Collective expert appraisal: summary and conclusions

Regarding the “expert appraisal for recommending occupational exposure limits for chemical agents”
on the evaluation of the health effects and methods for measuring exposure levels in the workplace atmosphere for acetic acid, CAS No. 64-19-7

This document summarises the work of the Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee) and the Working groups on health effects and on metrology.

Presentation of the issue

On 12 June 2007, the French Agency for Environmental and Occupational Health Safety (AFSSET) received a formal request from the French Directorate General for Labour to conduct the expert appraisal work required for establishing recommendations on measures to be taken in the event of specific exposure profiles such as those with peaks.

A first report\(^1\) published in June 2009 issued recommendations on measures to be taken in the event of an 8h-OELV with no short-term exposure limit (STELV).

A second report\(^2\) published in October 2010 addressed the second part of the issue, i.e. substances with a short-term exposure limit (15min-STELV) but no 8h-OELV. Among other things, it recommended studying the 36 French substances under French labour law with a short-term exposure limit with no 8h-OELV to recommend health values taken from the most recent scientific literature. This report on acetic acid was written in this context.

France currently has an indicative 15-minute exposure limit of 25 mg.m\(^{-3}\) (10 ppm) for acetic acid. This value was set in the Circular of 19 July 1982\(^3\). It should be noted that at European level, an indicative 8-hour occupational exposure limit of 25 mg.m\(^{-3}\) (10 ppm) was set by Directive 91/322/EEC.

Scientific background

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

- independent scientific expert appraisal (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

\(^1\) http://www.anses.fr/ET/DocumentsET/VLEP_Picsdexpo_Avis_0906.pdf
\(^2\) http://www.anses.fr/ET/DocumentsET/10_10_VLEP_Pics_exposition_Avis.pdf
\(^3\) Circular of 19 July 1982 relative to permitted values for concentrations of certain hazardous substances in workplace atmospheres.
implementation timetable, depending on any technical and economic feasibility problems.

The organisation of the scientific expertise phase required for the establishment of Occupational Exposure Limits (OELVs) was entrusted to AFSSET in the framework of the 2005-2009 Occupational Health Plan (PST) and then to ANSES after AFSSET and AFSSA merged in 2010.

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 the workplace atmosphere 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 (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:

- 8-hour occupational exposure limit (8h-OEL): this corresponds to the limit of the time-weighted average (TWA) of the concentration of a chemical in the worker's breathing zone over the course of an 8-hour work shift. In the current state of scientific knowledge (toxicology, medicine, epidemiology, etc.), 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;

- Short-term exposure limit (STEL): this corresponds to the limit of the time-weighted average (TWA) of the concentration of a chemical in the worker's breathing zone over a 15-minute reference period 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;

- Ceiling value: this is the limit of the concentration of a chemical in the worker's breathing zone that should not be exceeded at any time during the working period. This value is recommended for substances known to be highly irritating or corrosive or likely to cause serious potentially irreversible effects after a very 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 it exists, is not exceeded.

In addition to OELs, the OEL Committee assesses the need to assign a 'skin' notation, when significant penetration through the skin is possible (ANSES, 2014). 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 atmospheric limit levels, yet can potentially cause health effects even when the atmospheric levels are respected.

The OEL Committee assesses the need to assign an “ototoxic” notation indicating a risk of hearing impairment in the event of co-exposure to noise and the substance below the recommended OELs, to enable preventionists to implement appropriate measures (collective, individual and/or medical) (ANSES, 2014).

The OEL Committee also assesses the applicable reference methods for the measurement of exposure levels in the workplace. The quality of these methods and their applicability to the measurement of exposure levels for comparison with an OEL are assessed, particularly with regards to their compliance with the performance requirements in the NF-EN 482 Standard and their level of validation.

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 Committee mandated:

- The working group on health effects to conduct the expert appraisal work on health effects;
- The working group on metrology to assess measurement methods in workplace atmospheres.

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

The methodological and scientific aspects of the work of these groups 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”.

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 methodology
For the assessment of health effects
A summary report was prepared by the working group on health effects and submitted to the OEL Committee, which commented on it and added to it. The information in the summary report on the health effects of acetic acid was taken from Medline and Toxline databases queried up to January 2012 and summary documents written by the ACGIH (2004) and DECOS (Health Council of the Netherlands, 2004).

For the assessment of methods for measuring exposure levels in the workplace atmosphere

A summary report was prepared by the working group on metrology and submitted to the OEL Committee, which commented on it and added to it. The summary report presented the various protocols identified for measuring acetic acid in the workplace atmosphere grouped together based on the methods they use. These methods were then assessed and classified based on the performance requirements set out particularly in the French Standard NF EN 482: "Workplace atmospheres – General requirements for the performance of procedures for the measurement of chemical agents" and the decision-making criteria listed in the methodology report. A list of the main sources consulted is detailed in the methodology report (ANSES,2014).

These methods were classified as follows:

- Category 1A: the method has been recognised and validated (all of the performance criteria in the NF EN 482 Standard are met);
- Category 1B: the method has been partially validated (the essential performance criteria in the NF EN 482 Standard are met);
- Category 2: the method is indicative (essential criteria for validation are not clear enough);
- Category 3: the method is not recommended (essential criteria for validation are lacking or inappropriate).

A detailed comparative study of the methods in Categories 1A, 1B and 2 was conducted with respect to their various validation data and technical feasibility, in order to recommend the most suitable method(s) for measuring concentrations for comparison with OELs.

The collective expert appraisal work and its conclusions and recommendations were adopted on 30 May 2012 by the OEL Committee (term of office 2010-2013)

The collective expert appraisal work and the summary report were submitted to public consultation from 30/06/2014 to 02/09/2014. No comments were received. The OEL Committee (term of office 2014-2017) adopted this version on 14 October 2014.

Results of the collective expert appraisal on the health effects of acetic acid

Description of the SCOEL report

In a report dating from 2011, the SCOEL (Scientific Committee on Occupational Exposure Limits) concludes that the critical effect is irritation of the skin and mucous membranes and that there is a good dose-response relationship for sensory irritation in humans that can be used to establish OELs.

It considers that minor subjective irritating effects were reported for volunteers exposed to 10 ppm by Ernstgard et al. (2006 cited in SCOEL, 2011) but were not found in another study by Van Thriel et al. (2008).
The study by Van Thriel et al. (2008 cited in SCOEL, 2011) was published in a German journal not included in scientific databases (e.g. Pubmed and Scopus).

The SCOEL concludes that neither of these studies showed physiological changes related to irritation up to 10 ppm and therefore proposes an 8h-OEL of 10 ppm and an STEL of 20 ppm, offering no additional explanations.

**Kinetics and metabolism**

Acetic acid vapours are easily absorbed by the lungs. The acetate ion is then rapidly metabolised by many tissues as it plays a role in many metabolisms. Acetic acid, or its ionic form acetate, can be found in many foods of animal and plant origin.

**General toxicity**

**Toxicity in humans**

Acetic acid is corrosive when pure. It is also a powerful irritant for the skin, eyes and mucous membranes at lower concentrations. Many clinical cases of accidental exposure to pure acetic acid through skin and eye contact have been described in the literature.

Ernstgård et al. (2006) studied the effects of 2 hours of human exposure to low concentrations of acetic acid vapours. This study examined 12 healthy volunteer adult non-smokers (6 men and 6 women) between the ages of 20 and 40 years who had been exposed for 2 hours while at rest to 0, 5 and 10 ppm of acetic acid vapours in a 20 m³ exposure chamber (15 days between each exposure dose). The effects were assessed through a questionnaire on eye, nose and throat discomfort, respiratory difficulty, perceived odour, headaches, fatigue, dizziness and a 'poisoning sensation'. The questionnaires were filled out during and after exposure. During exposure, blinking frequency was measured as an indicator of eye irritation. Measurements of pulmonary function, swelling and resistance of nasal cavities and inflammatory markers in blood were also taken after exposure.

According to the assessments of symptoms, only the volunteers' ratings of nose discomfort and perceived odour were significantly higher during the 2 hours of exposure. Nasal passage discomfort was low but significant at 10 ppm. Odour was barely perceived at 5 ppm and was slight at 10 ppm. Measurements of pulmonary function during and after exposure did not reveal any significant dose-dependent effects. It should be noted however that the results for inflammatory markers in the blood were also taken after exposure.

Shusterman et al. (2005) exposed 16 adult subjects (aged 21 to 63 years) with allergic rhinitis to 15 ppm of acetic acid vapours for 15 min. daily over one week. The results showed that all of the allergic subjects had nasal obstruction shortly after or even during exposure, unlike the control group which showed no symptoms. This study thus identified an LOAEL of 15 ppm for a sensitive population for 15 min. of exposure to acetic acid.

In 1954, Parmeggiani and Sassi studied Italian workers continuously exposed to acetic acid at concentrations ranging from 26 to 92 ppm who were assigned to filter-unloading operations exposing them for approximately 30 minutes to high acetic acid concentrations of 139 and 260 ppm. They all had skin lesions (blackness, dryness, calluses, painful cracks, etc.), conjunctival hyperaemia and increased lachrymal secretion without corneal impairment, pharyngeal hyperaemia, blackened, eroded teeth and gastric and respiratory problems.

In 1957, Ghiringhelli and Fabio also studied a group of workers who had been employed at the same plant for 2 to 19 years and were exposed to 125 mg.m⁻³ of acetic acid vapours on average. These workers all had hyperkeratotic dermatoses on the exposed areas.
Toxicity in animals
There are few studies on the toxicity of acetic acid by inhalation in animals.
The data for animals show moderate acute toxicity for acetic acid with an oral LD$_{50}$ in rats and mice of 3310 and 4960 mg.kg$^{-1}$ respectively and an LC$_{50}$ of 5620 ppm in mice exposed for one hour (SCOEL, 2011). Concentrations above 1000 ppm cause transient symptoms of conjunctival and upper respiratory tract irritation.

Mutagenicity and genotoxicity
Mutagenicity tests for acetic acid in S. typhimurium TA97, TA98, TA100 and TA1535 strains for concentrations of 100 to 6666 µmol/plate were negative with and without metabolic activation (Zeiger et al., 1992).

Carcinogenicity
Acetic acid appeared to be a weak promoter that enhances tumour progression in a mouse skin carcinogenesis model (Rotstein, 1988).

Establishment of OELs
15-minutes short-term exposure limit
Based on the toxicological profile, irritation of the mucous membranes and upper respiratory tract has been selected as the critical effect. The study by Ernsgård et al. (2006) has been chosen as the key study.
This study undertaken in individuals exposed for 118 minutes showed that all of the results to identify an effect (functional and/or biochemical) were negative at 10 ppm. Although some participants mentioned having felt effects at 10 ppm (nose discomfort and perceived odour), the Expert Committee considered that such signs were subjective. They have therefore not been taken into account, considering that this dose of 10 ppm is a NOAEL.

According to Haber's rule$^4$, modified by ten Berge (1986), the toxicity of a substance is dependent on the concentration and exposure time. The concentration-time-response relationship can be expressed by the following equation:

\[ c^n \times t = k \]

where:
- \( c \) is the concentration of the substance in the air required to produce a given effect
- \( t \) is the exposure time required to produce a given effect
- \( k \) is a constant
- \( n \) is a correction factor

$^4$The equation given corresponds to an adaptation by ten Berge (1986) of Haber's equation which had initially described that the relationship between the concentration, exposure time and effect was constant (Haber's rule) and could be expressed by the equation \( C \times t = k \). While the equation has been modified, it is commonly agreed that the described relationship is called Haber's rule.
The OEHHA’s recommendations (1999) show that this corresponds to the typical scenario where a no-effect concentration has been estimated for a longer time than relevant for the reference value.

In this case n = 2.

Haber’s rule\(^6\) is applied to calculate an adjusted 15-min NOAEL of 28 ppm.

Thus, based on the adjusted 15-min NOAEL of 28 ppm, the experts propose applying a safety factor of 3 to take into account inter-individual variability.

This gives: 28 (ppm) / 3 = 9.3 ppm or 22.5 mg.m\(^{-3}\) (conversion factor at 20°C and 101 kPa).

This value of 22.5 mg.m\(^{-3}\) is rounded to recommend a 15min-STEL of 20 mg.m\(^{-3}\).

8h-OEL

In the study by Parmeggiani et al. (1954), the only available study for long-term human toxicity, late-onset local effects (dental erosion, calluses, chronic bronchitis, etc.) were observed during exposure to average values of 26 to 92 ppm with exposure peaks.

The Expert Committee considers that limiting exposure through an STEL will prevent the identified long-term effects from occurring.

It is therefore not proposing an 8h-OEL for acetic acid.

Skin notation

Since the substance does not produce any systemic effects and there are no quantitative data to calculate skin absorption, no skin notation can be assigned for acetic acid.

Conclusions

No recommended 8h-OEL

15min-STEL: 20 mg.m\(^{-3}\)

Skin notation: not assigned

\(^6\) \(10^2 \text{ (ppm)} \times 120 \text{ (minutes)} = (NOAEL_{\text{adjusted}})^2 \times 15 \text{ (minutes)}\)
Results of the collective expert appraisal on measurement methods in the workplace atmosphere

Assessment of methods for measuring acetic acid in the workplace atmosphere

The following table presents the methods for measuring acetic acid that were identified and assessed.

**Table 1: Summary table of methods for measuring acetic acid in the workplace atmosphere**

<table>
<thead>
<tr>
<th>No</th>
<th>Methods</th>
<th>Protocols</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Active sampling in a Florisil® tube, $\text{Na}_2\text{CO}_3/\text{NaHCO}_3$ desorption, Ion chromatography with suppressor column, conductivity detection</td>
<td>MétroPol 045 (2003)</td>
</tr>
<tr>
<td>3</td>
<td>Active sampling in an active charcoal tube, $\text{Na}_2\text{B}_4\text{O}_7$ desorption Ion chromatography with suppression, conductivity detection</td>
<td>OSHA ID-186SG (1993)</td>
</tr>
<tr>
<td>4</td>
<td>Active sampling in an activated charcoal tube, NaOH desorption Ion chromatography with suppression, conductivity detection</td>
<td>OSHA PV-2119 (2003)</td>
</tr>
<tr>
<td>5</td>
<td>Active sampling in a Florisil® tube, water desorption Ion-exclusion chromatography, conductivity detection</td>
<td>MétroPol 045 (2003)</td>
</tr>
<tr>
<td>6a</td>
<td>Active sampling in a quartz filter impregnated with Na2CO3, capillary electrophoresis</td>
<td>MétroPol 078 (2003)</td>
</tr>
<tr>
<td>6b</td>
<td>Active sampling in a Florisil® tube, water desorption, capillary electrophoresis</td>
<td>MétroPol 045 (2003)</td>
</tr>
<tr>
<td>7</td>
<td>Active sampling in a silica gel tube, HPLC, UV detection</td>
<td>BIA 7320 (1993)</td>
</tr>
<tr>
<td>8</td>
<td>Active sampling in an activated charcoal tube, formic acid desorption, GC, FID detection</td>
<td>NIOSH 1603 (1994)</td>
</tr>
<tr>
<td>9</td>
<td>Passive sampling in an activated charcoal badge, $\text{Na}_2\text{B}_4\text{O}_7$ desorption, NaOH, ion chromatography, conductivity detection. Formic acid desorption, GC, FID detection</td>
<td>NIOSH 1603 (1994)</td>
</tr>
<tr>
<td>10</td>
<td>Passive sampling in an Anasorb® GCB1 badge (equiv. to Carbopack™ B) Thermal desorption, GC, FID or Mass detection</td>
<td>NIOSH 1603 (1994)</td>
</tr>
</tbody>
</table>
The graph below presents the ranges for which the various methods have been validated and their limits of quantification.

Methods 3, 6a, 6b, 7, 9 and 10 have been classified in category 3 for the following reasons:
- Lack of sensitivity (method 3),
- Validation range not determined (method 7)
- Analytical performance criteria not provided (methods 6a and 6b)
- Lack of validation data (methods 9 and 10)

The methods classified in categories 1A, 1B and 2 are described in detail in part B of the report.

Conclusions and recommendations

The identified methods under study were developed to assess higher exposure concentrations of 25 and 37 mg.m⁻³ respectively with exposure times of 8 hours and 15 minutes. They were validated in a concentration range that was generally higher than that required to validate the value of 20 mg.m⁻³ proposed by the OEL Committee for 15 sampling minutes.

The methods described in the INRS MétroPol 045 (Florisil® sampling) and 078 (sampling in filters impregnated with carbonates) and OSHA PV-2119 (activated charcoal sampling) protocols and then analysis by ion-exclusion or ion chromatography comply with the recommendations and requirements of the NF-EN 482 Standard. They can assess the concentration of acetic acid in an atmosphere for comparison with the 15min-STEL provided that the desorption volume is reduced in some cases. Ion and ion-exclusion chromatography analyses are routine and reducing the desorption volume by a factor of 2 to 5 does not affect the quality of the analyses. These methods have been classified in categories 1B and 2.

For technical control of the STEL in a regulatory framework, the methods using an ion chromatography analysis with conductivity detection described in the INRS MétroPol 045 and 078 and OSHA PV-2119 protocols are sensitive enough to measure one-tenth of the 15min-STEL recommended by the Expert Committee. They have been classified in category 1B in this specific context.

NIOSH protocol 1603 gives a sufficiently sensitive estimate of exposure and uses a technique common to many laboratories. Intended to assess high concentrations, this protocol was validated in a range far from the one relevant here. The group has classified it in category 2, indicative methods.

The other described protocols cannot be recommended either due to a lack of sensitivity (OSHA ID-186SG, NIOSH 1603) or a total or critical lack of validation data (INRS MétroPol 078 for capillary electrophoresis and BIA 7320). Badge diffusion methods are only recommended by the manufacturer for 8 hours of exposure; they have no validation data and rely on a calculated sampling rate. For all of these reasons, the group has classified these protocols in category 3 and does not recommend them.

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6 Validation and performance criteria for methods for monitoring STELs are defined in the NF EN 482 Standard from 0.5 to 2 times the STEL. Under the French regulations, for the technical control of the exposure limit, the measurement method must be able to measure one-tenth of the 15min-STEL (Ministerial Order of 15 December 2009 on technical monitoring of occupational exposure limits in the workplace atmosphere and conditions for accrediting the organisations in charge of monitoring, published in the French Official Journal of 17 December 2009). As such, when a method cannot measure one-tenth of the 15min-STEL, it cannot be classified in category 1A or 1B for regulatory control of the 15min-STEL. However, it may be classified in category 1A or 1B solely for assessing occupational exposure.
The group recommends the following methods:

<table>
<thead>
<tr>
<th>Method</th>
<th>Protocol</th>
<th>Category for monitoring short-term exposure</th>
<th>Category for regulatory technical control of the 15min-STEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Active sampling by pumping through a Florisil® tube - Ion chromatography with conductivity detection</td>
<td>MétroPol 045 INRS (2003)</td>
<td>1B</td>
</tr>
<tr>
<td>2</td>
<td>Active sampling by pumping through a quartz filter impregnated with Na₂CO₃ Ion chromatography with conductivity detection</td>
<td>MétroPol 078 INRS (2003)</td>
<td>1B</td>
</tr>
<tr>
<td>4</td>
<td>Active sampling by pumping through an activated charcoal tube, NaOH desorption - Ion chromatography with conductivity detection</td>
<td>PV-2119 OSHA (2003)</td>
<td>1B</td>
</tr>
<tr>
<td>5</td>
<td>Active sampling by pumping through a Florisil® tube - Ion-exclusion chromatography with conductivity detection</td>
<td>MétroPol 045 INRS (2003)</td>
<td>1B 2</td>
</tr>
<tr>
<td>8</td>
<td>Active sampling by pumping through an activated charcoal tube. Gas chromatography with flame ionisation detection</td>
<td>NMAM 1603 NIOSH (1994)</td>
<td>2</td>
</tr>
</tbody>
</table>
References


Health effects section

American Conference of Governmental Industrial Hygienists (ACGIH). Acetic Acid: TLV Chemical Substances 7th Edition Documentation; 2004 6 pages


SCOEL: Recommendation from the Scientific Committee on Occupational Exposure Limits for Acetic Acid, SCOEL/SUM/98 September 2011


Metrology section (date of inventory of methods: July 2012)

AFNOR NF EN 482 (2012) Exposition sur les lieux de travail – Exigences générales concernant les performances des procédures de mesure des agents chimiques,


Date summary validated by the OEL Committee: 14 October 2014