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

boron trifluoride (CAS No. 7637-07-2)

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, which became ANSES in July 2010, received a formal request from 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 from AFSSET issued recommendations on measures to be taken in the event of an 8h-OELV with no short-term exposure limit (STELV) (Afsset, 2009).

A second report addressed the second part of the issue, i.e. substances with a short-term exposure limit (15min-STELV) but no 8h-OELV (Anses, 2010). 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. In this context, ANSES has published this report on boron trifluoride.

France currently has an indicative 15-minute exposure limit value of 3 $mg.m^{-3}$ (1 ppm) for boron trifluoride. It was set by the Circular of the Ministry of Labour of 13 May 1987.

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 recommending occupational exposure limits for chemical agents (Committee on Health Reference Values), 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 an “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 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, which commented on it.

The summary report results from bibliographic information taking into account the scientific literature published on this substance through to 2013. The literature search was undertaken in the following databases: Medline and Toxline. The source articles cited as references were reviewed as requested by the OEL Committee.

For assessment of methods for measuring exposure levels in workplace:

A summary report was prepared by the working group on metrology and submitted to the OEL Committee, which added its own comments.

The summary report presents the various protocols for measuring boron trifluoride 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, 2014).

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 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 collective expert appraisal work and its conclusions and recommendations were adopted on 10 march 2015 by the OEL Committee (term of office 2014-2017).

This collective expert appraisal work and the summary report were submitted to public consultation from 22/09/2017 to 22/11/2017. The people or organizations who contributed to the public consultation are listed in appendix 4 of the report (only available in French). The comments received were reviewed by the Committee on Health Reference Values (term of office 2017-2020) who finally adopted this version on the 8 march 2018.

Results of the collective expert appraisal on the health effects

This report deals with the non-combustible gas, marketed as boron trifluoride (BF_3). It should be noted that boron trifluoride dihydrate (CAS no. 13319-75-0) can also be found on the market.

Toxicokinetics

Rusch *et al.* (1986) reported that rats exposed as part of a study on the chronic inhalation of boron trifluoride dihydrate[1] showed a decrease in urinary calcium concentrations directly related to the administered concentrations and an increase in urinary fluoride concentrations. Less than half of the BF_3 broke down, while the other half was excreted in unchanged form. Bone concentrations of fluoride increased, even after the end of exposure. The authors concluded that bone deposition is related to serum fluoride concentrations.

General toxicity

Toxicity in humans

Acute toxicity

No data on mortality in humans following exposure to BF_3 were identified in the literature.

In a series of experimental studies by inhalation undertaken by Torkelson *et al.* (1961), the staff handling the animals perceived a rather pleasant odour when the animals were exposed to a concentration of 1.5 ppm (4 $mg.m^{-3}$).

Only one case of human poisoning has been reported in the literature, by Stewart and Waisberg in 1988. A scrap metal dealer, his young son and his pregnant wife were exposed to BF_3 in their garage. On admission to the hospital, hypoxaemia with slight acidosis was noted. The authors indicated that the patients did not have any sequelae. No other information regarding the duration, concentration or circumstances of exposure for these individuals was mentioned in the publication.

Subchronic and chronic toxicity

No data on chronic or subchronic exposure in humans were identified in the literature.

Toxicity in animals

Acute and subacute toxicity

Several studies on acute toxicity by inhalation in animals have been undertaken over the past fifty years.

The studies by Rusch *et al*. were the most recent, undertaken in accordance with current standards.

[1] Analytical concentrations of 2, 6 or 17 $mg.m^{-3}$, 6 hours/day, 5 days/week for 13 weeks

In the study by Rusch *et al.* (1986), four groups of five male and five female Fischer F344 rats were exposed to liquid aerosols of BF_3 dihydrate at concentrations of 1010, 1220, 1320 or 1540 $mg.m^{-3}$ for four hours[2].

The authors reported excessive production of tears, oral secretions and nasal discharge and dry and moist rales. The animals in the most heavily exposed group were panting. Four hours post-exposure, almost all the animals showed signs of respiratory distress. Six days post-exposure, the surviving rats recovered. A decrease in body weight and an increase in kidney and liver weight were also observed.

In 2008, Rusch and his collaborators undertook a second study in order to examine the irritant potential of BF_3. Groups of ten male and ten female Sprague-Dawley rats were exposed to boron trifluoride dihydrate for four hours, at (analytical) concentrations of 8.53, 24.6 or 74.4 $mg.m^{-3}$.

No effect on body weight or body weight gain was observed in the animals, irrespective of the exposure concentration; the same was true for water intake. Kidney and lung weights were normal. However, histological changes in the larynx, indicators of respiratory irritation, were noted (cartilage necrosis, epithelial hyperplasia, haemorrhage and inflammatory cell infiltration[3]). These effects were observed only at 74.4 $mg.m^{-3}$ and were more pronounced in the sub-group sacrificed after 24 hours. In the sub-group sacrificed after 14 days, only two rats (one male and one female) showed cartilage necrosis. The study's authors indicated that the concentration of 24.6 $mg.m^{-3}$ could be considered a NOAEL[4]. They added that these results were in line with those of a study undertaken a few years earlier (Rusch et al. 1986), in which rats were exposed by inhalation to BF_3 for 13 weeks and no respiratory tract irritation was observed at 17 $mg.m^{-3}$.

As part of a subacute study, Rusch *et al.* (1986) exposed four groups of ten F344 rats (five males, five females) to a liquid aerosol of BF_3 dihydrate at (analytical) concentrations[5] of 24 or 66 $mg.m^{-3}$, six hours/day for nine days (five days for the first week and four days for the second) or 180 $mg.m^{-3}$, six hours/day for five days. All the rats exposed to 180 $mg.m^{-3}$ died before the sixth day of exposure. Although no deaths were noted in the rats exposed to 24 or 66 $mg.m^{-3}$, they showed signs of respiratory distress and irritation similar to those observed in the acute toxicity study. Necrosis and pyknosis of the proximal tubular epithelium were found in the animals exposed to 180 $mg.m^{-3}$.

Subchronic and chronic toxicity

In 1961, Torkelson and his collaborators conducted a series of chronic toxicity studies exposing guinea pigs for seven hours a day, five days a week. In a first experiment, ten male guinea pigs were exposed to a (nominal) concentration[6] of 35 $mg.m^{-3}$ BF_3 for a period of 62 to 65 days. The authors noted that the animals had difficulty breathing and seemed asthmatic. Seven out of ten animals died following the 19^{th} exposure period, likely due to irritation of the respiratory tract and asphyxia. In a second experiment, ten male guinea pigs were exposed to a (nominal) concentration of 21 $mg.m^{-3}$ BF_3 for six weeks. Four animals developed what seemed to be asthma attacks and died during the 2^{nd}, 6^{th}, 7^{th} or 11^{th} exposure period. The six surviving animals had laboured breathing and died accidentally during the 29^{th} exposure period.

[2] Concentrations expressed as BF_3
[3] Number of animals involved not provided
[4] No Observed Adverse Effect Level
[5] The concentrations were expressed as BF_3
[6] Analytical concentrations were not reported

As part of a subchronic study, Rusch *et al.* (1986) exposed four groups of 40 F344 rats (20 males, 20 females) to liquid aerosols of BF_3 for six hours/day, five days/week for 13 weeks at (analytical) concentrations of 0, 2, 6 or 17 $mg.m^{-3}$ BF_3. The animals exposed to high concentrations showed red deposits around the nose and mouth, excessive lachrymation and dry rales. According to the US EPA (2013) document, in the group exposed to 2 $mg.m^{-3}$, irritation in the form of excessive lachrymation was noted in five animals from the 10th week of exposure. In the group exposed to 6 $mg.m^{-3}$, the same phenomenon was noted but in 16 animals from the 2nd week of exposure. According to Rusch *et al.* (1986), in the groups exposed to low concentrations, respiratory tract irritation described as "minimal" was reported. However, this respiratory tract irritation was not found in the histopathological examination (no changes in the cross-sections of lungs, nasal lining and other respiratory tract tissues).

According to the authors, necrosis of the tubular epithelium of the kidneys, observed in two rats exposed to 17 $mg.m^{-3}$, was the most significant clinical sign. Based on this study, Rusch *et al.* considered that exposing rats to 6 $mg.m^{-3}$ does not have harmful effects, even though an increase in blood fluoride was observed.

In 1961, Torkelson and his collaborators, in a third experiment similar to those described above, exposed ten male and ten female guinea pigs to a (nominal) concentration[6] of 8 $mg.m^{-3}$ (seven hours/day, five days/week) for 26 weeks. No exposure-related effects were observed on the heart, lungs, liver, thymus, testicles, adrenal glands or pancreas.

Carcinogenicity and genotoxicity

No data were found in the literature.

Reprotoxicity

No data were found in the literature.

Establishment of OELs

There are no data explaining the mechanism by which BF_3 exerts its toxic action.

8-hour occupational exposure limit

Considering its toxicological profile, BF_3 can induce systemic effects that only an 8h-OEL can limit.

Necrosis of the tubular epithelium of the kidneys in rats as reported in the study by Rusch *et al.* (1986) justifies the establishment of an 8h-OEL.

This study was considered the key study for the establishment of an OEL; the critical effect selected is necrosis of the tubular epithelium of the kidneys[7]. According to Rusch, contacted during the preparation of this report, the concentration of 6 $mg.m^{-3}$ can be considered a NOAEL. Furthermore, the respiratory tract irritation observed in the animals exposed to 2 and 6 $mg.m^{-3}$ was not demonstrated by the histopathological examination.

[7] Only "hyaline droplet" nephropathy associated with the accumulation of eosinophilic protein droplets in the proximal tube is specific to rats and has not been found in humans (Hard *et al.*, 2009; Green *et al.*, 2003)

Thus, based on the NOAEL of 6 $mg.m^{-3}$, the Committee recommends applying the following adjustment factors:

- an adjustment factor of 3 for the extrapolation of a subchronic study to a chronic effect;
- an adjustment factor of 3 to take into account inter-individual variability (Wolf, 1991);
- an adjustment factor of 3 for the extrapolation of a study undertaken in rats to humans (inter-species variability).

Thus, the calculated 8h-OEL is 0.2 $mg.m^{-3}$ (6/27), i.e. approximately 0.1 ppm.

Considering the exposure of the population to fluoride and boron, particularly through food, the committee has evaluated the additional intake that occupational exposure to BF_3 could generate according to the recommended value. This assessment shows that the total daily intake (fluoride and boron) remains below the EFSA recommendation.

15min-STEL

The four-hour study by Rusch *et al.* (2008) indicates a NOAEL of 24.6 $mg.m^{-3}$ for acute effects (irritation of the upper respiratory tract).

The equation of ten Berge can be used to adjust this NOAEL (24.6 $mg.m^{-3}$ for 240 minutes) to a period of 15 minutes. The value of n = 3 proposed by OEHHA for boron trifluoride (extrapolation of the health effects of over one hour of exposure to one hour of exposure) has been selected. The starting point adjusted to 15 minutes of exposure would then be 62 $mg.m^{-3}$.

Two adjustment factors have been selected:

- an adjustment factor of 3 to take into account inter-individual variability
- an adjustment factor of 3 for the extrapolation of a study undertaken in rats to humans (inter-species variability)

Thus, the recommended 15min-STEL is 7 $mg.m^{-3}$, i.e. 2.5 ppm.

"Skin" notation

In the absence of quantitative data for the calculation of dermal absorption, the "skin" notation cannot be assigned for boron trifluoride.

"Noise" notation

In the absence of scientific data on the ototoxic effect of boron trifluoride, no "noise" notation has been assigned for this substance.

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

Assessment of methods for measuring boron trifluoride in workplace atmospheres

Only one method for measuring boron trifluoride in workplace atmospheres was identified.

It involves sampling by absorption through a bubbler in an ammonium fluoride solution and then analysis of the formed BF_4^- fluoroborate ions by potentiometry using a BF_4^- fluoroborate ion specific electrode.

This method has been classified in category 3 due to the lack of data on sample storage conditions, measurement uncertainty, and non-compliance with the requirements of the NF EN 482 standard for accessible measurement ranges.

Given the category-3 classification of the only identified measurement method, research was undertaken into equipment for the continuous measurement of boron trifluoride concentrations.

The equipment identified uses an electrochemical cell to detect boron trifluoride.

The measurement ranges given seem to enable the measurement of the 8h-OEL and 15min-STEL recommended by the Committee. However, the data, taken from sales brochures and installation manuals, are very incomplete. In addition, no information is available as to the conditions of the tests for which the stated values were determined.

Table 1: Summary table of methods for measuring boron trifluoride in workplace atmospheres

No.	Methods	Similar protocols
1	Sampling by absorption in an NH_4F solution - analysis by potentiometry (specific electrode)	OSHA[8] ID 216 SG: 1989
2	Gas detector (electrochemical cell)	According to the supplier

Conclusion and recommendations

Method 1 identified for the measurement of boron trifluoride (OSHA method) has sampling and analysis characteristics that could enable it to take personal measurements.

However, the information presented in the OSHA method is insufficient. In particular, pre-analysis sample storage conditions, trapping capacity and measurement uncertainty are not specified. Furthermore, the measurement ranges that can be achieved, for the exposure limits recommended by the Committee, do not comply with the requirements of the NF EN 482 standard.

That is why the proposed method should be considered unsuitable and has been classified in category 3 for the monitoring of both the 8h-OEL and the 15min-STEL recommended by the Committee.

[8] Occupational Safety and Health Agency

In the absence of manufacturer and/or distributor feedback, Method 2 for measuring occupational exposure to boron trifluoride with a gas detector in real time has been classified in category 3 due to a lack of validation data.

Conclusions of the collective expert appraisal

On the basis of the data currently available, the Committee recommends setting an 8h-OEL for boron trifluoride of 0.2 $mg.m^{-3}$ (or approximately 0.1 ppm). This recommendation aims to protect against the occurrence of potential effects on the renal tubular epithelium.

The Committee also recommends setting a 15min-STEL of 7 $mg.m^{-3}$ in order to protect workers from possible irritation of the upper respiratory tract.

In the absence of quantitative data, no “skin” notation has been assigned.

In the absence of scientific on the ototoxic effect of boron trifluoride, no « noise» notation has been assigned.

As for the evaluation of methods for measuring boron trifluoride in workplace atmospheres, the only identified method for taking personal measurements is considered unsuitable and has been classified in category 3 for monitoring the 8h-OEL and 15min-STEL. Research into real-time measurement methods using gas detectors has also resulted in a category-3 classification for the two types of values. There are therefore no suitable methods for monitoring the recommended values. The Committee recommends developing a validated personal exposure measurement method of boron trifluoride for the monitoring and control of the recommended limit values.

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- Partie 1 : exigences générales et méthodes d'essai
- Partie 2 : exigences de performance pour les appareillages utilisés pour le mesurage des concentrations de l'ordre des valeurs limites
- Partie 3 : exigences de performance pour les appareillages utilisés pour le mesurage des concentrations très supérieures aux valeurs limites
- Partie 4 : guide de sélection, d'installation, d'utilisation et d'entretien