginning of exposure)**	**Half life**
Parent substance				
TCE in blood (TCEb)	100 ppm for 6 h (Muller *et al*., 1974)		From 2 h	
	Mathematic modelling (Sato *et al*., 1977)			Triphasic elimination **2.4 min**; **24.5 min** and **3.5 h**
	70 ppm, 4h/day, 5 day (Monster *et al*., 1979)			**14 h**
	54 or 97 ppm for 8 h (Fernandez *et al*., 1975)			**20 min** (highly vascularised tissue) then **3h** (muscles) then **30 h** (adipose tissue)
Metabolites				
TCA in blood	100 ppm for 6 h (Muller *et al*., 1974)		**24 h**	

(TCAb)	70 or 140 ppm for 2.5 or 4h (Monster *et al*., 1976) and 70 ppm for 4 h/day for 5 days (Monster *et al*., 1979)			**70 – 100 h**
TCA in urine (TCAu)	1042 mg·m^{-3}, i.e. 187 ppm for 5 h Bartonicek *et al*. (1962)	32%		
	Ikeda and Imamura, 1973 based on the results of Bartonicek *et al*., 1962			Monophasic: **55 h**
	170 ppm for 3 or 7h (Ogata *et al*., 1971)		**42 to 69 h** after the end of exposure	
	50 ppm, 6h/day for 5 days Muller *et al*., 1972			**100 h**
	70 or 140 ppm for 2.5 or 4h (Monster *et al*., 1976)	**18% to 24 %**	**22 to 46 h**	
	27, 81 and 201 ppm for 4h (Nomiyama and Nomiyama, 1977)		**2 days** after the end of exposure	
	250 to 380 ppm for 2h40 min (Ikeda and Imamura, 1973 based on the results of Nomiyama and Nomiyama, 1971)			**38 h** (men) and **36 h** (women)
	Workers intermittently exposed to 50 ppm TCE (Ikeda and Imamura, 1973)			Monophasic: **51 h**
TCOH in blood (TCOHb)	50 ppm or 100 ppm for 6h/day for 5 days (Ertle *et al*., 1972)			**12 h**
	100 ppm for 6 h (Muller *et al*., 1974)		**6 h**	**12 to 13 h**
	70 or 140 ppm for 2.5 or 4h (Monster *et al*., 1976)			**10 to 12 h**
	100 ppm for 4h (Fisher *et al*., 1998)		Free TCOH: at the end of exposure (**4h**)	
TCOH in urine (TCOHu)	1042 mg·m^{-3}, i.e. 187 ppm for 5 h (Bartonicek *et al*., 1962)	**45%**		
	Ikeda and Imamura, 1973 based on the results of Bartonicek *et al*., 1962			Monophasic: **30 h**
	50 ppm, 6h/day for 5 days Muller et al., 1972			Monophasic: **12 h**
	Inhalation	**40% to 43%**		

	70 or 140 ppm for 2.5 or 4h – 70 ppm, 4h/day for 5 days (Monster *et al*., 1976 and 1979)			
	250 to 380 ppm for 2h40min (Ikeda and Nomiyama, 1973 based on the results of Nomiyama and Nomiyama, 1971)			Monophasic: **19 h** (men) **26 h** (women)
	Workers intermittently exposed to 50 ppm TCE (Ikeda and Imamura, 1973)			Monophasic: **43 h**
	27, 81 and 201 ppm for 4h (Nomiyama and Nomiyama, 1977)		**1 to 4 h** after the end of exposure	
TCOH+ TCA in urine (TCOH+TCAu)	Ikeda and Imamura, 1973 based on the results of Nomiyama and Nomiyama (1971)			**31 h** (men) **36 h** (women)
	Workers intermittently exposed to 50 ppm TCE (Ikeda and Imamura, 1973)			**38 h** (women)
N-acetyl-DCVC in urine (NacDCVCu)	40, 80 or 160 ppm for 6 h (Bernauer *et al*., 1996)		Second concentration peak **36 h** after the end of exposure	Biphasic elimination

Selection of biomarkers of exposure and effect

Biomarkers of exposure (BME)

The analysis of the data in the literature led to nine BMEs being identified: TCE in blood (TCEb), TCE in urine (TCEu), TCE in exhaled air (TCEa), TCA in blood (TCAb), TCA in urine (TCAu), TCOH in blood (TCOHb), TCOH in urine (TCOHu), TCOH in exhaled air (TCOHa) and NAcDCVC in urine (NAcDCVCu). The sum of TCA and TCOH in urine was also considered.

The three BMEs that involve measuring TCE in exhaled air, blood or urine have their specificity as an advantage. It has been demonstrated that the analytical method for determining TCE concentrations in urine is a simple one that does not involve invasive sampling (Imbriani et al., 2001).

The measurement of TCE in exhaled air has disadvantages related to sampling difficulties. Moreover, a rapid decrease in levels in the first few minutes after the end of exposure requires strict compliance with the sampling time at the end of exposure, which is not necessarily easy to achieve in the occupational field.

Blood TCE seems to be a relevant BME for the biological monitoring of exposure to TCE. However, in addition to the invasive nature of sampling, no field studies or studies in volunteers focusing on the correlation between blood concentrations and atmospheric concentrations were identified in the literature. Nonetheless, there are validated PBPK models enabling blood concentrations to be predicted following exposure by inhalation.

TCA and TCOH are not specific to exposure to TCE. However, for these two metabolites, recommendations could be considered regarding their monitoring. Measurements from blood

samples will not be selected *a priori* for the biological monitoring of occupational exposure since, in addition to being invasive, they provide no more advantages than measurements in urine. However, TCOH and TCA in urine may be proposed as biomarkers of exposure. It should be noted that certain countries propose biological values for TCOH in blood, applicable to exposed workers, but not for TCOH in urine.

TCOH in exhaled air has also been proposed in the literature, but as with TCE measured in this same medium, there are also disadvantages related to sampling difficulties.

Measuring the sum of TCOH and TCA in urine, as has sometimes been reported in certain studies in volunteers, has no more advantages than measuring each of the two BMEs (there is not less variability). Moreover, although they are derived from the same metabolic pathway, these two metabolites have different kinetic behaviour (TCA binds to plasma proteins and has a much longer half-life than TCOH). Therefore, the sum of urinary TCOH and TCA was not selected as a relevant BME for the biological monitoring of occupational exposure to TCE.

Lastly, although N-acetyl DCVC has the advantage of following the same elimination pathway as the metabolite responsible for nephrotoxicity, and although urine concentrations may therefore be closely correlated with this effect, the information currently available in the literature is highly limited.

Therefore, only urinary TCE, urinary TCA and urinary TCOH were selected as relevant BMEs for the biological monitoring of occupational exposure to TCE.

Biomarkers of effect

Regarding nephrotoxic effects, several studies have shown changes in non-specific markers of nephrotoxicity. In particular, an increase in urinary concentrations of certain biological markers of tubular impairment has been reported in the literature. Brüning *et al.*, 1999 demonstrated an increase in the excretion of α-1 microglobulin and GST-α in workers exposed to TCE compared to the controls (Brüning *et al.*, 1999). In a report from 2003, DFG[4] indicated that α-1 microglobulin is the most relevant biomarker of effect for the biological monitoring of TCE due to its stability in urine, as opposed to β-2 microglobulin.

However, recommendations cannot be made for the monitoring of these biomarkers of effect since the identified studies do not enable a dose-response relationship to be characterised.

[4] Deutsche Forschungsgemeinschaft

Information on biomarkers of exposure identified as relevant for the biomonitoring of exposed workers

Name	TCE in urine
Other substances giving rise to this biomarker	None
Concentrations measured in exposed workers or volunteers (with exposure levels and sampling times)	• Field studies: *Rastkari et al. 2011* N = 30 male employees of dry-cleaning facilities, 3 groups of 10 subjects according to the capacity of the washing machines, non-smokers, mean age: 41 years (27-57 years) Analysis of TCEu LOQ = 20 $ng \cdot L^{-1}$: - 8 kg machine: mean [TCE]atmo = 1.56 $mg \cdot m^{-3}$ (standard deviation 0.68: *[TCEu] start of shift = 2.38 $\mu g \cdot L^{-1}$ (standard deviation 1.06); [TCEu] end of shift = 4.46 $\mu g \cdot L^{-1}$ (standard deviation 1.39) - 12 kg machine: mean [TCE]atmo = 1.75 $mg \cdot m^{-3}$ (standard deviation 0.74): *[TCEu] start of shift = 5.53 $\mu g \cdot L^{-1}$ (standard deviation 2.25); [TCEu] end of shift = 11.31 $\mu g \cdot L^{-1}$ (standard deviation 3.62) - 18kg machine: mean [TCE]atmo = 2.40 $mg \cdot m^{-3}$ (standard deviation 0.63): *[TCEu] start of shift = 8.18 $\mu g \cdot L^{-1}$ (standard deviation 2.42); [TCEu] end of shift = 4.46[5] $\mu g \cdot L^{-1}$ (standard deviation 1.39) *Imbriani et al. 2001* 49 workers (8 men, 41 women; mean age 38 years) [TCEatmo] exposure ($mg \cdot m^{-3}$): - Arithmetic mean (min – max): 83.31 (2.7 - 387.0) - Geometric mean (standard deviation): 44.05 (3.37) [TCEu] ($\mu g \cdot L^{-1}$) (middle of shift): - Arithmetic mean (min – max): 11.03 (0.8 - 43.90) - Geometric mean (standard deviation): 7.99 (2.46) • Studies on volunteers: Not Specified (NS)
Conversion factor (with molecular weight)	MW: 131.4 $g.mol^{-1}$ 1 $\mu mol.L^{-1}$ = 131 $\mu g.L^{-1}$ 1 $mg.L^{-1}$ = 7.63 $\mu mol.L^{-1}$
Concentrations in the general population	NS
Recommended limit values for exposed workers (INRS, 2018)	None

[5] Surprisingly, urinary concentrations of TCE at end of shift were lower than those measured at start of shift

Name	**TCA in urine**
Other substances giving rise to these biomarkers	Methylchloroform (1,1,1-trichloroethane) and tetrachloroethylene
Concentrations measured in exposed workers or volunteers (with exposure levels and sampling times)	• <u>Field studies:</u> *Ikeda et al. 1972* [TCEatmo] exposure (means) 8h/day, 6 days/week – [TCA u] (geometric means (SD range)) (end of week and end of shift): - (n = 9) 3 ppm – 12.7 mg.L^{-1} (8.8 – 18.2) - (n = 5) 5 ppm – 20.2 mg.L^{-1} (10 – 40.8) - (n = 6) 10 ppm – 17.6 mg.L^{-1} (10.3 – 30) - (n = 4) 25 ppm - 77.2 mg.L^{-1} (51.6– 115.6) - (n = 4) 40 ppm – 90.6 mg.L^{-1} (50.2 – 163.8) - (n = 5) 45 ppm – 138.4 mg.L^{-1} (83.2 – 216.5) - (n = 5) 50 ppm – 146.6 mg.L^{-1} (76.3 – 281.7) - (n = 5) 60 ppm – 155.49 mg.L^{-1} (104.3 – 231.4) - (n = 4) 120 ppm – 230.1 mg.L^{-1} (199 -267.4) - (n = 4) 175 ppm – 235.8 mg.L^{-1} (187.2 – 296.9) *Skender et al. 1991* [TCEatmo] exposure ranging from 25 to 40 ppm (never exceeding 50 ppm) [TCAu] (median for 10 employees of dry-cleaning facilities; start of week, start of shift) 32.47 mmol·mol^{-1} creat, i.e. 46.8 µg·g^{-1} creat [TCAu] (median for 10 employees of dry-cleaning facilities; Wednesday, end of shift) 37.15 mmol·mol^{-1} creat, i.e. 53.6 µg·g^{-1} creat *Imbriani et al. 2001* Exposure to TCEatmo (mg·m^{-3}): - Arithmetic mean (min – max): 83.31 (2.7 - 387.0) - Geometric mean (standard deviation): 44.05 (3.37) [TCAu] (µg·L^{-1}) (middle of day): - Arithmetic mean (min – max): 21.60 (0.4 - 57.3) - Geometric mean (standard deviation): 10.86 (4.48)

Concentrations measured in exposed workers or volunteers (with exposure levels and sampling times)	• <u>Studies on volunteers:</u> *Monster et al., 1979* [TCEatmo] exposure: 70 ppm (4 h/day; 5 days) [TCAu] (mean for 5 volunteers; end of exposure) increase in concentrations: - 1st day: 10 mg·24h^{-1} - 5th day: 82 mg·24h^{-1} *Kimmerle and Eben, 1973* [TCE]atmo exposure 50 ppm (4 h/day; 5 days) [TCAu] (mean for 4 volunteers; end of exposure) increase in concentrations: - 1st day: 4.75 mg·24h^{-1} - 5th day: 70.4 mg·24h^{-1}	
Conversion factor (with molecular weight)	MW: 163 g.mol^{-1} 1 µmol.L^{-1} = 163 µg.L^{-1} 1 mg.L^{-1} = 6 µmol.L^{-1}	
Concentrations in the general population	Reference value in the non-occupationally exposed working-age population = **0.07 mg.L^{-1}** end of exposure or end of shift after several shifts (BAR[6] value) (last modified in 2010). *Hajimiragha et al. 1986* [TCAu]: 95th percentile 177.6 µg·L^{-1} in adult subjects (N=43) from the German general population Skender *et al*. 1993 [TCAu]: 95th percentile 123.6 µg/24h in adult subjects (N=39) from the general population (Zagreb, Croatia) *Calafat et al. 2003* [TCAu][7]: 90th percentile 23 µg/L in a general population of adults (N=402) (detected in 76% of samples, LOD: 0.5 µg·L^{-1}) *Bevan et al. 2013* [TCAu]: 8.7 µg·g^{-1} creatinine (8.1 µg.L^{-1}) (95th percentile); adults from the English general population (United Kingdom; n=436) (50% of samples < LOD of 3 nM)	
Recommended limit values for exposed workers	SCOEL (2009)	20 mg·L^{-1} end of week and end of shift
	USA - ACGIH (BEI)	15 mg·L^{-1} end of shift and end of week (2008) (corresponding to a TLV-TWA of 10 ppm)

[6] Biologische Arbeitsstoff-Referenzwerte
[7] TCA: drinking water disinfection by product

	Germany - DFG (BAT) (2011)	For exposure to TCE: atmospheric concentration ($mg \cdot m^{-3}$)	EKA[8] [TCAu] ($mg.L^{-1}$)
		3.3 (0.6 ppm)	1.2
		33 (6 ppm)	12
		55 (10 ppm)	20
		60 (11 ppm)	22
		82 (15 ppm)	30
		109 (20 ppm)	40
		137 (25 ppm)	50)
	Quebec - IRSST (IBE)	End of shift and end of week: 100 $mg \cdot g^{-1}$ cr (corresponding to a weighted mean exposure value of 50 ppm, i.e. 269 $mg \cdot m^{-3}$) (2012)	
	Finland - FIOH (BAL)	End of shift and end of week: 120 $\mu mol.L^{-1}$ (19.5 mg. L^{-1}) (corresponding to a TWA of 10 ppm) (2012)	

[8] Expositionäquivalente für Krebserzeugende Arbeitstoffe ; Equivalents to exposures for carcinogens

Name	**TCOH in urine**
Other substances giving rise to these biomarkers	Methyl chloroform (1,1,1-trichloroethane), chloral hydrate, tetrachloroethane and tetrachloroethylene
Concentrations measured in exposed workers or volunteers (with exposure levels and sampling times)	• <u>Field studies:</u> *Ikeda et al., 1972* [TCEatmo] exposure (means) 8h/day, 6 days/week – [TCOH]u (geometric means and (SD range))[9] (end of week and end of shift) in 10 workshops: - (n = 9) 3 ppm – 25.1 $mg.L^{-1}$ (14.2 – 44.6) - (n = 5) 5 ppm – 24.9 $mg.L^{-1}$ (16.3 – 37.9) - (n = 6) 10 ppm – 42.0 $mg.L^{-1}$ (25.1 – 70.3) - (n = 4) 25 ppm – 77.3 $mg.L^{-1}$ (52.3 – 114.1) - (n = 4) 40 ppm – 220.3 $mg.L^{-1}$ (164.4 – 295.3) - (n = 5) 45 ppm – 256.7 $mg.L^{-1}$ (202.1 – 330.8) - (n = 5) 50 ppm – 267.3 $mg.L^{-1}$ (140 – 510.3) - (n = 5) 60 ppm – 307.9 $mg.L^{-1}$ (223 – 425.6) - (n = 4) 120 ppm – 681.8 $mg.L^{-1}$ (581.4 -799.5) - (n = 4) 175 ppm – 973.1 $mg.L^{-1}$ (596.9 – 1586.4) *Skender et al. 1991* Exposure ranging from 25 to 40 ppm (never exceeding 50 ppm) [TCOHu] (median for 10 employees of dry-cleaning facilities; start of week and start of shift) 9.7 $mmol \cdot mol^{-1}$ creat, i.e. 12.7 $\mu g \cdot g^{-1}$ creat [TCOHu] (median for 10 employees of dry-cleaning facilities; Wednesday, end of shift) 54.89 $mmol \cdot mol^{-1}$ creat, i.e. 72 $\mu g \cdot g^{-1}$ creat • <u>Studies in volunteers:</u> *Monster et al., 1979* [TCEatmo] exposure: 70 ppm (4 h/day; 5 days) [TCOHu] (mean for 5 volunteers; end of exposure) increase in concentrations: - 1st day: 142 $mg \cdot 24h^{-1}$ - 5th day: 217 $mg \cdot 24h^{-1}$ *Kimmerle and Eben, 1973* [TCEatmo] exposure: 50 ppm (4 h/day; 5 days) [TCOHu] (mean for 4 volunteers; end of exposure) increase in concentrations: - 1st day: 78.5 $mg \cdot 24h^{-1}$ - 5th day: 103 $mg \cdot 24h^{-1}$
Conversion factor (with molecular weight)	MW: 149 $g.mol^{-1}$ 1 $\mu mol.L^{-1}$ = 149 $\mu g.L^{-1}$ 1 $mg.L^{-1}$ = 6.7 $\mu mol.L^{-1}$

[9] These values are the geometric mean minus and plus one geometric standard deviation

Concentrations in the general population	NS
Recommended limit values for exposed workers (INRS, 2018)	None

Study of the relationship between concentrations of biomarkers of exposure and health effects

According to the analysis of the available scientific literature, no dose response relationship between the biological concentrations of the three selected BMEs (TCE in urine, TCA in urine and TCOH in urine) and health effects (nephrotoxicity and neurotoxicity) was identified.

Study of the relationship between concentrations of biomarkers of exposure and atmospheric concentrations

Several studies have examined the relationship between concentrations of BMEs of TCE and atmospheric concentrations of TCE. The main data on BMEs considered relevant/valuable are shown in the tables below.

- ***Urinary TCE***

Table 2 : Urine trichloroethylene concentrations, calculated from correlations enabling to link biological concentrations to atmospheric concentrations

Field studies

Exposure (atmosphericTCE)	**[TCEu] measured**	**Equation linking exposure to TCE concentrations in urine**	**Calculation of [TCEu]** for exposure at the 8h-OEL (40 $mg.m^{-3}$; 7 ppm)	**Reference**
Arithmetic mean (AM): 83.3 $mg·m^{-3}$ Geometric mean (GM): 44.0 $mg·m^{-3}$ (2.7 to 387.0) Sampling for 4 h	AM: 11.0 $mg·L^{-1}$ GM: 8 $mg·L^{-1}$ (0.8 to 43.9) **First day of week** **Middle of day**	[TCEu] ($µg.L^{-1}$) = 0.081 [TCEatm] ($mg.m^{-3}$) + 4.27 (n =49; r = 0.84)	7.51 $µg·L^{-1}$	Imbriani *et al.* (2001)

- ***Urinary TCA***

Table 3 : Urine trichloroacetic acid concentrations, calculated from correlations enabling to link biological concentrations to atmospheric concentrations

Field studies				
Exposure (atmosphericTCE)	**[TCAu] measured**	**Equation linking exposure to TCA concentrations in urine**	**Calculation of [TCAu]** for exposure at the 8h-OEL (40 $mg.m^{-3}$; 7 ppm)	**Reference**
AM: 83.3 $mg·m^{-3}$ (14 ppm) GM: 44.0 $mg·m^{-3}$ (7 ppm) (2.7 to 387.0) Sampling for 4 h	AM: 21.6 $mg·L^{-1}$ GM: 10.9 $mg·L^{-1}$ (0.4 to 57.3) **First day of week** **Middle of day**	[TCAu] ($mg·g^{-1}$ cr) = 0.06 [TCEatm] ($mg·m^{-3}$) + 17.03 (n = 49; r = 0.32) Issue of contamination without exposure: value 8 times greater than if calculated only with 0.06 x 40 $mg·m^{-3}$ According to the authors, the sampling time was not appropriate	**19.4 $mg.g^{-1}$.cr**	Imbriani *et al*. (2001)
8 to 60 ppm	NS	[TCAu] (**$mg·g^{-1}$ cr**) = 2.7 [TCEatm] (ppm) (n = 25; r = NS) **End of shift; End of week**	**18.9 $mg·g^{-1}$ cr** (26.5 $mg·L^{-1}$)*	Ogata *et al*. (1987)
AM: 5 ppm (n = 5) Sampling for 8 h	AM: 20.2 $mg·L^{-1}$ End of week End of shift	[TCAu] ($mg·L^{-1}$) = 2.74 [TCEatm] (ppm) + 0.7 (linear only below 50 ppm) (n = 51; regression based on mean concentrations for each exposure "class") **End of shift; End of week**	**19.88 $mg·L^{-1}$** (14.2 $mg·g^{-1}$ cr)*	Ikeda *et al*. (1972)
AM: 10 ppm (n = 6) Sampling for 8 h	AM: 17.6 $mg·L^{-1}$ End of week End of shift			

*use of default creatinine value of 1.4 $g.L^{-1}$ (Anses, 2017)

- ***Urinary TCOH***

Table 4 : Urine trichloroethanol concentrations, calculated from correlations enabling to link biological concentrations to atmospheric concentrations

Exposure (atmosphericTCE)	**[TCOH] measured**	**Equation linking exposure to TCOH concentrations in urine**	**Calculation of [TCOH]** for exposure at the 8h-OEL (40 $mg.m^{-3}$; 7 ppm)	**Reference**
Field studies				
8 to 60 ppm	NS	[TCOHu] ($mg.g^{-1}$ cr) = 4.0 [TCEatm] (ppm) (n = 25; r = NS) **End of shift; End of week**	**28 $mg·g^{-1}$ cr** (39 $mg·L^{-1}$) (total: free + conjugated)	Ogata *et al*. (1987)
AM: 5 ppm (n = 5) Sampling for 8 h	AM: 24.9 $mg·L^{-1}$ End of week End of shift	[TCOHu] ($mg·L^{-1}$) = 5.57 [TCEatm] (ppm) + 4.4 (n = 51; regression based on mean concentrations for each exposure "class") **End of shift; End of week**	**43.39 $mg·L^{-1}$** (31 $mg·g^{-1}$ cr) (total: free + conjugated)	Ikeda *et al*. (1972)
AM: 10 ppm (n = 6) Sampling for 8 h	AM: 42.0 $mg·L^{-1}$ End of week End of shift			

Toxicokinetic Modelling

Several physiologically based pharmacokinetic (PBPK) models have been published for TCE for various species. The most recent validated version in humans enabling exposure by inhalation to be connected to various BMEs was the one from Fisher *et al.* (1998). As published, the model does not enable urinary concentrations of unchanged TCE to be predicted. Fisher's model was therefore modified by a pharmacokinetic modelling expert from the Biomarkers WG to predict urinary concentrations depending on the state of bladder replenishment (addition of a bladder reservoir).

The model enabled urinary concentrations of TCE at the end of a work shift to be simulated after five consecutive days for exposure to 40 $mg·m^{-3}$. These simulations involved simulating bladder emptying (i.e. complete voiding) every eight hours, four hours and two hours, as a function of physical workload (0, 50 W and 100 W) (Table 5).

Table 5: Urinary concentrations of TCE simulated at the end of a work shift for 5 consecutive work days for exposure to 40 $mg·m^{-3}$

	[TCEu]($\mu g.L^{-1}$)				
Time	**8h emptying**	**4h emptying**	**2h emptying**	**4h at 50W emptying**	**4h at 100W emptying**
End of Day 1	10.01	11.28	11.52	13.72	19.68
End of Day 2	10.31	11.57	11.81	13.85	19.95
End of Day 3	10.48	11.74	11.98	13.91	20.07
End of Day 4	10.59	11.83	12.07	13.95	20.13
End of Day 5	10.65	11.89	12.12	13.97	20.16

The urinary concentrations obtained ranged from 10.01 $\mu g·L^{-1}$ (rest and emptying every eight hours) to 20.16 $\mu g·L^{-1}$ (workload of 100W and emptying every four hours).

Establishment of BLVs and choice of biological reference values

In the OEL collective expert appraisal report on TCE, the Committee took the view that TCE should be considered as a non-threshold carcinogen. In 2013, in the absence of sufficiently robust and adequate data, the OEL Committee recommended a pragmatic 8h-OEL of 40 mg·m^{-3} (i.e. 7 ppm) for an effect other than cancer, i.e. nephrotoxicity[10]**.**

Neurotoxic and nephrotoxic effects have been examined in several field studies. These studies failed to establish a dose-response relationship between urinary concentrations of TCE, TCA or TCOH and health effects (nephrotoxicity or neurotoxicity). Therefore, the decision was made to take into account studies linking atmospheric concentrations of TCE and urinary concentrations of the selected BMEs and establish pragmatic BLVs based on exposure to the 8h-OEL (40 mg·m^{-3}).

Urinary TCE

Establishment of a biological limit value (BLV)

TCEu is a specific indicator that has the advantage of not requiring invasive sampling.

Only one field study (Imbriani *et al.,* 2001) (cf table 2) established a strong correlation between atmospheric concentrations and urinary concentrations of TCE. Based on this study's results, the urinary concentration of TCE at middle of shift and start of week for exposure to the 8h-OEL (40 mg·m^{-3}) was 7.5 µg·L^{-1}.

Moreover, the model developed by Fisher *et al.*, 1998 (most recent validated version in humans) that linked atmospheric concentrations of TCE to concentrations of several BMEs was selected for the establishment of a BLV. As published, the model does not enable variations in TCEu to be predicted. It was therefore modified by a pharmacokinetic modelling expert from the Biomarkers WG to predict urinary concentrations with a bladder reservoir and without in humans. Adapting the model to exposure to the 8h-OEL of 40 mg·m^{-3} (7 ppm) for eight hours with an activity level of 50 or 100 W and various time periods between bladder emptying leads to urinary concentrations of TCE at end of shift ranging from 10 µg·L^{-1} (rest and emptying every eight hours) to 20 µg·L^{-1} (workload of 100W and emptying every four hours). The modelling results are consistent with those of the only available field study described above.

Due to differences in concentrations of TCE or its metabolites depending on the gender described in the literature, the modified PBPK model for TCE was also configured for women. One week of occupational exposure (8h/day) to 7 ppm TCE (scenario without exertion) was simulated for each gender. The results suggested that, for the same exposure, men will have around 25% higher blood concentrations at end of shift than women. However, the simulated urinary concentrations of unchanged TCE were more or less the same for both genders.

Thus, **a urinary concentration of TCE of 10 µg·L^{-1}** in samples at end of shift, regardless of the work day of the week, was selected for the establishment of a **BLV based on exposure to the 8h-OEL**. This is a protective value for both women and men.

Proposition of a biological reference value

There are no French data reporting urinary levels of TCE for large samples of the general population. Thus, by default, the study by Poli *et al.,* 2005 undertaken in 120 adult subjects from the Italian general population (from the city of Parma) can be used to propose a BRV. In this study, 72% of the urine samples were associated with a quantifiable concentration of TCE and the median concentration of TCE was 0.22 µg.L^{-1} (concentration range: 0.02 – 3.64 µg·L^{-1}). Based on the median and the concentration range, it was possible to estimate, by calculation, the 95th percentile (P95), assuming a log-normal distribution. Calculation led to a 95th percentile of 1.3 µg·L^{-1}, which was rounded up to **1.5 µg·L^{-1}**. This concentration was selected as the BRV.

[10] Selected critical effect: tubular cell cytokaryomegaly

It should be noted, however, that this value accounts for 13% of the BLV presented above. Considering that the atmospheric concentrations of TCE in the general environment[11] are generally several orders of magnitude lower than the OEL of 40 mg·m^3 that was used to establish the BLV, this BRV may not be truly representative of the French general population. However, it is the only value available for the non-occupationally exposed population at the time of writing of this report.

Urinary TCA

Establishment of a biological limit value (BLV)

Although the field studies from Ogata *et al*., 1987 and Ikeda *et al.,* 1972 have limitations (especially in terms of the estimated atmospheric concentrations), they gave similar results and were used to estimate the concentration of TCAu resulting from exposure to the 8h-OEL of 40 mg·m^{-3} at 16.5 mg·g^{-1} creatinine or 23.2 mg·L^{-1}, by calculating the mean concentration from each study[12]. The study by Imbriani *et al*. (2001) was not selected due to a very poor correlation between atmospheric and urinary levels, a very high intercept in the regression equation and an inappropriate sampling time (start of week, middle of shift).

The pragmatic BLV recommended for TCAu for sampling at end of week and end of shift was rounded down to 15 mg·g^{-1} creatinine or 21 mg·L^{-1}.

Proposition of a biological reference value

There are no French data reporting urinary levels of TCA for large samples of the general population. Thus, by default, the study by Bevan *et al.*, 2013 undertaken in 436 adult subjects from the English general population (United Kingdom) was selected to propose a BRV.

The 95th percentile of the distribution of measured urinary concentrations of TCA for the subjects in this study was *8.7 µg·g^{-1} creatinine or 8.1 µg·L^{-1}* (50% of samples < LOD of 3 nM) rounded to **9 µg·g^{-1} creatinine or 8 µg·L^{-1}**. This concentration was selected as the BRV.

[11] The 95th percentile of concentrations of trichloroethylene is 7.3 µg·m^{-3} according to the results of the French national housing campaign undertaken from 2003 to 2005 (OQAI, 2006)

[12] Use of a default creatinine value of 1.4 g·L^{-1} (ANSES, 2017)

Urinary TCOH

Establishment of a biological limit value (BLV)

Although the field studies from Ogata *et al*., 1987 and Ikeda *et al.,* 1972. have limitations (especially in terms of the estimated atmospheric concentrations), they gave similar results and were used to estimate the concentration of TCOHu resulting from exposure to the 8h-OEL of 40 $mg \cdot m^{-3}$ at 41 $mg \cdot L^{-1}$ or 29.5 $mg \cdot g^{-1}$ creatinine, by calculating the mean concentration from each study[13]. The **pragmatic BLV recommended for TCOHu for sampling at end of week and end of shift was rounded to 30 $mg \cdot g^{-1}$ creatinine, i.e. 40 $mg \cdot L^{-1}$.**

Proposition of a biological reference value

In the absence of data in the general population, it was not possible to recommend biological reference values for urinary TCOH.

Conclusions of the collective expert appraisal

The biological values proposed for monitoring occupational exposure to TCE are:

Urinary TCE at the end of shift:

BLV based on a health effect	None
Pragmatic BLV based on an 8h-OEL exposure (40 $mg.m^{-3}$ or 7 ppm)	10 $\mu g \cdot L^{-1}$
Biological reference value	1.5 $\mu g \cdot L^{-1}$

Urinary TCA at the end of week and end of shift:

BLV based on a health effect	None
Pragmatic BLV based on an 8h-OEL exposure (40 $mg.m^{-3}$ or 7 ppm)	15 $mg.g^{-1}$ creatinine or 21 $mg.L^{-1}$ (calculated value) [13]
Biological reference value	9 $\mu g.g^{-1}$ creatinine or 8 $\mu g.L^{-1}$ (measured value)

Urinary TCOH at the end of week and end of shift:

BLV based on a health effect	None
Pragmatic BLV based on an 8h-OEL exposure (40 $mg.m^{-3}$ or 7 ppm)	30 $mg.g^{-1}$ creatinine or 40 $mg.L^{-1}$ (calculated value)[13]
Biological reference value	None

These biological values do not allow to prevent the carcinogenic effects of TCE in the workplace.

Sampling method and factors that may affect the interpretation of results
Samples should be taken from workers outside the workplace in a non-polluted environment,

[13] Use of a default creatinine value of 1.4 $g \cdot L^{-1}$ (ANSES, 2017)

after hand-washing, a shower and a change of clothing, to avoid external contamination of the samples by trichloroethylene.

TCE in urine should be collected in headspace glass vials that are immediately sealed to limit evaporation[14]. Regardless of the analysed BME, samples should be stored in a refrigerator (+4°C). At this temperature they are stable for ≤ 7 days for TCA and ≤ 15 days for TCOH (UCL, 2018).

Samples should be transported at a temperature not exceeding +4°C and ideally at -20°C.

The absorption of TCE is influenced by physical load. The consumption of alcohol, the use of certain medications and co-exposure to certain substances can modulate the metabolism of TCE and thus be a source of interference in the interpretation of measurement results. Gender differences have also been reported with regard to the urinary excretion of TCE metabolites.

[14] Mainly applies to TCE

Biometrology

Some analytical methods described in the literature have been listed and are shown in the table below for the relevant BMEs. The objective of this section is not to recommend a measurement method, but to provide information on certain characteristics of the analytical methods.

URINARY TCE	
Analytical method	
Analytical technique	**Headspace gas chromatography and mass spectrometry detection (HS-GC-MS)**
References	Imbriani *et al*. (2001) Poli D et al. (2005)
Sensitivity	Limit of quantification (LOQ): 0.1 µg.L^{-1} (Imbriani et al., 2001) LOD: 0.005 µg.L^{-1} (Poli D et al., 2005)
Fidelity	Coefficient of variation (CV): 7.9 % at [C] = 15 µg.L^{-1}
Precision	97.9 – 102.5 %
Reference standard	TCE standard solution (dissolution of 1 mL, i.e. 1.4649 g of TCE in 100 mL of acetone and then dilution of 1 mL of this solution in 1 L of water)
Interlaboratory quality control programme	NS

URINARY TCA			
Analytical Methods			
	Method 1	**Method 2**	**Method 3**
Analytical technique	**Headspace gas chromatography and mass spectrometry detection (HS-GC-MSD)**	**Gas chromatography coupled with electron capture detection (GC-ECD)**	**High-performance liquid chromatography with tandem mass spectrometry detection (EI-HPLC-MS/MS)**
References	Imbriani *et al*. (2001) according to Ziglio et al. (1984)	Breimer *et al*. (1974), Singthong *et al.* (2015) according to Christensen et al. (1988), UCL (2018)	Bevan et al. (2013)
Sensitivity		LOD: 0.1 µg.L^{-1} (Breimer *et al*. 1974) LOD: 0.139 mg.L^{-1}	LOD: 0.5 mg·L^{-1}

		(Singthong *et al*. 2015) LOQ: 5 mg.L^{-1} (UCL, 2018)	
Fidelity		CV < 10 % (UCL, 2018)	CV: 15%
Precision			
Reference standard			
Interlaboratory quality control programme	G-EQUAS (German External Quality Assessment Scheme) for analyses in biological materials, University Erlangen-Nuremberg (Germany)		

URINARY TCOH	
Analytical method	
Analytical technique	**Gas chromatography coupled with electron capture detection (GC-ECD)**
References	Ertle *et al*. (1972), Breimer *et al*. (1974) UCL, 2018
Sensitivity	0.5 µg.L^{-1} (LOD) (Breimer *et al*. 1974) 5 mg.L^{-1} (LOQ) (UCL, 2018)
Fidelity	CV < 10 %
Precision	CV < 10 % (UCL, 2018)
Interlaboratory quality control programme	NS

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