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.