

The Director General

Maisons-Alfort, 11 May 2011

OPINION

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

**concerning the proposal for exposure limit values for chemical agents in
occupational environments**

**Evaluation of biological indicators for exposure to toluene with a view to setting biological
limit values or biological reference values**

ANSES's public health mission involves ensuring environmental, occupational and food safety as well as assessing the potential health risks they may entail.

It provides the competent authorities with the necessary information concerning these risks as well as the requisite expertise 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. This Opinion is a translation of the original French version. In the event of any discrepancy and ambiguity the French language text dated 11 May 2011 shall prevail.

This ANSES Opinion incorporates the expert appraisals undertaken by AFSSET. ANSES became legally operational on 1 July 2010 following the promulgation of the Ministerial Order dated 8 January 2010 enacting its creation, and adopted the missions, knowledge and values of AFSSET and AFSSA.

1. PRESENTATION OF THE ISSUE

ANSES received a formal request on 12 June 2007 from the French Directorate General of Labour to conduct an expert appraisal with the aim of determining occupational exposure limits for about 20 substances including toluene.

2. BACKGROUND

The French Ministry of Labour commissioned ANSES with the aim of determining the appropriate level to be used for occupational exposure limit values (OELVs) for toluene. This formal request was entrusted to the Expert Committee *on expert appraisal for setting*

exposure limits for chemical agents in occupational environments (OEL Committee), which submitted a report¹ on 19 May 2008, recommending for toluene:

- setting an 8-h OEL of 20 ppm (or 75.4 mg.m⁻³) to prevent any visual effects regarding alterations in color discrimination;
- setting a 15-minute short time exposure limit (STEL) of 100 ppm (or 377 mg.m⁻³) in order to prevent any short-term neurobehavioural effects;
- assigning the "skin" notation to prevent any systemic effects that may result from significant dermal absorption;
- supplementing the expert appraisal by developing biological reference values (BRVs) that may be used for biological monitoring of exposures in the workplace;

In order to comply with its latest recommendation, the Agency decided to supplement its expert appraisal on toluene with work on the establishment of biological limit values (BLVs).

3. ORGANISATION OF THE EXPERT APPRAISAL

This expert appraisal was carried out in accordance with the French standard NF X 50-110 "Quality in Expertise - General Requirements of Competence for Expert Appraisals (May 2003)" to ensure compliance with the following points: competence, independence, transparency, and traceability.

This issue falls under the responsibility of the Expert Committee (CES) on *expert appraisal for setting exposure limits for chemical agents in occupational environments* (OEL CES). This committee mandated five experts from the CES (of whom two were appointed rapporteurs specifically for this dossier) and two officers from the agency to form a working sub-group focused specifically on biomarkers (Biomarkers WG).

The Biomarkers WG met three times to complete the necessary work and review the existing data likely to answer this question.

The methodological and scientific aspects of the work were regularly submitted to the CES. This expert appraisal is therefore the result of a group of experts with complementary skills.

The scientific aspects of this Opinion are based on the final report released following this collective expert appraisal: "Collective expert report for setting exposure limit values for chemical agents in occupational environments: evaluation of biological exposure indicators for toluene", which was approved by the CES at the meeting held on 10 June 2010.

4. OPINION AND RECOMMENDATIONS

Reminder of the role of biological monitoring in the worker health protection programme

Biological monitoring of exposure involves measuring, in the biological media (tissues, excretions, secretions or exhaled air) of workers exposed to chemical products, biological exposure indicators which may be:

¹ AFSSET, June 2008. Toluene - Evaluation of the effects on health and techniques for measuring exposure levels in the workplace.

- the toxin itself;
- one or more of its transformation products or metabolites.

Depending on the type of toxin and its fate in the body, the result of the analysis shows either acute recent exposure, or cumulative chronic exposure.

Biological monitoring, atmospheric metrology, and measurement of surface contamination, are complementary approaches which contribute to assessing the extent to which workers are exposed to various substances. One of the specific features of biological monitoring is that it covers all the pathways by which a chemical agent may enter the body (lungs, skin and digestive tract).

Proposal for setting BLVs

Relevance of implementing biological monitoring for toluene

ANSES recommends biological monitoring of occupational exposure to toluene for the following reasons:

- toluene in liquid form may be absorbed by the skin, and dermal absorption can contribute significantly to the overall exposure of workers;
- systemic effects of the neurosensory type have been demonstrated, particularly regarding impairment of color discrimination (dyschromatopsia) in some field studies in occupational environments, which may be due to both exposure through inhalation and dermal absorption.

Choice of biomarkers of exposure (BMEs) and biological limit values

Assessment of the available BMEs for toluene resulted in three biomarkers of exposure being selected that were considered relevant for the biological monitoring of occupational exposure with a view to constructing biological limit values: toluene in blood, toluene in urine and ortho-cresol (o-cresol) in urine.

Biological limit values in the occupational environment, based on exposure to the 8-h OEL and biological reference values for non-occupationally exposed persons, were recommended for these three biomarkers.

For biological monitoring of workers exposed to toluene, ANSES therefore recommends selecting:

- 1) for toluene in blood
 - a biological limit value (BLV) of **20 µg.L⁻¹** with samples taken at the end of the week and at start of shift to assess exposure during the working week;
 - a biological reference value (BRV) of **1 µg.L⁻¹** for the non-occupationally exposed population.
- 2) for toluene in urine
 - a BLV of **30 µg.L⁻¹** with samples taken at the end of the day to assess exposure during the working day;
 - a BRV of **0.4 µg.L⁻¹** for the non-occupationally exposed population.

It should be noted that this biomarker is the most sensitive one and shows good correlation with atmospheric concentrations even at low exposure levels (below 20 mg.m⁻³).

- 3) for ortho-cresol (o-cresol) in urine
 - a BLV of **300 µg.g⁻¹ of creatinine** with samples taken at the end of the week and at end of shift to assess exposure during the working week;
 - two BRVs for the non-occupationally exposed population: a value of **50 µg.g⁻¹ of creatinine for non-smokers** and a value of **250 µg.g⁻¹ of creatinine for smokers**.

It should be noted that this biomarker is the least sensitive one: its correlation with low atmospheric concentrations (below 30 mg.m⁻³) is not very strong.

Additional information

ANSES stresses that:

- recent methods are available for determining these three BMEs. As an example, gas chromatography methods, combined with detection by mass spectrometry, flame ionisation, or photoionisation, are suitable for toluene in blood or urine, as well as for o-cresol;
- assaying benzylmercapturic acid (a metabolite of toluene) in urine is also relevant since urine concentrations of this metabolite at end of shift are well correlated with atmospheric conditions provided that they exceed its sensitivity level² (approximately 15 mg.m⁻³). However, the currently available data are not sufficiently robust and complete to establish a BLV.

the Director General

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² The sensitivity limit corresponds to the lowest atmospheric concentration that can distinguish exposed workers from non-exposed controls (in other words, the atmospheric concentration for which the blood toluene concentrations measured at end of shift are significantly higher in exposed workers than in the non-occupationally exposed controls).