Maisons-Alfort, 22 July 2011

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

concerning the 'reference value for hydrocyanic acid – HCN'

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 made public.[1]

On 23 April 2010 the Agency received a request from the Directorate General for Risk Prevention and the Directorate General for Health to "determine the toxicity reference values for Hydrogen cyanide (HCN) for the protection of the general public as part of aircraft rodent control by means of fumigation," including sensitive individuals such as children.

1. BACKGROUND AND PURPOSE OF THE REQUEST

Conditions for using HCN for fumigation of rodents in aircraft are governed by regulations.

Article 7 of Decree 2009-1685 of 30 December 2009 lays down the conditions for use of fumigants based on HCN as products mentioned in Article L. 522-1 of the Environmental Code. In applying this decree, the Order of 14 June 2010 (Official Journal of 4 July 2010), on which the Agency has issued an Opinion on 2 November 2009, specifies the conditions for carrying out aircraft fumigation operations. The aim of the provisions of Article 10 of this Order is to control the access of workers and the general public to the aircraft following fumigation procedures.

In this context, on 23 April 2010, the Agency received a request from the Directorate General for Risk Prevention and the Directorate General for Health to "determine the HCN toxicity reference values to be taken into account for protection of the general public as part of aircraft rodent control by means of fumigation."

Moreover, in the framework of Directive 98/8/EC, the active substance, hydrocyanic acid, is currently being evaluated by the Czech Republic (Member State, Rapporteur) for TP8 (wood

[1] This document is a translation of the original French version; the French language text shall prevail.

preservatives), TP14 (rodenticides) and TP18 (insecticides, acaricides and to control other arthropodes).

2. EXPERT APPRAISAL METHOD

Since this concerns a potential exposure of airline passengers to hydrocyanic acid residues resulting from fumigation, and the maximum exposure time being the duration of the flights concerned, the Agency considered that the appropriate reference value to meet this request was an Indoor Air Quallitiy Guideline (IAQG) Value for short-term exposure to hydrocyanic acid.

The IAQGs, as defined by the Agency, are air concentrations of a chemical substance below which no health effect, or (in the case of odorous compounds), no nuisance or significant indirect effect on health is normally expected for the general population. They thus aim to protect the population from any adverse effects associated with exposure to this substance.

The expert appraisal was entrusted to an Expert Committee (CES) on assessment of the risks related to air environments and the 'Indoor air quality guideline values' Working Group. The results of the Working Group were submitted to the CES, concerning both the methodological and the scientific aspects, on several occasions from September 2010 to May 2011. The report of this expert appraisal, entitled 'Guide to Indoor Air Quality Guideline Values: Hydrogen Cyanide was approved by the Working Group at its meeting on 6 May 2011. This report was adopted by the CES at its meeting of 19 May 2011.

The expert appraisal was carried out in accordance with the French Standard NF X 50-110 'Quality in Expertise Activities - General competence requirements for an expert appraisal activity (May 2003).'

3. ANALYSIS AND CONCLUSIONS OF THE CES

The main elements of this expert appraisal are the following:

- ✓ **Toxicity of HCN**

HCN is very easily absorbed by inhalation and to a lesser extent by skin penetration. Once absorbed, it is distributed rapidly and evenly throughout the body. Because of its affinity for heme, HCN is mostly sequestered in red blood cells. When poisoning is significant, the red blood cells are rapidly saturated and free HCN is massively transported at the cellular level, where it exerts its toxicity..

Toxicity data for short-term respiratory exposure is scarce and insufficiently documented . All of the available literature concerns exposures characterised by high concentrations associated with severe effects (loss of consciousness, asphyxia, coma, etc.), including death.

There are no precise data linking concentrations and short-term exposure times which do not cause health effects.

The only short-term toxicity values available for humans are estimates of exposure values relative to severe effects. They were published by British authors in 1987. These values have been referred to in several health agency reports on the toxicity of hydrogen cyanide (DECOS 2002, IPCS 2004 , ATSDR 2006), which observe that:

- mild effects can be observed at exposure levels of 20 to 40 mg/m^3,
- exposure levels of 50 to 60 mg/m^3 are tolerable for 20 minutes to one hour without immediate or delayed effects,
- an exposure of about 120 to 150 mg/m^3 may cause death in half an hour to an hour,
- beginning at 150 mg/m^3, death can occur in just 30 minutes,
- exposure to 200 mg/m^3 is probably fatal after 10 minutes,
- beginning at 300 mg/m^3, death is immediate.

There are also some toxicity data for long-term exposures, which are however insufficiently documented. They are mainly related to exposures in the workplace. On this basis, some European and American health agencies have developed toxicity reference values for chronic exposure.

✓ **Survey of guideline values, reference values, and other toxicity values**

No guideline value for acute exposure to HCN in the air has been identified in the literature.

Similarly, no health-based reference value for acute inhalation has been published.

However, there are three reference values for chronic exposure by inhalation, published by three health agencies, which are all based on the same study[2] of exposure to HCN in the workplace:

Agency	**Denomination**	**TRV**
US-EPA 2010	Reference Concentration for Chronic Inhalation Exposure (RfC)	8 x10^{-4} mg/m^3
OEHHA 1999	Chronic Reference Exposure Level (REL)	8 x10^{-3} mg/m^3
RIVM 2001	Tolerable Concentration in Air (TCA)	25 x10^{-3} mg/m^3

There are also guideline values for acute exposure to HCN, called 'Acute Exposure Guideline Levels AEGL-1', developed in the United States, under the umbrella of the National Research Council (NRC). They were determined for several short-term exposure times, but do not guarantee a total absence of effects, particularly for susceptible individuals. They are primarily intended for use as preventive measures and precautions to be taken in case of possible HCN emission in the air under accidental conditions.

The authors define the AEGL-1 as 'air concentrations of a substance above which it is expected that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic effects'

[2] El Ghawabi SH, Gaafar MA, El-Saharti AA, *et al.* 1975 Chronic cyanide exposure: A clinical, radioisotope, and laboratory study. Br J Ind Med 32:215-219.

Their values for HCN, according to different exposure times, are given in the following table:

(Time in min)	**10**	**30**	**60**	**240**	**480**
AEGL 1 in ppm	2.5	2.5	2.0	1.3	1.0
AEGL 1 in mg/m^3	2.8	2.8	2.3	1.5	1.1

✓ **Elaboration of the IAQG**

The Working Group did not propose an IAQG, on the basis that there were no precise quantitative data on acute exposures to HCN which would enable them to determine a reference value for short-term inhalation exposure capable of avoiding any effect on health.

✓ **Metrology of HCN in the air**

A survey of the main measurement methods for HCN in air was carried out by the experts. These methods include:

- Direct measurements, which can give on-site sampling results.
- Indirect measurement, requiring the transport of a sample to the laboratory to determine the result.

These methods are described in the Annex of the Working Group's report. It should be noted that the description of direct methods is based on commercial 'manufacturer' data and that the metrological performances announced are given for information only.

The Working Group indicates that the direct measurement method, called ‘adjustable resonant-cavity laser diode’ seems to be the only one that enables detection at limits well below 1 ppm, while allowing rapid reading. It specifies that this method is not very widely used in the context of industrial hygiene, and is probably very expensive.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The expert appraisal covered all data for HCN inhalation toxicity, both in humans and in animals. The acute toxicity of HCN by inhalation is well known at high exposures, as it has been observed in many cases of poisoning. The dose-response relationship indicates that serious consequences, such as asphyxia leading to death, may occur in the short term after exposure, when the defence capabilities of the organism are exceeded.

HCN directly and quickly affects several vital functions, including pulmonary respiration, blood circulation, and cellular respiration.

The expert appraisal found that:

- Data for acute inhalation toxicity in humans are poorly documented and lack precision. This is particularly true of low levels of exposure that cause only mild and reversible effects. In fact, the available toxicity data are mostly related to doses and exposure times causing severe effects.
- exposure data available in animal experiments cannot be used to develop an IAQG.

Given all these elements, and in accordance with the opinion of the WG experts' 'Indoor air guideline values ' and the CESs' 'assessment of the risks related to air environments ', ANSES does not propose IAQG values for short-term exposures by inhalation to hydrogen cyanide present in indoor air.

ANSES notes that the conditions for use of hydrogen cyanide fumigants for aircraft treatment are regulated by the Order of 14 June 2010. It specifies that:

- the entry of crew members in the aircraft is authorised after verification that forced or natural ventilation has decreased the gas concentration below occupational exposure limits (OEL);
- the entry of passengers in the aircraft is authorised after a minimum period of six hours following the entry of aircraft personnel. During this period, the fuselage is mechanically ventilated.

The Agency notes that the limit values[3] in force for hydrogen cyanide are respectively 2 ppm (2.2 mg/m^3) for the occupational exposure limit (8 hours of exposure), and 10 ppm (11 mg/m^3) for the short-term exposure limit (15 minutes of exposure). It points out that the SCOEL (Scientific Committee responsible for proposing OELs to the European Commission) has proposed an OEL of 1 ppm (1.1 mg/m^3) for 8 hours of exposure, and a short-term exposure limit (STEL) of 5 ppm (5 mg/m^3) for 15 minutes of exposure.

To date, the Agency considers that there is no data indicating that the recommendations of the Order of 14 June 2010 are insufficient to ensure the safety of the procedure in regards to aircraft passengers.

However, it appears that the devices, after their treatment, should be naturally or mechanically ventilated for a sufficient time, and at a temperature of at least 25.7° C, to ensure complete desorption of HCN residues from the different materials. In fact, hydrogen cyanide only exists in the gaseous state when the ambient temperature is equal to 25.7° C or higher. Below this temperature, part of the hydrocyanic acid may remain adsorbed to different materials of the aircraft, following the ventilation of the aircraft.

Finally, given the known toxicity of HCN, and due to the fact that the threshold for lack of short-term effect could not be precisely defined, the Agency recommends studying the feasibility of another method of aircraft rodent control which is sufficiently effective and safer with regard to the general public.

The Director General

Marc Mortureux

[3] Decree No. 88-448 of 26 April 1988, as amended by Decree No. 95-608 of 6 May 1995 (OJ 7)