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Dermal absorption of vaporous and liquid 2-methoxyethanol and 2-ethoxyethanol in volunteers

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Abstract

***Objectives*—To estimate dermal absorption of vaporous and liquid 2-methoxyethanol (ME) and 2-ethoxyethanol (EE) in volunteers.**

***Methods*—Five volunteers (two men and three women) were dermally exposed to vaporised and liquid ME and EE. Dermal exposure on an area of about 1000 cm^2 (forearm and hand) to vapours of ME and EE (4000 mg/m^3 ME and 3700 mg/m^3 EE) lasted for 45 minutes. Duration of exposure to liquid ME and EE on an area of 27 cm^2 (forearm) was 15 minutes. Dermal uptake was assessed by measurement of the main metabolites in urinary methoxyacetic acid (MAA) and ethoxyacetic acid (EAA). For each volunteer, excretion of metabolites was compared with a reference inhalatory exposure.**

***Results*—Mean (SD) absorption rates of ME and EE vapour were 36 (11) and 19 (6) cm/h respectively. The mean (SD) absorption rates of the liquid ME and EE amounted to 2·9 (2·0) and 0·7 (0·3) $mg/cm^2.h$.**

***Conclusions*—Vaporised and liquid ME and EE are readily absorbed through the skin. In the combined inhalatory and dermal exposure when whole body surface is exposed to vapour, the uptake through the skin is estimated to be 55% of the total uptake of ME and 42% of EE. Dermal uptake resulting from skin contact of both hands and forearms (about 2000 cm^2) with liquid ME and EE for 60 minutes would exceed inhalatory uptake of the eight hour occupational exposure limit by 100 times at 16 mg/m^3 of ME and 20 times at 19 mg/m^3 of EE. The substantial skin uptake of ME and EE indicates that in assessing the health risks biological monitoring and use of biological exposure indices are preferable to environmental monitoring.**

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Although often comprising < 10% of the final product, 2-methoxyethanol (ME) and 2–ethoxyethanol (EE) are key ingredients in water or solvent based paints and coatings and industrial and domestic hard surface cleaning products.[1] The usefulness of glycol ethers can be attributed to their physical properties, particularly their miscibility or high solubility in water and organic solvents, and their low vapour pressure. Studies on rodents indicate that ME and EE are compounds causing teratogenic, fetotoxic, haematotoxic, and testicular effects.[1] The toxic metabolites of ME and EE are the corresponding alkoxyacetic acids, methoxyacetic acid (MAA) and ethoxyacetic acid (EAA).[2–4] In humans, 85·5% of absorbed ME is excreted as urinary MAA with a half life of 77 hours.[4] On average, within 42 hours, 22% of absorbed EA was excreted as EAA with a mean (SD) half life of 42 (4·7) hours.[3]

The main concern for human exposure is the occupational environment. The occupational exposure limits (OEL) of ME and EE are set in The Netherlands[5] and United States[6] at 5 ppm (16 and 19 mg/m^3, respectively). A skin notation assigned to ME and EE in these OEL documents implies that skin absorption might be an important route of entry.

Despite hard evidence that both glycol ethers as liquids are readily absorbed through human skin in vitro[7] there are few human data on skin absorption of ME and EE in the liquid as well as in the vapour phase. Human data for skin uptake of another glycol ether 2-butoxyethanol have been published,[8 9] reporting that dermal exposure to 2-butoxyethanol, both liquid and vapour, was even more important than respiratory uptake. The purpose of this study was, therefore, to estimate the percutaneous absorption of ME and EE in volunteers under controlled experimental conditions.

Subjects and methods

SUBJECTS

The volunteers (two men and three women) ranged in age from 22 to 25. All were without a history of serious diseases and their skins appeared normal. None of them took medicines or alcohol from at least 12 hours before exposure until the end of collection of urine. The experimental protocol was submitted to and approved by the medical ethics committee of the Academic Medical Center, University of Amsterdam. An informed consent form was signed by each subject.

Given the very long half life of MAA (74 hours)[4] and of EAA (44 hours),[3] the period between the two exposures in each volunteer was at least three weeks.

GENERATION OF GLYCOL ETHER VAPOUR

Medical air at a flow rate of about 31/min

from a compressed air cylinder was led through a bottle filled with neat ME or EE. The vapour stream was led through teflon tubes into and out of the exposure cylinder.

EXPERIMENTAL SETTING

Dermal exposure to vapour and liquid

The volunteer was situated in a clean air cabin with a slightly increased pressure to avoid additional inhalatory exposure. The exposure lasted for 45 minutes. The arm of the subject was the only part of the body outside the cabin. During the vapour exposure experiments, the subject placed the lower arm into the exposure cylinder into which the glycol ether vapour was led. The exposure cylinder (volume 6·5 l) was provided with one large opening for the forearm and five small openings of about 3 mm internal diameter: two inlets, two outlets, and an opening for the vapour sampling. The vapour concentrations of ME and EE were about 10 times below the saturation concentration. To minimise the influence of temperature and humidity in the cylinder on the skin absorption and to prevent condensation on the skin, the flow of ME and EE of about 31/min was used. The temperature varied from 22°C to 25°C and the relative humidity from 60% to 65%. To avoid contamination of inhaled air through leakage, the opening in the cylinder and on the cabin were provided with cuffs. The concentrations of ME and EE in the cylinder were measured every five minutes throughout exposure.

During exposure to liquid ME and EE, a glass chamber with an area of 27 cm^2 was placed on the volar forearm and filled with ME or EE. After 15 minutes the exposure vessel was removed and the remaining solvent gently wiped off with a tissue. At the end of exposure the subject stayed for another 15 minutes in the cabin to allow the glycol ether to evaporate from the skin surface and to prevent possible inhalatory uptake.

Inhalatory exposure

Each volunteer was exposed during four periods of 15 minutes to a concentration of about three times the current OEL value in The Netherlands (16 and 19 mg/m^3 for ME and EE respectively). The time between the exposures was 10 minutes. Volunteers were in a sitting position and inhaled through a mouthpiece with a one way valve connected to a Tedlar (DuPont, Delaware, USA) bag containing ME and EE. During exposure the total amount of exhaled air was collected in another Tedlar bag. To prevent condensation of water in the exhaled air bag, a cold water trap (held at 0°C) was placed between the mouthpiece and exhaled air bag. To correct for the amount of ME and EE possibly absorbed in the water trap, we measured the amount of ME and EE absorbed in the condensate in the cold trap after consecutive 15 minute exposures of four subjects; this amount was taken into account when calculating the respiratory uptake. To determine the actual exposure concentration, air samples were taken from the inhalation bag before and during exposure from a point situated in the system before the mouthpiece.

Urine collection

All urine was collected for the first two days; for practical reasons, on days three to five only a morning and last evening sample were taken. One person collected all urine for seven days. For each sample, volume, creatinine, and specific gravity were measured and the samples were stored at −20°C until analysis.

Analysis

Analysis of inhaled and exhaled air was performed by gas chromatography. Air samples were injected with gas tight syringes into a gas chromatograph.

The MAA and EAA in urine were measured by a slightly modified version of the method of Groesenken *et al.*[10]

To 100 µl urine 25 µl butoxyacetic acid (20 mg/l)(internal standard) and 100 µl phosphate buffer (pH = 7) were added. Thereafter, samples were left at 60°C under slightly reduced pressure (20 mm Hg) to evaporate to dryness (about 20 minutes). After cooling down to room temperature 500 µl 5% derivatisation reagent (2,3,4,5,6-pentafluorobenzyl bromide) (Aldrich Chemie, Germany) in methanol was added. Derivatisation was allowed to proceed for three hours at 70°C; after cooling down to room temperature, 500 µl water was added then 500 µl n-hexane. Samples were vortexed for one minute and then centrifuged for two minutes at 3000 *g*. One µl hexane extract was injected into the gas chromatograph. Under these conditions, the detection limit of the method was 10 µg/l for both MAA and EAA.

Gas chromatographic conditions for the analysis of metabolites in urine

The gas chromatograph used was a Hewlett Packard Model 5890 A, equipped with an electron capture detector and a CP-SIL-13CB column (25 m; 0·25 mm internal diameter; film thickness 0·2 µm) (Chrompack, Middelburg, The Netherlands). Nitrogen was used as the carrier gas at a flow rate of 1 ml/min. The oven temperature was initially set at 60°C, increased to 166°C at a rate of 15°C/min, and subsequently to 200°C at a rate of 70°C/min and the column temperature was then kept at 200°C for 10 minutes.

Gas chromatographic conditions for the analysis of inhaled and exhaled air

The gas chromatograph used was a Carlo Erba Mega 5000 (Interscience, The Netherlands) equipped with a flame ionisation detector and a DB-WAX column (30 m; 0·53 mm internal diameter; 1 µm film thickness)(J and W Scientific). The analysis was performed isothermally at 80°C.

Measurement of skin area

The skin area of the forearm exposed to vapour was measured with the formula for calculation of the curved area of the frustum of a right cone.[11] The area of the hand was measured as

Table 1 Inhalatory exposure to ME and EE (4 times for 15 minutes): exposure conditions, respiratory retention, and uptake of ME and EE and 48 h cumulative urinary excretion of MAA and EAA

	Exposure (mg/m³)		Respiratory retention (%)		Inhalatory uptake, U_{inh} (mg)		MAA (EAA)$_{inh,48\,h}$ (mg)		Inhalatory uptake extrapolated to 8 h exposure at OEL (mg)	
Subject	ME	EE	ME	EE	ME	EE	MAA	EAA	ME	EE
1	41	52	85	85	18	23	3·3	5·9	54	67
2	39	46	80	75	18	20	1·2	1·8	54	58
3	44	60	77	75	18	24	2·4	5·2	54	70
4	44	49	92	86	23	24	3·1	5·3	69	70
5	42	59	67	86	16	29	3·7	6	48	84
Mean	42	53	80	81	19	24	2·7	4·8	57	70
SD	2·2	5·9	9	6	2·6	3·2	0·98	1·8	7·8	9·3

follows: the subject put on a rubber glove which fitted as well as possible without stretching on the hand. The area was then assessed by comparing the weights of the glove and of a piece of glove of a known area.

Calculation of uptake

The respiratory uptake (U_{inh}) and dermal uptake ($U_{der,vap}$ and $U_{der,liq}$) of ME and EE was calculated from the equations (1) and (2):

$$U_{inh}\,(mg) = (c_{inh} - c_{exh}) \times V \quad (1)$$

where c_{inh} = concentration ME or EE in inhaled air bag; c_{exh} = concentration in exhaled air bag (corrected for the amount absorbed in the water trap); V = volume inhaled (= exhaled) air; and

$$U_{der}(mg) = (MAA(EAA)_{der,48\,h}/MAA(EAA)_{inh,48\,h}) \times U_{inh} \quad (2)$$

where $MAA(EAA)_{der,48\,h}$ = amount of excreted MAA(EAA) in urine during the 48 hours after dermal exposure; $MAA(EAA)_{inh,48\,h}$ = amount of excreted MAA(EAA) in urine during the 48 hours after inhalatory exposure.

Permeability parameters

Exposure to vapour—The absorbtion rate (cm/h) was calculated by dividing the absorbed amount of ME and EE ($U_{der,vap}$) (mg) by the exposed area (cm²), the duration of exposure (h), and the exposure concentration (mg/cm³).

Exposure to liquid—The dermal penetration rate (dermal flux) (mg/cm².h) was calculated by dividing the total absorbed amount ($U_{der,liq}$)(mg), by the skin exposure area (cm²) and the exposure duration (h).

Results

Table 1 shows the experimental conditions of inhalatory exposure to ME and EE. For each volunteer, the calculated respiratory uptake (U_{inh}) of ME and EE and the 48 hour cumulative excretion of the corresponding acid metabolite are presented along with the respiratory uptake and retention defined as $(C_{inh} - C_{exh})/C_{inh}) \times 100\%$.

Estimation of dermal uptake of vaporised and liquid ME and EE was based on the 48 hour MAA and EAA urinary excretion, $MAA(EAA)_{der,48\,h}$. Tables 2 and 3 show the amounts absorbed dermally and calculated on an individual basis by comparison with a reference inhalatory exposure and exposure conditions. Tables 2 and 3 also show the permeability parameters for MA and EA vapour (absorbtion rate, cm/h) and for liquid (absorption rate, mg/cm².h). The results indicate that ME vapour penetrated the skin faster then EE; the absorbtion rate for ME amounted to 36 cm/h and to 19 cm/h for EE (table 2). The difference in penetration between ME and EE is even more pronounced after exposure to liquid; the absorption rate amounted to 2·9 for ME and 0·7 mg/cm².h for EE (table 3).

Table 2 Dermal exposure to vaporised ME and EE for 45 min: exposure conditions, 48 h cumulative urinary excretion of MAA and EAA and calculated dermal uptake and absorbtion rates of ME and EE

	Exposure (mg/m³)		Exposed area (cm²)		MAA (EAA)$_{der,48\,h}$ (mg)		Dermal uptake U_{der} (mg)		Absorbtion rates (cm/h)		Dermal uptake extrapolated to 8 h whole body exposure at OEL (mg)		Dermal/total uptake (%)	
	ME	EE	ME	EE	MAA	EAA	ME	EE	ME	EE	ME	EE	ME	EE
1	3835	2959	954	868	12	11	67	42	27	22	40	40	42	37
2	5782	4458	905	883	10	4	153	39	40	13	92	37	63	39
3	3082	2520	1210	1134	18	14	137	67	49	31	82	64	60	48
4	6190	4600	1032	1228	30	24	219	109	46	19	131	104	66	60
5	5032	3705	1086	1086	15	7	66	35	16	12	40	33	45	28
Mean	4854	3648	1037	1040	17	12	128	58	36	19	77	55	55	42
SD	1307	910	119	159	8	8	64	31	14	8	38	29	11	12

Table 3 Exposure to liquid ME and EE for 15 minutes: exposure conditions, cumulative urinary excretion of MAA and EAA, and calculated dermal uptake and absorption rate of ME and EE

	MAA (EAA)$_{der,48\,h}$ (mg)		Dermal uptake, U_{der} (mg)		Absorption rate (mg/cm².h)		Dermal uptake extrapolated to 1 h exposure and to exposed area of 2000 cm² (mg)		Dermal/inhalatory uptake (8 h, OEL)	
	MAA	EAA	ME	EE	ME	EE	ME	EE	ME	EE
1	3·9	0·8	14	3	2·1	0·4	4144	888	76	13
2	2·2	0·6	35	7	5·2	1·0	10360	2072	192	36
3	2·8	0·9	21	4	3·1	0·6	6216	1184	115	17
4	—	0·8	—	4	—	0·5	—	1184	—	17
5	2·4	1·7	10	8	1·6	1·1	2960	2368	62	28
Mean	2·8	0·96	20	5·2	2·9	0·7	5920	1539	111	22
SD	0·8	0·43	11	2·2	2·0	0·3	3256	651	58	10

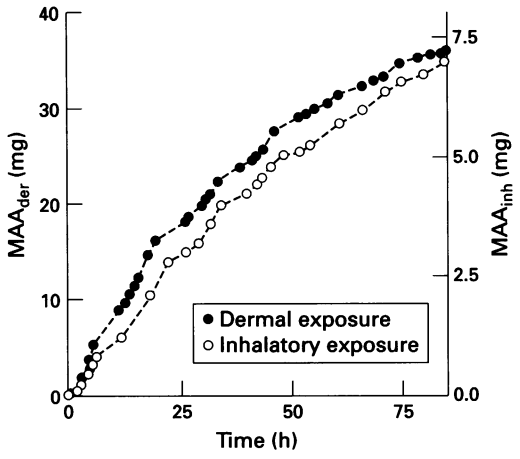

Figure 1 Cumulative urinary excretion of MAA after dermal and inhalatory exposure to vaporised ME.

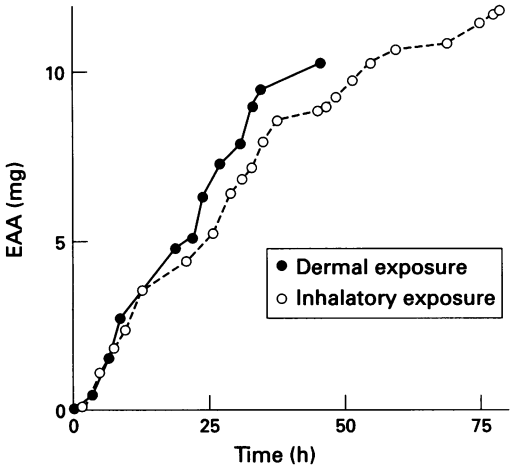

Figure 2 Cumulative urinary excretion of EAA after dermal and inhalatory exposure to vaporised EE.

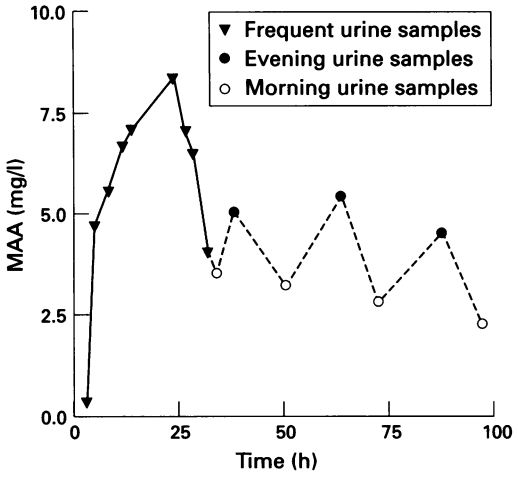

Figure 3 Urinary excretion of MAA after dermal exposure to vaporised ME.

To compare dermal uptake and uptake by inhalation from the same atmosphere we extrapolated the amount of $MAA(EAA)_{der,48\ h}$ in both experiments to the identical exposure conditions assuming constant absorbtion rates: eight hours of exposure at OEL (16 mg/m³ ME and 19 mg/m³ EE). Assuming that the entire skin area of the body is exposed, the forearm surface area is linearly extrapolated to the whole body surface area of 1·8 m² (tables 1 and 2).

To compare dermal uptake of liquid ME and EE with inhalatory uptake, we extrapolated the uptake determined in our study (exposed area of 27 cm² and exposure duration of 15 minutes) to a skin area of 2000 cm² (both forearms and hands) and exposure duration of 60 minutes. Table 3 shows this extrapolated uptake compared with the inhalatory uptake after exposure for eight hours at the OEL (table 1). These exposure conditions are proposed by the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) as a criterion for assigning a "skin notation" in the OEL documents. According to that criterion a skin notation should be applied if dermal uptake is > 10% of the eight hour inhalatory uptake at the OEL.

The use of inhalatory exposure as reference is based on the assumption that the toxicokinetics of ME and EE once absorbed in the systemic circulation is identical for both exposure routes. The excretion of both metabolites showed a similar pattern independent of exposure route: an initially fast increase in the concentration then slow and highly irregular excretion (figs 1–3). Before exposure neither MAA nor EAA was present in the urine in concentrations exceeding the detection limit of the analytical method (0·01 mg/l). The mean (SD) elimination half life calculated from the slope of the log linear excretion time curve 72 (24) hours for MAA and 44 (8) hours for EAA. Consequently, in morning urine samples lower concentrations were found; a day and night rhythm was illustrated for MAA after dermal exposure to ME vapour (fig 3). Correction for creatinine or specific density did not affect this excretion pattern. Slow urinary excretion of MAA and EAA is reflected in the shape of the cumulative excretion curves: even after seven days there was hardly any levelling off (measured in a person who collected all urine for seven days).

Discussion

Estimation of dermal uptake by comparison of urinary excretion of MAA and EAA after dermal and respiratory exposure is based on the assumption that their biokinetics is not affected by different routes of entry. The elimination pattern of MAA and EAA seemed to be similar for both exposure routes (figs 1 and 2) and it gave us the opportunity to measure dermal absorption by comparing it with a reference inhalatory exposure on an individual basis. Excretion of MAA and EAA was highly variable within individual people and there was a day and night rhythm; morning concentrations were always lower than those in the evenings (fig 3). The half lives were 72 hours for MAA and 42 hours for EAA and agreed closely with previously reported values of 77 and 42 hours for ME and EE.[3,4] As a consequence of such long half lives, the excretion of MAA and EAA was far from complete 48 hours after the start of exposure; on a molar equivalent basis only 12% and 14% of the dose was recovered within this period as MAA and EAA, respectively. This was lower than the reported values of 28% for ME[4] and 23% for EE.[3]

The long half life of MAA and EAA and a circadian excretion pattern could probably be explained by protein binding of MAA and EAA in blood or their reabsorption in the kidneys. Binding to proteins and elimination by saturable kinetics in the kidneys were reported by Corely and Bormett[12] for butoxyacetic acid (BAA), a compound with a comparable chemical structure to MAA and EAA. A similar urinary excretion pattern, with a circadian variation and a long half life, was also reported by Monster *et al*[13] for trichloroacetic acid, a metabolite of trichloroethylene. Circadian excretion rhythm is important if MAA and EAA are used as generally accepted biological exposure indices. A consistent sampling time has, therefore, to be applied.

Respiratory retention of both ME and EE was high, about 80%, as could be expected from the very high blood/air partition coefficients of 32 836 and 22 093 for ME and EE, respectively.[14] Respiratory retentions estimated in our study were somewhat higher than the values of 76% and 64% for ME and EE reported by Groesenken *et al.*[3 4] These differences could be explained by different exposure conditions (mouth only in our study versus nose and mouth exposure in the studies of Groesenken *et al.*[3 4]

This study showed that vaporised and liquid ME and EE are readily absorbed through the skin. The absorbtion rates into the skin normalised by cocentration of ME vapour is 36 cm/h and 19 cm/h for EE. Higher absorption of ME was more pronounced in exposure to liquid where an absorption rate of 2·9 for ME and 0·7 mg/cm^2.h for EE was estimated. Theoretically, the same ratio in permeability of ME and EE could be expected in exposure both to liquid and vapour. However, a high variation between people in both permeability parameters precludes speculation about the source of this discrepancy. Dugard and Walker[7] reported that liquid ME has a higher skin damage ratio than EE. This could possibly affect the skin integrity, and consequently increase the absorption of ME, in relation to EE. The absorption rate of liquid ME and EE estimated in our study is in close agreement with findings reported from the in vitro studies of Dugard and Walker[7] who reported mean (SD) values of 2·82 (2·63) for ME and 0·796 (0·46) mg/cm^2.h for EE.

In risk assessment it is important to estimate the relevance of skin uptake in relation to the other exposure routes. Inhalation exposure is assumed to be the most important uptake route for most organic solvents. However, ME and EE penetrate the skin so easily that skin contact of both hands and forearms (about 2000 cm^2) with liquid for one hour, greatly exceeds the respiratory uptake at OEL for eight hours (ME 100-fold and EE 20-fold). The question arises as to how realistic is such extensive skin contact with liquid ME and EE in occupational settings. It has to be stressed, however, that if spilling of ME and EE on clothing occurs, an even higher exposed area and exposure time can be expected. This exposure scenario (2000 cm^2 exposure area for one hour) was proposed by the ECETOC[15] as a criterion for assigning a skin notation. According to that criterion, a skin notation should be given if the dermal uptake under these conditions amounted to > 10% of the inhalatory uptake.

Dermal absorption of vapours is generally considered to be of minor importance compared with pulmonary uptake. However, it should be realised that a whole body skin area of 1·8 m^2 confronted with a mean air velocity of 2 km/h was swept by a volume of 28 800 m^3 in eight hours,[15] considerably more than the corresponding inhaled volume of 10 m^3. On the other hand, difference in the relative surface areas (1·8 m^2 for the skin *v* 30–100 m^2 for the lungs),[16] percentages of the cardiac output (100% for the lungs *v* 3% for the skin), and the distance that the compound must penetrate to reach the blood favour the lungs, generally speaking, as the primary site of absorption in a whole body exposure. However, our study shows that the skin is a significant uptake route for ME and EE vapour. If we assume whole body dermal and inhalatory exposure to vapour, the contribution of the skin to the total uptake would amount to 55% for ME and 42% for EE. Of course, this approach is simplified and some assumptions have been used in making these calculations. Firstly, that skin penetration characteristics of the forearms and hands (about 10 % of the total body area) are representative for the whole body, and secondly that clothing and possibly higher temperature and humidity under the clothing does not notably affect skin penetration. It is well known, however, from several experimental studies, that these factors could have an impact on the skin permeability.[17] Previously, Johanson and Boman[8] reported that dermal uptake of butoxyethanol accounts for about 75% of the total uptake during whole body exposure to butoxyethanol vapour with a tendency towards increased percutaneous absorption rate under conditions of increased temperature and humidity (33°C, 71% relative humidity in comparison with 23°C and 29% relative humidity) although the differences were not significant. However, with physiologically based pharmacokinetics models, Corely and Bormett[12] estimated the contribution of dermal uptake to be 21% of the total uptake, pointing out that the dermal uptake of butoxyethanol in the study of Johanson and Boman[8] was overestimated due to the method of calculating uptake. The contribution of 21% would be more consistent with the assumption that permeability of homologous glycol ethers decreases with the number of C atoms in the chain, as found in the present study and in the study of Dugard and Walker.[7] Applying another mathematical model from the literature,[18] based on the octanol/water partition coefficient, molecular weight and vapour pressures, we estimated contribution of whole body dermal uptake to be 32%, 40%, and 61% of the total uptake for ME, EE, and BE, respectively. Although these values are of the same order of magnitude as our results,

the permeability coefficient calculated with this model seems to increase with the number of C atoms and thus contrasts with our results and the in vitro study reported by Dugard and Walker.[7]

In summary, results of the present study show that dermal absorption associated with exposure to ME and EE vapour and liquid is of major importance. In the mixed inhalatory and dermal exposure when the whole body surface is exposed to vapour, dermal uptake would contribute 55% of the total uptake for ME and 42% for EE. Skin contact of both hands and forearms for 15 minutes with liquid ME and EE would considerably exceed the eight hour inhalatory uptake at the OEL. In monitoring exposure at the workplace, substantial skin uptake of ME and EE indicates that biological monitoring is to be preferred over environmental monitoring.

Also, the experimental set up used in the present study proved to be suitable for measurement of dermal absorption of chemical vapours and liquids in humans, providing the necessary data for the assessment of the health risks of exposure to these solvents.

1 National Institute for Occupational Safety and Health. *Occupational exposure to ethylene glycol monomethyl ether, ethylene glycol monoethyl ether, and their acetates.* Cincinnati, OH: NIOSH, 1991.

2 Groesenken D, Veulemans H, Masschelein R. Respiratory uptake and elimination of ethylene glycol monoethyl ether after experimental human exposure. *Br J Ind Med* 1986;**43**:544–9.

3 Groesenken D, Veulemans H, Masschelein R. Urinary excretion of ethoxyacetic acid after experimental human exposure to ethylene glycol monoethyl ether. *Br J Ind Med* 1986;**43**:615–9.

4 Groesenken D, Veulemans H, Masschelein R, Van Vlem E. Experimental human exposure to ethylene glycol monomethyl ether. *Int Arch Occup Environ Health* 1989; **61**:243–7.

5 *De Nationale MAC-lijst.* Den Haag: Arbeidsinspectie, 1994.

6 American Conference of Governmental Industrial Hygienists. *Threshold limit values for chemical substances and physical agents and biological exposure indices.* Cincinnati, OH: ACGIH, 1992.

7 Dugard PH, Walker M. Absorption of some glycol ethers through human skin in vitro. *Environ Health Perspect* 1984;**57**:193–7.

8 Johanson G, Boman A. Percutaneous absorption of 2-butoxyethanol vapour in human subjects. *Br J Ind Med* 1991;**48**:788–92.

9 Johanson G, Boman A, Dynesius B. Percutaneous absorption of 2-buthoxyethanol in man. *Scand J Work Environ Health* 1988;**14**:101–9.

10 Groesenken D, Veulemans H, Masschelein R, Van Vlem E. An improved method for the determination in urine of alkoxyacetic acids. *Int Arch Occup Environ Health* 1989; **61**:249–54.

11 Hursh JB, Clarkson TW, Miles EF, Goldsmith LA. Percutaneous absorption of mercury vapour by men. *Arch Environ Health* 1989;**44**:122–7.

12 Corely RA, Bormett GA. Physiological based pharmacokinetics of 2-butoxyethanol and its major metabolite, 2-butoxyacetic acid, in rats and humans. *Toxicol Appl Pharmacol* 1994;**129**:61–79.

13 Monster AC, Boersma G, Duba WC. Kinetics of trichloroethylene in repeated exposure of volunteers. *Int Arch Occup Environ Health* 1979;**42**:283–92.

14 Johanson G. Dynesius B. Liquid/air partition coefficients of six commonly used glycol ethers. *Br J Ind Med* 1988;**45**: 561–4.

15 European Centre for Ecotoxicology and Toxicology of Chemicals. *Percutaneous absorption.* Brussels: ECETOC, 1993.

16 International Commission on Radiological Protection. *Report of the task group on reference man.* New York: ICRP, 1975.

17 Scheuplein RJ, Blank I. Permeability of the skin. *Physiological Reviews* 1971;**51**:702–47.

18 Wilschut A, ten Berge WF, Robinson PJ, McKone TE. Estimating skin permeation. The validation of five mathematical skin permeation models. *Chemosphere* 1995;**30**: 1275–96.