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ANSES opinion
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The Director General

Maisons-Alfort, 2 February 2018

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

on the revision of ANSES's reference values for formaldehyde: occupational exposure limits (OELs), derived no-effect levels (DNELs) for professionals, toxicity reference values (TRVs) and indoor air quality guidelines (IAQGs)

ANSES undertakes independent and pluralistic scientific expert assessments.
ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.
It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its opinions are published on its website.
This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 2 February 2018 shall prevail.

At the end of 2015, ANSES issued an internal request regarding a possible revision of the reference values for formaldehyde: occupational exposure limits (OELs) and occupational derived no-effect levels (DNELs) (Internal Request No 2016-SA-0257), toxicity reference values (TRVs) (Internal Request No 2017-SA-0040), and indoor air quality guidelines (IAQGs) (Internal Request No 2017-SA-0041).

1. BACKGROUND AND PURPOSE OF THE REQUEST

In November 2015, the European Commission (Directorate General for Employment, Social Affairs and Inclusion) held a public consultation on the recommendations issued by the European Scientific Committee on Occupational Exposure Limits (SCOEL) relating to formaldehyde. The consultation phase ran until 17 February 2016. ANSES, in the context of its permanent mission on OELs, usually gives its opinion of the recommendations issued by the SCOEL, relying on the contributions of its Expert Committee on Expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee).

ANSES had previously undertaken several expert appraisals on reference values for formaldehyde.

- Regarding the workplace
    - In 2008, a short-term exposure limit (15min-STEL) of 500 µg.m^{-3} (0.4 ppm) was recommended by the OEL Committee based on the study by Lang *et al.* (2008) to protect against the irritant effects of formaldehyde. An 8-hour occupational exposure limit (8h-OEL) of 250 µg.m^{-3} (0.2 ppm) was also recommended. The critical effects were sensory irritation and eye irritation. For this value, the studies by Paustenbach

et al. (1997) for eye irritation and Arts *et al.* (2006) for sensory irritation were used as the key studies.

- In 2014, during the formaldehyde evaluation for workers under the REACH Regulation[1], the ANSES Committee on Chemicals covered by the REACH and CLP Regulations (REACH Committee) proposed, as a first approach, a long-term DNEL by inhalation of 123 µg.m^{-3} (0.1 ppm) based on the key study by Lang *et al.* (2008). A short-term DNEL of 246 µg.m^{-3} (0.2 ppm), based on the same key study, was also proposed. ANSES, which was responsible for assessing risks for workers, concluded that there were risks relating to the occupational use of formaldehyde in several sectors. At the end of 2015, in accordance with the implementing practices of the REACH Regulation, ANSES initiated a Risk Management Option Analysis (RMOA) for the management of occupational risks generated by formaldehyde.

- Regarding the general population
  - In 2007, the Agency selected TRVs for formaldehyde by inhalation with the aim of assessing risks for the general population. The TRVs of the OEHHA[2] and ATSDR[3], of respectively 94 and 50 µg.m^{-3} for acute exposure and 3 and 10 µg.m^{-3} for chronic exposure were selected.
  - Further to this expert appraisal, the Agency recommended IAQGs of 50 µg.m^{-3} for short-term exposure and of 10 µg.m^{-3} for long-term exposure. This proposal relied on the choice of the ATSDR's TRVs. The acute TRV was based on the study by Pazdrack *et al.* (1993) indicating the appearance of sub-clinical inflammatory nasal signs. The ATSDR's chronic TRV was based on the study by Wilhelmsson and Holmstrom (1992), indicating histological nasal changes in individuals specifically exposed to formaldehyde as part of their job.

With the aims of responding to the aforementioned public consultation launched by the European Commission at the end of 2015 and of harmonising and updating ANSES's reference values for workers (15min-STEL, 8h-OEL and occupational DNELs) (Internal Request No 2016-SA-0257), ANSES created an Emergency Collective Expert Assessment Group (GECU) on Formaldehyde.

In light of the GECU's conclusions, it was deemed relevant to revise the reference values for the general population by conducting an updated review of the toxicity data on formaldehyde by inhalation. As a result, the Agency issued an internal request in 2017 to revise the TRVs and IAQGs proposed in 2007 (Internal Requests Nos 2017-SA-0040 and 2017-SA-0041).

This Opinion sets out the results and conclusions of the expert appraisal on the toxicity of formaldehyde and an update on the following reference values for formaldehyde: OELs, occupational DNELs, TRVs and IAQGs. The expert appraisal reports on OELs and IAQGs are thus replacing the Agency's reports published in 2008 and 2007:

- French Agency for Environmental and Occupational Health Safety (AFSSET). 2007. Indoor air guideline values. Formaldehyde.
- AFSSET. 2008. Occupational exposure limits. Assessing the health effects and methods for measuring occupational exposure for formaldehyde [CAS No 50-00-0].

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French Standard NF X 50-110 "Quality in Expert Appraisals – General Requirements of Competence for Expert Appraisals (May 2003)".

[1] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

[2] Office of Environmental Health Hazard Assessment (United States).

[3] Agency for Toxic Substances and Disease Registry (United States).

⇨ Regarding Internal Request No 2016-SA-0257 (OELs)

The report on the health effects of formaldehyde was prepared with the support of the aforementioned GECU on Formaldehyde, which met on five occasions between 5 January and 15 February 2016. The applicable methods for measuring exposure levels for formaldehyde in the workplace were assessed by the Working Group on Metrology. These assessments were submitted to the OEL Committee, which commented on them.

The report on "Expert appraisal for setting exposure limits for chemical agents in occupational environments. Assessing the health effects and methods for measuring occupational exposure for formaldehyde" and the conclusions of the updated collective expert appraisal were adopted by the OEL Committee on 13 March 2017.

The report and conclusions were submitted for public consultation from 5 August to 30 September 2017. The received comments were considered and discussed by the OEL Committee, which adopted the finalised version on 17 October 2017.

⇨ Regarding the Risk Management Option Analysis (RMOA) for occupational risks generated by formaldehyde (DNELs)

The analysis was undertaken by the REACH Committee. The work of the GECU on Formaldehyde led to the proposal of new OELs used as DNELs in the context of the RMOA. The French Ministry of the Environment held a public consultation on this document from 7 July to 31 October 2016. Following this consultation, on 29 March 2017, ANSES adopted an "Opinion on the Risk Management Option Analysis for occupational risks generated by formaldehyde", accompanying the final RMOA.

⇨ Regarding Internal Request No 2017-SA-0040 (TRVs)

The collective expert appraisal was undertaken by the ANSES Committee on Characterisation of substance hazards and toxicity reference values (Substances Committee) between May 2016 and May 2017. The toxicological profile of formaldehyde by inhalation was updated with the support of expert rapporteurs from the Substances Committee and the ANSES Committee on Assessment of the risks related to air environments (Air Committee). Acute and chronic TRVs were proposed by these expert rapporteurs and validated by the Substances Committee on 11 May 2017.

⇨ Regarding Internal Request No 2017-SA-0041 (IAQGs)

The collective expert appraisal was undertaken by the Air Committee. The existing IAQGs were updated according to the updated method for establishing IAQGs in light of the TRVs proposed by the Substances Committee, leading to the updating of the 2007 collective expert appraisal report recommending IAQGs for formaldehyde.

Methods for measuring formaldehyde in indoor air were assessed by the Working Group on Metrology and gave rise to recommendations based on the proposed IAQGs. The IAQGs and the assessment of the measurement methods were validated by the Air Committee on 15 June 2017.

Data from previously published ANSES reports were gathered in full to update the toxicological profile of formaldehyde. These reports were as follows:

- Indoor air guideline values. Formaldehyde (2007);
- Assessment of the health risks associated with the presence of formaldehyde in indoor and outdoor environments. Toxicity of formaldehyde. State of knowledge on the characterisation of hazards and selection of toxicity reference values (2008);
- Occupational exposure limits. Assessing the health effects and methods for measuring occupational exposure for formaldehyde [CAS No 50-00-0] (2008);

- CLH report. Proposal for Harmonised Classification and Labelling. Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2. Substance Name: FORMALDEHYDE (2011);
- Substance Evaluation Report (SeV Report) on Formaldehyde (2014): unpublished expert appraisal, prepared in the framework of the REACH Regulation;
- ANSES Opinion on a Risk Management Option Analysis for occupational risks generated by formaldehyde (CAS No 50-00-0) (2017).

Regarding the toxicological profile used for the establishment of OELs and occupational DNELs: the literature data used in the aforementioned ANSES reports were supplemented by a literature review on Medline and Toxline covering the period between 2008 and 2016, the IARC report[4] (2012) and the SCOEL document "SCOEL/REC/125 Formaldehyde Recommendation from the Scientific Committee on Occupational Exposure Limits" published in 2016.

Regarding the toxicological profile used for the establishment of TRVs and IAQGs: the literature data used in the aforementioned SeV report were supplemented by the documentary references identified for establishing OELs and occupational DNELs, by a search on Medline and Scopus covering the period between 2014 and 2016, and by the contributions of the experts involved in this work.

Lastly, regarding metrology, the assessment of methods for measuring formaldehyde in indoor air was undertaken according to the harmonised approach developed by ANSES in its methodology report (ANSES, 2016). The previously published assessment of methods for measuring formaldehyde in workplace atmospheres (ANSES, 2008) was updated using the same methodology.

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals.
The experts' declarations of interests are made public via the ANSES website (www.anses.fr).

3. ANALYSIS AND CONCLUSIONS OF THE EXPERT COMMITTEES

3.1. TOXICITY DATA ON FORMALDEHYDE

The data presented below relate to the updated toxicological profile of formaldehyde, which was used to establish the various reference values. This part was adopted by the Substances and the OEL Committees and presented to the Air and the REACH Committees.

3.1.1. Toxicokinetics

Formaldehyde is an endogenous compound formed naturally by the body through amino acid catabolism. Its physiological blood concentration is around 100 µmol.L^{-1} (BfR, 2006b).
Whether in animals or humans and regardless of the route of exposure, the retention of formaldehyde is limited to the site of first contact in the body, due to its reactivity with biological macromolecules, which limits its systemic availability (ATSDR, 1999). Several studies have shown no differences between blood levels of formaldehyde before and after respiratory exposure to formaldehyde, in humans and rats (Heck *et al.*, 1985; Casanova *et al.*, 1988).
Formaldehyde is rapidly metabolised into formate and then CO_2 by several enzymes, the most important being NAD+-dependent formaldehyde dehydrogenase (FDH). Formaldehyde reacts rapidly with glutathione (GSH) to form hydroxymethylglutathione (GS-CH_2OH), which is subsequently oxidised in the presence of FDH into S-formylglutathione (G-S-CHO). The hydrolysis of this compound releases glutathione and a formate ion ($HCOO^-$), which is either eliminated in the urine or oxidised into CO_2 and eliminated primarily in the lungs (ATSDR 1999; BfR, 2006b). This

[4] International Agency for Research on Cancer

mechanism is saturable: the sharp increase in toxicity in rats at concentrations above 6 ppm can be interpreted as being due to saturation of FDH or depletion of GSH (BfR, 2006).
When it is not metabolised, because of its high reactivity with the functional groups of the molecules, formaldehyde may bind covalently with the nucleophilic sites of proteins, small- and medium-sized molecules, and DNA (ATSDR, 1999; National Institute for Working Life, 2003). This route is responsible for the formation of DNA-protein cross-links (DPXs) in the nasal mucosa, playing a crucial role in the carcinogenic mode of action of formaldehyde in the nasopharynx. No increase in DPXs related to exogenous formaldehyde was observed in bone marrow or away from the absorption site (Heck and Casanova, 2004; Lu *et al.*, 2010; Golden, 2011).
Expired air is the primary route of elimination, with around 40% of formaldehyde eliminated in the form of carbon dioxide. Regardless of the concentration of formaldehyde to which animals are exposed, the rates of elimination through the three routes are of the same order of magnitude (Heck *et al.*, 1983; IARC, 2006).

3.1.2. Acute toxicity

While serious effects can be observed above 12,000 µg.m^{-3} (respiratory difficulties, oedema, lung congestion, etc.), most of the effects observed at lower concentrations are irritant effects (INRS, 2006).

3.1.3. Irritation

Many studies have been undertaken to describe and assess the irritant potential of formaldehyde in humans. These are case-control and controlled exposure studies.
Some studies have also investigated sensory irritation. This is defined as a chemosensory effect, i.e. an interaction between the chemical substance and the sensory nerve endings of the trigeminal nerve. It is an extremely rapid process, occurring in a few milliseconds between stimulation and reaction. With regard to dose-response relationships in humans and animals, this sensory irritation occurs at lower levels than actual irritation inducing tissue damage. At very low concentrations, therefore, acute effects such as discomfort or itching, burning or stinging sensations are unpleasant but completely reversible. It now seems, however, that prolonged nerve stimulation can lead to a cascade response causing chronic adverse effects. In particular, neurogenic inflammation seems to play an important role: it reflects the transition from reversible, purely sensory effects to more general effects and inflammatory defence mechanisms, such as those observed in tissue irritation. At a certain level of response, tissue irritation and sensory irritation can therefore become indistinguishable from one another. As sensory irritation can therefore be a precondition for tissue irritation, Brüning *et al.* (2014) suggest considering the first observed sensory irritation effects as a NOAEC[5] (Brüning *et al.*, 2014).

Pazdrack *et al.* (1993) conducted a controlled exposure study in nine people with skin hypersensitivity to formaldehyde through occupational exposure (with no other signs of allergy or rhinitis but with signs of eye irritation at the work station) and a second group of 11 men with no history of allergy, all of whom were exposed to 500 µg.m^{-3} for two hours. The authors concluded that there were pro-inflammatory effects on the nasal mucosa in both groups.

In two recent studies (Lang *et al.,* 2008 and Mueller *et al.,* 2013), objective tests to measure sensory irritation such as eye blinking frequency and nasal airflow and resistance were evaluated. These tests helped overcome any distorted perception of irritation, due for example to the smell of formaldehyde. In addition, these studies incorporated exposure with peaks, closer to actual conditions of occupational exposure.

An analysis matrix showing the results of these two studies is available in Annex 1 of this Opinion.

[5] No Observed Adverse Effect Concentration

The study by Lang *et al.* (2008) was conducted with 21 volunteers (11 male and 10 female). Measurements consisted in conjunctival redness, blinking frequency, nasal resistance and flow, and pulmonary function. Ten different exposure conditions, described below, were put in place, corresponding to different concentrations of formaldehyde in air. Exposure lasted four hours and included or excluded peaks over a 15 minutes period:

- 0 $\mu g.m^{-3}$; 185 $\mu g.m^{-3}$; 369 $\mu g.m^{-3}$; 615 $\mu g.m^{-3}$;
- 369 $\mu g.m^{-3}$ + four 738 $\mu g.m^{-3}$ peaks; 615 $\mu g.m^{-3}$ + four 1230 $\mu g.m^{-3}$ peaks;
- With masking agent (ethyl acetate): 0 $\mu g.m^{-3}$; 369 $\mu g.m^{-3}$; 615 $\mu g.m^{-3}$; 615 $\mu g.m^{-3}$ + four 1230 $\mu g.m^{-3}$ peaks.

All the subjects were exposed to each of the exposure conditions.
No significant changes were reported following exposure to formaldehyde for nasal resistance and flow, pulmonary function, or reaction time. Regarding conjunctival redness, the only statistically significant observation was found at the highest exposure level of 615 $\mu g.m^{-3}$ + four 1230 $\mu g.m^{-3}$ peaks. The increase in blinking frequency became significant with the same exposure condition, also with the masking agent. Subjective effects (ocular, nasal, respiratory irritation, olfactory symptoms, discomfort) occurred from 369 $\mu g.m^{-3}$ but were not always significant with the masking agent.

The study by Mueller *et al.* (2013) was conducted with 41 male volunteers. The measured effects were conjunctival redness, eye blinking frequency, tear film breakup time (reflecting ocular dryness) and nasal flow. ANOVA was used for the statistical analysis with a repeated-measures cross-over design. Five different exposure conditions, described below, were put in place. Exposure lasted four hours and included or excluded peaks over a 15 minutes period:

- 0 $\mu g.m^{-3}$; 615 $\mu g.m^{-3}$; 861 $\mu g.m^{-3}$;
- 369 $\mu g.m^{-3}$ + four 615 $\mu g.m^{-3}$ peaks; 492 $\mu g.m^{-3}$ + four 984 $\mu g.m^{-3}$ peaks.

All the subjects were exposed to each of the five exposure conditions for five consecutive days. It should be noted that this study divided the volunteers into "hypersensitive" and "hyposensitive" groups, using a test of sensitivity to CO_2.
No significant changes were observed regarding conjunctival redness or eye blinking frequency compared to the controls. Tear film breakup time was reduced in the "hyposensitive" subjects exposed to 369 $\mu g.m^{-3}$ + four 615 $\mu g.m^{-3}$ peaks and 861 $\mu g.m^{-3}$ compared to the controls. However, no dose-response relationship was seen and the same observations were not found with the "hypersensitive" subjects. Similarly, nasal flow increased only at 369 $\mu g.m^{-3}$ + four 615 $\mu g.m^{-3}$ peaks for "hyposensitive" subjects. Regarding subjective effects, no statistically significant difference was reported for the nasal and ocular irritation tests. For olfactory symptoms and the perception of "impure air", an increase in effects, primarily in "hypersensitive" subjects, was observed.

Only two cross-sectional studies have investigated the irritant effects of formaldehyde: those by Holmstrom *et al.* (1989) and Wilhelmsson and Holmstrom (1992). These were epidemiological studies in workers, distinguishing between various exposure groups. The irritant effect of formaldehyde was analysed using nasal biopsies and biological tests performed at the end of the studied exposure period.
In the study by Holmstrom *et al.* (1989), the difference compared to the control group was considered significant ($p < 0.05$). The authors indicated that the average 500 $\mu g.m^{-3}$ concentration of formaldehyde did not cause long-term effects different from the short-term effects.
In the other study run by the same team (Wilhelmsson and Holmstrom, 1992), work-related nasal discomfort was observed in more than half of the workers exposed to formaldehyde. Among the subjects experiencing these symptoms, atopic individuals did not represent a larger share than non-atopic individuals. Irritation affected the eyes, lungs and nose (cough and rhinorrhoea). The authors concluded that formaldehyde may induce a nasal type 1 hypersensitivity response (mediated by IgE) but that, in most of the cases reported in this study, the symptoms were caused by hyper-responsiveness induced by formaldehyde itself.

3.1.4. Sensitisation

Regarding respiratory sensitisation, the study results are inconsistent.

Some studies showed a potentiating effect of formaldehyde on immediate and delayed bronchial response during exposure to allergens (Casset *et al.*, 2006). Moreover, delayed response and asthma were found to be significantly more severe after inhalation of formaldehyde (Casset *et al.*, 2006; Marchand, 2005).

However, several recent reviews of the literature relating specifically to the indoor air of homes or occupational environments led to the conclusion that respiratory sensitisation caused by formaldehyde was highly unlikely, in particular at low concentrations (MAK, 2014; Golden, 2011; Schram-Bijkerk *et al.*, 2013). In fact, the associations between formaldehyde and respiratory symptoms may have been due to the influence of co-exposure or confounding factors such as psychosocial factors.

Regarding skin contact, under the CLP Regulation (EC) No 1272/2008, formaldehyde has a harmonised classification as a Category 1 skin sensitiser, with the H317 statement "may cause an allergic skin reaction" (ECHA, 2016).

3.1.5. Chronic toxicity

The irritant effects related to chronic exposure to formaldehyde are similar to those observed during acute exposure.

In humans, eye, throat and respiratory tract irritation, fatigue and headaches have been reported in the workplace and in the general population, in many studies undertaken in particular in mobile homes. These symptoms occur from 120 $\mu g.m^{-3}$ in the general population (non-significant increase of around 1% to 2%) (IPCS, 2002; Ritchie *et al.*, 1987).

Of the recent epidemiological studies focusing specifically on indoor air pollution, four found a statistically significant relationship between the occurrence of respiratory symptoms and exposure to the highest concentrations of formaldehyde; however, five did not observe such a relationship.

Some studies identified sensitisation phenomena and asthmatic diseases, but had a number of confounding biases, making the results difficult to interpret. Moreover, many other studies failed to observe any such relationships.

3.1.6. Effects on reproduction and development

Duong *et al.* (2011) conducted a systematic review of the data on the reproductive and developmental effects of formaldehyde as well as a meta-analysis. The results of this meta-analysis (which were consistent with those of the meta-analysis by Collins *et al.,* 2001) showed that maternal exposure to formaldehyde was associated with a risk of spontaneous abortion. The authors themselves specify that confounding factors (co-exposure with other compounds that can induce effects on reproduction in the studies, and non-adjusted relative risks - RRs) and recall biases may have caused these RRs to be overestimated, but they did not consider they were able to assess them (Duong *et al.*, 2011).

3.1.7. Genotoxicity

Formaldehyde has shown *in vitro* genotoxicity at high concentrations in bacteria and mammalian cell genotoxic assays (IARC, 1997; Health Canada, 2001). The mutagenic potential of formaldehyde is reduced by adding an exogenous metabolic activation system, which suggests that formaldehyde itself is probably genotoxic (INRS, 2006). Formaldehyde also forms DPX cross-links whose incomplete repair can lead to mutations (Barker *et al.*, 2005) or clastogenic effects (ANSES, 2011).

Regarding the genotoxic effects of formaldehyde away from the contact site, the results of the various studies undertaken in humans are conflicting and ambiguous. The European Chemicals Agency (ECHA) considered they could not be used to assess the mutagenic potential of formaldehyde. It recalls that, from a biological point of view, systemic effects are not expected

since exposure to formaldehyde does not increase blood concentrations of formaldehyde (ECHA, 2012).
In conclusion, there is insufficient evidence to confirm whether formaldehyde has systemic genotoxicity in humans. The results of micronucleus tests with circulating lymphocytes from various studies in workers exposed to formaldehyde indicate a correlation between the level and duration of exposure to formaldehyde and the occurrence of genetic instability in circulating lymphocytes in the form of micronuclei when the lymphocytes are cultured *ex vivo*. However, these tests were unable to identify whether the observed micronuclei were due to the effect of formaldehyde on lymphocytes circulating in the blood, which would be a marker of exposure to formaldehyde, or if they were caused by an effect on lymphoid progenitor cells located in bone marrow, which by accumulating mutations, may generate circulating lymphocytes with greater genetic instability. It therefore appears difficult to conclude with certainty as to the systemic genotoxic potential of formaldehyde, as the weight of evidence is considered average or low.
As stated above, it is very unlikely that formaldehyde can be distributed in gonadal cells after inhalation. The few studies available on germ cells suffer from methodological biases and could not be used.

3.1.8. Carcinogenicity

3.1.8.1. Nasopharynx

In its 2004 monograph, the IARC concluded that formaldehyde was carcinogenic to humans (classification in Group 1). In 2014, under the European regulations, formaldehyde was classified as Category 1B carcinogenic, presumed to have carcinogenic potential for humans (ATP 06 - Regulation (EC) No 1272/2008).

The numerous data prove that formaldehyde causes nasopharyngeal cancer in humans. The genotoxicity of formaldehyde is observed experimentally only at high concentrations. The carcinogenic effect of formaldehyde on the nasopharynx relies on its cytotoxicity and genotoxicity. A review by Gaylor *et al.* (2004) of the results of the study by Monticello *et al.* (1996) confirmed that the occurrence of nasopharyngeal cancer is the result of two separate events showing a threshold dose-response relationship: a) the cytotoxicity of formaldehyde, responsible for regenerative cellular proliferation, b) the combined genotoxic effects of formaldehyde including the formation of DPX which becomes irreversible at high concentrations (BfR, 2006).
Studies measuring the DPX formation rate in animals conclude that there is a 2.5 $mg.m^{-3}$ threshold above which this rate increases significantly. At lower concentrations, the cross-links are rapidly repaired and therefore cannot accumulate (WHO, 2010). Still in animals, regenerative cellular proliferation in response to formaldehyde cytotoxicity did not increase below 2.5 $mg.m^{-3}$, in rats exposed for two years (Monticello *et al.*, 1991; Connolly *et al.*, 2002).
Epidemiological studies in occupational environments indicate that the relative risk of nasopharyngeal cancer due to formaldehyde is increased only at the highest exposure concentrations (peaks > 5 $mg.m^{-3}$). Average exposure levels below 1.25 $mg.m^{-3}$ are not associated with an increase in this risk.

The carcinogenic effects of formaldehyde on the nasopharynx are therefore observed in contexts of repeated exposure to high concentrations, first causing cytotoxicity manifested as local irritation.

3.1.8.2. Leukaemia

Numerous studies undertaken in humans have assessed the association between leukaemia mortality and occupational exposure to formaldehyde. The results are equivocal but tend to show an association between leukaemia and formaldehyde exposure at high concentrations only.

More recent studies have sought to assess the toxic potential of formaldehyde in peripheral blood stem cells taken from workers exposed to formaldehyde. One of these studies' limitations is related to the difficulty of reliably characterising exposure to formaldehyde. Some studies do not or only

inadequately indicate the exposure levels associated with the studied effects. In particular, one of the major biases in some of these studies is the lack of data on co-exposure to other compounds. The results are therefore difficult to interpret since the observed effects cannot be attributed with certainty to formaldehyde alone. Lastly, some studies have used a questionable methodological approach involving the establishment of reference groups. In fact, as concluded by the ECHA's Committee for Risk Assessment (RAC) in 2012, the authors of occupational cohort studies used workers in the group exposed to low concentrations of formaldehyde as the reference group, while subsequent studies and updates used individuals outside the workplace, not specifically exposed, as the reference group. Considering the major differences between workers exposed to formaldehyde and individuals outside the workplace, the methodological choice of these reference groups is a bias influencing the interpretation of results.

Assumptions describing the leukaemogenic mode of action of formaldehyde have not yet been verified by experimental animal and/or *in vitro* studies. In fact, blood concentrations of formaldehyde increase only slightly or insignificantly after exogenous exposure to formaldehyde, even at high concentrations. In addition, the assumption that formaldehyde has cytotoxic action targeting bone marrow cells is questionable since formaldehyde is cytotoxic regardless of the cell type.

Lastly, animal studies provide no evidence of leukaemia occurring at the formaldehyde exposure levels associated with the occurrence of nasal cancers. In fact, the incidence of leukaemia or lymphoma in animals increased only in the groups with the highest tested concentrations. Experimental studies conducted orally lead to the same conclusion.

The published data indicate that:

- no excess leukaemia mortality was observed with average concentrations below 0.93 $mg.m^{-3}$ or exposure peaks below 5 $mg.m^{-3}$ (Hauptmann *et al.*, 2003);
- no excess Hodgkin's lymphoma mortality was observed with average concentrations below 0.63 $mg.m^{-3}$ or exposure peaks below 2.5 $mg.m^{-3}$ (Marsh *et al.*, 2004);
- no excess myeloid leukaemia mortality was observed with average concentrations below 1.23 $mg.m^{-3}$ or exposure peaks below 5 $mg.m^{-3}$ (Beane-Freeman *et al.*, 2009);
- no excess mortality from non-Hodgkin's lymphoma, multiple myeloma, leukaemia or myeloid leukaemia was observed with exposure levels above 2.5 $mg.m^{-3}$ (the group the most exposed to formaldehyde in the study by Coggon *et al.*, 2014);
- effects of formaldehyde on circulating myeloid stem cells (genetic anomalies, reduction in cellular growth) and haematological parameters in exposed workers were observed at average concentrations of 1.6 to 5.18 $mg.m^{-3}$ (Zhang *et al.*, 2010).

Despite uncertainties regarding mechanistic data and the lack of consolidated data in animals, and considering the results of epidemiological studies in humans, the association between formaldehyde exposure and the occurrence of leukaemia in humans cannot be ruled out. Even so, the causal relationship cannot be confirmed (due to confounding biases and uncertainties regarding the characterisation of exposure in particular). In addition, the association is observed at higher concentrations than those associated with the occurrence of nasopharyngeal cancer whose causal relationship with formaldehyde is certain. The carcinogenic effects on the nasopharynx are therefore the most sensitive critical effect of chronic exposure to formaldehyde in humans.

3.1.9. Susceptible population groups

No particular susceptibility to formaldehyde has been found in asthmatic or atopic individuals (Wilhelmsson and Holmstrom, 1992; Pazdrack *et al.*, 1993; Paustenbach *et al.*, 1997; Krakowiak *et al.*, 1998; Arts, 2006; WHO, 2010).
In studies investigating a relationship between the occurrence of respiratory effects in children and exposure to formaldehyde at home or school, no conclusions could be drawn with certainty as to

whether there was an association, due to exposure co-factors (animal allergens, mould, road traffic, socio-economic factors) (Paustenbach, 1997; IPCS, 2002; AFSSET, 2008; WHO, 2010; Golden, 2011).
No studies have reported increased susceptibility in elderly people (Doty *et al.*, 2004).
Nonetheless, regarding eye irritation, several ophthalmologists contacted in the framework of this Opinion reported inter-individual variability for eye irritation to chemicals, especially formaldehyde. Ocular dryness is one of the aggravating factors and can be correlated with the existence of diseases (e.g. dry eye syndrome) or specific physiological states (e.g. menopause, contact lens users). The study by Wolkoff *et al.* (2016) listed a number of risk factors associated with ocular dryness including age.

3.2. UPDATING OF ANSES's REFERENCE VALUES

Since ANSES's earlier publications dealing with reference values for formaldehyde, new data have been identified. They relate to toxicokinetics, irritant effects (controlled exposure studies in humans), respiratory sensitisation, association between indoor air pollution and respiratory effects (epidemiological studies), genotoxicity (human studies) and carcinogenic effects of formaldehyde (nasopharyngeal cancer and leukaemia). An analysis of these data enabled the updating of the following reference values: OELs, occupational DNELs, TRVs and IAQGs adopted by the OEL, REACH, Substances and Air Committees.

3.2.1. Selection of the acute critical effect

Sensory or cellular eye irritation is an early effect compared to nasal and respiratory irritation. The results of human studies indicate that eye irritation is the most sensitive effect induced by formaldehyde exposure. It is observed at concentrations below those associated with nasal and respiratory irritation (Paustenbach *et al.*, 1997; AFSSET, 2008; Doty *et al.*, 2004; WHO, 2010; ANSES, 2017). It was thus appropriate to select it as the acute critical effect.

3.2.2. Selection of the key study for acute reference values

The literature update was an opportunity to closely examine two new controlled exposure studies determining a dose-response relationship associating formaldehyde exposure with the occurrence of acute effects in humans: those by Lang *et al.* (2008) and Mueller *et al.* (2013). These two studies, financed by industrial consortia (formaldehyde producers and users), are of good quality and were conducted with a large number of subjects. Each has a rigorous and detailed study design (standardised exposure indicators, rigorously completed questionnaires) and a high-quality statistical data analysis. Their results are consistent with those published earlier.

In the study by Lang *et al.* (2008), the subjects were exposed to 10 different concentrations of formaldehyde, continuously for four hours, with or without 15-minute exposure peaks. The concentrations ranged from 185 to 615 $\mu g.m^{-3}$, corresponding to the lowest tested concentrations in the available controlled exposure studies.

The study by Mueller *et al.* (2013) supplemented the results obtained by Lang *et al.* (2008). It had a higher number of subjects (41 individuals) exposed for one week but was undertaken with male subjects only. In addition, the division of the subjects into two separate groups of subjects "hypersensitive" and "hyposensitive" to sensory nasal irritation was not considered relevant. Lastly, the CO_2 irritation test used for this division was considered a pain test that was not appropriate for identifying individuals susceptible to the effects of formaldehyde. Lastly, the study was conducted for one week instead of two consecutive weeks in the study by Lang *et al.* (2008).

The study by Lang *et al.* (2008) was thus chosen as the key study for the proposal of acute reference values for professionals and the general population.

3.2.3. Selection of the chronic critical effect

The selected critical effect of chronic exposure to formaldehyde was nasopharyngeal cancer. It is the best described carcinogenic effect of formaldehyde, for which a causal relationship has been well established based on numerous human, animal and mechanistic data. The development of nasopharyngeal cancer is linked to repeated and prolonged changes in the nasal epithelium, and therefore to sufficiently high and prolonged exposure first causing irritation. The data on the mode of action enable a threshold dose-response relationship to be determined, with a series of key events leading to the formation of nasopharyngeal tumours of which the first is eye and nose irritation.

Regarding leukaemia, the level of evidence is considered sufficient by the IARC for exposure to formaldehyde at high concentrations at which nasopharyngeal cancer is also observed. Even so, the causal relationship could not be confirmed due to confounding biases and uncertainties regarding the characterisation of exposure in particular. Furthermore, assumptions describing the mode of action have not yet been verified by experimental animal and/or *in vitro* studies. Animal studies provide no evidence of leukaemia at the formaldehyde exposure levels associated with the occurrence of nasal cancers. Experimental studies conducted orally lead to the same conclusion.
The carcinogenic effects on the nasopharynx were therefore the most sensitive critical effect of chronic exposure to formaldehyde in humans.

As indicated above, eye irritation is observed at formaldehyde concentrations below those associated with nasal and respiratory irritation. Moreover, these effects are generally reversible after the end of exposure in human controlled exposure studies. Eye irritation is therefore the first key event and is a precursor of more severe irreversible effects such as nasopharyngeal carcinogenic effects of formaldehyde. Its selection as the critical effect for the establishment of a chronic value appeared as the most conservative for preventing the occurrence of long-term effects.

In order to protect against the occurrence of nasopharyngeal cancers, the selected effect was therefore eye irritation.

3.2.4. Selection of the key study for chronic reference values

Regarding the irritant effects of formaldehyde for chronic exposure, only two studies in humans sought to assess these effects by performing nasal biopsies and biological tests, which are objective criteria (Holmstrom *et al.*, 1989; Wilhelmsson and Holmstrom, 1992). However, these past studies relied on a series of poorly documented measurement campaigns and included little information about sampling strategies. The irritant effects of formaldehyde were not monitored continuously but assessed only when the studies were put in place, which meant that the dose-response relationship was not explored. The description of the groups and justification of the recruiting method for the subjects were limited. Aside from smoking and exposure to wood dust in the study by Holmstrom *et al.* (1989), the authors did not look for other confounding factors. In the study by Wilhelmsson and Holmstrom (1992), the presence of co-factors was not taken into account in the interpretation of the results. In addition, the statistical data analysis was limited. All the above are biases lowering the quality of these studies.

Considering the recent data on the irritant effects of formaldehyde documented by controlled exposure studies, the study by Lang *et al.* (2008) was thus selected as the key study for the proposal of chronic reference values for professionals and the general population.

3.2.5. Reference values for the general population adopted by the Substances and Air Committees

3.2.5.1. Critical concentrations and uncertainty factors

3.2.5.1.1. Acute exposure

According to the table attached in Annex 1, objective ocular irritant effects (increase in eye blinking frequency and eye redness and therefore sensory and cellular effects) were observed from 615 $\mu g.m^{-3}$ with four 1230 $\mu g.m^{-3}$ peaks. This concentration is therefore considered as a LOAEC[6]. No effects were observed at the lower concentration. The NOAEC is therefore defined as the lower test concentration, i.e. 369 $\mu g.m^{-3}$.

No temporal or allometric adjustment was applied, as the study by Lang *et al.* (2008) was conducted in humans for acute exposure times of four hours (15-minute peaks).
Since the key study was undertaken in humans, only an uncertainty factor taking into account inter-individual variability (UF_H) was applied (ANSES, 2015). Indeed, compared to a general population, a limited number of subjects were included in the study by Lang *et al.* (2008): 21 young male and female volunteers with no specific susceptibility to chemical substances. Thus, the results of this study cannot be transposed to the entire general population including subjects with different ages, health status and susceptibilities. The application of an inter-individual uncertainty factor thus appeared justified.
The UF_H value could be reduced in relation to ANSES's default recommendations (2015) (value of 10). In fact, inter-individual toxicokinetic variability was considered negligible since eye irritation is a purely local effect (Wolkoff, 2016). Regarding the existence of susceptible populations, no particular susceptibility to formaldehyde has been found. Nevertheless, it was considered that physiological and exogenous factors can cause increased ocular sensitivity to chemical irritants, especially in the general population. Inter-individual toxicodynamic variability ($UF_{H\text{-}TD}$) should therefore be taken into account.

The inter-individual uncertainty factor UF_H, for the establishment of an acute TRV, was therefore 3.

3.2.5.1.2. Chronic exposure

The NOAEC of 369 $\mu g.m^{-3}$, determined for the establishment of the acute TRV based on objective acute ocular irritant effects, was chosen for the establishment of a chronic TRV.

Since the subjects in the study by Lang *et al.* (2008) were exposed for four hours, the relevance of applying a temporal adjustment to chronic exposure was discussed. Several arguments were in favour of a concentration-dependent effect of formaldehyde depending on the duration of exposure.

For acute exposure, the intensity and severity of ocular and nasal irritation observed after exposure to formaldehyde are comparable, regardless of the duration of exposure.

- An increase in the severity of this irritation is generally observed only as the tested concentrations increase, but not the duration of exposure (AFSSET, 2007; Belkebir *et al.*, 2011; Wilmer *et al.*, 1987, 1989).
- In animals, an increase in cytotoxicity and cell proliferation in the nasal epithelium is influenced by the exposure concentration, not the duration. Indeed, for the same concentration applied according to three different exposure protocols (13.5 $mg.m^{-3}$ for three hours; 6.7 $mg.m^{-3}$ for six hours; and 3.4 $mg.m^{-3}$ for 12 hours), the effects were more severe in the highly exposed animals (Swenberg *et al.*, 1983; Belkebir *et al.*, 2011).

[6] Lowest Observed Adverse Effect Concentration

- Human controlled exposure studies have shown a decrease in or even disappearance of irritation symptoms after several hours of exposure (Paustenbach *et al.*, 1997), which does not rule out the persistence of histological effects.

The same conclusion can be made for sub-chronic exposure.

- Five groups of 10 male Wistar rats were continuously exposed to 0, 5.6 and 11.2 $mg.m^{-3}$ of formaldehyde for eight hours per day and intermittently to 11.2 and 22.4 $mg.m^{-3}$ of formaldehyde (30-minute cycle followed by 30 minutes of rest, for eight hours per day), five days per week for four weeks. Nasal lesions (rhinitis, metaplasia of the respiratory epithelium) were more severe in the animals exposed intermittently. These results were corroborated by a complementary study exposing male Wistar rats continuously to 0, 1.1 and 2.2 $mg.m^{-3}$ of formaldehyde (eight hours/day) and intermittently to 2.2 and 4.5 $mg.m^{-3}$ of formaldehyde (30-minute cycle followed by 30 minutes of rest, eight hours per day, five days per week for 13 weeks). Nasal lesions were more severe in the animals exposed intermittently (Belkebir *et al.*, 2011).
- Several studies undertaken in the workplace have shown a decrease in the susceptibility of individuals exposed to formaldehyde based on the duration of exposure. The occurrence of ocular, nasal and respiratory irritation tends to decrease over time, which does not rule out the persistence of histological effects.

Following chronic exposure, the development of nasopharyngeal cancer relies on prolonged and repeated changes in the nasal epithelial cells (cytotoxicity) at high and repeated concentrations of formaldehyde (genotoxicity).

- In animals
  - Regenerative cellular proliferation in response to cytotoxicity of formaldehyde did not increase below 2.5 $mg.m^{-3}$, in rats exposed for two years (Monticello *et al.*, 1991; Connolly *et al.*, 2002).
  - The same threshold was determined from the results of a study exposing rats for nine days, proving that the concentration of 2.5 $mg.m^{-3}$ associated with the lack of regenerative cellular proliferation in animals remains constant regardless of the exposure period (Swenberg *et al.*, 1983).
  - In the nasal cavity, formaldehyde induces the formation of DPX in animals, rapidly eliminated at concentrations below 2 $mg.m^{-3}$. There is no accumulation of DPX over time after repeated exposure to formaldehyde; only the formaldehyde concentration impacts the increase in the formation of these cross-links in animals (IARC, 2006; WHO, 2010).
  - Monticello *et al.* (1996) concluded that the carcinogenic effect of formaldehyde on the nasopharynx is correlated with the quantity of cells exposed to formaldehyde, not the duration of exposure. In fact, the number and location of cells exposed to formaldehyde are decisive parameters in the increase in regenerative cellular proliferation (BfR, 2006b).
- In humans
  - The results of epidemiological studies all indicate an increase in mortality from nasopharyngeal cancer in individuals exposed with peaks but not with cumulative exposure, suggesting an effect related to repeated high concentrations rather than to a longer exposure period. The study by Holmstrom *et al.* (1989) indicates that no correlation was found between the duration of exposure to formaldehyde or the concentration-year variable and histopathological changes. In fact, the study showed that longer cumulative exposure to formaldehyde did not cause more severe histopathological nasal changes in the exposed workers (Holmstrom *et al.*, 1989; AFSSET, 2007).
  - Lastly, the results from controlled exposure up to 2.2 $mg.m^{-3}$ of formaldehyde in healthy individuals on the one hand and in laboratory technicians chronically exposed in the workplace on the other hand led to the same conclusions. Repeated exposures of

laboratory technicians to formaldehyde did not increase susceptibility to formaldehyde during controlled short-term exposure. Rather, the proportion of individuals reporting ocular and nasal irritation was lower than in healthy individuals (Paustenbach *et al.*, 1997).

Considering all of these justifications, the chronic irritant effects of formaldehyde show a concentration-dependent relationship. Thus, the application of a temporal adjustment to the NOAEC defined above was not justified.

As for the establishment of the acute TRV, only an uncertainty factor for inter-individual variability (UF_H) was applied. The justifications regarding the lack of toxicokinetic variability (UF_{H-TK}) were the same, i.e. the lack of a more susceptible population to the irritant effects of formaldehyde and the local site of these effects.
For toxicodynamic variability (UF_{H-TD}), the study by Firestone *et al.* (2008) modelled the rate of DNA-protein cross-link (DPX) formation generated by exposure to formaldehyde comparatively for adults and children. This model led to the conclusion that DPX formation due to formaldehyde exposure is 1.5 times higher in adults than in children, for the same level of exposure. Considering the decisive role of genotoxicity of formaldehyde in the occurrence of nasopharyngeal cancer, children are thus not more susceptible to the carcinogenic effects of formaldehyde than adults (WHO, 2010).
The inter-individual uncertainty factor UF_H, for the establishment of a chronic TRV, was therefore 3.

3.2.5.2. TRVs proposed by the Substances Committee

The Substances Committee recommends an acute TRV by inhalation of 123 µg.m^{-3}.
The overall confidence level was assigned to this TRV based on the following criteria:

- Level of confidence in the nature and quality of the data: **high**: numerous monographs, publications and expert appraisal reports supporting the assumptions for the establishment of the acute TRV;
- Level of confidence in the selection of the critical effect and the mode of action: **high**: substantiated data from the literature, choice of the ocular irritant effect as the most sensitive critical effect of formaldehyde exposure, protecting against nasal and respiratory irritant effects;
- Level of confidence in the selection of the key study: **high**: detailed, good-quality key study, solid experimental protocol, high number of tested concentrations, advanced statistical analysis, numerous justifications provided supporting the authors' conclusions. However, financing by an industrial consortium.
- Level of confidence in the selection of the critical concentration: **moderate**: critical concentration determined from an objective sensitive critical effect. However, the results are difficult to interpret, especially for subjective effects with exposure conditions with and without a masking agent. In addition, the critical condition corresponds to the condition with exposure peaks.

Thus, the overall level of confidence for this TRV is **high**.

Critical effect (key study)	Critical concentration	UF	Acute TRV
Eye irritation (Lang *et al.*, 2008)	NOAEC = 369 µg.m^{-3}	3 UF_H = 3	**TRV = 123 µg.m^{-3}** **Confidence level High**

A chronic TRV is also proposed, based on the same effect and the same critical concentration as the acute TRV, but protecting against carcinogenic effects on the nasopharynx considered as a threshold effect.

The Substances Committee recommends a chronic TRV by inhalation of 123 µg.m^{-3}.
The overall confidence level was assigned to this TRV based on the following criteria:

- Level of confidence in the nature and quality of the data: **moderate**: numerous monographs, publications and expert appraisal reports supporting the assumptions for the establishment of the chronic TRV. Only two studies investigated the chronic irritant effects of formaldehyde and were not chosen due to methodological limitations;
- Level of confidence in the selection of the critical effect and the mode of action: **high**: substantiated data from the literature, choice of a precursor key event to protect against a threshold carcinogenic effect;
- Level of confidence in the selection of the key study: **moderate**: lack of a good-quality study with an experimental protocol assessing chronic irritant effects of formaldehyde. Failing that, choice of a detailed, good-quality key study, solid experimental protocol, high number of tested concentrations, advanced statistical analysis, numerous justifications provided supporting the authors' conclusions. However, financing by an industrial consortium.
- Level of confidence in the selection of the critical concentration: **moderate**: critical concentration determined from an objective sensitive and precursor critical effect. However, the results are difficult to interpret, especially for subjective effects with exposure conditions with and without a masking agent.

Thus, the overall level of confidence for this TRV is **moderate**.

Critical effect (key study)	Critical concentration	UF	Chronic TRV
Eye irritation (Lang *et al.*, 2008)	NOAEC = 369 µg.m^{-3}	3 UF_H = 3	**TRV = 123 µg.m^{-3}** **Confidence level Moderate**

As the acute TRV is the same as the chronic TRV, only compliance with this value, regardless of the duration of exposure, can guarantee a lack of effect.
The epidemiological data do not show a risk of nasopharyngeal cancer below average formaldehyde concentrations 10 times higher than the chronic TRV.

3.2.5.3. IAQGs proposed by the Air Committee

The Air Committee reiterates that:

- there are many indoor sources of formaldehyde since it is found in manufactured products. Formaldehyde is also formed by combustion (cooking, chimney fires, burning of incense, candles, cigarettes) and chemical reactions from other pollutants;
- formaldehyde is frequently measured in indoor air, primarily over periods of several days, to characterise long-term exposure. The formaldehyde concentration levels usually measured in indoor air are around a few dozen µg.m^{-3}: median at 19.6 µg.m^{-3} and 75th percentile at 28.3 µg.m^{-3} in the national "Housing" campaign of the Indoor air quality observatory (OQAI) conducted between 2003 and 2005. Higher concentration levels of about 200 µg.m^{-3} have been reported, in particular with tobacco smoke. Very few formaldehyde measurements over short periods stand out from the data in the scientific literature;

- exposure to formaldehyde in indoor air often occurs in tandem with exposure to other chemical substances, especially other aldehydes including acetaldehyde and acrolein which are also upper airway irritants. They may have combined or even potentiated effects. The Air Committee is currently contributing to ANSES's expert appraisal work aiming to establish IAQGs for a mixture of pollutants. Firstly, existing methods for health risk assessments of mixtures will be reviewed. This will be followed by the establishment and implementation of reference values for the proposal of IAQGs for a mixture of substances.

Based on the expert appraisal results, the Air Committee concluded that:

- regarding the updating of IAQGs for formaldehyde, a single IAQG for short-term exposure is proposed for the protection of the general population for acute and chronic effects.

  The reasons justifying this proposal are as follows. Eye irritation was chosen for the establishment of the acute and chronic TRVs. This effect is the first key event and is a precursor of more severe irreversible effects such as nasopharyngeal carcinogenic effects of formaldehyde. Considering the threshold mode of action for nasopharyngeal cancer, compliance with the acute value, characterised by a high confidence level, will protect against the occurrence of long-term effects. For this to happen, as underlined by the WHO in 2010, the proposed value should be complied with for repeated and continuous short-term exposure over a day.

  Given the TRVs of 123 $\mu g.m^{-3}$ and for consistency with the IAQG proposed by WHO in 2010 of 100 $\mu g.m^{-3}$, the Air Committee proposed a short-term IAQG of 100 $\mu g.m^{-3}$.

- regarding the methods for measuring formaldehyde in indoor air, they were assessed in view of sampling durations of 30 minutes, one hour and four hours considering a concentration range from 0.1 to 2 times the newly proposed IAQG[7]:
  - thirty minutes considering the duration of application of the WHO IAQG that is applied every 30 minutes for a day but with no particular justification;
  - one hour in order to be pragmatic and ensure some logic with regard to the sampling time usually adopted for short-term exposure in the context of investigations or campaigns in indoor environments;
  - four hours corresponding to the controlled exposure conditions in Lang *et al*. (2008) on which the proposed short-term IAQG is based.

  Of the nine identified methods for measuring formaldehyde in air (see Annex 2), three deal more specifically with indoor air measurement:
  - two of the three identified measurement methods for indoor air are recommended for comparison with the IAQG for formaldehyde of 100 $\mu g.m^{-3}$ for one to four hours of sampling (see Annex 2): active or passive sampling on a 2,4-DNPH-coated adsorbent tube, solvent desorption and analysis by liquid chromatography and UV detection. They have been classified in Category 1B, corresponding to the "partially validated method" classification. However, these methods are not recommended for 30 minute sampling due to limits of quantification above one-tenth of the short-term IAQG;
  - the third method is not recommended since no specific validation data for formaldehyde are available.

  It should be noted that this assessment of measurement methods applies only to short-term measurements whose results would be compared with the short-term IAQG of 100 $\mu g.m^{-3}$.

[7] For monitoring the short-term IAQG: 10 – 200 $\mu g.m^{-3}$ (0.1 to 2 x ST-IAQG).

In the past few years, several continuous-measurement, direct-reading devices have been developed. Some have been marketed. However, the technical characteristics and performance of these instruments remain insufficiently documented to date to enable an assessment of the related measurement methods.

- Recommendations

In light of this update, the Air Committee recommended a single IAQG of 100 µg.m^{-3} to be complied with for repeated and continuous short-term exposure over a day.

Critical effect (key study)	Critical concentration	UF	IAQG	Duration of application
Eye irritation (Lang *et al.*, 2008)	NOAEC = 369 µg.m^{-3}	3 UF_H = 3	**100 µg.m^{-3} (rounded value in keeping with the WHO IAQG (2010))**	**1 to 4 hours**

In addition, the Air Committee recommended:

- measuring formaldehyde in indoor air preferably with sampling times of one to four hours by active or passive sampling on a 2,4-DNPH-coated adsorbent tube followed by solvent desorption and analysis by liquid chromatography and UV detection;
- defining a sampling strategy capable of identifying formaldehyde exposure peaks in confined spaces given that sources of formaldehyde in indoor air can lead to variations in concentrations;
- documenting variations in formaldehyde concentrations including peaks and their determinants in confined spaces;
- experimentally validating, especially in terms of specificity, continuous-measurement and direct-reading instruments which are particularly useful for the identification of sources.

3.2.6. Reference values in the workplace adopted by the OEL and REACH Committees

3.2.6.1. Critical concentrations and uncertainty factors

3.2.6.1.1. Chronic exposure

A NOAEC of 369 µg.m^{-3} (0.3 ppm) for chronic effects, based on the formaldehyde exposure level of 369 µg.m^{-3} + 4 x 738 µg.m^{-3} (0.3 + 4 x 0.6 ppm) in the study by Lang *et al.* (2008), was selected.
As indicated above (see 3.1.9.), the data show that no particular susceptibility to formaldehyde was noted. In addition, the selected critical effect (sensory irritation) appears at lower concentrations than those producing cellular irritation. Considering the carcinogenic mode of action of formaldehyde, this cellular irritation is a precursor of events that can lead to the occurrence of nasopharyngeal cancer.
In view of this precursor effect, the low inter-individual variability and the concordance of the numerous studies on formaldehyde, it was not deemed necessary to apply an uncertainty factor.

As the duration of exposure in the key study was four hours, the relevance of applying a temporal adjustment to match the duration of a working day (eight hours) was discussed. However, as stated above, the irritation phenomena are concentration-dependent rather than time-dependent effects (Belkebir *et al.*, 2011). This is also confirmed by studies with longer exposure durations in which the effects are observed at comparable doses. A temporal adjustment was therefore not considered necessary.

3.2.6.1.2. Acute exposure

A NOAEC of 738 µg.m^{-3} (0.6 ppm) for acute effects, based on the formaldehyde exposure level of 369 µg.m^{-3} + 4 x 738 µg.m^{-3} (0.3 + 4 x 0.6 ppm), was selected for measurable eye irritation effects. The application of an uncertainty factor was discussed for this value considering the very likely inter-individual variability in eye irritation and especially ocular dryness. Nevertheless, in the workplace, this had already been taken into account by the many available studies on formaldehyde (total number of exposed subjects in the two key studies and the epidemiological studies). As no other uncertainty factor was deemed relevant, the decision was made not to apply an uncertainty factor.

3.2.6.2. OELs proposed by the OEL Committee

- 8h-OEL

The OEL Committee recommended an 8h-OEL of 369 µg.m^{-3} rounded to 350 µg.m^{-3}.

Critical effect (key study)	Critical concentration	UF	8h-OEL
Sensory irritation (Lang *et al.*, 2008)	NOAEC = 0.3 ppm (369 µg.m^{-3})	/	**8h-OEL = 350 µg.m^{-3} (rounded)**

- 15min-STEL

The OEL Committee recommended a 15min-STEL of 738 µg.m^{-3} rounded to 700 µg.m^{-3}.

Critical effect (key study)	Critical concentration	UF	15min-STEL
Eye irritation (Lang *et al.*, 2008)	NOAEC = 0.6 ppm (738 µg.m^{-3})	/	**15min-STEL = 700 µg.m^{-3} (rounded)**

- "Skin" notation

Due to the very high reactivity of formaldehyde at the contact site, penetration by the dermal route seems very low, and the contribution of this route to a possible systemic effect (not currently demonstrated for formaldehyde) seems negligible. The "skin" notation is therefore not selected for formaldehyde.

- "Noise" notation

None of the available studies suggest an ototoxic effect of formaldehyde. Accordingly, the "noise" notation is not assigned.

- Assessment of measurement methods for OELs

Of the nine identified methods for measuring formaldehyde in air, eight involve workplace atmospheres and were assessed in relation to the OELs (see Annex 2). The OEL Committee recommended, for monitoring the 8h-OEL, for regulatory technical control of the 15min-STEL or for monitoring short-term exposure, using the following two methods classified in Category 1B:

- the method, described in numerous protocols, which involves performing active sampling on a 2,4-DNPH-coated silica gel sampling tube, desorption in acetonitrile and then determination by liquid chromatography (UV/visible detector). In contrast, use of this method with a 2,4-DNPH-coated glass filter as the sampling medium is not recommended;
- the method that involves performing passive sampling on a 2,4-DNPH/H_3PO_4-coated badge, acetonitrile desorption, then determination by liquid chromatography (UV/visible detector). For implementation of this method for controlling the 15min-STEL, the OEL

Committee recommended using the ChemDisk or DSD-DNPH badges, or validating a lower limit of quantification for the UMEX 100 badge.

Note that these two methods are also those recommended for monitoring the short-term IAQG.

Of the six other methods:

- Five measurement methods were not recommended for monitoring the 8h-OEL and short-term exposure, or for the technical control of the 15min-STEL since their limits of quantification are too high, they do not have validation data, or they do not provide for individual measurements of formaldehyde in air.
- One method is classified in Category 2, i.e. considered as indicative, for monitoring the 8h-OEL and short-term exposure, but in Category 3 for regulatory technical control of the 15min-STEL and was therefore not recommended for that purpose.

3.2.6.3. Occupational DNELs proposed by the REACH Committee

- Long-term DNEL

The REACH Committee recommended a long-term DNEL of 369 µg.m^{-3}. This value protects against irritation symptoms in people exposed in the workplace but may not provide enough protection against subjective irritation symptoms related to the smell of formaldehyde as confirmed by the data of Lang *et al.* (2008) and Mueller *et al.* (2013).

Critical effect (key study)	Critical concentration	UF	Long-term DNEL
Sensory irritation (Lang *et al.*, 2008)	NOAEC = 0.3 ppm (369 µg.m^{-3})	/	**Long-term DNEL = 0.3 ppm (369 µg.m^{-3})**

- Short-term DNEL

The REACH Committee recommended a short-term DNEL of 738 µg.m^{-3}.

Critical effect (key study)	Critical concentration	UF	Short-term DNEL
Eye irritation (Lang *et al.*, 2008)	NOAEC = 0.6 ppm (738 µg.m^{-3})	/	**Short-term DNEL = 0.6 ppm (738 µg.m^{-3})**

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The French Agency for Food, Environmental and Occupational Health & Safety endorses the conclusions of the OEL, REACH, Substances and Air Committees on the revision of the reference values for formaldehyde. These values are presented in the summary table in Annex 3 of this Opinion.

Moreover, the Agency underlines the following points.

◆ **Regarding toxicity reference values (TRVs)**

In the event that a quantitative risk assessment is undertaken in relation to formaldehyde exposure, ANSES recommends paying special attention when analysing the representativeness of chronic exposure levels for this substance. In fact, exposure data generally correspond to average concentrations. In that case, their representativeness should be discussed and questions asked regarding formaldehyde emission sources, in order to assess the potential occurrence of exposure peaks. There are various possible configurations:

1. The sources of formaldehyde are clearly identified and result in continuous emissions: the comparison of average concentrations with the chronic TRV is appropriate;

2. The sources of formaldehyde are clearly identified and some can result in intermittent emissions that can generate varying concentrations over time and concentration peaks for example; the comparison of average concentrations with the chronic TRV should be discussed;
3. The sources of formaldehyde are not known: the comparison of average concentrations with the chronic TRV should be discussed related to this uncertainty in particular.

◆ **Regarding the indoor air quality guideline (IAQG)**

The updating of knowledge on the health effects of formaldehyde led ANSES to recommend a single short-term IAQG of 100 µg.m^{-3} to protect the general population from acute and chronic effects. This value should be complied with for repeated and continuous short-term exposure over a day.

ANSES insists on the need to develop suitable measurement methods for comparison with the single short-term IAQG of 100 µg.m^{-3} to be complied with for repeated and continuous short-term exposure over a day.

The current French regulations on the surveillance of indoor air quality in public-access buildings rely on regulatory IAQGs on the one hand and on a sampling strategy aiming to characterise long-term exposure with samples taken over several days, repeated in two different periods of the year, on the other hand[8]. These surveillance methods, especially the required sampling times, cannot be used to assess the variability of concentrations over time, in particular the existence of exposure peaks, and thus ensure compliance with the IAQG for formaldehyde set at 100 µg.m^{-3} with a duration of application of one to four hours.

Pending the possible definition of new surveillance methods in light of the proposal of a single short-term IAQG, a pragmatic option could be considered to interpret measurement results for concentrations obtained over several days with the aim of characterising long-term exposure as currently recommended in the regulations. For this to happen, the authorities could apply an additional safety factor to the single short-term IAQG. This would enable a comparison with measurements obtained over several days by reducing the risk of the single IAQG of 100 µg.m^{-3} being exceeded over short periods (concentration peaks).

◆ **Regarding occupational exposure limits (OELs)**

ANSES reiterates that at European level, formaldehyde is classified as a Category 1B carcinogenic compound, presumed to have carcinogenic potential for humans (ATP 06 - Regulation (EC) No 1272/2008). In this respect, the substitution of carcinogenic substances by less harmful substances or processes is a priority for chemical risk prevention in the workplace that applies to formaldehyde. When substitution is impossible, exposure should be reduced to a level as low as technically possible.

On 9 October 2014, ANSES received a formal request to assess the benefits of formaldehyde substitutes in various sectors: pathological anatomy and cytology, embalming, and the production and use of food products in animal and human nutrition. Moreover, on 8 February 2016, ANSES, *via* the French Agency for Veterinary Medicinal Products (ANMV), issued an internal request to include the use of formaldehyde in fish farming activities in the scope of the request. The expert appraisal, consisting in comparing alternatives with one another and with formaldehyde, was entrusted to the Working Group on Formaldehyde and substitutes. These studies should be completed in 2018.

[8] French Decree No 2012-14 of 5 January 2012 on the assessment of aeration methods and the measurement of pollutants undertaken for the surveillance of indoor air quality in certain establishments open to the public

Furthermore, on ANSES's www.substitution-cmr.fr website, a few companies have accepted to share information on the substitution processes they have put in place: 11 examples[9] are given of substitution for formaldehyde.

Dr Roger Genet

KEYWORDS

Valeur toxicologique de référence, valeur guide de qualité d'air intérieur, valeur limite d'exposition professionnelle, formaldéhyde, inhalation, irritation, cancer, métrologie, méthodes de mesure, lieux de travail, air intérieur

Toxicity reference value, air quality guideline, occupational exposure limit value, formaldehyde, inhalation, irritation, cancer, metrology, measurement methods, workplaces, indoor air

[9] ANSES does not undertake risk assessments for the substitutes identified on this website. These substitution examples must not be understood as direct models of substitution by the substances mentioned but only as an incentive to undertake a substitution process.

ANNEX 1

Analysis matrix of the results of the studies by Lang *et al.* (2008) and Mueller *et al.* (2013)

Study	Conc. ($\mu g.m^{-3}$)	Number of subjects	Ocular effects								Nasal effects										Respiratory effects				Discomfort					
			Conjunctival redness		Eye irritation		Blinking frequency		Tear film breakup time		Nasal irritation		Nasal lavage markers	Nasal airflow measurement		Nasal airflow resistance	Olfactory sympt.		SPES questionnaire - olfactory sympt.		Respiratory sympt.		Pulmonary function	Metha-choline test	Discomfort		SPES questionnaire - complaints		SPES questionnaire - "perception of impure air"	
			Objective		Subjective		Objective		Subjective		Subjective		Objective	Objective		Objective	Subjective		Subjective		Subjective		Objective	Objective	Subjective		Subjective		Subjective	
			- EA	+ EA	- EA	+ EA	- EA	+ EA	hypo	hyper	- EA	+ EA		hypo	hyper		- EA	+ EA	hypo	hyper	- EA	+ EA			- EA	+ EA	hypo	hyper	hypo	hyper
Lang et al. 2008	0	21																												
Lang et al. 2008	185	21																												
Lang et al. 2008	369	21			*												*				*	*				**				
Mueller et al., 2012	369 + 738	41					hypo	hyper	*					*													*			
Lang et al. 2008	369 + 738	21			*												*								**					
Mueller et al., 2012	492 + 984	41					hypo	hyper												*								***		
Krakowiak et al., 1998	492	10E + 10C									*		*																	
Pazdrack et al., 1993	492	20											*																	
Lang et al. 2008	615 + 1230	21	*		**	**	*	*			**	**					**	**			*	**			**	**				
Lang et al. 2008	615	21			*												*					**			*					
Kulle et al., 1987	615	19			*												*													
Mueller et al., 2012	615	41					hypo	hyper																						
Mueller et al., 2012	861	41					hypo	hyper	*																					
Kulle et al., 1987	1230	19			**												**													
Kulle et al., 1987	2460	19			**												**													
Kulle et al., 1987	3690	19			**											*	**													

	No data
	No significance
*	Low significance (significant with p between 0.05 and 0.01)
**	High significance (significant with p below 0.01)

** EA: ethyl acetate; hypo/hyper: populations with hypo- or hypersensitivity to the CO_2 test.*

ANNEX 2

Classification of methods for measuring formaldehyde in indoor air and workplace atmospheres for comparison with the ST-IAQG and the OELs

No.	Method	Protocol		OELs			ST-IAQG		
	Medium	Workplace atmospheres	Indoor air	8h-OEL	15min-STEL	Short-term exposure	30 mins of exposure	1 hr of exposure	4 hr of exposure
1	Active sampling on a DNPH-coated silica gel in a sampling tube – Determination by HPLC/UV/visible detector	INRS M-4 (2011), INSHT-MTA/MA-062/A08 (2008), DFG Aldehyde Method 2 (1995), NIOSH 2016 (2003), Standard NF X 43-264 (2011), HSE MDHS 102 (2010), DFG Aldehyde Method 1 (1989), BGIA 6045 (2007), BGIA 7520 (2007)	NF ISO 16000-3 (2011) US EPA IP-6A (1990) US EPA 0100/8315A (1996) US EPA TO11A (1999)	1B			2	1B	1B
	Active sampling on a DNPH-coated filter – Determination by HPLC/UV/visible detection	DFG–Aldehyde Method 1 HSE MDHS 102 BGIA 7520	/	2	3	2	/		
2	Active sampling on XAD-2 adsorbent resin coated with 2-HMP – Determination by GC/FID-NDP or MS	NIOSH 2541 (1994) OSHA 52 (1989) IRSST 295-1	/	2	3	2	/		
3	Active sampling in a lithium hydroxide solution – Determination by differential pulse polarography (Hg electrode)	DFG Method 3 (1989)	/	*3 (* - method cannot be evaluated, classified in Category 3 due to the absence of validation data)*			/		
4	Active sampling on a filter + sodium bisulphite solution sampler – Determination by spectrophotometry	NIOSH 3500.2 (1994) INSHT- MTA/MA-018/A89 (1989)	/	3			/		
5	Active sampling on a filter – Determination by HPLC/UV	NIOSH 5700 – Dust (1994)	/	3			/		
6	Active sampling on silica gel	DFG – Formaldehyde – Method 2 (1977)	/	3 (*)			/		
7	Passive sampling on a sodium bisulphite-impregnated badge – Determination by spectrophotometry	OSHA ID 205 (1990)	/	3			/		
8	Passive sampling on a DNPH/H3PO4-coated badge (DSD – DNPH, UMEX 100, ChemDisk, Radiello 165) – Determination by HPLC/UV or HPLC/DAD	OSHA 1007 (2005) IRSST 357-1	NF ISO 16000-4 (2012) OSHA 1007 US EPA IP-6C (1990) – Indoor Air	1B (Classification of this method in Category 1B for technical control of the 15min-STEL is only valid when using the ChemDisk or DSD-DNPH badge)			3	1B	1B
							3 if use of ChemDisk, Umex 100 or Radiello 165 badges		
9	Bubbling in water, determination by DNPH and detection by spectrophotometry or HPLC/UV	/	US EPA – TO-5 (1984) – Ambient Air *abandoned for TO-11A*	/			3 (*)		

ANNEX 3

Summary of the reference values established by ANSES

	Type of value	Critical effect (key study)	Critical concentration	UF	Value	Duration of application	Additional observations and/or recommendations	Comments
OELs	8h-OEL	Eye irritation (Lang *et al.*, 2008)	NOAEC = 369 µg.m^{-3}	/	350 µg.m^{-3} (rounded value)	8 hours	Recommended measurement methods (Category 1) Active sampling on a DNPH-coated silica gel in a sampling tube – Determination by liquid chromatography using a UV/visible detector or Passive sampling on a DNPH/H_3PO_4-coated badge – Determination by liquid chromatography using a UV/visible detector**	
	15min-STEL		NOAEC = 738 µg.m^{-3}		700 µg.m^{-3} (rounded value)	15 min		
Occupational DNELs*	Long-term DNEL		NOAEC = 369 µg.m^{-3}		0.3 ppm			
	Short-term DNEL		NOAEC = 738 µg.m^{-3}		0.6 ppm			
TRVs	Chronic TRV		NOAEC = 369 µg.m^{-3}	3 UF_H= 3	Acute TRV = chronic TRV: 123 µg.m^{-3}		Pay special attention to the characterisation of chronic exposure to formaldehyde especially for assessing exposure peaks	Confidence level: Moderate
	Acute TRV							Confidence level: High
IAQG					100 µg.m^{-3} (rounded value)	1 to 4 hours	Recommended measurement methods (Category 1) Active sampling on a DNPH-coated silica gel in a sampling tube – Determination by liquid chromatography using a UV/visible detector or Passive sampling on a DNPH/H3PO4-coated badge (DSD-DNPH cartridge) – Determination by liquid chromatography using a UV/visible detector	To be complied with for repeated and continuous short-term exposure over a day.

* The DNELs expressed in ppm correspond to the same values as those of the OELs expressed in µg.m^{-3}.
** This method is recommended for technical control of the 15min-STEL only when using the ChemDisk or DSD-DNPH badge.

COLLECTIVE EXPERT APPRAISAL: SUMMARY AND CONCLUSIONS

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

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

Formaldehyde (CAS No. 50-00-0)

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 group on metrology.

Presentation of the issue

On 12 June 2007, AFSSET, which became ANSES on 1 July 2010, was formally asked by the Directorate General for Labour to conduct the expert appraisal work required for setting occupational exposure limit values (OELVs) for around 20 substances, including formaldehyde. In its collective expert appraisal report of 2008, the Agency therefore recommended for formaldehyde:

- setting an 8-hour occupational exposure limit (TWA) of 0.2 ppm (i.e. 0.25 mg.m^{-3}) to prevent possible irritant effects on the respiratory tract, which are precursor events in the threshold mechanism considered for the development of nasopharyngeal cancer associated with this substance;
- setting a 15-minute short-term exposure limit (STEL) of 0.4 ppm (i.e. 0.5 mg.m^{-3}) to limit peaks of exposure and prevent possible eye irritation effects (the most sensitive effect in terms of irritation for formaldehyde);
- not assigning a “skin" notation.

It was also concluded that there are validated measurement methods suitable for assessing occupational exposure. These methods can be used not only to measure the 8-hour exposure limit value of 0.2 ppm (0.25 mg.m^{-3}) but also the 15-min STEL of 0.4 ppm (0.5 mg.m^{-3}).

From November 2015 to February 2016, the SCOEL[1] held a public consultation on its recommendations for new occupational exposure limit values for formaldehyde, which it ultimately adopted on 30 June 2016[2].

1 Scientific Committee on Occupational Exposure Limits

2 SCOEL/REC/125 Formaldehyde. Recommendation from the Scientific Committee on Occupational Exposure Limits, 30 June 2016

As the OEL Committee experts are also mandated to take position on the recommendations issued by the SCOEL during the public consultation phase, the analysis of the European document led ANSES to update its collective expert appraisal report of 2008.

France currently has an indicative 8-hour time-weighted average (TWA) exposure value for formaldehyde of 0.5 ppm and an indicative short-term exposure limit of 1 ppm. They were set in a Ministry of Labour Circular of 12 July 1993 (not published in the Official Journal)[3].

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 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

[3] DRT Circular no. 93-18 of 12 July 1993 amending and supplementing the annex to the Circular of 19 July 1982 on the acceptable values for concentrations of certain hazardous substances in workplace atmospheres

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 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, 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 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 OEL 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”.

Prevention of 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).

Methodology

For the assessment of health effects:

A summary report on the health effects was prepared by the working group on health effects and submitted to the OEL Committee, which commented on it and added to it.

The summary report is essentially based on two AFSSET collective expert appraisal reports: "Expert appraisal for setting exposure limits for chemical agents in occupational environments. Assessment of the health effects and methods for measuring occupational exposure levels for formaldehyde" published in 2008, and "Toxicity of formaldehyde. State of knowledge on the characterisation of hazards and selection of toxicity reference values", also published in 2008. The data have been updated, mainly on the basis of the opinion of ECHA's Risk Assessment Committee (RAC) published in 2012 and France's proposal for a harmonised classification, which led to the RAC's document, as well as the IARC report, also published in 2012, for all the carcinogenicity and genotoxicity aspects. The SCOEL document "SCOEL/REC/125 Formaldehyde Recommendation from the Scientific Committee on Occupational Exposure Limits", published in 2016, was also used to prepare this report. The data and information were supplemented by a literature review on Medline and Toxline, which mainly took place between 2008 (date of publication of the AFSSET reports) and 2016.

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 formaldehyde in workplace atmospheres, grouped together according to the methods they use. These methods were then assessed and classified based on the performance requirements set out 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 13 March 2017 by the OEL Committee. They were submitted to public consultation from the 05/08/2017 to 30/09/2017. The people or organizations who contributed to the public consultation are listed in an appendix of the report (available only in French). Comments received were reviewed by term of office by the Committee on Health Reference Values (2017-2020) who finally adopted this version on 17/10/2017.

Results of the collective expert appraisal on the health effects

Toxicokinetics

Formaldehyde is an endogenously compound formed naturally by the organism by catabolism of glycine and serine (amino acids). It is then used for the synthesis of purine bases (BfR, 2006).

Absorption

Whether in animal or human studies and regardless of the route of exposure, the retention of formaldehyde seems to be limited to the site of first contact in the body, due to its reactivity with biological macromolecules, which limits its systemic exposure (ATSDR, 1999).

Distribution/Metabolism

After inhalation of carbon-14 radiolabelled formaldehyde by rats, the radioactivity is located primarily in the oesophagus and the trachea, and to a lesser extent in the kidneys, the liver, the intestines and the lungs (Heck *et al.*, 1983).

In reality, it is the metabolites and reaction products of formaldehyde that are distributed in the body (INRS 2006). Indeed, at the contact sites, formaldehyde is rapidly metabolised into formate and then carbon dioxide (CO_2) by several water-soluble cellular enzymes, the most important being NAD+-dependent formaldehyde dehydrogenase (FDH). Formaldehyde reacts rapidly with glutathione (GSH) to initially form hydroxymethylglutathione ($GS\text{-}CH_2OH$), which is subsequently oxidised in the presence of FDH into S-formylglutathione (G-S-CHO). The hydrolysis of this compound releases glutathione and a formate ion (HCOO-), which is either eliminated in the urine, or oxidised into CO_2 and eliminated primarily in the lungs or incorporated in the C1 compound pool via the tetrahydrofolate (THF) dependent pathway (ATSDR 1999, BfR 2006). This mechanism is saturable: the sharp increase in carcinogenicity observed in rats at formaldehyde concentrations above 6 ppm can be interpreted as being due to saturation of FDH or depletion of GSH (BfR, 2006). Other similar enzymes (other aldehyde dehydrogenases) with a strong affinity with free formaldehyde can contribute to its metabolism at a higher concentration. When it is not metabolised, because of its high reactivity with the functional groups of the molecules, formaldehyde may bind covalently with the nucleophilic sites of proteins, small- and medium-sized molecules, and DNA (ATSDR 1999, Nordic Council of Ministers, 2003).

Excretion

Rats were exposed by inhalation to 0.63 and 13.1 ppm for 6 hours: the percentages of total radioactivity found in the urine were 17.6% and 17.3% respectively, and in the faeces were 4.2 and 5.3%. Expired air is therefore the primary route of elimination, with respectively 39.4% and 41.9% of formaldehyde eliminated in the form of carbon dioxide. Lastly, the quantity of ^{14}C remaining in the carcass after 70 hours was respectively 39.9% and 35.2% of the total radioactivity (Heck *et al.*, 1983).

The average concentrations of urinary formic acid in a non-occupationally exposed population are around 12 mg/L and are extremely variable from one individual to another (Nordic Council of Ministers, 2003).

Toxicity data

Acute toxicity

Concerning acute exposure, no deaths have been observed in humans following inhalation or dermal exposure. While serious effects can be observed above 10 ppm (respiratory difficulties, oedema, lung congestion, etc.), most of the effects observed at lower doses are irritant type effects (INRS, 2006).

Irritation

Data in humans

There are many available studies in humans (case-control and controlled exposure studies) on the irritant potential of formaldehyde.

Some studies have also investigated sensory irritation. This is defined as a chemosensory effect, i.e. an interaction between the chemical substance and the sensory nerve endings of the trigeminal nerve. It is an extremely rapid process, occurring in the space of a few milliseconds between stimulation and reaction. With regard to dose-response relationships in humans and animals, this sensory irritation occurs at lower levels than irritation itself inducing tissue damage. At very low concentrations, therefore, the acute effects such as discomfort or itching, burning or stinging sensations are unpleasant but completely reversible. It now seems, however, that prolonged nerve stimulation can lead to a cascade response leading to chronic adverse effects. In particular, neurogenic inflammation seems to play an important role: it reflects the transition from reversible, purely sensory effects to more general effects and inflammatory defence mechanisms, such as those observed in irritation itself or tissue irritation. For example, when the sensation of pain is felt, the nervous system will secrete chemical mediators such as substance P, which will stimulate the cells of the immune system. At a certain level of response, tissue irritation and sensory irritation can therefore become indistinguishable from one another. As sensory irritation can therefore be a precondition for tissue irritation, Brüning *et al.* (2014) suggest, in their review of the literature on the subject, considering the first observed sensory irritation effects as a NOAEL (Brüning *et al.*, 2014).

In general, to examine these tissue and sensory irritations, controlled exposure studies on volunteers were preferred, since they are considered more reliable than epidemiological studies, primarily because exposure data are better controlled. Observations from controlled clinical studies in different categories of individuals (workers, healthy or asthmatic volunteers) confirm the irritant nature of formaldehyde. In the available studies, which are numerous but of unequal quality, with varied exposure patterns, the authors provide points of departure for the irritation in humans (Table 1).

Table 1 : Benchmark doses from the literature for the irritant effects in humans

References	Critical effect	Dose	Point of departure
(Arts *et al.*, 2006)	**Sensory irritation**	0.24 ppm	BMDL[4]
(Bender, 2002)		1 ppm	LOAEL[5]
(Paustenbach *et al.*, 1997)	**Eye irritation**	<0.3 ppm 0.3 ppm	LOEL[6] NOAEL[7]
(Arts *et al.*, 2006)		0.56 ppm	BMDL
(Lang *et al.*, 2008)	**Sensory irritation**	0.3 ppm + 0.6 ppm and 0.5 ppm peaks 0.5 ppm + 1 ppm peaks	NOAEL LOEL
(Mueller *et al.*, 2013)		0.4 ppm + 0.8 ppm peaks 0.7 ppm	NOAEL

An expert panel, the "Industrial Health Foundation (IHF) panel" carried out a meta-analysis of 150 scientific articles with the aim of establishing an OEL based on irritation. The experts concluded that the most sensitive deleterious effect is eye irritation. For most people, this effect is indeed observed at lower concentrations than nasal or throat irritation (Paustenbach *et al.*, 1997).

Two recent studies in particular stand out: Lang *et al.* (2008) and Mueller *et al.* (2013). The authors set up "objective" tests to measure sensory irritation, such as eye blinking frequency, nasal airflow and resistance, etc. This helped overcome any distorted perception of irritation, due for example to the strong smell of formaldehyde. In addition, under certain exposure conditions, these studies incorporated peaks, making them correspond more closely to actual conditions of occupational exposure.

The study by Lang *et al.* (2008) was conducted with 21 volunteers (11 men and 10 women). Ten different exposure conditions were put in place. Exposure lasted 4 hours and included or excluded peaks lasting 15 min:

- 0 ppm;
- 0.15 ppm;
- 0.3 ppm;
- 0.3 + 4 x 0.6 ppm;
- 0.5 ppm;
- 0.5 + 4 x 1 ppm;
- 0 ppm + masking agent;
- 0.3 ppm + masking agent;
- 0.5 ppm + masking agent;
- 0.5 + 4 x 1 ppm + masking agent.

All the subjects were exposed to each of the exposure conditions.

[4] BMDL: generally corresponds to the lower limit of the 95% confidence interval of the dose (BMD) associated with a 10% response rate ($BMD_{10\%}L_{95\%}$).

[5] LOAEL: Lowest Observed Adverse Effect Level

[6] LOEL: Lowest Observed Effect Level

[7] NOAEL: No Observed Adverse Effect Level

The study by Mueller *et al.* (2013) was conducted with 41 male volunteers. Five different exposure conditions were put in place. Exposure lasted 4 hours and included or excluded peaks lasting 15 min:

- 0 ppm;
- 0.3 + 4 x 0.6 ppm;
- 0.4 + 4 x 0.8 ppm;
- 0.5 ppm;
- 0.7 ppm.

All the subjects were exposed to each of the 5 exposure conditions for 5 consecutive days. It should be noted that this study divided the volunteers into "hypersensitive" and "hyposensitive" groups, using a test of sensitivity to CO_2. This enabled the authors to analyse the results on the basis of each volunteer's sensitivity to chemicals.

In the study by Lang *et al.* (2008), the first statistically significant objective effects (eye redness and eye blinking frequency, namely eye irritation) appeared with the exposure condition 0.5 ppm + 4 x 1 ppm. The NOAEL is therefore the exposure condition 0.3 + 4 x 0.6 ppm. Concerning the study by Mueller *et al.* (2013), the authors consider that they did not see any adverse effects (no significant difference was observed for eye redness and eye blinking frequency in comparison with control group) and that the NOAEL was therefore 0.4 ppm + 4 x 0.8 ppm.

Experimental data

Sensory irritation has been examined in animals in many studies, through an analysis of the decrease in respiratory rate.

Rats and mice were exposed for 4 days, 6h/d, to 2, 6 or 15 ppm of formaldehyde. The RD_{50} concentrations were 4.9 ppm for mice and 31.7 ppm for rats. Another study showed that at the RD_{50} (established at 3.1 ppm by the authors), mice exposed for 5 days, 6h/d had moderate histopathological lesions in the anterior part of the nasal cavity (Buckley *et al.*, 1984).

All the available studies have shown that mice are more sensitive than rats to the effects of formaldehyde (IARC, 2006).

Sensitisation

Data in humans

Some data show that formaldehyde can cause respiratory effects from 3 $mg.m^{-3}$ in certain highly sensitive subjects with respiratory hyper-responsiveness (BfR 2006; DECOS, 2003; NICNAS, 2006). A study of sensitisation by formaldehyde, conducted with12 asthmatic subjects also allergic to pollen and exposed to formaldehyde, was unable to corroborate these findings. In this study, exposure to 500 $\mu g.m^{-3}$ of formaldehyde did not significantly aggravate the allergic response of the asthmatic subjects, with a trend in the opposite direction even being observed (Ezratty, 2007).

Several recent reviews of the literature relating specifically to indoor air or the occupational environment all concluded that an immune-mediated respiratory reactions caused by formaldehyde was highly uncertain, in particular at low concentrations (MAK, 2014, Golden, 2011, Schram-Bijkerk *et al.*, 2013).

Experimental data

A study by Lee *et al.* (1984) in guinea pigs assessed skin (measurement of antibodies) and respiratory sensitisations after exposure to 7.2 $mg.m^{-3}$ for 6 hours or 12 $mg.m^{-3}$ for 8 hours over 5 consecutive days. The authors did not observe any sensitisation phenomena in the lungs.

Chronic toxicity

Data in humans

Neurological disorders (memory loss, concentration disorders) have been described in several studies where the presence of formaldehyde was concomitant with that of other neurotoxic solvents. There seems to be a correlation between exposure to formaldehyde and a decrease in performance assessed by a battery of tests combining dexterity, memory and coordination (Kilburn *et al.*, 1985; Kilburn, 1994). Despite these results, it can be considered that not enough research has been conducted on the effects of formaldehyde on the central nervous system and on the cognitive behaviour of exposed individuals, and that the few publications available do not enable any conclusions to be drawn as to the proven effects of occupational exposure (INVS, 2007).

Experimental data

In rodents, for 90-day exposure periods, histopathological changes have been observed in the nasal cavity, larynx, trachea and bronchi (rhinitis, metaplasia and hyperplasia of the respiratory epithelium, inflammation) for concentrations above 2.4 $mg.m^{-3}$. The NOAELs are usually between 1.2 and 2.4 $mg.m^{-3}$. However, a LOAEL of 0.36 $mg.m^{-3}$ for the same type of effects was reported in a 2-year study in male rats and was attributed to exposure to formaldehyde (effect not statistically significant compared to the control but dose-response relationship clearly established) (Kamata *et al.*, 1997). Other literature summaries reported irritation of the upper airways (NICNAS, 2006). During the course of a study in mice, immunological functions involving the B and T lymphocytes were not impaired after 3 weeks of exposure (Dean *et al.*, 1984).

Genotoxicity

The available data on the genotoxicity of formaldehyde were recently analysed by ECHA's RAC (ECHA, 2012).

Regarding the data on local genotoxicity in humans, the results of different studies appear contradictory, and ECHA considered that it was not possible to use them to assess the mutagenic potential of formaldehyde. Concerning genotoxicity at distant sites, the results of the available studies are also contradictory. ECHA recalls in its report that, from a purely biological point of view, systemic effects are not expected since exposure to formaldehyde does not increase blood levels of formaldehyde. In conclusion, there is insufficient evidence to confirm whether formaldehyde induces systemic genotoxicity in humans. Lastly, no studies are available concerning the genotoxic effects of formaldehyde on germ cells.

Regarding experimental data, the available studies show that formaldehyde induces mutagenic and genotoxic effects on cells that are directly exposed. It can therefore be considered as a mutagen *in vitro* with a clastogenic mode of action (Speit *et al.*, 2011). *In vivo*, formaldehyde is genotoxic in somatic cells at the site of contact. In particular, DNA-protein cross-links were induced in the nasal mucosa of rats and in the nasal turbinates of monkeys exposed by inhalation. However, the *in vivo* studies did not show any genotoxic potential of formaldehyde in somatic cells at distant sites. As mentioned previously, ECHA considers it very unlikely that formaldehyde is available in the gonads after inhalation. The few studies available on germ cells suffer from methodological biases and could not be used.

Carcinogenicity

Data in humans

Many studies have investigated the relationship between exposure to formaldehyde in humans and the incidence of cancer (cohort studies, case-control studies and meta-analyses).

- Nasopharyngeal cancer

The most informative cohort study (in terms of size and follow-up) is one of 25,619 industry workers exposed to formaldehyde in the United States, conducted by the NCI (Hauptmann *et al.*, 2004). The average duration of follow-up in this study is 35 years. The median ages when entering and leaving the study were 26 and 64 years, respectively. Among the workers in this cohort, 17.5% had never worked in jobs involving exposure to formaldehyde, 4.7% had always been employed in jobs involving exposure to formaldehyde of an intensity of 2 ppm or higher, and 22.6% had always been employed in jobs involving formaldehyde exposure peaks of 4 ppm or more.

The relative risk of nasopharyngeal cancer is increased two-fold with evidence in favour of a dose-response relationship for both the exposure peaks and for cumulative exposure. These results are confirmed when comparing nasopharyngeal cancer with the local mortality rates, to take regional environmental factors into account.

The IARC considered that not all the positive results highlighted for nasopharyngeal cancer (mainly in the NCI study) could be explained by bias or confounding factors. Thus, the results of this study were deemed conclusive and are borne out by those of many other positive studies (case-control and cohort), providing sufficient epidemiological evidence to assert that formaldehyde causes nasopharyngeal cancer in humans (IARC, 2012). In its opinion on the classification of formaldehyde, the RAC confirms that a positive association between exposure to formaldehyde and the frequency of nasopharyngeal cancer was observed in a cohort study, for which a causal relationship seems plausible. However, the RAC specifies that some uncertainties persist, and that bias or confounding factors cannot be ruled out with sufficient confidence. The additional evidence comes from case-control studies (ECHA, 2012).

- Leukaemia

In humans, the IARC considered that there was sufficient evidence that formaldehyde causes leukaemia, in particular the myeloid type. It pointed to the fact that in two of the three largest industrial cohort studies (NCI and NIOSH), a positive association for leukaemia was observed, in particular myeloid leukaemia. Despite the positive association observed by the authors in the NCI cohort (Hauptmann *et al.*, 2004), the RAC underlined the absence of any association demonstrated by a re-analysis or updating of the data for this cohort. The RAC also indicated that the meta-analyses carried out all concluded as to a lack of association between exposure to formaldehyde and the emergence of leukaemia in the industrial cohorts (ECHA, 2012). Since the assessments by the RAC and the IARC, three publications have studied the link between formaldehyde and leukaemia. One of them found no excess mortality among exposed workers (Pira *et al.*, 2014), and the other two mentioned limited evidence (Meyers *et al.*, 2013), or doubts about the causal link (Checkoway *et al.*, 2015).

In humans, concerning systemic carcinogenicity and increased incidence of leukaemia, the available studies show conflicting results. Furthermore, when an association is shown, it is at high concentrations.

- Other cancers

Paget-Bailly *et al.* (2012) conducted a systematic review and then a meta-analysis on 99 publications: 30 case-control studies, 65 cohort studies and four record-linkage studies. The purpose was to review occupational exposure to a number of substances and cancer of the larynx. No association was found between exposure to formaldehyde and cancer of the larynx.

Experimental data

In studies in rats, formaldehyde causes nasal tumours in both sexes at concentrations greater than 2 ppm. The dominant type of tumour is the squamous cell carcinoma, whose incidence increases from 5.6 ppm. Adenocarcinomas, rhabdomyosarcomas and squamous cell papillomas can also be observed in these studies.

At 2 ppm, malignant tumours in the nasal tissues are generally not observed, but the study by Kerns *et al.* (1983) showed an increase in benign tumours. An increase in signs of inflammation and regenerative proliferation phenomena in the nasal cavity were also observed.

The only available study in mice (Kerns *et al.*, 1983) is questionable from a qualitative point of view. Nevertheless, from 5.6 ppm inflammation of the nasal mucosa, squamous metaplasia and epithelial dysplasia could be observed, which do not seem to be reversible (ECHA, 2012).

The study conducted in hamsters did not show any significant effect (ECHA, 2012).

The RAC concludes that formaldehyde via inhalation is carcinogenic in rats, and that evidence of carcinogenicity has been observed in mice (ECHA, 2012). The IARC concluded that the evidence in animals is sufficient (Group 1) regarding the carcinogenicity of formaldehyde (IARC, 2012).

Reproductive and developmental toxicity

The NIH conducted a systematic review of the data on reproduction and development for formaldehyde as well as a meta-analysis (Duong *et al.*, 2011).

Data in humans

The results of the NIH's meta-analysis (which are also consistent with those of the meta-analysis by Collins *et al.*, 2001) show that maternal exposure to formaldehyde is associated with a risk of spontaneous abortion and effects on reproduction. The authors themselves specify that confounding factors (co-exposure with other compounds that can induce effects on reproduction in the studies, and non-adjusted relative risks - RRs) and "differential recall" may be behind the overestimation of these RRs. However, the authors do not consider they are able to assess them (Duong *et al.*, 2011).

Experimental data

In animals, two studies, of 13 and 52 weeks, in Wistar rats (Woutersen *et al.*, 1987, Appelman *et al.*, 1988) showed no morphological changes to the testicles or ovaries linked to exposure to formaldehyde. However, ovarian lesions have been observed in mice exposed for 13 weeks to 50 $mg.m^{-3}$. According to the authors, however, this may be a consequence of a general weakening of the mice (without any more precise explanations) (Maronpot *et al.*, 1986).

The IARC attributed the effects observed in pregnant females and on embryofoetal development to maternal toxicity: they have not been clearly observed at doses that are not toxic for the mother (IARC 2006). For its part, following its systematic review, the NIH considered that the data from the animal studies showed a strong association between the effects on reproduction and development and exposure to formaldehyde (Duong *et al.*, 2011).

Mechanism of action

Formaldehyde is a highly electrophilic compound (a property linked to the carbonyl group). It can thus react with the amine, thiol and hydroxyl groups of the body's macromolecules (nucleophilic sites of proteins, small- and medium-sized molecules – cysteine, glutathione – and DNA).

The genotoxic mechanism of formaldehyde is not yet completely elucidated. It forms DNA and DNA-protein adducts in the cells with which it is in contact, a response that seems to be concentration-dependent and non-linear. The incomplete repair of these adducts can then lead to mutations (Barker *et al.*, 2005) or clastogenic effects (Anses, 2011).

The currently accepted hypothesis within the scientific community is an increase in the regenerative proliferation of epithelial cells of the nasal mucosa resulting from cytotoxicity, a key step in the induction of cancer by formaldehyde (DECOS, 2003; IARC, 2006; McGregor *et al.*, 2006). This proliferation induces an increase in the number of DNA replications and thus an increased probability of formation of DNA and DNA-protein adducts. This chain reaction leads to more frequent replication errors, then to mutations. Point mutations at the GC base pairs of several codons (including codon 271) of the conserved region of the *p53* gene of nasal tumours in rats have been shown (Health Canada, 2001). The CpG dinucleotide of the p53 codon 273 (codon 271 in the rat) is a point of high mutation frequency in many human cancers. This hypothesis was confirmed by the identification of local genotoxicity *in vitro* and *in vivo* only at the higher doses causing cytotoxicity.

At high doses, formaldehyde also inhibits the mucociliary clearance function. Thus, the development of nasopharyngeal cancer may be linked to a repeated and prolonged deterioration of the nasal epithelium, and therefore to sufficiently high and prolonged exposures first causing irritation.

From the experimental and epidemiological data, it can be concluded that the mode of action of formaldehyde as a local carcinogen in rodents and humans is similar, although the target tissue is not exactly the same. The exact site of the tumour depends on the place where the substance is deposited, which is determined by the air flow.

Thus, in the current state of knowledge, formaldehyde can therefore be considered as a genotoxic carcinogen with a threshold effect for nasopharyngeal cancer.

Concerning the systemic toxicity of formaldehyde, this is unlikely, due to its low absorption. Moreover, there are few studies available that assess these aspects.

Establishment of OELs

8h-OEL

The objective of the 8h-OEL is to protect workers from nasopharyngeal cancer, the chronic effect regarded as the most sensitive. The association between exposure to formaldehyde and leukaemia in humans when observed occurs at higher concentrations that those associated with certainty to nasopharyngeal cancer. The causal link between this cancer and irritation of the respiratory tract is well established. Two distinct properties of formaldehyde contribute to the occurrence of this cancer: on the one hand, because of its irritant property, it induces cytotoxicity, which leads to histological changes to the epithelium and greater cell renewal. On the other hand, formaldehyde is a genotoxic compound recently evaluated by ECHA, and classified in category 2. Greater cell renewal allows the expression of the genotoxic potential of formaldehyde, leading in a higher probability of malignant cell proliferation. Thus, by avoiding this irritation (in particular the sensory irritation, which occurs earlier than the tissue irritation) and therefore this cytotoxicity, it is estimated that the probability of occurrence of a nasopharyngeal cancer is negligible. However, sensory irritation is generally studied through questionnaires, which include a large degree of subjectivity in the answers, and therefore uncertainty in the results. As mentioned previously, in the studies by Lang *et al.* (2008) and Mueller *et al.* (2013), the authors set up "objective" tests to

measure sensory irritation, such as eye blinking frequency, nasal airflow and resistance, etc. Overall, these studies are also consistent with the epidemiological data.

These studies therefore seem to be the most robust for establishing an OEL. Because Mueller *et al.* (2013) conducted their study only on male volunteers, the decision was taken to select the study by Lang *et al.* as the key study for establishing the 8h-OEL.

A NOAEL of 0.3 ppm for the chronic effects, based on the exposure condition 0.3 + 4 x 0.6 ppm, was therefore chosen for the sensory irritation effects.

At the critical dose proposed above, no particular sensitivity to formaldehyde was shown by the study of asthmatic populations (Krakowiak *et al.*, 1998). In addition, the critical effect selected (sensory irritation) appears at lower doses than tissue irritation, which is predictive, according to the selected mechanism of action, of cytotoxicity that can lead to the occurrence of nasopharyngeal cancer.

In view of this early effect, the low interindividual variability and the concordance of the many studies available on the substance, the OEL Committee did not find it necessary to apply an adjustment factor.

As the duration of exposure in the key study was 4 hours, the question of applying a temporal adjustment to match the duration of a working day was also raised. However, it was considered that the irritant effects are concentration-dependent and not time-dependent effects (Belkebir *et al.*, 2011). This is also confirmed by studies with longer exposure durations in which the effects are observed at comparable doses. A temporal adjustment was therefore not considered necessary.

Thus, the OEL Committee recommends an 8h-OEL of 0.3 ppm, i.e. 0.37 $mg.m^{-3}$, rounded down to 0.35 $mg.m^{-3}$.

15min-STEL

The short-term exposure limit should be able to protect workers from the occurrence of the irritant effects of formaldehyde.

As with the establishment of the 8h-OEL, the data on volunteers in controlled exposure conditions are more precise for establishing benchmark doses. The studies by Lang *et al.* (2008) and Mueller *et al.* (2013) include brief exposure peaks in some groups of continuous 4-hour exposure. Thus, these studies seem to be closer to the actual acute exposure situations in the workplace. They have therefore also been chosen as the key studies for establishing the 15min-STEL.

It is generally observed, and this was confirmed in these studies, that eye irritation is an early phenomenon compared to respiratory irritation. This eye irritation has the advantage of having been investigated by objective tests in these two studies, for example by measuring eye redness or eye blinking frequency over 90 seconds.

A NOAEL of 0.6 ppm for the acute effects, based on the exposure condition 0.3 + 4 x 0.6 ppm, was therefore chosen for the objective eye irritation effects.

The application of an adjustment factor, mainly for interindividual variability, was discussed for this value.

In particular, ophthalmologists were contacted during the course of the work, and they indicated the very likely existence of interindividual variability concerning ocular irritation, and more particularly, eye dryness. Nevertheless, the OEL Committee considered that this had already been taken into account by the many available studies on formaldehyde (taking account of the total number of workers considered in the two key studies and the epidemiological studies). As no other

adjustment factor was deemed relevant, the decision was therefore made not to apply an adjustment factor.

Thus, the OEL Committee recommends a 15min-STEL of 0.6 ppm, i.e. 0.74 $mg.m^{-3}$, rounded down to 0.70 $mg.m^{-3}$.

"Skin" notation

Due to the very high reactivity of formaldehyde at the contact site, penetration by the dermal route seems very low, and the contribution of this route to a possible systemic effect (not currently demonstrated for formaldehyde) seems negligible. The "skin" notation is therefore not assigned to formaldehyde.

"Noise" notation

None of the available studies suggest an ototoxic effect of formaldehyde. Accordingly, the "noise" notation is not assigned.

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

Assessment of the measurement methods for formaldehyde in workplace atmospheres

The following table presents the eight measurement methods identified and assessed, as well as their classification.

Table 2 : Classification of the measurement methods for formaldehyde in workplace atmospheres

Method		Protocols	Category		
			Regulatory technical control of the 8h-OEL	Monitoring of short-term exposure	Regulatory technical control of the 15min-STEL
1	Active sampling on a DNPH-coated silica gel in a sampling tube – Determination by liquid chromatography using a UV/visible detector	NF- X43-264, INRS M-4, INSHT MTA/MA-062/A08, NIOSH 2016, HSE MDHS 102, DFG – Aldehyde Method 2, BGIA 6045	1B		
	Active sampling on a DNPH-coated filter – Determination by liquid chromatography using a UV/visible detector	DFG – Aldehyde Method 1, HSE MDHS 102, BGIA 7520	2		3
2	Active sampling on XAD-2 adsorbent resin coated with 2-HMP – Determination by gas chromatography – FID/NDP/mass detector	OSHA 52 NIOSH 2541 IRSST 295-1	2		3
3	Active sampling in a lithium hydroxide solution – Determination by differential pulse polarography (mercury electrode)	DFG Method 3	3 (*)		
4	Active sampling on a filter + sodium bisulphite solution sampler – Determination by spectrophotometry	NIOSH 3500 MTA/MA-018/A89	3		
5	Active sampling on a filter – Determination by liquid chromatography (UV/visible detector)	NIOSH 5700	3		
6	Active sampling on silica gel	DFG - Formaldehyde Method 2	3 (*)		
7	Passive sampling on a sodium bisulphite-impregnated badge – Determination by spectrophotometry	OSHA ID 205	3		
8	Passive sampling on a DNPH/H_3PO_4-coated badge – Determination by liquid chromatography using a UV/visible detector	OSHA 1007 IRSST 357-1	1B		

(*) method classified in Category 3 due to the absence of validation data

The two graphs below show the range of validation of the different methods classified in Categories 1B and 2, as well as their limit of quantification with regard to the 8h-OEL and the 15min-STEL recommended by the OEL Committee.

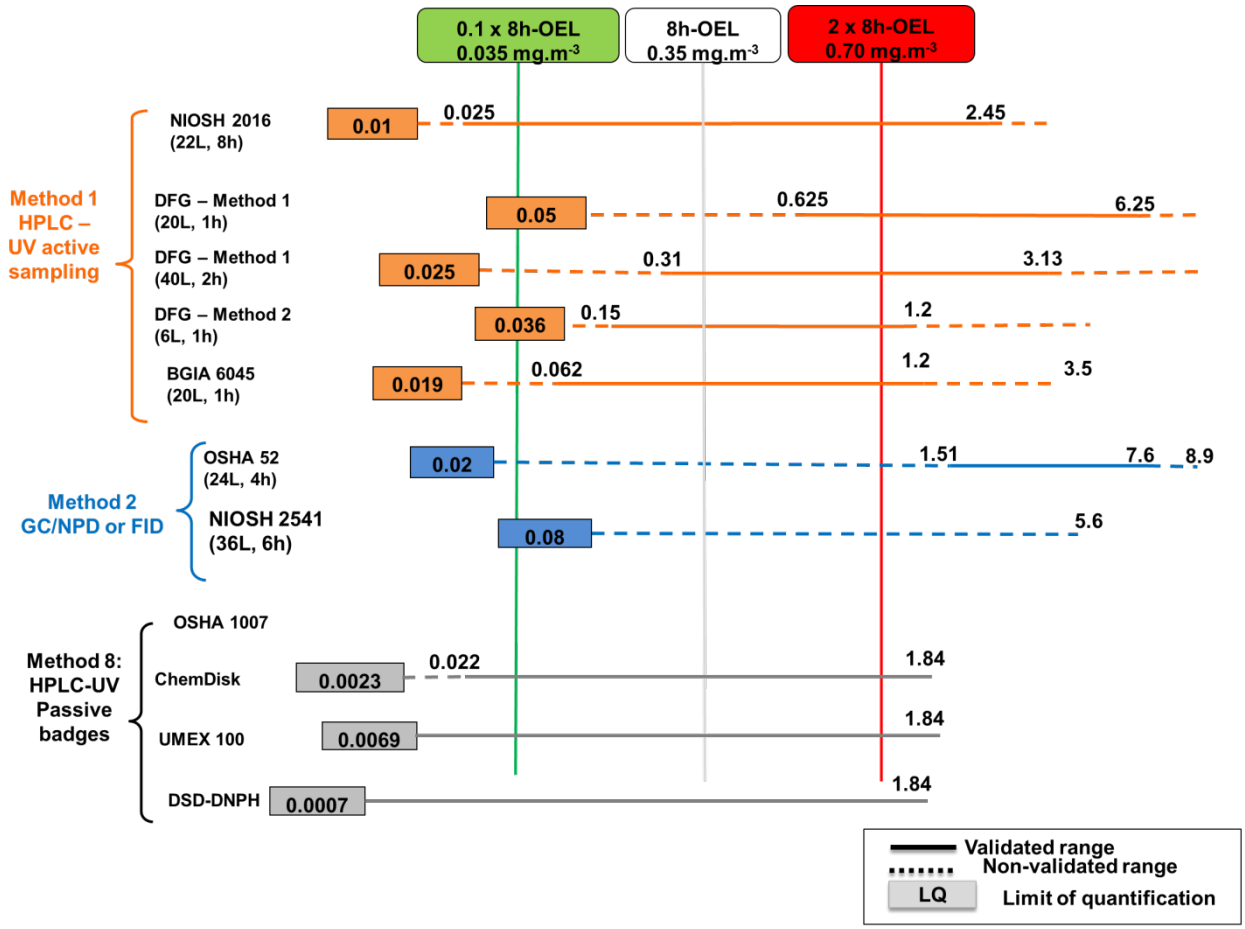

Figure 1: Range of validity and limit of quantification of the methods classified in Categories 1B and 2 compared to the range from 0.1 to 2 times the 8h-OEL recommended by the OEL Committee

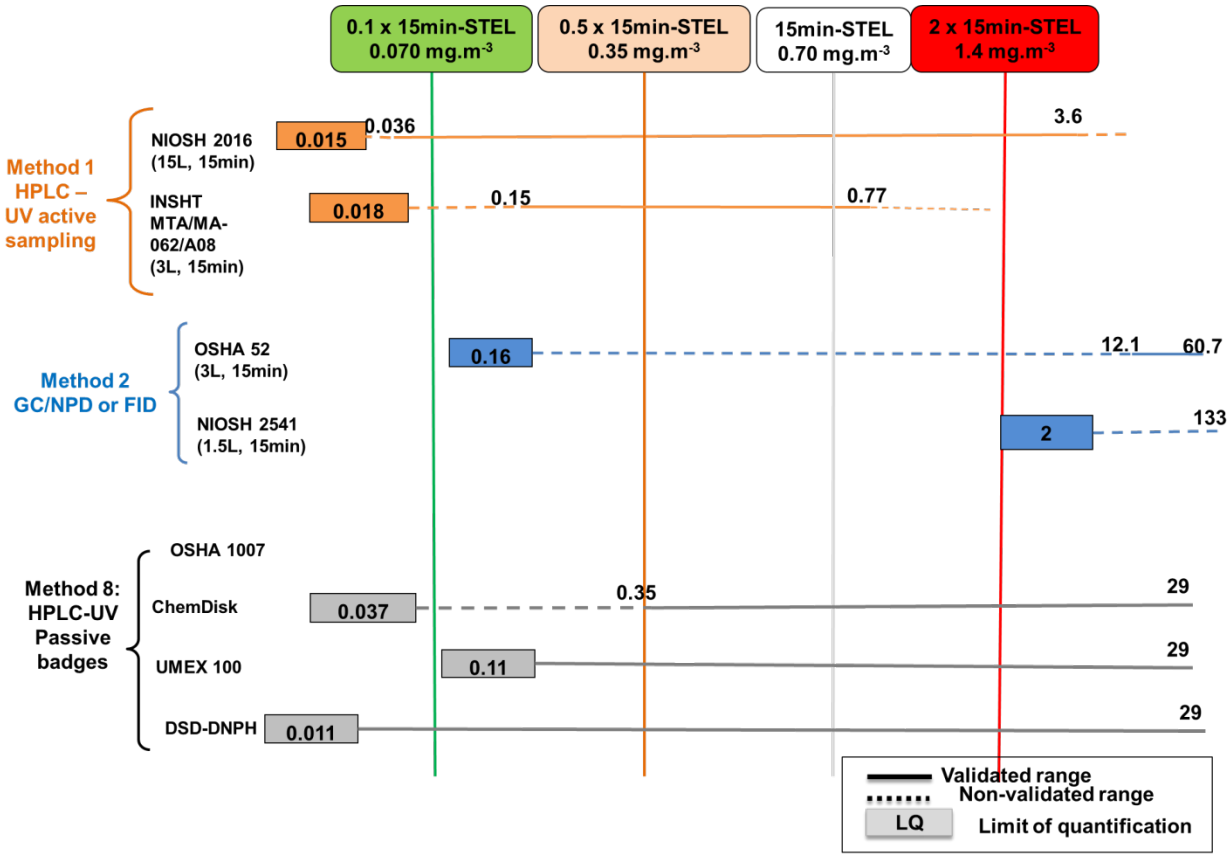

Figure 2: Range of validity and limit of quantification of the methods classified in Categories 1B and 2 compared to the range from 0.1 to 2 times the 15min-STEL recommended by the OEL Committee

Method 1:

Method 1 involves performing active sampling on a 2,4-DNPH-coated medium (silica gel sampling tube or glass fibre filter), desorption with acetonitrile and then analysis by HPLC/UV.

The validation data for the method show that most of the requirements of the NF EN 482 Standard are met for monitoring the 8h-OEL with 8h sampling, whether with a sampling medium comprising a DNPH-coated silica gel sampling tube or a DNPH-coated glass fibre filter. Nevertheless, the influence of interfering compounds (ozone, NO_2, carbonyl compounds) is mentioned without any details on the studies carried out for the two sampling media, and no information is provided on the influence of environmental conditions on sampling on a coated filter. These elements led to the method using a 2,4-DNPH-coated silica gel sampling tube being classified in Category 1B, and the method using a 2,4-DNPH-coated glass fibre filter being classified in Category 2, for technical control of the 8h-OEL.

The method using a coated silica gel sampling tube provides detailed validation information through the protocols studied and can cover the concentration range from 0.1 to 2*15min-STEL. It is therefore classified in Category 1B for regulatory technical control of the 15min-STEL. However, the alternative with a coated glass fibre filter is unable to reach one tenth of the 15min-STEL; it is therefore classified in Category 2 for monitoring short-term exposure and in Category 3 for regulatory technical control of the 15min-STEL.

Method 2:

Method 2 involves performing sampling on XAD-2 adsorbent resin coated with 2-(hydroxymethyl)piperidine (2-HMP), desorption in toluene and then analysis by gas chromatography (with an NDP detector).

Most of the validation data are available and meet the requirements of the NF EN 482 Standard but have been determined on concentration ranges higher than 0.1 to 2*8h-OEL and 0.5 to 2*15min-STEL. Moreover, the limit of quantification is less than 0.1*8h-OEL but between 0.1 and 0.5*15min-STEL. Therefore, the method is classified in Category 2 for regulatory technical control of the 8h-OEL and for monitoring short-term exposure, but in Category 3 for regulatory technical control of the 15min-STEL.

Method 3:

Method 3 involves performing sampling by pumping in an aqueous lithium hydroxide solution, then directly performing quantification in the solution by differential pulse polarography with a mercury drop electrode.

The method is classified in Category 3 for regulatory technical control of the 8h-OEL and the 15min-STEL, as well as for monitoring short-term exposure, because most of the validation data are unavailable, in particular on the breakthrough volume. The desorption coefficient was determined for a single concentration only, and the only data on uncertainty come from one dataset on reproducibility also determined for a single concentration only. In addition, the method gives no information on storage of the samples (conditions and recovery rate). It only states that the analysis should be carried out within two days of sampling.

Method 4:

Method 4 involves conducting sampling by bubbling through 20 mL of sodium bisulphite solution, then spectrophotometric determination of the derivative formed with chromotropic acid.

This method is classified in Category 3 due to the mode of sampling, which intends the method to be used for static sampling and not personal sampling**.**

Method 5:

Method 5, cited as a method for quantifying formaldehyde in dust collected in the atmosphere of industrial premises of the textile industry, involves collecting the inhalable fraction of dust, consisting of textile fibres. This method has been classified in Category 3 due to the fact that it does not correspond to the objective of measuring formaldehyde vapours in the atmosphere**.**

Method 6:

Method 6 involves performing sampling on a silica gel tube, and then carrying out the spectrophotometric analysis in the presence of sodium tetrachloromercurate, sodium sulphite and pararosaniline, after desorption in distilled water.

This method is classified in Category 3 due to the absence of validation data, in particular on the desorption coefficient, the breakthrough volume and the shelf life of samples.

Method 7:

Method 7 involves conducting passive sampling on a badge consisting of sodium bisulphite-impregnated paper, desorption in distilled water, the addition of chromotropic acid in a sulphuric acid medium, then determination by spectrophotometry of the complex formed at the 580 nm wavelength.

This method has numerous validation data over a concentration range corresponding to 1 to 16*8h-OEL, although the tests are not always described. However, the limit of quantification is unable to reach one tenth of the 8h-OEL. In addition this method cannot be used to take samples over short durations and is therefore not suited to monitoring short-term exposure. The method is therefore classified in Category 3 for regulatory technical control of the 8h-OEL and the 15min-STEL, as well as for monitoring short-term exposure.

Method 8:

Method 8 involves performing passive sampling on a medium coated with a mixture of 2,4-DNPH and phosphoric acid, desorption in acetonitrile and then determination by liquid chromatography (UV/visible detector). This method has very comprehensive validation data for three media tested (ChemDisk badge consisting of a glass fibre filter, UMEX 100 badge consisting of a silica tape, and a DSD-DNPH badge consisting of silica gel).

The method is validated on the range from 0.1 to 2*8h-OEL for 4h sampling for the three types of badges cited, and the requirements of the NF EN 482 Standard are met. However, the sample flow rate of the badges was only determined at a single concentration, greater than 2*8h-OEL. Therefore, the method is classified in Category 1B for regulatory technical control of the 8h-OEL.

The method is also validated for monitoring short-term exposure for the three types of badges. Nevertheless, only two out of the three tested badges (ChemDisk and DSD-DNPH) are able to reach one tenth of the 15min-STEL. The method is therefore classified in Category 1B for monitoring short-term exposure and for regulatory technical control of the 15min-STEL, provided that the ChemDisk or DSD-DNPH badges are used, or that a lower limit of quantification is validated for the UMEX 100 badge.

Conclusions and recommendations

Among the eight methods identified,

- Five methods were classified in Category 3 for monitoring the 8h-OEL, monitoring short-term exposure and technical control of the 15min-STEL:
    - Methods 3 and 6 because of the absence of validation data.
    - Method 4, because of the mode of sampling, which enables formaldehyde to be measured in ambient air but does not enable personal sampling.
    - Method 5 because it is used to determine the concentration of formaldehyde not in air but in dust from the textile industry.
    - Method 7 because the limit of quantification is too high.
- Method 2 is classified in Category 2 for monitoring the 8h-OEL and short-term exposure, and in Category 3 for regulatory technical control of the 15min-STEL, due to:
    - validation data determined at concentrations often higher than the ranges 0.1 to 2*8h-OEL and 0.5 to 2*15min-STEL
    - a limit of quantification that is unable to reach one tenth of the 15min-STEL.

- Method 1 with a coated silica gel sampling tube and Method 8 were classified in Category 1B for monitoring the 8h-OEL, monitoring short-term exposure and regulatory technical control of the 15min-STEL.
    - These methods' different characteristics do indeed meet most of the requirements of the EN 482 Standard for measuring formaldehyde in air over durations of 15 min or 8 h.
    - Concerning the classification of Method 8 in Category 1B for technical control of the STEL, it should be noted that only two out of the three tested badges (ChemDisk and DSD-DNPH) are able to reach one tenth of the 15min-STEL.
- Method 1 with a coated glass fibre filter has been classified in Category 2 for monitoring the 8h-OEL and short-term exposure, and classified in Category 3 for regulatory technical control of the 15min-STEL, because no information is provided on the influence of environmental conditions on sampling, and the method is not able to reach one tenth of the 15min-STEL.

Methods 1 and 8 are therefore recommended for measuring formaldehyde in workplace atmospheres for the purposes of comparison with the OELs (see Table below).

Table 3: recommended methods for measuring formaldehyde in workplace atmospheres for the purposes of comparison with the OELs

Method	Protocols	Category		
		For regulatory technical control of the 8h-OEL	For monitoring of short-term exposure	For regulatory technical control of the 15min-STEL
Method 1: Active sampling on 2,4-DNPH-coated silica gel – Determination by liquid chromatography (UV/visible detector)	NF X43-264 INRS M-4 INSHT MTA/MA-062/A08 NIOSH 2016 HSE MDHS 102 DFG Aldehyde Method 2 BGIA 6045	1B	1B	1B
Method 8: Passive sampling on a DNPH/H_3PO_4-coated badge (3 types of badge) – Determination by liquid chromatography using a UV/visible detector	OSHA 1007	1B	1B	1B (*)
(*) Classification of this method in Category 1B for technical control of the STEL is only valid when using the ChemDisk or DSD-DNPH badges.				

Conclusions of the collective expert appraisal

On the basis of the data currently available for formaldehyde, the OEL Committee recommends setting an 8h-OEL of 0.3 ppm, i.e. 0.35 $mg.m^{-3}$ as well as a 15min-STEL of 0.6 ppm, i.e. 0.70 $mg.m^{-3}$.

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

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

Concerning the methods for measuring formaldehyde in the workplace, the OEL Committee recommends, for monitoring the 8h-OEL, for regulatory technical control of the 15min-STEL or for monitoring short-term exposure, using the two methods classified in Category 1B:

- Method 1, which involves performing active sampling on a 2,4-DNPH-coated silica gel sampling tube, desorption in acetonitrile and then determination by liquid chromatography (UV/visible detector). This method is described in many protocols. In contrast, use of this method with a 2,4-DNPH-coated glass filter as the sampling medium is not recommended.
- Method 8, which involves performing passive sampling on a 2,4-DNPH/H_3PO_4-coated badge, acetonitrile desorption, then determination by liquid chromatography (UV/visible detector). This method is described in OSHA Protocol 1007. For implementation of this method for controlling the 15min-STEL, the OEL Committee recommends using the ChemDisk or DSD-DNPH badges, or validating a lower limit of quantification for the UMEX 100 badge.

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