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French agency for food, environmental and occupational health & safety

COLLECTIVE EXPERT APPRAISAL: SUMMARY AND CONCLUSIONS

regarding the expert appraisal on recommending occupational exposure limits for chemical agents

Application on substances already reviewed by the OEL Committee of the methodological document aiming at preventing the effects of occupational co-exposure to noise and chemicals

This document summarises and presents the work of the Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee)

1- Presentation of the issue

ANSES has been mandated by the French Directorate General for Labour to conduct the expert appraisal work required for setting occupational exposure limit values (OELVs) for a number of substances.
The Agency decided to go ahead and conduct assessments to establish limit values for the substances included in its work programme and methodological work on topics of concern or emerging issues in occupational health, falling within its sphere of competence and the missions assigned to it by its supervisory ministries.

The OEL committee has conducted methodological work aiming at preventing the effect of occupational co-exposure to noise and chemicals. The results of this work led the OEL committee to review the substances for which it had already recommended exposure limits by considering co-exposure to noise, with a view to assigning an “ototoxic” notation where appropriate.

2- Organisation of the expert appraisal

ANSES entrusted examination of this internal request to the Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee). This Committee mandated three rapporteurs (one OEL Committee expert, one expert in ototoxicity and one ANSES officer) to conduct this expert work.
The findings of this work led to the drafting of this document, which was discussed by the experts of the OEL Committee on three occasions before being adopted on 9 July 2013. The result of the collective expert appraisal described below takes account of the observations and additional information provided by the Committee members.

This expert appraisal was therefore conducted by a group of experts with complementary skills. It was carried out in accordance with the French Standard NF X 50-110 “Quality in Expert Appraisals – General requirements of Competence for Expert Appraisals (May 2003)”.

3- Description of the method

On the basis of the available knowledge, the OEL Committee reviewed certain substances for which it had already recommended exposure limits, by considering co-exposure to noise, with a view to assigning an “ototoxic” notation where appropriate.

This document was prepared based on reports from several expert organisations (CONCAWE 2005, WHO 2005, EU-OSHA 2009, IRSST 2009, NEG 2010). Source articles were consulted when it was deemed necessary. In addition, a review of the literature on Medline, Toxline and Scopus was carried out for 2010-2012.

The collective expert appraisal work and its conclusions and recommendations were adopted on 9 July 2013 by the OEL Committee (term of office 2010-2013)
This work was submitted to a public consultation from 27/08/2013 to 27/10/2013. The list of persons or organizations who contributed to the public consultation is listed in appendix. The comments received were reviewed by the OEL Committee who adopted this version on 12 December 2013.

4- Result of the collective expert appraisal

4-1 Styrene

In 2010, the OEL Committee had recommended for styrene (ANSES 2010):

- setting an **occupational exposure limit value for 8 hours** (8-h OEL) **of 100 mg.m^{-3}** (or 25 ppm) with the aim of preventing any possible neurotoxic effects in the workplace. This recommendation is derived from a review of the scientific literature and is consistent with the analyses conducted by other committees such as the SCHER[1] in 2008 and the ACGIH[2] in 2007. This would lead to a halving of the indicative value currently in force;
- setting a **short-term limit value for 15 minutes** (15-min STEL) of **200 mg.m^{-3}** to avoid exposure peaks that may cause irritation of the respiratory system's mucous membranes. This recommendation is based on a study in humans (Stewart et al., 1968) which concluded that a maximum concentration of styrene does not produce any irritation effects at 50 ppm;
- assigning a **“skin” notation,** as quantitative information indicates that dermal exposure can contribute substantially to the body burden.

Moreover, in 2012, a new expert appraisal on styrene led to certain biological indicators of exposure being selected, with a view to setting a biological limit value. The results of this appraisal are summarised in the table below.

Urinary styrene at end of shift	BLV based on exposure to the 8h-OEL: 40 µg.L^{-1} BLV based on a health effect: None Biological reference values: Not specified

[1] SCHER: Scientific Committee on Health and Environmental Risks of the European Union.
[2] ACGIH: American Conference of Governmental Industrial Hygienists

Sum of the urinary concentration of mandelic acid and phenylglyoxylic acid at end of shift	BLV based on exposure to the 8h-OEL: 600 $mg.g^{-1}$ cr BLV based on a health effect: None Biological reference values: 3 $mg.g^{-1}$ cr

Table 1: Results of the expert appraisal on "Evaluation of biological indicators of exposure to styrene with a view to establishing BLVs"

Some experiments have shown that noise interacts with styrene in a synergistic manner (Lataye, 2000 and 2007, Mäkitie 2003). Based on the available studies in rats, the NOAEL for styrene alone as an ototoxic substance is estimated about 250 ppm by inhalation (Chen, 2007; NEG, 2010). In inhalation studies in rats, 300 ppm (for 4 weeks) was identified as a no ototoxic effect level, both with and without exposure to noise (100 dB SPL) (Mäkitie 2002, 2003). However, in active rats, a LOAEL of 300 ppm for styrene alone as an ototoxic substance was obtained (Lataye et al., 2005).
In occupational studies, currents levels of styrene averaged approximately 3,5 - 50 ppm.. Even at the lowest average exposures recorded among employees (3.5 to 22 ppm), significant hearing loss was observed (Johnson, 2006; Mascagni 2007; Morata 1993, 2002). Groups exposed to styrene were subjected to noise below 85 dBA at the time of the study. However, exposure to styrene and louder noise levels in the past, as well as high concentration peaks in the present and the past, are likely to aggravate this effect and contribute to greater hearing loss.
Sliwinska-Kowalska (2003, 2005) found a positive correlation between the average life-long concentration of styrene of 14 ppm and hearing loss.
The influence of long-term exposure was demonstrated in the study by Triebig et al., which showed hearing impairment among employees exposed to 30-50 ppm for at least 10 years with concentrations above 50 ppm in the past (Triebig, 2009).
The current OEL recommended by the OEL Committee is 25 ppm, in order to prevent neurotoxic effect of this substance, the critical effect upon which the OEL is based.
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The OEL Committee recommends to assign the “ototoxic” notation for styrene.

4.2 Toluene
The OEL Committee recommended setting for toluene (AFSSET 2008, ANSES 2011) :
- an **exposure limit value (8h) of 20 ppm** (or 75.4 mg/m^3);
- a **STEL of 100 ppm** (or 377 mg/m^3);
- and maintaining a **"skin" notation**.

Setting a limit (8h) of 20 ppm for toluene in the workplace was recommended, to prevent any visual impairment such as colour discrimination.
Furthermore, in order to limit exposure peaks, setting a STEL of 100 ppm (or 377 mg/m^3) was recommended, which is also relevant for preventing possible short-term neurobehavioural effects. This value is identical to the one recommended by the SCOEL in 2001.
The "skin" notation for toluene should be maintained because of the existence of occupational situations that could lead to dermal exposure to liquid toluene for which skin penetration is likely to contribute substantially to an increase in body burden.
Three biomarkers of exposure were considered relevant for the biological monitoring of occupational exposure with a view to establishing biological limit values; blood toluene, urinary toluene and urinary ortho-cresol (*o*-cresol).

	Blood toluene	Urinary toluene	Urinary *o*-cresol
Biological limit values in the workplace	20 $\mu g.L^{-1}$ Samples to be taken at the end of the week and start of the shift	30 $\mu g.L^{-1}$ Samples to be taken at the end of the shift	300 $\mu g.g^{-1}$ of creatinine Samples to be taken at the end of the week and end of the shift
Biological reference	1 $\mu g.L^{-1}$	0.4 $\mu g.L^{-1}$	50 $\mu g.g^{-1}$ of

value for the general population			creatinine for non-smokers and a value of 250 µg.g^{-1} of creatinine for smokers

Several animal studies have shown the effects of toluene on the auditory receptor.
Inhalation of high concentrations of toluene disrupts the auditory system and causes a permanent rise in hearing thresholds in animal experiments (mainly in rats) (Pryor et al., 1983, 1984a, 1984b; Pryor & Howd, 1986; Rebert et al., 1983; Johnson & Canlo, 1994a, 1994b; Campo et al., 1997, 1999; Lataye et al., 2003).
Repeated exposure to toluene at concentrations ranging from 600 to 1500 ppm, depending on the test used to identify the hearing loss, seems to be necessary to cause ototoxicity in rats.
Some indications suggest that this ototoxicity is a long-term irreversible effect: even after one year, auditory function was not restored (Nylen et al., 1994a, 1994b).
It should be noted that there are currently no experimental data on the hearing impairment of active rats exposed to toluene. Therefore, the exposure values reported in the literature to identify an animal NOAEL or LOAEL following co-exposure to toluene and noise are certainly overestimated.
In some epidemiological studies, the ototoxic effects of toluene were associated with exposure levels currently identified in the workplace of 10-50 ppm (Bernardi, 2000; Morata, 1997; Vrca 1996). The histories of exposure to toluene and/or noise are not well characterised and certain groups of employees were co-exposed to other solvents. Moreover, it is likely that in most cohorts described, participants were exposed to higher concentrations in the past, as well as exposure peaks in the present or the past that could explain the observed effects.
Compliance with the 8h-OEL recommended by the OEL Committee, associated with the average regulatory value of 80 dBA at which preventive measures must be initiated, seems to offer protection from the synergistic effect of concomitant exposure to noise and toluene. Auditory damage occurs only with long-term exposure to toluene concentrations well above the recommended 8h-OEL even when accompanied by exposure to noise at around 80 dBA.
The OEL Committee recommends to assign the “ototoxic” notation for toluene.

4-3 Trichloroethylene (TCE)

The OEL Committee (ANSES 2012, draft) considers TCE **as a non-threshold carcinogen.** Different studies calculating excess risk were analysed (from epidemiological studies for the US EPA and the BAuA, and from animal studies for the WHO, OEHHA and Health Canada).
The OEL Committee found that it was not possible to use the results of the epidemiological or animal studies to calculate the excess cancer risk associated with occupational exposure to TCE. **They proposed establishing a pragmatic OEL,** which is not intended to prevent the carcinogenic effects of TCE but to implement a management tool to limit occupational exposure.
The OEL Committee selected the renal effect as the critical effect and the study by Maltoni et al. (1988) in rats as the key study: the authors observed a karyocytomegaly in renal tubular cells at 300 and 600 ppm in male rats (significant results for both doses, $p < 0.01$). The NOAEC for renal effects was 100 ppm, to which two safety factors were applied (SF_A for transposition from animals to humans = 2.5, and SF_H for intra-species variability = 5) hence **an 8h-OEL of 40 mg/m^3 or 7 ppm**.
In inhalation studies in rats, no effect on hearing was observed after exposure to 1600 ppm TCE alone (for 12 or 13 weeks) (NOAEL) (Crofton, 1997; Rebert, 1982). Reference concentrations causing a 15 dBA increase in the hearing threshold were 1418 ppm (data from 4 weeks of exposure) and 1707 ppm (data from 13 weeks of exposure) (Crofton, 1997). Combined exposure to 3000 ppm of TCE (only dose tested) and 95 dBA of noise leads to synergistic interactions (Muijser, 2000).
The few available studies in humans indicate that TCE can be ototoxic in humans, but the exposure concentrations in these studies could not be evaluated (Szulc-Kuberska, 1976; Tomasini, 1971).

The 8h-OEL for trichloroethylene recommended by the OEL Committee aims to protect from kidney damage. The NOAEL of 100 ppm for this effect is much lower than that at which hearing loss is observed in rats. Thus protecting from the renal effect equates to de facto protection from the ototoxic effect of TCE.
However, there are no human data in the literature to date that indicate a possible synergistic or additive effect of co-exposure to TCE and noise.
The OEL Committee doesn't recommend to assign the "ototoxic" notation for trichloroethylene.

4-4 Carbon monoxide (CO)

Carbon monoxide's toxicity is due to its capacity to bind to haemoglobin to form carboxyhaemoglobin, which inhibits the transport of oxygen in the blood.
The OEL Committee recommended (ANSES 2011) setting an 8-hour occupational exposure limit value for CO of **20 mg.m^{-3}**, **or about 17 ppm.**
This recommendation is designed to prevent, in the workplace, any tissue hypoxia caused by the conversion of oxyhaemoglobin to carboxyhaemoglobin (COHb).
In humans, numerous studies conducted in healthy adults show that when COHb levels reach 5%, maximum oxygen consumption is reduced, resulting in reduced capacity to work and neurobehavioral disturbances.
However at COHb levels of 2.9%, no effect is observed in the healthy adult population which can be compared to the worker population.
The mathematical model used for modelling the toxicokinetic profile of CO in the body (Coburn-Foster-Kane, 1965) shows that 2.9% of COHb corresponds to exposure to a CO concentration of 19.5 mg.m^{-3}.
For better protection of worker health, the OEL Committee recommends for CO not a 15min-STEL but a ceiling value of 200 ppm (or 230 mg.m^{-3}). This value must not be exceeded at any time in the working day.

In inhalation studies in rats, carbon monoxide alone had no effect on the auditory system at concentrations of up to 1500 ppm (the NOAEL) (Chen, 1999). However, it may potentiate the effects of noise, even when noise levels are not sufficient to cause a change in hearing.
In combination with noise (95 dBA at 100 kHz), the experimental NOAEL was 300 ppm and the LOAEL was 500 ppm (Chen, 1999; Fechter, 2000; Lund, 2004).
Acute human poisoning by carbon monoxide was associated with hearing loss, even in the absence of exposure to excessive noise.
There is no evidence that chronic occupational exposure to carbon monoxide potentiates the effects of noise.
Human exposure to carbon monoxide and noise at levels above 90 dBA increases hearing thresholds (Lacerda, 2007). In a small subgroup, hearing loss was significant for exposures to between 16 and 35 ppm of CO in combination with noise (Lacerda, 2007).
The 8h-OEL for CO is 17 ppm. It was established to keep the carboxyhaemoglobin rate in blood below 3% and prevent adverse neurobehavioral and cardiovascular effects, while maintaining the exercise capabilities necessary for work. At this 8h-OEL a pilot study shows hearing loss associated with noise levels above the regulatory value of 80 dBA that leads to the implementation of preventive measures.
In addition, the benchmark dose calculated at the lower bounds gives reference doses in rats for hearing thresholds of 194 and 320 ppm; this value is very close to the ceiling value recommended by the OEL Committee without taking into account any exposure to noise.
The OEL Committee recommends to assign the "ototoxic" notation for carbon monoxide.

5- Conclusions and recommendations of the OEL Committee :

The OEL Committee considers it necessary to pay special attention to the effects of co-exposure to chemicals and noise. In conclusion, it recommends assigning the "ototoxic" notation to the following substances: styrene, toluene and carbon monoxide.

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