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# Setting of French indoor air quality guidelines for chronic exposure to benzene

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## SUMMARY

Indoor air quality guidelines (IAQGs) provide safe levels of indoor pollutant concentrations below which adverse health effects are not expected to occur in the general population, including susceptible groups.

The development of French IAQGs has been on-going since 2005 in the framework of the National Environment and Health Action Plan (NEHAP, 2004-2008).

According to toxicological and epidemiological data, benzene inhalation leads to acute and chronic effects. For long-term exposure, haematological effects and leukaemia have been observed in the Pliofilm cohort. Benzene is classified as carcinogenic for humans and its genotoxic effects have been demonstrated.

Considering non carcinogenic effects and available toxicological reference values for benzene, the IAQG of 10  $\mu\text{g}\cdot\text{m}^{-3}$  is proposed to protect the general population for long-term exposure. To protect from carcinogenic effects, the proposed IAQGs are based on WHO's potency slope factor: 2 and 0.2  $\mu\text{g}\cdot\text{m}^{-3}$  respectively associated with an excess lifetime risk of  $10^{-5}$  and  $10^{-6}$ .

## KEYWORDS

Benzene, Indoor air, Health effect, Guideline, General population

## INTRODUCTION

In France, indoor pollutant levels have been considerably investigated in different environments (homes, schools, offices...) over the last few years. While the health effects of outdoor air pollution have been widely studied, health effects of indoor exposures need to be assessed. There is also a lack of reference values to facilitate management of indoor air quality. In this context, it seems necessary to promote the development of specific health-based indoor air quality guidelines (IAQGs).

Many countries already have guideline values, and the World Health Organization is currently developing IAQGs (WHO, 2006). At the European Union level, the INDEX project (supported by the Directorate General for Health and Consumers DG-SANCO) elaborated IAQGs for 13 priority chemical pollutants in 2004 (Koistinen *et al.*, 2008). In order to update if necessary, or to extend the approach to other compounds, the French Agency for Environmental and Occupational Health Safety (AFSSET) and the French Scientific and Technical Centre for Building (CSTB) have been leading a multi-partner working group in charge of the development of IAQGs based on health criteria.

As a first step, the methodological approach was developed and a list of substances of concern was established; this list included benzene as high priority compound (AFSSET, 2007a).

Benzene comes from outdoor air (exhaust fumes from mobile sources) and from indoor sources such as combustion (heating, cooking, incense burning, smoking...), attached garages, building materials and furniture, storage of solvents, etc. Inhalation is the main route of exposure for the general population (EC-JRC, 2004). In French residences, benzene concentrations in bedrooms range from 0.4 to 22.8  $\mu\text{g}\cdot\text{m}^{-3}$  (mean over 7 days), with a median of 2.1  $\mu\text{g}\cdot\text{m}^{-3}$  (study in 2003-2005, passive sampling, 541 residences) (Kirchner *et al.*, 2007).

## **METHODS**

According to the WHO, IAQGs correspond to safe levels of pollutant concentrations below which adverse health effects are not expected to occur in the general population, including subgroups considered susceptible due to their health status or age (WHO, 2000). For genotoxic carcinogenic compounds, guideline values are expressed as risk levels corresponding to a probability of cancer occurring.

The methodological approach developed by the working group is based on three steps for any given substance. First, the human and/or animals health effects for inhalation exposure are described, taking into account associated durations of exposure (acute, sub-chronic or chronic). Susceptible subgroups of populations are identified (AFSSET, 2007). The consistency of toxicokinetic and toxicodynamic data, and related effects, is analysed.

Secondly, existing guideline values and toxicological reference values (TRVs) are collected and described: guideline values established within international bodies such as the WHO or by the European Commission are collected; guideline values established at a national scale (proposed by other bodies or countries) are summarized. In addition, available TRVs for inhalation from the US-Environmental Protection Agency-Integrated Risk Information System (US-EPA, IRIS), the Agency for Toxic Substances and Disease Registry (ATSDR), the Office of Environmental Health Hazard Assessment (OEHHA), Health Canada and the Dutch Agency for environmental health (RIVM) are also collected.

Finally an in-depth critical analysis of available values (guidelines and TRVs) is carried out. Duration of exposure, critical health effects, studied populations, point of departure doses (NOAEL or LOAEL), safety factors, low-dose extrapolation are specified and discussed. IAQGs are proposed if there is one or more already existing guideline value established exclusively on health considerations and/or one or more TRV for inhalation. The choice among the reliable values is made on a case-by-case basis according to additional criteria (e.g. establishment date, animal or human data, etc.). If there is neither a guideline value, nor a reliable TRV for inhalation, the working group does not set any IAQG, indicating that additional assessment and research are required.

## **RESULTS AND DISCUSSION**

The available toxicological and epidemiological data indicate that benzene inhalation leads to both acute and chronic effects, and allow for a good description and comprehension of benzene toxicokinetics and mode of action.

The observed chronic effects are bone marrow depression expressed as leukopenia, anaemia, thrombocytopenia, leading to pancytopenia and aplastic anaemia. A causal relationship exists between exposure to benzene or solvents containing benzene at the workplace and the development of leukaemia in a rubberworker cohort (Pliofilm). The International Agency for Research on Cancer (IARC), the US-EPA and the European Commission have classified benzene as a known human carcinogen, respectively, group 1 in 1987, category A in 1998, and category 1 in 2004. The analysis of benzene's mode of action indicates that benzene and

the reactive metabolites cause chromosomal aberrations in humans after chronic exposure. Data in animals support the genotoxic action of benzene.

The AFSSET-CSTB working group has considered benzene as a carcinogenic compound via a genotoxic mechanism. Available guidelines and toxicological reference values for genotoxic-carcinogenic haematological effects are presented in Table 1.

Table 1. Available guideline and toxicological reference values for non-carcinogenic and genotoxic-carcinogenic haematological effects following chronic exposure (scientific review until September 2007):

organization	date	value	study	construction
<b>Chronic exposure – Non carcinogenic effects</b>				
OEHHA	1999	REL = 60 $\mu\text{g.m}^{-3}$	Tsai <i>et al.</i> 1983	UF =10
US EPA	2003	RfC = 30 $\mu\text{g.m}^{-3}$	Rothman <i>et al.</i> 1996	UF =300
ATSDR	2007	MRL = 9.7 $\mu\text{g.m}^{-3}$	Lan <i>et al.</i> 2004	UF =10
<b>Chronic exposure – Genotoxic- carcinogenic effects</b>				
WHO	2000	ERU <sub>i</sub> = 6.10 <sup>-6</sup> ( $\mu\text{g.m}^{-3}$ ) <sup>-1</sup>	Rinsky <i>et al.</i> 1981 – 1987	linear and non-linear mathematical models
US EPA	1998	ERU <sub>i</sub> = 2.2 – 7.8.10 <sup>-6</sup> ( $\mu\text{g.m}^{-3}$ ) <sup>-1</sup>	Rinsky <i>et al.</i> 1981 – 1987	linear mathematical model
RIVM	2001	Cr = 2.10 <sup>-2</sup> mg.m <sup>-3</sup>	no information	no information
OEHHA	2005	ERU <sub>i</sub> = 2.9 .10 <sup>-3</sup> ( $\mu\text{g.m}^{-3}$ ) <sup>-1</sup>	not clear	no information
Health Canada	1991	CT <sub>0.05</sub> = 15 mg.m <sup>-3</sup>	Rinsky <i>et al.</i> 1987	mathematical model

An analysis of the studies used for the construction of these values was performed. All values were determined on the basis of human epidemiological data.

For non-carcinogenic effects, the ATSDR and the US EPA used a benchmark dose as a critical dose to derive the TRV. 240 exposed subjects versus 44 were respectively taken into account. Moreover, the study of Lan *et al.* (2004), which was chosen by ATSDR, was considered more appropriate because the characterisation of exposure at low concentrations is divided into three levels. The working group proposed the IAQG of 10  $\mu\text{g.m}^{-3}$  to protect the general population for long-term exposure (conventionally over 1 year of exposure).

For carcinogenic-genotoxic effects, the unit risk values for which sufficient data were available were discussed. The WHO's value is based on different models (concentration-dependent model and multiplicative risk model), using the Pliofilm cohort (Rinsky, 1981; Rinsky, 1987) and different exposure matrixes (Crump and Allen, 1984; Paustenbach *et al.*, 1992; Paustenbach *et al.*, 1993). The geometric mean of the range of excess lifetime risk of leukaemia estimates is 6 10<sup>-6</sup> ( $\mu\text{g.m}^{-3}$ )<sup>-1</sup>. Since the dose-response relationship remains unknown at low concentrations, the use of a concentration-dependent model and a multiplicative risk model is considered relevant. The WHO unit risk value of 6 10<sup>-6</sup> ( $\mu\text{g.m}^{-3}$ )<sup>-1</sup>, published in 2000, was considered as being the most relevant unit risk value by the group. The concentrations of benzene associated with an excess lifetime risk of 10<sup>-5</sup> and 10<sup>-6</sup> are respectively 2 and 0.2  $\mu\text{g.m}^{-3}$ . The group considers that then the choice of an acceptable risk level is the responsibility of policy makers.

## CONCLUSIONS

The methodological approach is relevant to set IAQG recommendation for chronic exposure, whatever the health effect is. This approach also allows IAQGs for other exposure duration :

- for short-term exposure: 30  $\mu\text{g.m}^{-3}$ , mean over 14 days;
- for subchronic exposure: 20  $\mu\text{g.m}^{-3}$  mean over 1 year.

This method was tested and consolidated on several substances. Formaldehyde and carbon monoxide IAQGs for acute and chronic exposure were published in 2007. Elaboration of IAQGs for tetrachloroethylene, trichloroethylene and naphthalene is ongoing; they will be published in 2009. These elaborated guideline values may then be used by policy makers to set regulatory levels.

This work is now also contributing to the development of WHO guidelines for indoor air quality initiated by WHO-Europe in 2006.

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