Hematological Follow-up of an Intervention Program Adding Rubber Glove-Wearing to Local Ventilation for 2-Ethoxyethanol Acetate-Exposed Workers

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Abstract: Hematological Follow-up of an Intervention Program Adding Rubber Glove-Wearing to Local Ventilation for 2-Ethoxyethanol Acetate-Exposed Workers: Hong-I CHEN, *et al.* Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, Taiwan, R.O.C.—The objective of this study was to evaluate

an intervention program, implemented in year 1999, of wearing rubber gloves in addition to engineering control, and to follow-up the hematological effects of 2-ethoxyethanol acetate (2-EEA) exposure among workers in a silk-screening factory. All workers from the printing department with direct exposure to 2-EEA were recruited as the exposed group. Workers from the other departments were recruited as the comparison group. Hematological parameters were measured during health surveys conducted 3 times every two years. Information on personal characteristics and working habits was obtained through a structured questionnaire. More female workers were involved in manual printing resulting in higher exposure to 2-EEA. Hemoglobin and haematocrit levels in female exposed workers were significantly lower than those of female comparison workers in the 1st (1998) health survey, but not in the 2nd (2000) and 3rd (2002) health surveys. No difference was found between male exposed and

comparison workers for all three surveys. Longitudinal analysis after adjusting for confounders using the general estimating equation model showed the hemoglobin, haematocrit, and RBC count were significantly higher for 2-EEA exposed workers than comparison workers across the 3 surveys (n=42). The results show that wearing rubber gloves in addition to local ventilation was effective at preventing direct dermal exposure to 2-EEA and ameliorated the hematological effects of 2-EEA exposure.

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2-Ethoxy ethanol (2-EE) and its acetate ester, 2-ethoxyethanol acetate (2-EEA), are solvents with properties of medium-high boiling points and low evaporation rates, and are suitable for manufacturing of coating materials¹. Although use of 2-EEA has been banned in the semiconductor industry, 2-EE and 2-EEA is still used in paints, thinners, and inks products^{1–13}. Data from a hazard survey showed that the annual consumption rates of 2-EE and 2-EEA are 1,200–1,800 and 5,000–8,000 tons, respectively, in Taiwan¹⁴. In particular, 2-EEA is used in silk-screening printing shops as a diluent or detergent¹⁴.

Overexposure to 2-EE or 2-EEA leads to toxic effects in animal experiments and human epidemiological studies via inhalation or percutaneous absorption^{1, 6–13}. Percutaneous uptake is the main route of exposure for 2-EEA^{1, 4, 5, 12, 13}. The toxic effects of 2-EEA include neurological toxicities^{1, 6}, reproductive toxicities^{1, 7–9}, and

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Table 1. Timeframe of major events in the silk-screening printing shop

Year	Events	Description
1994	1st environmental monitoring	All 17 samples in printing lines > PEL (10 ppm). The levels in the non-printing departments were also high.
1994–1997	Engineering control	Installation of local & general ventilation
1998	2nd environmental monitoring	Only 2 out of 29 samples in printing lines > PEL (10 ppm). The levels in the non-printing departments were quite low.
1998	1st Health survey	High exposure: 17/12 (Male/Female); Low exposure: 29/27 (M/F)
1999	Intervention with rubber glove	half-elbow-length butyl rubber gloves
2000	2nd Health survey	High exposure: 25/11 (M/F) Low exposure: 21/24 (M/F)
2002	3rd Health survey	High exposure: 29/11 (M/F); Low exposure: 28/19 (M/F)

hematological abnormalities^{1, 6, 10–13}). Our recent paper showed lower mean hemoglobin and haematocrit levels in a 2-EEA high-exposure group than in a low-exposure group¹³). However, the red blood cell (RBC), white blood cell (WBC), and platelet counts were found not to be decreased in the high-exposure group. A difference was only found in female workers, not in male workers, due to the fact that females had high exposure to 2-EEA during cleaning work and potential dermal absorption of 2-EEA from skin contact¹³). Since cleaning work in the surveyed printing shop is usually done by female workers, a lack of protective gloves was resulting in dermal contact and absorption of 2-EEA. Male workers were usually assigned to mixing jobs, and a respirator was provided by the company. Therefore, hematopoietic effects were not found in male workers¹³). Based on these findings, an intervention program of wearing rubber protective gloves during work was implemented in addition to engineering control. The objective of the study is to evaluate the impacts of this wearing rubber gloves intervention program on hematological toxicity of 2-EEA exposed workers.

Materials and Methods

Job description and operation processes

The silk-screening printing shop had fifteen printing lines. Four were automatic and eleven were manual. In the automatic printing lines, workers spend 70% of their work time in a control room with fresh air supply. For the manual printing lines, workers stay 8 h a day by the printing machine area. New design samples and small complicated pictures are often tested or printed on the manual printing machines. Therefore, manual printing often needs more delicate skills and more frequent cleaning of the screen with high solvent exposures.

Every day, the printing workers have to mix the solvents with inks and to clean the printing machines with solvents. The main component of screen-cleaning solvent is 2-EEA. The amount of 2-EEA used in the

surveyed factory was about 1,000 kg per month. In addition to 2-EEA, the workers may also be exposed to small amounts of methyl isobutyl ketone (MIBK), and toluene. A qualitative confirmation of 2-EEA, toluene, and MIBK in raw materials was reconfirmed by gas chromatography/mass spectrometry (GC/MS G1, 800A, GCD, Hewlett Packard, CA, USA). No benzene was found in the raw materials¹³).

In addition to the printing lines, 7 workers worked in the final product room, cutting room and design room. Some other workers were also engaged in the administration office. Due to the volatility of solvents, workers working outside the printing rooms may be indirectly exposed to 2-EEA.

Cross-sectional and longitudinal study population

Table 1 showed the timeframe of major events of this silk-screening printing shop. Workers in the silk-screening shop during the 3 health surveys were recruited as the cross-sectional study population¹³). But only workers had presented themselves for all three health surveys were recruited in the longitudinal analysis. All workers from the printing department (29, 36, 40 workers for three consecutive health surveys, respectively) with direct exposure to 2-EEA were recruited as the exposed group. Workers from the photo-sensitizing, design, product compiling, cutting rooms, and the administration office (56, 45, 47 workers for three consecutive health surveys, respectively) were recruited as the comparison group. All participants were informed about the study and signed consent forms.

Only workers presenting for all 3 consecutive health surveys were included in the longitudinal analysis (n=42). The study population present in all 3 health surveys consisted of 12 male and 5 female workers in the exposed group (n=17) and 13 male and 12 female workers in the comparison group (n=25).

Table 2. Air concentration of 2-EEA in the silk-screen shop stratified by sampling year among high exposure and comparison groups

Time	Year 1994			Year 1998		
	High-exp. group		Comparison group	High-exp. group		Comparison group
	Automatic printing	Manual printing		Automatic printing	Manual printing	
n	4	13	6	17	12	7
GM(GSD) (ppm)	45.71 (1.32)	17.38 (3.24)	8.51 (3.31)	4.87 (1.74)	9.34 (4.51)	0.07 (5.84)
Range (ppm)	33.09–60.59	10.07–38.97	3.16–22.9	1.35–8.69	4.1–16.5	ND–3.62

Intervention program (Table 1)

In 1994, the first environmental monitoring of air concentrations of 2-EEA had been performed in this shop¹⁵⁾ (Table 2). Since the exposure level were much higher than the permissible exposure limit (PEL) in Taiwan (10 ppm before 2003), the printing shop owner was ordered to reduce workers' exposures by the Institute of Occupational Safety and Health, Taiwan. Engineering controls including: local ventilation installed over the coating and heating ovens of each printing line and more fresh air provided for general ventilation in the entire exposure working areas were implemented. The installation of engineering control took about 4 yr and finished in early 1998. In middle of 1998, we conducted the 2nd environmental monitoring and found the exposure level was still high (exceeding the US OSHA PEL=5 ppm) (Table 2). In late of 1998, we conducted the first health survey to examine the hematological effects and found lower mean hemoglobin and hematocrit levels in the female exposure group than in the female comparison group¹³⁾.

Our previous experience showed that wearing impermeable rubber gloves during high-risk tasks could reduce major 2-ME exposure¹⁶⁾. Therefore, in 1999, a further intervention program of wearing half-elbow length butyl rubber gloves (B131R; thickness, 17 mm; length, 14 inches; North Safety Product, USA) during work was implemented after the first (1998) health survey. Before the intervention in 1999, only cotton gloves were available and were worn during the printing work. The percentage of workers always wearing cotton gloves doubled from 28% (8 of 29) at the time of the first (1998) health survey, while the proportion of workers always wearing rubber gloves was 55% (22 of 40) at the third (2002) health survey. Not all the workers wore the rubber gloves all the time, because some design works require speed and very delicate skills. However, they always wore the rubber gloves during the cleaning job. Due to the hot and humid environment, all workers refused to wear respirators during their work except for during the mixing jobs. Only cotton masks were worn during the work.

Data collection

Questionnaires were used to collect information on

personal characteristics, personal habits (e.g., alcohol consumption and smoking), reproductive history, disease and drug histories, a detailed occupational history, and related symptoms. About 10 ml of blood was collected from each worker for hematological examinations during 3 surveys. Hematological parameters in this study included hemoglobin, hematocrit, red blood cells (RBCs), white blood cells (WBCs), neutrophils, lymphocytes, platelets, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and the mean corpuscular hemoglobin concentration (MCHC). The hematological examinations during these 3 surveys were performed at the same hospital. Randomly selected blood samples were split and sent to a second hospital to analyze the hemoglobin value as a quality control check¹³⁾.

Statistical analysis

Student's *t*-test and Chi-squared test were used to compare differences between the exposed and comparison groups. A test of the equality of variance was performed using Student's *t*-test, and the adjusted variance and degrees of freedom were applied if the variances were not equal. For non-parametric statistics, the Mann-Whitney U test was used to compare hematological parameters stratified by gender due to the small sample sizes. The generalized estimating equation (GEE) model was used to evaluate the trend of repeated measurements between the exposed and comparison groups.

Results*Environmental monitoring data*

The sampling method of 2-EEA in this silk-screening shop was described elsewhere¹⁵⁾. Briefly, 3M 3500 passive samplers were used for 8-h personal sampling. The 2-EEA was analyzed using a gas chromatograph (Hewlett-Packard 5890 Series II, CA, USA) equipped with a HP 7673A auto-sampler and a flame ionization detector (FID). Table 2 showed the results of two environmental monitoring. In 1994, the environmental measuring of the air concentration of 2-EEA¹⁵⁾ showed the air 2-EEA concentration (GM) was highest in the automatic printing line (45.71 ppm, n=4) (Table 2), followed by the manual printing line (17.38 ppm, n=13),

Table 3. Distribution of characteristics in 2-EEA high exposure and comparison groups in the third survey

Variables	High Exposure n=40	Comparison group n=47	p value [#]
Male (%)	26 (65%)	21 (44.7%)	0.06
Age (yr)	32.20 ± 4.12	34.32 ± 7.55	0.10
20–30	15 (37.5%)	15 (31.9%)	
30–40	25 (62.5%)	28 (59.6%)	
>40	0 (0%)	4 (8.5%)	
Duration of employment (yrs)	10.46 ± 5.46	10.62 ± 4.95	0.89
<5 yr	7 (17.9%)	12 (25.5%)	
5–10 yr	17 (43.6%)	11 (23.4%)	
10–15 yr	8 (20.5%)	14 (29.8%)	
>15 yr	7 (17.9%)	10 (21.3%)	
BMI (kg/m ²)	22.62 ± 3.26	23.03 ± 3.27	0.56
Married (%)	30 (75%)	40 (85.1%)	0.39
Race			
Hakka	2 (5%)	3 (6.4%)	1
Mainlander	2 (5%)	2 (4.3%)	
Taiwanese	36 (90%)	42 (89.4%)	
Education			
None	0 (0%)	1 (2.1%)	0.008*
Elementary school	1 (2.5%)	1 (2.1%)	
Junior school	15 (37.5%)	4 (8.5%)	
Senior high school	20 (50%)	34 (72.3%)	
College	4 (10%)	7 (14.9%)	
Smoker	14 (35%)	10 (21.7%)	0.27
Alcohol			
>1 time/per week	2 (5.0%)	3 (6.4%)	0.37
Coffee			
>1 time/per day	8 (20%)	11 (23.4%)	0.68
Tea			
>1 time/per day	7 (17.5%)	11 (23.4%)	0.81

[#]by Student's *t*-test and chi-square test. **p*<0.05.

the cutting room (9.98 ppm, n=2), and the office and design room (2.71 ppm, n=4). Since then, the authority initiated a four years engineer control program (such as installation of local & general ventilation). In middle of 1998, we conducted the 2nd environmental evaluation. The geometric mean (GM) of air concentration of 2-EEA in the printing room (exposed group) was reduced to 7.41 ppm (n=29), with maximum of 16.5 ppm (Table 2)¹³. After installation of engineering control, the air 2-EEA concentration (GM) in the manual printing line (9.34 ppm) was higher than that in the automatic printing line (4.87 ppm)¹³. The air 2-EEA concentrations (GM) in the low exposure (comparison) departments of this printing shop were reduced to an average 0.07 ppm (n=7), with a maximum of 3.62 ppm.

The distribution of characteristics among study subjects

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in the 1st (1998) health survey has been published elsewhere¹³. The distribution of characteristics among study subjects in the third survey is given in Table 3. There were no differences in the distributions of age, gender, duration of work, marital status, personal habits, or smoking status between the exposed and comparison groups for all 3 surveys. However, the distribution of education significantly differed between these 2 groups. The comparison workers had a higher educational level than the exposed workers (*p*=0.008).

Cross-sectional studies of hematological effects

Since the criteria for hematological abnormalities varied with gender, the analysis in this study was stratified by gender. The means of hematological parameters for the 1st (1998), 2nd (2000) and 3rd (2002) health surveys stratified by gender are shown in Tables 4 and 5. For male workers, there were no significant differences

between the exposed and comparison workers of the 1st, 2nd and 3rd surveys, except for significantly higher platelet counts in the exposed group than in the comparison groups of the 2nd and 3rd surveys (Table 4). But for female workers, there were significantly lower values of hemoglobin and haematocrit in the female exposed workers than in the female comparison workers of the 1st survey (Table 5), as reported previously¹³. However, the decrements in hemoglobin and haematocrit in female exposed workers were not evident in the 2nd and 3rd surveys (Table 5). Except for hemoglobin and hematocrit, there were no significant differences in RBC, WBC, or platelet counts between female exposed and female comparison workers in all 3 surveys.

Longitudinal study of hematological effects over the three surveys

Since significantly reduced values of hemoglobin and haematocrit in the female exposed workers were only found in the 1st (1998) health survey, but not in the 2nd (2000) and 3rd (2002) health surveys (Table 5). This might have been the results may be due to the dilution effect from new employees in the factory. A longitudinal analysis was performed to investigate the changes of hematological parameters in 42 workers (12 male and 5 female workers in the exposed group and 13 male and 12 female workers in the comparison group) present in all 3 surveys. The GEE multiple regression models for comparison of repeated hematological measurements over the 3 surveys of these 42 workers are shown in Table 6. Changes in hemoglobin, hematocrit, and the RBC count were significantly associated with exposure status, after adjustment for potential confounders. The significantly positive coefficients mean the increasing temporal trends of hemoglobin, hematocrit, and RBC count in the exposed group were significantly higher than the temporal trends in the comparison group. However, the temporal trends for WBC and platelets were not significantly associated with exposure. These results suggest an amelioration of red blood cell damage among 2-EEA-exposed workers after the intervention.

Discussion

In the 1st (1998) health survey, it was found significantly lower values of hemoglobin and haematocrit in the female exposed workers than in the female comparison workers (Table 5). However, there were no significant differences between the 2 groups of male workers (Table 4). Meanwhile, the decrements in hemoglobin and hematocrit in the female exposed workers were not evident in the 2nd (2000) and 3rd (2002) health surveys (Table 5). Longitudinally, increasing temporal trends of hemoglobin, haematocrit, and the RBC count were found in the exposed workers during the follow-up period (Figures have not shown). The

increasing temporal trends of hemoglobin, hematocrit, and RBC count in the exposed group were significantly higher than those in the comparison group (positive coefficients in Table 6). These findings indicate that 2-EEA is a hematological toxin. After reducing dermal exposures through wearing rubber gloves, in addition to local ventilation and general ventilation, the hematological toxicities in the female exposed workers disappeared and a gradual recovery and increasing temporal trends of hemoglobin, haematocrit, and RBC count appeared in the total exposed group.

Female workers have higher solvent exposures because they clean screens more frequently¹³. The air of the manual printing lines had higher air 2-EEA concentrations (Table 2) and produced greater hematological toxic effects (Table 5). Our previous experience showed that wearing impermeable rubber gloves during high-risk tasks could reduce major 2-ME exposure¹⁶. Before the intervention in 1999, only cotton gloves were available and wore during the printing work. Therefore, an intervention program of wearing rubber gloves during work was implemented immediately after the first survey. Since some design works require speed and delicate skills, some workers did not always wear the rubber gloves during the printing work. The percentage of workers always wearing rubber gloves was increased to 55% in the third (2002) health survey. Although the internal doses or metabolites of 2-EEA exposure, 2-ethoxyacetic acid (2-EAA), were not measured in this study, improvements of hematological effects in the female exposed workers and increasing temporal trends of hemoglobin, haematocrit, and RBC count in the total exposed group support the evidence of reduced exposure during this follow-up period. These results may be related to the increased proportion of workers wearing rubber gloves during work which reduced dermal contact and absorption of 2-EEA. Installation of local ventilation over printing machines, and more fresh air provided for the general ventilation of the entire working area, kept the mean 2-EEA levels down to acceptable levels. However, the lowered 2-EEA air level did not protect workers from dermal contact, since significantly lower values of hemoglobin and haematocrit in the female exposed workers than in the female comparison workers was still shown at the 1st (1998) health survey (Table 5). These findings suggest that skin absorption rather than inhalation was the major route of exposure to 2-EEA. An intervention program to avoid direct dermal contact with 2-EEA by wearing rubber gloves is an important protective measure in the silk-screen printing industry.

Several studies have reported the importance of dermal absorption of ethylene glycol ether¹⁷⁻²³. However, most studies have focused on 2-EE rather than 2-EEA. Some *in vitro* studies have found that 2-EE absorption by human skin was about one-third of that in rat skin^{17, 18}, while

Table 4. Comparison of hematological parameters between male high exposure and comparison groups at the baseline, second and third surveys

Items	Male (1st survey)			Male (2nd survey)			Male (3rd survey)		
	High Exposure n=17	comparison group n=29	p value [#]	High Exposure n=25	comparison group n=21	p value [#]	High Exposure n=29	comparison group n=28	p value [#]
Hemoglobin (g/dl)	15.31 ± 0.97	15.72 ± 1.08	0.2	14.86 ± 1.09	15.14 ± 1.05	0.27	15.73 ± 1.00	15.76 ± 1.01	0.78
Haematocrit (%)	46.52 ± 2.61	47.00 ± 2.75	0.08	42.70 ± 2.46	42.99 ± 2.72	0.68	46.52 ± 2.61	46.82 ± 2.56	0.40
RBC (106/ μ l)	5.11 ± 0.38	5.33 ± 0.56	0.16	4.91 ± 0.47	4.85 ± 0.30	0.68	5.28 ± 0.40	5.31 ± 0.50	0.93
WBC (103/ μ l)	6.51 ± 1.73	6.19 ± 1.34	0.49	7.52 ± 1.97	6.78 ± 1.38	0.38	6.93 ± 1.79	6.86 ± 1.46	0.91
Platelets (103/ μ l)	254.1 ± 76.7	271.5 ± 64.5	0.41	238.4 ± 46.4	207.1 ± 45.5	0.04*	269.6 ± 51.4	233.8 ± 42.5	0.008*
MCV (fl)	90.13 ± 7.99	89.34 ± 7.52	0.74	86.39 ± 7.50	88.62 ± 2.89	0.46	88.53 ± 7.45	88.66 ± 7.52	0.87
MCH (pg)	1.90 ± 0.19	1.87 ± 0.20	0.68	30.12 ± 3.15	31.24 ± 1.14	0.27	29.99 ± 2.86	29.89 ± 2.94	0.93
MCHC (g/ μ l)	0.33 ± 0.009	0.33 ± 0.01	0.68	34.84 ± 1.03	35.24 ± 0.83	0.25	33.79 ± 0.63	33.66 ± 0.74	0.34

#Mann-Whitney U test, * $p < 0.05$.**Table 5.** Comparison of haematological parameters between female high exposure and comparison groups at the baseline, second and third surveys.

Items	Female (1st survey)			Female (2nd survey)			Female (3rd survey)		
	High Exposure n=12	comparison group n=27	p value [#]	High Exposure n=11	comparison group n=24	p value [#]	High Exposure n=11	comparison group n=19	p value [#]
Hemoglobin (g/dl)	13.07 ± 0.76	13.77 ± 0.99	0.03*	12.77 ± 0.81	12.82 ± 1.06	0.97	13.35 ± 0.91	13.43 ± 1.02	0.94
Haematocrit (%)	40.00 ± 2.69	42.00 ± 3.00	0.02*	36.68 ± 2.04	37.38 ± 2.58	0.62	39.00 ± 2.69	38.79 ± 5.45	0.64
RBC (106/ μ l)	4.42 ± 0.57	4.62 ± 0.65	0.36	4.23 ± 0.28	4.31 ± 0.38	0.78	4.30 ± 0.363	4.49 ± 0.44	0.34
WBC (103/ μ l)	6.69 ± 1.24	6.61 ± 1.77	0.89	6.05 ± 1.67	6.07 ± 1.29	0.71	6.88 ± 2.14	6.79 ± 2.27	0.98
Platelets (103/ μ l)	239.4 ± 65.9	261.8 ± 56.0	0.28	232.6 ± 41.1	238.6 ± 43.5	0.80	241.4 ± 36.1	262.0 ± 55.1	0.17
MCV (fl)	90.70 ± 8.33	91.78 ± 7.16	0.68	86.78 ± 3.11	85.89 ± 7.83	0.56	91.02 ± 3.16	88.73 ± 5.85	0.12
MCH (pg)	1.89 ± 0.20	1.90 ± 0.16	0.86	30.27 ± 1.27	30.08 ± 2.81	0.59	31.13 ± 1.00	30.07 ± 2.26	0.09
MCHC (g/ μ l)	0.33 ± 0.01	0.33 ± 0.01	0.57	34.73 ± 0.79	34.38 ± 1.21	0.48	34.20 ± 0.35	33.86 ± 0.72	0.11

#Mann-Whitney U test, * $p < 0.05$.

Table 6. The GEE model in longitudinal analysis of impact of 2-EEA exposure on the changes of hematological parameters

Dependent variables	Independent variables	Coefficient	SE*	p value
Hemoglobin	Intercept	12.3476	1.1519	
	Age	0.1211	0.0320	<0.001
	Sex	0.9329	0.3504	<0.05
	BMI	0.0698	0.0573	0.2234
	Education	-0.5421	0.3148	0.08
	High exposure vs. comparison	1.55	0.42	<0.001
Haematocrit	Intercept	35.17	3.43	
	Age	0.38	0.10	<0.001
	Sex	3.87	1.04	<0.001
	BMI	0.15	0.17	0.37
	Education	-1.24	0.94	0.19
	High exposure vs. comparison	4.39	1.26	<0.001
Red blood cells	Intercept	3.37	0.52	
	Age	0.03	0.01	0.02
	Sex	0.45	0.16	<0.05
	BMI	0.05	0.03	0.08
	Education	-0.10	0.14	0.47
	High exposure vs. comparison	0.55	0.19	<0.05
White blood cells	Intercept	4.59	3.34	
	Age	-0.18	0.09	0.05
	Sex	0.05	1.02	0.96
	BMI	0.15	0.17	0.38
	Education	1.02	0.91	0.26
	High exposure vs. comparison	-1.37	1.22	0.26
Platelets	Intercept	103.06	50.09	
	Age	-1.58	1.39	0.26
	Sex	-61.94	15.24	<0.001
	BMI	12.46	2.49	<0.001
	Education	-37.05	13.69	<0.05
	High exposure vs. comparison	24.65	18.35	0.18

*SE: Standard Error

others have shown that skin absorption is higher for 2-BE and 2-ME than for 2-EE^{19, 20}. Kenzic *et al.* experimentally studied the dermal absorption of vaporous and liquid 2-ethoxyethanol in 5 volunteers²⁰. Although their approach was simplified and some assumptions were used in making calculations, they found that both vaporized and liquid 2-EE were readily absorbed through the skin, and dermal absorption of 2-EE vapor and liquid was considered to be the most important route of 2-EE exposure²⁰. In combined inhalatory and dermal exposure when the entire body's surface was exposed to vapor, the uptake through the skin was estimated to be 42% of 2-EE²⁰. Dermal uptake resulting from skin contact of both hands and forearms (about 2000 cm²) with liquid EE for 60 min would exceed the inhalatory uptake of the 8-h occupational exposure limit by 20-fold at 19 mg/m³ 2-EE²⁰. These experimental findings indicate that skin

absorption rather than inhalation is the major route of exposure to 2-EEA.

Another compound, 2-methoxyethanol (2-ME), an ethylene glycol ether structurally similar to 2-EEA, has been shown to possess hematological toxicity and dermal absorption characteristics^{1, 16, 24}. One of our coauthors previously used an automated concentration and humidity-controlled system to measure the real-time percutaneous absorption of 2-ME vapor of 7 volunteers²⁴. Because the permeability constant of ME vapor (14.0 ± 5.3 cm/h) is much higher than that of many widely used organic chemicals, the authors concluded that vapor absorption through the skin was a significant contributor to overall ME exposure. Another coauthor evaluated the protective effectiveness of gloves against occupational exposure to 2-ME using the biomarkers of 2-methoxyacetic acid levels in urine and plasma¹⁶. They

found that wearing impermeable rubber gloves during high-risk tasks reduced major 2-ME exposure if engineering controls were also provided to diminish worker exposure to 2-ME in occupational environments¹⁶⁾.

Although many workers are potentially exposed to 2-EE or 2-EEA, reports on their hematological toxicity are very limited. A case of 2-EE poisoning was reported in Russia⁶⁾. A case of aplastic anemia was reported in a lithographer with potential exposure to dipropylene glycol monomethyl ether, 2-EE, and a range of aliphatic, aromatic, and halogenated hydrocarbons used for offset and ultraviolet-cured multicolor printing¹⁰⁾. Kim *et al.* reported decreased WBCs, but normal RBCs, among a group of shipyard painters exposed to 2-EEA¹²⁾. Johnson in his final report on the safety assessment of 2-EE and 2-EEA stated that mild anemia has been reported in individuals exposed occupationally to 2-EE, which resolved when the chemical was no longer used²⁵⁾. Several animal studies have also reported hematological toxicity induced by 2-EEA and 2-EE^{26–28)}.

As far as we could determine, there are no reports on recovery from the hematological effects of 2-EE or 2-EEA in humans. Human case reports state that the hematological effect of 2-methoxy ethanol (2-ME), a structurally similar ethylene glycol ether to 2-EEA, quickly dissipates to normal, within 4 wk to 3 months after cessation of exposure^{29–34)}. Our recent paper also showed that subjects recovered very quickly from the 2-ME-induced hematological effects as the airborne concentrations of 2-ME and its major toxic metabolite, MAA (2-methoxy acetic acid), were reduced^{35, 36)}. Since the half-life of MAA in humans (77–100 h)^{37–39)} is much longer than that of EAA (23–42 h)^{40, 41)}, we speculate that the toxic metabolite, EAA, stays in humans a shorter time than MAA, and human subjects can recover more quickly from the 2-EEA-induced hematological effects than those induced by 2-ME. Since increasing temporal trends of hemoglobin, haematocrit, and the RBC count were found in this study for the exposed workers during the follow-up period, these findings suggest that reducing exposures through dermal contact can lead to the gradual amelioration of the hematological effects in 2-EEA-exposed workers.

Conclusions

2-EEA is a hematological toxin. In addition to installation of local ventilation and general ventilation, reducing exposure through avoidance of direct dermal exposure to 2-EEA by wearing rubber gloves is an important protective measure in the silk-screen printing industry. Depression of hemoglobin, haematocrit, and the RBC count in the exposed workers gradually recovered after reduction of dermal exposure.

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