

## Percutaneous absorption of 2-butoxyethanol in man

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JOHANSON G, BOMAN A, DYNÉSIUS B. Percutaneous absorption of 2-butoxyethanol in man. *Scand J Work Environ Health* 14 (1988) 101–109. The percutaneous absorption of the commonly used glycol ether 2-butoxyethanol (ethylene glycol monobutyl ether) was investigated in 12 exposure experiments with five men. The subject kept two or four fingers immersed in neat butoxyethanol for 2 h. Arterialized capillary blood samples were collected from the other hand before, during, and up to 4 h after the exposure and analyzed for butoxyethanol by gas chromatography. Urine was collected for 24 h and analyzed for the metabolite butoxyacetic acid, also by gas chromatography. The presence of butoxyethanol in blood and of butoxyacetic acid in urine confirmed that butoxyethanol enters the systemic circulation in man in vivo during dermal exposure. Percutaneous uptake rates were calculated from measured blood levels of butoxyethanol with the use of kinetic parameters (clearance and volume of distribution) obtained in earlier experiments with the same subjects. The uptake rates ranged from 7 to 96 nmol · min<sup>-1</sup> · cm<sup>-2</sup>. The results indicate that persons exposing large portions of their skin to butoxyethanol are at risk of absorbing acutely toxic doses.

**Key terms:** blood, butoxyacetic acid, cellosolve, glycol ether, gas chromatography, toxicokinetics, urine.

The glycol ether 2-butoxyethanol (ethylene glycol monobutyl ether) is frequently used in cleansing products, paints, and lacquers (13). The compound causes hemolysis and reduced hemoglobin concentration and red blood cell count in laboratory animals (15, 21). In contrast to the lower homologues 2-methoxyethanol and 2-ethoxyethanol, butoxyethanol does not appear to be teratogenic (15, 20). The low vapor pressure of butoxyethanol, combined with the high preference for water — a water/air partition coefficient of about 8 000 has been reported (9) — reduces the risk of attaining very high vapor concentrations in the atmosphere. On the other hand butoxyethanol may readily penetrate the skin, as shown with the guinea pig (10, 11) and the rat (1) in vivo and with human, pig, and rat skin in vitro (1, 5).

This paper deals with the percutaneous uptake of butoxyethanol in man in vivo. The aims of the investigation were (i) to confirm qualitatively that percutaneous uptake occurs in man in vivo and (ii) to obtain a quantitative estimate of the percutaneous uptake rate in order that comparisons with other routes of exposure and exposure levels and other species could be made. The main tool was the analysis of butoxyethanol in blood. In addition, the urinary excretion of the acid metabolite butoxyacetic acid was studied. Butoxyacetic acid is a major metabolite in urine from men exposed to butoxyethanol (8, 12).

## Materials and methods

### Subjects

The experiment was approved by the Ethical Committee at the Karolinska Institute, Stockholm. Five healthy men volunteered for the study. They had approximately one and a half years earlier participated in a study involving inhalation exposure to butoxyethanol (12). Thus toxicokinetic data, such as estimates of the respiratory uptake, apparent blood clearance, and apparent volume of distribution, were available for these individuals. None of them had experienced any occupational exposure to solvents. All were non-smokers and stated low or no alcohol consumption. One of the volunteers (subject B) was allergic to chlorpromazine and had atopic eczema on his chest, back, face, and the cubital fossa, and one (subject C) had neurodermatitis on his left leg. The subjects were told not to consume alcoholic beverages during the preceding 24 h and throughout the experiment and also to avoid activities that might cause exposure to organic solvents or induce irritation or damage to the skin.

### Chemicals

Butoxyacetic acid and pentoxyacetic acid were synthesized in our laboratory (12). All other chemicals were of analytical grade and purchased from Merck (Darmstadt, Federal Republic of Germany), unless otherwise stated. Butoxyethanol was distilled prior to use.

### Experimental procedure

Prior to the experiment the fingers were carefully examined for skin disorders (in one experiment, the ex-

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posure was switched to the right-hand fingers because of a small wound on one of the left-hand fingers). Blood and urine samples were collected, and finger diameter, skinfold thickness, and finger volume were measured as described below.

The subjects were exposed to neat butoxyethanol for 2 h by placing four fingers of the left hand through cut holes in a polyethylene cap into a polyethylene jar filled with pure solvent. The temperature in the room and the solvent jar was approximately 21°C. The subject sat in a comfortable chair with a good support for the left arm and hand throughout the exposure. The solvent jar and the left arm were kept in a separately ventilated hood to eliminate the risk of additional dermal exposure or inhalation or contamination of blood samples. At the end of the exposure, each subject rinsed the exposed hand thoroughly under running tap water and then washed both hands with a mild soap. They were thereafter allowed to move freely in the building, except when finger measurements and inspections were performed and blood and urine were sampled.

At regular intervals, the skinfold thickness of the dorsal skin on the third phalanx of the exposed fingers was measured with a Harpenden caliper (British Indicators Ltd, St Albans, Great Britain). In parallel, the finger volume was assessed with a simple plethysmograph, a test tube filled to the edge with water. The finger volume was determined by weighing the tube before and after the dipping of each finger. In all experiments the corresponding unexposed fingers served as the control.

#### Blood analysis

Arterialized capillary blood samples were repeatedly collected from the fingers of the unexposed hand after the hand had been rinsed and warmed for 1 min in freshly prepared hot tap water. The blood samples (2 · 200 µl) were rapidly transferred to screw-cap vials and extracted into toluene, derivatized with pentafluorobenzoyl chloride (Pierce, Beijerland, Holland), and analyzed by gas chromatography with electron capture detection as described earlier (12). The method error was estimated to be 11 %, expressed as the standard deviation of 43 duplicate samples of blood spiked to 1–10 µmol/l with butoxyethanol.

**Table 1.** Body weight, age, and estimates of the blood clearance ( $CL_b$ ) and steady-state volume of distribution ( $V_{ss}$ ) for 2-butoxyethanol.

| Subject | Body weight (kg) | Age (years) | $CL_b^a$ (l/min)  | $V_{ss}^a$ (l)    |
|---------|------------------|-------------|-------------------|-------------------|
| A       | 86               | 34          | 1.12              | 40.4              |
| B       | 72               | 40          | 1.11              | 48.4              |
| C       | 76               | 35          | 0.88              | 24.3              |
| D       | 80               | 37          | 1.52 <sup>b</sup> | 77.0 <sup>b</sup> |
| E       | 84               | 22          | 1.07              | 40.1              |

<sup>a</sup> From Johanson et al (12).

<sup>b</sup> Unpublished observation.

#### Urine analysis

All urine was quantitatively collected for approximately 24 h, in the same manner as previously described (12), and stored at –20°C until analyzed. Butoxyacetic acid, the urinary metabolite of butoxyethanol, was determined as follows. Urine (200 µl) was added to a teflon-lined screw-cap vial containing 2 ml of tetrabutylammonium hydrogen sulfate (0.1 M) buffered to pH 6 with potassium phosphate (0.2 M), with 25 µl of an aqueous solution of pentoxyacetic acid (1 mmol/l) as the internal standard, 2 ml of methylene chloride, and 10 µl of pentafluorobenzyl bromide (Pierce, Beijerland, Holland). The vial was capped, vigorously shaken, and then rotated for 1 h at room temperature. The methylene chloride phase was collected and evaporated under nitrogen at 40°C. The residues were dissolved in 2 ml of hexane, and aliquots of 1 µl were injected into the gas chromatograph (Varian 3400 equipped with a <sup>63</sup>Ni electron capture detector, Varian 8000 autosampler and Vista 402 integrator) by the split/splitless technique. A fused silica capillary column [Oribond SE-30, 25 m · 0.32 mm (inner diameter), 0.25-µm phase layer] was used. The column was identical to the one used for the analysis of butoxyethanol. Nitrogen was used as the carrier (2.0 ml/min) and make up (30 ml/min) gas. The temperatures were: injector 220°C, column 130°C, detector 260°C. The concentration of butoxyacetic acid was calculated from the pentafluorobenzyl butoxyacetate:pentafluorobenzyl pentoxyacetate peak area ratio. The described method is a further development of previous ones (12, 19) and comprises a reduced number of extractions, less use of reagent, close to neutral pH, and increased sensitivity. Urine samples spiked to 5–500 µmol/l were used as the standard. Fresh standard curves were prepared for each experiment. The slope of the curve was obtained by linear regression on log-log values. The method error was estimated to be 14 %, expressed as the standard deviation of 60 duplicate urine samples.

#### Calculations

The cumulated systemic uptake of a substance ( $a_{\text{uptake}}$ ) may be expressed as a function of time. Thus, on the assumption of linear kinetics, the cumulated uptake at a given time may be calculated during steady state once the concentration in blood ( $C_b$ ), the steady state volume of distribution ( $V_{ss}$ ), the blood clearance ( $CL_b$ ), and the “area under the concentration time curve” ( $AUC_{(0-t)}$ ) for the substance are known. Accordingly, the uptake of butoxyethanol may be calculated as:

$$a_{\text{uptake}} = C_b \cdot V_{ss} + CL_b \cdot AUC_{(0-t)}$$

This approach has been discussed in more detail in a previous paper (10). Estimates of  $V_{ss}$  and  $CL_b$  were obtained in previously performed inhalation experiments (12) and are listed in table 1.  $C_b$  was determined by gas chromatography, as has already been

described. Obviously, if steady state is not reached (such as when changes in  $C_b$  are rapid) or if the value of  $V_{ss}$  is incorrect, the first term in the equation will contribute inadequately to the calculated uptake. Such contribution is illustrated by peaks in some of the "invasion curves" in figure 4 in the Results section. However, the contribution of the first term, and thus of this error, will gradually decrease with time and eventually become zero. The  $AUC_{(0-t)}$  was calculated by the trapezoidal method up to 360 min. To obtain the  $AUC_{(0-\infty)}$ , a residual term was added on the assumption of monoexponential decay (17). The slope constant used in the residual term was an average of all 12 experiments, with values from 180 to 360 min. The systemic uptake of butoxyethanol was obtained as the product of  $AUC_{(0-\infty)}$  and  $CL_b$ . The uptake rate was calculated as the uptake divided by the exposure time and the exposed area.

The excretion rate and cumulated excretion of butoxyacetic acid in urine were calculated from the product of the measured concentration of acid and the urine volume of each sampling period.

The half-times of butoxyethanol and butoxyacetic acid were obtained by linear regression on the semi-log values from the decay phases.

The exposed area was calculated with the use of a cylindrical shape for the fingers. The average of the measured diameters of the first and third phalanges was taken as the diameter of the cylinder.

Skinfold thickness and finger volume were expressed as a quotient of the average value of the exposed fingers to that of the control fingers. The effect of exposure to butoxyethanol was graphically visualized from the quotient, expressed as a percentage of the initial (preexposure) quotient, at various times after the end of the exposure. The statistical significance of deviations from 100 % were tested with the two-tailed Student's t-test.

## Results

None of the subjects complained about or showed any signs of discomfort during or after the exposure to butoxyethanol. The skin of the exposed fingers was not irritated but appeared somewhat more rigid and less elastic after exposure and had a wrinkled appearance. This effect continued to develop, reached a maximum about 2–4 h after the end of the exposure, and then gradually disappeared. In parallel to the visible changes, the volume and skinfold thickness of the exposed fingers decreased and then returned to normal, as seen in figures 1 and 2. A dry, reticulate pattern with small fissures developed within a few hours after the exposure. In some cases the fissures became slightly erythematous. This reaction disappeared within 1 or 2 d. One subject (C) developed white fingers during the exposure in the second experiment. This occur-

rence appeared not to be an effect of low temperature only, as a similar but less prominent response was obtained when the subject was exposed to butoxyethanol heated to 30°C in a third experiment.

As seen in figure 3, the solvent could be detected in the blood of all the subjects when their fingers were exposed to liquid butoxyethanol. This is direct evidence of systemic uptake of butoxyethanol via the skin in man in vivo. The shape of the concentration profile varied considerably between individuals and also between experiments for some of the individuals. Esti-

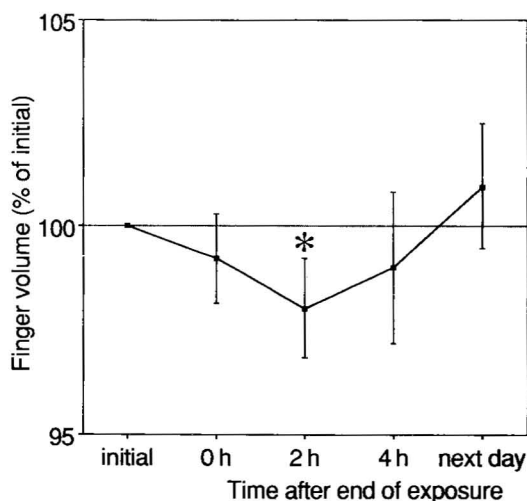


**Figure 1.** Relative finger volume (exposed/control) as measured by plethysmography after exposure to neat 2-butoxyethanol. The squares represent the average of 11 experiments with five subjects. The vertical bars represent the 95 % confidence interval (\*  $p < 0.01$  in Student's t-test versus the initial value).

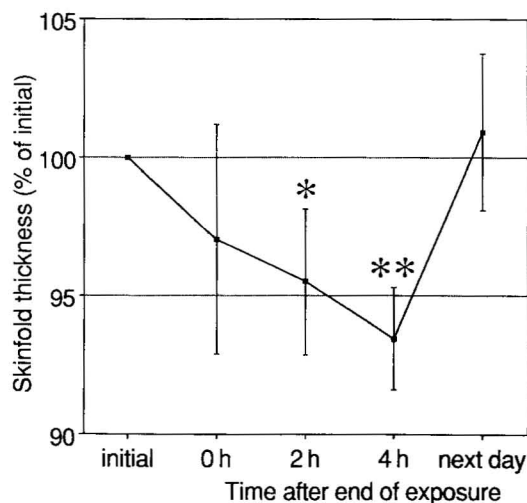


**Figure 2.** Relative skinfold thickness (exposed/control) after exposure to neat 2-butoxyethanol. The filled squares represent the average of 11 experiments with five subjects. The vertical bars represent the 95 % confidence interval (\*  $p < 0.01$  and \*\*  $p < 0.001$  in Student's t-test versus the initial value).

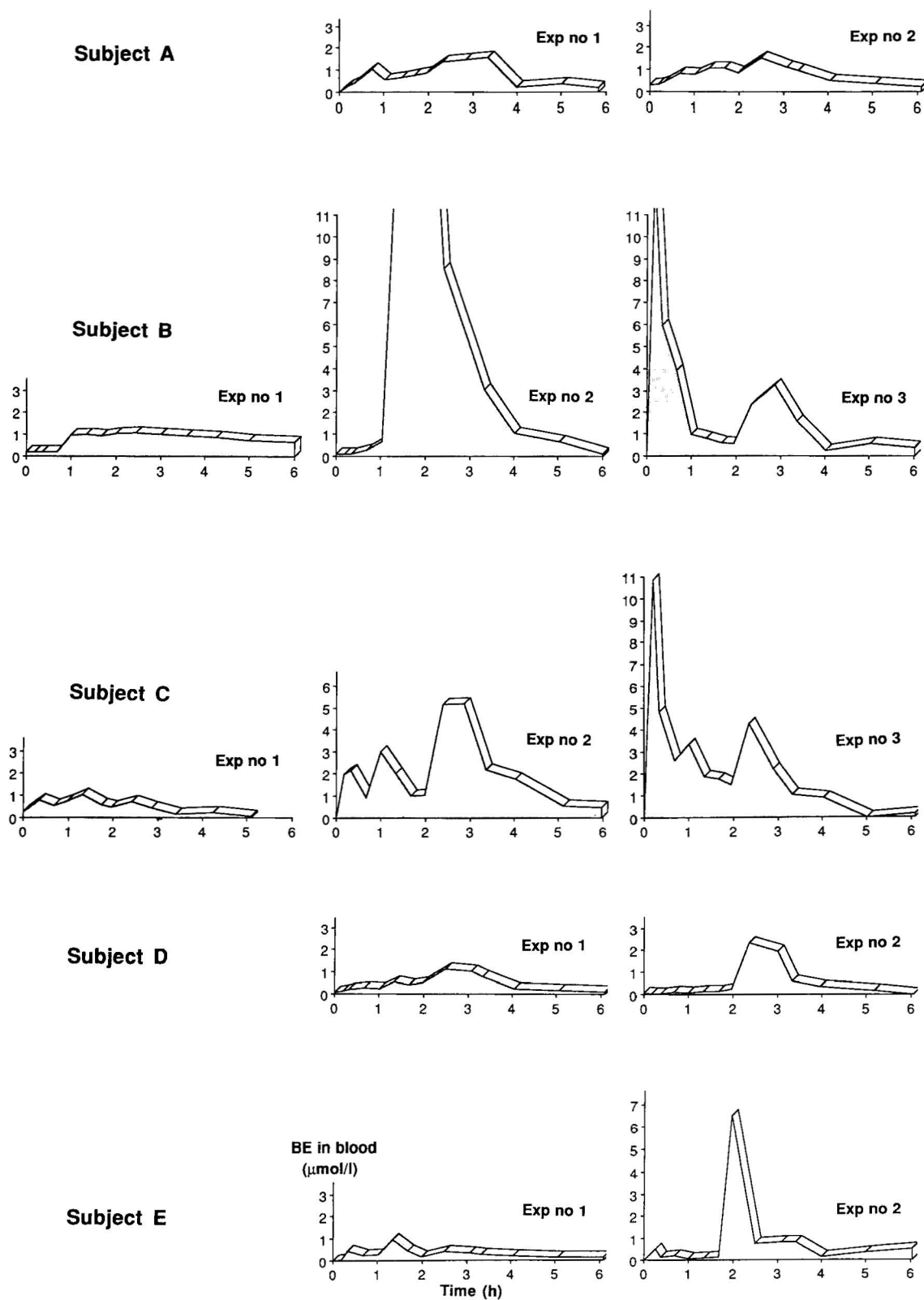


**Figure 3.** Time course of the concentration ( $\mu\text{mol/l}$ ) of 2-butoxyethanol (BE) in arterialized capillary blood during and after a 2-h immersion of four fingers in neat solvent (only two fingers of subject C, first experiment). Each curve represents one experiment.

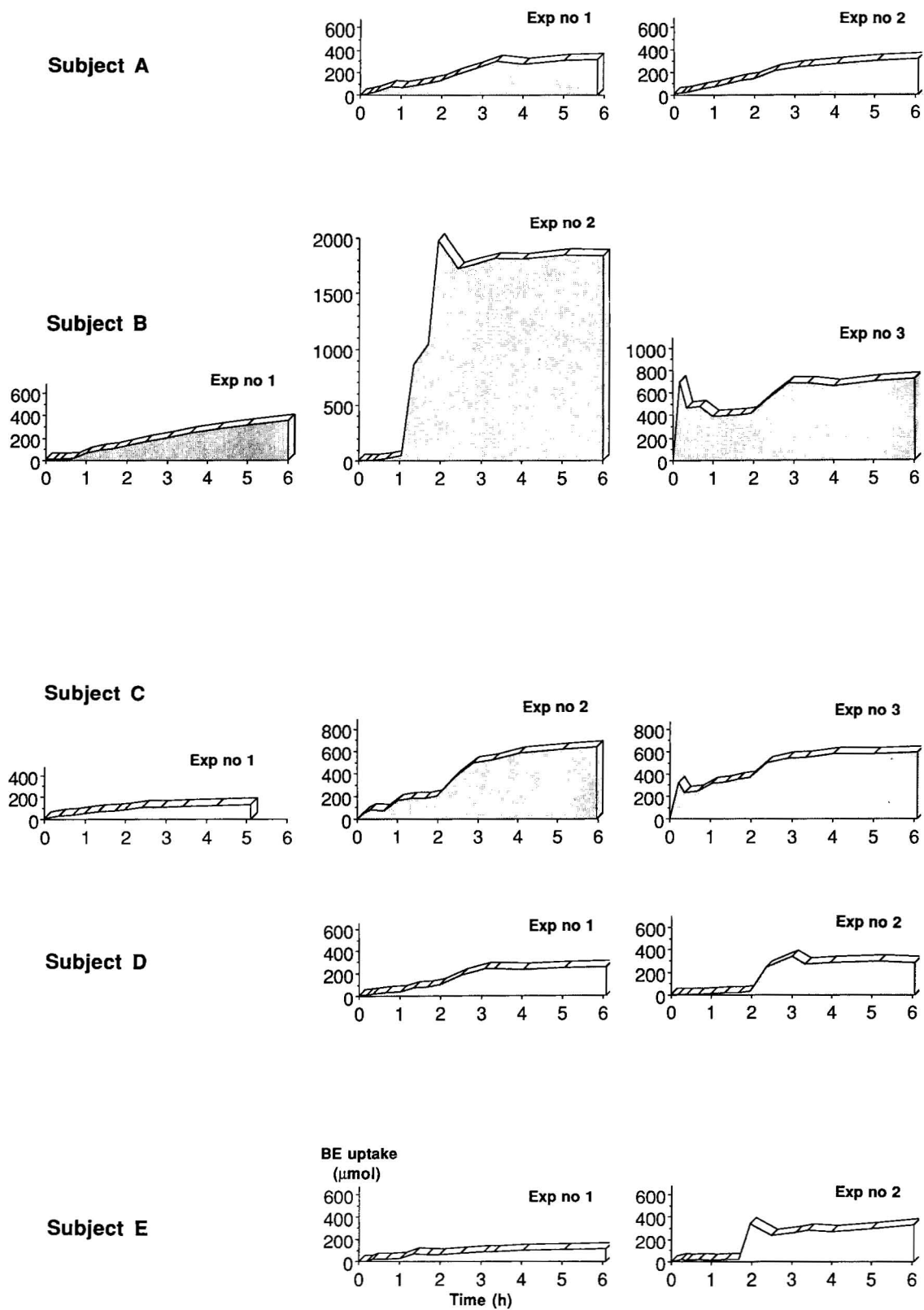


**Figure 4.** Time course of the calculated percutaneous uptake ( $\mu\text{mol}$ ) of 2-butoxyethanol (BE) during and after a 2-h immersion of four fingers in neat solvent (only two fingers of subject C, first experiment). Each curve represents one experiment.

mates on the skin uptake of butoxyethanol for each experiment are given in figure 4 and table 2. The percutaneous uptake varied more than tenfold, from 127 to 1 891  $\mu\text{mol}$ , corresponding to 7–96  $\text{nmol} \cdot \text{min}^{-1} \cdot \text{cm}^{-2}$ , with a geometric mean of 20  $\text{nmol} \cdot \text{min}^{-1} \cdot \text{cm}^{-2}$ . The half-time of butoxyethanol during the decay phase ranged from 0.6 to 4.8 (geometric mean 1.3) h.

The acid metabolite butoxyacetic acid was found in the urine after dermal exposure to butoxyethanol. As seen in figure 5, the excretion rate increased during the first hours after the exposure, reached a maximum at about 5 h (3 h postexposure), and then declined with an average half-time of 3.1 h (geometric mean). The calculated total uptake of butoxyethanol has been compared with the cumulated 24-h urinary excretion of

butoxyacetic acid in figure 6. Linear regression analysis for all the experiments, as well as the geometric mean, suggest that, on the average, 17 % of the absorbed dose of butoxyethanol was excreted as butoxyacetic acid in 24 h. However, there was a large variation between experiments. The cumulated excretion of butoxyacetic acid ranged from 8.7 to 313  $\mu\text{mol}$  (table 2), corresponding to 2.5–39 % of the uptake of butoxyethanol.

## Discussion

A possible source of error in the presently used method to calculate the percutaneous uptake of butoxyethanol is the clearance ( $CL_b$ ) values. Their correctness depends on the accuracy of the estimated respiratory uptake and the AUC in the inhalation experiments performed more than one year earlier. Metabolic clearance may change due to enzyme induction, liver changes, etc. However, there was nothing to indicate the occurrence of such a change, as the eating, smoking and drinking habits, body weight, health status, and occupation of the volunteers had remained unchanged.

The calculations presented in this study are valid only when linear kinetics may be applied. In experiments performed with perfused rat liver, the elimination kinetics of butoxyethanol were concentration dependent, the estimated values on the apparent Michaelis constant ranging from 0.32 to 0.70  $\text{mmol/l}$  (14). The blood concentrations of butoxyethanol were one or two orders of magnitude lower in the present study, and linear kinetics were thus indicated under the present conditions, when the results were extrapolated from rat to man.

**Table 2.** Estimates of the percutaneous uptake of 2-butoxyethanol (BE) and excretion of butoxyacetic acid (BAA) in urine during and after 2 h of exposure of four fingers.

| Subject | Experiment no  | Exposed area ( $\text{cm}^2$ ) | Uptake of BE ( $\mu\text{mol}$ ) | BE uptake rate ( $\text{nmol} \cdot \text{min}^{-1} \cdot \text{cm}^{-2}$ ) | BAA excreted ( $\mu\text{mol}$ ) |
|---------|----------------|--------------------------------|----------------------------------|-----------------------------------------------------------------------------|----------------------------------|
| A       | 1              | 175                            | 330                              | 15.7                                                                        | 41                               |
|         | 2              | 189                            | 315                              | 13.9                                                                        | 114                              |
| B       | 1              | 162                            | 390                              | 20.1                                                                        | 77                               |
|         | 2              | 164                            | 1891                             | 95.8                                                                        | 313                              |
|         | 3              | 161                            | 743                              | 38.5                                                                        | 65                               |
| C       | 1 <sup>a</sup> | 79                             | 128                              | 13.4                                                                        | 25                               |
|         | 2              | 182                            | 683                              | 31.3                                                                        | 39                               |
|         | 3 <sup>b</sup> | 176                            | 620                              | 29.4                                                                        | 222                              |
| D       | 1              | 180                            | 264                              | 12.2                                                                        | 102                              |
|         | 2              | 184                            | 274                              | 12.4                                                                        | 78                               |
| E       | 1              | 149                            | 127                              | 7.1                                                                         | 47                               |
|         | 2 <sup>c</sup> | 159                            | 346                              | 18.2                                                                        | 8.7                              |

<sup>a</sup> Two fingers exposed.

<sup>b</sup> Solvent heated to 30°C.

<sup>c</sup> Fingers of right hand exposed.

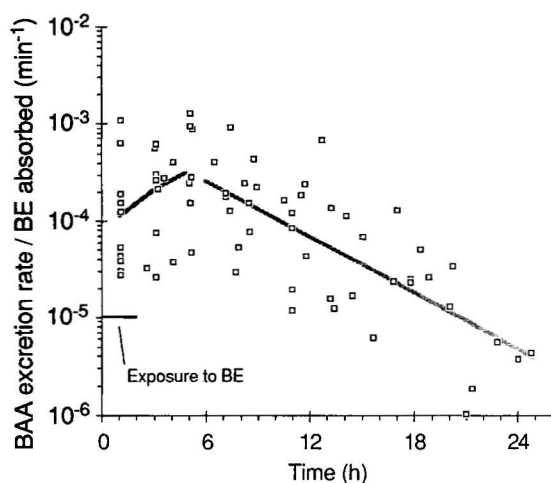


**Figure 5.** Time course of the excretion rate of butoxyacetic acid (BAA) in urine, expressed as the fraction of the total percutaneous uptake of 2-butoxyethanol (BE). Each data point represents one urine sample. The shaded curve was constructed from geometric means up to 5 h, and thereafter by linear regression.

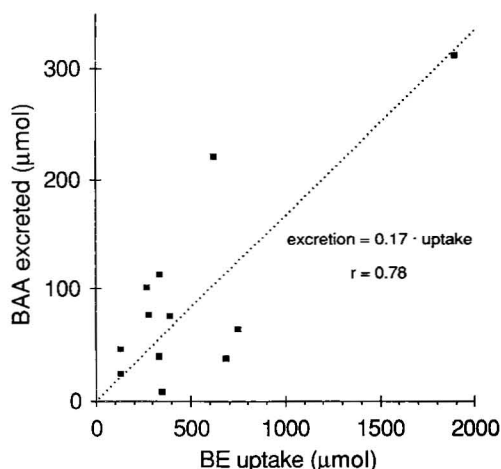


**Figure 6.** Cumulated 24-h excretion of butoxyacetic acid (BAA) in urine versus calculated dermal uptake of 2-butoxyethanol (BE). Each data point represents one experiment. The broken line was obtained by linear regression.

The time course of the concentration of butoxyethanol in blood during and after dermal exposure varied widely between the experiments, both regarding the shape of the curve and the levels reached. The reasons for the large fluctuations during the exposure are not known to us, but they appear to be related to changes in the uptake rate of the solvent. Diffusion through the stratum corneum is generally considered to be the rate-limiting factor in skin absorption (2), but other factors such as reduced peripheral blood flow may also be important. One subject developed "white fingers" when dipping his fingers in solvent at room temperature. This effect was less pronounced when the experiment was repeated with the solvent heated to 30°C. However, with the limited data available, no relationship between the uptake rate of butoxyethanol and the development of white fingers could be determined.

Other explanations of the variability, such as changes in distribution or metabolic rate, are not supported by the results of earlier inhalation experiments (12). Contamination of blood samples was unlikely because of the precautions undertaken in the blood sampling procedure, and exposure by inhalation was prevented. The strikingly high uptake of butoxyethanol in the second experiment with subject B is supported by a similarly high 24-h excretion of butoxyacetic acid (table 2 and figure 6).

The slope of the "invasion curve" was used to calculate the rate of uptake into the systemic circulation in previous guinea pig experiments (10). This approach could not be used in the present study because of the variable uptake pattern. Instead, total uptake was divided by exposure time. In the guinea pig, uptake rates calculated from the total uptake were approximately twice as high as those calculated from the slope of the "invasion curve" (unpublished observation). However, this difference is considerably smaller than the tenfold variation in skin uptake rates of butoxyethanol obtained for both guinea pig and man.

The estimated uptake rate of butoxyethanol of  $7\text{--}96\text{ nmol} \cdot \text{min}^{-1} \cdot \text{cm}^{-2}$  in the present study is comparable to that obtained in vitro with human skin by Dugard et al [28 (SD 99)  $\text{nmol} \cdot \text{min}^{-1} \cdot \text{cm}^{-2}$  (5)] and by Bartnik et al [approximately  $24\text{ nmol} \cdot \text{min}^{-1} \cdot \text{cm}^{-2}$  (1), our estimate from their table 6]. The uptake rate of another polar solvent, namely, methyl n-butyl ketone ( $0.05$  and  $0.08\text{ } \mu\text{mol} \cdot \text{min}^{-1} \cdot \text{cm}^{-2}$ ) in two men (4) was of similar magnitude.

The skin uptake of butoxyethanol in man is also comparable to that observed in the guinea pig [ $52\text{--}462\text{ nmol} \cdot \text{min}^{-1} \cdot \text{cm}^{-2}$  (10)] and the hairless rat [approximately  $170\text{ nmol} \cdot \text{min}^{-1} \cdot \text{cm}^{-2}$  (1), our estimate from their table 4], considering the known species differences with regard to the percutaneous uptake of xenobiotics (24).

The skin of the fingers exposed to butoxyethanol developed visible changes, as indicated by a decreased finger volume and skinfold thickness and a wrinkled and less elastic appearance. Generally, if skin is ex-

posed to an organic solvent, lipids are extracted, and permeability to water increases. The most effective in skin delipidization is chloroform or a 2:1 mixture of chloroform and methanol (16). The properties of butoxyethanol resemble those of the chloroform: methanol mixture in its ability to extract both hydrophilic and hydrophobic substances. Skin delipidization and dehydration may account for the development of the rigid, wrinkled, dry, and fissured appearance of the skin, as well as for the observed decrease in finger volume and skinfold thickness.

In most experiments the concentration in blood continued to increase after the exposure to butoxyethanol had ceased. This increase may partly be due to a depot effect. An additional explanation may be that the barrier properties of the skin were impaired by rehydration of the stratum corneum when the hands were washed at the end of the exposure (23). A similar effect was seen in guinea pigs dermally exposed to neat butoxyethanol (11).

With the possible exceptions of four experiments (with subjects B, D, and E), no lag time in the absorption of butoxyethanol could be seen. The absence of a lag time contrasts the 21–60 min observed for the guinea pig (10) and the < 1 h reported for human skin in vitro (5).

The percutaneous uptake of butoxyethanol was comparable to the respiratory uptake observed in the same men. The percutaneous uptake rate ranged from approximately 1 to  $16\text{ } \mu\text{mol}/\text{min}$  when four fingers were exposed, while the respiratory uptake rate ranged from 8 to 14 (average 10)  $\mu\text{mol}/\text{min}$  when they were exposed to butoxyethanol vapor at 20 ppm (the current Swedish occupational exposure limit) during light physical exercise at 50 W on a bicycle ergometer (12). Thus, exposing four fingers to liquid butoxyethanol corresponds roughly to being exposed to butoxyethanol vapor at 20 ppm.

However, care should be exercised when dermal and respiratory uptake rates are compared, for several reasons. First, variability in the dermal uptake rate may exist both between and within individuals, as suggested by the limited number of experiments presented in this paper. The uptake rates obtained in this investigation may not be representative of a large population. Second, the skin uptake of butoxyethanol may be considerably higher in other regions of the human body (22). Third, the condition of the skin may heavily influence the uptake rate, as has been shown for several compounds (18, 22). Fourth, butoxyethanol is mostly used together with water or other solvents (13). The presence of water has been shown to enhance the percutaneous uptake of butoxyethanol in guinea pigs (1, 11).

Feelings of discomfort and increased erythrocyte osmotic fragility have been reported after experimental exposure to 98 ppm, 113 ppm, and 195 ppm of butoxyethanol vapor (3). Exposure to 98–195 ppm corresponds to an absolute respiratory uptake rate of ap-

proximately 23–46  $\mu\text{mol}/\text{min}$ , if the ventilation rate and the relative respiratory uptake are assumed to be 10 l/min and 60 %, respectively. It is very probable that such uptake rates may be obtained with skin exposure if the exposed area is larger than in the present study or if other regions of the body, more permeable to solvents, are exposed.

The pattern of excretion for the urinary excretion of butoxyacetic acid (time to reach maximum excretion rate and half-time of the decay) was comparable to that determined in previous inhalation experiments (12). However, the excretion rate, as well as the cumulated 24-h excretion of acid metabolite, varied considerably both within and between experiments and between individuals, as seen in figures 5 and 6. Consequently, analysis of the acid metabolite in urine appears to be an unreliable method for assessing the percutaneous uptake of butoxyethanol in man.

Glycine conjugates of the butoxyacetic acid homologues ethoxyacetic acid and isopropoxyacetic acid have been detected in urine from experimental animals exposed to ethoxyethanol and isopropoxyethanol, respectively (6, 7). The presently used derivatization method was carried out at pH 6 to avoid the hydrolysis of conjugates, if present. The previous methods involved an extraction step at pH 2 followed by derivatization at pH 11 (12, 19). Acid-catalyzed hydrolysis of butoxyacetic acid conjugates in the urine may therefore explain the higher percentage of acid metabolite found in the previous inhalation experiments [geometric mean 41 (range 15–55) %, as compared to 17 (range 2.5–39) %]. This possibility is presently being further investigated.

In conclusion, our study clearly shows that butoxyethanol is absorbed through human skin in vivo and enters the systemic circulation. From calculations of the dermal uptake rate, a comparison with inhalatory uptake could be made. The comparison suggested that both skin and respiratory uptake should be considered when chemical products containing butoxyethanol are handled. Exposure of large areas of the skin to butoxyethanol may cause acute toxic effects in man.

## Acknowledgments

We wish to express our gratitude to Professor JE Wahlberg for performing the medical examinations, and to him and to Dr M Byfält Nordqvist for their valuable discussions and criticism of the manuscript.

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Received for publication: 10 December 1987