COLLECTIVE EXPERT APPRAISAL: SUMMARY AND CONCLUSIONS

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

Assessment of health effects and methods for the measurement of exposure levels in workplace atmospheres for acetic anhydride (CAS Nº 108-24-7)

This document summarises the work of the Expert Committees “health reference values”, “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, AFSSET was requested by the 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.

In 2010, ANSES published a report that recommended studying the 36 substances in France with a short-term exposure limit but no time-weighted average (TWA) to recommend health values taken from the most recent scientific literature (ANSES, 2010).

France currently has an indicative 15-minute exposure limit value for acetic anhydride of 20 $mg.m^{-3}$ (or 5 ppm). This was set by the Circular dated 5 March 1985[1].

Scientific background

The French system for setting OELVs consists of three clearly distinct phases:

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

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.

[1] Circular of 5 March 1985 completing and amending the annex to the Circular of 19 July 1982 relative to permitted levels for concentrations of certain hazardous substances in the workplace atmosphere.

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

These concentration levels are determined by the OEL Committee experts based on information available from epidemiological, clinical, animal toxicology studies, etc. Identifying concentrations that are safe for human health generally requires adjustment 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 the OELs, the OEL Committee assesses the need to assign a "skin" notation, when significant penetration through the skin is possible (ANSES, 2014a). This notation indicates the need to consider the dermal route of exposure in the exposure assessment and, where necessary, to implement appropriate preventive measures (such as wearing protective gloves). Skin penetration of substances is not taken into account when determining the atmospheric limit levels, yet can potentially cause health effects even when the atmospheric levels are respected.

The OEL Committee assesses the need to assign an "ototoxic[2]" 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, 2014a).

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). The Agency also 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.

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 Committee.

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

For the assessment of health effects

A summary report was prepared by the working group on health effects and submitted to the OEL Committee (term of office 2010-2013), which commented on it and added to it.

[2] Since the publication of the ANSES report of 2014, the "ototoxic" notation has been replaced by the "noise" notation as the "noise" notation has been adopted by the European Scientific Committee and has been adopted in the French regulation for styrene.

The information in the summary report on the health effects of acetic anhydride was taken from the Medline and Toxline databases consulted up to January 2012, and from summary documents written by the ACGIH (last revised in 2001).

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

A summary report was prepared by the working group on metrology and submitted to the OEL committee (term of office 2010-2013), which added its own comments.

The summary report presented the various protocols identified for measuring acetic anhydride in workplace atmospheres 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.

The methods were classified as follows:

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

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

The OEL Committee (term of office 2014-2017) adopted

- the assessment of health effects at its meeting on 12 October 2015
- the evaluation of measurements methods in workplace atmospheres at its meeting on 12 October 2015.

The OEL Committee (term of office 2014-2017) adopted the collective expert appraisal work and its conclusions and recommendations on 12 October 2015.

The collective expert appraisal work and the summary report were submitted to public consultation from 30/06/2017 to 30/08/2017. No comments were received.

The Health Reference Values Committee (term of office 2017-2020) adopted this version on 17 October 2017.

Results of the collective expert appraisal on the health effects

Occupational uses

Acetic anhydride is mainly used as:

- an acetylating agent for the manufacture of acetic esters (in particular cellulose acetates), pharmaceutical products (aspirin, etc.) and agrochemical products;

- a dehydrating agent.

(Source: Toxicological data sheet No 219, INRS-2004)

Toxicokinetics data

Inhaled acetic anhydride is absorbed by the upper and lower respiratory tracts. It hydrolyses into an acetate ion. In aqueous solution, acetic anhydride hydrolyses rapidly, with a half-life at 25°C of 4.40 min (ECHA 2011).

General toxicity

Toxicity in humans

Exposure to acetic anhydride in liquid or vapour forms causes severe irritation of the skin, eyes and mucous membranes (ACGIH 2001).

A study by Sinclair *et al*. (1994) describes the consequences of accidental contact with acetic anhydride following the explosion of a container. The worker developed a pulmonary oedema within 24 hours of the accident and died on the 69th day. The authors suggest degradation and necrosis of the pulmonary tissues following an exothermic reaction between the acetic anhydride and the water in the tissues.

There are no studies available of the effects of chronic exposure to acetic anhydride vapours in humans.

Toxicity in animals

There are few studies on the toxicity of acetic anhydride by inhalation in animals.

The two studies described below and mentioned later in the report were not described in peer-reviewed scientific literature but were described in the REACh registration dossier for acetic anhydride, available on the ECHA website, and are the subject of a report (in the screening information dataset - SIDS) by the OECD as part of the United Nations Environment Program (UNEP)[3] (OECD 1997 , ECHA 2011).

A study of acute toxicity by inhalation in rats, prior to a toxicity study on reproduction, was carried out by a group of industrial producers of acetic anhydride in 1994. Mated Charles River male and female rats were exposed, 6 hours a day, 5 days a week for two weeks for the male rats and from the 6th to the 15th day after mating for the female rats. In each group, 5 animals were exposed to high concentrations of acetic anhydride of 0 – 104 – 418 – 1670 mg.m^{-3}, or respectively 0 – 24 – 104 – 407 ppm. The exposure at 407 ppm only took place once as it resulted in the death of 2 animals and a poor general condition for the surviving animals. The autopsy revealed severe degeneration of all the tissues in the respiratory tracts. The animals exposed at 104 ppm showed less severe irritation of the respiratory tracts and significant weight loss. Lastly, the animals exposed at 24 ppm also showed signs of irritation of the respiratory tracts. A lower level of irritation and signs of discomfort (eyes half closed) were also observed in these animals during exposure (OECD 1997, ECHA 2011).

A study of sub chronic toxicity by inhalation over 90 days in rats was carried out by the same group of industrial producers (OECD 1997, ECHA 2011). A control group was included in the

[3] For “high production volume” (HPV) substances (produced or imported into Member States in volumes exceeding 1000 tonnes per year).

study (15 male and 15 female rats) and three levels of exposure were tested, 1, 5 and 20 ppm or 4.2, 21 and 83.5 mg.m^{-3} (target concentrations) (15 rats per dose and per sex). The animals exposed to the highest concentrations of acetic anhydride (20 ppm) all presented clinical and histopathological signs of severe irritation of the respiratory tracts (local inflammatory lesions with hyperplasia and squamous metaplasia of the underlying respiratory epithelium) in the nose, larynx, trachea and lungs as well as in the eyes. At 5 ppm, some minor signs of irritation in the nose, larynx and eyes were observed in some of the animals exposed. Slight haematological modifications were observed at 5 ppm but are described as being without toxicological significance. No clinical, biochemical or haematological signs were observed in the animals exposed at 1 ppm. The study also shows that the signs of irritation in the animals exposed had been reversed 13 weeks after exposure. The study led to a proposed NOAEL of 1 ppm.

Genotoxicity

Genotoxicity tests on bacteria gave negative results for acetic anhydride.

Carcinogenic effects

No data were found in the literature concerning potential carcinogenicity.

Reproductive toxicity

A reprotoxicity study by inhalation of acetic anhydride in rats followed the study of maternal toxicity described in the section on acute toxicity (OECD 1997, ECHA 2011). Female Charles River rats were exposed to acetic anhydride vapours for six hours a day, five days a week from the 6th to the 15th day after mating. In this study the female rats were only exposed to concentrations of 0 – 104 – 418 mg.m^{-3}, respectively 0 – 24 – 104 ppm. Exposure of the female rats to 104 ppm of acetic anhydride was interrupted after seven exposures because of the observed general toxicity (weight loss, low feed consumption, and noisy, gasping respiration) leading to litter resorption in two of the animals. In the group exposed to 24 ppm, the animals also showed signs of maternal toxicity, but to a lesser extent, and no foetal toxicity was observed.

Establishment of OELs

15min-STEL

The critical effect selected is severe irritation of the eyes and respiratory tract following exposure to acetic anhydride vapours.

The available data cannot be used to establish a short-term limit value for acetic anhydride.

In the event of missing or insufficient data, the profile of substances with a similar structure can be considered for establishing the limit values, as indicated in the methodological document on *the establishment of limit values for irritating or corrosive substances (*ANSES 2014b*)*.

An analogy can be made with the acetic acid produced during the hydrolysis of acetic anhydride. The moistening and warming of the inhaled air by the mucous membranes of the upper airways, with their abundant blood vessels, provides a suitable environment for the rapid hydrolysis of acetic anhydride. The same is true for the mucous membranes of the eyes. Accordingly, exposure to acetic anhydride of skin tissue in the presence of moisture,

and of eye and respiratory tract tissue in a humid atmosphere, is comparable to exposure of these tissues to acetic acid vapours.

The ANSES collective expert appraisal on acetic acid carried out in 2014 led to a proposed short-term limit value for this substance of 22.5 mg.m^{-3}, rounded to 20 mg.m^{-3}. Calculation of the limit value for acetic anhydride is based on the molar balance of its hydrolysis reaction in the presence of water, giving rise to two molecules of acetic acid:

$$15\text{min-STEL}_{\text{acetic anhydride}} = \frac{\text{STEL}_{\text{acetic acid}} \times \text{M}_{\text{acetic anhydride}}}{2 \times \text{M}_{\text{acetic acid}}}$$

With the molar masses of acetic anhydride and acetic acid equal to 102.09 g.mol^{-1} and 60.05 g.mol^{-1} respectively.

This gives: (22.5 x 102.09) / (2 x 60.05) = 19.1 mg.m^{-3}, rounded up to 20 mg.m^{-3}

Thus, a 15min-STEL of 20 mg.m^{-3} is recommended for acetic anhydride, or 4 ppm (conversion factor at 20°C and 101 kPa).

8h-OEL

The literature review carried out identified no long-term effect for acetic anhydride.

As a result, no 8h-OEL is recommended for acetic anhydride.

"Skin" notation

As the substance does not cause any systemic effect and there are no quantitative data to calculate skin absorption, the "skin" notation is not assigned for acetic anhydride.

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"Noise" notation

In the absence of scientific data on the ototoxic effect of acetic anhydride, the "noise" notation was not assigned for this substance.

Conclusions

No 8h-OEL recommended

15min-STEL = 20 mg.m^{-3}

"Skin" notation: not assigned

"Noise" notation: not assigned

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

Three methods for measuring acetic anhydride in the air at the workplace were identified and assessed (see Table 1).

Table 1: Assessment of methods for measuring acetic anhydride in workplace atmospheres

No	Methods	Similar protocols	Category	
			For monitoring short-term exposure	For regulatory technical control of the 15min-STEL [4]
1	Active sampling by bubbling through an alkaline solution of hydroxylamine – addition of a ferric chloride solution – analysis by visible spectrophotometry of the acetic anhydride/hydroxylamine-ferric chloride complex	NIOSH 3506: 1994	3	
2	Active sampling through a glass fibre filter impregnated with 1-(2-pyridyl)piperazine – extraction with a mixture of 2-propanol/toluene – analysis by GC/NPD	OSHA 82: 1990	1B	
3	Active sampling through a glass fibre filter impregnated with veratrylamine and di-n-octyl phthalate – extraction with a mixture of 2-propanol/toluene – analysis by GC/NPD	OSHA 102: 1993	1B	

The graph below presents the ranges for which the various methods were validated as well as their limits of quantification.

[4] Validation and performance criteria for methods for monitoring STELs are defined in the NF EN 482 Standard over an interval 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 controls of occupational exposure limits in workplace atmospheres and conditions for accrediting the organisations in charge of controls, 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 might be classified in Category 1A or 1B solely for assessing occupational exposure.

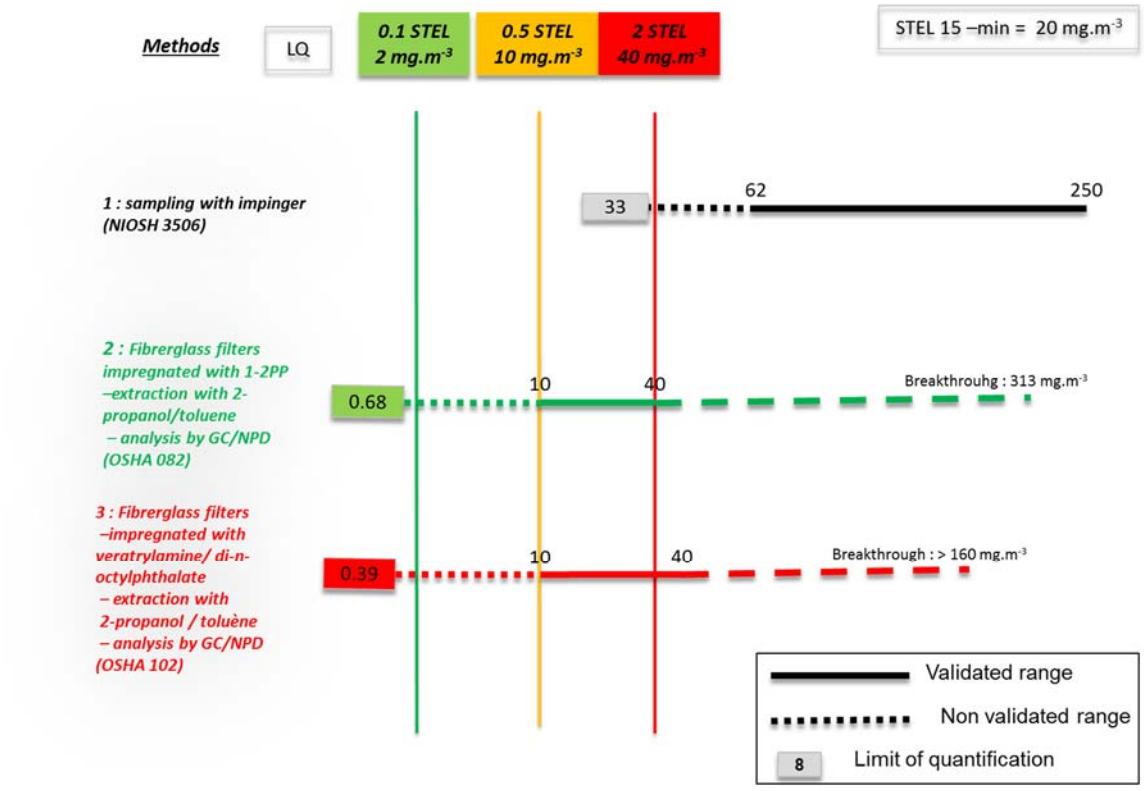

Figure 1: Ranges of validity and limits of quantification for the various methods from 0.1 to 2 times the 15min-STEL recommended for acetic anhydride

Method 1, described by the NIOSH 3506 protocol, was classified in Category 3 because it is not suitable for assessing the atmospheric concentration of acetic anhydride for the purposes of comparison with the 15min-STEL of 20 mg.m^{-3} recommended by the OEL Committee, given that its limit of quantification is too high and the lack of validation data, in particular on the breakthrough volume.

Method 2, described by the OSHA 082 protocol, is validated between 1 and 2 times the 15min-STEL with a limit of quantification below 0.1 of the 15min-STEL. The OSHA 082 protocol mentions possible interferences but does not examine their influence on collection efficiency. The method is classified in category 1B for the monitoring of short-term exposure. For technical control of the 15min-STEL in a regulatory framework, this method can be used to measure one tenth of the 15min-STEL, and is classified in category 1B.

Method 3, described by the OSHA 102 protocol, is validated between 1 and 2 times the 15min-STEL with a limit of quantification below 0.1 of the 15min-STEL. The extraction efficiency was also studied over the range of 0.1 to 2 times the 15min-STEL. The OSHA 102 protocol mentions possible interferences but does not examine their influence on the trapping ability. The method is classified in category 1B for the monitoring of short-term exposure. For technical control of the 15min-STEL in a regulatory framework, this method can be used to measure one tenth of the 15min-STEL, and is classified in category 1B.

It should be noted that recovery in the method described by the OSHA 102 protocol is higher than that of the method described by the OSHA 082 protocol.

Conclusions of the collective expert appraisal

Based on the data currently available, the OEL Committee:

- recommends a 15min-STEL of 20 $mg.m^{-3}$ for acetic anhydride
- does not recommend setting an 8h-OEL for acetic anhydride
- does not recommend a "skin" notation
- does not recommend an "noise" notation

Regarding the assessment of the methods for measuring acetic anhydride in the workplace, the OEL Committee recommends Methods 2 and 3, for the regulatory technical control of the 15min-STEL and the monitoring of short-term exposure. These two methods, both classified in category 1B, consist of active sampling on glass fibre filters impregnated with either 1-(2-pyridyl) piperazine (OSHA 082) or veratrylamine (OSHA 102), extraction with a mixture of 2-propanol/toluene, and then quantification by gas chromatography with a thermionic-specific nitrogen-phosphorus detector (GC/NPD).

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