COLLECTIVE EXPERT APPRAISAL: SUMMARY AND CONCLUSIONS

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

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

Chlorine [CAS No: 7782-50-5]

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

Presentation of the issue

On 12 June 2007, AFSSET, which became ANSES in July 2010, 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.

A first report, published in June 2009, issued recommendations on measures to be taken in the event of an existing 8h-OELV without short-term exposure limit (STELV) (Afsset, 2009).

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).

It is within this framework that the assessment was undertaken for chlorine, which has currently in France a 15-minute binding exposure limit value of 1.5 $mg.m^{-3}$ (0.5 ppm).

This value was set by the decree n°2007-1539 of 26 October 2007 setting binding occupational exposure limit values for some chemicals and amending the Labour Code.

Scientific background

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

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

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 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 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 Committee assesses the need to assign a "skin" notation, when significant penetration through the skin is possible (ANSES, 2017). 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 Committee assesses the need to assign a “noise 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, 2017).

The 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 latter 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 these groups were regularly submitted to the OEL Committee. The report produced 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 then term of office 2014-2017), which added its own comments.

The summary report was based on bibliographic information taking into account the scientific literature that had been published on this substance up to 2013. The literature search was carried out using the report written by ATSDR in 2010, the summary document written by ACGIH (in 2001) and articles found in the Medline, Toxline and HSDB databases.

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

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 presents the various protocols for measuring chlorine 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 (ANSES, 2017).

A list of the main sources consulted is detailed in the methodology report (ANSES, 2017).

These methods were classified as follows:

- Category 1A: the method has been recognized 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 OEL Committee (term of office 2014-2017) adopted:

- the assessment of health effects at its meeting on 15 December 2015
- the evaluation of measurement methods in workplace atmospheres at its meeting on 10 October 2016.

The OEL Committee (term of office 2014-2017) adopted the collective expert appraisal work and its conclusions and recommendations on 13 December 2016.

The collective expert appraisal work and the summary report were submitted to public consultation from 30/01/2018 to 30/03/2018. No comments were received.

The Health Reference Values Committee (term of office 2017-2020) adopted this version on 21 June 2018.

Result of the collective expert appraisal on the health effects

Chlorine is a greenish yellow gas that has a pungent odour[1].

Occupational uses[2]

Chlorine is a substance used in the synthesis of numerous organic and mineral compounds:

- Manufacture of polyvinyl chloride (PVC) and other organic products (solvents, pesticides, herbicides, refrigerants);
- Synthesis of isocyanates;
- Environment: disinfection and sterilisation (water treatment);
- Paper pulp: paper pulp bleaching processes;
- Electronics: manufacture of semiconductors for the plasma etching of aluminium and other metal films;
- In mineral chemistry: production of titanium oxide using the rutile process. Aluminium purification.

In 2015, 996,706 tonnes of chlorine were produced in France, in 10 plants belonging to eight different companies. In the same year, 76,524 tonnes of chlorine were exported (36% to Switzerland, 19% to Italy, 27% to Germany) and 9219 were imported (39% from Belgium, 23% from Spain, 19% from the United Kingdom and 11% from Germany).

Toxicokinetics data

Chlorine is a highly reactive oxidising agent that, in contact with the mucosa, forms hydrochloric acid and hypochlorous acid. In biological media having a pH of 6 to 8, the most abundant chemical species is HOCl, in equilibrium with ClO^- (EC, 2007).

In humans, more than 95% of inhaled molecular chlorine is absorbed in the airways. Only 5% reaches the lower respiratory tract (Nodelman and Ultman, 1999b cited in ATSDR, 2010).

No data were found in the scientific literature regarding the distribution of chlorine after inhalation by humans or animals.

There are few data on the metabolism of chlorine. In the study by Abdel-Rahman *et al.* (1983), in rats exposed by gavage to a single dose of $HO^{36}Cl$, 81% of the radioactivity detected in the plasma corresponded to chloride ions (Cl^-) (ASTDR, 2010).

No data on the elimination of chlorine after exposure by inhalation were identified in the literature. In metabolism studies, hypochlorous acid is converted and then eliminated in chloride form primarily by urinary excretion (NTP, 2005).

No data on the toxicokinetics of chlorine following dermal exposure were identified in the literature.

[1] *Source: INRS Toxicological Data Sheet FT9, 2011 edition*
[2] *Source: Société Chimique de France,* http://www.societechimiquedefrance.fr/extras/Donnees/mine/cl/texcl.htm, consulted on 30/08/2013 and 24/11/2016

General Toxicity

Molecular chlorine (Cl_2) has very high oxidation potential resulting in the dehydrogenation of water in tissues. This leads to the production of oxygen, which induces most tissue lesions, and of hydrochloric acid, which aggravates the effect. In addition, in the body, hydrochloric acid is rapidly converted into hypochlorous acid (HOCl). This hypochlorous acid increases the permeability of the cell membranes and reacts with cellular proteins to form chloramines. These destroy the cellular structure, inducing corrosive lesions and oedema (INRS, 2008).

Chlorine is a highly water-soluble gas. Due to its high reactivity and its irreversible reactions with the tissues of the respiratory tract, molecular chlorine does not accumulate in blood (Walsh and Bouchard, 2002).

Toxicity in humans

Acute toxicity

According to the Toxicological Data Sheet of the INRS, exposure to moderate concentrations (< 15 ppm) causes irritation of the nasal, ocular and pharyngeal mucosa with no clinical consequences. Exposure to concentrations above 30 ppm is immediately associated with burning sensations and pain affecting the ocular mucosa (lacrimation), respiratory tract (cough, rhinorrhoea) and mouth (hypersalivation). More general symptoms have also been described: feeling of suffocation combined with anxiety and retrosternal pain or burning, headaches, and abdominal pain with nausea and vomiting. In severe cases, respiratory distress, cyanosis and haemoptysis are observed. Reactive bronchospasm may occur. At higher levels of exposure, the main complication is acute pulmonary oedema, which is sometimes immediate but is generally delayed. Infectious complications such as bronchopneumonia and lung abscess may also occur. After suitable treatment, the outcome is favourable and there may be no sequelae. Most of the time, however, functional respiratory disorders still remain with a decrease in vital capacity and diffusion capacity. Chronic obstructive bronchopneumonia, fibrosis and asthma have also been described further to accidents. The minimum lethal concentration in humans is around 430 ppm for more than 30 minutes of exposure. Exposure to 1000 pm is rapidly fatal (INRS, 2008).

Several studies in volunteers as well as workplace studies (describing accidents) reporting the effects of acute chlorine exposure were identified in the literature. The studies' characteristics and main findings are given in the table below.

Table 1: Summary table of studies dealing with acute chlorine exposure

Study	Protocol	Advantages & Limitations	Comments
Rotman *et al.* 1983 (study in volunteers)	**N=** 8 **Exposure**: inhalation chamber; 0 - 0.5 - 1 ppm; 4 - 8 hrs **Investigated effects:** - Symptoms/signs: data collected by questionnaire. - Pulmonary function: FEV1, FVC, TLC, PEFR, FEF25-75, Raw[3]	**Advantages**: - Chlorine gas - Healthy adults (population similar to workers) - 2 concentrations tested **Limitations:** - Small number of subjects	Critical effect: transient pulmonary insufficiency including *increased airway resistance* LOAEL = 1 ppm/4 hrs for effects on the airways (measured by their resistance) (0.5±0.76 $cm.H_20^{-1}.s$ before exposure, 2.96±1.72 $cm.H_20^{-1}.s$ 4 hrs after exposure) **NOAEL = 0.5 ppm for 8 hrs**
D'Alessandro *et al.* 1996 (study in volunteers)	**N: 10 subjects** (5 healthy subjects + 5 subjects with airway hyperreactivity) **Exposure**: inhalation chamber; hyperreactive subjects: 0.4 - 1 ppm; healthy subjects: 1 ppm; 1 hr **Investigated effects:** - Symptoms/signs: not specified - Pulmonary function: FEV1, SRaw, etc.)	**Advantages**: - Chlorine gas - Adults - Range of concentrations includes a point below 0.5 ppm (lowest concentration tested in several studies) **Limitations:** - Small number of subjects	LOAEL = 1 ppm (transient increase in airway resistance [more significant in hyperreactive individuals]) No change in airway resistance for hyperreactive subjects exposed to 0.4 ppm (0.14 $mg.m^{-3}$) **NOAEL = 0.4 ppm for 1 hr**
Schins *et al.*	**N:** 8	**Advantages:**	Airways: no inflammatory or irritant response

[3] FEV1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; PEFR: peak expiratory flow rate; FEF25-75: forced expiratory flow measured between 25% and 75% of forced vital capacity, airway resistance (Raw or SRaw)

2000 (study in volunteers)	**Exposure**: inhalation chamber; 0 - 0.1 - 0.3 - 0.5 ppm; 6 hrs/day, 3 days **Investigated effects**: - Well-being of the patient evaluated by a physician (symptoms/signs: ocular irritation, cough, nasal congestion, throat irritation, nasal discharge, etc.) - Measurement of inflammatory parameters in the nasal lavage: IL-8, albumin, etc. - Respiratory function: FVC, FEV1, FEF25-75, etc.	- Chlorine gas - Healthy adults - Range of concentrations has points lower than those used in the protocols of the other studies **Limitation:** - Small number of subjects	Pulmonary function: no effect observed **NOAEL = 0.5 ppm for 6 hrs** for effects on the airways (inflammation and irritation)
Anglen, 1981 (university thesis cited in ACGIH, 2015; study in volunteers)	**N:** 29 adults **Exposure**: inhalation chamber; 0 - 0.5 - 1 - 2 ppm; 4 - 8 hrs **Investigated effects**: - Symptoms: subjective measurements of irritation (subjects invited to describe and rate the sensations felt (itching or burning of the eyes and throat, lacrimation, need to cough, nasal discharge)) Pulmonary function: FVC, FEV1, etc.	**Advantages:** - Chlorine gas - 29 adults - Extended exposure range **Limitations:** - Thesis not available - Eye irritation: unconventional test	Study difficult to use due to the implementation of subjective tests and the unavailability of the source document
Joosting and Verberk, 1974 (cited in NRC,	**N:** 8 healthy adults **Exposure**: inhalation chamber; 0 - 0.5 - 1 - 2 - 4 (n=3) ppm; 2 hrs	**Advantages**: - Chlorine gas	2 ppm: slight irritation of the eyes, nose and throat. No significant effect on pulmonary function

2004)	**Investigated effects**: - Signs/symptoms collected every 15 mins. (eye, nose, throat irritation, cough) Pulmonary function: FEV1, FVC, TLC, electrocardiogram (ECG), forced inspiratory volume	- Adults **Limitation:** - Small number of subjects	4 ppm: severe irritation of the eyes, nose and throat, cough. Pulmonary function not tested because there were not enough subjects
Shusterman *et al.* 2003 (study in volunteers)	**N:** 25 adults without allergic rhinitis + 27 with allergic rhinitis **Exposure**: inhalation chamber; 0 - 1 ppm; 15 mins **Investigated effects**: - Symptoms/signs: olfactory perception, nasal irritation and congestion, rhinorrhoea, rhinopharyngitis - Nasal airway resistance (rhinomanometry)	**Advantages:** - Chlorine gas - Recent study - Large number of subjects - 52 Adults - Short exposure time (short-term effect of chlorine) **Limitations:** **- 1 concentration tested** - Critical dose = LOAEL and not NOAEL	Critical effect: increase in nasal airway resistance **LOAEL = 1 ppm for 15 mins** in a susceptible population

Shusterman *et al.* 1998 (study in volunteers)	**N:** 8 adults without allergic rhinitis + 8 with allergic rhinitis **Exposure:** inhalation chamber; 0 - 0.5 ppm; 15 mins **Investigated effects**: - Symptoms/signs: olfactory perception, nasal irritation and congestion, rhinorrhoea, rhinopharyngitis - Nasal airway resistance (rhinomanometry)	**Advantages:** - Chlorine gas - Adults - Short exposure time (short-term effect of chlorine) - Objective measurement of the clinical effect (nasal airway resistance) **Limitations:** - **1 concentration tested** (0.5 ppm) - Subjective measurements of nasal symptoms	Subjects without rhinitis: no increase in nasal airway resistance Subjects with rhinitis: increase in nasal airway resistance with slight nasal congestion ; no effect on the pulmonary peak flow Critical effect: increase in nasal airway resistance resulting in nasal congestion in subjects with allergic rhinitis **NOAEL = 0.5 ppm for 15 mins** in subjects without allergic rhinitis No relationship between the increase in nasal airway resistance measured objectively and the symptoms described by the subjects. No significant changes for rhinorrhea, postnasal drip or headache whatever the status of the subject (with or without rhinitis)
Gautrin *et al.* 1999	**N: 211** **Exposure:** Inhalation **Accidental exposure** Unknown concentration **Investigated effects**: Pulmonary function (FEV1, FVC, etc.)	**Advantages:** - Chlorine gas - 211 Workers - Large number of subjects **Limitations:** - Cases of chlorine gas poisoning: unknown exposure doses.	This study cannot be used due to lack of exposure concentration data

Chronic toxicity

Prolonged exposure to chlorine mainly induces effects associated with its irritant properties (conjunctivitis, keratitis and blepharitis, enamel and dentin erosion (role of hydrochloric acid), anorexia, pyrosis, nausea and vomiting). More general disorders can be observed such as weight loss, anaemia, headaches and dizziness. The most severe effects occur in the lungs with respiratory signs such as those of "chronic bronchitis" (Centerwall, 1986; Lauwerys, 1992 cited in INRS, 2008).

Several studies undertaken in pulp mills have described respiratory infections in workers chronically exposed to chlorine (Ferris *et al.*, 1967; Ferris *et al.*, 1979; Enarson *et al.*, 1984 cited in SCOEL, 1998). The studies by Ferris *et al.* had the following limitations: respiratory infections were determined by analysing questionnaires completed by workers, levels of exposure to chlorine were not described in detail, and there was concomitant exposure to sulphur dioxide and chlorine dioxide. In the study by Enarson *et al.*, respiratory infections were more common in younger workers than in older workers. This observation may have been due to the "healthy worker effect" (Enarson *et al.*, 1984 cited in SCOEL, 1998).

Hyback (1999) investigated changes in vital capacity (VC) and FEV1 over 10 years in 44 workers exposed to chlorine and 33 "white collar" subjects matched for age and smoking habits. According to the author, the concentration of chlorine measured during this study was below 0.5 ppm. A more significant decrease in VC and FEV1 was observed for the white-collar workers than for the workers exposed to chlorine; this difference was statistically significant for FEV1. Hyback (1999) made the assumption that low concentrations of chlorine gas may protect workers from respiratory infections, which cause respiratory function to decline over time.

Toxicity in animals

Acute toxicity

The following data were taken from the Toxicological Data Sheet of the INRS (2008). Chlorine causes severe irritation of the eyes, nose, throat and respiratory tract. The following lethal concentrations for 50% of animals (LC_{50}) have been reported: 414 ppm for rats, 256 ppm for mice, and 650 ppm for dogs for 30 minutes of exposure by inhalation (INRS, 2008).

Chlorine is a sensory irritant able to stimulate the trigeminal nerve endings of the eyes and respiratory tract mucosa, causing a decrease in respiratory rate in mouse (Barrow, 1977). The concentration of chlorine that induces a 50% decrease in respiratory rate (RD_{50}) is around 25 ppm for 10 minutes of exposure in rats (Barrow et Steinhagen 1982). The RD_{50} is 3.5 ppm for 60 minutes of exposure in mice (Gagnaire, 1994). After the end of exposure, recovery is rapid. Tolerance to respiratory irritation is induced in rats previously exposed to chlorine for one to 10 days; it depends on the dose and the pre-treatment time (Chang, 1984). Rats and mice exposed to concentrations equivalent to the RD_{50} (around 10 ppm, 6 hrs/day, for 1 to 5 days) showed inflammation of the upper and lower respiratory tract. It was bilateral and mainly affected the olfactory and respiratory epithelium of the nasal cavity. Effects on the larynx, trachea and lungs are less severe (Jiang *et al.*, 1983 cited in INRS, 2008).

More significant lung damage was observed in rats after repeated exposure (24-hour intervals) to much higher concentrations of chlorine (50-1500 ppm for 1 to 10 minutes). The authors indicated that the lesions induced by exposure partially healed during the time interval before the next exposure period (Demnati *et al.*, 1995).

In rats exposed to 1330 ppm of chlorine for 15 minutes, the pulmonary changes observed 45 days after exposure included interstitial fibrosis and thickening of the alveolar *septa* due to the thickening of the basal membrane (Yildirim *et al.*, 2004).

Exposure of mice to 221-289 ppm chlorine for 60 minutes caused severe lung inflammation as evidenced by widespread neutrophil influx into the lung parenchyma six hours after exposure, followed by a clustering of neutrophils in the damaged airways 24 hours after exposure (Tian *et al.*, 2008). Histologically, exposure to chlorine caused massive sloughing of the airway epithelium that was evident six hours after exposure (ATSDR, 2010).

Subchronic and chronic toxicity

Repeated exposure to chlorine causes airway inflammation to worsen; the rate of aggravation depends on the species, sex and dose.

In rats, subchronic exposure (1 and 3 ppm, 6 hrs/day, 5 days/week, for 6 weeks) caused inflammation of the tracheal submucosa to spread to the bronchioles and alveolar ducts; exposure to 9 ppm led to erosion of the epithelium lining the nasal mucosa, with epithelial hyperplasia in the trachea, bronchioles and alveolar ducts. The alveoli contained a higher level of secretions and macrophages. An increase in some biological parameters was observed: haematocrit and the number of white blood cells, the activity of certain serum enzymes showing hepatic modifications, the level of urea in the blood, and urinary density with some histological signs of degenerative lesions in the proximal tubules of the kidney (INRS, 2008).

Rats and mice exposed for two years (0.4 - 1 - 2.5 ppm, 6 hrs/day, 5 days/week) showed a decrease in weight gain with no change in survival time. No effects were observed in terms of brain, liver or kidney weight, haematological or clinical parameters, or macroscopic findings. Degenerative and inflammatory histological lesions were limited to the nasal cavities (Wolf, 1995).

Compared to monkeys, rats are more susceptible to the irritant effect of chlorine since they are obligate nasal breathers. Rhesus monkeys were exposed to chlorine for one year (0.1 - 0.5 - 2.3 ppm, 6 hrs/day, 5 days/week). For some animals, at the concentration of 2.3 ppm, conjunctival irritation was observed in addition to moderate focal lesions of the epithelium lining the nasal cavities and trachea (epithelial hyperplasia, loss of hair cells). Effects limited to the nasal mucosa were observed at lower concentrations (Klonne *et al.*, 1987 cited in INRS, 2008).

Genotoxicity

According to the ATSDR (2010) document, no studies on the genotoxic potential of chlorine in gas form in humans have been identified in the literature. The only available data come from a study in rats exposed to chlorine by inhalation for 62 days. This study showed no evidence of increased incidence of sister chromatid exchanges, or of chromosomal aberrations or cellular proliferation (ATSDR, 2010).

Carcinogenicity

A study exposed rats and mice (of both sexes) by inhalation for 6 hrs/day, 5 days/week, over a period of two years, to 0, 0.4, 1 or 2.5 ppm of chlorine (purity: 99.7%). No increase in the incidence of neoplasms was found in the exposed animals compared to the controls (Wolf, 1995).

Reproductive toxicity

There are few data on the effects of chlorine exposure on reproduction. Only one very old study on exposure by inhalation is reported in the ATSDR (2010) document. Rabbits exposed *in utero*

to low concentrations of chlorine (0.6-1.6 ppm) were healthy at birth (Skljanskaja and Rappoport 1935 cited in ATSDR, 2010).

Establishment of OELs

Regarding the acute toxicity of chlorine, a gradation in the severity of effects is observed depending on the exposure level. In humans, exposure to low concentrations causes irritation of the nasal, ocular and pharyngeal mucosa. Exposure to concentrations above 30 ppm is immediately associated with burning sensations and pain affecting the ocular mucosa (lacrimation), respiratory tract (cough, rhinorrhoea) and mouth (hypersalivation). In severe cases, respiratory distress, cyanosis and haemoptysis are observed. At higher exposure levels, the main complication is acute pulmonary oedema (APO). Infectious complications such as bronchopneumonia and lung abscess may also occur. Due to its high reactivity and its irreversible reactions with the tissues of the respiratory tract, molecular chlorine does not accumulate in blood.

Therefore, in accordance with the methodological document of the OEL Committee (ANSES, 2017), the Committee considers there is justification for recommending a 15min-STEL and a ceiling value (CV) for chlorine. The recommended 15min-STEL will aim to protect workers from short-term effects such as irritation phenomena. Moreover, the potentially irreversible serious effects (such as APO) observed following exposure to chlorine can only be prevented by recommending a ceiling value.

15min-STEL

Based on the toxicological profile, irritation of the upper airways has been selected as the critical effect.

In order to choose the most relevant key study for the establishment of the 15min-STEL, studies in humans dealing with the short-term effects of chlorine were selected by the Committee (for more details about the advantages and limitations of these studies, see Table 1).

The various studies analysed gave consistent information (NOAEC of 0.5 ppm); the study by Shusterman *et al.* (1998) was selected as the most relevant key study for the establishment of the 15min-STEL.

This study was undertaken with 16 volunteers (eight subjects with seasonal allergic rhinitis and eight healthy subjects). The healthy subjects exposed for 15 minutes to 0.5 ppm of chlorine did not show any effect on nasal airway resistance (measured by rhinomanometry). In subjects with allergic rhinitis, an increase in nasal airway resistance was observed, resulting in nasal congestion. Nevertheless, regardless of the subject's status (with or without rhinitis), no significant changes were observed regarding the following symptoms: rhinorrhea, postnasal drip and headaches. The peak flow measurement also showed no change. It should be noted, however, that no relationship could be established between the objective measurements on the one hand and the subjective symptoms described by the subjects on the other hand.

This study was chosen for the following reasons: it was a controlled study in humans dealing with the short-term effects of chlorine on the airways. It provided well-documented exposure data and was thus considered to be a reliable study, as the clinical effect observed was measured objectively. In addition, the population selected for the study included subjects with and without allergic rhinitis. In light of all of these criteria taken together, this study can be considered as sufficient to establish an OEL.

Based on these findings, starting from a NOAEC of 0.5 ppm in healthy subjects, no adjustment factor was applied. Several studies that investigated the same critical effect with longer exposure times (4-8 hrs) supported this choice:

- Schins (2000): NOAEL = 0.5 ppm for respiratory effects (inflammation and irritation) on the airways after exposure for 6 hrs/day
- Rotman (1983): NOAEL = 0.5 ppm for 8 hrs (LOAEL = 1 ppm for 4 hrs for effects on the airways)
- D'Alessandro (1996): NOAEL = 0.4 ppm for 60 mins (1 hr) (no change in airway resistance was observed in the hyperreactive subjects)

Thus, a 15min STEL of 0.5 ppm or 1,5 $mg.m^{-3}$ is recommended.
Furthermore, it should be noted that this value also protects against ocular irritation (Anglen, 1981 cited in ACGIH, 2001 and ATDSR, 2010).

Ceiling value

Only a ceiling value can protect workers from potentially irreversible serious effects (such as APO) following a short exposure period. The 15min-STEL is a value averaged over a 15-minute period that does not rule out the occurrence of peaks.

The potentially irreversible serious effects (such as APO) justifying the recommendation of a ceiling value are likely to occur at exposure levels much higher than the 15min-STEL of 0.5 ppm. The data in the literature reporting exposure levels causing these effects often come from secondary sources. In humans, reports of poisoning following accidental exposure seldom provide data about exposure levels.

In the absence of scientific data providing a point of departure (NOAEC or LOAEC) to establish a ceiling value and in accordance with its methodology, the OEL Committee recommends a "pragmatic" ceiling value.

The information available in the scientific literature (described below) does not show irreversible effects up to 4 ppm over longer periods than those to be considered for instantaneous values.

Table 2: information available for the proposal of a ceiling value

Concentration	Duration	NOAEL/LOAEL	Effect	Reference
1 ppm	15 mins → 4 hrs	LOAEL	↗ airway resistance ≠ lower respiratory tract effect	Rotman 1983 D'Alessandro 1996 Shusterman 2003
0 - 0.5 - 1 - 2 - 4 ppm 2 ppm	2 hrs 2 hrs	NOAEL NOAEL	Respiratory rate, spirometry Throat irritation	Joosting Verberk 1974 (cited in NRC, 2004)
0.5 or 3 ppm	Bolus	NOAEL	No details about the observed signs and symptoms are reported	Nodelman Ultman 1999a, b

Moreover, based on the studies by Rotman *et al.*, 1983, Shusterman *et al.*, 1998 and D'Alessandro *et al.*, 1996, AEGL-1[4] and AEGL-2[5] values were recommended by the NRC in 2004:

Table 3: AEGL-1 and AEGL-2 values

Concentration	Duration	NOAEL/LOAEL	Effect	Reference
0.5 ppm	10 mins → 8 hrs	NOAEL	Reversible effects	AEGL-1 (NRC, 2004)
2.8 ppm	10 and 30 mins	NOAEL	Irreversible effects, serious adverse effects	AEGL-2 (NRC, 2004)

The OEL Committee thus proposes a pragmatic ceiling value of 4 ppm, i.e. 11.8 mg.m^{-3} rounded up to 12 mg.m^{-3} corresponding to the application of a multiplicative factor of 8 to the 15min-STEL, in accordance with the methodology of the OEL Committee which recommends that this factor fall within the range of 3 to 10.

"Skin" notation

Chlorine is indeed likely to have an irritant effect on the skin but there is no information suggesting it may have any systemic toxicity following dermal absorption.

Therefore, the "skin" notation is not justified for this substance.

"Noise" notation

In the absence of scientific data on the ototoxic effects of chlorine, the "noise" notation has not been assigned for this substance.

Conclusion

8h-OEL: not recommended

15-min STEL: 1.5 mg.m^{-3}

Pragmatic ceiling value: 12 mg.m^{-3}

"Skin" notation: not assigned

"Noise" notation: not assigned

[4] Acute Exposure Guideline Level 1 (AEGL-1): airborne concentration (expressed in ppm or mg.m^{-3}) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic non-sensory effects. These effects are not disabling and are transient and reversible upon cessation of exposure.

[5] Acute Exposure Guideline Level 2 (AEGL-2): airborne concentration (expressed in ppm or mg.m^{-3}) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects.

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

Assessment of methods for measuring chloride in workplace atmospheres

Assessment in relation to the 15min-STEL

Five methods for measuring concentrations of chlorine in workplace atmospheres were identified and assessed in relation to the 15min-STEL. Table 4 shows the classification of these five measurement methods and Figure 1 gives ranges of validity and limits of quantification for the methods classified in Category 1B.

Table 4: Classification of methods for measuring chlorine in workplace atmospheres for comparison with the 15min-STEL

Method		Protocol	Category	
			For monitoring the 15min-STEL	For monitoring short-term exposure[6]
1	Active sampling by pumping through a three-piece cassette and silver membrane – Desorption in sodium thiosulphate and analysis by ion chromatography	NIOSH 6011	1B	
2	Active sampling by pumping through a glass bubbler containing a sulfamic acid solution – Electrochemical analysis with a residual chlorine electrode after adding an aliquot to a buffered potassium iodide solution	OSHA ID101	3	1B
3	Active sampling by pumping through a glass bubbler containing a potassium iodide solution – Titration with a sodium thiosulphate solution and a coloured indicator	OSHA ID126SGX	3(*)	
4	Active sampling by pumping through a glass bubbler containing a solution of sulphuric acid and methyl orange – Analysis by spectrometry	MAK-Chlor	3 (*)	
5	Active sampling in a silica gel tube impregnated with sulfamic acid – Analysis by potentiometry	INRS MétroPol M-104	3 (*)	
(*) *classified in Category 3 due to the lack of essential validation data*				

Method 3 was classified in Category 3 for comparison with the 15min-STEL and for monitoring short-term exposure due to the incompatible recommended sampling time (100 mins) and the lack of validation data. The same was true for Method 4, which does not specify the range of validity for the method or the trapping capacity; only dispersion was calculated, but not made explicit. Method 5 was also classified in Category 3 due to the lack of certain essential validation data (range of validity for the method, uncertainty data, trapping ability).

[6] 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.

Method 2 was classified in Category 1B for monitoring short-term exposure, and in Category 3 for regulatory control of the 15min-STEL: even though the method includes detailed validation data and can measure from 0.3*15min-STEL to 2*15min-STEL, the limit of quantification is above 0.1*15min-STEL. In addition, uncertainty data are described but not calculated in accordance with the NF EN 482 standard.

Method 1 was classified in Category 1B for monitoring short-term exposure and for control of the 15min-STEL since it fulfils the essential requirements of the NF EN 482 standard and can measure 0.1*15min-STEL as well as the value of 2*15min-STEL.

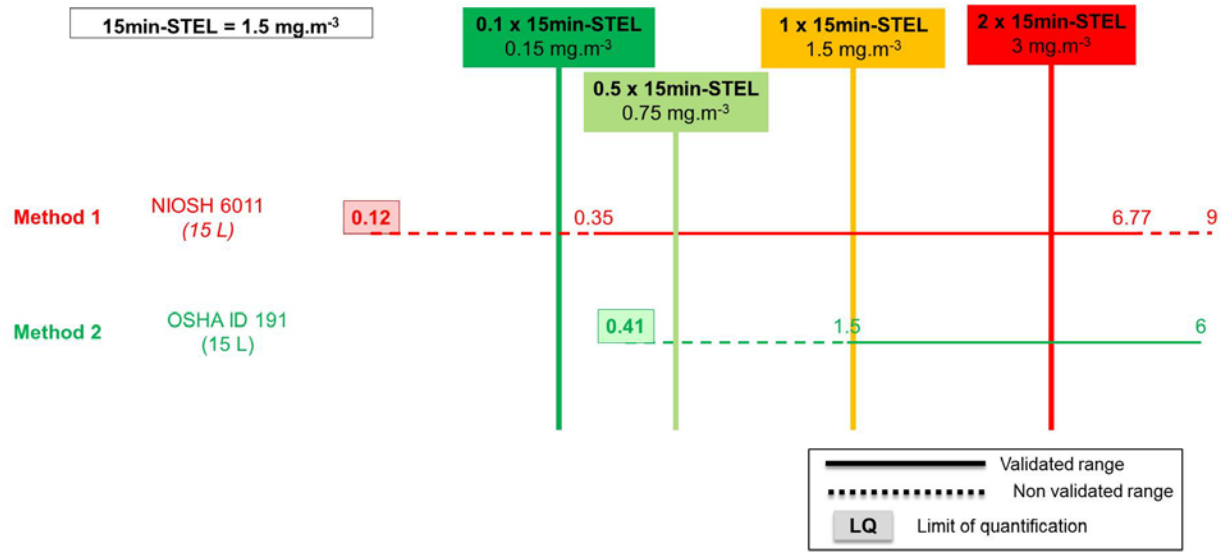

Figure 1: Range of validity and limit of quantification of the methods classified in Category 1B compared to the range from 0.1 to 2 times the 15min-STEL recommended by the Committee

Assessment in relation to the ceiling value (CV)

The continuous measurement of exposure is the only reliable type of method for monitoring the ceiling value for chlorine recommended by the Committee.

Three continuous analysis methods were identified and are given in the table below:

Table 5: Summary table of methods for measuring chlorine in workplace atmospheres for comparison with a ceiling value

No.	Method	Similar sensors (non-exhaustive list)
6	Portable electrochemical cell sensor	Dräger: X-am 5000; Pac® 7000
		Crowcon: Gasman
		Honeywell: ToxiPro®
		Oldham: Ibrid™ MX6
		Rae Systems: ToxiRae II
7	Fixed electrochemical cell sensor	Honeywell: Gas Point II, Signal Point
		Dräger®: Plytron 7000
8	Portable tape-based sensor	Honeywell: SPM Chemcassette®

Regarding Method 6, the user manuals for these sensors provide information regarding certain validation data (T90, influence of environmental conditions, zero drift, interferences, etc.). However, it is not possible to rule as to its compliance with the requirements of the NF EN 45544 standard, since the test methods are not specified. Furthermore, these data were obtained using a test gas with 5 or 10 ppm of chlorine and the NF EN 45544 standard stipulates that the concentration in the reference test gas should be 0.5 ppm for chlorine (Annex A of the NF EN 45544-1 standard). Therefore, this type of sensor is classified in Category 3 for control of the CV.

Regarding Method 7, based on the same principle as Method 6, additional validation data were found in the study undertaken by INERIS in collaboration with Exera aiming to evaluate the effectiveness, response time and drift over time of various fixed chlorine sensors (INERIS, 2006). The results of this study provide certain validation data (T90, T50, influence of environmental conditions and certain interferences), but do not make it possible to rule as to compliance with the requirements of the NF EN 45544 standard, since the test methods are different and uncertainty data are not specified. Moreover, since the tested devices are not identified, the models and suppliers are not known. Therefore, this type of sensor is classified in Category 3.

Regarding Method 8, the data provided by the manufacturer in its various manuals are not sufficient to conclude as to its compliance with the NF EN 45544 standard. In addition, these sensors are unable to measure the CV (measurement range from 0.05 to 1.5 ppm whereas CV = 4 ppm). Calibration is not performed with the gas to be measured. Therefore, this type of sensor is classified in Category 3.

Conclusion and recommendations

Five methods for measuring concentrations of chlorine in workplace atmospheres were identified and assessed in relation to the 15min-STEL (Methods 1 to 5), and three methods for the continuous, real-time measurement of chlorine concentrations in workplace atmospheres were identified and assessed in relation to the CV (Methods 6 to 8).

Of the five methods assessed in relation to the 15min-STEL, only Method 1 is recommended by the Committee. Since it fulfils the essential requirements of the NF EN 482 standard and can measure 0.1*15min-STEL as well as the value of 2*15min-STEL, it was classified in Category 1B for regulatory technical control of the 15min-STEL and for monitoring short-term exposure. However, considering the interference of hydrochloric and hydrobromic acids (and undoubtedly of other mineral acids), it is first necessary to ensure they are absent when measuring concentrations of chlorine with this method.

Method 2, although classified in Category 1B for monitoring short-term exposure, has a limit of quantification above one-tenth of the 15min-STEL. As such, the method is not suitable for the regulatory technical control of the 15min-STEL. Furthermore, since the sampling system comprises a bubbler, the method can be difficult to implement in the field. For these reasons, the method is not recommended for monitoring short-term exposure.

Methods 3, 4 and 5 were classified in Category 3 and are not recommended for monitoring short-term exposure or for the regulatory technical control of the 15min-STEL due to the lack of essential validation data (range of validity for the method, uncertainty data, trapping capacity).

The three methods for the continuous, real-time measurement of chlorine concentrations in workplace atmospheres assessed in relation to the ceiling value were classified in Category 3 due to the inability to rule as to their compliance with the requirements of the NF EN 45544 standard.

The Committee thus does not recommend any method for monitoring the ceiling value but recommends validating or developing methods in accordance with the NF EN 45544 standard.

Conclusions of the collective expert appraisal

Based on the currently available data, the Committee:

- recommends a 15-min STEL of 1.5 $mg.m^{-3}$ for chloride
- recommends a pragmatic ceiling value of 12 $mg.m^{-3}$ for chloride
- does not recommend establishing an 8h-OEL for chloride
- does not recommend a "skin" notation.
- does not recommend a "noise" notation.

Regarding the assessment of methods for measuring chloride in workplaces, the Committee:

- recommends, for the regulatory technical control of the 15min-STEL or for monitoring short-term exposure, the implementation of the measurement method consisting of active sampling by pumping through a three-piece cassette and a silver membrane, then desorption in sodium thiosulphate and lastly analysis by ion chromatography. This method is described in the NIOSH 6011 protocol. The lack of interfering substances such as mineral acids should be verified before implementing this method.
- does not recommend any measurement method for monitoring the ceiling value. Of the three identified measurement methods, none have been validated or enable continuous measurement of chlorine concentrations to reliably monitor the ceiling value in workplace air.
- recommends encouraging research to be able to continuously measure chlorine in workplace atmospheres in order to enable monitoring of the ceiling value.

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- Part 2: Performance requirements for apparatus used for measuring concentrations in the region of limit values
- Part 3: Performance requirements for apparatus used for measuring concentrations well above limit values
- Part 4: Guide for selection, installation, use and maintenance

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Date summary validated by the Health reference values Committee: 21 June 2018