

Field study of the urinary excretion of ethoxyacetic acid during repeated daily exposure to the ethyl ether of ethylene glycol and the ethyl ether of ethylene glycol acetate

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VEULEMANS H, GROESENENKEN D, MASSCHELEIN R, VAN VLEM E. Field study of the urinary excretion of ethoxyacetic acid during repeated daily exposure to the ethyl ether of ethylene glycol and the ethyl ether of ethylene glycol acetate. *Scand J Work Environ Health* 13 (1987) 239–242. The urinary excretion of ethoxyacetic acid (EAA) was studied in a group of five women daily exposed to the ethyl ether of ethylene glycol (EGEE) and the ethyl ether of ethylene glycol acetate (EGEE-Ac) during 5 d of normal production and 7 d after a 12-d production stop. The mean combined exposure concentration of EGEE and EGEE-Ac (expressed in equivalent weight of EGEE) was 14.0 mg/m³ with occasional slight excursions above the current Belgian occupational exposure limit. The daily combined exposure profiles for EGEE and EGEE-Ac were rather constant during the first observation period, but they tended to decrease during the last week. The urinary EAA excretion clearly increased during the work week. Over the weekends the elimination was far from complete, and even after a prolonged nonexposure period of 12 d traces of the metabolite were still detectable. Based on the observations from the first period, a good linear correlation ($r = 0.92$) was found between the average exposure over 5 d (14.4 mg/m³) and the EAA excretion at the end of the week (105.7 mg/g creatinine). An EAA estimate of 150 ± 35 mg/g was found to correspond with repeated 5-d full-shift exposures to the respective occupational exposure limit of EGEE (19 mg/m³) or EGEE-Ac (27 mg/m³).

Key terms: biological monitoring, environmental monitoring, silk-screen printing.

Animal studies in recent years have caused great concern about the potential toxicity of certain glycol ethers (1, 2, 4, 5, 11, 12, 14, 15). Surveys on occupational exposures to these solvents and human epidemiologic findings are still scarce. Recently we studied the urinary excretion of ethoxyacetic acid after short-term (4 h) experimental exposures of volunteers to the ethyl ether of ethylene glycol (EGEE) and the ethyl ether of ethylene glycol acetate (EGEE-Ac) (6, 7). We established that ethoxyacetic acid could be used as a specific and sensitive biological exposure parameter for both products. However, in view of its relatively long biological half-time in urine (21–24 h) (6, 7), it was thought that the accumulation of this metabolite during the work week or even over a longer period had to be considered. The present field study was undertaken to investigate this assumption further.

Subjects and methods

Subjects

A group of five women (ages 29–54 years) daily exposed to EGEE and EGEE-Ac participated in the

study. These women were employed as operators of silk-screen printing installations for the surface marking of a variable assortment of plastic containers. The subjects were working in weekly alternating morning and evening shifts. For the duration of this study, the subjects agreed to wear protective rubber gloves at all times in order to avoid occasional skin contact with inks and thinners.

Sampling procedures

Air and urine samples were taken each day for an entire week (from Monday through Friday) during a normal production period in December and again during the first seven workdays in January (from Thursday through Friday of the next week) after a 12-d production stop.

Air samples were collected as individual half-shift samples on standard charcoal tubes (100/50 mg, SKC Inc, lot 120) with the aid of accuhaler pumps from MDA Scientific Inc (type 808, 100 ml/min).

Urine samples were collected twice a day, immediately before and after work, and on the Monday morning after the second observation period.

Analysis

The air samples were analyzed on a Hewlett-Packard gas chromatograph (model 5880 A) equipped with a dual wall-coated open tubular (WCOT) capillary column system [dimethyl polysiloxane, inner diameter

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25 m × 0.32 mm, and 1,2,3-tris-(2-cyano-ethoxy)-propane, inner diameter 25 m × 0.32 mm, custom made by Chrompack, Middelburg, The Netherlands], a dual flame ionization detector, electronic integrator-recorders, a carbon dioxide cooling system, and an automatic injector (0.5 µl) with an inlet splitter (ratio 1 : 10). All the samples were analyzed simultaneously on both columns under a linear temperature program from 15 to 105°C at a rate of 2.5°C/min. Sample preparation was done by chemical desorption in two steps. First, the samples were treated with 1 ml of carbon disulfide (JT Baker 8395) for a preliminary qualitative analysis without interference from a second solvent peak.

Afterwards, the analyses were repeated after the addition of 5 % ethanol (analytical grade, Union Chimique Belge 1115) to obtain complete desorption of the glycol ethers.

The urine samples were analyzed for ethoxyacetic acid, the main urinary metabolite of both EGEE and EGEE-Ac (6, 7), as described elsewhere (9). All ethoxyacetic acid values are expressed in milligrams per gram of creatinine.

Results

Exposure concentrations

The subjects were exposed to a complex solvent mixture containing different ethylene glycol derivatives, esters, alcohols, ketone, and trichloroethane (table 1). Among the glycol ethers the most important were EGEE, EGEE-Ac, and the butyl ether of ethylene glycol. On a few occasions traces of the methyl ether of ethylene glycol acetate were also found.

Most of the absolute exposure concentrations were fairly low, with the exception of exposure to methyl ethyl ketone (191.2 mg/m³) during cleaning operations. Relative to the current Belgian occupational exposure limits, however, the values of EGEE and EGEE-Ac were not negligible, with a mean combined concentration of 14.0 mg/m³ (EGEE-Ac expressed in equivalent weight of EGEE) and occasional excursions

above the limit value in the half-shift samples (21 out of 111 samples, maximal combined concentration 31.8 mg/m³).

The daily exposure profiles for EGEE and EGEE-Ac (combined value) proved to be rather constant during the first observation period, but they showed a tendency to decrease during the last week, due to normal fluctuations in the production cycle (figure 1).

Metabolite excretions

The urinary ethoxyacetic acid excretion showed a clear increase during the workweek (figure 1). This metabolite accumulates because of its relatively long biological half-time. Over the weekends the elimination proved to be far from complete. In the last observation period, the values on Monday morning still attained about half the urinary concentration on Friday evening (30 mg/g versus 64 mg/g). Even after a prolonged nonexposure period of 12 d, traces of the metabolite (1.2–2.6 mg/g) were still detectable. A more precise calculation of the urinary half-time from the difference between postshift and preshift concentrations would not be reliable as, surprisingly, on a number of days the latter were even higher than the immediate postexposure values on the preceding day and on the same day.

From our results it would also appear that maximum urinary concentrations of ethoxyacetic acid are not reached after a single week of exposure. On the average the urinary concentrations remained lower during the second period in comparison with the first, although on most of the days the exposure concentrations were at least as high or higher.

For this reason, and because of the more constant exposure profiles, an estimation of the maximum ethoxyacetic acid levels in a population with prolonged daily exposure to the glycol ethers studied in our investigation was made on the basis of the results of the first period. For this week a good linear correlation ($r = 0.92$) was found between the average exposure over the five exposure days (14.4 mg/m³) and the ethoxyacetic acid excretion at the end of the week (105.7

Table 1. Exposure profiles from 111 half-shift personal samples in units of milligrams per cubic meter.

Product	Number of occurrences	Mean	SD	Maximum	Belgian occupational exposure limit
Ethyl ether of ethylene glycol	111	5.8	2.8	15.3	19
Ethyl ether of ethylene glycol acetate	111	12.2	7.5	34.5	27
Butyl ether of ethylene glycol	108	3.2	1.1	5.7	120
Methyl ether of ethylene glycol acetate	5	0.8	0.3	1.1	24
Methyl ethyl ketone	101	13.6	35.4	191.2	590
Isobutanol	65	1.5	0.5	3.4	150
1-Butanol	73	1.6	0.5	3.6	150
Ethanol	8	2.2	1.0	4.3	1 900
Ethyl acetate	71	2.1	0.9	4.9	1 400
n-Butyl acetate	5	2.8	2.2	6.1	710
1,1,1-Trichloroethane	9	2.5	1.4	4.9	1 900

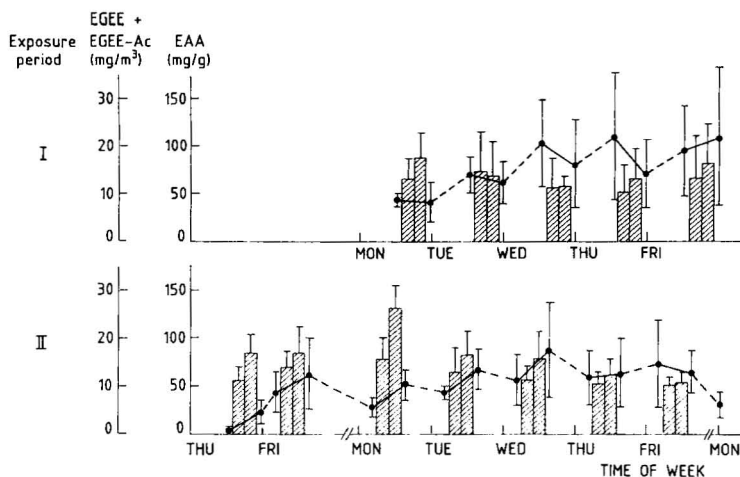


Figure 1. Combined exposures to the ethyl ether of ethylene glycol (EGEE) and the ethyl ether of ethylene glycol acetate (EGEE-Ac) (hatched columns) over shift halves and the urinary concentrations of ethoxyacetic acid (EAA) (•) before and after work. Depicted are the mean values and standard deviations for five subjects.

mg/g). The regression equation indicated that an estimated amount of ethoxyacetic acid of 150 ± 35 mg/g corresponds with repeated 5-d full-shift exposures to an EGEE air concentration of 19 mg/m^3 or an EGEE-Ac air concentration of 27 mg/m^3 .

Discussion

This field study on a group of five women daily exposed to a mixture of EGEE and EGEE-Ac confirms the conclusions from our short-term experiments regarding the relatively long biological half-time of the main metabolite ethoxyacetic acid and the expected accumulation effect (6, 7). From these experiments with single 4-h exposure periods, a half-time of 21–24 h was estimated. The present results seem to indicate that this half-time may even be longer. The reason remains unclear why on some days, especially during the first observation period, the preshift urinary concentrations of ethoxyacetic acid exceeded the end-shift values. In our experiments a delayed excretion maximum was also detected, but only 3–4 h after the exposure.

Furthermore, the excellent correlation of the ethoxyacetic acid concentration at the end of the week with the average individual exposures over the week proves the usefulness of this biological parameter for exposure monitoring purposes. To combine the exposures to EGEE and EGEE-Ac, as was done in this case, may be justified by the results from our experimental data. It was shown that the metabolic elimination kinetics of EGEE and EGEE-Ac in equimolar amounts were very similar (6, 7), probably due to the rapid and nonrate-limiting ester cleavage of EGEE-Ac by the plasma esterases (8, 10). The accumulation of ethoxyacetic acid in humans, due to its relatively long biological half-time, could also prove to be important from the toxicological point of view, especially if ethoxyacetic acid itself were the causative agent of the toxic effects (5, 13). It would certainly warrant extra caution in the extrapolation of experimental data from

laboratory animals to man, since comparable accumulation effects apparently are not found in all species, eg, rats (3) and beagle dogs (10).

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