COLLECTIVE EXPERT APPRAISAL: SUMMARY AND CONCLUSIONS

Regarding the "expert appraisal for recommending occupational exposure limits for chemical agents"

Assessment of health effects and methods for the measurement of exposure levels in workplace atmospheres for

methyl ethyl ketone peroxide (CAS No. 1338-23-4)

This document summarises the work of the Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee) and the Working groups on health effects and on metrology.

Presentation of the issue

On 12 June 2007, AFSSET, which became ANSES in July 2010, was requested by the Directorate General for Labour to conduct the expert appraisal work required for establishing recommendations on measures to be taken in the event of specific exposure profiles such as those with peaks.

In 2010, ANSES published a report that recommended studying the 36 substances in France with a short-term exposure limit but no time-weighted average (TWA) to recommend health values taken from the most recent scientific literature (ANSES, 2010).

In this context, an assessment was undertaken for methyl ethyl ketone peroxide (MEKP), which has a short-term exposure limit in France set at 1.5 $mg.m^{-3}$ in a Circular[1] of 1987 but no TWA.

Scientific background

The French system for establishing OELVs has three clearly distinct phases:

- Independent scientific expertise (the only phase entrusted to ANSES);
- Proposal by the Ministry of Labour of a draft regulation for the establishment of limit values, which may be binding or indicative;
- Stakeholder consultation during the presentation of the draft regulation to the French Steering Committee on Working Conditions (COCT). The aim of this phase is to discuss the effectiveness of the limit values and if necessary to determine a possible implementation timetable, depending on any technical and economic feasibility problems.

The organisation of the scientific expertise phase required for the establishment of Occupational Exposure Limits (OELVs) was entrusted to AFSSET in the framework of the 2005-2009

[1] Circular of 13 May 1987 supplementing the annex to the Circular of 19 July 1982 on the acceptable values for concentrations of certain hazardous substances in workplace atmospheres.

Occupational Health Plan (PST) and then to ANSES after AFSSET and AFSSA merged in 2010.

The OELs, as proposed by the Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee), are concentration levels of pollutants in workplace atmospheres that should not be exceeded over a determined reference period and below which the risk of impaired health is negligible. Although reversible physiological changes are sometimes tolerated, no organic or functional damage of an irreversible or prolonged nature is accepted at this level of exposure for the large majority of workers. These concentration levels are determined by considering that the exposed population (the workers) is one that excludes both children and the elderly.

These concentration levels are determined by the OEL Committee experts based on information available from epidemiological, clinical, animal toxicology studies, etc. Identifying concentrations that are safe for human health generally requires adjustment factors to be applied to the values identified directly by the studies. These factors take into account a number of uncertainties inherent to the extrapolation process conducted as part of an assessment of the health effects of chemicals on humans.

The Committee recommends the use of three types of values:

- 8-hour occupational exposure limit (8h-OEL): this corresponds to the limit of the time-weighted average (TWA) of the concentration of a chemical in the worker's breathing zone over the course of an 8-hour work shift. In the current state of scientific knowledge (toxicology, medicine, epidemiology, etc.), the 8h-OEL is designed to protect workers exposed regularly and for the duration of their working life from the medium- and long-term health effects of the chemical in question;
- Short-term exposure limit (STEL): this corresponds to the limit of the time-weighted average (TWA) of the concentration of a chemical in the worker's breathing zone over a 15-minute reference period during the peak of exposure, irrespective of its duration. It aims to protect workers from adverse health effects (immediate or short-term toxic effects such as irritation phenomena) due to peaks of exposure;
- Ceiling value: this is the limit of the concentration of a chemical in the worker's breathing zone that should not be exceeded at any time during the working period. This value is recommended for substances known to be highly irritating or corrosive or likely to cause serious potentially irreversible effects after a very short period of exposure.

These three types of values are expressed:

- either in $mg.m^{-3}$, i.e. in milligrams of chemical per cubic metre of air and in ppm (parts per million), i.e. in cubic centimetres of chemical per cubic metre of air, for gases and vapours;
- or in $mg.m^{-3}$, only for liquid and solid aerosols;
- or in $f.cm^{-3}$, i.e. in fibres per cubic centimetre for fibrous materials.

The 8h-OELV may be exceeded for short periods during the working day provided that:

- the weighted average of values over the entire working day is not exceeded;
- the value of the short term limit value (STEL), when it exists, is not exceeded.

In addition to the OELs, the OEL Committee assesses the need to assign a "skin" notation, when significant penetration through the skin is possible (Anses, 2014a). This notation indicates the need to consider the dermal route of exposure in the exposure assessment and, where necessary, to implement appropriate preventive measures (such as wearing protective gloves).

Skin penetration of substances is not taken into account when determining the atmospheric limit levels, yet can potentially cause health effects even when the atmospheric levels are respected.

The OEL Committee assesses the need to assign an “ototoxic” notation indicating a risk of hearing impairment in the event of co-exposure to noise and the substance below the recommended OELs, to enable preventionists to implement appropriate measures (collective, individual and/or medical) (Anses, 2014a).

The OEL Committee also assesses the applicable reference methods for the measurement of exposure levels in the workplace. The quality of these methods and their applicability to the measurement of exposure levels for comparison with an OEL are assessed, particularly with regards to their compliance with the performance requirements in the NF-EN 482 Standard and their level of validation.

Organisation of the expert appraisal

ANSES entrusted examination of this request to the Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee). The Agency also mandated:

- The working group on health effects to conduct the expert appraisal work on health effects;
- The working group on metrology to assess measurement methods in workplace atmospheres.

The methodological and scientific aspects of the work of this group were regularly submitted to the Expert Committee.

The report produced by the working group takes account of 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 Expertise Activities”.

Preventing risks of conflicts of interest

ANSES analyses interests declared by the experts before they are appointed and throughout their work in order to prevent potential conflicts of interest in relation to the points addressed in expert appraisals.

The experts’ declarations of interests are made public on ANSES's website (www.anses.fr).

Description of the method

For the assessment of health effects:

A summary report on the health effects of MEKP was prepared by the working group on health effects and submitted to the OEL Committee, which commented on it and added to it.

The summary report was based on bibliographic information taking into account the scientific literature that had been published on this substance up to 2013 and the ECHA[2] database providing information about substances registered under the REACH Regulation. The literature search was carried out using the summary report written by the Health Council of the Netherlands (2002), the summary document written by ACGIH (2001) and articles found in the Medline, Toxline and HSDB (ToxNet) databases.

For assessment of methods for measuring exposure levels in workplace:

A summary report was prepared by the working group on metrology and submitted to the OEL Committee, which added its own comments.

The summary report presents the various protocols for measuring methyl ethyl ketone peroxide in workplace atmospheres grouped together based on the methods they use. These methods were then assessed and classified based on the performance requirements set out particularly in the French Standard NF EN 482: "Workplace atmospheres - General requirements for the performance of procedures for the measurement of chemical agents" and the decision-making criteria listed in the methodology report (Anses, 2014a).

A list of the main sources consulted is detailed in the methodology report (Anses, 2014a).

These methods were classified as follows:

- Category 1A: the method has been recognized and validated (all of the performance criteria in the NF-EN 482 Standard are met);
- Category 1B: the method has been partially validated (the essential performance criteria in the NF-EN 482 Standard are met);
- Category 2: the method is indicative (essential criteria for validation are not clear enough);
- Category 3: the method is not recommended (essential criteria for validation are lacking or inappropriate).

A detailed comparative study of the methods in Categories 1A, 1B and 2 was conducted with respect to their various validation data and technical feasibility, in order to recommend the most suitable method(s) for measuring concentrations for comparison with OELs.

The collective expert appraisal work and its conclusions and recommendations were adopted on 13 May 2014 by the OEL Committee.

The collective expert appraisal work and the summary report were submitted to public consultation from 21/05/2015 to 21/07/2014. No comments were received. The OEL Committee (term of office 2014-2017) adopted this version on 09 May 2016.

Results of the collective expert appraisal on the health effects

Kinetics

No data were found in the scientific literature regarding the absorption, distribution, metabolisation or excretion of MEKP in humans or animals.

[2] European Chemicals Agency

General toxicity

The mechanism of toxicity for MEKP is related to the formation of free radicals inducing lipid peroxidation, which in the event of ingestion, causes damage to the gastrointestinal mucosa and liver in particular (Bates *et al*., 2001; Karhunen *et al*., 1990). MEKP breaks down to form various hydroxyl, ethyl and methyl radicals as well as alkoxy radicals (RO°) and peroxyl radicals (ROO°). These radical forms can in turn react with biological macromolecules and thus cause lipid peroxidation, protein modification and inactivation, and nucleic acid adducts (Graham *et al*., 2011; Andо and Tappel, 1985; Summerfield and Tappel, 1984).

Toxicity in humans

Workers can be exposed to MEKP aerosols or solutions by inhalation and skin and/or eye contact. This substance is highly irritative and corrosive to the skin and mucosa.

Acute and subacute toxicity

Fraunfelder *et al.,* 1990 studied the ocular lesions of 13 patients who had been accidentally exposed to MEKP vapour or solvent with varying degrees of dilution. The ocular lesions, primarily located on the cornea, were associated with photophobia, watery eyes and decreased or even absent conjunctival and corneal sensitivity. The most severe ocular lesions corresponded to persistent keratitis (exacerbations and remissions) and resembled, according to the authors, keratitis observed after exposure to mustard gas.

Decreased pulmonary function, nose and throat irritation, headaches, vertigo and respiratory difficulty were observed in some workers exposed by inhalation primarily to MEKP (concentrations of 0.19 to 1.24 $mg.m^{-3}$) as well as to other chemical compounds including toluene isocyanate. One of the workers had hyperreactivity to toluene diisocyanate (McGlothlin and Thoburn, 1981 cited by Health Council of the Netherlands, 2002). Due to co-exposure, it was not possible to distinguish between the effects of MEKP and those of the other substances.

A few cases of allergic contact dermatitis have been reported in workers who had positive reactions to MEKP upon patch testing (Bourne and Milner, 1963; Stewart *et al.,* 1992; Bhushan *et al.,* 1997).

Several cases of accidental and deliberate MEKP ingestion have been reported, with acute toxic symptoms such as gastrointestinal bleeding, abdominal burns, necrosis, stomach perforation, oesophageal stricture, severe metabolic acidosis, rapid hepatic failure, rhabdomyolysis and respiratory failure.

Subchronic and chronic toxicity, and carcinogenicity

No data were found in the literature regarding the chronic or subchronic toxicity or carcinogenicity of MEKP in humans.

Toxicity in animals

The data on the toxicity of MEKP in animals have primarily been taken from the publication by Floyd and Stokinger (1958) and secondary sources (some publications were not found in the scientific literature).

Acute and subacute toxicity

In rats, Floyd and Stokinger (1958) determined a lethal concentration for 50% of animals (LC_{50}) of 1460 $mg.m^{-3}$ for four hours of exposure by inhalation to MEKP (in a 60% solution in dimethyl phthalate (DMP)). It should be noted that the authors of an industrial study of 1976 described by ECHA (2012) determined a higher LC_{50} than the previous study (17 $mg.L^{-1}$, i.e. 17,000 $mg.m^{-3}$) in rats exposed for four hours to MEKP by inhalation.

In mice, Floyd and Stokinger (1958), using the same protocol as in rats (exposure to MEKP by inhalation for four hours in a 60% solution in DMP), determined a LC_{50}[3] of 1240 $mg.m^{-3}$.

Dermal tests in rabbits showed that a single application on shaved skin of a 60% MEKP solution (in dimethyl phthalate) induced erythema, oedema and vesiculation within two or three days. However, solutions containing no more than 1.5% MEKP caused no skin irritation in rabbits.

Ocular tests showed that exposing the eyes of rabbits to solutions containing 3% MEKP (in dimethyl phthalate) induced extensive effects in the cornea, iris and conjunctiva while solutions containing 0.6% MEKP had an effect on the conjunctiva only.

According to Floyd and Stokinger (1958), MEKP appeared to be more irritating to the skin and eyes than the other organic peroxides tested.

Repeated dose toxicity

No repeated dose toxicity studies by inhalation were identified in the literature.

All of the rats (n=5) exposed orally to 97 mg/kg of MEKP (diluted in DMP), three days a week for seven weeks, died during the exposure period. The authors interpreted this result as a cumulative effect of MEKP following repeated exposure to low doses. Changes in the body weight of animals were also reported (Floyd and Stokinger, 1958).

In the NTP[4] (1993) report, the effects of repeated dermal exposure to MEKP (in a 45% solution in DMP) were studied in Fischer rats and $B6C3F_1$ mice. The animals were administered respective daily doses of 1.07 to 107 mg/rat and 0.357 to 35.7 mg/mouse, five days a week for 13 weeks (plus two consecutive days during the 14th week). The animals exposed to the highest doses died or had to be sacrificed early due to the severity of the observed dermal lesions. Necrosis, inflammation and acanthosis (epidermal hyperplasia) were noted on the application site in rats and mice. Dermal lesions were observed from exposure to the low doses.

The other reported effects included a dose-dependent decrease in the body weight of the animals with the exception of female mice, changes in the weights of certain organs (such as a decrease in liver weight in rats only), and histopathological changes (spleen and bone marrow lesions). These were considered secondary responses and were observed almost exclusively in the animals sacrificed early.

Genotoxicity

Two studies showed that MEKP (diluted to 45% in dimethyl sulphoxide) was not mutagenic in *S.* Typhimurium strains TA100, TA1535, TA1537 or TA98, with or without S9 metabolic activation (Mortelmans *et al.,* 1986 and NTP, 1993).

[3] Lethal concentration 50
[4] National Toxicology Program

However, a study by Levin *et al*., 1984 reported by the Health Council of the Netherlands (2002) showed that MEKP (diluted to 50% in DMP) induced a weakly positive response with *S.* Typhimurium strain TA102, a strain known to be sensitive to oxidative mutagens.

A few data taken from *in vitro* tests appear to indicate that MEKP induces an increase in the frequency of sister chromatid exchanges in Chinese hamster ovary (CHO) cells (NTP, 1993 and Health Council of the Netherlands, 2002). An increase in the percentage of chromosome aberrations was also found in an *in vitro* test in CHO cells exposed to MEKP (NTP, 1993).

In vivo, the authors of the NTP (1993) report conclude that there was no statistically significant increase in the frequency of micronuclei induced by MEKP in the conditions of the study, and there were no cytotoxic effects on bone marrow based on the percentage of polychromatic erythrocytes in the total analysed blood sample. Given the date on which this study was undertaken, its methodological conditions and its imprecise data, it is not possible to take a firm position as to the merits of these conclusions; however, there are no specific arguments to refute them. In conclusion, this study has fairly limited significance in the overall assessment of the potential genotoxic effects of MEPK.

Summerfield and Tappel (1984) showed DNA interstrand crosslinks and DNA-protein crosslinks in the brains of rats exposed intraperitoneally to MEKP. However, pretreatment of the rats with vitamin E reduced the numbers of both types of crosslinks, presumably by acting as a scavenger of free radicals produced by MEKP (Summerfield and Tappel, 1984).

Carcinogenic effects

A study undertaken by Logani *et al.* (1984) showed that MEKP (diluted to 50% in dibutyl phthalate) had weak tumour-promoting activity after 25 weeks of dermal application in hairless mutant mice irradiated with UVB. The authors conclude that lipid peroxidation may have an impact on the promotion of skin tumours, given that the promoting activity of MEKP was enhanced by pretreatment with diethyl maleate, which is known to deplete intracellular glutathione in several tissues (including the skin of mice) and increase lipid peroxidation.

Data from secondary sources describe the development of tumours (subcutaneous sarcoma, pulmonary adenoma, malignant lymphoma) in mice exposed to MEKP (unknown route and duration of exposure).

Reproductive toxicity

No studies on the reproductive toxicity of MEKP by inhalation were identified in the literature.

No effects on sperm morphology or the vaginal cytology parameters examined were observed in rats or mice following daily dermal exposure to doses of MEKP (diluted in DMP) of up to 10.7 mg (rats) and 3.57 mg (mice) for 13 weeks.

With oral exposure (gavage), an industrial study of 2006 described by ECHA and undertaken in accordance with OECD[5] Guideline 421 showed no reproductive effects on the F0 generation. Moreover, there were no observed effects on litter size, the percentage of male pups, post-natal survival or growth after exposure to MEKP in the F0 parental generation. The rats were exposed by gavage to 0, 25, 50 and 100/75 mg/kg/day for 28-29 days (including 14 days before mating) for males and for 39-45 days (from 14 days before mating to day 3 of lactation) for females. It should be noted that due to the mortality/morbidity observed in some animals exposed to 100 mg/kg/day, the authors lowered the dose to 75 mg/kg/day after two days of

[5] Organisation for Economic Cooperation and Development

exposure. For the F0 parental generation, the systemic toxicity effects reported only in the group exposed to the dose of 100/75 mg/kg/day were mortality/morbidity, decreases in weight gain and food intake and macroscopic and microscopic effects on the stomach.

Establishment of OELs

8h-OEL

Given the small database for MEKP, the literature was analysed in order to verify whether the mechanism of action and toxicity of MEKP could be compared to those of hydrogen peroxide (H_2O_2), as indicated by ACGIH. Several data regarding their mechanisms of action and health effects prove that it is difficult to compare these two substances (for more information, see Annex 1 of the collective expert appraisal report).

MEKP is irritative and corrosive to the skin and mucosa.

No conclusions can be drawn from the few data available in the literature as to the medium- or long-term systemic toxicity of this substance. Thus, in accordance with the methodological document on the establishment of limit values for irritants and corrosives (ANSES, 2014b), a 15min-STEL can be recommended to protect workers from the irritating and corrosive effects MEKP but it does not appear relevant to recommend an 8h-OEL.

15min-STEL

No relevant data are available in the literature to establish a 15min-STEL, even considering similar compounds such as hydrogen peroxide and benzoyl peroxide.

Based on the current bibliographic data, no scientifically sound numerical values can be recommended for MEKP. However, it should be noted that there is a French indicative Occupational Exposure Limit (OEL) of 1.5 $mg.m^{-3}$ (0.2 ppm) (Circular of 13 May 1987) for which no supporting documents were found. The available data that were examined do not confirm or contradict the validity of this 1.5 $mg.m^{-3}$ value.

"Skin notation"

In the absence of a conclusion on systemic toxicity, the "skin" notation was not assigned for MEKP.

"Ototoxic" notation

In the absence of scientific data on the ototoxic effects of MEKP, the "ototoxic" notation was not assigned for this substance.

Results of the collective expert appraisal on measurement methods in workplace atmospheres

Assessment of methods for measuring MEKP in workplace atmospheres

Two methods for measuring concentrations of MEKP in workplace atmospheres were identified and assessed (see Table 1).

In the absence of OELs recommended by the OEL Committee, the measurement methods were assessed in relation to the non-regulatory indicative short-term exposure limit of 1.5 mg.m^{-3} set by the Circular of 13 May 1987.

Table 1: Assessment of methods for measuring concentrations of MEKP in workplace atmospheres

No.	Methods	Similar protocols[6]	Category[7] In relation to the 15-minute value of 1.5 mg.m^{-3}	
			For regulatory technical control	For monitoring short-term exposure
1	Active sampling in an XAD-4 tube, 2-propanol solvent desorption, high-performance liquid chromatography with ultra-violet detection (HPLC/UV)	**Protocol 1:** OSHA-77 Method (1989): Methyl Ethyl Ketone Peroxide	**2**	**1B**
2	Active sampling in an impinger in 15mL dimethyl phthalate, visible absorption spectrometry	**Protocol 2:** NIOSH Method 3508, issue 2 (1994): Methyl Ethyl Ketone Peroxide	**3**	

The graph below presents the ranges for which the various methods were tested, as well as their limits of quantification in relation to this 15-min. value of 1.5 mg.m^{-3}.

[6] NIOSH: National Institute for Occupational Safety and Health; OSHA: Occupational Safety and Health Administration

[7] Validation and performance criteria for methods for monitoring STELs are defined in the NF EN 482 Standard from 0.5 to 2 times the STEL. Under the French regulations, for the technical control of the exposure limit, the measurement method must be able to measure one-tenth of the 15min-STEL (Ministerial Order of 15 December 2009 on technical controls of occupational exposure limits in workplace atmospheres and conditions for accrediting the organisations in charge of controls, published in the OJ of 17 December 2009). As such, when a method cannot measure one-tenth of the 15min-STEL, it cannot be classified in category 1A or 1B for regulatory control of the 15min-STEL. However, it may be classified in category 1A or 1B solely for assessing occupational exposure.

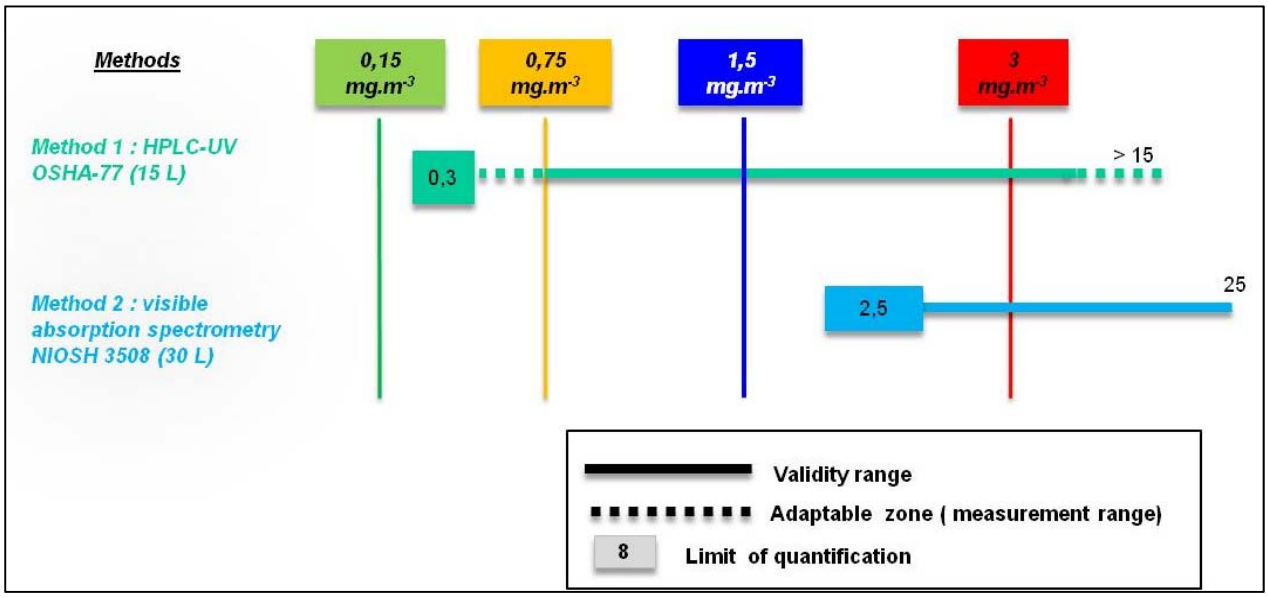

Figure 1: Ranges of validity and limits of quantification for the various compared methods from 0.1 to 2 times the 15-min. value of 1.5 mg.m^{-3} for MEKP

Method 1 is classified in category 1B for the monitoring of short-term exposure, and category 2 for the regulatory technical control of the 15-min. value of 1.5 mg.m^{-3}. The requirements of the NF EN 482 Standard in relation to the ranges of measurement and measurement uncertainty are met, and while this method cannot reach one-tenth of this value, technological advances since 1989 suggest that the limit of quantification can be lowered.

Method 2 is classified in category 3 for the control of the 15-min. value of 1.5 mg.m^{-3} due to the use of a sampling system that cannot measure individual exposure in satisfactory conditions of safety for workers equipped with the system, the area of work which is not appropriate for measuring this value and the lack of uncertainty data.

Conclusions of the collective expert appraisal

Based on the data that are currently available, the OEL Committee:

- does not recommend setting an 8h-OEL for methyl ethyl ketone peroxide considering the lack of expected medium- or long-term systemic effects.
- cannot recommend a 15min-STEL for methyl ethyl ketone peroxide due to poor bibliographic data to establish a value even when considering those for similar compounds such as hydrogen peroxide and benzoyl peroxide.
- does not recommend the "skin" notation.
- does not recommend the "ototoxic" notation.

Lastly, the OEL Committee would like to emphasise that:

- methyl ethyl ketone peroxide is an irritating, corrosive substance. Thus, while recommending a 15min-STEL appears justified, no data are available in the literature to

establish this value. It notes that there is currently a French indicative Occupational Exposure Limit (OEL) of 1.5 mg.m^{-3} (set by the Circular of 13 May 1987) for which no supporting documents were found and for which the available data that were examined do not confirm or contradict the relevance of this concentration level.

In light of the assessment of measurement methods in relation to the non-regulatory indicative limit value of 1.5 mg.m^{-3} established by the Circular of 13 May 1987, the OEL Committee:

- underlines that none of the identified measurement methods are validated for the regulatory technical control of this value.
- recommends, for the regulatory control of this value and the monitoring of short-term exposure, the method described in the OSHA-77: 1989 protocol. This method involves active sampling in an XAD-4 tube, desorption with 2-propanol and analysis by HPLC/UV. It is indicative (category 2 classification) for regulatory control and partially validated (category 1B classification) for the monitoring of short-term exposure.

Moreover, the OEL Committee recommends undertaking studies that could support scientifically sound recommendations for the establishment of a 15min-STEL for MEKP.

Further details: General information on the substance

1) Identification of the substance:

Name:	Methyl ethyl ketone peroxide (MEKP)
Synonyms:	2-butanone peroxide
CAS No:	1338-23-4
EINECS No:	215-661-2
Empirical formula:	$C_8H_{16}O_4$
Physical form, appearance:	Colourless liquid, slightly pungent odour

2) Physico-chemical properties:

Molecular weight:	176.24 g/mol
Melting point:	< -10°C
Flash point:	75°C at 1.013 hPa
Decomposition temperature:	60°C
Density (D420):	1.14
Solubility:	Insoluble in water but soluble in particular in phthalates and alcohols
Explosion risk:	Organic and inorganic acids, strong bases, amines, sulphur compounds, etc.

Conversion factor: 1 ppm = 7.2 mg.m-3

3) Professional uses:

Methyl ethyl ketone peroxide is mainly used in the plastics industry as a hardener or polymerisation agent. It is regularly used in the form of a commercial solution, diluted 50-60% (i.e. 9-11% active oxygen), containing mixtures of several isomers of peroxides and hydroperoxides derived from 2-butanone.

(Source: Toxicological Fact Sheet FT 50 INRS[8] - 1997)

[8] French National Research and Safety Institute

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Metrology section (date of inventory of methods : September 2013)

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