Collective Expert Report

Glycol ethers

New toxicological data

Synthesis

2006

Inserm

Institut national de la santé et de la recherche médicale

(National Institute for Health and Medical Research)

This document summarizes the work of the expert group formed by Inserm in the context of the collective expertise procedure in response to the request from the French Agency for Environmental Health Safety (Afsse) which became the French Agency for Environmental and Occupational Health Safety (Afsset) on September 1, 2005. The present report follows on from the collective expertise report implemented in 1999: 'Glycol esters: what health risks?' and appraises the new toxicological data on glycol ethers generated since the initial review. The document is based on the scientific data available as at the first quarter 2005. Some 150 documents (articles and evaluation reports) constituted the document base for the expert review.

The Inserm collective expertise center ensured coordination of this collective expertise report.

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Foreword

Glycol ethers are molecules forming a series of over 80 derivatives. Because of their solubility in both water and organic solvents, some 30 glycol ethers are used in numerous industrial applications, in particular as solvents in paint and coating manufacture. Glycol ethers are also incorporated in numerous products such as adhesives, inks, varnishes, diluents, cosmetics, cleaning products and products for mechanics and metallurgy.

The chemical profiles of the glycol ethers used have markedly changed in recent years. In France, since 1997, numerous regulatory provisions have been formulated with respect to the derivatives of the ethylene series (classified as products endowed with reproductive toxicity [CMR classification]; restriction of use in industrial environments and prohibition of use in products for household use for certain derivatives) with a view to promoting their gradual replacement by derivatives of the propylene series, which are reported to be less toxic.

In 2003, the French Authority General of Health (DGS) made public the governmental action plan for glycol ethers. In this context, the Minister of Health asked Afsse[1] to review the new toxicological data that had emerged since the Inserm collective expertise report of the subject published in 1999. In the context of a partnership agreement with Inserm, Afsse asked Inserm to update the toxicological and epidemiological data of the 1999 collective expert report on the basis of the scientific and gray literature published from 1998 to 2005.

In response to that request, Inserm formed a group of experts with skills in ecotoxicology, clinical and environmental toxicology, developmental biology and reproduction, and epidemiology.

The following questions were raised to the expert group:

- What are the toxicokinetics of the glycol ethers first marketed since 1998?
- What are the recent data on the mutagenic and genotoxic effects of all glycol ethers?
- What are the recent data on the effects of glycol ethers with respect to reproduction, embryonic and fetal development, and teratogenicity?
- What are the recent data on the bone marrow toxicity, immunotoxicity and hemotoxicity of glycol ethers?
- What are the results of the epidemiological studies published since 1998 and addressing the occupational environment and overall population?
- What are the new effects of glycol ethers on human health that have been evidenced since 1999?
- What is the assessment of the effects of new glycol ethers on humans?
- Which glycol ethers were not taken into account in the 1999 expert review and have since been incorporated in the analysis?

The databases of the following institutions were searched: the Agency for Toxic Substances and Disease Registry (ATSDR); the National Toxicology Program (NTP), a program incorporating the toxicological work of the National Institute of Health / National Institute of Environmental Health Sciences (NIH/NIEHS), the Center for Disease Control and prevention / National Institute for Occupational Safety and Health (CDC/NIOSH), and the Food and Drug Administration / National Center for Toxicological Research (FDA/NCTR);

[1] The French Agency for Environmental Health Safety (Afsse) became the French Agency for Environmental and Occupational Health Safety (Afsset) on September 1, 2005.

the European Chemical Bureau (ECB) of the International Program on Chemical Safety (IPCS); the Organization for Economic Cooperation and Development (OECD); the Hazardous Substances Data Bank (HSDB); etc. The search enabled retrieval of 21 reports published since 1998 together with 4 risk assessment reports undergoing finalization (two glycol ethers and their acetates), for which France is the rapporteur, and which were supplied by the French National Institute for Research and Safety (INRS). In addition, the document base included scientific publications obtained by searching French and international databases (Medline, Embase, Toxline, Pascal, Biosis) and consisted of 130 references. The most recent editions of the technical report on the toxicology of glycol ethers[2] issued by the European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC) and Patty's Toxicology[3] were also consulted.

Lastly, glycol ethers manufacturers were contacted through the French Oxygenated solvent producers association (OSPA), the French Chemical industry association (UIC), and the French Federation of the paint, ink, color, dye and adhesive industries (FIPEC) in order to provide the expert group with the toxicological data obtained since 1999 with respect to all the substances, including the new compounds.

In the course of six working sessions held from October 2004 to July 2005, the experts formulated a critical analysis and review of the work published on the various aspects addressed.

[2] ECETOC WORKING GROUP. The Toxicology of Glycol Ethers and its Relevance to Man (4th Edition), Volumes 1 & 2. Technical Report 95. European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels, 2005

[3] Patty's Toxicology, 6th ed., John Wiley & Sons, New York, (in preparation)

Synthesis

Updating the toxicological and epidemiological data from the 1999 collective expert review of glycol ethers has enabled, first, the confirmation of the effects (hemotoxicity, reproductive toxicity, etc.) of the compounds already studied and identification of new effects, and, secondly, a review of the data on compounds for which no data had been published prior to 1999.

Toxicokinetics

Due to their amphiphilic nature, glycol ethers readily cross membranes and are distributed in the aqueous and lipid compartments. Strongly absorbed irrespective of the penetration route (oral, cutaneous, pulmonary), glycol ethers are distributed through most biological tissues, including fetal tissues. However, the precise distribution data on each of the glycol ethers remain fragmentary. The distribution studies on EGBE in the mouse have enabled quantification of EGBE and its metabolites in various gastric compartments. Data from pharmacological studies of DEGEE in the rat support the finding that glycol ethers are distributed through all tissues and particularly the liver, kidneys and bone marrow. Following absorption, the enzyme systems convert glycol ethers to water-soluble compounds that are more readily eliminated or to reactive metabolites responsible for toxic effects. Nonetheless, with regard to di- or triethylene derivatives, the proportions of intermediate and final metabolites formed have yet to be fully elucidated. Toxicokinetic studies conducted on DEGEE in the rat have, for example, shown that the main metabolite is ethoxyethoxyacetic acid (EEAA) and not the final metabolite, ethoxyacetic acid (EAA). Associated with toxicity studies on the metabolites themselves, this type of data enables, first, enhanced evaluation of the toxic potential of di- or triethylene derivatives and, secondly, determination of the metabolite to be assayed in the context of human exposure studies.

Hemotoxicity

With regard to the hematological toxic effects of glycol ethers, the data published since 1999 do not fundamentally modify our knowledge of those effects but provide some valuable complementary informations. These data confirm the hemolytic effects of EGBE in the rat and elucidate the natural history of hemolytic accidents: these accidents are preceded by a decrease in erythrocyte plasticity, erythrocyte deformation (spherocytosis, stomatocytosis) and an increase in corpuscular volume. When hemolysis is marked, it is complicated by intravascular coagulation giving rise to disseminated thromboses and infarctions, hemoglobin precipitation in renal tubules inducing tubular necrosis, and the emergence of hematopoietic foci outside of the bone marrow. The hemolysis induced by EGBE in the rat is not, in fact, of a specific nature and very similar phenomena are observed in the course of all hemolytic diseases. EGBE-induced hemolysis in the rat thus constitutes a good animal model of hemolytic disease. Use of the model has enabled enhanced elucidation of the procoagulant effects of hemolytic accidents. In addition, recent publications confirm that the main metabolite of EGBE, butoxyacetic acid (BAA), is responsible for the hemolysis. Human

erythrocytes are highly resistant to the hemolytic effects of BAA. In the rat, females are more sensitive than males to the effects of EGBE, but the difference does not reflect a greater fragility of female erythrocytes: it results from toxicokinetic differences between the sexes. The mechanism underlying the effects of EGBE on erythrocytes has yet to be fully elucidated but the *primum movens* appears to be increased sodium and water influx.

Recently published data have also confirmed the ability of EGiPE, EGPhE and DEGBE to induce hemolysis. The hemolytic potential of those three compounds is nonetheless less marked than that of EGBE. The hemolytic potential of EGiPE is much greater than that of EGPhE or DEGBE. An *in vitro* study has shown that the hemolysis induced by the latter is probably due to its main metabolite, butoxyethoxyacetic acid (BEAA). Human erythrocytes are only weakly sensitive to the hemolytic effect of BEAA.

New epidemiological studies have confirmed the bone marrow hypoplasia-inducing effect of EGME, EGEE and EGEEA by demonstrating an increased risk of peripheral cytopenia correlated with the exposure of workers in various industrial sectors. An animal study has demonstrated the hemotoxicity of TEGDME in the rat: in that species, repeated high dose administration of the glycol ether induced a decrease in platelet and leukocyte counts together with thymic impairment. Another recent study in the rat confirmed the hypoplastic effect of DEGDME with respect to the bone marrow and established its toxicity for lymphoid organs.

Two studies have confirmed that the toxicity of EGME with respect to the bone marrow and lymphoid organs is mediated by its two main metabolites, methoxyacetic acid (MAA) and, especially, methoxyacetaldehyde (MALD). The studies have generated arguments in favor of an apoptotic mechanism for stem cell impairment.

Experimental mutagenicity, genotoxicity and carcinogenicity

Study of the mutagenicity of ethylene glycol and propylene glycol ethers has shown equivalent profiles for the two series of solvents, which appear to be devoid of mutagenic activity in bacteria and mammalian cells.

It is difficult to state that the ethers of the propylene series are less dangerous in terms of genotoxicity than the ethers of the ethylene series. Effects such as aneuploidy, inhibition of metabolic cooperation, and sister chromatid exchange, for which EGME, EGEE and EGBE tested positive, have, apart from a few exceptions, not been investigated. When tests were conducted, they were positive: PGME and DPGnBE inhibit metabolic cooperation; PGME also increases sister chromatid exchanges. Moreover, two propylene glycol ethers, DPGtBE and 2PG1PhE, unlike other glycol ethers, have generated positive *in vivo* micronucleus test results.

The carcinogenicity of EGBE, PGtBE and PGME has been demonstrated in animals. However, the hypothetical mechanisms advanced to explain the neoplastic effects in animals are considered not transposable to man. CIRC[4] has classified EGBE and PGtBE in category 3. The European Union reports that there is no proof of the human carcinogenicity of EGBE and has not classified that compound in any of the three carcinogenic agent categories.

[4] CIRC category 3: group of unclassifiable agents ("the agent is not classifiable as to its carcinogenicity to humans due to inadequate evidence in humans and inadequate or limited evidence in animals")

Effects on reproductive function and development in animals

Since the 1999 collective expert report, an enhanced understanding of the apoptotic mechanisms induced by glycol ethers endowed with reproductive toxicity at testicular level and during gestation and development has been acquired. The uncertainties with respect to the testicular toxicity of DEGBE and DEGEE have been resolved thanks to new animal toxicology studies demonstrating the absence of effects. In contrast, other assessments have confirmed the testicular toxicity of DEGDME and TEGME.

New studies have also shown that DEGBE, DEGDME and TEGME are devoid of adverse effects on female gonads. A few glycol ethers have been studied with respect to their potential impact on development. DEGEE was shown to have no toxic effects other than the emergence of delayed ossification at very high doses. New studies on DEGDME have, in contrast, validated the previous results indicating developmental toxicity. With regard to propylene glycol ethers, new research has focused on the minor β-isomer of PGME (1PG2ME). These studies confirmed its developmental toxicity and showed, for the first time, testicular toxicity. Compared to ethylene glycol ethers, propylene glycol ethers, particularly the β-isomers that are metabolized to alkoxyacids, have been little studied with respect to reproductive toxicity. New investigations should be conducted.

Epidemiological studies of the effects on reproduction and development

The effects of occupational exposure to glycol ethers on male fertility would appear to have been confirmed and to be restricted to those compounds and exposure levels observed in France before 1995. Studies from Asia, where the most toxic glycol ethers are still in use, suggest an impact on ovarian function. However, a number of contradictions in the results need to be elucidated before a definitive conclusion with respect to this risk can be formulated. Several epidemiological studies on congenital malformations such as neural tube defects and oral clefts, together with reports of cases subsequent to very high dose maternal exposures, associate (estimated) maternal exposure to glycol ethers with an increased risk of malformation. Concomitant exposure to multiple solvents makes causal relationships difficult to establish. However, the existence of a risk of malformation increased by exposure to certain glycol ethers that are teratogenic in animals indicates that the hypothesis cannot be ruled out for humans. Prospective epidemiological studies are ongoing and should relate objective assessment of glycol ethers exposure at the start of pregnancy (by urinary metabolite assay) to the quality of intrauterine development (miscarriage, low birth weight, congenital malformation).