Evaluation of exposure to ethylene glycol monoethyl ether acetates and their possible haematological effects on shipyard painters

Yangho Kim, NaRoo Lee, Tadashi Sakai, Kyoo-Sang Kim, Jeong Sun Yang, Seunghyun Park, Choong Ryeol Lee, Hae-Kwan Cheong, Younghahn Moon

Abstract

Objectives—To evaluate exposure to mixed solvents containing ethylene glycol monoethyl ether acetate (EGEEA) in shipyard painters, to determine if EGEEA is toxic to the bone marrow.

Methods—An industrial hygiene survey was performed to identify exposure to EGEEA of two groups of shipyard painters, a low exposure group (n=30) and a high exposure group (n=27). Urinary ethoxyacetic acid and methyl hippuric acid as well as haemoglobin, packed cell volume, red cell indices, total and differential white blood cell counts (WBCs), and platelet count for the shipyard painters and the control subjects were measured.

Results—The mean (range) exposure concentration (ppm) to EGEEA in the high and low exposure groups were 3.03 (not detectable to 18.27), 1.76 (not detectable to 8.12), respectively. The concentrations of methyl hippuric acid and ethoxyacetic acid in the high exposure group were significantly higher than those in the control group. The mean WBCs in the high exposure group were significantly lower than in the control group, and a significant proportion, six (11%) of the 57 painters, were leucopenic; none of the controls were affected.

Conclusion—The high rate of possible haematological effects among shipyard painters and a hygienic evaluation of their working environment in the present study suggests that EGEEA might be toxic to bone marrow.

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Keywords: leucopenia; hypocellular marrow; granulocytopenia; ethoxyacetic acid; ethylene glycol monoethyl ethers

Ethylene glycol ethers—such as ethylene glycol monoethyl ether (EGEE), ethylene glycol monomethyl ether (EGME), ethylene glycol monoethyl ether acetate (EGEEA), and ethylene glycol monomethyl ether acetate (EGMEA)—are colourless liquids, and are miscible with water and many organic solvents. They are widely used as industrial solvents for resins, lacquers, dyes, paints, and inks. Animal experiments and human case reports show that ethylene glycol ethers have a potentially important impact on the haematopoietic and reproductive systems.1 2

Although many workers are potentially exposed, the published airborne exposure data on ethylene glycol ethers, especially EGEEA, are limited. It is also important to note that air sampling only poorly identifies the potential for exposure to ethylene glycol ethers. They are rapidly absorbed through the skin, and some studies suggest that skin absorption may be a more important route of exposure than inhalation.3 4 Hence, the rare biological monitoring of workers exposed to EGEEA by measurement of ethoxyacetic acid (EAA) excreted in urine is particularly important for assessing occupational exposure.5 6 In the animal study by Nagano et al,1 EGEEA administered orally to mice for 5 weeks produced leucopenia in peripheral blood as well as marked testicular atrophy, with a dose-response relation. In another animal experiment, EGEEA applied to rats by skin contact caused a considerable decrease in peripheral white blood cell count (WBC).3 However, the health effects of EGEEA on humans have not been reported.

A cross sectional study of shipyard workers with and without potential occupational exposures to mixed solvents containing EGEEA was conducted. The objectives of the study were to evaluate exposure to mixed solvents containing EGEEA in shipyard painters, and to find if EGEEA is toxic to the bone marrow.

Materials and methods

JOB DESCRIPTION

Painters, mostly men, employed at the shipyard were separated into two types of crews—tank crews and deck house crews. Tank crews (group A) apply paint to block units of assembled ships. The main tank crew workers wear respirators as they apply paint primarily in spray form in tanks or other closed spaces. The assistant tank crew workers are those who mix paint or assist the main crews. The assistant workers seldom wear half face cartridge respirators.

The deck house crews (group B) are involved in various jobs—such as spraying or brush painting, wiping, or surface preparation for painting. Half face cartridge respirators are available to these men, but their use is at the discretion of the individual painters.

SUBJECTS

The shipyard employed about 900 painters, consisting of many groups. From each of these groups in the factory, we randomly selected
one tank crew, total 32 workers, as a high exposure group, and one deck house crew, total 29 workers, as a low exposure group. The few women randomly selected were not included in the study population, thus leaving for examination 30 and 27 workers in groups A and B, respectively.

As controls, we examined all 41 workers in one non-production section of the same factory. They worked mainly in the office in a building separated from the production section, and sometimes patrolled the factory to prevent industrial accidents. We thought that they had no potential exposure to EGEEA, and thus they were not monitored with personal air samplers.

ENVIRONMENTAL MONITORING
For personal breathing zone air samples two trained industrial hygienists selected 18 and 12 painters from groups A and B, respectively; their exposures were thought to be representative for each group. Personal sampling pumps connected to two types of charcoal tube were used. One was for sampling and analysis of hydrocarbons at a flow rate of 50–200 ml/min (NIOSH method 1501), the other for alcohols of which the flow rate was 10–50 ml/min (NIOSH method 1403).

All pumps were calibrated before and after use. Sampling was carried out for at least 6 hours excluding breaks. Bulk samples of some paints and thinners, representative of those most used during the sampling period and in the recent past, were taken on site in the workplace and were put into vials. Samples were sent to the Industrial Health Research Institute of the Korean Industrial Safety Corporation, designated as the reference laboratory by the Korean government. This laboratory has been proficient in the analytical testing programme of the American Industrial Hygiene Association since 1992 and has performed internal quality control programmes. Analysis was performed by gas chromatography (5890 II, Hewlett Packard, CA, USA) according to NIOSH analytical methods 1501 and 1403.

Gas chromatographs with a mass selection detector (GC-MSD, 5871 II, Hewlett Packard, CA, USA) were used to assess the contents of bulk samples. A detailed industrial hygiene investigation was done on current work practices and control measures including ventilation.

BIOLOGICAL MONITORING
Urine samples were collected to measure EAA, hippuric acid (HA), and methyl hippuric acid (MHA) from the exposed and control groups at the end of the shifts at the end of the workday. Urinary EAA was measured with gas chromatography and flame ionization detection (GC-FID, Shimazu GC-9AM, Shimazu, Kyoto, Japan) and a capillary column (HR-20M, 50 m long, 0.25 mm internal diameter, 0.25 μm film thickness, Shinwa Kako, Kyoto, Japan) by the Sakai method. Urinary HA and MHA were measured by high performance liquid chromatography (Shimazu LC-3A, Shimazu, Kyoto, Japan). Urinary metabolites were corrected for the concentration of urinary creatinine. The lead concentration of whole blood was analysed with flameless atomic absorption spectrometry (Varian SpectraAA, Varian Technology Pty, Victoria, Australia). The laboratory in the Industrial Health Research Institute has participated in the comparison programme in Germany for occupational and environmental medicotoxicological analyses, and has fulfilled the requirements for two variables, blood lead and urinary hippuric acid, for 2 years.

QUESTIONNAIRES AND LABORATORY TESTING
Each participant was seen at the factory clinic. We administered a questionnaire and collected samples of blood and urine. The questionnaire elicited basic demographic information and information about smoking, alcohol consumption, medications, and recent medical history. Each participant was asked about his work history, environmental exposure, and leisure time exposure in detail.

A sample of blood was obtained for a complete blood count. The count was run within 8 hours with a Coulter counter to reduce variation of WBCs, and the following data were collected: WBCs, haemoglobin (Hb), red blood cell count (RBC), packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), differential count, peripheral blood smear (PBS). Bone marrow aspiration was done in the iliac crest on three consistently leucopenic workers. Liver function testing—such as aspartate aminotransferase, alanine aminotransferase, and γ-glutamyltransferase—was done to rule out chronic liver disease. The laboratory tests were analysed at a nearby university hospital.

STATISTICAL ANALYSES
Mean values for Hb, Hct, RBC, WBC, Plt, MCV, MCH, and MCHC for the two exposure groups and one control group were compared by one way analysis of variance (ANOVA). If the ANOVA showed significance at p<0.05, Scheffe's multiple comparison test was used to identify which group was significantly different from which other group. Correlations among variables were evaluated with Pearson's correlation coefficients.

The proportion of men with leucopenia in each group was compared by Fisher's exact test.

Analytical regression modelling on WBCs were also performed to control for the influence of age, alcohol consumption, smoking, and duration of work.

For leucocyte count, 4500–11 000 cells/μl is generally regarded as the normal range in adults. We used a value of <4500 cells/μl as a cut off point for leucopenia to detect the early changes of leucocyte count, although many laboratories worldwide define leucopenia as <4000 cells/μl.

Results
Toluene, ethyl benzene, xylenes, butanol, isopropanol, ethanol, ethyl acetate, butyl acetate,
methyl isobutyl ketone, EGEEA, and nonane were identified in the bulk samples. These were also detected in air samples. Benzene, and other kinds of ethylene glycol ethers were not found. Thus, no benzene has been used currently or in the recent past. The peaks in the air samples were confirmed in the bulk samples by GC-MSD. The levels of detection of toluene, ethyl benzene, xylene, butanol, isopropanol, ethanol, ethyl acetate, butyl acetate, methyl isobutyl ketone, and EGEEA were 0.004, 0.007, 0.014, 0.012, 0.003, 0.006, 0.011, 0.001, 0.007, and 0.003 mg/sample, respectively. EGME, EGEE, EGMEA, and benzene were not detected in conditions for which limits of detection were 0.005, 0.004, 0.004, and 0.004 mg/sample. According to our hygienist’s evaluation of past environmental exposure records, EGEEA had been used for several years.

Thirty (18 group A+12 group B) samples were analysed, and major peaks found were toluene, xylene, methyl isobutyl ketone, and EGEEA. Overall data, summarised in table 1, showed means (ranges) of 3.03 (non-detectable to 18.27), and 1.76 (ND–8.12) for EGEEA in groups A and B, respectively. Nine (50%) out of 18 workers in group A had values for xylene exceeding 100 ppm, its TLV, one had values for toluene exceeding 50 ppm, its TLV, and one had values for methyl isobutyl ketone exceeding 50 ppm, its TLV.

Table 2 summarises the urinary concentrations of three acids in control subjects and workers exposed to the paints. Detection limits for EAA, HA, and MHA were 0.1, 50, and 10 mg/l urine, respectively. The concentrations of MHA and EAA in the high exposure group A were significantly higher than those in the control subjects (p<0.05), in whom very low concentrations of EEA and MHA supported non-exposure to mixed solvents. The correlation coefficient of EAA with log EGEEA was 0.40. The mean (range) of blood lead concentrations was 7.5 (3.3–19) µg/dl, indicating non-exposure to lead.

As shown in table 3, there were no significant differences in mean age, the duration of work, and the proportion of smokers and drinkers among the three groups (p>0.05). The mean WBC and granulocyte counts in the two exposure groups were not significantly different. There was a significant difference, however, between the more exposed group A and the control group. The mean for MCV in the more exposed group was also higher than that for the control group (p<0.05), although the mean concentrations of Hb or packed cell volumes did not differ among the subjects. (table 3). A significant proportion, six (11%) of 57, painters were leucopenic (<4500), but none of the controls were affected (p<0.05, table 4). In the leucopenic workers WBCs were 3200, 3800, 4300, and 4400 cells/µl in group A, and 4200 cells/µl in group B.

Table 3 Demographic and hematological findings of the study population (mean (SD))

Table 4 Proportion of low leucocyte count (cells/µl) in the study population

Table 1 Summary of airborne exposure (ppm) in shipyard painters (geometric mean (range))

Table 2 Urinary hippuric acid (g/g creatinine), methyl hippuric acid (g/g creatinine), and ethoxyacetic acid concentrations (mg/g creatinine) of control subjects and painters exposed to EGEEA (geometric mean/geometric SD (range))

*p<0.05.
** p<0.01
ND=non-detectable.
Table 5. Results of multiple regression analysis modelling WBC counts.

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<tr>
<th>Variables</th>
<th>β coefficients (95% CI)</th>
<th>p Value</th>
<th>Mode R²</th>
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<tr>
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<tr>
<td>Study group (group A v control group)</td>
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<td>Study group (group B v control group)</td>
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<td>Model 2 (with log EAA):</td>
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<tr>
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<td>Alcohol consumption</td>
<td>-344.5 (-959.1 to 355.2)</td>
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</table>

Discussion

The glycol ethers (EGEE, EGME) and their acetates (EGEEA, EGMEA) are widely used as industrial solvents because of their chemical and physical properties. Animal experiments and human case studies have shown that glycol ethers have the potential for a considerable impact on the haematopoietic and reproductive systems. Although some data on airborne exposure for EGEE or EGME have been reported, the data on EGEEA are severely limited. Reported exposure concentrations vary depending on the work process. The exposure concentrations in the present study were lower than those reported in a situation of acute poisoning, or when used as a cleaning solvent, but were close to the concentrations reported when EGEE was used in painting.

Firstly, EGEEA and EGMEA are converted to EGEE and EGME by esterases. Then EGEE and EGME are metabolised to the corresponding alkoxyacetic acids (EAA, MAA; methoxyacetic acids) by oxidation through alcohol dehydrogenase and aldehyde dehydrogenase. The alkoxyacetic acids produce the same degree of testicular toxicity as the parent compounds. Biological monitoring by means of alkoxyacetic acids is very important in occupational exposure, because of their low vapour pressure and high rate of dermal absorption.

The biological monitoring data are, however, scarce. The concentrations of EAA in group A were significantly higher than those in the control subjects, which indicates that tank crews in group A were widely exposed to EGEEA. The concentration of EAA (mean (SD)) in group A is lower than the 25.0 (20.7) mg/g creatinine in the shipyard painters reported by Lowry. The correlation coefficient (0.40) of EAA with EGEEA is lower than that (0.85) reported by Groeseneken et al. These differences might be due to personal respiratory protective equipment and percutaneous absorption.

The possible effects of EGEEA on the haematological system in humans have been reported for the first time in the present study, although the toxic effects of EAA on the WBCs have been reported. Whereas normal values for the erythrocyte count and haemoglobin concentration remain quite stable, the normal leucocyte count may show considerable variation within an individual subject. To minimise these problems we examined the workers at the same time, ran the complete blood count within 8 hours of blood sampling, and ruled out such factors as viral infections and medications. Our study showed a significant difference in the mean leucocyte count between the more exposed group A and the control group, although the difference was not clinically significant. Multiple linear regression showed that subjects in groups A and B had lower WBCs than the control group after controlling for smoking and alcohol consumption; EAA concentrations also decreased WBCs. Smoking was, however, shown to increase WBCs. The present study also showed a higher proportion of leucopenia in the shipyard painters. Bone marrow aspiration was done on the three leucopenic workers, and they were shown to have bone marrow hypoplasia. Hence the haematological effects in the painters could be due to bone marrow depression. Our study also showed that granulocytopenia may affect peripheral leucopenia, findings also reported by Larese et al. Increases in MCV (macrocytosis) without anaemia have also been described recently in workers exposed to organic solvents.

The importance of this finding remains obscure, but may provide a clue to the mechanism for solvent induced haematopoietic hazards. The reason leucocytes but not RBCs, are affected by EGEEA in the present study might be explained by the report of Nagano et al., in which leucocytes were affected by a lower dose, and RBCs only by a higher dose of EGEEA. It was found that EGEEA had been used for several years and other myelotoxic factors such as benzene, ionising radiation, and lead were ruled out by detailed hygiene evaluations including analyses of blood lead concentrations, and evaluation of exposure in the environment and during leisure time. Chronic liver disease was also ruled out.

The high rate of possible haematological effects among shipyard painters and a hygienic evaluation of the working environment suggests that EGEEA might be toxic to bone marrow. The present study is important as it is the first report suggesting a possible haematological effect despite the fact that the work has such limitations as lack of haematological data before the start of employment and is a cross sectional study.

Further study to confirm the haematological effects in workers exposed to these compounds must be carried out, in view of their implications for future haematological health, and the widespread use of these solvents in industrial processes.

The shipyard painters were exposed to mixtures of EGEEA, toluene, xylene, and methyl isobutyl ketone, etc, and the possible combined effects on human health also remain to be studied.


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