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 2-ethoxyethanol (CAS n° 110-80-5) and 2-ethoxyethyl acetate (CAS n° 111-15-9)

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

Presentation of the issue

ANSES was requested from the Directorate General for Labour to conduct the scientific expert appraisal work required for setting occupational exposure limit values (OELVs) for incorporation into French law. During the consultation organised by the European Commission in 2007 on the SCOEL reports for 2-ethoxyethanol (EGEE) and 2-ethoxyethyl acetate (EGEEA)[1], experts from AFSSET's working group in charge of "assessment of French exposure to glycol ethers"[2] had expressed their disagreement with the recommended values. For this reason, ANSES conducted a re-assessment of the toxic effects of 2-ethoxyethanol and its acetate to enable the Ministry of Labour to update if necessary the indicative European limit values established by Directive 2009/161/EU[3].

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.

[1] SCOEL/SUM 116 of October 2006

[2] AFSSET Opinion and Collective Expert Report of September 2008. Glycol ethers: summary of knowledge on exposure of the general and professional populations in France.

[3] Commission Directive 2009/161/EU of 17 December 2009 in implementation of Council Directive 98/24/EC and amending Commission Directive 2000/39/EC

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 and animal toxicology studies. Identifying concentrations that are safe for human health generally requires correction 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:
- an 8-hour occupational exposure limit (8h-OEL): unless otherwise indicated, this corresponds to the limit of the time-weighted average (TWA) of the concentration of a chemical, in the air in the worker's breathing zone, over the course of an 8-hour working day.
In the current state of scientific knowledge (in toxicology, medicine and epidemiology), 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.
- a short-term exposure limit (STEL): This is a limit corresponding to exposure measured over a 15-minute reference period (unless otherwise indicated) 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.
- a ceiling value: This is an atmospheric concentration in workplace that should not be exceeded at any time during the day. This value is recommended for substances known to be highly irritating or corrosive or likely to cause serious potentially irreversible effects after a 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. 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 also evaluates the applicable reference methods for the measurement of exposure levels in workplace atmospheres. The different protocols are classified according to the methods used. These methods are then assessed and ranked according to their compliance with the European Standard EN 482: 2006: "Workplace atmospheres - General requirements for the performance of procedures for the measurement of chemical agents".

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). This body mandated:

- a working group on health effects to conduct the expert appraisal work on the health effects;
- a rapporteur from among the OEL Committee experts to update the expert appraisal work on the assessment of measurement techniques already published[4].

Three ANSES officers contributed to this work and were responsible for scientific coordination of the different expert groups.
The methodological and scientific aspects of the work of this group and rapporteur were regularly submitted to the OEL Committee. The final report takes account of all their observations.
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 - General Requirements of Competence for Expert Appraisals (May 2003)" to ensure compliance with the following points: competence, independence, transparency, and traceability.

Description of the method

For the assessment of health effects:

A summary report was prepared by ANSES and submitted to the working group on health effects, which commented on and added to it.
Much of this summary report on the health effects of 2-ethoxyethanol and 2-ethoxyethyl acetate comes from the "Risk Assessment Report" of the European Chemicals Bureau (ECB) published in August 2010 and the document from the US National Institute for Occupational Safety and Health (NIOSH) published in 1991. The OEL Committee returned to the original articles for all the key publications to which it referred for establishing its recommendations. Furthermore, the literature review was supplemented by searches on Medline, Toxline HSDB, ToxNet (CCRIS, GENE-TOX, IRIS) and ScienceDirect conducted between November 2010 and June 2011. Throughout this document, 2-ethoxyethanol will be referred to as EGEE and 2-ethoxyethyl acetate as EGEEA.

For the assessment of the methods for measuring exposure levels in workplace atmospheres:

The different protocols for measuring EGEE and EGEEA in workplace atmospheres were identified and grouped according to the methods used. These methods are then assessed and ranked according to their compliance with the European Standard EN 482: 2006: "Workplace atmospheres - General requirements for the performance of procedures for the measurement of chemical agents". A list of the main sources consulted is detailed in the report.

These methods were classified into two categories:

- Category 1 for validated methods: these satisfy a majority of the validation criteria (range of measurements, uncertainties, sensitivity, storage of samples, etc.)
- Category 2 for indicative methods: here, the protocols do not specify or do not sufficiently explain the major validation criteria.

[4] ANSES Opinion and collective expert report of May 2011 - Evaluation of techniques for measuring atmospheric levels in the workplace of the substances listed in European Directive 2009/161/EU.

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

The Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents adopted:

- the summary report for the evaluation of the health effects, at its meeting on 15 June 2011;
- the summary report on the methods for measuring exposure levels in workplace atmospheres, at the meeting on 12 March 2010.

The summary and conclusions of the collective expert appraisal were adopted by the Committee on expert appraisal for recommending occupational exposure limits for chemical agents on 9 September 2011.

The collective expert appraisal work and the summary report were submitted to public consultation from 18/10/2012 to 20/12/2012. No comments were received. The OEL Committee adopted this version on 4 April 2013.

Results of the collective expert appraisal of health effects of EGEE and EGEEA

General information and summary of the SCOEL document

EGEE is mainly used as an intermediate in chemical synthesis or as a solvent. There are still a few uses of this product in the formulation of paints, lacquers, varnishes and printing inks. Only one EGEE production site can still be found in EU territory and there are no known imports from outside the European Union (EU-RAR, 2009).

General information collected on these substances highlights their identical classification both at European level and in tables of occupational diseases, as shown in the table below.

	EGEE	EGEEA
European classification 1st ATP (Commission Regulation (EC) 790/2009 of 10 August 2009)	Flam. Liq. 3; H226 Repr. 1B; H360FD Acute Tox. 4; H302 (oral) Acute Tox. 4; H312 (dermal) Acute Tox. 4; H332 (inhalation)	Flam. Liq. 3; H226 Repr. 1B; H360FD Acute Tox. 4; H302 (oral) Acute Tox. 4; H312 (dermal) Acute Tox. 4; H332 (inhalation)
IARC classification	Not classified	Not classified
Table of occupational diseases	General scheme: Table No. 84 Agricultural scheme: Table No. 48	General scheme: Table No. 84 Agricultural scheme: Table No. 48

The NIOSH (National Institute for Occupational Safety and Health) is the organisation currently recommending the lowest OELVs, namely an 8h-TWA of 0.5 ppm for both substances, i.e., 1.8 mg/m^3 for EGEE and 2.7 mg/m^3 for EGEEA.

The SCOEL 2007 report estimates that EGEE and EGEEA have the same toxicity, because of their common metabolite, 2-ethoxyacetic acid (EAA). The critical effects of EGEE and its acetate

are reprotoxic and haematotoxic effects, which have been demonstrated by experimental studies in animals and epidemiological studies in humans. As humans are more sensitive than animals, only the studies in humans (despite their limited validity) were used to derive an OEL.
The haematopoietic effects in humans, with effect levels of 2.6 ppm (maximum 21.5 ppm; Welch and Cullen (1988)) and 3.0 ppm (maximum 18.3 ppm) and a no significant effect level of 1.8 ppm (maximum 8.1 ppm; Kim *et al.* (1999)) were used to establish the 8h-OEL.
Thus, an 8h-OEL of 2 ppm is considered to protect from the effects on both haematopoiesis and fertility.
The available data are insufficient for recommending a 15-min STEL.
A skin notation is recommended due to dermal absorption which contributes significantly to the total concentration levels in the body.

Toxicokinetics – Metabolism

EGEE and EGEEA are well absorbed by the respiratory tract and rapidly metabolised and eliminated in humans, as in animals. Groeseneken *et al.* (1986), who exposed healthy volunteers during rest, noted that lung retention of EGEE rapidly reached equilibrium.

In humans as in animals, EGEEA is rapidly hydrolysed to EGEE by esterases present in various body tissues (Stott and McKenna (1985), Gargas *et al.* (2000)).
EGEE is metabolised in humans as in animals by two main oxidative pathways:

- the action of alcohol and aldehyde dehydrogenase, which leads to the formation of EAA;
- the action of O-dealkylase leading to the formation of ethylene glycol (EG).

Both these metabolic pathways can lead to the formation of CO_2 which is exhaled.
The first pathway is likely responsible for the toxicity of EGEE and EGEEA due to the formation of EAA, the potentially toxic metabolite.
The second pathway may be a detoxification pathway (Medinsky *et al.,* 1990).
It should be noted that ethanol has a higher affinity for alcohol dehydrogenase than EGEE. Thus, populations with relatively inactive alcohol-degrading enzymes metabolise alcohol more slowly and tend to eliminate EGEE and EGEEA much more slowly. This is the case for almost 50% of Asians, who have an inactive aldehyde dehydrogenase variant which is unable to metabolise acetaldehyde to acetate (Chen *et al.,* 1999).

EGEE is mainly excreted via urine in the form of several metabolites, the main ones being EAA and EG.

Kezic *et al.* (1997) sprayed from 2520 to 4600 mg/m^3 (average 3648 mg/m^3) of EGEE for 45 minutes on an average skin surface area of 1040 cm² (forearms and hands). Dermal absorption was determined by measuring the amount of EAA excreted in 48-h urine, corrected for the fraction excreted in urine following pulmonary exposure to 53 mg/m^3 for four 15-minute periods.
The results of this study indicate that EGEE is rapidly absorbed through the skin, either in liquid or vapour form. The average absorption fluxes were 0.7 mg/cm²/h for exposure to EGEE liquid and 0.074 mg/cm²/h for exposure to EGEE vapour. The authors concluded that if the whole body was exposed to EGEE vapour for 8h at a concentration of 19 mg/m^3, dermal penetration of EGEE would account for an average of 42% of overall exposure (pulmonary and dermal).

General toxicity
In humans
Welch and Cullen (1988) analysed the relationship between exposure to glycol ethers in shipyard painters and the effects on certain blood parameters, in a cross-sectional exposed versus non-exposed study of 94 workers.
Clinical investigations, including a medical questionnaire and a blood count, were conducted in the two study populations.

The study authors reported an average exposure level to EGEE and ethylene glycol monomethyl ether (EGME) of 2.7 and 0.8 ppm respectively.
The blood test results indicated that 14 of the 94 painters presented haematological abnormalities. The cross-sectional design, low participation (risk of selection bias), lack of individual exposure assessment (co-exposure to EGEE, EGME and many other pollutants, absence of biomonitoring, risk of misclassification, measurement bias), non-comparability of the exposed and non-exposed groups, particularly from an ethnic standpoint, use of a relatively high anaemia threshold (14 g/dL) and finally the tenuous results, are the main limitations of this study.

Kim *et al.* (1999) conducted a cross-sectional study in two groups of shipyard painters exposed to mixtures of solvents containing, among others, EGEEA. The exposed individuals had worked for an average of 9.4 years in the company.
Group A consisted of 30 individuals considered as highly exposed: the principal painters and their assistants. Group B consisted of 27 individuals involved in various tasks such as surface preparation. Wearing of personal protective equipment (PPE) was left to their discretion. A control group of 41 individuals was included in the study. They worked in offices in a building separate from the production section. According to the study authors, they were never exposed to EGEEA. Eighteen individuals from group A and 12 from group B were equipped with an active sampler for 6 hours and all participants provided a urine and blood sample and answered a questionnaire about their health and lifestyle.
On average, the individuals from group A were exposed to EGEEA concentrations of 3 ppm and group B to 1.8 ppm. Compared with the control group, group A showed a significant reduction in the average number of granulocytes and the mean corpuscular volume. In three leukopenic subjects (<4000/µL), bone marrow aspiration confirmed the hypoplasia. Thus, the study authors suggest that EGEEA is probably toxic to bone marrow. These results were confirmed by measurement of urinary EAA.
This publication has many limitations that impede its use: the cross-sectional design, the small numbers, exposure to a mixture of solvents (EGEEA, toluene, xylene, methyl ethyl ketone) whose combined effects are unknown, a poor correlation between atmospheric data and data from biomonitoring (r=0.40), the value of 1.76 ppm as a LOAEL from a geometric mean of all the exposure data, and the inability to identify workers wearing PPE from the others. Furthermore, the study author contacted for information on the level of atmospheric exposure of the three workers with leukopenia, on the PPE they were wearing and on the exact type of activities they were working on, was unable to respond.

In conclusion, despite the relatively large number of epidemiological studies of workers handling EGEE and/or EGEEA, it was considered that none of the studies were of sufficient quality to allow establishment of the OELs.

In animals
One study reported that following exposure of two groups of six female rats for 8 hours to Cellosolve vapours, the LC_{50} is 7.36 mg/L (4.01-13.5 mg/L) for EGEE and 12.1 mg/L (9.1-16.1 mg/L) for EGEEA (Pozzani *et al.*, 1959).
Exposure of male rats to EGEE vapours (4500 ppm, or 17 mg/L) for 3 hours caused a significant reduction in the weight of their testes, as well as haematuria (Doe, 1984).
The work by Barbee *et al.* (1984) involved groups of 30 Sprague-Dawley rats (15 males and 15 females) and groups of 20 New Zealand white rabbits (10 males and 10 females) exposed to vapours containing 0, 25, 100 and 400 ppm EGEE, i.e. 0, 93, 390 and 1480 mg/m^3 respectively, for 6 hours/day, 5 days a week for 13 weeks. Rabbits were more sensitive than rats; those exposed to 400 ppm EGEE presented anaemia characterised by decreased weight gain during 13 weeks of exposure, and changes in haematological parameters (haemoglobin, erythrocyte and hematocrit counts). The authors suggest that this anaemia may be related to a haemolytic effect rather than a decrease in erythropoiesis.

In the exposed rats, no change in weight gain was observed. Only a decrease in the number of leukocytes in female rats exposed to 400 ppm EGEE was observed as well as significant changes in plasma constants. The study authors concluded that the NOAEL of EGEE by inhalation was 100 ppm in rabbits and 400 ppm in rats (Barbee *et al.,* 1984).
This study is interesting because it shows haematological effects in two different species and identifies the doses at which these effects occur.

The work by Tyl *et al.* (1988) focused on the effects of exposure to EGEEA vapours in rabbits and rats during gestation. Twenty-four pregnant rabbits and 30 pregnant rats were exposed to vapours of 0, 50, 100, 200 and 300 ppm of EGEEA (i.e. respectively 0, 271, 541, 1082 and 1623 mg/m^3) for 6h/day from the 6th to the 18th day of gestation for rabbits, and from the 6th to the 15th day for rats.
The study showed that exposure of animals to EGEEA vapours during pregnancy leads to significant changes in certain blood constants from 100 ppm, with a decrease in the number and volume of erythrocytes, and in haemoglobin and hematocrit counts, and from 200 ppm an increase in the number of leukocytes and a decreased platelet count. These changes appear to be related to the exposure dose. In rabbits, exposure to EGEEA vapours resulted in a decrease in the platelet count from 100 ppm and an increase in erythrocyte volume from 300 ppm. The study authors concluded that the NOAEL for EGEEA by "subacute" inhalation is 50 ppm in rabbits and rats, with regard to maternal and developmental toxicity. (Tyl *et al.,* 1988.)
This was a development study, whose protocol was not intended to investigate haematological effects, which were only described from a blood test on the rats at the end of gestation. However the study is still of interest, because it shows that exposure to EGEEA vapours has a haematotoxic effect, as was the case with EGEE in the study by Barbee (1984).

The available data indicate that neither EGEE nor its acetate appear to have a mutagenic effect when tested on bacteria.
Several studies of reprotoxicity by different routes of exposure are available in the literature (Barbee *et al.,* 1984; Oudiz *et al.,* 1984, Doe *et al.,* 1984; Tyl *et al.,* 1988).
They show significant decreases in testicular weight, reduced sperm motility and changes to their morphology. Moreover, EGEE like EGEEA induced maternal toxicity and developmental effects at 100 ppm, and teratogenicity at 200 ppm. No effects were reported at 50 ppm, the concentration proposed by the authors as the NOAEL for maternal toxicity and for developmental effects.

Establishment of occupational exposure limit values
The results of epidemiological and toxicological studies show that the critical effects observed following administration of EGEE and/or EGEEA are similar, as they are due to a common metabolite.
The critical effects adopted are both haematotoxicity observed in humans and animals, and reproductive toxicity which has only been observed in animals. It should be noted that the doses at which these effects are observed are of the same order of magnitude, regardless of the administered compound, if ppm are used.
Therefore, the OELs were established from studies considering either EGEE or EGEEA.
The haematologic effects were demonstrated by several epidemiological studies, particularly that of Kim *et al.* (1999) which, because of its many limitations, could not be retained as the key study.
The study by Barbee *et al.* (1984) was chosen as the key study because it is a subchronic exposure study conducted in male and female rabbits and rats, where the observed effects were also noted in workers. The NOAEL for haematological effects is 100 ppm.

Choice of safety factors

Type of factor	Rationale	Value applied
SF_A	Transposition from animals (rabbits) to humans	3
SF_H	Variation in enzymatic metabolism according to ethnic origin: Caucasian/Asian polymorphism	10
SF_S	Extrapolation from the subchronic exposure in the study (15 weeks) to whole life exposure	3

This leads to the recommendation of **an 8h-OEL of 1 ppm i.e. 3.75 mg/m^3 at 20°C and at 101 kPa for EGEE and 5.49 mg/m^3 for EGEEA**.

The short-term deleterious effects of EGEE/EGEEA are not substantiated. Irritation was mentioned in some animal studies. However, given the reprotoxicity of these substances, special attention should be paid to women of childbearing age, to avoid exposure peaks during specific windows of exposure.
Under these conditions and in accordance with its previous work (AFSSET, 2008), the OEL Committee recommends a STEL equal to five times the 8h-OEL, i.e. 5 ppm **(18.75 mg/m^3 for EGEE and 27.45 mg/m^3 for EGEEA).**

The study by Kesic *et al.* (1997) conducted in volunteers clearly indicates significant dermal absorption of EGEE. Therefore, **the skin notation should be attributed both to EGEE and EGEEA.**

Results of the collective expert appraisal on the assessment of the methods for measuring exposure levels in workplace atmospheres

The OEL Committee states **that there is a suitable validated measurement method** for assessing occupational exposures for the purpose of comparison with the limit values. This method can be used for controlling the 8h-OEL of 3.75 mg.m^{-3} for EGEE and of 5.49 mg.m^{-3} for EGEEA. It is also suitable for controlling the 15-min STEL of the two substances.
Therefore, the Committee recommends **the active pumping method, based on trapping EGEE or EGEEA vapours on activated carbon, followed by desorption in a solvent or mixture of solvents and analysis by GC/FID.**

Because of their significant percutaneous absorption, the OEL Committee considers it necessary to continue work on EGEE and EGEEA by identifying the biological reference values that can be used in biological monitoring. These values could then enhance the current French regulatory scheme for evaluation of exposures to chemicals in workplace atmospheres.

Conclusions

<u>Recommended limit values:</u>

For EGEE:
8h-OEL: 1 ppm i.e. 3.75 mg/m^3
STEL: 5 ppm i.e. 18.75 mg/m^3

Skin notation: yes

For EGEEA:
8h-OEL: 1 ppm i.e. 5.5 mg/m^3
STEL: 5 ppm i.e. 22.45 mg/m^3
Skin notation: yes

Recommended sampling and measurement techniques

The active pumping method, based on trapping EGEE or EGEEA vapours on activated carbon, followed by desorption in a solvent or mixture of solvents and analysis by GC/FID is to be used for assessing occupational exposures for the purpose of comparison with the occupational exposure limit values.

References

- AFSSET-2008: Recommendations relating to occupational exposure limit values (OELVs) in order to limit the size and number of exposure peaks over the working day (Part 1). Collective expert report for recommending occupational exposure limit values for chemical agents, December 2008.
- Barbee SJ, Terrill JB, DeSousa DJ, Conaway CC (1984): Subchronic inhalation toxicology of ethylene glycol monoethyl ether in the rat and rabbit. Environmental Health Perspectives 57: 157-163.
- Chen CC, Lu RB, Chen YC, Wang MF, Chang YC, Li TK, Yin SJ (1999). Interaction between the functional polymorphisms of the alcohol-metabolism genes in protection against alcoholism. Am J Hum Genet 65: 795-807.
- Doe JE (1984): Ethylene glycol monoethyl ether and ethylene glycol monoethyl ether acetate teratology studies. Environ Health Perspect 57: 33-41
- EU RAR draft, 2008: Risk assessment 2-Ethoxyethanol. Draft of 21.11.2008. Rapporteur Germany, Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA). http://echa.europa.eu/documents/10162/17228/trd_rar_germany_ethoxyethanol_en.pdf (Consulted on 15 June 2011)
- Gargas ML, Tyler TR, Sweeney LM, Corley RA, Weitz KK, Mast TJ, Paustenbach DJ and Hays SM (2000) A toxicokinetic study of inhaled ethylene glycol ethyl ether acetate and validation of a physiologically based pharmacokinetic model for rat and human. Toxicol Appl Pharmacol 165:63-73.
- Groeseneken D, Van Vlem E, Veulemans H, Masschelein R (1986). Gas chromatographic determination of methoxyacetic and ethoxyacetic acid in urine. Br J Ind Med 43:62-65.
- Kezic S, Mahieu K, Monster AC and de Wolff FA (1997). Dermal absorption of vaporous and liquid 2-methoxyethanol and 2-ethoxyethanol in volunteers. Occupational and Environmental Medicine 54: 38-43.
- Kim Y, Lee N, Sakai T, Yang K-S, Park S, Lee CR, Cheong H-K, Moon Y (1999). Evaluation of exposure to ethylene glycol monoethyl ether acetates and their possible hematological effects on shipyard painters. Occup Environ Med. 56: 378–382.
- Medinsky MA, Singh G, Bechtold WE, Bond JA, Sabourin PJ, Birnbaum LS, Henderson RF (1990). Toxicol Appl Pharmacol.;102(3):443-55.
- Oudiz DJ, Zenick H, Niewenhuis RJ, McGinnis PM (1984) Male reproductive toxicity and recovery associated with acute ethoxyethanol exposure in rats. J Toxicol Environ Health.13(4-6):763-75.
- Pozzani UC, Weil CS, Carpenter CP (1959): The toxicological basis of threshold limit values: 5. The experimental inhalation of vapour mixtures by rats, with notes upon the relationship between single dose inhalation and single dose oral data. Ind Hyg J; 364-369
- SCOEL 2007: Recommendation from the Scientific Committee on Occupational Exposure Limits for 2-Ethoxyethanol and 2-Ethoxyethyl acetate. SCOEL/SUM/116 final rev, August 2007 (SCOEL, 2007)
- Stott WT and McKenna MJ (1985) Hydrolysis of several glycol ether acetates and acrylate esters by nasal mucosal carboxylesterase in vitro. *Fundamental and Applied Toxicology* **5:**399-404.
- Pritts IM, France KA, Fisher LC, (1988). Developmental toxicity evaluation of inhaled 2-ethoxyethanol acetate in Fischer 344 rats and New Zealand white rabbits. Fundamental and applied toxicology : official journal of the Society of Toxicology 10(1):20-39.
- Welch LS, Cullen MR (1988): Effect of exposure to ethylene glycol ethers on shipyard painters. III. Hematological effects. Am J Ind Med 14: 527-536