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

Butan-1-ol (CAS nº. 71-36-3)

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

Presentation of the issue

On 3 February 2012, AFSSET, which became ANSES in July 2010, was requested by the Directorate General for Labour to conduct the expert appraisal work required for setting occupational exposure limit values (OELVs) for butan-1-ol.

France currently has a short-term exposure limit for butan-1-ol of 150 mg.m^{-3} (50 ppm) that was set in a Circular[1] but does not have an 8-hour time-weighted average (TWA).

The Directorate General for Labour requested ANSES to re-assess this value and, if necessary, propose new occupational exposure limits based on health considerations for butan-1-ol.

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.

[1] Circular of 19 July 1982 on the acceptable values for concentrations of certain hazardous substances in workplace atmospheres (not published in the OJ).

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

The OELs, as proposed by the Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee), are concentration levels of pollutants in 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 2014). This notation indicates the need to consider the dermal route of exposure in the exposure assessment and, where necessary, to

implement appropriate preventive measures (such as wearing protective gloves). Skin penetration of substances is not taken into account when determining 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” notation indicating a risk of hearing impairment in the event of co-exposure to noise and the substance below the recommended OELs, to enable preventionists to implement appropriate measures (collective, individual and/or medical) (Anses 2014).

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

Organisation of the expert appraisal

ANSES entrusted examination of this request to the Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee). 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.

The methodological and scientific aspects of the work of these Groups were regularly submitted to the Expert Committee.

The report produced by the Working Groups takes account of observations and additional information provided by the Committee members.

This expert appraisal was therefore conducted by 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 on the health effects of butan-1-ol was prepared by the Working Group on Health effects and submitted to the OEL Committee, which commented on it.

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 summary document written by ACGIH[2] (2002) and articles found in the Medline, Toxline and HSDB (ToxNet) databases.

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 butan-1-ol 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 04/07/2014 by the OEL Committee.

The collective expert appraisal work and the summary report were submitted to public consultation from 11/05/2015 to 13/07/2015. The people or organizations who contributed to the public consultation are listed in appendix of the report (only available in French). The comments received were reviewed by the OEL Committee who adopted this version on 12 October 2015.

Results of the collective expert appraisal on the health effects

Toxicokinetics

The experimental studies undertaken in humans and animals show that butan-1-ol is rapidly absorbed irrespective of the route of absorption (dermal, pulmonary or digestive).

Percutaneous absorption of butan-1-ol has been assessed in several in vitro tests. According to the available data, the flow of dermal absorption of pure butan-1-ol probably ranges from 0.5 to

[2] American Conference of Governmental Industrial Hygienists

2.5 mg.cm^{-2}.hour^{-1}. Bowman and Maibach (1996) reported an absorption flow for pure butan-1-ol through dermatomed human thigh skin of 2.3 mg.cm^{-2}.hour^{-1}.

A study on exposure by inhalation in volunteers by Astrand et al. (1976)[3] showed pulmonary uptake of 47% at rest and of 37 to 41% in exercise after two hours of exposure to butan-1-ol. A low arterial blood concentration was measured 30 minutes after the start of exposure. In a study in dogs, lung uptake of 55% was determined and butan-1-ol could no longer be detected in exhaled air one hour after the end of exposure (Di Vincenzo and Hamilton 1979).

Once absorbed, butan-1-ol is widely distributed through the body.

The unchanged product is primarily metabolised in the liver by alcohol dehydrogenase and then by aldehyde dehydrogenase, leading to the formation of 1-butanal and then butyric acid, the final metabolite being carbon dioxide (CO_2). Moreover, butan-1-ol can also be marginally transformed into sulpho- and glucuro-conjugates. It should be noted that n-butyl acetate is rapidly hydrolysed into butan-1-ol by esterases found in the nasal cavities, blood and liver.

After metabolisation, butan-1-ol is primarily excreted in exhaled air in the form of CO_2. Low amounts are eliminated in the urine in unchanged or sulpho-/glucuro-conjugated form.

General toxicity

Toxicity in humans

Acute toxicity

By inhalation, the main effects observed in humans are related to the irritating properties of butan-1-ol on the skin and mucosa (ocular and respiratory). General symptoms have also been described such as headaches, vertigo and drowsiness.

Several studies undertaken in the workplace have shown eye irritation in workers exposed to butan-1-ol. Complaints of eye irritation were reported by workers in plants manufacturing rainwear when concentrations of butan-1-ol ranged from 60 to 115 ppm (Tabershaw et al. 1944 cited by ACGIH 2002). In another study where eye irritation was determined by ophthalmological examination, the effects observed in workers exposed to concentrations ranging from 15 to 100 ppm included epiphora, eye burning and itching, eyelid swelling and reversible corneal inflammation (Cogan and Grant 1945, cited by ACGIH 2002). However, a causal relationship between the observed effects and exposure to other compounds could not be ruled out.

The eye irritation potential of butan-1-ol was also assessed in the study by Sterner et al. (1949). The subjects included in this study had coated photographic paper with barite and used butan-1-ol as a solvent for ten years. The study protocol included the collection of clinical data (medical examinations, lung x-rays, laboratory tests), measurements of butan-1-ol concentrations in the workers' breathing zones and occupational exposure histories. The main effects observed in the workers exposed to average concentrations of 200 ppm were blurred vision, tears, photophobia, burning, moderate corneal oedema and oedematous conjunctivitis. However, when levels of exposure to butan-1-ol were reduced to 100 ppm, very few complaints of irritation were reported. These short-term complaints were associated with short exposure times frequently exceeding 100 ppm. Moreover, ophthalmological examination of these cases showed only slight oedema in

[3] Two groups of 6 healthy volunteers (aged from 21 to 34 years) were exposed by inhalation of butan-1-ol at 300 or 600 mg.m^{-3} of butan-1-ol for 2 hours.

the cornea and conjunctiva. No changes in clinical biochemical parameters or lung x-rays could be linked to exposure to butan-1-ol.

Three cases of severe vertigo and two cases showing transient signs of vestibular vertigo with nausea, vomiting and headaches were observed in seven workers exposed by inhalation to unknown but likely high concentrations of butan-1-ol for 18 to 24 months (Seitz et al. 1972). However, the workers were exposed to at least one other solvent, including isobutanol, in a non-ventilated photographic laboratory.

Several studies in volunteers were also identified in the literature.

Nelson et al. (1943) undertook a study in volunteers exposed by inhalation to butan-1-ol for three to five minutes. The concentration of 50 ppm was considered intolerable by the subjects due to pronounced irritation of the eyes, nose and throat and headaches. Mild irritation of the respiratory tract was felt in the subjects exposed to 25 ppm, who considered they were capable of working for an 8-hour period at concentrations below 25 ppm.

Conjunctival hyperaemia was observed in subjects exposed to 990 ppm of butan-1-ol in a study assessing eye irritation related to this substance in non-smoking naive volunteers (Hempel-Jorgensen et al. 1998).

For workers exposed to acetone and naive subjects, Wysocki and Dalton (1996 cited in ACGIH 2002) determined a median olfactory detection threshold for butan-1-ol of 0.17 ppm and a median nasal irritation threshold of 2042 ppm. The lowest nasal irritation threshold in all of the tested subjects was 289 ppm. The nasal lateralisation method was used to objectively distinguish between the olfactory detection threshold and the sensory irritation threshold (the concentration required to stimulate the trigeminal nerve).

Furthermore, in normosmics, the olfactory threshold and the intra-nasal irritation threshold determined for butan-1-ol were respectively 28.8 ppm and 4163 ppm (Cometto-Muñiz and Cain 1998). This study suggests that the olfactory threshold may be used in some cases to determine the irritation threshold.

Several inhalation studies in humans (workers and volunteers) were thus identified in the literature. However, in most cases, no dose-response relationships could be determined due to limitations primarily related to co-exposure to several solvents and inadequate study descriptions.

Erythema was reported in volunteers who had received dermal applications of butan-1-ol (3% in a solution, held in place with an occlusive swab) (ACGIH 2002). In addition, dermatitis has been associated with exposure to butan-1-ol in industrial settings.

A clinical case corresponding to deliberate ingestion by a man of butan-1-ol (unknown dose) was described by Bunc et al. (2006). The reports mention general symptoms (headaches, abdominal pain, vomiting) followed by muscular hypotonus, coma, hypotension, respiratory insufficiency and acidosis. The patient fully recovered 30 hours after the start of treatment.

Chronic toxicity

There are very few data on the chronic toxicity of butan-1-ol in humans.

A study by Velasquez et al. (1969 cited by ACGIH 2002) suggests that butan-1-ol may have ototoxic properties. More significant hearing loss was found in workers exposed to 80 ppm of butan-1-ol for a period of three to eleven years compared to the control group, exposed to industrial noise only. However, according to an unpublished report, this study is believed to have

methodological limitations (uncertainties as to the measured exposure levels and hearing measurements) that would compromise its validity.

Regarding the possibility of a psycho-organic syndrome occurring after exposure to butan-1-ol, no reported cases and no relevant epidemiological studies were identified in the literature.

Carcinogenicity

Butan-1-ol was classified by the US EPA[4] as a group D compound meaning that it cannot be classified as a human carcinogen due to a lack of human and animal data (US EPA 1991).

Reprotoxicity

No data on the reprotoxic potential of butan-1-ol in humans were found in the literature.

Toxicity in animals

Acute and subacute toxicity

In animals, irrespective of the route of exposure, the observed symptoms show that butan-1-ol primarily acts on the central nervous system with ataxia, prostration and coma.

The acute toxicity values (LD_{50} and LC_{50})[5] for butan-1-ol reported in the literature show that this compound has low acute toxicity. In rats, it was reported that exposure by inhalation to 8000 ppm of butan-1-ol for four hours is not lethal but induces narcosis.

Korsak and Rydzynski (1994, cited by DFG 2003) assessed the effects of acute exposure to butan-1-ol on neuromuscular function (rotarod test). A decline in motor performance was reported in Wister rats exposed by inhalation to butan-1-ol for four hours (EC_{50} = 7759 ppm)[6].

Acute exposure to butan-1-ol can also cause eye, skin and respiratory irritation. Sensory irritation caused by butan-1-ol was assessed by De Ceaurriz et al. (1981), using a test based on the reflex decrease in respiratory rate at the beginning of exhalation. A RD_{50}[7] of 1268 ppm was calculated in OF1 mice exposed by inhalation (in a chamber) to butan-1-ol for five minutes.

Regarding the ototoxic potential of butan-1-ol, no hearing loss was found in Long Evans rats exposed by inhalation to 4000 ppm of butan-1-ol for six hours/day for five days (Crofton et al. 1994).

Subchronic and chronic toxicity

In animals, studies have examined the effects of repeated exposure to butan-1-ol by inhalation and ingestion.

[4] United-States Environmental Protection Agency

[5] Lethal dose for 50% of animals and lethal concentration for 50% of animals

[6] EC_{50}: the effective concentration 50 measures the concentration of a toxicant that induces a response halfway between the baseline and the maximum effect after a specified exposure time.

[7] Concentration that induces a 50% decrease in respiratory rate.

A decline in motor performance (assessed by the rotarod test) was observed in male Wister rats exposed by inhalation to 50 or 100 ppm of butan-1-ol (vapours) six hours/day, five days/week for three months in a chamber (Korsak et al. 1994). This effect was due to central nervous system depression, as has also been found with organic solvents. Minor haematological changes (decrease in concentrations of haemoglobin and in numbers of red blood cells) and increased lipid peroxidation in liver microsomes were also reported. However, no changes were observed in the investigated biochemical parameters, the activity of monooxygenases (aniline p-hydroxylase and cytochrome P450) or sensitivity to pain (hot plate test). It should be noted that no histological examinations were undertaken in this subchronic toxicity study.

Transient ataxia and hypoactivity[8] were observed in rats exposed by gavage to 500 $m.kg^{-1}.day^{-1}$ for 13 weeks (Toxicity Research Laboratories 1986 cited by ACGIH 2002 and ECETOC 2003). As in the study by Korsak et al. (1994), changes in haematological parameters were noted in females from 125 $mg.kg^{-1}.day^{-1}$. However, these changes were transient and were no longer observed at the end of the study. No dose-effect relationships were found in relation to mortality, body/organ weight or food intake. Ophthalmological and histological examinations did not show any differences between the exposed rats and the rats in the control group.

Genotoxicity

It is reported in the ACGIH document (2002) that several in vitro mutagenicity studies did not show genotoxic activity for butan-1-ol. In an in vivo test in mouse micronuclei, butan-1-ol did not show clastogenic activity.

Carcinogenicity

No data were found in the literature on the carcinogenicity of butan-1-ol in animals.

Reprotoxicity

In the study by Nelson et al. (1989a), no foetotoxic effects were observed after pregnant rats had been exposed by inhalation to up to 6000 ppm. The only foetotoxic effect reported in this study was an increase in the incidence of rudimentary cervical rib lesions with maternal toxicity at 8000 ppm. In another study by inhalation, no link was found between in utero exposure (up to 6000 ppm) and newborn behaviour (Nelson et al, 1989b).

With oral exposure, abnormalities in the skeleton and central nervous system (dilation of the subarachnoid space and brain ventricles, hydrocephalus) were observed in the foetuses of pregnant rats exposed to butan-1-ol (300, 1000 and 5000 $mg.kg^{-1}.day^{-1}$) via drinking water for eight weeks (before mating and during gestation). A decrease in foetal crown-rump length was also noted in the group exposed to 5000 $mg.kg-^{1}.day^{-1}$. Note that in the exposed pregnant rats, no effects were found on body weight gain, feed intake, organ weight or the assessed haematological parameters (Sitarek et al. 1994).

Unlike in the study by Sitarek et al. (1994), no effects on foetal development without maternal toxicity were found by Ema et al. (2005). They had used a similar protocol (exposure of pregnant rats through drinking water to doses of 316, 1454 and 5654 $mg.kg^{-1}.day^{-1}$) with the aim of reproducing the results of the previous study (morphological foetal abnormalities in particular).

[8] These effects appeared 2 to 3 minutes after administration and disappeared within one hour.

The differences in the observed results were no doubt related to the use of different rat strains (the strain used in the study by Sitarek et al. 1994 was an atypical one, making it difficult to compare the results with those from other studies).

Additional data on the toxicity of butyl acetate

Since n-butyl acetate is rapidly hydrolysed into butan-1-ol in the body, data on the systemic toxicity of acetate, particularly in rats, were taken into account in the assessment of the health effects of butan-1-ol.

Based on the available studies on subchronic toxicity by inhalation (Bernard et al. 1996 cited by DECOS 2001 , David et al. 1998 , David et al. 2001), the effects observed following repeated exposure to butyl acetate vapours in rats are as follows:

- a transient decrease in motor activity (effect on the nervous system);
- a decrease in body weight and feed intake;
- signs of nasal irritation (slight necrosis of the olfactory epithelium);

These effects are observed starting at 1500 ppm.

However, no persistent neurotoxic effects could be detected by a set of functional tests, behavioural tests and neurohistopathological examinations. In addition, no specific systemic effects have been observed in animals exposed by inhalation to n-butyl acetate.

Establishment of OELs

In humans, exposure to butan-1-ol vapours primarily causes irritation of the eyes, skin, nose and throat. General symptoms are also described: headaches, vertigo and drowsiness. These effects are due to the acute narcosis caused by this substance with high exposure.

A decrease in motor activity and changes in certain haematological parameters were also found in rats after subchronic exposure by inhalation to 50 or 100 ppm of butan-1-ol. Doubts regarding the validity of the observations on the motor performance of animals were raised by the results of an acute toxicity study (by the same team) that did not show such effects in rats exposed for four hours to 2500 ppm. Moreover, in rats, oral exposure caused nervous system depression (ataxia and hypoactivity) as well as changes in certain haematological parameters. However, these effects were temporary. The changes in certain haematological parameters observed in animals were not found in a study in humans (Sterner et al. 1949).

Due to the rapid hydrolysis of n-butyl acetate in the body, the assessment of the systemic effects of butan-1-ol was supplemented by studies dealing with n-butyl acetate. The effects shown in these studies on subchronic toxicity by inhalation in rats were irritation of the eyes and upper respiratory tract, reduced body weight and a decrease in motor activity from 1500 ppm.

The animal weight loss observed for high concentrations of n-butyl acetate was associated with a decrease in feed intake. It is difficult to draw a conclusion regarding this type of effect in animals, which can be related to the experimental conditions.

Regarding neurological effects, only a decrease in motor activity was found. The results of the functional and behavioural tests and neurohistopathological examinations did not show any other changes providing evidence of damage to the central nervous system as suggested by the publication's authors.

In conclusion, no specific medium- or long-term systemic effects were found. Therefore, there is no proposed 8h-OEL and only a 15min-STEL is recommended in order to prevent acute local effects such as irritation of the ocular mucosa and upper respiratory tract.

15min-STEL

Based on the toxicological profile, irritation of the ocular mucosa was chosen as the critical effect and the study by Sterner et al. (1949), considered of sufficient quality, was used to establish the 15min-STEL.

This study undertaken in a cohort of workers monitored over a ten-year period coating photographic paper with barite showed that those exposed to average concentrations of 200 ppm complained of blurred vision, tears, photophobia, a burning sensation, moderate corneal oedema and oedematous conjunctivitis. When the concentrations of butan-1-ol were reduced to 100 ppm or less, very few complaints of irritation were reported. It should be noted that these short-term complaints were associated with short exposure times frequently exceeding 100 ppm. Moreover, ophthalmological examination of these cases showed only slight oedema in the cornea and conjunctiva. There were no changes in the biochemical or clinical parameters or lung x-rays.

The value of 100 ppm can be considered a LOAEL[9].

Thus, based on the LOAEL of 100 ppm, the experts propose only applying a LOAEL-to-NOAEL[10] adjustment factor of 3 given that it was a study in humans and that the complaints of irritation were associated with short exposure times.

Thus: 100 ppm / 3 = 33.3 ppm or 101 $mg.m^{-3}$ value rounded to 100 $mg.m^{-3}$.

A 15min-STEL of 100 $mg.m^{-3}$ is recommended.

“Skin” notation

The available quantitative data indicate that the percutaneous absorption of butan-1-ol is not negligible.

However, according to the methodology of the OEL Committee for assigning the "skin" notation, it is not assigned for acute toxicants. Thus, in the absence of medium- or long-term systemic effects, the OEL Committee does not consider that butan-1-ol can cause medium- or long-term specific systemic toxicity. Therefore, the skin notation is not assigned.

However, the CES would like to draw the attention of preventionists to the potential dermal penetration of butan-1-ol.

“Ototoxic” notation

[9] Lowest Observed Adverse Effect Level

[10] No Observed Adverse Effect Level

Examination of the studies by Crofton et al. (1994) and Velazquez et al. (1969, cited by ACGIH 2002) led the OEL Committee to question the relevance of assigning the ototoxic notation to butan-1-ol.

The study by Crofton undertaken in rats did not show any ototoxic effects. As for the study by Velazquez, it is not conclusive as to the causal relationship between exposure to butan-1-ol together with noise and hearing loss since in this study, the subjects were exposed not only to butan-1-ol but also to cellulose acetate.

Thus, the limited scientific data available in the literature do not allow to conclude on the ototoxic effect of butan-1-ol with co-exposure to noise. Therefore, an "ototoxic" notation is not recommended.

Results of the collective expert appraisal on measurement methods in workplace atmospheres for butan-1-ol

Nine methods for measuring concentrations of butan-1-ol in workplace atmospheres were identified and assessed. (See Table 1)

Table 1: Assessment of methods for measuring concentrations of butan-1-ol in workplace atmospheres

N°	Methods	Similar protocols11	Category for the 15min-STEL (for the monitoring of short-term exposure and regulatory technical control)
1	Passive sampling in active charcoal badges, solvent desorption, GC/FID analysis (Dräger ORSA-5, SKC 575-001, 3M-3500 and 3520, Radiello 130 badges)	ISO 16200-2 (2000) HSE MDHS 88 (1997) IRSST 90-1 (1988)	3
2	Passive sampling in Tenax TA, Chromosorb 106 or Porapack thermodesorbable tubes, thermal desorption, GC/FID analysis	MDHS 80 (1995) DFG (E) Solvent mixtures 5 (1997)	3
3	Active sampling in an active charcoal tube Isopropanol/CS_2 desorption GC/FID analysis	NIOSH 1401 (1984, rev. 1994), NIOSH 1405 (2003), IRSST90-1 (1988), OSHA 7 (2000), MDHS 96 (2000), ISO 16200-1 (2001)	1B
4	Active sampling in an active charcoal tube Isobutanol/CS_2 desorption GC/FID analysis	MTA/MA-016/A89 (1989)	1B
5	Active sampling in an active charcoal tube Dichloromethane/CS_2 desorption GC/FID analysis	MétroPol 077/V01.02 (2013)	1B
6	Active sampling in an active charcoal tube Dichloromethane/CS_2/MeOH desorption GC/FID analysis	BIA 6385 (1997)	2
7	Active sampling in a silica gel tube Deionised water desorption Head-Space/GC/FID analysis	DFG (D) Lösungsmittelgemische (1998) DFG (E) Solvent mixtures 6 (1997)	3

11 BIA: Berufsgenossenschaftliches Institut für Arbeitsschutz; DFG: Deutsche Forschungsgemeinschaft; HSE: Health and Safety Executive; IRSST: Institut de recherche Robert-Sauvé en santé et en sécurité du travail; ISO: International Standard Organization; MDHS: Methods for the Determination of Hazardous Substances; NIOSH: National Institute for Occupational Safety and Health; OSHA: Occupational Safety and Health Administration.

8	Active sampling in a silica gel tube Deionised water desorption GC/FID analysis	MétroPol 018 (2003) Described in NF X 43-267 (2004)	3
9	Active sampling Tenax TA or Chromosorb 106 Thermal desorption GC/FID analysis	MDHS 72 (1993) DFG (E) Solvent mixtures 5 (1997) NF EN ISO 16017-1 (2001)	2

The following graph presents the ranges for which the various methods were tested, as well as their limits of quantification in relation to the 15min-STEL recommended by the OEL Committee.

Ranges of validity and limits of quantification for methods 1, 2 and 8 do not appear since they are not specified or are difficult to extrapolate to a 15-minute period.

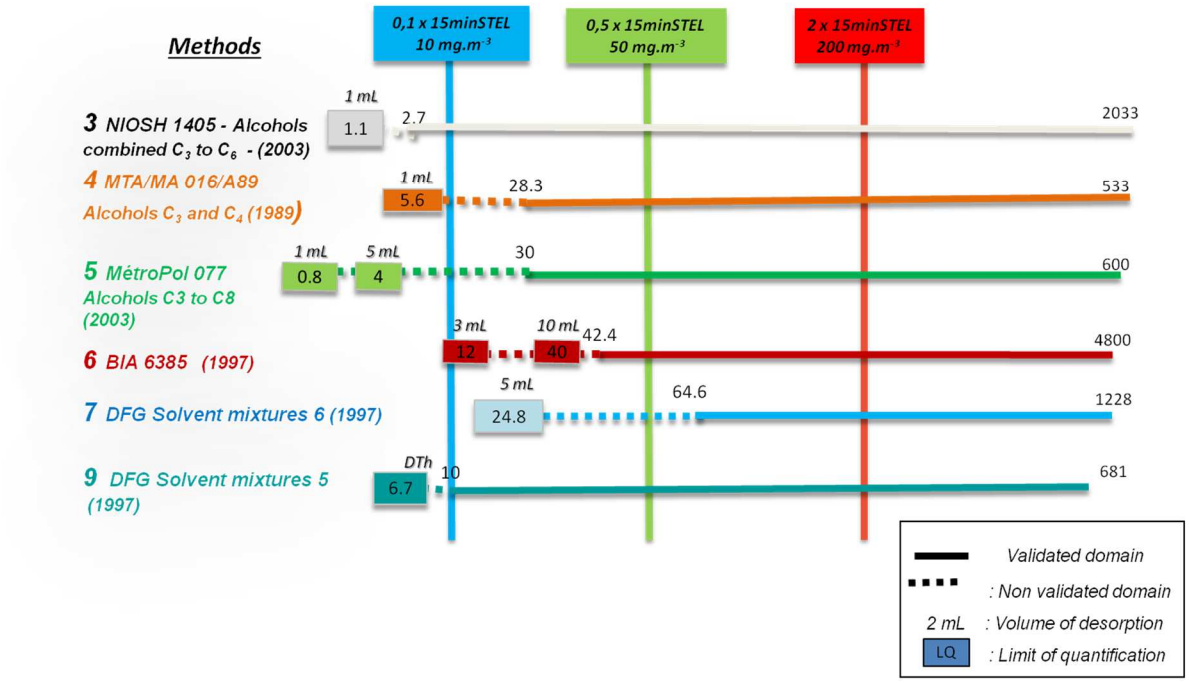

Figure 1: Ranges of validity and limits of quantification for the various compared methods from 0.1 to 2 times the 15 min-STEL recommended by the OEL Committee for butan-1-ol

None of the identified methods perfectly meet the requirements of the NF EN 482 Standard to be classified in category 1A.

Methods 3, 4 and 5 were classified in category 1B, for measuring the 15min-STEL for butan-1-ol of 100 mg.m^{-3} recommended by the OEL Committee.
These three methods rely on the same principle, i.e. active sampling from an active charcoal tube followed by desorption in an organic solvent then analysis by gas chromatography with flame

ionisation detection. These sensitive and selective methods differ only in the desorption solvent used, i.e. isopropanol/CS_2, isobutanol/CS_2 and dichloromethane/CS_2 respectively.
The various characteristics of these methods fulfil most of the requirements of the NF EN 482 Standard, although they were validated in a range more suitable for the estimation of an 8h-OEL (methods 3 and 4) and the uncertainty data cannot be compared with the requirements of the NF EN 482 Standard (methods 3, 4 and 5).

Two other methods were classified in category 2:

- Method 6: this method uses a large-capacity (300/700 mg) active charcoal tube, which results in a significant loss of sensitivity and is not suitable for 15-minute sampling. Moreover, the uncertainty data cannot be compared with the requirements of the NF EN 482 Standard and it should be noted that there is a lack of information about potential interferences and the impact of environmental conditions.
- Method 9: this method, based on thermal desorption and sampling at 4 $mL.min^{-1}$, was declassified due to difficulties in adjusting the settings for the pump, controlling it and performing calibration from spiked tubes and due to the lack of data on the impact of environmental conditions.

The following were classified in category 3:

- methods 1 and 2 relying on the principle of diffusion, due to the lack of validation data compatible with the range of 0.1 to 2 times the 15min-STEL and due to the lack of a diffusion rate specific to butan-1-ol.
- methods 7 and 8 using active sampling in silica gel and desorption with deionised water and Head-Space GC/FID (method 7) or GC/FID (method 8) analysis, due to a lack of sensitivity, the influence of interferences such as hydrocarbons polluting the analytical system (method 7) and a lack of validation data (method 8).
- portable monitors for direct measurement and tubes with colour reagent, due to lack of sensitivity.

Conclusions of the collective expert appraisal

Based on the data currently available, the OEL Committee recommends establishing a 15min-STEL of 100 $mg.m^{-3}$ and does not recommend an 8h-OEL considering the lack of expected medium- or long-term specific systemic effects.

The OEL Committee does not recommend a "skin" notation.

The OEL Committee does not recommend an "ototoxic" notation.

In light of the assessment of measurement methods, the OEL Committee recommends, for the regulatory technical control of the 15min-STEL[12] and the monitoring of short-term exposure, methods 3, 4 and 5. These three methods, classified in category 1B, are based on the same principle, i.e. active sampling from an active charcoal tube, solvent desorption and gas chromatography with flame ionisation detection. They differ only in the desorption solvent used.

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

Further details: General information on the substance:

1) Identification of the substance:

Name:	Butan-1-ol
Synonyms:	n-butanol, n-butyl alcohol, n-propylcarbinol
CAS No:	71-36-3
EINECS No:	200-751-6
Empirical formula:	$C_4H_{10}O$ [isomers]
Semi-structural formula:	CH_3-CH_2-CH_2-CH_2OH
Classification:	Primary alcohol
Physical form, appearance:	Translucent liquid, slightly syrupy, slightly pungent alcoholic odour.

(Source: GESTIS Substance Database and Toxicological Fact Sheet No 80, INRS)

2) Physico-chemical properties

Molecular weight:	74.12 g/mol
Boiling point:	117°C at atmospheric pressure
Melting point:	-90°C
Closed cup flash point:	26 to 37°C
Autoignition temperature:	340 to 380°C
Relative density (water=1):	0.810
Vapour density (air=1)	2.60
Vapour pressure:	6 hPa at 50°C
Solubility:	Partially soluble in water (74 to 80 g.L-1), miscible with most of the usual organic solvents, alcohols, esters, ketones, etc.
Log $K_{o/w}$ partition coefficient	0.88
Odour threshold:	2.4 to 45 $mg.m^{-3}$
Conversion factors:	1 ppm = 3.03 $mg.m^{-3}$ (1063 hPa and 20°C)

(Source: Toxicological Fact Sheet No 80, INRS)

3) Professional uses:

Global demand for butan-1-ol is growing. It is used primarily for its solvent qualities:

- solvent for paints, varnishes, resins and rubber-based glues,
- solvent for cleaning products, degreasers and brake fluids,
- solvent for coatings of textiles, imitation leather, rayon, and for waterproofing fabrics and leathers,
- industrial solvent for the extraction and purification of vegetable oils, gums, waxes, fragrances, alkaloids, antibiotics, hormones, etc.

Butan-1-ol is also an organic feedstock for the manufacture of esters used as solvents. Finally, it is increasingly used as a biofuel and is tending to replace bioethanol.

(Source: Toxicological Fact Sheet No 80, INRS and http://www.inchem.org/ consulted on 6/09/2013)

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