ANSES Opinion
Request No. 2021-MPEX-0006
Related Request No 2021-MPEX-0005

The Director General

Maisons-Alfort, 8 July 2024

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

on updating the indoor air quality guideline values for benzene (CAS No. 71-43-2)

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 8 July 2024 shall prevail.

1. BACKGROUND AND PURPOSE OF THE REQUEST

As with outdoor air quality, the quality of air inside buildings is a public health concern in France, given that people spend on average 85% of their time in enclosed environments. There are a wide variety of pollution situations in the indoor environment due to chemical or microbiological contaminants or physical agents, mainly related to the nature of the building materials, the fixtures, the immediate external environment and the occupants' activities. These pollutants can have consequences on people's health, although they cannot all be precisely quantified.

The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) undertakes expert appraisal work in order to produce indoor air quality guideline values (IAQGs) based on health criteria.

An IAQG is a numerical value, associated with an exposure time, that corresponds to a concentration in air of a chemical agent below which no health effect (or, in the case of odorous compounds, no hazard with health consequences) is normally expected for the general population. This definition is generally applicable for guideline values established to provide protection from threshold-dose effects (the IAQG is expressed in mass per volume of air (mg

or µg per m^3)). In the case of effects without a threshold dose, the IAQGs are expressed as risk levels corresponding to the probability of occurrence of the effect.

Benzene has been the subject of a number of expert appraisals as part of ANSES's ongoing work on reference values, in particular the proposals for an IAQG in 2008 and a toxicity reference value (TRV) in 2014, which are designed to protect the general population. New data available, in particular on the carcinogenic effects of benzene, has led ANSES to update these inhalation reference values.

2. ORGANISATION OF THE EXPERT APPRAISAL

Different groups were called on to conduct this expert appraisal work:

- the Expert Committee on "Health Reference Values" (CES VSR), which is responsible for drawing up and validating the various reference values on which ANSES is consulted (TRVs, occupational exposure limits (OELs), biological limit values (BLVs), biological reference values (BRVs), IAQGs, derived no effect levels (DNELs));
- the Working Group (WG) on "Metrology", which assessed the measurement methods available for monitoring exposure levels in indoor air in light of the proposed IAQGs;
- the CES on "Assessment of the risks related to air environments" (CES Air), which adopted the work of the WG on "Metrology" and made recommendations based on existing data on benzene measurement methods for comparing concentration levels with IAQGs.

Expert appraisal method

The general approach to developing IAQGs is summarised below (ANSES, publication pending):

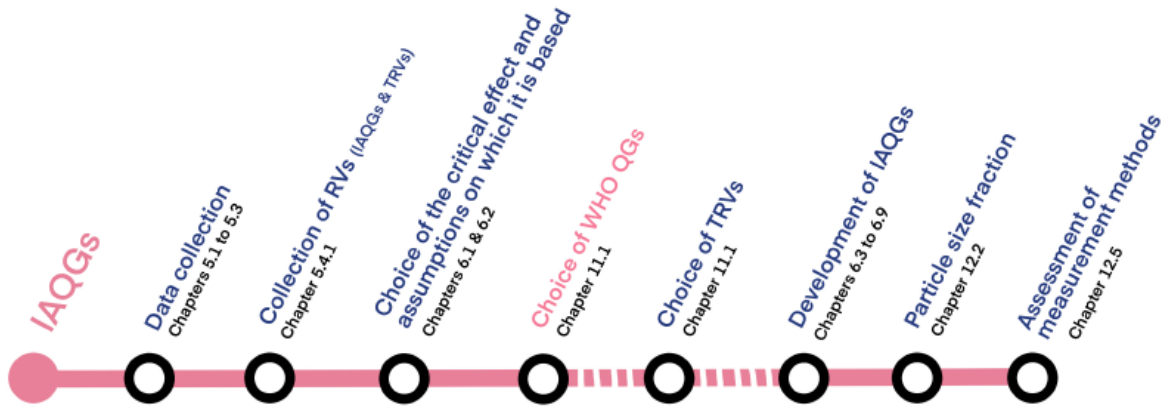

Figure 1: Proposed IAQGs (ANSES, publication pending)

NB: WHO QGs: WHO quality guideline value. If there is no WHO QGs or respiratory TRV available, or if these are deemed unsatisfactory, ANSES develops an IAQG. The particle size fraction to be considered concerns the development of IAQGs for chemical agents in aerosol form and is mainly applied to assist in recommending measurement methods.

The work was presented to the two CESs mentioned above in March and May 2024. The CES VSR validated the updated IAQGs for benzene on 15 March 2024. The CES Air validated the recommendations on benzene measurement methods in relation to the proposed IAQGs at its meeting on 27 May 2024.

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 website: https://dpi.sante.gouv.fr/.

3. ANALYSIS AND CONCLUSIONS OF THE CES VSR AND THE CES AIR

3.1. Updating of the IAQGs for benzene by the CES VSR

- **Summary of the data on health effects**

A summary of the expert appraisal work, based on the CES VSR's analysis and conclusions on the development of TRVs for benzene, is presented below (ANSES, 2024). As inhalation is the main route of human exposure to benzene, only data on toxicity following inhalation exposure are presented.

Data on the **health effects in humans** are described below.

Toxicokinetics

Benzene is rapidly absorbed after inhalation exposure. In humans exposed by inhalation to 47 and 110 ppm (150 to 351 $mg \cdot m^{-3}$, respectively) of benzene for three to four hours, the absorption rate measured in the first five minutes after exposure was between 70 and 80%. After one hour of exposure, the absorption rate fell to between 20% and 60%. Data on workers indicate that benzene is also absorbed through the skin (ATSDR, 2007).

Due to its high lipophilicity, benzene is then distributed throughout the body and tends to accumulate in lipid-rich tissues (ATSDR, 2007). The highest levels of benzene have been observed in human adipose tissue and bone marrow after inhalation. Benzene also crosses the blood-brain and placental barriers and is found in umbilical cord blood at concentrations equal to or greater than those found in maternal blood (Winek and Collom, 1971; Dowty *et al.*, 1976).

Benzene metabolism does not appear to depend on the route of absorption. Benzene is mainly metabolised in the liver, although metabolism can also take place in other organs where it has accumulated, such as bone marrow.

The data available for humans following inhalation exposure have shown that exhalation is the main route of elimination for non-metabolised benzene. Absorbed benzene is also excreted via urine in the form of phenols (phenol, catechol, hydroquinone, trihydroxybenzene in free, sulpho- and glucuroconjugated forms), muconic acid and S-phenylmercapturic acid, as well as in unchanged form. Some of these urinary metabolites, like urinary benzene, can be used as biomarkers of benzene exposure.

Acute effects

A few older case reports in humans stated that inhalation of benzene at a concentration of 20,000 ppm (64,980 $mg \cdot m^{-3}$) for 5 to 10 minutes was generally fatal (Flury *et al.*, 1928; Gerarde, 1960). Death following exposure to benzene is often attributed to asphyxiation, respiratory arrest or depression of the central nervous system. In mild forms of poisoning, excitation followed by speech problems, headaches, dizziness, insomnia, nausea, paraesthesia of the hands and feet and fatigue have been reported. These symptoms were generally observed at concentrations of between 300 and 3000 ppm (975 and 9750 $mg \cdot m^{-3}$) (Cronin, 1924; Flury, 1928; Midzenski *et al.*, 1992).

Irritation

High concentrations of benzene in the air cause irritation of the mucous membranes of the eyes, nose and respiratory tract (ATSDR, 2007). Liquid benzene is irritating to the skin in the event of prolonged or repeated contact.

Subchronic and chronic non-carcinogenic effects:

- Haematological effects

Numerous epidemiological studies of workers exposed to different concentrations of benzene over the medium or long term have revealed a number of haematological effects. Bone marrow damage is one of the first signs of chronic benzene toxicity. Most of the blood-related effects (thrombocytopaenia, granulocytopaenia, lymphopaenia, anaemia, pancytopaenia and leukaemia) were associated with inhalation exposure.

Aplastic anaemia is one of the most severe effects induced by benzene inhalation. It occurs when bone marrow function is impaired and stem cell maturation is affected. Aplastic anaemia can progress to myelodysplastic syndrome and then to leukaemia. The presence of chromosomal abnormalities may be associated with the occurrence of myeloproliferative syndrome, the transition from aplastic anaemia to myelodysplastic syndrome and the development of leukaemia.

- Immunological effects

Benzene impairs humoral immunity by inducing changes in blood concentrations of immunoglobulins (Ig). A reduction in IgG and IgA was observed in several studies. Benzene also impairs cellular immunity (ATSDR, 2007). Cases of lymphopaenia were reported in a series of studies of workers exposed to benzene in different industries.

- Respiratory effects

The results of studies into the respiratory effects of benzene are equivocal. Some studies have found positive associations between exposure to benzene and reduced lung function, particularly in children, while others have found no association between benzene exposure and children's respiratory health (Health Canada, 2023).

- Reprotoxicity and developmental toxicity:

Studies conducted in the workplace suggest that benzene reduces female fertility. In particular, studies have revealed menstrual cycle disruptions in women occupationally exposed to benzene.

Some studies also report a decrease in male fertility related to the duration of exposure to benzene (significant decrease in sperm count and motility, significant increase in percentages of morphologically abnormal sperm and sperm DNA fragmentation) (ATSDR, 2015).

Studies indicate a significant association between maternal exposure to benzene and the occurrence of premature births (Wilhelm *et al.*, 2011; Estarlich *et al.*, 2016; Dos Santos *et al.*, 2019) and reduced birth weight (Zahran *et al.*, 2012), but no association has been reported between *in utero* environmental exposure to benzene and the occurrence of birth defects, cognitive effects or the child's psychomotor development (Lertxundi *et al.*, 2015; Vinceti *et al.*, 2016; Janitz *et al.*, 2018).

Genotoxicity

Benzene has the main characteristics of a carcinogen. In particular, there is strong evidence from both animal and human studies that benzene is metabolised to active electrophilic metabolites that can induce oxidative stress and oxidative damage. It is also described as genotoxic, immunosuppressive and haematotoxic (IARC, 2018). In addition, there is evidence from experimental studies that benzene alters DNA repair, causing genomic instability by inhibiting topoisomerase II, which is involved in DNA replication. Benzene metabolites, in particular 1,4-benzoquinone and hydroquinone, have been shown to directly inhibit topoisomerase II in *in vitro* studies on human cells and in mice.

In studies on workers, benzene induced oxidative DNA damage, single- and double-strand DNA breaks, gene duplications, chromosomal aberrations and micronuclei. The specific cytogenetic changes induced include aneuploidy, translocations and various other structural changes to chromosomes. These conclusions, based on epidemiological studies, are largely confirmed by *in vitro* and *in vivo* studies. The formation of DNA adducts in bone marrow, chromosomal aberrations and micronuclei have been shown in animals following exposure to benzene. Similarly, after treatment of human cells *in vitro*, benzene or its metabolites induced DNA adducts and damage, as well as chromosomal aberrations (IARC, 2018).

The available data show that it is the metabolites of benzene that lead to genotoxic effects. It is possible that each metabolite produces its own effects, which would explain the differences observed in the results of the various tests carried out (ANSES, 2014).

Carcinogenic effects

Benzene has been classified as a human carcinogen (Group 1) by the International Agency for Research on Cancer (IARC) since 1979, on the basis of sufficient evidence in humans and animals that it causes leukaemia. This assessment was confirmed specifically for acute myeloid leukaemia (AML) and/or acute non-lymphocytic leukaemia (ANLL) in adults, in the IARC monographs published in 2012 and then in 2018[1]. In 2012, the IARC also concluded that there were positive associations between benzene exposure and the risks of acute lymphocytic leukaemia (ALL), chronic lymphocytic leukaemia (CLL), multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL)[2]. In addition, the IARC concluded in 2018 that there were positive

[1] In 2018, the IARC clarified that ANLL was included in the AML category due to changes in classification (WHO, 2017).
[2] In 2018, the IARC clarified that ALL, CLL and MM were included in the NHL category (WHO, 2017)

associations with the risk of chronic myeloid leukaemia (CML), lung cancer and AML in children.

The vast majority of the available studies have been carried out in the workplace. The first occupational cohort studies carried out on workers in the rubber and petroleum industries revealed excess mortality from leukaemia and other malignant diseases of the lymphatic and haematopoietic tissues (Rinsky *et al.*, 2002; Glass *et al.*, 2003; Richardson, 2008; Hayes *et al.*, 1997).

The most recent studies confirm the excess mortality risk found previously, particularly for AML and ANLL (Stenejhem *et al.*, 2015; Rhomberg *et al.*, 2016; Linet *et al.*, 2019). These studies have refined the assessment of benzene exposure and report positive results at relatively low levels of exposure compared with previous studies.

Two recent meta-analyses and meta-regressions confirmed the risk of AML associated with occupational exposure to benzene (IARC, 2018; Scholten *et al.*, 2022).

- **Updating of the IAQGs for benzene**

The updating of the IAQGs for benzene drew on the expert appraisal on the proposed inhalation TRVs for benzene adopted by the CES VSR in January 2024 and presented in Annex 1. On the basis of this work, it was proposed that the IAQGs for benzene be updated to protect the general population from acute, sub-chronic and chronic effects (Table 1). As in 2008, given all the possible exposure situations, three exposure durations – short-term, medium-term and long-term – were considered. For long-term exposure, both non-carcinogenic (threshold) and carcinogenic (no-threshold) haematological effects were taken into account.

The haematological effects observed in humans and animals were selected as critical effects for the short-, medium- and long-term TRVs, established on the assumption of a threshold dose (threshold effects). The analysis of existing guideline values and TRVs led to the values proposed by the ATSDR in 2007 being selected, which had already been the case for the IAQGs proposed in 2008. The overall level of confidence was moderate for the short- and medium-term TRVs, and moderate-high for the long-term TRV. **The short-term IAQG of 30 µg·m^{-3}, medium-term IAQG[3] of 20 µg·m^{-3} and long-term IAQG of 10 µg·m^{-3} were therefore maintained.**

For the carcinogenic effects, the critical effect selected was AML. According to the IARC, this is the type of leukaemia for which the level of evidence of a causal association with benzene exposure is the highest. A new no-threshold TRV was developed by ANSES in 2024 based on the meta-regression by Scholten *et al.* (2022) including six epidemiological studies and considering AML as the critical effect. Combining the results of several epidemiological studies is therefore beneficial for increasing the robustness and accuracy of AML risk estimates. The approach adopted for developing the TRV was based on the use of a life table, which should be favoured when the necessary data (incidence or mortality by age group in France for the critical effect) are available, according to ANSES's recommendations (ANSES, publication pending). This is because life tables allow for the calculation of probabilities conditional on survival from one age group to the next, taking account of potential competing risks over a

lifetime that are different from the health event of interest, i.e. risks linked to diseases or causes of death other than the one of interest.

The excess unit risk (ERU) proposed by ANSES in 2024 was therefore selected for updating the IAQG designed to provide protection from the carcinogenic effects of benzene. This ERU is $1.6.10^{-6}$ $(\mu g \cdot m^{-3})^{-1}$. IAQGs are expressed in the form of concentrations corresponding to the probability of the disease occurring of 1 in 100,000 and 1 in 1,000,000. They are equal to 6 $\mu g \cdot m^{-3}$ and 0.6 $\mu g \cdot m^{-3}$, respectively.

Table 1: IAQGs for benzene proposed by ANSES (2024)[4]

Reference	Critical effect	IAQG	Application period	TRV confidence level
Short-term (ST) IAQG				
ATSDR, 2007 (Rozen *et al.*, 1984)	Haematotoxicity Decrease in the proliferative response of B lymphocytes (mitogenic action induced by LPS), decrease in circulating lymphocytes	**30 µg·m^{-3}**	For exposure from 1 to 14 days	Moderate
Medium-term (MT) IAQG				
Rosenthal and Snyder, 1987	Haematotoxicity Delayed *in vitro* alloreactivity of lymphocytes	**20 µg·m^{-3}**	For exposure from 14 days to 1 year	Moderate
Long-term (LT) IAQG				
Lan *et al.*, 2004	Haematotoxicity Decrease in the number of lymphocytes	**10 µg·m^{-3}**	For exposure > 1 year	Moderate-high
ANSES, 2024 (Scholten *et al.*, 2022)*	Acute myeloid leukaemia (mortality)	**6 µg·m^{-3}** for a risk level of 10^{-5} **0.6 µg·m^{-3}** for a risk level of 10^{-6}	For lifetime exposure	Moderate-high
*: Meta-regression of six epidemiological studies in the workplace (inhalation exposure)				

3.2. Metrological assistance with IAQGs from the CES Air

- **Emission sources and concentrations in indoor environments**

Inside premises, tobacco smoke and, more generally, any processes involving the combustion of organic materials are known sources of benzene emissions. Building and furnishing materials, as well as DIY and cleaning products, are also potential sources. According to Health Canada (2023), the main factors associated with benzene concentrations in homes were the presence of an attached garage, the storage of paints, solvents and petrol in the garage or house, smoking indoors, and the intake of outside air from open windows or ventilation.

In outdoor air, annual benzene emissions are quantified by the Interprofessional Technical Centre for Studies on Air Pollution (Citepa). Between 1990 and 2021, atmospheric benzene

[4] The terminology used to describe IAQGs has changed. "Intermediate" IAQGs are now referred to as "medium-term" IAQGs. The application period is unchanged (see ANSES methodological guide for developing RVs, publication pending).

emissions in France fell by 70%. In 2020, the main emitter was the residential-tertiary sector (65.1%), particularly due to wood combustion, followed by transport (20.2%), agriculture (7.4%), industry (6.9%) and waste treatment (0.4%) (Citepa, 2023). Benzene is found in fuels (particularly unleaded petrol, which can contain up to 1% by volume) in the European Union (INRS 2019).

Concentrations measured in various indoor environments in France during campaigns conducted by the French Indoor Air Quality Observatory (OQAI) are shown in Table 2. In France, the regulations governing the monitoring of indoor air quality in certain establishments open to the public set an IAQG of 2 µg·m^{-3} for benzene (Article R221-29 of the French Environmental Code) and a value of 10 µg·m^{-3} above which additional investigations must be carried out (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).

Table 2: Benzene concentrations measured in various indoor environments in France

Reference (Environment)	Measurement period	N	LD and LQ (µg·m^{-3}), Percentage of detection and quantification	Concentrations measured (µg·m^{-3})
OQAI, 2006 (Homes)	2003-2005	541 homes (adjusted number = 23,392,236 homes)	LD = 0.4 LQ = 1.1 % > LD = 98.6% %>LQ = 85.1%	Min. < LD P25 = 1.4 Med. = 2.1 P75 = 3.3 Max. = 22.8
OQAI, 2016 (Energy-efficient buildings, EEBs)	2013-2014	68 EEBs	LD = 0.05 LQ = 0.17 %>LQ = 99%	Min. = 0.5 P25 = 1.0 Med. = 1.5 P75 = 2.2 Max. = 7.0 Arithmetic mean (+/- SD) = 1.8 +/- 1.0
OQAI, 2019 (Schools)	2012-2017	296 schools (adjusted number = 66,044 schools)	LD = 0.3 LQ = 0.3 % > LD = 100% %>LQ = 99%	P5 = 0.4 P25 = 0.9 Med. = 1.2 P75 = 1.6 P95 = 3.1 Arithmetic mean (+/- SD) = 1.4 +/- 0.1
OQAI, 2023 (Health and medical-social establishments - HMSEs)	2019-2020	97 HMSEs	LD = 0.2 LQ = 0.2 % > LD = 85% %>LQ = 85%	P5 < LD P25 = 0.3 Med. = 0.6 P75 = 1.1 P95 = 2.2 Arithmetic mean (+/- SD) = 0.8 +/- 0.7
LD: Limit of detection, LQ: Limit of quantification, SD: standard deviation				

According to GEOD'AIR[5], the annual average measured in outdoor air in metropolitan France in 2023 was between 0.26 and 2.82 µg·m^{-3} depending on the type of measuring station considered.

[5] National database on air quality: Data consultation | Geod'air: data and statistics on air quality in France (geodair.fr)

Outdoor air is a major contributor to the benzene concentrations measured in indoor air. Average concentrations measured in outdoor air are generally of the same order of magnitude as those measured in indoor air. Overall, the population is more exposed to benzene via the respiratory route indoors than outdoors, given the respective amounts of time spent in these environments. Moreover, indoor sources can increase concentration levels in indoor air and therefore play an important role in the general population's exposure to benzene.

- **Assessment of the methods for measuring benzene concentrations**

The general principle for assessing measurement methods is presented in Annex 2

Seven methods for measuring benzene in indoor air and in workplace air were identified and assessed according to the harmonised ANSES approach of 2020 (Annex 3):

- Method A: Active sampling on adsorbent support, chemical desorption, analysis by GC/FID or GC/MS;
- Method B: Active sampling on adsorbent support, chemical desorption, analysis by Headspace GC/FID;
- Method C: Sampling by diffusion on adsorbent support, chemical desorption, analysis by GC/FID or GC/MS;
- Method D: Active sampling on adsorbent support, thermal desorption, analysis by GC/FID or GC/MS;
- Method E: Sampling by diffusion on adsorbent support, thermal desorption, analysis by GC/FID or GC/MS;
- Method F: Canister sampling, pre-concentration, GC-MS analysis;
- Method G: Automatic analyser.

Of the seven benzene measurement methods listed, four are common to both indoor air and workplace air, one is specific to workplace air and two are specific to indoor air. Method G is mainly used to measure the concentration of benzene in ambient air. Commercial analysers can be transported to a site, but they systematically require several hours or even a few days to set up, taking into account pre-heating and the preliminary checks needed. It is important to consider this on-site preparation time for any measurements to be carried out in an indoor environment. The same is true if the analyser is moved, for example to another room.

Details of the methods and their classification resulting from the assessment of the measurement methods in accordance with the approach of the WG on "Metrology", considering sampling periods of seven days and concentration ranges from 0.1 to 2 times the IAQGs[6], are presented in Annex 3.

In the remainder of this document, IAQGs are referred to as follows:

- Short term: ST IAQG = 30 $\mu g \cdot m^{-3}$
- Medium term: MT IAQG = 20 $\mu g \cdot m^{-3}$
- Long-term, threshold effects: LT1 IAQG = 10 $\mu g \cdot m^{-3}$

[6] For comparison with the short-term IAQG: 3 to 60 $\mu g \cdot m^{-3}$ over 7 days
For comparison with the medium-term IAQG: 2 to 40 $\mu g \cdot m^{-3}$ over 7 days
For comparison with the long-term IAQG: 1 to 20 $\mu g \cdot m^{-3}$ over 7 days
For comparison with the long-term IAQG for a risk level of 10^{-5}: 0.6 to 12 $\mu g \cdot m^{-3}$ over 7 days
For comparison with the long-term IAQG for a risk level of 10^{-6}: 0.06 to 1.2 $\mu g \cdot m^{-3}$ over 7 days

- Long-term, no-threshold effects for a risk level of 10^{-5}: LT2 IAQG = 6 µg·m^{-3}
- Long-term, no-threshold effects for a risk level of 10^{-6}: LT3 IAQG = 0.6 µg·m^{-3}

- **Conclusions of the CES Air**

The CES Air concludes that:

- Indoor air contributes more than outdoor air to the general population's respiratory exposure to benzene.
- The available data tend to show a decline in benzene concentrations in indoor environments over the last 20 years. Concentrations are of the order of the µg·m^{-3}. These conclusions are confirmed by the results of the Second National Housing Campaign (CNL2), which will be published in 2024. Nevertheless, when the IAQGs are compared with the distribution percentiles, some IAQGs are still exceeded: for example, according to the results of the OQAI's "schools" campaign, the LT2 IAQG of 6 µg·m^{-3} was exceeded in nearly 5% of schools, and the LT3 IAQG of 0.6 µg·m^{-3} was exceeded in more than 95% of schools.

Regarding the methods used to measure benzene concentrations for comparison with the proposed IAQGs, the CES Air concludes that of the seven measurement methods assessed:

- four are recommended for comparison with one or more IAQGs, with varying degrees of validation:
  - Method A using active sampling on adsorbent support, solvent desorption with CS_2 and analysis by GC/FID or GC/MS is recommended (Cat. 1B, partially validated) for comparison with the LT1 and LT2 IAQGs;
  - Method D using active sampling on adsorbent support, thermal desorption and analysis by GC/FID or GC/MS is recommended (Cat. 1B, partially validated) for comparison with the ST IAQG, MT IAQG and LT1 and LT2 IAQGs;
  - Method E using passive sampling on adsorbent support, thermal desorption and analysis by GC/FID or GC/MS is recommended (Cat. 1B, partially validated) for comparison with the LT1 IAQG;
  - Method G using an automatic analyser is recommended (Cat. 1A, validated) for comparison with the MT IAQG and LT1 and LT2 IAQGs. However, the CES stresses that this method is difficult to implement.
- Method C (passive sampling, chemical desorption and analysis by GC/FID or GC/MS) is classified as Category 2, i.e. indicative for comparison with the ST, MT and LT1 IAQGs;
- the other two methods (Method B using active sampling, chemical desorption and analysis by GC/FID or GC/MS and Method F using canister sampling, pre-concentration, GC/FID or GC/MS analysis) are unsuitable or could not be assessed for comparison with each of the IAQGs;
- no measurement method is suitable for comparison with the LT3 IAQG.

Sampling times are seven days for comparison with each of the IAQGs.

- **Recommendations of the CES Air**

Regarding the measurement of benzene in indoor air, in light of the proposed IAQGs, the CES Air recommends the use of the following methods:

- For comparison with the short-term IAQG: **Method D**, consisting of active sampling on an adsorbent tube, thermal desorption and analysis by GC/MS or GC/FID;
- For comparison with the medium-term IAQG: **Method D** consisting of active sampling on an adsorbent tube, thermal desorption and analysis by GC/MS or GC/FID, **or Method G** using an automatic analyser, which is nevertheless more complex to implement;
- For comparison with the long-term IAQG (LT1): **Method A** consisting of active sampling on an adsorbent tube followed by desorption using CS_2 and analysis by GC/FID or GC/MS, or **Method D** consisting of active sampling on an adsorbent tube followed by thermal desorption and analysis by GC/MS or GC/FID, or **Method E** consisting of passive sampling on an adsorbent tube followed by thermal desorption and analysis by GC/MS or GC/FID, or **Method G** using an automatic analyser, which is nevertheless more complex to implement;
- For comparison with the long-term IAQG associated with a risk level of 10^{-5} (LT2): **Method A** consisting of active sampling on an adsorbent tube followed by desorption using CS_2 and analysis by GC/FID or GC/MS, or **Method D** consisting of active sampling on an adsorbent tube followed by thermal desorption and analysis by GC/MS or GC/FID, or **Method G** using an automatic analyser, which is nevertheless more complex to implement.

The recommended sampling periods are seven days for comparison with each of the IAQGs.

No method is recommended for comparison with the long-term IAQG for a risk level of 10^{-6} (LT3). The CES therefore calls for a measurement method that can achieve the required sensitivity to be developed.

The CES stresses that particular attention should be paid to the very high purity of the CS_2 used as the desorption solvent in Method A. **The CES draws users' attention to the fact that CS_2 is classified as a Category 2 reprotoxic substance.**

Lastly, **the CES Air recommends** that French regulations on monitoring indoor air quality in the relevant establishments open to the public be revised to take account of the updated IAQGs.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The French Agency for Food, Environmental and Occupational Health & Safety endorses the conclusions and recommendations of the CES on "Health Reference Values" and the CES on "Assessment of the risks related to air environments" presented above.

The Agency reiterates that an indoor air quality guideline (IAQG) offers a framework of reference based exclusively on health criteria and intended to protect the general population from the health effects of exposure to pollution through inhalation of an air contaminant. IAQGs

are intended primarily for public authorities, to enable them to set risk management values. As such, the results of the Second National Housing Campaign (CNL2), which will be published in 2024, will help illustrate changes in benzene concentrations in indoor environments and the extent to which the proposed IAQGs are exceeded.

On the basis of new knowledge about the carcinogenic effects of benzene, in particular acute myeloid leukaemia (AML), for which the level of evidence of a causal association with exposure to benzene is the highest, ANSES has updated the reference values for the general population, namely the toxicity reference values (TRVs) and IAQGs. It now recommends two new long-term IAQGs of 6 $\mu g \cdot m^{-3}$ and 0.6 $\mu g \cdot m^{-3}$, corresponding to concentration levels associated with an individual excess risk (IER) of 10^{-5} and 10^{-6}, respectively.

The short-term, medium-term and long-term IAQGs for non-carcinogenic effects are unchanged from the values proposed in 2008.

The Agency notes that the measurement methods cannot be used to measure benzene in indoor air for comparison with the lowest guideline value of 0.6 $\mu g \cdot m^{-3}$ (ERI of 10^{-6}). It therefore stresses the need to validate suitable measurement methods for comparison with this IAQG.

Lastly, the Agency points out that with the 2024 launch of the Indoor Environment Quality Observatory (OQEI), supported jointly by ANSES and the Scientific and Technical Centre for Building (CSTB), it will be possible to provide knowledge and even solutions to all stakeholders, to improve the management of risks associated with these environments.

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KEY WORDS

Valeur guide de qualité de l'air intérieur, VGAI, benzène, 71-43-2, inhalation, aiguë, subchronique, chronique, cancer, métrologie, méthodes de mesure, logements, écoles, expertise

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ANNEX 1: ANSES TRVs (2024) FOR RESPIRATORY EXPOSURE TO BENZENE

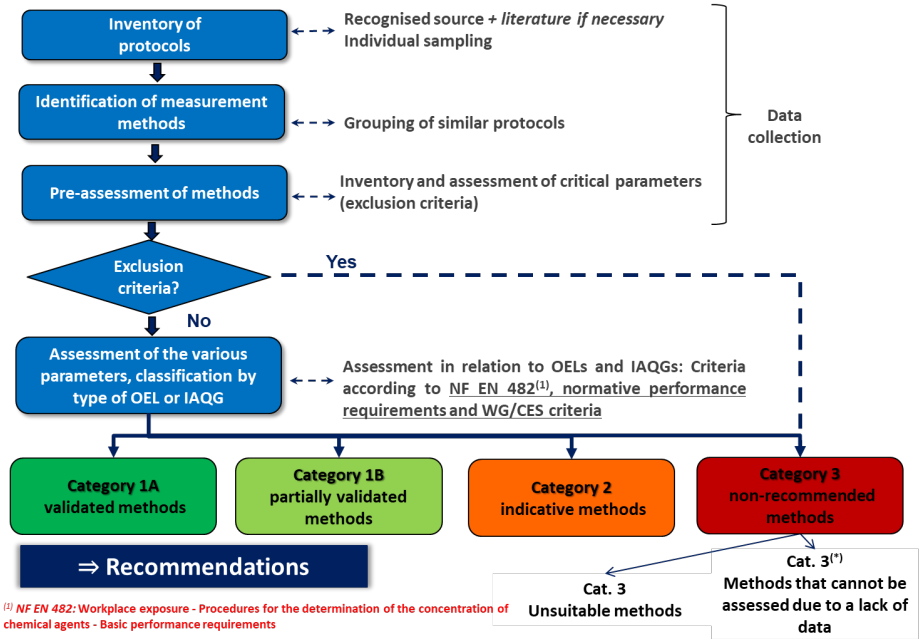
Table 3: Short-, medium- and long-term threshold TRVs by the respiratory route for benzene (ANSES, 2024)

Type of reference value		Short term	Medium term	Long term
TRV	Organisation	ATSDR	ATSDR	ATSDR
	Year	2007	2007	2007
	Name	MRL_{acute}	$MRL_{intermediate}$	$MRL_{chronic}$
	Value	**29 µg·m^{-3}**	**19 µg·m^{-3}**	**9.6 µg·m^{-3}**
Target population		General population	General population	General population
Critical effect		Decrease in the proliferative response of B lymphocytes (mitogenic action induced by LPS), decrease in circulating lymphocytes	Delayed *in vitro* alloreactivity of lymphocytes	Decrease in the number of lymphocytes
Key study	Reference	Rozen *et al.*, 1984	Rosenthal and Snyder, 1987	Lan *et al.*, 2004
	Study population or species	Male mice	Male mice	Men (workers)
	Exposure (duration, route)	6h/d for 6 consecutive days Respiratory route	6 h/d, 5 d/w for 20 days Respiratory route	On average 6.1 years
Point of departure (PoD)		LOAEC = 33 mg·m^{-3}	LOAEC = 32.5 mg·m^{-3}	$BMCL_{(0,25sd)}$ = 0.32 mg·m^{-3}
Time adjustment		$LOAEC_{ADJ}$ = 8.0 mg·m^{-3}	$LOAEC_{ADJ}$ = 5.8 mg·m^{-3}	$BMCL_{0.25sd\ ADJ}$ = 0.1 mg·m^{-3}
Allometric adjustment		$LOAEC_{ADJ\ HEC}$ = 8.0 mg·m^{-3}	$LOAEC_{ADJ\ HEC}$ = 5.8 mg·m^{-3}	-
Uncertainty factors (UF)		300 UF_A: 3, UF_H: 10, UF_L: 10	300 $UF_{A\text{-}TD}$: 3, UF_H: 10, UF_L: 10	10 UF_H: 10
Confidence level		Moderate	Moderate	Moderate-high

Table 4: No-threshold carcinogenic TRVs by the respiratory route for benzene (ANSES, 2024)

Critical effect (key study)	Concentration-risk relationship	TRV
Acute myeloid leukaemia (mortality) Scholten *et al.*, (2022): meta-regression of six epidemiological studies in the workplace (inhalation exposure)	Ln $RR_{UB95\%}$ = $\beta_{UB95\%}$ x [benzene] $\beta_{UB95\%}$ = upper bound of the 95% confidence interval for the β coefficient = 0.0037 (unitless) [benzene] = occupational exposure concentration for benzene (ppm-years) Life table with time adjustment Linear model with intercept and intercept subtracted ELR of 1%	**ERU = 1.6.10^{-6} (µg·m^{-3})$^{-1}$** For a risk of: 10^{-4}: 60 µg·m^{-3} 10^{-5}: 6 µg·m^{-3} 10^{-6}: 0.6 µg·m^{-3} **Confidence level: Moderate-High**

ANNEX 2: GENERAL PRINCIPLE FOR ASSESSING MEASUREMENT METHODS



ANNEX 3: CLASSIFICATION OF THE METHODS FOR MEASURING THE CONCENTRATION OF BENZENE IN AIR FOR MONITORING IAQGs

Methods		Protocols	Classification for verifying the IAQG				
			Short term (ST)	Medium term (MT)	Long term (LT1)	Long term (10^{-5}) (LT2)	Long term (10^{-6}) (LT3)
			30 µg·m^{-3}	20 µg·m^{-3}	10 µg·m^{-3}	6 µg·m^{-3}	0.6 µg·m^{-3}
A	Active sampling on an activated charcoal tube (100/50) CS_2 desorption Analysis using GC/MS or FID	INRS-MétroPol M-40 (2019) INSST MTA/MA-030 (1992) NIOSH 1501 (2003) OSHA 1005 (2020) OSHA 5000 (2021) IRSST 369 (2012) HSE MDHS 96 (2020) HSE MDHS 104 Method 3 (2016) NF ISO 16200-1 (2001) NF X43-267 (2014)	3*	3*	3*	3*	3*
		NF EN 14662-2 (2005)	2	2	1B	1B	3
	Active sampling on an activated charcoal tube (300/600) CS_2 desorption Analysis using GC/MS or FID	DGUV 213-504 (2019) BGIA 6265 Method 1 (2019) MAK DFG Method 1 (1995)	2	2	2	2	3
B	Active sampling on an activated charcoal tube (300/600) Desorption solvent mixture Analysis using Headspace GC/FID	MAK DFG Solvent mixtures Method 4 (1995)	3*	3*	3*	3*	3*
C	Passive sampling on an activated charcoal badge CS_2 desorption Analysis using GC/MS or FID	INRS MétroPol M-237 (2016), M-243 (2015) OSHA 1005 (2020) HSE MDHS 88 (1997) EN ISO 16200-2 (2000) NF EN 14662-5 (2005)	2 (SKC 575-001 or ORSA-5)	2 (SKC 575-001, ORSA-5 or Radiello-130)	2 (ORSA-5 or Radiello-130)	3	3
D	Active sampling on an adsorbent tube Thermal desorption Analysis using GC/MS or FID	MAK DFG Solvent mixtures 5 (2005) DGUV 213-504 (2019) BGIA 6265 Method 2 (2019) EN ISO 16017-1 (2001) HSE MDHS 72 & 104 Method 1 (1993-2016) NF EN 14662-1 (2005) EN ISO 16000-6 (2012) EPA TO-1, TO-2 & TO-17 (1984,1999 & 1999) INRS-MétroPol M-338 (2016) NIOSH 2549 (1996)	1B (Chromosorb 106 or Carbopack X)	1B (Chromosorb 106 or Carbopack X)	1B (Carbopack B or Carbopack X)	1B (Carbopack B or Carbopack X)	3

Methods		Protocols	Classification for verifying the IAQG				
			Short term (ST)	Medium term (MT)	Long term (LT1)	Long term (10^{-5}) (LT2)	Long term (10^{-6}) (LT3)
			30 µg·m^{-3}	20 µg·m^{-3}	10 µg·m^{-3}	6 µg·m^{-3}	0.6 µg·m^{-3}
E	Passive sampling on an adsorbent tube Thermal desorption Analysis using GC/MS or FID	MAK DFG Method 5 (2005) INSST MTA/MA-066 (2019) EN ISO 16017-2 (2003) HSE MDHS 80 & 104 Method 2 (1995-2016) NF EN 14662-4 (2005)	3	3	1B (Carbopack B or Carbopack X)	2 (Carbopack B)	3
F	Canister sampling Pre-concentration Analysis using GC/MS	EPA TO-14A (1999) US EPA TO-15 (1999)	3	3	3	3	3
G	Automatic analyser	NF EN 14662-3 (2005) US EPA TO-3 (1984)	2	1A	1A	1A	3

NOTE: Category 1A: validated methods, Category 1B: partially validated methods, Category 2: indicative methods, Category 3: unsuitable methods, Category 3*: methods that cannot be assessed due to a lack of data.