

The Director General

Maisons-Alfort, 1 October 2010

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 the monitoring of biological exposure indicators and establishment of
biological limit values and biological reference values for

2-butoxyethanol and its acetate

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).

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 13 June 2005 from the Directorate General of Labour to conduct an expert appraisal with the aim of determining occupational exposure limits for 2-butoxyethanol and the corresponding acetylated derivative, 2-butoxyethanol acetate.

2. BACKGROUND

The French Ministry of Labour submitted a formal request to ANSES in order to decide the appropriate occupational exposure limit values (OELVs) to select for 2-butoxyethanol and its acetate. This formal request was entrusted to the Expert Committee (CES) on *expert appraisal for setting exposure limits for chemical agents in occupational environments* (OEL CES). The committee produced two reports¹ on 3 July 2008, in which it recommended for both 2-butoxyethanol and 2-butoxyethanol acetate:

¹ AFSSET, December 2008. 2-butoxyethanol - Evaluation of the health effects and methods for measuring exposure levels in the workplace.

- setting an occupational exposure limit value for 8 hours (8-h OEL) of 10 ppm (or 49 mg.m⁻³ for 2-butoxyethanol and 66.5 mg.m⁻³ for its acetylated derivative) in order to prevent any chronic irritant effects in the workplace, potentially leading to impaired respiratory function;
- setting a short-term limit value for 15 minutes (15-min STEL) of 50 ppm (or 246 mg.m⁻³ for 2-butoxyethanol and 333 mg.m⁻³ for its acetylated derivative) to limit exposure peaks and prevent any acute irritant effects;
- assigning the "skin" notation to prevent any potential systemic haemolytic effects;
- supplementing the expert appraisal by developing biological reference values that may be used for biological monitoring of exposure.

In order to comply with its latest recommendation, ANSES decided to supplement its expert appraisal on 2-butoxyethanol and 2-butoxyethanol acetate 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 Committee). The CES mandated five experts from the CES and an ANSES officer to form a working sub-group focused specifically on the subject of biological exposure indicators (BEI WG).

The BEI WG met three times to complete the necessary work and review the existing measurements that might provide an answer to this problem.

The methodological and scientific aspects of the work were regularly submitted to the CES, and the conclusions were presented and approved at the OEL Committee meeting held on 12 March 2010.

This expert appraisal was therefore conducted by 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 ("Expert report for setting exposure limit values for chemical agents in occupational environments" dated March 2010, concerning the evaluation of biological exposure indicators for 2-butoxyethanol and 2-butoxyacetic acid) which was approved by the CES at its meeting held on 12 March 2010.

4. OPINION AND RECOMMENDATIONS

Reminder of the role of biological monitoring within 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:

- 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 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 2-butoxyethanol

Due to the lack of relevant biomarkers of effect, ANSES recommends monitoring of biomarker of exposure (BEI) for 2-butoxyethanol in the workplace, for the following reasons:

- dermal penetration of 2-butoxyethanol is significant, in vapour or liquid form. Dermal penetration is particularly high when the product is diluted and it can greatly contribute to the body burden;
- 2-butoxyethanol has low volatility;
- 2-butoxyacetic acid, a metabolite of 2-butoxyethanol, has been shown to have a systemic haemolytic effect *in vitro* and in animals.

Choice of the biomarker of exposure and of the biological limit value

For biological monitoring of workers exposed to 2-butoxyethanol, ANSES recommends:

- using 2-butoxyacetic acid as the biological exposure indicator. This substance has been identified as the metabolite responsible for the appearance of a systemic effect (haemolysis) both *in vitro* and in animals;
- assaying 2-butoxyacetic acid in urine after hydrolysis in order to take into account intra- and inter-individual variations;
- selecting as the BLV a maximum concentration **of urinary 2-butoxyacetic acid after hydrolysis of 100 mg.g⁻¹ of creatinine**. This concentration, which is consistent with the limited data available from studies on volunteers, was obtained from modelling data (PBPK model) and corresponds to the expected concentration

for exposure to the 8-h OEL taking into account absorption (of vapours) by pulmonary and dermal routes:

- for the non-occupationally exposed population, setting a biological reference value (BRV) equal to **0.05 mg.g⁻¹ of creatinine for urinary 2-butoxyacetic acid after hydrolysis**;
- taking samples at end of shift (irrespective of the day of the week), due to a 4 to 6 hour half-life of 2-butoxyacetic acid in urine;
- applying the same BEIs, BLVs and BRVs for both 2-butoxyethanol and its acetate.

Additional information

ANSES stresses that:

- 2-butoxyacetic acid can be considered as a specific biological exposure indicator for exposure to 2-butoxyethanol and its acetate;
- recent methods are available for assaying 2-butoxyacetic acid in urine after hydrolysis. For example, the separation technique using gas chromatography (GC) coupled with negative-ion chemical ionisation mass spectrometry produces no analytical interference and can follow G-EQUAS inter-laboratory quality control procedures.

Produced in six copies,

The Director General

Marc Mortureux