U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES ■ Public Health Service
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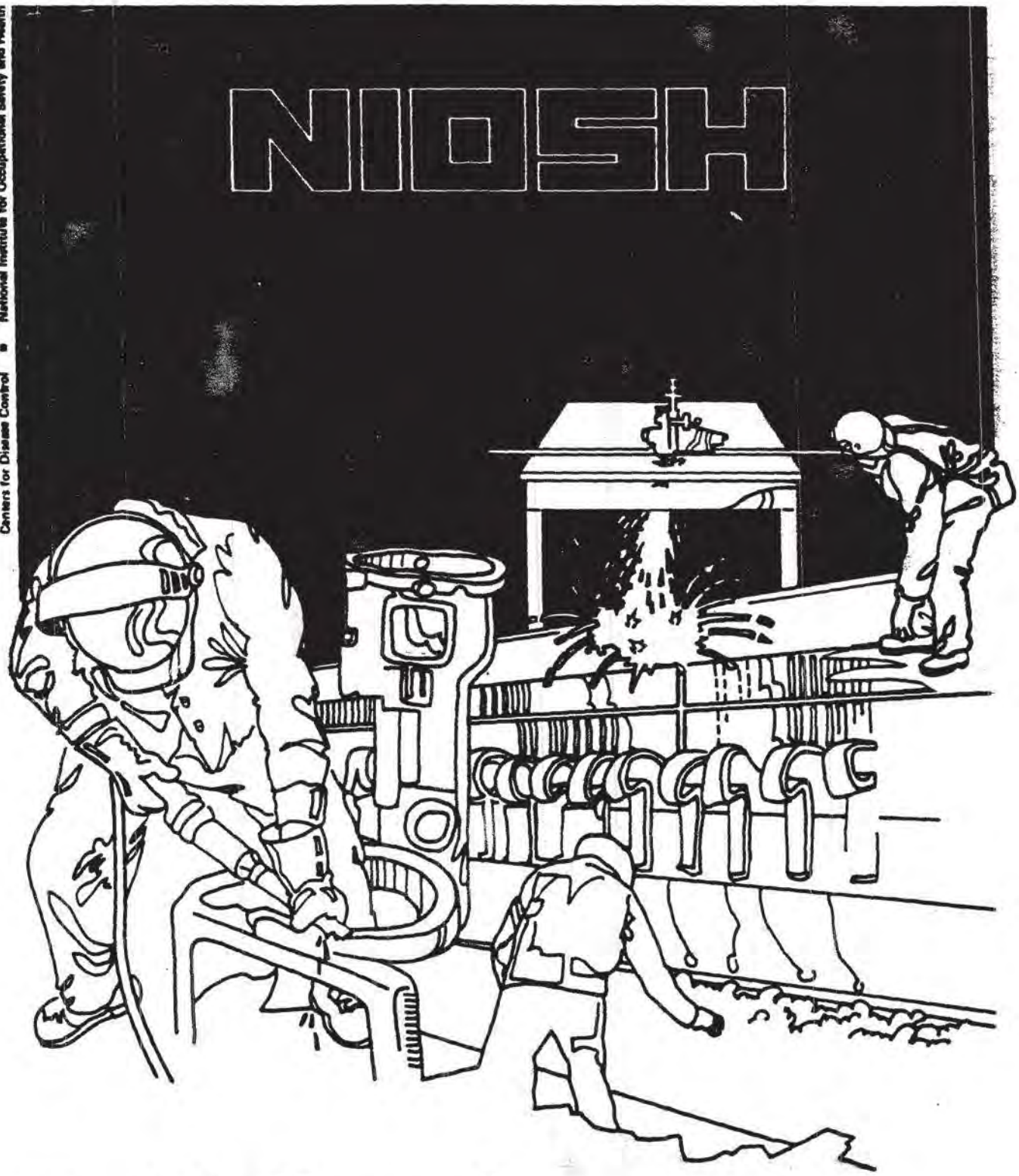
NIOSH



Health Hazard Evaluation Report

HETA 84-474-1946
ELECTRIC BOAT DIVISION
GENERAL DYNAMICS CORPORATION
GROTON, CONNECTICUT

PREFACE

The Hazard Evaluations and Technical Assistance Branch of NIOSH conducts field investigations of possible health hazards in the workplace. These investigations are conducted under the authority of Section 20(a)(6) of the Occupational Safety and Health Act of 1970, 29 U.S.C. 669(a)(6) which authorizes the Secretary of Health and Human Services, following a written request from any employer or authorized representative of employees, to determine whether any substance normally found in the place of employment has potentially toxic effects in such concentrations as used or found.

The Hazard Evaluations and Technical Assistance Branch also provides, upon request, medical, nursing, and industrial hygiene technical and consultative assistance (TA) to Federal, state, and local agencies; labor; industry and other groups or individuals to control occupational health hazards and to prevent related trauma and disease.

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ELECTRIC BOAT DIVISION
GENERAL DYNAMICS CORPORATION
GROTON, CONNECTICUT

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I. SUMMARY

On August 14, 1984, the National Institute for Occupational Safety and Health (NIOSH) received a request for a Health Hazard Evaluation from the painters union at Electric Boat Division of General Dynamics Corporation, Groton, Connecticut. The request concerned the potential for adverse reproductive effects among male workers exposed to glycol ethers (Cellosolves, 2-ethoxyethanol, 2-butoxyethanol, 2-methoxyethanol) during ship painting operations at this facility. The NIOSH study consisted of assessing exposures. A separate medical evaluation was conducted by Yale University and is reported elsewhere.

2-ethoxyethanol (2EE) is the primary solvent in epoxy paints used this shipyard. Approximately 800 painters are potentially exposed to 2EE during the application of coatings at various stages in the construction of nuclear submarines. An industrial hygiene survey conducted by NIOSH between December 3-7, 1984, showed full-shift breathing zone airborne exposures to 2EE ranging from non-detectable to 84.3 mg/m^3, with a mean concentration of 9.9 mg/m^3. Personal exposures to 2-methoxyethanol (2ME) ranged from non-detectable to 17.2 mg/m^3, with a mean of 2.6 mg/m^3. NIOSH recommends minimizing exposure to 2EE and other glycol ether solvents. Because of the potential for skin exposure to 2EE adding to the workers' overall exposure, urine specimens were collected from workers being monitored before and after each work shift for measurement of the metabolite of 2EE, ethoxyacetic acid (EAA). Results showed urine excretion of EAA ranging from non-detectable to 144 mg/g creatinine. The difference between pre and post-shift EAA levels in urine indicated a correlation to the measured air exposure level, as explained in the body of this report.

Based on the results of this survey, NIOSH has determined that a potential health hazard existed as a result of workers' exposure to 2-ethoxyethanol. Recommendations are made to minimize employee exposure to 2EE during painting operations in the shipyard.

KEYWORDS: SIC 3731 (Ship Building and Repairing), Cellosolve, 2-ethoxyethanol, ethylene glycol monoethyl ether, 2-ethoxyacetic acid, reproductive health.

II. INTRODUCTION

On August 14, 1984, the National Institute for Occupational Safety and Health (NIOSH) received a request for a Health Hazard Evaluation from the International Brotherhood of Painters and Allied Trades of United States and Canada (painters union) at Electric Boat Division of General Dynamics Corporation, Groton, Connecticut. The request was concerned with the potential for reproductive effects among male workers exposed to glycol ethers (Cellosolves: 2-ethoxyethanol, 2-methoxyethanol, 2-butoxyethanol) during ship painting operations at this facility. The request was a result of published information implicating glycol ethers as having the potential for causing adverse reproductive effects in both male and females.

2-ethoxyethanol (2EE) is the primary solvent in epoxy paints used at this shipyard. Approximately 800 painters are potentially exposed to 2EE during the application of coatings at various stages in the construction of nuclear submarines. An industrial hygiene survey was conducted by NIOSH between December 3-7, 1984. A separate medical evaluation was conducted by Yale University and is reported elsewhere.

III. BACKGROUND

The Electric Boat Division of General Dynamics Corporation constructs and retrofits nuclear submarines under contractural agreement with the United States Navy. The two types of submarines manufactured at Electric Boat are the Trident class and the Fast Attack Class. Electric Boat employs about 25,000 workers (predominantly trades people), approximately 800 of whom are painters.

Painters are engaged full-time in a variety of painting operations including brush painting, spray painting, mixing, and sand blasting. They use a significant amount of paints and thinners which contain from 5-60% 2-ethoxyethanol (2EE) and 2-methoxyethanol (2ME). They often work in enclosed spaces. The glycol ethers are found as constituents and thinners for epoxy paints. These paints are used extensively in ship building. At Electric Boat, over 40,000 gallons of one epoxy paint alone (Savapon), containing 10% 2ME have been used. The same paint contains 5% 2EE in the color component, 25% 2EE in the cure component and 25% 2EE in the thinner. Epoxy paints are used to paint inside tanks and missile tubes, as well as the exterior of the ships. Mixing and brush painting often take place without respiratory protection; spray painting is usually done with an air supplied respirator. NIOSH previously conducted a health hazard evaluation (HETA 78-135-1333) in this shipyard and measured 108 mg/m^3 of 2ME and 27-475 mg/m^3 of 2EE during painting operations. Industrial hygiene sampling performed by General Dynamics indicated: up to 30 ppm (93 mg/m^3) of 2ME during a mixing operation, levels up to 27 ppm (84 mg/m^3) of 2ME in areas 10 feet from a spray operation, and one sample with 400 ppm (1474 mg/m^3) of 2EE in a closed space operation.

Respirators are required during spray painting in closed locations but not during mixing and brush painting operations or nearby the spray painting. Significant skin contact can occur in all of these operations.

IV. EVALUATION DESIGN AND METHODS

A. Environmental

In order to assess potential exposure to solvents during painting operations, personal breathing zone air samples were collected with activated charcoal sampling media and portable air sampling pumps.

Air samples were collected at either 20 cc/min or 50 cc/min, depending on the type of sampling pump used. Pumps used included SKC Model 222 and Sipin low flow. Sampling pumps were calibrated before and after each sampling period. Employees reported to the paint shop at the beginning of each shift to pick up their assignments, and then reported directly to the industrial hygiene lab where they (1) provided a pre-shift urine specimen, and (2) were fitted with the air sampling apparatus. At the end of each shift, employees returned to the lab where the sampling train was removed and a post-shift urine specimen was collected.

One hundred-two (102) air samples were collected during this survey. Samples were analyzed by gas chromatography according to NIOSH Method P&CAM 127.[1] All air samples were analyzed for 2EE, 2ME and 2BE.

For 2-4 consecutive days, a total of 36 workers were monitored. Information was gathered from each employee as to the amount of time actually spent painting during each shift, whether or not a respirator was worn, whether other types of personal protective clothing were worn, and the temperature in the work area. A somewhat subjective rating was assigned to each employee's physical activity, and estimate of skin contact. Work areas were visited twice during each shift to check the operation of the sampling pumps, and work practice observations were noted at this time. A rating system of 0-3 was used to describe employees' physical activity, with 0 being sedentary, and 3 being strenuous labor. Similarly, skin contact was assigned a rating based on 0 = no, 1 = little, 2 = significant, amounts of paint on the skin of the worker. Information was recorded as to the location of each worker while painting, how much time during the shift was actually spent painting, whether or not the painter wore a respirator, what type of paint was used and how much paint the worker applied.

Bulk samples were taken of 7 of the paints, representative of those most used during the sampling period, and of a cleaner. Gas chromatography-mass spectrometry (GC-MS) analysis was used to assess the contents of 6 with distinctive chromatograms.

B. Biological

Urine specimens were collected in a polyethylene cup and then split into two separate scintillation vials, labeled and frozen for shipment to the analytical laboratory. Samples were analyzed for the glycol ether metabolites 2-ethoxyacetic acid (EAA), 2-methoxyacetic acid (MAA), and 2-butoxyacetic acid (BAA) accordingto the method developed by Smallwood, et. al.[2] Urine samples were also analyzed for creatinine. (The urine creatinine concentration, by itself, has no medical interpretation, it is used to standardize the measured concentrations of the other substances.) Two hundred fifty-four (254) specimens were submitted for analysis (total 508 vials). Pre- and post-shift urine specimens were collected from the 36 workers being air monitored on 2-4 consecutive work days in an attempt to determine if any correlation could be demonstrated between exposure to the glycol ethers and excretion of the metabolites in urine.

V. EVALUATION CRITERIA

As a guide to the evaluation of the hazards posed by workplace exposures, NIOSH field staff employ environmental evaluation criteria for assessment of a number of chemical and physical agents. These criteria are intended to suggest levels of exposure to which most workers may be exposed up to 10 hours per day, 40 hours per week for a working lifetime without experiencing adverse health effects. It is, however, important to note that not all workers will be protected from adverse health effects if their exposures are maintained below these levels. A small percentage of workers may experience adverse health effects because of individual susceptability, a pre-existing medical condition and/or by a hypersensitivity (allergy).

In addition, some hazardous substances may act in combination with other workplace exposures, the general environment, or with medications or personal habits of the worker to produce health effects even if the occupational exposures are controlled at the level set by the evaluation criteria. These combined effects are often not considered in the evaluation criterion. Also, some substances are absorbed by direct contact with the skin and mucous membranes, and thus potentially increase the overall exposure. Finally, evaluation criteria may change over the years as new information on the toxic effects of an agent become available.

The primary sources of environmental evaluation criteria considered for this study were: (1) NIOSH criteria documents and recommendations, (2) the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV's), and (3) the U.S. Department of Labor (OSHA) federal occupational health standards. Often, the NIOSH recommendations and ACGIH TLV's are lower than the corresponding OSHA standards. Both NIOSH recommendations and ACGIH TLV's usually are based on more recent information than are the OSHA standards. The OSHA standards also may be required to take into account the feasibility of

controlling exposures in various industries where the agents are used; the NIOSH recommended exposure limits, by contrast, are based primarily on concerns relating to the prevention of occupational disease. In evaluating the exposure levels and the recommendations for reducing these levels found in this report, it should be noted that industry is legally reguired to meet those levels specified by an OSHA standard. A time weighted average (TWA) exposure refers to the average airborne concentration of a substance during a normal 8-10 hour workday. Some substances have recommended short-term exposure limits or ceiling values which are intended to supplement the TWA where there are recognized toxic effects from high short-term exposures.

The Occupational Safety and Health Administration (OSHA) has promulgated an 8-hour time weighted average permissible exposure limit (PEL) of 200 ppm (740 mg/m^3) for 2EE, 25 ppm (80 mg/m^3) for 2ME, and 50 ppm (240 mg/m^3) for 2BE.[3] The ACGIH recommends a TLV of 5 ppm (19 mg/m^3) for 2EE, 5 ppm (16 mg/m^3) for 2ME, and 25 ppm (120 mg/m^3) for 2BE.[4] Both the OSHA PEL's and ACGIH TLV's bear the "skin" notation indicating the potential for absorption of toxic amounts of 2EE, 2ME and 2BE through the intact skin (see also Reference #5). NIOSH does not recommend a specific exposure limit for 2EE, 2ME or 2BE, but recommends that exposure to glycol ethers be reduced to the lowest extent feasible.[6]

Toxicology

2-Ethoxyethanol is one of a family of glycol ethers, several of which have been shown to produce adverse reproductive effects in both male and female animals.[6] With respect to the male reproductive toxicity of 2EE, testicular atrophy and microscopic testicular changes (including degeneration of seminiferous tubules and damage to dividing spermatocytes and spermatids) have been reported in rats given 900 mg/kg 2EE in the diet for two years;[7] in rats and dogs treated orally with 186 mg 2EE/kg/day for 13 weeks and rats given 372 and 744 mg 2EE/kg/day subcutaneously for four weeks.[8]

Similar effects were shown in rats dosed orally with 460-1000 mg 2EE/kg/day for 11 days; in mice given 1000-2000 mg/kg/day orally for five weeks and in rabbits exposed to 400 ppm 2EE (6-hr/day, 5 days/week) by inhalation for 13 weeks.[9,10,11,12]

Oudiz, et al intubated rats with 936, 1872, and 2808 mg 2EE/kg/ for five days and analyzed semen at periods ranging from 1-14 weeks after cessation of dosing, and found azoospermia or severe oligiospermia among the two highest dose groups and a significant increase in abnormal sperm morphology in the lowest dose group by the seventh week.[13] Partial or complete recovery of sperm counts and morphology were observed by the fourteenth week. Finally, Lamb, et al found dose related decreases in sperm motility, an increase in the percentage of morphologically abnormal sperm and decreases in testicular weight in mice given 1-2% 2EE in their drinking water for 14 weeks.[14] A significant reduction in fertility (number of live pups per litter) among untreated females mated with males treated with 2% 2EE was also observed.

Based on the animal evidence of the reproductive toxicity of 2EE, NIOSH has recommended that the current OSHA PEL of 200 ppm (8-hour TWA) be reexamined and that exposures to 2EE be reduced to the lowest extent feasible.[6]

VI. RESULTS AND DISCUSSION

A. Environmental

Glycol ethers were found only in those bulk samples expected to contain glycol ethers although some discrepancies existed between hazard communication listings of components and those identified by analysis. 2-Methoxyethanol, for example, was not found in any of the bulks though it was expected, and appeared in some of the air samples.

All of the blank samples (not exposed to 2EE but handled as field samples) were analyzed as non-detectable. Fourteen blank samples were submitted for analysis. The absence of any detectable quantities of 2EE on the blank samples confirms the absence of contamination either in preparation, shipping, and laboratory analysis.

The results of environmental air samples for 2-ethoxyethanol are shown in Table 1. The Table also includes the results of pre and post-shift concentrations of ethoxyacetic acid for each worker. Other variables presented in the Table include: numerical values ratings for physical activity, skin exposure, and respirator usage; method of painting; which paint was used; temperature in the work environment; actual number of hours spent painting; and the location where the painting took place.

Of the 102 samples analyzed for 2EE, 14 were below the detection limit of 0.01 mg/sample. With the same analytical sensitivity for 2ME, 50 out of 102 samples were undetectable. Only one sample, that of a painter performing brush painting out-of-doors, contained butoxy ethanol (6.01 mg/m^3). This sample contained no detectable 2EE or 2ME.

None of the sample results exceeded the OSHA PEL's for 2EE, 2ME, or 2BE. Only one (1) sample exceeded the ACGIH TLV for 2ME, but eleven (11) sample results exceeded the TLV for 2EE.

A summary of exposure by work location appears in Table 3. However, since workers' assignments are constantly changing, this information is of little use in determining cumulative exposure potential. On any given day, any worker could be assigned to any area. Nonetheless, the highest measured exposures seemed to cluster in the most confined spaces and in those being intensively painted.

A review of the subjective ratings of skin contact at the end of each shift revealed that the vast majority of workers had "little" or "no" skin contact with the paints.

B. Biological

The urine samples collected during this study allowed NIOSH to validate a biological monitoring method which can detect human exposure to glycol ethers. The method is described in a separate publication by Smallwood, et al (1988).[15]

The results of the ethoxyacetic acid (EAA) metabolite in urine analyses are presented in Table 1 along with the environmental data. All EAA excretion data were corrected for variation in the rate of excretion of water by dividing the measured EAA concentrations by the concentration of creatinine in the urine sample.

The purpose of these analyses was to evaluate potential worker biological exposure to EE by various routes of occupational exposure, specifically through breathing air containing EE and skin contacts with EE. Here, biological exposure refers to the entry of EE into the blood stream, from which it could interact with the body and possibly cause health effects. This evaluation was carried out by determining how the concentration of ethoxyacetic acid (EAA, a chemical that is produced from EE in the body) in workers' urine is related to EE exposure in the workplace. This was done by considering the available data and the current scientific knowledge about the human body's ability to process and react to EE. Since both data and knowledge are limited, these analyses should not be considered precise, although they do represent the best effort possible by Hattis and Berg. For a more detailed explanation of these analyses, see pages 8-36 in the Hattis and Berg report that is attached as Appendix 1.

The results and conclusions of these analyses can be found on page 37-70 of Appendix 1. Basically, Hattis and Berg showed that there was evidence of biological exposure from breathing and having skin contact with EE. Further, their study showed that the largest portion of the biological exposure was explained by breathing air containing EE, although their study indicated that a smaller portion of the biological exposure may come from skin contact with EE. The importance of this study is not only that it demonstrates that biological exposure does result from both breathing and having skin contact with EE, but that it also shows this method may help in the future in estimating the total biological exposure resulting from various routes of occupational exposure. If adverse health effects are proven to result from occupational exposure to EE, then the results of studies of biological exposure may be useful in the future to help assure a safe working environment.

The data was also analyzed to compare the activity adjusted air concentration to the effect of wearing a respirator vs. not wearing a respirator. The results indicated a respiratory protection factor of somewhat less than two, which is at the lower end of in-use protection factors measured for other agents in other industries.[17,18,19] This finding could be explained if skin absorption proved to be a significant route of entry for EE in these workers.

A similar analysis of the data was performed to assess the relative importance of direct inhalation exposure and skin absorption (as indicated by visible contamination of the skin with paint at the end of the shift) on total EE absorption. Overall, the researchers reported that although some skin absorption was indicated, this factor did not achieve statistical significance. It was estimated that of the total amount of EE absorbed, inhalation was likely to have been 3-5 times as large a source as dermal absorption for this group of workers. It would not be inconsistent to report that direct air inhalation could have accounted for essentially all of the total EE absorption observed.

VII. CONCLUSIONS AND RECOMMENDATIONS

Conclusions

Based on the results of this investigation it is concluded that a potential health hazard existed at the time of this study due to painters' exposure to 2-ethoxyethanol.

In the effort to study the health effects of workplace chemical exposures, estimation of the dose received is always the most elusive term. Historical exposure data is often scarce, inadequate, not comparable with current methods of data collection, or inaccessible. In a shipyard situation such as this, accurate assessment of even current exposures is exceptionally hard to attain because of the extreme variability of conditions. Different materials are used and even the configuration of the work spaces changes as a ship progresses toward completion. Even the number of painters assigned to the same space can change exposure levels. Because of the variability of the jobs, with painters moved freely from location to location, and working with different paints, it is a difficult task to attempt to categorize a worker's potential exposure level by any of these factors. As a result of this investigation, NIOSH has developed an additional tool to aid in the evaluation of worker exposure to glycol ethers: a biological monitoring method. This method, together with the pharmacokinetic models tested by Dr. Hattis, et al, provides a useful measure of an employee's total exposure to these solvents.

Recommendations

1. Worker exposure to glycol ethers should be reduced to the lowest extent feasible. In this regard, substitution for the glycol ethers with less toxic materials would achieve the optimum result.

However, it is understood that the paints must meet strict Department of the Navy specifications and substitution may not be possible until the Navy changes their specifications.

2. Employees who are required to use glycol ether based paints should be provided with, and required to use, proper personal protective equipment, including respirator with organic vapor cartridge, impervious coveralls and gloves.

3. A continuous program of industrial hygiene assessment should be instituted for the painters. Since solvents are used in varying quantities and conditions, frequent sampling for exposures is essential.

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IX. AUTHORSHIP AND ACKNOWLEDGEMENTS

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X. DISTRIBUTION AND AVAILABILITY OF REPORT

Copies of this report are temporarily available upon request from NIOSH, Hazard Evaluations and Technical Assistance Branch, 4676 Columbia Parkway, Cincinnati, Ohio 45226. After 90 days, the report will be available through the National Technical Information Service (NTIS), 5285 Port Royal, Springfield, Virginia 22161. Information regarding its availability through NTIS can be obtained from NIOSH Publications Office at the Cincinnati address. Copies of this report have been sent to:

1. Electric Boat Division, General Dynamics
2. Painters' Union, Groton, Connecticut
3. NIOSH, Boston Region Office
4. OSHA, Region I

For the purpose of informing affected employees, copies of this report shall be posted by the employer in a prominent place accessible to the employees for a period of 30 calendar days.

Table 1
Electric Boat Division
General Dynamics Corporation
Groton, Connecticut

ID	DAY	PRE mg EEA/ g creat	POST mg EEA/ g creat	AIR CON mg EE/ cu m	Activity 1=light 3=heavy	SKIN EX 0=none 2=signif	RESP USE 1=no respirator	Type	Paint	TEMP	HOURS	Location
	3		6	1.70	3	1	1	brush	Savapon	80	3	ER 719
1	4	<7	<4	4.10	1	1	0	brush	Savapon	80	5	EVW 719
	5	ND	ND	2.18	2	0	0	brush	Savapon	85	5	ER 719
	6		<3									
	4	36	64	44.01	2	1	1	brush	Savapon	80	4	ER 719
2	5	61	54	16.99	1	0	1	brush	Savapon	85	4	ER 720
	6	57	44	<1.1	1	0	1	none	none	85	0	ER 720
	7	39										
	4	ND	<5	5.23	1	1	1	brush	83&84	35	3	Sail 720
3	5	ND	11	56.03	1	0	1	brush	Savapon	45	4	Sail 720
	6	16	13	4.83	1	1	1	brush	83&84	45	5	Sail 720
	7	7										
	4	14	11	<1.2	1	1	1	brush	Savapon	80	4	AMR 719
4	5	7	17	2.12	2	2	1	brush	Savapon	85	6	ER 719
	6	<10		3.23	1	0	1	brush	Savapon	85	6	ER 719
	7	20										
	4	A,B		22.94	2	1	1	brush	Savapon	80	3	AMR 720
5	5	A,B		7.14	2	1	1	brush	Savapon	85	3	AMR 720
	6		no		1	0	1					
	4	36	38	7.58	2	1	1	brush	Hi Heat	80	4	Reac 720
6	5	47	47	6.38	2	1	1	brush	Savapon	85	3	ER 720
	6		55	8.30	1	0	1	none	none	85	0	torp720
	7	34										
	3	<8	6	2.91	1	0	1	brush	Savapon	80	2	ER 719
7	4	ND	6	4.79	1	1	1	brush	Savapon	80	3	ER 732
	5	<10	9	6.59	1	0	0	brush	Savapon	85	3	ER 732
	6	<11	13									
	4	ND	ND	<3.1	1	1	1	brush	Savapon	35	5	Sail 719
8	5	ND	ND	1.06	2	1	1	brush	Sav,83&	45	4	Sail 719
	6	ND	ND	1.55	1	1	1	brush	Sav,83&	85	2	ER 719
	7	ND										
	3	<6	ND	6.21	2	0	1	spray	Savapon	90	6	AMR 719
9	4	<8	21	18.89	2	2	1	brush	Sav, Oi	80	7	ER 731
	5	23	18	8.63	2	1	1	brush	Savapon	85	3	ER 731
	6	15	14									
	4	ND	ND	1.10	1	0	0	brush	Savapon	80	4	AMR 719
10	5	ND	ND	<1.1	2	2	1	brush	Savapon	85	6	UL 719
	6	ND	ND	<7.4	1	1	1	brush	Savapon	85	6	UL 719
	7	ND										

TABLE 1 - Electric Boat - HETA 84-474 (Continued)

ID	DAY	PRE ug EEA/ g creat	POST ug EEA/ g creat	AIR CON ug EE/ cu m	Activity 1=light 3=heavy	SKIN EX 0=none 2=signif	RESP USE 1=no respirator	Type	Paint	TEMP	HOURS	Location
	4	12	14	3.99	2	1	1	brush	Savapon	80	5	ER 724
11	5	13	12	2.43	1	0	1	brush	Savapon	85	5	ER 725
	6	12		1.96	1	0	1	brush	Savapon	85	5	ER 725
	7	9										
	4	ND	<9	<8.8	2	1	0	spray	oil	80	5	ER 719
12	5	ND		<1.1	1	0	1	brush	Savapon	85	4	ER 719
	6	5		<1.4	1	0	1	brush	Interni	85	4	EVW 719
	7	ND										
	4		69	39.05	1	1	1	brush	Savapon	80	3	Torp 720
13	5		144 no		2	2	1	brush	Savapon	85	4	720
	6			3.82	1	0	1	none	none	85	0	Aft 720
	7	66										
	4	46	47	<1.1	1	1	1	brush	Sav,83&	35	4	top 720
14	5	31	45	0.96	1	1	1	brush	Amercda	45	4	Top 720
	6	36	33 no		1	1	1	brush	Savapon	45	5	Top 720
	7	24										
	4		9	7.38	2	1	1	brush	Savapon	80	4	AMR 720
15	5	11	15	19.51	1	0	0	brush	Savapon	85	5	AMR 720
	6		9	3.09	1	0	1	none	none	85	0	AMR 720
	7	9										
	3	<5	ND	0.52	3	1	0	brush	Vinyl 1	40	5	Dome 719
16	4	<5	8	84.34	1	0	0	brush	Savapon	80	4	AMR 719
	5	11	9	7.88	1	0	1	brush	Savapon	85	4	AMR 719
	6	13	11									
	4	9	11	6.64	2	1	0	brush	Savapon	80	4	ER 719
17	5	<7	14	2.15	2	1	0	brush	Savapon	85	7	ER 719
	6	11	17	5.74	1	0	1	brush	Savapon	85	7	ER 719
	7	10										
	3	9		79.00	2	0	0	spray	Savapon	90	1	AMR 719
18	4	31	23	1.05	1	0	1	brush	Savapon	80	2	AMR 719
	5	13	10	11.52	1	0	1	spray	Savapon	85	4	AMR 719
	6	27	12									
	3	ND	<6	2.19	1	0	1	brush	Savapon	70	6	MR 731
19	4	ND	ND	2.08	3	1	0	brush	Savapon	35	7	Dock 731
	5	<4	ND	0.00	2	2	0	brush	Savapon	40	4	Dock 731
	6	ND	<4									
	4	26	26	40.12	2	1	0	brush	Savapon	90	4	Torp 719
20	5	66	49	59.20	1	1	1	brush	Savapon	85	5	Torp 719
	6	41	38	9.29	1	1	1	brush	oil	85	5	Torp 719
	7	43										

TABLE 1 - Electric Boat - HETA 84-474 (Continued)

ID	DAY	PRE ug EEA/ g creat	POST ug EEA/ g creat	AIR CON ug EE/ cu m	Activity 1=light 3=heavy	SKIN EX 0=none 2=signif	RESP USE 1=no respirator	Type	Paint	TEMP	HOURS	Location
	4		20	15.83	1	1	1	brush	Savapon	80	4	AMR 720
21	5	29	40	38.54	1	0	1	brush	Savapon	85	6	AMR 720
	6	35	30	no	1	0	1	none	none	85	0	Torp 720
	4	6	<5	3.33	2	0	1	brush	Blac Po	80	8	MR 720
22	5	<7	6	4.42	1	0	1	brush	Blac Po.	85	1	MR 731
	6	6	7									
	3	12	14	8.19	1	0	1	brush	Savapon	80	3	ER 719
23	4	16	10	3.13	2	1	1	brush	Savapon	80	6	ER 719
	5	16	10	7.29	1	0	1	brush	Savapon	85	6	ER 719
	6	16	8									
	4	ND	ND	4.11	1	1	1	brush	Savapon	80	3	ER 719
24	5	ND	<7	2.17	1	0	1	brush	Savapon	85	6	ER 719
	6	<7	ND	0.99	1	0	1	none	none	85	0	ER 719
	7	ND										
	3		<9	0.92	3	1	1	brush	Vinyl 1	40	5	Dome 719
25	4	6	<7	1.05	1	0	1	brush	oil	80	2	SES 719
	5	<10	<8	6.85	1	1	1	brush	Savapon	85	6	SES 719
	6	<7	10									
	4	<9	8	3.08	2	1	1	brush	Savapon	80	6	ER 719
26	5	11	16	6.27	1	0	1	brush	Savapon	85	2	ER 719
	6	10	16	9.49	1	0	1	brush	Savapon	85	4	ER 719
	7	13										
	3	<8	16	7.45	3	1	1	brush	Savapon	75	5	LL 719
27	4		<8	2.17	1	0	1	brush	Savapon	80	4	ER 719
	5	10										
	3	ND	ND	2.60	1	0	1	brush	Blac Po	80	5	GBC 731
28	4	ND	<7	3.21	2	2	0	spray	oil	80	7	Study 731
	5	ND	ND	3.91	2	2	0	spray	oil, un	85	5	Study 731
	6	ND	ND									
	3	ND	<5	11.64	1	0	1	brush	Sav,Int	70	7	CQ 732
29	4	6	8	3.33	2	1	1	brush	Blac Po	80	6	Aft 732
	5	ND	5	1.31	2	0	1	brush	Savapon	85	5	ER 732
	6	<4	4									
	3		<6	8.95	1	0	1	brush	Savapon	70	6	MR 731
30	4	ND	<6	7.64	2	0	0	brush	Savapon	80	6	MR 731
	5	<6	<5	4.08	1	0	1	brush	oil	85	1	MR 731
	6		6									
	4	57	47	<0.45	2	1	1	brush	Savapon	35	3	Top 720
31	5	78	42	<2.00	2	1	1	brush	Savapon	45	5	Top 720
	6	54		<1.20	1	0	1	brush	vinyl 1	45	4	Top 720
	7	39										

TABLE 1 - Electric Boat - HETA 84-474 (Continued)

ID	DAY	PRE mg EEA/ g creat	POST mg EEA/ g creat	AIR CON mg EE/ cu m	Activity 1=light 3=heavy	SKIN EX 0=none 2=signif	RESP USE 1=no respirator	Type	Paint	TEMP	HOURS	Location
	3	26	16	7.17	1	0	1	spray	Sav, Un	80	1	AMR 719
32	4	35	10	3.02	2	2	0	spray	oil	80	6	Fan 719
	5	27	24	5.71	2	0	0	spray	oil	85	4	Fan 719
	6	26	20									
	4	18	14	<0.45	2	0	1	brush	Savapon	80	2	AMR 720
33	5	25	16	10.96	1	0	1	brush	Savapon	85	3	AMR 720
	6	20	13	3.60	1	0	1	none	none	85	0	AMR 720
	3	<6	13	3.20	1	0	1	brush	Blac Po	75	6	D'head 73
34	4	ND	13	2.11	2	1	1	brush	Blac Po	80	6	Fan 731
	5	<6	6	4.00	1	1	1	brush	Blac Po	85	6	Fan 731
	6	ND	6									
	3	<8	<7	2.28	1	0	1	brush	Savapon	80	4	ER 720
35	4	<7	10	48.61	2	0	0	brush	Savapon	80	7	ER 720
	5	12	15	2.67	1	0	0	none	none	85	4	UL 720
	6	10										
	3	ND	<4	4.09	1	0	1	brush	Savapon	80	1	CR 732
36	4	ND	<3	5.04	1	0	1	brush	Savapon	80	4	EVW 732
	5	ND	<7	11.13	2	1	1	brush	Savapon	85	4	ER 732
	6	8	10									

Summary of Airborne Exposures

	2-ethoxyethanol		2-methoxyethanol	
	mg/m^3	(ppm)	mg/m^3	(ppm)
n	90		81	
Mean ± S.D.	9.9±15.7	(2.6±4.2)	2.6±3.2	(0.8±1.0)
Median	4.4	(1.2)	1.4	(0.44)
Range	0-84.3	(0-21.5)	0-17.2	(0-5.6)
Geometric Mean*	1.6		1.1	
Geometric S.D.	1.1		0.7	

*Geometric statistics based on non-zero terms only.

Summary of Airborne Exposures by Location

	2-ethoxyethanol		2-methoxyethanol	
	mg/m^3	(ppm)	mg/m^3	(ppm)
TORPEDO ROOM				
n	5		5	
Mean ± S.D.	30.0±21.3	(8.0±5.7)	60.0±4.5	(1.9±1.4)
Median	37.1	(9.9)	7.3	(2.3)
Range	8.1-58.3	(2.2-15.6)	0-11.0	(0-3.5)
Geometric Mean*	3.1		1.9	
Geometric S.D.	0.9		0.6	
AMR				
n	17		16	
Mean ± S.D.	13.9±19.5	(3.7±5.2)	3.6±4.5	(1.1±1.4)
Median	7.3	(1.9)	2.4	(0.8)
Range	0-84.3	(0-21.5)	0-17.2	(0-5.6)
Geometric Mean*	2.1		1.4	
Geometric S.D.	1.1		0.7	
ER				
n	33		26	
Mean ± S.D.	7.4±10.4	(2.0±2.8)	1.9±2.6	(0.6±0.8)
Median	3.9	(1.0)	1.1	(0.3)
Range	1.0-45.6	(0.3-12.2)	0-8.7	(0-2.7)
Geometric Mean*	1.5		0.8	
Geometric S.D.	0.9		0.8	
OTHER				
n	35		34	
Mean ± S.D.	7.4±15.1	(2.0±4.0)	2.1±2.4	(0.7±0.7)
Median	3.9	(1.0)	1.6	(0.5)
Range	0-77.8	(0-20.7)	0-9.4	(0-3.0)
Geometric Mean*	1.3		1.0	
Geometric S.D.	1.0		0.6	

*Geometric statistics based on non-zero terms only.

Table 3.1
Shipyard Painter Database

WORKER NUMBER	DAY	PRESHFT mg EAA / g creatinine	POSTSHIFT mg EAA / g creatinine	AIRCONC mg EE / cubic meter	ACTIVITY (1=standing 3 = heavy lift.)	RESPUSE (1 = No respirator)	SKINEX (0 = none 2=signif.)
1	3	-99*	6	1.70	3	1	1
	4	5	3	4.10	1	0	1
	5	2	1	2.18	2	0	0
	6	2	-99	-99.00	9**	9	9
2	4	36	64	44.01	2	1	1
	5	61	54	16.99	1	1	0
	6	57	44	.60	1	1	0
	7	39	-99	-99.00	9	9	9
3	4	1	4	5.23	1	1	1
	5	1	11	56.03	1	1	0
	6	16	13	4.83	1	1	1
	7	7	-99	-99.00	9	9	9
4	4	14	11	.60	1	1	1
	5	7	17	2.12	2	1	2
	6	7	-99	3.23	1	1	0
	7	20	-99	-99.00	9	9	9
5	4	-99	-99	22.94	2	1	1
	5	-99	-99	7.14	2	1	1
	6	-99	-99	-99.00	1	1	0
6	4	36	38	7.58	2	1	1
	5	47	47	6.38	2	1	1
	6	-99	55	8.30	1	1	0
	7	34	-99	-99.00	9	9	9
7	3	5	6	2.91	1	1	0
	4	-99	6	4.79	1	1	1
	5	6	9	6.58	1	0	0
	6	8	13	-99.00	9	9	9

* -99 signifies missing data for the urinary measurements of ethoxyacetic acid and the air measurements of ethoxyethanol.

** 9 signifies missing data for the activity, respirator use, and skin exposure ratings.

Table 3.1, Continued

WORKER NUMBER	DAY	PRESHFT mg EAA / g creatinine	POSTSHIFT mg EAA / g creatinine	AIRCONC mg EE / cubic meter	ACTIVITY (1=standing 3 = heavy lift.)	RESPUSE (1 = No respirator)	SKINEX (0 = none 2=signif.)
8	4	1	2	1.60	1	1	1
	5	2	1	1.06	2	1	1
	6	1	2	1.55	1	1	1
	7	1	-99	-99.00	9	9	9
9	3	4	2	6.21	2	1	0
	4	6	21	18.89	2	1	2
	5	23	18	8.63	2	1	1
	6	15	14	-99.00	9	9	9
10	4	1	2	1.10	1	0	0
	5	2	2	.60	2	1	2
	6	3	1	3.70	1	1	1
	7	2	-99	-99.00	9	9	9
11	4	12	14	3.99	2	1	1
	5	13	12	2.43	1	1	0
	6	12	-99	1.96	1	1	0
	7	9	-99	-99.00	9	9	9
12	4	2	6	4.40	2	0	1
	5	2	-99	.60	1	1	0
	6	5	-99	.70	1	1	0
	7	1	-99	-99.00	9	9	9
13	4	-99	69	39.05	1	1	1
	5	-99	144	-99.00	2	1	2
	6	-99	-99	3.82	1	1	0
	7	66	-99	-99.00	9	9	9
14	4	46	47	.60	1	1	1
	5	31	45	.96	1	1	1
	6	36	33	-99.00	1	1	1
	7	24	-99	-99.00	9	9	9

Table 3.1, Continued

WORKER NUMBER	DAY	PRESHFT mg EAA / g creatinine	POSTSHIFT mg EAA / g creatinine	AIRCONC mg EE / cubic meter	ACTIVITY (1=standing 3 = heavy lift.)	RESPUSE (1 = No respirator)	SKINEX (0 = none 2=signif.)
15	4	-99	9	7.38	2	1	1
	5	11	15	19.51	1	0	0
	6	-99	9	3.09	1	1	0
	7	9	-99	-99.00	9	9	9
16	3	3	2	.52	3	0	1
	4	3	8	84.34	1	0	0
	5	11	9	7.88	1	1	0
	6	13	11	-99.00	9	9	9
17	4	9	11	6.64	2	0	1
	5	5	14	2.15	2	0	1
	6	11	17	5.74	1	1	0
	7	10	-99	-99.00	9	9	9
18	3	9	-99	79.00	2	0	0
	4	31	23	1.05	1	1	0
	5	13	10	11.52	1	1	0
	6	27	12	-99.00	9	9	9
19	3	2	4	2.19	1	1	0
	4	3	1	2.08	3	0	1
	5	3	1	.00	2	0	2
	6	1	3	-99.00	9	9	9
20	4	26	26	40.12	2	0	1
	5	66	49	59.20	1	1	1
	6	41	38	9.29	1	1	1
	7	43	-99	-99.00	9	9	9
21	4	-99	20	15.83	1	1	1
	5	29	40	38.54	1	1	0
	6	35	30	-99.00	1	1	0
22	4	6	3	3.33	2	1	0
	5	5	6	4.42	1	1	0
	6	6	7	-99.00	9	9	9

Table 3.1, Continued

WORKER NUMBER	DAY	PRESHFT mg EAA / g creatinine	POSTSHIFT mg EAA / g creatinine	AIRCONC mg EE / cubic meter	ACTIVITY (1=standing 3 = heavy lift.)	RESPUSE (1 = No respirator)	SKINEX (0 = none 2=signif.)
23	3	12	14	8.19	1	1	0
	4	16	10	3.13	2	1	1
	5	16	10	7.29	1	1	0
	6	16	8	-99.00	9	9	9
24	4	1	1	4.11	1	1	1
	5	2	5	2.17	1	1	0
	6	5	2	.99	1	1	0
	7	1	-99	-99.00	9	9	9
25	3	-99	6	.92	3	1	1
	4	6	5	1.05	1	1	0
	5	7	6	6.85	1	1	1
	6	5	10	-99.00	9	9	9
26	4	6	8	3.08	2	1	1
	5	11	16	6.27	1	1	0
	6	10	16	9.48	1	1	0
	7	13	-99	-99.00	9	9	9
27	3	5	16	7.45	3	1	1
	4	-99	5	2.17	1	1	0
	5	10	-99	-99.00	9	9	9
28	3	1	1	2.60	1	1	0
	4	2	5	3.21	2	0	2
	5	1	1	3.91	2	0	2
	6	1	1	-99.00	9	9	9
29	3	1	3	11.64	1	1	0
	4	6	8	3.33	2	1	1
	5	2	5	1.31	2	1	0
	6	3	4	-99.00	9	9	9

Table 3.1, Continued

WORKER NUMBER	DAY	PRESHFT mg EAA / g creatinine	POSTSHIFT mg EAA / g creatinine	AIRCONC mg EE / cubic meter	ACTIVITY (1=standing 3 = heavy lift.)	RESPUSE (1 = No respirator)	SKINEX (0 = none 2=signif.)
30	3	-99	4	8.95	1	1	0
	4	1	4	7.64	2	0	0
	5	5	3	4.08	1	1	0
	6	-99	6	-99.00	9	9	9
31	4	57	47	.23	2	1	1
	5	78	42	1.00	2	1	1
	6	54	-99	.60	1	1	0
	7	39	-99	-99.00	9	9	9
32	3	26	16	7.17	1	1	0
	4	35	10	3.02	2	0	2
	5	27	24	5.71	2	0	0
	6	26	20	-99.00	9	9	9
33	4	18	14	.23	2	1	0
	5	25	16	10.96	1	1	0
	6	20	13	3.60	1	1	0
34	3	4	13	3.20	1	1	0
	4	2	13	2.11	2	1	1
	5	4	6	4.00	1	1	1
	6	2	6	-99.00	9	9	9
35	3	6	5	2.28	1	1	0
	4	5	10	48.61	2	0	0
	5	12	15	2.67	1	0	0
	6	10	-99	-99.00	9	9	9
36	3	2	3	9.09	1	1	0
	4	2	2	5.04	1	1	0
	5	3	5	11.13	2	1	1

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PHARMACOKINETICS OF ETHOXYETHANOL IN HUMANS

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SUMMARY

This is the fourth in a series of research efforts to improve the state of the art of risk assessment by making use of more detailed information on the biological mechanisms by which specific agents are processed and cause harm in biological systems. Based on clinical experiments of Groseneken et al. (1986a,b) we have constructed four different pharmacokinetic models of the uptake of ethoxyethanol (EE, ethylene glycol ethyl ester), metabolism of EE via ethoxyacetaldehyde to ethoxycacetic acid (EAA), and the urinary excretion of EAA.*

---

* The four models fall into two groups. Our two "simplest" models are both constructed with only a single kinetically homogeneous body compartment for ethoxyacetaldehyde and EAA. Within this group,

> For the "best-estimate simplest" model we chose values of our two adjustable parameters (ethoxyacetaldehyde oxidation and EAA excretion) that minimized the sum of the squares of the logarithms of the ratios of our model "predictions" and the EAA excretion observations of Groseneken et al. This resulted in a half-time for EAA excretion of 26 hours, and an estimate that about 49% of retained EE is metabolized by the aldehyde dehydroganase pathway. The peak of EAA excretion, however, occured only an hour and forty minutes after the end of exposure--in contrast to the 3-4 hours than Groseneken et al. (1986b) observed.
>
> To achieve a later peak EAA excretion time, our "alternative simplest" model incorporated a much slower rate of ethoxyacetaldehyde oxidation than was found optimal for the "best-estimate simplest" model. The result, however, was a peak time that was still only 2 hours and 20 minutes after the end of exposure. The half-time for EAA excretion became 31 hours, and 54% of retained EE was estimated to be metabolized by the aldehyde dehydrogenase pathway.

By contrast, for ethoxyacetaldehyde and EAA, our two "less simple" models incorporated tissue compartments and diurnally-varying blood flows adapted from our earlier physiologically-based pharmacokinetic models for perchloroethylene (Hattis et al., 1986). Tissue/blood partition coefficients were estimated from observations of other hydrophilic chemicals (Fiserova-Bergerova and Diaz, 1986). Within this group,

> Our overall best-estimate "less simple" model was tuned to the Groseneken et al. (1986b) urinary EAA excretion observations as above without further adornment. This resulted in a peak of urinary EAA just under three hours after the end of exposure, and a half-time for urinary EAA excretion of 33 hours. About 42% of retained EE was estimated to be metabolized via the aldehyde dehydrogenase pathway.
>
> Finally, we noticed that comparisons of the two points in the Groseneken et al. (1986b) data that were exactly 24 hours apart led to a much longer estimate for the urinary EAA excretion half-life--about 70 hours. We therefore constructed a "70-hour model" assuming this was the true excretion half-time, but that EAA excretion is 20% greater during waking hours than during sleep. This resulted in a peak of

We tested the performance of these models with data on the EE exposure, and preshift and postshift urinary EAA excretion/g creatinine in a group of 36 painters studied over several successive days by McManus (1987) and DeBord and Lowry (1986). In many cases the data allowed two separate estimates to be made of EE absorption on a particular workshift for each model--one estimate based on a comparison of preshift urinary EAA with postshift urinary EAA, and another estimate based on comparison of preshift urinary EAA with EAA excretion in the next day's preshift urine collection. In each case, the dynamic models were used to predict the EAA excretion that would have been expected at various subsequent times if there had been no further exposure to EE during the workshift. The observed excess of urinary EAA over this prediction was then used with the same model to infer the indicated moles of EE that had been absorbed during the workshift.

Unfortunately, when we initially used this methodology to compare the aggregate moles of EE estimated to have been absorbed on all available worker-days with complete information, we found that all of the models produced estimates of EE absorption from the preshift-postshift comparison that were only about 31-33% of the corresponding estimates made from the preshift-next day's preshift comparison. This difficulty was greatly reduced when we corrected our estimation procedures for diurnal changes in urinary creatinine excretion using the observations of Lakatua et al. (1982). After correction, the aggregate absorption estimated by the models for the preshift-postshift comparison was 70 - 118% of the aggregate absorption estimated for the preshift-next day's preshift comparison. For subsequent regression analyses of the effects of various environmental factors on EE absorption, we used the average of the preshift-postshift and preshift-next day's preshift absorption estimates as our dependent variable.

A second criterion that was used to compare the performance of the different models was the strength of the association between measured EE air concentrations* and estimated absorption. On this test, all of the models produced highly statistically significant relationships,** although the "70-hour"

EAA excretion three and a half hours after the end of exposure for the Groseneken et al. (1986b) exposure pattern, and an estimate that a much greater proportion (72%) of retained EE is metabolized by tha aldehyde dehydrogenase pathway.

* With a modest adjustment for different activity levels.

** Ratios of the regression coefficients to their standard errors ranged from 4.27 to 4.78--see Table 3.5 on p.54.

model performed a little more poorly than the others. In the end we could not completely rule out any of the models on the bases of the available data. Because the 70-hour model results in a greater conversion of EE to activated ethoxyacetaldyde and EAA metabolites, and also for a greater persistence of EAA in the body, it may serve in later work to provide a plausible high estimate of internal body exposure to testicular toxins.

Of all the models we believe the "less simple" model is somewhat to be preferred to the others for the following reasons:

- o It incorporates plausible features used in full physiologically-based pharmacokinetic models (blood flows and organ sizes) and is therefore inherently somewhat more plausible.

- o It fits no worse to the primary Groseneken et al. (1986b) urinary EAA excretion data than the "best estimate-simplest" model, and somewhat better than the "alternative-simplest" model using the logarithmic least-squares criterion.

- o It shows a later peak of urinary EAA excretion than the two "simplest" models, which is more in keeping with the peak times observed by Groseneken et al. (1986b and 1987b).

- o It perfoms slightly better than the two "simplest" models in reconciling the moles EE absorbed as calculated by the two methods explored in Section 3.3 (comparing post-shift with preshift urinary EAA vs. comparing next-day's preshift urinary EAA with preshift EAA.)

Multiple regression analyses relating model estimates of absorbed EE to activity-adjusted air concentrations and ratings of visible skin absorption were performed for worker-days where respirators were and were not used. Surprisingly, the regression coefficients for absorption as a function of adjusted air concentration for worker days where respirators were worn was about 60% of the coefficient found for the worker days when respirators were not worn. The indicated respiratory protection factor of somewhat less than two-fold is at the lower end of in-use protection factors measured for

other agents in other industries (Smith, et al., 1980; Harris et al., 1974; Goble et al., 1983).

The same regression analyses were used to assess the relative importance of direct inhalation exposure and skin absorption (as indicated by visible contamination of the skin with paint at the end of the shift) on EE absorption. Overall the "skin" regression coefficients, although indicative of some skin absorption did not quite achieve statistical significance. The relative magnitudes of the adjusted air and skin coefficients suggested that direct air inhalation is likely to have been 3-5 times as large a source of EE absorption as dermal absorption for the group of shipyard painters that were studied. Calculations comparing the total absorption inicated by the models with the total adjusted air exposures were not inconsistent with the possibility that direct air inhalation could have accounted for essentially all of the observed absorption.

The relatively long half life of EAA in the body, and the delayed appearance of peak EAA excretion after the end of exposure means that the use of urinary EAA concentrations to estimate worker exposure requires a dynamic model. There is appreciable carryover of EAA from day to day,* and it can be expected that EAA excretion rates build up in the course of a work-week with constant 8-hour exposure on each day. Table S-1 shows the day to day buildup as predicted by our favored "less simple" model, and the '70-hour" model. This table also shows the effects of expressing EAA excretion in ug/min vs mg/g creatinine, given the diurnal changes in creatinine excretion. In Section 4.4 (p. 64 below) we recommend formulas for calculating equivalent TWA EE air exposure levels from urinary EAA excretion data.

The modeling we have done with the information available to date has left many unanswered questions about the pharmacokinetics of ethoxyethanol and related compounds. For the construction of full physiologcially-based pharmacokinetic models it would be desirable to have:

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* See Table 2.9 on page 36 for the pattern of excretion expected after a single day's exposure. Also see Figures 1.2 and 1.3 for the original observations of Groseneken et al. (1986b and 1987b).

Table S-1
Predicted Urinary Excretion Of Ethoxyacetic Acid at Various Times During Successive Daily 8-Hour Occupational Exposure to 5.65 ppm Ethoxyethanol (20 mg/m^3)

Time After Start of Exposure (min.)	"Less Simple Model" Predictions (Best Estimate Model). (ug EAA/min. excreted)	(mg EAA/g creatinine*)	"70-Hr Model Predictions (Plausible Upper Bound) (ug EAA/min. excreted)	(mg EAA/g creatinine)
Day 1 Post-shift (420 min)**	15.73	12.52	12.39	9.86
Day 2 Pre-shift (1380 min)***	12.67	12.54	13.27	13.14
Day 2 Post-shift (1860 min)	24.33	19.37	24.65	19.62
Day 3 Pre-shift (2820 min)	20.37	20.17	23.72	23.48
Day 3 Post-shift (3300 min)	30.88	24.58	34.32	27.32
Day 4 Pre-shift (4260 min)	25.04	24.79	31.96	31.64
Day 4 Post-shift (4740 min)	34.85	27.75	41.93	33.38
Day 5 Pre-shift (5700 min)	27.88	27.60	38.46	38.08
Day 5 Post-shift (6180 min)	37.27	29.67	47.93	38.16
4 Day Ave Pre-shift	21.49	21.28	26.85	26.59
5 Day Ave Post-shift	28.61	22.78	32.24	25.67

* Assuming 1.7 g per day of overall creatinine excretion, and diurnal changes in creatinine exccretion as given by Lakatua et al. (1982)--See Table 3.3 on p. 50. This results in expected creatinine excretion rates of (.8559*1700 mg/day)/1440 min/day = 1.01 mg/min for the two hours preceeding a 9:00 A.M. "preshift" collection, and (1.034*1700)/1440 = 1.256 mg/min for the two hours preceeding a 5:00 P.M. "postshift" collection.

** The data given here are the expected instantaneous rates of delivery of ethoxyacetic acid to the bladder. The 420 minute point is approximately the average rate that might be seen in a urine collection after an 8 hour shift, assuming that the urine has accumulated in the bladder between the 6- and 8-hour time points after the start of the workday.

*** By the same reasoning as given for the post-shift time points, the pre-shift urine samples are assumed to represent a two-hour accumulation of urine that was delivered to the bladder on average 23 hours after the start of the previous day's workshift.

(1) Measurements of relevant blood/air and tissue/air partition coefficents for EE, ethoxyacetaldehyde, and EAA.

(2) In clinical settings such as those used by Grosenekent et al. (1986a,b; 1987a,b), measurements of blood concentrations of ethoxyacetaldehyde and EAA. This might allow more definitive estimation of

(a) rates of the two steps of metabolism for the aldehyde dehydrogenase pathway (from EE to ethoxyacetaldeyde, and from ethoxyacetaldehyde to EAA),

(b) the fraction of EE that is metabolized via the aldehyde dehydrogenase vs "other" pathway(s)

(c) rates of tissue storage and release of ethoxyacetaldehyde, and return from storage. (Some aspects of the Groseneken et al. 1986a,b results suggest that the usual pharmacokinetic modeling assumption of equilibration between tissue levels of EE, ethoxyacetaldehyde, and EAA, and the levels in venous blood exiting the tissues may be leading to inaccuracies.)

(3) Analogous pharmacokinetic studies in animal systems where male and female reproductive effects have been measured.

(4) Observations in human workers of the decline in urinary EAA excretion rates over several days of no exposure (including diurnal fluctuations in excretion). This would both allow resolution of some important uncertainties in the construction of human pharmacokinetic models, and assessment of human interinidividual variability in EAA excretion.

TABLE OF CONTENTS

1. INTRODUCTION

1.1 Goals of the Analysis

This is the fourth in a series of research efforts to improve the state of the art of risk assessment by making use of more detailed information on the biological processes by which specific agents are processed and cause harm in biological systems.*

Ethoxyethanol (ethylene glycol ethyl ether) (EE) and other glycol ethers are widely used as solvents in inks, paints, varnishes and products used in servicing automobiles (Veulemans et al., 1987; US EPA, 1984). Extensive animal studies indicate that the aldehyde and/or acid metabolites of glycol ethers produce testicular toxicity and infertility in males (Beattie et al., 1984; Chapin and Lamb, 1984; Creasy and Foster, 1984; Creasy et al., 1985; Foster et al., 1984, 1986, 1987; Hardin et al., 1984; Hurtt and Zenick, 1986; Moss et al., 1985; Oudiz and Zenick, 1986) and embryotoxicity and developmental anomalies in pregnant females (Anderson et al., 1987; Andersen and Hardin et al., 1984, 1987; Hawley et al., 1984a,b; Hardin and Eisenman, 1987; Johnson et al., 1984; Nelson et al., 1984; Toraason et al., 1986; Tyler et al., 1984; Wier et al, 1987; Zenick et al., 1984). This report lays the groundwork for a quantitative assessment of these effects in human workers. We construct and test a series of semi-empirical** pharmacokinetic models of the processing of

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* The three previous analyses (on perchloroethylene, butadiene, and ethylene oxide) all applied physiologically-based pharmacokinetic modeling techniques to chemicals where the primary concern is carcinogenesis. Moreover in each of those cases it was reasonable to postulate a primary genetic mechanism for the carcinogenic action--direct reaction of the agent (ethylene oxide) or a metabolite (perchloroethylene, butadiene) with DNA. The ideal goal of the modeling in those cases was therefore to calculate the integrated sum of concentration X time of DNA-reactive material available in the different species as a function of the levels and durations of external exposure. Although the precise mechanism of action of the glycol ethers in producing reproductive effects is not known, it seems reasonable to suspect that damage may result from maintaining a critical concentration of active metabolites at the site(s) of action for a defined time. In this case, therefore, it may be much more important to have a dynamic model capable of determining peak levels of internal exposure, and the duration over which alternative hypothesized critical internal concentrations are maintained.

** As discussed in Section 2, due to the complexity of the two-step metabolism of ethoxyethanol (via ethoxyacetaldehyde to ethoxyacetic acid), some peculiarities of the findings of Groseneken et al. (1986a,b), and the lack of relevant data on partition coefficients, construction of a full physiologically-based pharmacokinetic model would require estimation of too many unknown parameters for the available information.

ethoxyethanol into its putative active metabolites--ethoxyacetaldehyde and ethoxyacetic acid--and the measurable excretion of ethoxyacetic acid in the urine. The final results at this stage are:

- o General formulas for assessment of overall human dosage as a function of dermal and inhalation exposure,

- o Guidelines for the use of urinary metabolite excretion data to determine overall absorption of ethoxyethanol from both inhalation and dermal routes of exposure. This may be helpful as a supplement for routine environmental air monitoring for control of exposures.

- o A case study of the likely relative importance of dermal and inhalation routes of exposure, and the efficacy of respirator use in reducing exposure, under at least one type of pattern of use (painting).

In later work we will also use the final models to help express the human and animal delivered dosage of the putative active metaobolites (ethoxyacetaldehyde and ethoxyacetic acid) in comparable terms for purposes of interspecies projection of effects.

1.2 Data Available for Analysis and Structure of the Report

We will use two primary sources of information. First, Groseneken et al. (1986a,b) have provided data from experimental clinical studies of the absorption of ethoxyethanol at various dose- and activity-levels during four hour exposure periods of exposure. They also report the pattern of later excretion of the minor amount (.1-.4%) of ethoxyethanol that is exhaled unchanged (Figure 1.1). Finally, in the same subjects, they also provide extensive measurements of the urinary excretion of ethoxyacetic acid--for a period of 42 hours after the start of the exposures (Figure 1.2). Our pharmacokinetic models will be primarily fit to the results of these well controled clinical experiments. Nevertheless, as will be seen, there are significant ambiguities that can lead to a number of different plausible interpretations of the data which we will represent in alternative model

controled clinical experiments. Nevertheless, as will be seen, there are significant ambiguities that can lead to a number of different plausible interpretations of the data which we will represent in alternative model formulations. The construction and fiitting of the alternative models from these data will be the subject of Section 2. Still more recently, the same research group has reported similar studies of the acetate ester of ethoxyethanol (Groseneken et al., 1987a,b), with generally similar results (Figure 1.3).* We have not yet incorporated these new data into the processes for fitting the alternative models.

The second primary source of data is a set of industrial hygiene and biological monitoring results for a group of painters using ethoxyethanol-based products in a shipyard (Sparer, et al., 1987; Welch et al., 1987; DeBord and Lowry, 1986; McManus, 1987). For 2-4 consecutive days, the authors measured pre- and post-shift concentrations of ethoxyacetic acid and creatinine in urine, and 8-hour time-weighted air concentrations of ethoxyethanol, in a group of 36 male workers. In addition, the workers were classified according to their use of respirators, and ratings were made of the strenuousness of their activity during the workday and of the degree of hand/arm skin exposure that was apparent at the end of each shift. In Section 3 we use these results to test the models, and then in Section 4 we use them together with the models to assess ethoxyethanol absorption in relation to air and dermal exposure, activity levels, and the use of respirators.

The shipyard painter data set offers two kinds of opportunities to use the different models to estimate daily worker absorption of ethoxyethanol. Each model can be used to predict

(1) the decline in urinary excretion of ethoxyacetic acid that would have been expected from each worker's preshift urine collection to the same day's postshift collection. Any excess of the observed to the predicted postshift excretion can then be interpreted in terms of ethoxyethanol absorption.

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* The acetate ester bond is evidently hydrolyzed quite rapidly relative to the time course of the oxidation to ethoxyacetic acid. Groseneken et al. (1987a) estimate a half-life for the ester hydrolysis of about 8-11 minutes.

Figure 1.1
Groseneken et al., 1986a--Breath Concentrations of Ethoxyethanol in Humans After 4-Hour Exposures

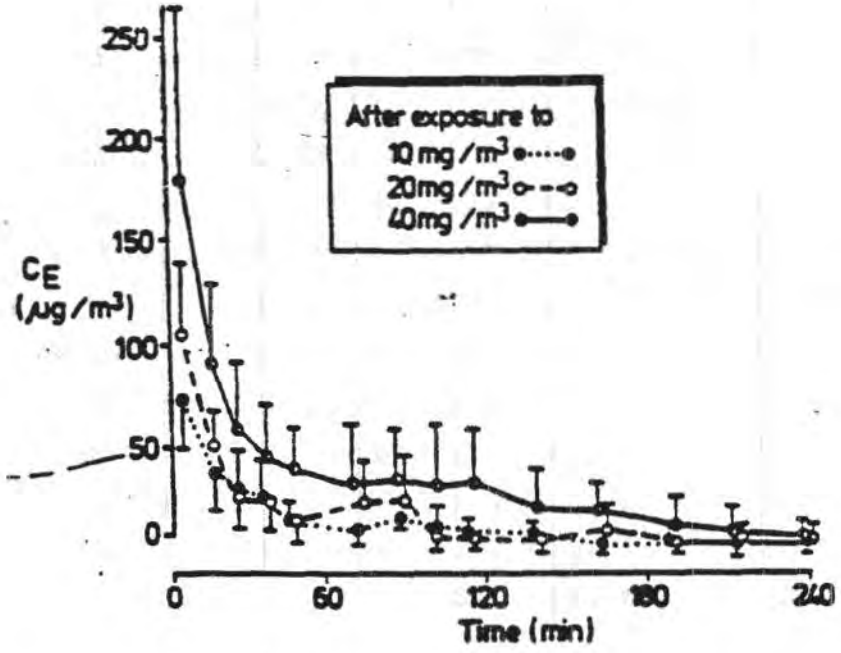


Fig 3 *Respiratory elimination of EGEE after exposure at rest. Data are mean ± SD for five subjects.*

Figure 1.2
Groseneken et al., 1986b--Urinary Ethoxyacetic Acid Excretion During and After 4-Hour Exposures to Ethoxyethanol

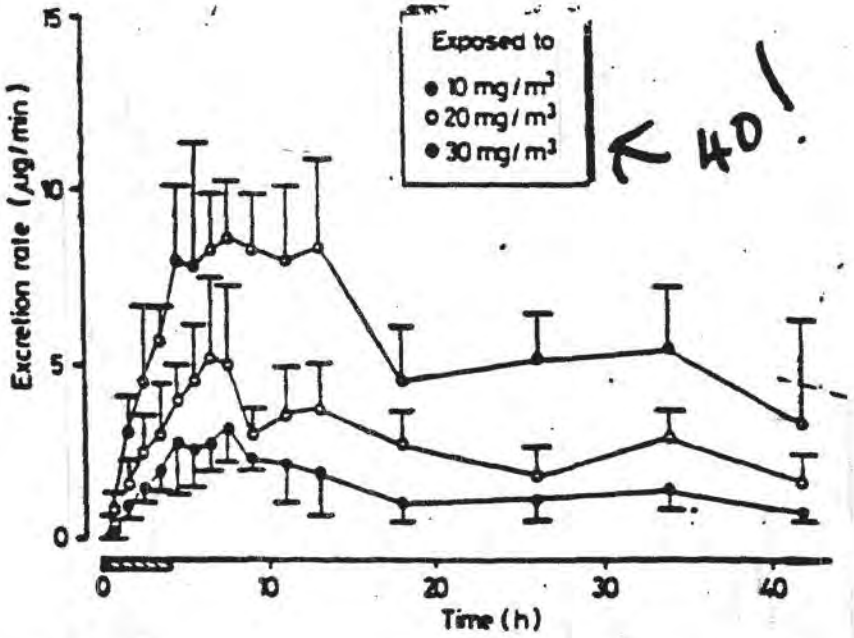


Fig 1 *Urinary excretion of ethoxyacetic acid during and after exposure to EGEE at rest. Data are means ± SD for five subjects. Shaded area indicates exposure period.*

Figure 1.3
Groseneken et al., 1987b--Urinary Ethoxyacetic Acid Excretion During and After 4-Hour Exposures to Ethoxyethanol Acetate

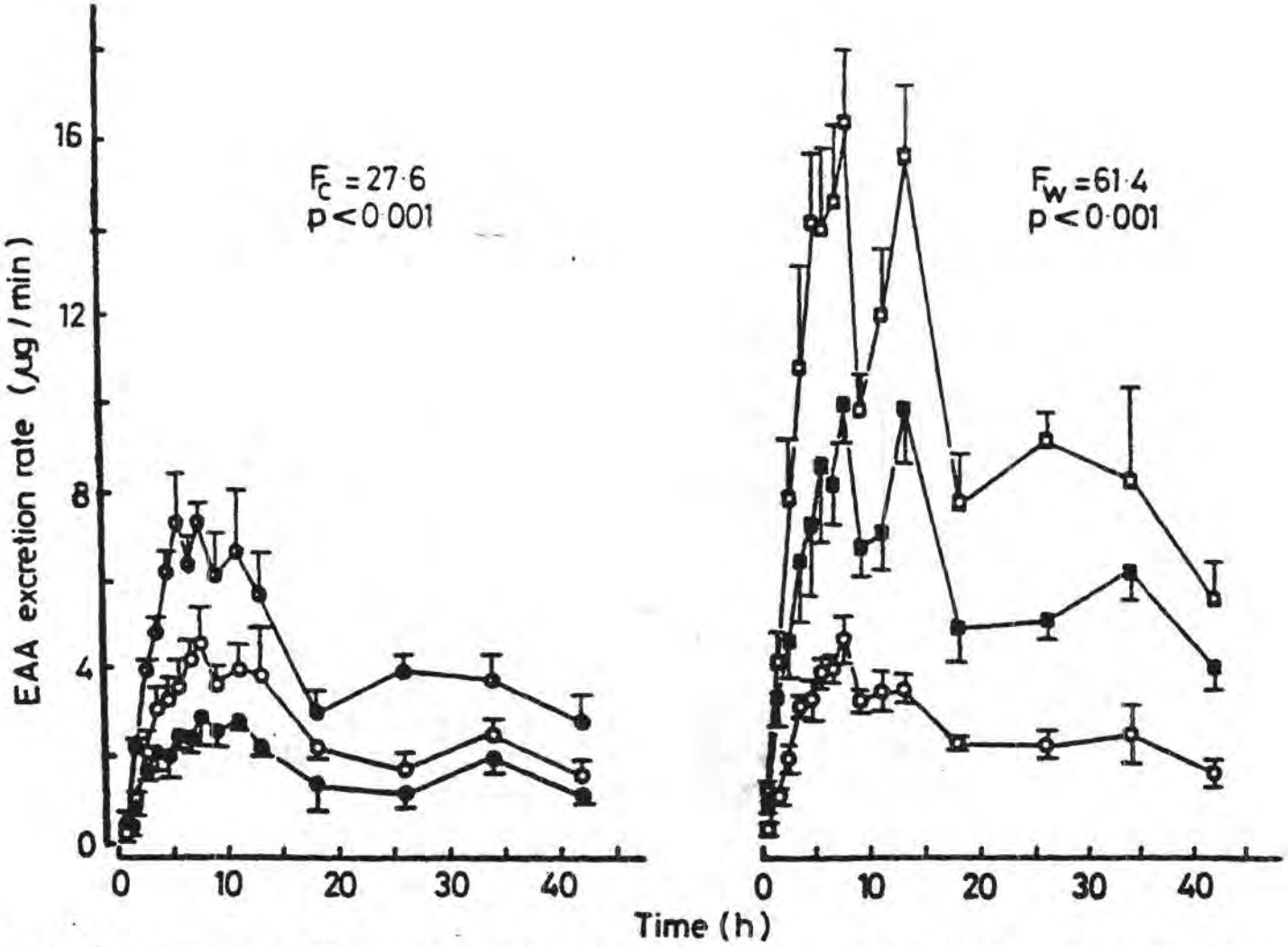


Fig 1 *Urinary excretion of ethoxyacetic acid during and after a four hour exposure to EGEE-Ac under various conditions: 14 mg/m³ (●), 28 mg/m³ (○), and 50 mg/m³ (◑) at rest or 28 mg/m³ at 30 W (■) and 60 W (□). Data are means ± SEM for five subjects. Statistical data are F ratios from three way ANOVA: c = exposure concentration, w = workload.*

(2) the decline in urinary excretion of ethoxyacetic acid that would have been expected from each worker's preshift urine collection to the next day's preshift collection. Again, any excess of observed over expected ethoxyacetic acid excretion can be used to make a second estimate of ethoxyethanol absorption during the workday.

A key test of the models is whether, in aggretate, the absorption estimates of the first type (preshift-postshift) agree with the absorption estimates of the second type (preshift-next day's preshift). As it happens, for several months we were unable to obtain reasonable agreement (within a factor of two) on this test for any of the model variants we tried. In the end, however, we were able to obtain agreement for our simplest models when we used the data of Lakatua et al. (1982) to correct for dirunal changes in creatinine excretion. It appears that failure to correct for this dirunal rhythm led to a significant distortion in the model predictions of post-shift ethoxyacetic acid excretion from preshift measurements.

2. BUILDING PHARMACOKINETIC MODELS USING THE GROSENEKEN ET AL. (1986a,b) DATA

2.1 Basic Description of the Groseneken et al. (1986a,b) Experiments

As mentioned earlier, Groseneken et al. (1986a,b) have recently provided two series of experimental clinical studies on groups of 5 young male volunteers exposed to ethoxyethanol (EE). The first group was exposed under resting conditions (seated in an arm chair) to three different concentrations (at three different sessions separated by at least a week)--10, 20, and 40 mg/m^3. The second group was exposed to 20 mg/m^3 at each of three different activity levels (0, 30 and 60 watts) on a bicycle ergometer. Each exposure session consisted of four 50-minute periods separated by 10-minute breaks.

During the exposures, the authors measured a number of respiratory parameters, including total ventilation and the percentage of inhaled ethoxyethanol that was retained (Table 2.1). A number of initial conclusions about the pharmacokinetics of ethoxyethanol are apparent from these data:

(1) The data in the final column for group 1 show no evidence of nonlinearities in the absorption of ethoxyethanol or ethoxyethanol acetate as a function of exposure level.

(2) The data on the fraction of inhaled ethoxyethanol that is absorbed are very nearly what one would expect if nearly all ethoxyethanol that reaches the alveoli is absorbed. [Alveolar ventilation at rest is generally assumed to be about 2/3 of total ventilation. This is compatible with the .59-.65 fractions absorbed seen for Group 1 in Table 2.1a. As for the data for Group 2, it is known that the fraction of total ventilation reaching the alveoli generally rises with increasing exercise. Therefore the increasing trend of fraction absorbed with energy expenditure (the differences are significant at $P < .05$) further supports the notion of nearly complete absorption from the alveoli.]

Table 2.1a
Ventilation and Absorption of Ethoxyethanol During Exposure (Groseneken et al., 1986a,b)

Group and Conditions	Total Ventilation (Liters/min.)	Fraction EE Absorbed*	Air Cleared (Liters/min.)	Total Absorbed (mg)
Group 1 (at rest)				
10mg/m3	12.7 +/- 1.6	.617	7.90 +/- 1.5	16.7 +/- 4.2
20mg/m3	13.0 +/- 1.6	.646	8.45 +/- 1.4	35.1 +/- 7.6
40mg/m3	12.4 +/- 1.6	.590	7.34 +/- 1.4	64.1 +/-14.5
Group 2 (20mg/m3)				
0 watts	13.1 +/- 2.0	.633	8.25 +/- 1.4	33.3 +/- 8.4
30 watts	21.8 +/- 3.8	.696	15.18 +/- 2.7	57.0 +/-11.8
60 watts	31.3+/-4.4	.706	22.13+/- 3.3	94.4 +/-13.9

Table 2.1b
Ventilation and Absorption of Ethoxyethanol Acetate During Exposure (Groseneken et al., 1987a,b)

Group and Conditions	Total Ventilation (Liters/min.)	Fraction EEac Absorbed***	Air Cleared (Liters/min.)	Total Absorbed (mg)
Group 1 (at rest)				
14mg/m3	14.4 +/- 0.9**	.562	8.09	23.3 +/- 2.0
28mg/m3	13.7 +/- 0.8	.585	8.01	44.9 +/- 1.3
50mg/m3	13.2 +/- 1.1	.645	8.51	85.1 +/- 5.5
Group 2 (28mg/m3)				
0 watts	12.2 +/- 1.1	.553	9.45	37.8 +/- 2.4
30 watts	22.3 +/- 1.1	.676	15.07	84.4 +/- 2.4
60 watts	29.1+/- 1.3	.746	21.7	121.5 +/- 5.5

*The fraction retained is (Ci - Ce)/Ci where Ci = the concentration in inhaled air, and Ce is the concentration in expired air.

***The data in this column for fraction cleared, and the liters/minute clearance in the next column were not given by Groseneken et al. (1987a) but were calculated by us from the data in the other three columns.

** Standard deviation, based on 5 observations in each case.

2.2 Initial Puzzles and Possible Interpretations of the Exhalation Data

The concentration of ethoxyethanol in expired air was measured over a four hour period after the end of exposure (Figure 1.1 above). These data were fit to a classical (empirical) two-compartment pharmacokinetic model. For group 1 (at rest) the best fitting equations were:

$10\ mg/m^3$ exposure--$Ce = 114\ e^{-.117t} + 25\ e^{-.0065t}$
$20\ mg/m^3$ exposure--$Ce = 218\ e^{-.128t} + 36\ e^{-.0070t}$
$40\ mg/m^3$ exposure--$Ce = 417\ e^{-.149t} + 59\ e^{-.0068t}$

where t = time in minutes and Ce is the expired air concentration in ug/m^3. For group 2 (exposures to $20\ mg/m^3$ at various activity levels) the best fitting equations were:

0 watts-- $Ce = 191\ e^{-.122t} + 34\ e^{-.0074t}$
30 watts-- $Ce = 224\ e^{-.108t} + 33\ e^{-.0069t}$
60 watts-- $Ce = 246\ e^{-.122t} + 44\ e^{-.0084t}$

The most recent data (Groseneken et al., 1987a), of exposure to ethoxyethanol acetate, show a quite similar pattern. For exposure at rest:

$14\ mg/m^3$ exposure--$Ce = 128\ e^{-.107t} + 54\ e^{-.0078t}$
$28\ mg/m^3$ exposure--$Ce = 232\ e^{-.112t} + 86\ e^{-.0072t}$
$50\ mg/m^3$ exposure--$Ce = 414\ e^{-.139t} + 119\ e^{-.0080t}$

For exposure to $28\ mg/m^3$:

30 watts-- $Ce = 332\ e^{-.119t} + 108\ e^{-.0083t}$
60 watts-- $Ce = 246\ e^{-.109t} + 93\ e^{-.0075t}$

These equations and Figure 1.1 both indicate that EE is lost very rapidly from the central circulation following the end of exposure. The average exponent of .131 in the group 1 equations for the first (faster) compartment in the original (Groseneken 1986a) experiments corresponds to

a half-life of only about five minutes. The average exponent for the second (presumably peripheral) compartment of .0068 corresponds to a half-life of slightly over 100 minutes.

Theoretically, the rapid loss of EE from the central circulation could be the result of (1) exhalation of unchanged EE, (2) storage of EE in tissues with a high tissue/blood partition coefficient, or (3) metabolism. The first of these can be ruled out as a major contributor immediately. Groseneken et al. (1986a) report that in all groups the total amount of EE exhaled accounts for less than 0.4% of the amount retained.

On the basis of the modeling we have done, it seems that the second process, reversible storage, is also unlikely to be a major contributor to the rapid depletion of the central compartment. In order for continuing storage in the periphery to significantly deplete the central compartment (relative to metabolism) after the end of exposure, the second compartment must be relatively far from its equilibrium level at that time. With the second compartment having a half life of on the order of 100 minutes, however, the 200 minutes of total exposure in the Groseneken et al. experiments can be expected to bring the system fairly near to equilibrium, unless transfer from the central to the peripheral compartment is extraordinarily slow relative to the capacity of the second compartment. With slow transfer to the second compartment, however, it is difficult for the continuing transfer to still be an appreciable fraction of the approximately 0.131 min^{-1} total loss rate from the central compartment.

The EE exhalation equations reproduced above pose some other serious puzzles for modeling, however. In the equations for group 1, although the amount of EE stored in the first compartment at the end of exposure appears to go up linearly with the external exposure level (with coefficients of 114, 218, and 417 for the 10, 20 and 40 mg/m^3 sessions) the coefficients for the second compartment do not quite show the same fourfold increase with the fourfold increase in exposure. This is also seen in the equations for exposure to ethoxyethanol acetate from Groseneken et al. (1987a). It is not certain from the papers whether the departure from linearity for this coefficient is statistically significant, but given two separate observations of the same phenomenon, it would seem likely. Even more puzzling is the failure of the exhalation equations for the "group 2's" (with exercise) to linearly reflect the nearly three-fold increase in overall absorption that occurs with increasing

exercise (compare with the data in the last column of Tables 2.1a and 2.1b). There are a couple of possible explanations for this:

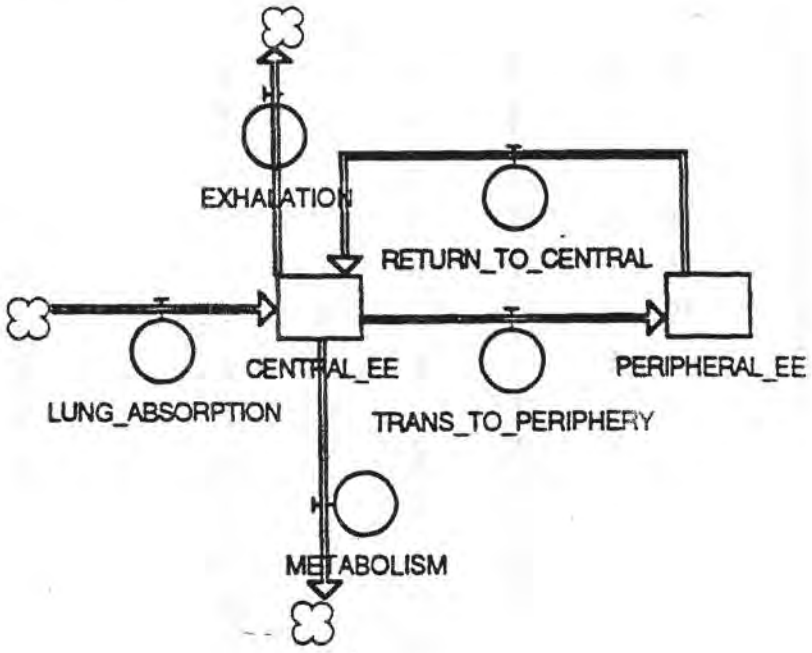
(1) The exercising subjects could have increased their rates of metabolism of EE during exposure, so that the increased absorption was not reflected in any appreciable increase in EE in the body at the end of the exposure periods. One possible type of mechanism for this might involve metabolism of EE in muscle tissue (muscle receives a greatly increased amount of blood flow with increasing exercise). Arguing against this is the very low activity of muscle tissue of alchohol dehydrogenase--the enzyme responsible for the initial oxidation of both ethanol and EE (Romer et al., 1986).

(2) The physiological conditions produced by increasing exercise (perhaps the greater transfer of alcoholic sugars etc. to be burned in muscle tissue) might somehow interfere with the transfer of ethoxyethanol to the slower-exchanging compartment. A relative increase in metabolism occurs because with the decrease in transfer to the peripheral compartment, relatively more ethoxyethanol is available in the central compartment (where metabolism presumably takes place)

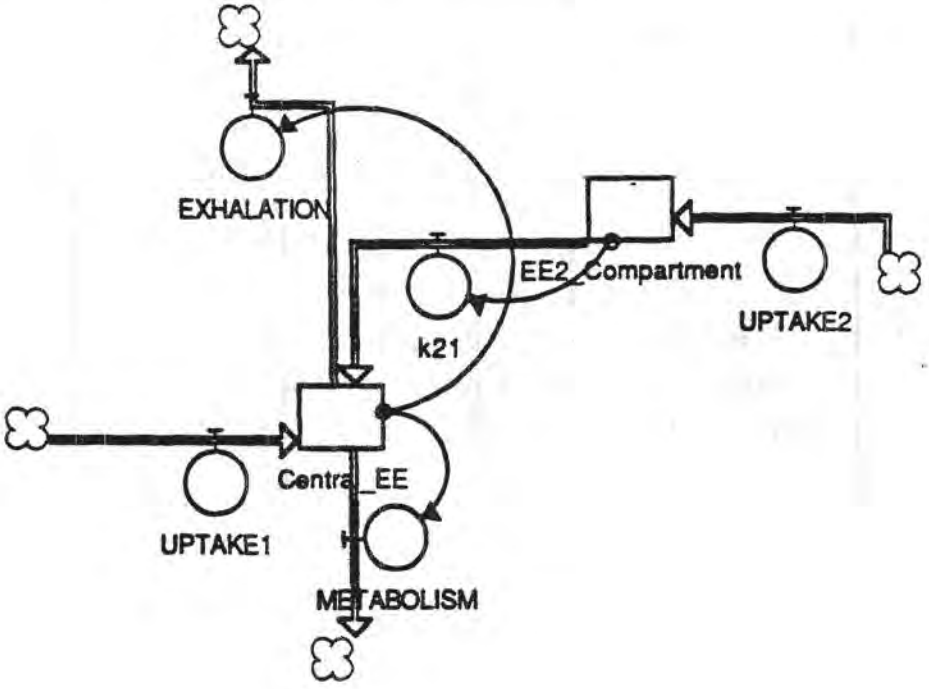
Whatever the true explanation, after trying out a number of possibilities, we concluded that we simply did not have enough information to build a full physiologically-based pharmacokinetic model that would reproduce this particular behavior. Moreover, because of the relatively rapid metabolism of ethoxyethanol when compared to the dynamics of excretion of ethoxyacetic acid (see below), it was our judgment that the modest suggested nonlinearities in the distribution of ethoxyethanol between the central and peripheral compartments are not critical for our main problem--which is the prediction of ethoxyacetic acid excretion. The key point is that the net absorption of ethoxyethanol and ethoxyethanol acetate is linear with external air concentration. Therefore, the enzymes responsible for metabolism cannot be appreciably saturated. For present purposes we believe it is sufficient to represent the uptake and storage of ethoxyethanol in our models with a simple empirical equation derived from the Groseneken (1986a) results. We named the models constructed on this basis our "simplest" models.

The usual way in which two-compartment empirical pharmacokinetic models are represented is with a central comparment that receives material

from the external exposure, and a peripheral compartment that exchanges with the central compartment:



In building our "simplest" models, we found that a somewhat modified structure would be more tractable mathematically:



As can be seen in this formulation, ethoxyethanol is delivered directly from the external air to both central and peripheral compartments, although all metabolism and exhalation depend only on the material in the central compartment.

The advantage of this is that the rate constant for transfer from the slow to the central compartment ("return to central" or "k21") is simply the regression coefficient found for the slower compartment in the Groseneken et al. (1986a) regression equations--about .0068 on average. Further, the sum of the metabolism and exhalation rate constants must simply be the regression coefficient found for the faster compartment--about .131 on average. The exhalation rate constant needed to achieve reasonable correspondence with the absolute levels of exhaled ethoxyethanol was .0027 or about 0.2% of the total loss from the central compartment (this is compatible with the reported range of total recovery of ethoxyethanol in exhaled air of 0.1-0.4%). The ratio of "uptake1" to total absorption ("uptake1" + "uptake2") needed to achieve the right balance of accumulation in the two compartments at the end of exposure was found to be about 83%. Table 2.2 shows the overall correspondence of the pattern of exhalation exhibited by our "simplest" models to the composite equation derived from the Groseneken et al. (1986a) experiments. The overall fit is clearly good enough that we will not be making gross errors by using this formlation to represent the availability over time of ethoxyethanol in the central compartment. This is what is required for the subsequent modeling of metabolism and excretion.

As can be seen in the notes at the bottom of Table 2.2, the results for our "simplest" model formulation suggest that the great bulk of absorbed ethoxyethanol is metabolized quite rapidly--90% or so is processed by the end of the exposure period. The remainder is delivered to the central compartment and metabolized at a modest rate, according to the dynamics of the slower "peripheral" compartment. At the end of the exposure, about 70% of the unmetabolized ethoxyethanol is contained in the peripheral compartment.

Table 2.2

Correspondence Between The Pattern of Air Exhalation for the "Simplest" Model and the Composite Equation* For the Groseneken et al. (1986a) Observations

(EE Exhalation after 20 mg/m^3 exposre for four 50-minute periods separated by ten minute breaks.)

Time After End of Exposure (min.)	Composite Equation ug/m^3 Exhaled	"Simplest" Model ug/m^3 Exhaled
10	94.25	97.82
20	47.29	48.20
30	33.64	33.47
40	28.58	28.18
50	25.94	25.50
60	24.02	23.60
80	20.90	20.53
100	18.24	17.91
120	15.92	15.63
140	13.89	13.65
160	12.13	11.91
180	10.59	10.40
200	9.24	9.07
220	8.06	7.92
240	7.04	6.91

Total Absorption = 3.896 X 10^{-4} moles
Total EE remaining unmetabolized at the end of exposure--10.4%
Total EE remaining unmetabolized one hour after exposure--5.9%

* Air exhalation = 218 $e^{-.131t}$ + 36 $e^{-.0068t}$.

2.3 Initial Inferences from the Data on Urinary Excretion of Ethoxyacetic Acid (EAA) and Construction of the "Simplest" Pharmacokinetic Models

Table 2.3 shows the total recovery of EAA in the urine over 42 hours of observation from the start of exposure in the two series of experiments (Groseneken et al., 1986b, 1987b). Again it can be seen that the excretion of EAA is essentially linear with absorbed dose. There is no evidence, therefore, that either the processes of metabolism of ethoxyethanol or the excretion of EAA are appreciably saturated at the doses studied. Overall, 23.6% of the absorbed ethoxyethanol was recovered as EAA in the original experiments, and 22.2% of the absorbed ethoxyethanol acetate was recovered as EAA in the later experiments. In order to reproduce this result, in addition to the pattern of decline of EAA excretion with time, we found it necessary to postulate that not all of the absorbed EE is metabolized to EAA.* In constructing the models, we adjusted the fraction of EE processed by the alcohol dehydrogenase vs "other" pathways to agree with the average of 23.6% excretion as EAA by 42 hours after the start of exposure observed by Groseneken et al. (1986b).

Figures 1.2 and 1.3 on pp. 4-5 above show the dynamics of urinary EAA excretion observed by Groseneken et al (1986b and 1987b). Qualitatively the observations indicate that urinary excretion (and thus the body levels of EAA) do not reach their peak until about three to four hours after the end of the exposures.** Thereafter, they decline slowly--with a half-life of approximately 21-24 hours according to Groseneken et al. (1986a). As will be seen below, our analysis of the same data suggests that the half-life of EAA may be even somewhat longer than this.

---

* One alternative route of metabolism might involve primary attack on the ether linkage, possibly yielding ethanol and ethylene glycol. In rats Cheever et al. (1984) found approximately 75-80% of administered ^{14}C-labeled EE was eventually excreted in the urine as EAA and a glycine ester of EAA.

** The more recent data (Groseneken 1987b), where exposure was to ethoxyethanol acetate, suggest that there may even be a second peak of excretion a few hours after the first. This suggests that like ethoxyethanol, EAA may be distributed between a central and peripheral pharmacokinetic compartment and that the dynamics of transter among the compartments may be unusual (involve some discrete lags). However, to date we have been unable to develop a two-compartment model for ethoxyacetic acid excretion that appreciably improves on the performance of the models in fitting the Groseneken et al. (1986b) observations.

Table 2.3a

Overall Excretion of Ethoxyacetic Acid Over 42 Hours in Relation to the Absorption of Ethoxyethanol (Groseneken et al., 1986b)

Group and Conditions	EE Absorbed (mg)	EAA Excreted in 42 hr (mg-Equiv of EE)	% of Absorbed Dose Excreted As EAA in 42 Hr
Group 1 (at rest)			
10mg/m3	16.7+/-4.2*	3.5+/-0.9	21.1+/-7.5
20mg/m3	35.1+/-7.6	7.4+/-0.7	21.7+/-3.9
40mg/m3	64.1+/-14.5	12.2+/-2.4	21.0+/-7.8
Group 2 (20mg/m3)			
0 watts	33.3 +/- 8.4	8.4+/-2.1	25.6+/-5.2
30 watts	57.0 +/-11.8	16.2+/-4.4	28.5+/-5.5
60 watts	94.4 +/-13.9	21.0+/-5.9	23.5+/-5.5
			Average 23.6%

Table 2.3b

Overall Excretion of Ethoxyacetic Acid Over 42 Hours in Relation to the Absorption of Ethoxyethanol Acetate (Groseneken et al., 1987b)

Group and Conditions	EE-Ac Absorbed (mg)	EAA Excreted in 42 hr (mg-Equiv of EE-Ac)	% of Absorbed Dose Excreted As EAA in 42 Hr
Group 1 (at rest)			
14mg/m3	23.3+/-2.1	5.34+/-0.64	22.9+/-1.3
28mg/m3	44.9+/-1.3	8.76+/-0.88	19.7+/-2.4
50mg/m3	85.1+/-5.5	15.47+/-0.68	18.3+/-0.7
Group 2 (28mg/m3)			
0 watts	37.1 +/- 2.4	8.77+/-0.85	23.2+/-1.6
30 watts	84.4 +/- 2.5	19.94+/-1.86	23.5+/-1.9
60 watts	121.5 +/- 5.4	30.83+/-3.32	25.9+/-3.4
			Average 22.2%

* The numbers following the +/- symbols are the standard errors of the means for each group.

When combined with the findings of the previous section--that nearly 90% of the absorbed ethoxyethanol may have already been metabolized at the end of exposure--the delayed peak of EAA excretion after exposure implies that either there may be appreciable storage of an intermediate form between EE and EAA or there may be a lag in the delivery of EAA from the tissues where it is metabolized to the renal excretory aparatus.

On the basis of the known metabolism of EE by aldehyde dehydrogenase, the intermediate form is presumably ethoxyacetaldehyde. Ethoxyacetaldehyde is potentially of considerable toxicological interest in the light of recent in vitro findings by Foster et al. (1986) which imply that methoxyacetaldehyde may be on the order of fifty times more potent than methoxyacetic acid in causing detachment of Sertoli-germ-cells (presuming that this is a good model of toxicity in vivo). For some time it has been known that metabolism is essential for the toxic action of glycol ethers on testicular cells (Moss et al., 1985).

Unfortunately there are no measurements of the levels of ethoxyacetaldehyde or ethoxyacetic acid in human blood, exhaled air, or any other body tissue. There are also no measurements of partition coefficients, or association constants for the reversible reactions forming covalent linkages to -SH, -NH_2 or -OH groups (on proteins or other molecules in blood or elsewhere). In short, we have little to go on to help us construct a full physiologically based pharmacokinetic model involving the aldehyde derivatives of glycol ethers. For our "simplest" models, we have therefore chosen to represent the oxidation of ethoxyethanol to ethoxyacetaldehyde and then to ethoxyacetic acid, and the later excretion of the EAA, in the most straightforward possible way--as simple linear rate constants, acting on total body stores of ethoxyacetaldehyde and EAA in each case. The full diagram of our "simplest" model is shown in Figure 2.1, and the corresponding equations are given in Table 2.4.

The system shown has two parameters that can be adjusted to fit the ethoxyacetic acid excretion data (in addition to the proportion of ethoxyethanol that is metabolized by alcohol dehydrogenase vs. hypothesized other routes--which was discussed earlier):

(1) the rate of oxidation of ethoxyacetaldehyde to ethoxyacetic acid

(2) the rate of urinary excretion of body stores of ethoxyacetic acid.

Figure 2.1
Diagram for the "Simplest" Models

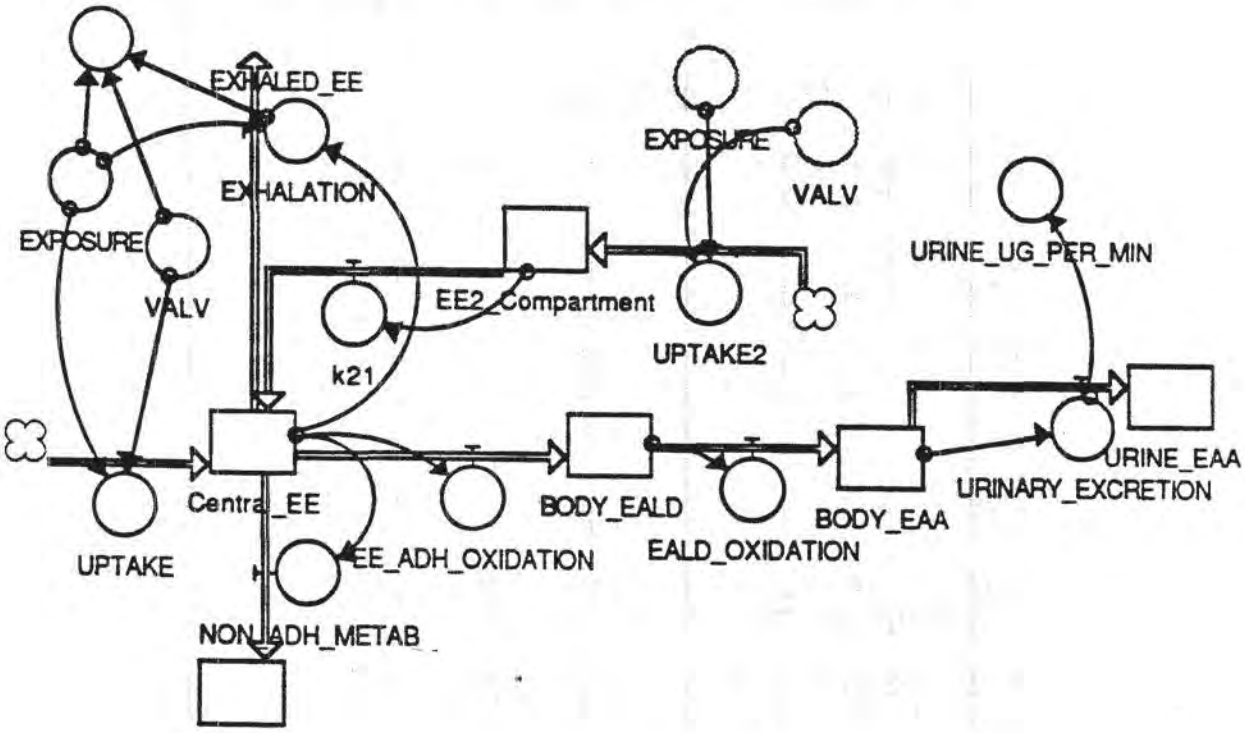


Table 2.3
Equations for the "Best-Estimate Simplest" Model

Equations for Accumulators:

BODY_EAA = BODY_EAA + dt * (EALD_OXIDATION - URINARY_EXCRETION)
INIT(BODY_EAA) = 0{initial value...}

BODY_EALD = BODY_EALD + dt * (EE_ADH_OXIDATION - EALD_OXIDATION)
INIT(BODY_EALD) = 0{initial value...}

Central_EE = Central_EE + dt * (UPTAKE - EE_ADH_OXIDATION -
NON_ADH_METAB - EXHALATION + k21)
INIT(Central_EE) = 0{initial value...}

EE2_Compartment = EE2_Compartment + dt * (-k21 + UPTAKE2)
INIT(EE2_Compartment) = 0{initial value...}

EXHALED_EE = EXHALED_EE + dt * (EXHALATION)
INIT(EXHALED_EE) = 0 {initial value...}

OTHER_METABOLITES = OTHER_METABOLITES + dt * (NON_ADH_METAB)
INIT(OTHER_METABOLITES) = 0{initial value...}

TOTAL_ABS = TOTAL_ABS + dt * (ABSORPTION)
INIT(TOTAL_ABS) = 0{initial value...}

URINE_EAA = URINE_EAA + dt * (URINARY_EXCRETION)
INIT(URINE_EAA) = 0{initial value...}

Equations for Converters:

ABSORPTION = UPTAKE + UPTAKE2 {MOLES/MIN}

EALD_OXIDATION = .14*BODY_EALD {MOLES/MIN}

EE_ADH_OXIDATION = .0624*Central_EE

EXHALATION = IF (EXPOSURE = 0) THEN (2.7E-3)*Central_EE ELSE 0
{MOLES/MIN}

EXPOSURE = IF (TIME <= 480) THEN 5.65 ELSE 0 {PPM}

k21 = .0068*EE2_Compartment

NON_ADH_METAB = .0659*Central_EE {HYPOTHESIZED ALTERNATIVE ROUTE
OF METABOLISM}

Table 2.3, CONTINUED
EQUATIONS FOR THE "Best-Estimate SIMPLEST" MODEL

```
UGM3_EXHALED = IF (EXPOSURE = 0) AND (TIME <= 960) THEN
 (EXHALATION/12.7)*9.01E10 ELSE IF (EXPOSURE = 0) THEN
.74*(EXHALATION/VALV)*9.01E10 ELSE 0
{ASSUMES 35% DEAD SPACE, AND THEREFORE CORRRESPONDING DILUTION
OF ALVOLAR AIR CONC. 1/1.35 = .74}

UPTAKE = .83*VALV*EXPOSURE*1E-6/25.45 {MOLES/MIN}

UPTAKE2= .17*EXPOSURE*VALV*1E-6/25.45 {MOLES/MIN}
URINARY_EXCRETION = (3.7E-4)*BODY_EAA
URINE_UG_PER_MIN = URINARY_EXCRETION*1.041E8

VALV = IF (TIME <= 960) OR (1440 < TIME) AND (TIME <= 2400) OR (2880 < TIME)
AND (TIME <= 3840) OR (4320 < TIME) AND
(TIME <= 5280) OR (5760 < TIME) AND (TIME <= 6720) OR
(7200 <TIME) AND (TIME <= 8160) OR (8640 < TIME) AND
 (TIME <= 9600) THEN 11.38 ELSE 4.
```

The fitting of these two parameters to the available urinary excretion data is outlined in the next section.

2.4 Defining and Fitting Alternative Models to the Groseneken et al. (1986b) Urinary EAA Excretion Data

2.4.1 Numerical Data and Fitting Tecniques

Table 2.4 shows the Groseneken et al. (1986b) ethoxyacetic acid excretion data in numerical form, as well as we could recover them from the figures in their paper. It can be seen that the standard deviations of the measurements of urinary EAA tended to be larger for larger absolute concentrations of EAA. This suggested that the measurement errors are more likely to be well described as lognormal, rather than normal distributions. In fitting the data, we therefore wished to choose values of our adjustable parameters so as to minimize the sum of the squares of the logarithms of the ratios of the observed and model-"predicted" EAA excretion rates. In addition, it can be seen in the final column of the second part of Table 2.4 that the coefficients of variation for the very earliest time point (30 minutes after the start of exposure) were considerably larger than was seen for later time points. Rather than develop a complex weighting scheme for this one set of points, we elected to exclude the 30 minute points from the model fitting.

The fitting process was facilitated by the fact that there are no elements in the models that produce nonlinearities with absorbed dose of EE. This allowed us to run each model variant only once (for the 20 mg/m^3 exposure at rest condition) and then use the results at each time point to linearly project the ethoxyacetic acid excretion rates as a function of time for other exposure conditions. A similar linear adjustment was made to bring the average urinary excretion for all six exposure conditions to 23.6% as discussed in Section 2.3 (implicitly this was simply an adjustment of the proportion of total absorbed EE that was processed via the alcohol dehydrogenase pathway.)

Table 2.4
Urinary Ethoxyacetic Acid Excretion Observations
Groseneken et al. (1986b)

Time After Start of Exposure (min.)	Groups Exposed At Rest 10 ug/m^3	20 ug/m^3	40 ug/m^3	Groups Exposed to 20 ug/m^3 0.W	30.W	60.W
30	.15	.39	.88	.76	.99	1.48
90	.88	1.48	2.96	2.05	2.47	5.21
150	1.35	2.45	4.41	4.08	4.39	8.76
210	1.87	2.96	5.66	4.59	7.23	12.27
270	2.69	3.89	7.87	4.86	8.91	14.49
330	2.51	4.51	7.73	5.82	11.34	15.97
390	2.74	5.13	8.21	5.80	12.55	17.51
450	3.16	4.91	8.52	6.00	10.79	17.13
540	2.42	2.96	8.25	5.55	8.97	12.37
660	2.19	3.56	7.96	5.06	9.98	13.43
780	1.93	3.75	8.36	5.09	9.40	12.99
1080	1.10	2.72	4.57	3.53	7.73	8.35
1560	1.18	1.87	5.24	3.78	8.71	9.11
2040	1.47	3.03	5.57	3.33	6.17	8.49
2520	.89	1.79	3.48	2.67	4.86	7.87

Standard Deviations of the Measurements (5 Subjects):

Time After Start of Exposure (min.)	Groups Exposed At Rest 10 ug/m^3	20 ug/m^3	40 ug/m^3	Groups Exposed to 20 ug/m^3 0.W	30.W	60.W	Geom. Mea Coef. Var.*
30	.26	.28	.53	.50	.42	.97	.718
90	.39	.67	1.03	.42	1.65	3.80	.437
150	.37	1.11	2.14	.69	1.19	5.34	.345
210	.64	1.49	.94	1.51	3.60	8.15	.382
270	1.42	1.04	2.16	1.76	4.49	6.76	.386
330	1.12	1.57	3.60	1.51	3.56	4.29	.341
390	.90	2.32	1.57	2.18	3.36	4.49	.300
450	1.02	2.20	1.65	1.66	4.62	3.73	.300
540	.37	.79	1.60	2.12	1.60	4.24	.239
660	1.16	1.42	2.10	1.40	5.18	5.56	.391
780	1.22	1.37	2.59	1.14	3.61	4.79	.362
1080	.57	.91	1.52	1.63	2.94	2.89	.390
1560	.67	.90	1.31	1.38	2.86	2.02	.349
2040	.61	.84	1.68	.99	1.51	3.06	.311
2520	.24	.81	2.94	1.18	1.68	.84	.345
	Grand Geometric Mean (Excluding 30 Min. Point)						**.345**

* The coefficient of variation is the standard deviation of each measurement divided by the mean (in the corresponding position in the upper part of the table). The numbers in this column represent the geometric means of all six coefficients of variation at each time point.

2.4.2 Fitting the Adjustable Parameters for the "Best Estimate" and "Alternative" "Simplest" Models

The upper part of Table 2.5 shows the sums of the squares of the differences between the logarithms$_{10}$ of the observed and model-predicted EAA excretion rates for our "simplest" models for various trial values of the rate constants for ethoxyacetaldehyde oxidation and EAA excretion. To place these numbers in perspective, a sum of log squares of 5 represents, for the average of the 84 points, a ratio of about 1.75 between a typical point and the model prediction.* Similarly, a sum of log squares of 4.3 (the best fit we achieved) represents a typical ratio of 1.68. It can be seen that the optimum value for the ethoxyacetaldehyde oxidation rate is affected by the value chosen for the EAA excretion rate.

The lower portion of Table 2.5 shows the times at which EAA excretion reached its peak, for the various combinations of parameter values. We were not entirely pleased to notice that optimizing on our primary criterion for fit--minimizing the sum of the squared log deviations--drove us to set the ethoxyaldehyde oxidation rate at such a high level that the peak of EAA excretion was predicted to happen at 330 minutes--only an hour and forty minutes after the end of exposure. It will be recalled that Groseneken et al. (1986a) observed the true peak at 3-4 hours after the end of exposure. We therefore decided to explore in parallel the implications of an "Alternative" variant of the "Simplest" model in which the ethoxyacetaldehyde oxidation rate was set at a relatively low value (.03/min), which, after optimization of the EAA excretion rate, led to a peak EAA excretion at 370 minutes (2 hours and 20 minutes after the end of exposure).

For the "Best Estimate-Simplest" model, the requirement for 23.6% EAA excretion over 42 hours led us to allocate 48.6% of the metabolized EE to the alcohol dehydrogenase pathway (rate constants of .0624/min. and .0659/min. for the ADH and non-ADH pathways, respectively). For the "Alternative-Simplest" model, 53.5% was allocated to the ADH pathway (rate constants of .0687/min. and .0596/min. for the ADH and non-ADH routes).

---

* $10^{(5/84)^{1/2}} = 1.754$

Table 2.5
Fitting the Adjustable Parameters for the "Simplest" Models

(First criterion: the sum of the squares of the differences between the model-predicted and observed $\log_{10}$(EAA excretion rates):

Ethoxyacetaldehyde Oxidation Rate	Urinary EAA Excretion Rate (x 10^{-4})/min.						
(min^{-1})	3.26	3.5	3.7	4.0	4.4	4.5	5.0
.025	6.412						
.03	5.742			5.145	**5.059***		5.225*
.035	5.343						
.04	5.089						
.045	4.914						
.05	4.805						
.06	4.658						
.07	4.576						
.09	4.496		4.3860				
.10	4.486	4.400	4.3814	4.433		4.710	5.234
.11		4.460					
.12			**4.3809****				

(Second Criterion: the times of peak EAA excretion--minutes after start of exposure)

Ethoxyacetaldehyde Oxidation Rate	Urinary EAA Excretion Rate (x 10^{-4})/min.						
(min^{-1})	3.26	3.5	3.7	4.0	4.4	4.5	5.0
.025	415						
.03	395			375	370*		360
.035	385						
.04	375						
.045	370						
.05	365						
.06	355						
.07	355						
.09	350		335				
.10	350	340	335	320		305	300
.11		340					
.12			**330****				

---

* This combination of ethoxyacetaldehyde oxidation rate and urinary EAA excretion rate was chosen as the "Alternative-Simplest" model.

** This combination of ethoxyacetaldehyde oxidation rate and urinary EAA excretion rate was chosen as the "Best Estimate-Simplest" model.

The calculated optimal urinary excretion rates correspond to terminal half-lives for urinary excretion of 31.2 hours in the case of the "Best Estimate-Simplest" model and 26.2 hours in the case of the "Alternative-Simplest" model. The latter is somewhat closer to the range of 21-24 hours reported by Groseneken et al. (1986b) themselves (using calculation methods that unfortunately were not described).

2.4.3 Defining and Fitting the Adjustable Parameters for the "Less Simple" Models (With and Without Diurnal Changes in EAA Excretion)

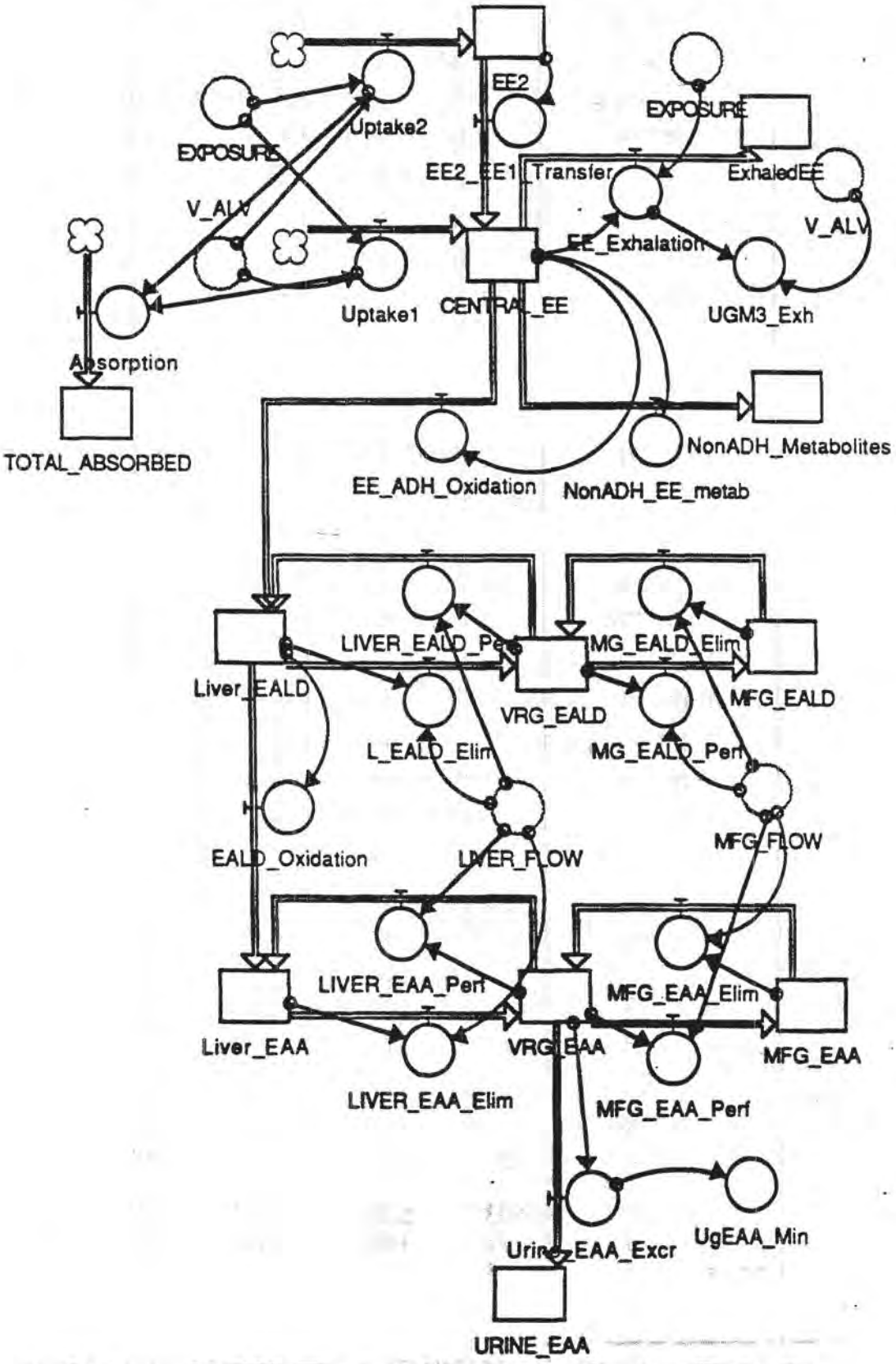
2.4.3.1 "Less Simple" Model Without Diurnal Changes in EAA Excretion

We were still not entirely happy with the relatively early appearance of the peak in EAA excretion, even in the "Alternative-Simplest" model. We therefore explored the implications of a "less simple" model structure (Figure 2.2) which has many features borrowed from our earlier physiologically-based pharmacokinetic models. By having both steps of metabolism occur in the liver, while excretion originated in the central "vessel-rich-group" compartment, we hoped to allow some ethoxyacetic acid to be excreted at early time points after the start of exposure while still producing a broadening of the time pattern of release of the EE metabolites from the large combined muscle/fat compartment, and hence a later peak EAA excretion time. Tissue/blood partition coefficients for the model were derived from Fiserova-Bergerova et al. (1986) assuming that ethoxyacetaldehyde and EAA would both have parition coefficients equal to the average for the seven hydrophilic chemicals studied by those authors:*

Liver and Vessel-Rich Group	.749
Fat Group	.68
Muscle Group	.726
Muscle/Fat Groups Combined (weighted average)	.712

* This assumption is particularly questionable in the case of ethoxyacetaldehyde because of the possibility of reversible covalent binding with amino-, sulfhydryl, and hydroxyl groups.

Figure 2.2
Diagram for the "Less Simple" Models



These models also incorporate a daily change of blood flow and alveolar ventilation rates between waking and sleeping periods.

The optimization of the adjustable parameters for this model structure is shown in Table 2.6, and the resulting equations are given in Table 2.7. It can be seen that with this structure, we were able to achieve a peak as late as 400 minutes, with no worse an overall fit to the EAA excretion data, as judged by the sum of the squares of the log ratios criterion. For this model, the terminal half-life for urinary excretion of EAA was 33.4 hours, and 42.4% of the metabolized EE was allocated to the alcohol dehydrogenase pathway (rate constants of .05445/min. and .07385/min. for the ADH and non-ADH pathways, respectively).

2.4.3.2 "Less Simple" Model With Diurnal Changes in EAA Excretion (The "70-Hour" Model)

In observing the pattern of deviations of the EAA excretion rates from the model predictions, we noticed that the points at 1560 and 2040 minutes after the start of exposure tended to be higher than the adjacent points at 1080 and 2520 minutes (see Figures 1.2 and 1.3, and Table 2.4). This suggested that there might be a diurnal pattern of change in the excretion of EAA. that could prove misleading. If we compare the excretion half-life implied by pairs of the last four points in the Groseneken et al. (1986b) data set we see:

Time After Start of Exposure (min.)	Groups Exposed At Rest			Groups Exposed to 20 ug/m^3			Geom. Mean of $T_{1/2}$
	10 ug/m^3	20 ug/m^3	40 ug/m^3	0 W	30 W	60 W	
1080	1.10	2.72	4.57	3.53	7.73	8.35	
2520	.89	1.79	3.48	2.67	4.86	7.87	
$T_{1/2}$* (hours)	78.5	39.8	61.0	59.6	35.8	281	69.7
1560	1.18	1.87	5.24	3.78	8.71	9.11	
2520	.89	1.79	3.48	2.67	4.86	7.87	
$T_{1/2}$* (hours)	39.32	254	27.1	31.9	19.0	75.8	48.1
2040	1.47	3.03	5.57	3.33	6.17	8.49	
2520	.89	1.79	3.48	2.67	4.86	7.87	
$T_{1/2}$* (hours)	11.0	10.5	11.8	25.1	23.2	281	19.7

* $T_{1/2}$ in hours = (ln 2)*(T_2 - T_1)/[60*ln (EAA excretion rate at T_2/EAA excretion rate at T_1), where the T's are times after the start of exposure in minutes.

Table 2.6
Fitting the Adjustable Parameters for the "Less Simple" Model (Without Diurnal Changes in Urinary EAA Excretion)

(First criterion: the sum of the squares of the differences between the model-predicted and observed $\log_{10}$(EAA excretion rates):

Ethoxyacetaldehyde Oxidation Rate (Moles EAA produced Mole Eald in liver-Min.)	Urinary EAA Excretion Rate*			
	.003	.0038	.004	.006
0.2				6.863
0.3	8.238			5.266
0.4				4.932
0.5	5.956		4.846	4.929
0.75	5.216			
1.0	4.972	4.430	**4.378****	5.438
1.2		4.412		

(Second Criterion: the times of peak EAA excretion--minutes after start of exposure)

Ethoxyacetaldehyde Oxidation Rate (Moles EAA produced Mole Eald in liver-Min.)	Urinary EAA Excretion Rate ($min.^{-1}$)			
	.003	.0038	.004	.006
0.2				545
0.3	550			475
0.4				440
0.5	490		450	410
0.75	450			
1.0	425	400	**400****	360
1.2		395		

* Moles EAA excreted/(Moles EAA in the Vessel-Rich Group-Min.).

** This combination of values for the adjustable parameters was selected as the best fit for the "less simple" model.

Table 2.7
Equations for the "Less Simple" Model (Without Diurnal Changes in EAA Excretion)

Equations for Accumulators:

CENTRAL_EE = CENTRAL_EE + dt * (Uptake1 + EE2_EE1_Transfer - EE_Exhalation - EE_ADH_Oxidation - NonADH_EE_metab)
INIT(CENTRAL_EE) = 0{initial value...}

EE2 = EE2 + dt * (Uptake2 - EE2_EE1_Transfer)
INIT(EE2) = 0{initial value...}
ExhaledEE = ExhaledEE + dt * (EE_Exhalation)
INIT(ExhaledEE) = 0{initial value...}

Liver_EAA = Liver_EAA + dt * (EALD_Oxidation - LIVER_EAA_Elim + LIVER_EAA_Perf)
INIT(Liver_EAA) = 0{initial value...}

Liver_EALD = Liver_EALD + dt * (EE_ADH_Oxidation - L_EALD_Elim + LIVER_EALD_Perf - EALD_Oxidation)
INIT(Liver_EALD) = 0{initial value...}

MFG_EAA = MFG_EAA + dt * (MFG_EAA_Perf - MFG_EAA_Elim)
INIT(MFG_EAA) = 0{initial value...}

MFG_EALD = MFG_EALD + dt * (MG_EALD_Perf - MG_EALD_Elim)
INIT(MFG_EALD) = 0{initial value...}
NonADH_Metabolites = NonADH_Metabolites + dt * (NonADH_EE_metab)

INIT(NonADH_Metabolites) = 0{initial value...}
TOTAL_ABSORBED = TOTAL_ABSORBED + dt * (Absorption)
INIT(TOTAL_ABSORBED) = 0

URINE_EAA = URINE_EAA + dt * (Urine_EAA_Excr)
INIT(URINE_EAA) = 0{initial value...}

VRG_EAA = VRG_EAA + dt * (LIVER_EAA_Elim - LIVER_EAA_Perf - MFG_EAA_Perf + MFG_EAA_Elim - Urine_EAA_Excr)
INIT(VRG_EAA) = 0{initial value...}

VRG_EALD = VRG_EALD + dt * (L_EALD_Elim - LIVER_EALD_Perf - MG_EALD_Perf + MG_EALD_Elim)
INIT(VRG_EALD) = 0 {initial value...}

Equations for Convertors:

Absorption = Uptake1 + Uptake2 {Moles/min}

AWAKE_TIME = 960 {minutes}

DAY = DAY1_5 + RESTDAY + DAY9_12 - 1

Table 2.7, Continued
Equations for the "Less Simple" Model (Without Diurnal Changes in EAA Excretion)

DAY1_5 = IF (TIME≥0) AND (TIME<1440) THEN 1 ELSE IF (TIME ≥ 1440) AND (TIME< 2880) THEN 2 ELSE IF (TIME ≥ 2880) AND (TIME < 4320) THEN 3 ELSE IF (TIME ≥ 4320)AND (TIME<5760) THEN 4 ELSE IF (TIME≥5760) AND (TIME<7200) THEN 5 ELSE 0

DAY9_12 = IF (TIME >= 11520) AND (TIME < 12960) THEN 9 ELSE IF (TIME >=12960) AND (TIME< 14400) THEN 10 ELSE IF (TIME >= 14400) AND (TIME < 15840) THEN 11 ELSE IF (TIME >=15480)AND (TIME<17280) THEN 12 ELSE 0

EALD_Oxidation = Liver_EALD

EE2_EE1_Transfer = .0068*EE2

EE_ADH_Oxidation = .0624*CENTRAL_EE

EE_Exhalation = IF (EXPOSURE = 0) THEN 2.7E-3*CENTRAL_EE ELSE 0

EXPOSURE = IF (TIME < 50) AND (DAY < 1) or (60 <=TIME) and (TIME < 110) or (120 <=TIME) AND (TIME < 170) OR (180 <= TIME) AND (TIME < 230) THEN 5.65 ELSE 0 (ppm)

LIVER_EAA_Elim = LIVER_FLOW*Liver_EAA/(2.476*.749)

LIVER_EAA_Perf = LIVER_FLOW*VRG_EAA/3.551

LIVER_EALD_Perf = LIVER_FLOW*VRG_EALD/3.551

LIVER_FLOW = IF (DAY * 24 * 60 <= TIME) AND
(TIME < DAY * 24 * 60 + AWAKE_TIME)
THEN 1.25 ELSE 1.4

L_EALD_Elim = Liver_EALD*LIVER_FLOW/(2.476*.749)

MFG_EAA_Elim = MFG_EAA*MFG_FLOW/(49.78*.712)

MFG_EAA_Perf = MFG_FLOW*VRG_EAA/3.551

MFG_FLOW = IF (DAY * 24 * 60 <= TIME) AND
(TIME < DAY * 24 * 60 + AWAKE_TIME)
THEN 2.91 ELSE 1.45

MG_EALD_Elim = MFG_EALD*MFG_FLOW/(49.78*.712)

MG_EALD_Perf = MFG_FLOW*VRG_EALD/3.551

NonADH_EE_metab = .0659*CENTRAL_EE

Table 2.7, Continued
Equations for the "Less Simple" Model (Without Diurnal Changes in EAA Excretion)

RESTDAY = IF (TIME >=7200) AND (TIME<8640) THEN 6 ELSE IF (TIME >=8640) AND (TIME<10080) THEN 7 ELSE IF (TIME >= 10080) AND (TIME<11520) THEN 8 ELSE IF (TIME >=17280) AND (TIME<18720) THEN 13 ELSE IF (TIME >= 18720) THEN 14 ELSE 0

UgEAA_Min = Urine_EAA_Excr*1.041E8

UGM3_Exh = .74*(EE_Exhalation/V_ALV)*9.01E10
{Assumes 35% dead space, and therefore corresponding dilution of alveolar air conc. 1/1.35 = .74}

Uptake1 = .83*V_ALV*EXPOSURE*1E-6/25.45

Uptake2 = .17*V_ALV*EXPOSURE*1E-6/25.45

Urine_EAA_Excr = .004*VRG_EAA

VRG_FLOW = IF (DAY * 24 * 60 <=TIME) AND
(TIME < DAY * 24 * 60 + AWAKE_TIME)
THEN 3.24 ELSE 2.95

V_ALV = IF (TIME < 230) THEN 8.772 ELSE IF (DAY * 24 * 60 <= TIME) AND (TIME < DAY * 24 * 60 + AWAKE_TIME)
THEN 8.5 ELSE 4.8

It can be seen that the comparison of the points that were separated by exactly twenty-four hours (both based on early morning urine collections) seems to yield much longer estimates of the half life of EAA in the body than the comparisons between waking-hour urine collections and the final morning point.

The suggested diurnal effect would not have to be very large to produce an appreciable distortion in the apparent half life of EAA in the body. If we assume that the true half life of EAA in the body is in fact about 70 hours, then the geometric mean of the ratio of the observed EAA excretion rates at 2520 minutes to those that would have been predicted from the 1580 minute points is about .867. Similarly, if we calculate from the 2080 minute point, the EAA excretion at 2520 appears to be only about .772 of what we might expect from simple exponential decline with a 70 hour half life. In the end, we decided to base a variant of our "less simple" model on an assumption that the true EAA body half life is 70 hours, but that urinary excretion during 16 waking hours is 20% more than during 8 hours of sleep. This yields rates for EAA excretion of .00202*(VRG EAA)/minute during waking hours, and .00168*(VRG EAA)/minute while asleep.

The fit of the remaining adjustable parameter (ethoxyacetaldehyde oxidation) using this assumption is shown in Table 2.8. It can be seen thatwith this model structure the peak of EAA excretion is extended to 440 minutes, although the best fit achieved to the EAA excretion data (with a rather high rate of ethoxyacetaldehyde oxidation) is a little worse than was achieved for the earlier model structures. An interesting feature of the 70-hour model is that it implies that a greater proportion (72.2%) of the metabolized EE will go via the non-ADH pathway (the rate constants for ADH and non-ADH metabolism are .0926/min. and .0357/min., respectively).

Table 2.8

Fitting the Adjustable Parameters for the "70-Hour" Model (With Diurnal Changes in Urinary EAA Excretion)

Ethoxyacetaldehyde Oxidation Rate (Moles EAA produced / Mole Eald in liver-Min.)	Sum of the Squares of Differences Between Model Predicted and Observed $\log_{10}$(EAA excretion rates)	Peak EAA Excretion Time (minutes after start of exposure)
.8	5.445	490
1.0	5.193	470
1.2	5.062	450
1.5	4.953	450
2.0	4.864*	440

* This combination of values for the adjustable parameters was selected as the best fit for the "70-hour" model.

2.5 Long Term Excretion of EAA Under the Different Models After a Single Day of Occupational Exposure to Ethoxyethanol

Table 2.9 shows the different models' predicted EAA excretion rates at various times following exposure of model workers for eight hours to 20 mg/m^3 ethoxyethanol.* In the next major section, we will use these model-predicted excretion rates (and rates for other time points) as alternative bases for inferring the amounts of EE absorbed by workers in the shipyard painter population.

* After our earlier work, based on Brugnone et al. (1980), we assume a normal alveolar ventilation rate of 11.38 liters/minute during occupational exposure with relatively light exertion. Given nearly complete absorption of the EE reaching the alveoli, this leads to an expectation that 1.213×10^{-3} moles of EE would be absorbed. Because the system as we have represented it is completely linear, greater or lesser air concentrations of EE, or alveolar ventilation rates, would lead to proportionately greater or lesser EE absorption.

Table 2.9

Predicted Urinary Excretion Of Ethoxyacetic Acid at Various Times After 8-Hour Occupational Exposure to 5.65 ppm Ethoxyethanol (20 mg/m^3) on a Single Day

Time After Start of Exposure (min.)	Best Estimate Model Pred. (ug EAA/min. excreted)	Alternative Model Pred. (ug EAA/min. excreted)	Less Simple Model Pred. (ug EAA/min excreted)	Diurnal Excretion Model Pred. (ug/EAA/min excreted)
Day 1 Post-shift (480 min)	19.22	23.44	15.55	14.23
Day 2 Pre-shift (1440 min)	14.79	18.08	12.41	13.18
Day 2 Post-shift (1920 min)	12.39	14.64	10.55	12.13
Day 3 Pre-shift (2880 min)	8.68	9.60	7.54	10.39
Day 3 Post-shift (3360 min)	7.27	7.77	6.41	9.56
Day 4 Pre-shift (4320 min)	5.10	5.09	4.58	8.18
Day 4 Post-shift (4800 min)	4.27	4.12	3.89	7.54
Day 5 Pre-shift (5760 min)	2.99	2.70	2.78	6.45
Day 5 Post-shift (6240 min)	2.50	2.19	2.37	5.94

3. ASSESSING THE PERFORMANCE OF THE MODELS USING THE SHIPYARD PAINTER DATA (SPARER ET AL., 1987, MCMANUS, 1987, DEBORD AND LOWRY, 1986, AND WELCH ET AL., 1987)

3.1 Basic Description of the Data Set

In a series of studies sponsored by NIOSH in conjunction with a NIOSH Health Hazard Evaluation, Sparer et al. (1987), Welch et al. (1987), K. McManus (1987) and L. Lowry have measured a variety of indices of EE exposure, and semen characteristics in a group of painters working in a large shipyard. In this report we will only be examining data from an initial HHE study of 36 workers by K. McManus and C. Moseley. Data were taken from McManus (1987) and DeBord and Lowry (1986).

A unique feature of the study is that both industrial hygiene and biological monitoring were performed over several successive days for each individual studied. Ethoxyacetic acid in the urine was measured by a modification of the method of Smallwood et al. (1984). Attempts were also made to measure methoxyacetic acid and butoxyacetic acid, however MAA was only detected in a single sample. All EAA excretion data were corrected for the time between urine collections and variation in the rate of excretion of water by dividing the measured EAA concentrations by the concentration of creatinine in the urine sample. Data points for which creatinine concentrations fell outside the range where this correction was considered reliable (0.5 to 3.0 g/liter) were not used. The coefficient of variation of both the EAA and the creatinine measurements was about 3-5%.

In order to express all the information as numerical data, we made a number of interpretations of notations in the data set that specific values were "less than" a particular number, or "non-detectable":

Table 3.1
Shipyard Painter Database

WORKER NUMBER	DAY	PRESHFT mg EAA / g creatinine	POSTSHIFT mg EAA / g creatinine	AIRCONC mg EE / cubic meter	ACTIVITY (1=standing 3 = heavy lift.)	RESPUSE (1 = No respirator)	SKINEX (0 = none 2=signif.)
1	3	-99*	6	1.70	3	1	1
	4	5	3	4.10	1	0	1
	5	2	1	2.18	2	0	0
	6	2	-99	-99.00	9**	9	9
2	4	36	64	44.01	2	1	1
	5	61	54	16.99	1	1	0
	6	57	44	.60	1	1	0
	7	39	-99	-99.00	9	9	9
3	4	1	4	5.23	1	1	1
	5	1	11	56.03	1	1	0
	6	16	13	4.83	1	1	1
	7	7	-99	-99.00	9	9	9
4	4	14	11	.60	1	1	1
	5	7	17	2.12	2	1	2
	6	7	-99	3.23	1	1	0
	7	20	-99	-99.00	9	9	9
5	4	-99	-99	22.94	2	1	1
	5	-99	-99	7.14	2	1	1
	6	-99	-99	-99.00	1	1	0
6	4	36	38	7.58	2	1	1
	5	47	47	6.38	2	1	1
	6	-99	55	8.30	1	1	0
	7	34	-99	-99.00	9	9	9
7	3	5	6	2.91	1	1	0
	4	-99	6	4.79	1	1	1
	5	6	9	6.58	1	0	0
	6	8	13	-99.00	9	9	9

* -99 signifies missing data for the urinary measurements of ethoxyacetic acid and the air measurements of ethoxyethanol.
** 9 signifies missing data for the activity, respirator use, and skin exposure ratings.

Table 3.1, Continued

WORKER NUMBER	DAY	PRESHFT mg EAA / g creatinine	POSTSHIFT mg EAA / g creatinine	AIRCONC mg EE / cubic meter	ACTIVITY (1=standing 3 = heavy lift.)	RESPUSE (1 = No respirator)	SKINEX (0 = none 2=signif.)
8	4	1	2	1.60	1	1	1
	5	2	1	1.06	2	1	1
	6	1	2	1.55	1	1	1
	7	1	-99	-99.00	9	9	9
9	3	4	2	6.21	2	1	0
	4	6	21	18.89	2	1	2
	5	23	18	8.63	2	1	1
	6	15	14	-99.00	9	9	9
10	4	1	2	1.10	1	0	0
	5	2	2	.60	2	1	2
	6	3	1	3.70	1	1	1
	7	2	-99	-99.00	9	9	9
11	4	12	14	3.99	2	1	1
	5	13	12	2.43	1	1	0
	6	12	-99	1.96	1	1	0
	7	9	-99	-99.00	9	9	9
12	4	2	6	4.40	2	0	1
	5	2	-99	.60	1	1	0
	6	5	-99	.70	1	1	0
	7	1	-99	-99.00	9	9	9
13	4	-99	69	39.05	1	1	1
	5	-99	144	-99.00	2	1	2
	6	-99	-99	3.82	1	1	0
	7	66	-99	-99.00	9	9	9
14	4	46	47	.60	1	1	1
	5	31	45	.96	1	1	1
	6	36	33	-99.00	1	1	1
	7	24	-99	-99.00	9	9	9

Table 3.1, Continued

WORKER NUMBER	DAY	PRESHFT mg EAA / g creatinine	POSTSHIFT mg EAA / g creatinine	AIRCONC mg EE / cubic meter	ACTIVITY (1=standing 3 = heavy lift.)	RESPUSE (1 = No respirator)	SKINEX (0 = none 2=signif.)
15	4	-99	9	7.38	2	1	1
	5	11	15	19.51	1	0	0
	6	-99	9	3.09	1	1	0
	7	9	-99	-99.00	9	9	9
16	3	3	2	.52	3	0	1
	4	3	8	84.34	1	0	0
	5	11	9	7.88	1	1	0
	6	13	11	-99.00	9	9	9
17	4	9	11	6.64	2	0	1
	5	5	14	2.15	2	0	1
	6	11	17	5.74	1	1	0
	7	10	-99	-99.00	9	9	9
18	3	9	-99	79.00	2	0	0
	4	31	23	1.05	1	1	0
	5	13	10	11.52	1	1	0
	6	27	12	-99.00	9	9	9
19	3	2	4	2.19	1	1	0
	4	3	1	2.08	3	0	1
	5	3	1	.00	2	0	2
	6	1	3	-99.00	9	9	9
20	4	26	26	40.12	2	0	1
	5	66	49	59.20	1	1	1
	6	41	38	9.29	1	1	1
	7	43	-99	-99.00	9	9	9
21	4	-99	20	15.83	1	1	1
	5	29	40	38.54	1	1	0
	6	35	30	-99.00	1	1	0
22	4	6	3	3.33	2	1	0
	5	5	6	4.42	1	1	0
	6	6	7	-99.00	9	9	9

Table 3.1, Continued

WORKER NUMBER	DAY	PRESHFT mg EAA / g creatinine	POSTSHIFT mg EAA / g creatinine	AIRCONC mg EE / cubic meter	ACTIVITY (1=standing 3 = heavy lift.)	RESPUSE (1 = No respirator)	SKINEX (0 = none 2=signif.)
23	3	12	14	8.19	1	1	0
	4	16	10	3.13	2	1	1
	5	16	10	7.29	1	1	0
	6	16	8	-99.00	9	9	9
24	4	1	1	4.11	1	1	1
	5	2	5	2.17	1	1	0
	6	5	2	.99	1	1	0
	7	1	-99	-99.00	9	9	9
25	3	-99	6	.92	3	1	1
	4	6	5	1.05	1	1	0
	5	7	6	6.85	1	1	1
	6	5	10	-99.00	9	9	9
26	4	6	8	3.08	2	1	1
	5	11	16	6.27	1	1	0
	6	10	16	9.48	1	1	0
	7	13	-99	-99.00	9	9	9
27	3	5	16	7.45	3	1	1
	4	-99	5	2.17	1	1	0
	5	10	-99	-99.00	9	9	9
28	3	1	1	2.60	1	1	0
	4	2	5	3.21	2	0	2
	5	1	1	3.91	2	0	2
	6	1	1	-99.00	9	9	9
29	3	1	3	11.64	1	1	0
	4	6	8	3.33	2	1	1
	5	2	5	1.31	2	1	0
	6	3	4	-99.00	9	9	9

Table 3.1, Continued

WORKER NUMBER	DAY	PRESHFT mg EAA / g creatinine	POSTSHIFT mg EAA / g creatinine	AIRCONC mg EE / cubic meter	ACTIVITY (1=standing 3 = heavy lift.)	RESPUSE (1 = No respirator)	SKINEX (0 = none 2=signif.)
30	3	-99	4	8.95	1	1	0
	4	1	4	7.64	2	0	0
	5	5	3	4.08	1	1	0
	6	-99	6	-99.00	9	9	9
31	4	57	47	.23	2	1	1
	5	78	42	1.00	2	1	1
	6	54	-99	.60	1	1	0
	7	39	-99	-99.00	9	9	9
32	3	26	16	7.17	1	1	0
	4	35	10	3.02	2	0	2
	5	27	24	5.71	2	0	0
	6	26	20	-99.00	9	9	9
33	4	18	14	.23	2	1	0
	5	25	16	10.96	1	1	0
	6	20	13	3.60	1	1	0
34	3	4	13	3.20	1	1	0
	4	2	13	2.11	2	1	1
	5	4	6	4.00	1	1	1
	6	2	6	-99.00	9	9	9
35	3	6	5	2.28	1	1	0
	4	5	10	48.61	2	0	0
	5	12	15	2.67	1	0	0
	6	10	-99	-99.00	9	9	9
36	3	2	3	9.09	1	1	0
	4	2	2	5.04	1	1	0
	5	3	5	11.13	2	1	1

- o The "not detected" data points resulted when the EAA concentrations were too small to be detected by the gas chromatography column. Depending on the column used for the sample, the limit of detection (LOD) was either 3 or 4 mcg/ml. We halved these numbers, divided by the creatinine concentration, and rounded to the nearest whole number.

- o The "range" data points (i.e. "less than 5") resulted when the sample had an amount of EAA that was detected, but was below the GC columns' level of quantification (LOQ). In this case, we averaged the LOD and LOQ (7 and 10 mcg/ml), getting 5 or 7 mcg/ml, then proceeded as above. Similarly in the case of the air data, where results were express as "less than x", the value 0.5x was entered into the data base after rounding to the nearest .1 (i.e. "less than 3.1" became 1.6).

With these transformations, the data are shown in Table 3.1.* "PRESHIFT" and "POSTSHIFT" refer to urinary concentrations of EAA/g creatinine. "AIRCONC" reflects an 8-hour Time Weighted Average air measurement using a personal sampler. For the "ACTIVITY" ratings, "1" reflects mostly standing, "2" indicates moderate climbing over objects, bending, and stretching, while "3" indicates heaving lifting and carrying. According to K. McManus it might be reaonable to assign the "2" rating an alveolar ventilation rate about 1.5X that prevailing for activity level "1"; and the "3" rating might correspond to approximately a doubling of respiratory rate over "1". The skin exposure ratings (SKINEX) were done by visual examination of the hands and forearms at the end of the shift. "Some" dermal exposure (rating of "1") corresponded to roughly 10-50% of the hand area covered by paint spots.

* The data were stored and analysed on the MIT IBM mainframe as a FOCUS (Information Builders, 1983) database.

3.2 Methodology for Inferring Ethoxyethanol Absorption From the Urinary Data and the Alternative Models

The model results presented in Table 2.9 (p. 36 above) show the rates of EAA excretion expected for the different models at various times after a single 8-hour exposure to 20 mg/m^3 EE (with total absorption of 1.213×10^{-3} moles EE). Larger and smaller air concentrations or alveolar ventilation rates would be expected to produce proportionately larger or smaller absorption and EAA excretion at every time point.*

There are two steps to using the urinary excretion data to calculate EE absorption over a workday:

(1) Based on the "preshift" EAA excretion rate, calculate the amount of EAA excretion that would be expected at the "postshift" collection time, and at the next day's preshift collection time in the absence of any further exposure. These "carryover" EAA excretion rates are then subtracted from the EAA excretion observed at the two collection times after the day's exposure.

(2) Multiply the remaining EAA excretion (not explained by simple continued excretion from the stores of EAA from previous days) by the appropriate constant factor to convert to units of moles EE absorbed during the workday.

To derive the appropriate preshift-to-postshift multipliers for the first step, we simply need to observe the ratio of the day 2 postshift EAA excretion rates to the day 2 preshift excretion rates. Similarly, the preshift-to-next-day's-preshift multipliers are calculated as the ratio of the day 3 preshift to the day 2 preshift:

* There would be some differences in the pattern of EAA excretion if the EE exposure were not (as implicitly assumed) uniform over the 8 hour period. This would particularly affect the EAA excretion rate for the first day's post-shift urine collection.

Comparison	Best Estimate Simplest Model	Alternative Simplest Model	Less Simple Model	70-Hr Model
Post/Pre	12.39/14.79 =.838	14.64/18.08 =.810	10.55/12.41 =.850	12.13/13.18 =.920
Nextpre/Pre	8.68/14.79 =.587	9.6/18.08 =.531	7.54/12.41 =.608	10.39/13.18 =.788

Deriving the second factor requires an assumption about when exactly the urine collected at the pre- and post-shift time points was delivered into the bladder. The data listed in Table 2.9 are the instantaneous rates of EAA excretion at particular time points.* However, the sample delivered represents a weighted average of the kidneys' output since the last time the worker urinated. For this purpose we assumed that the urine collections represented an average model excretion rate over the previous two hours.** Given this, the multiplicative conversion factors (moles EAA absorbed/"excess" mg EAA/g creatinine in urine) for the second step are derived from the each model's day 1 post-shift and day 2 preshift excretion rates, assuming an average of 1.7 g/day of creatinine excretion (ICRP Reference Man, 1975, p. 355). For example, for the postshift measurement for the "Best-Estimate Simplest" model:

$$\text{moles EAA absorbed} = \text{"excess" mg EAA/g creatininine} * \frac{1.213 \times 10^{-3} \text{ moles EAA absorbed} * 1.7 \text{ g creatinine/day} * 1000 \text{ ugEAA/mg}}{(16.79 \text{ ug EAA/min}) * (1440 \text{ min/day})}$$

$$= 8.53 \times 10^{-5}$$

The corresponding conversion factors for all eight situations are:

---

* The times listed for the original urinary excretion data of Groseneken et al. (1986b) appear to reflect the midpoints between the adjacent times when urine was collected. Therefore we have been fitting our model to what implicitly are the ongoing rates of delivery of EAA to the bladder.

** These two-hour average EAA excretion rates for the various models are:

Time	Best Estimate Simplest Model	Alternative Simplest Model	Less Simple Model	70-Hr Model
Day 1 Postshift	16.80	20.33	13.55	12.39
Day 2 Preshift	15.18	18.57	12.75	13.33

Comparison	Best Estimate Simplest Model	Alternative Simplest Model	Less Simple Model	70-Hr Model
Post/Pre	8.53×10^{-5}	7.04×10^{-5}	10.57×10^{-5}	11.56×10^{-5}
Nextpre/Pre	9.43×10^{-5}	7.71×10^{-5}	11.23×10^{-5}	12.90×10^{-5}

3.3 Comparison of Model Performance Using Criterion#1: Similarity of Absorption Calculated From Preshift/Postshift and Preshift/Next-Day-Preshift Data

3.3.1 Analysis Without Correction for Diurnal Cycles of Creatinine Excretion

An obvious first step in assessing the models' performance is to ask whether the two independent calculations that are possible for a single day's exposure under each model give reasonably comparable results. Table 3.2 shows the sum of total calculated EE absorption for all worker-days where preshift, postshift, and next-day's-preshift urinary EAA excretion data were available.

As can be seen in Table 3.2, for all of the model variants the comparisons are miserable--the total absorption of the workers (on the 77 days with complete information) calculated from the preshift/postshift data is less than a third of the total absorption calculated from the preshift/next-day's preshift comparison. These data are, however, based on what turns out to be an assumption that is not quite correct--that urinary creatinine is an appropriate normalizing measure which is comparable between pre-shift and post-shift time points. The next section shows how we have managed to do better by using available data on diurnal changes in creatinine excretion.

Table 3.2
Total Absorption Evaluated by the Different Models Without Correction for Diurnal Changes in Creatinine Excretion

Moles of EE Absorbed by the Entire Population, Based on 77 Person-Days of Observation, Where Preshift, Postshift, and Next-Day's Preshift Urinary EAA Levels Were All Available

Comparison	Best Estimate Simplest Model	Alternative Simplest Model	Less Simple Model	70-Hr Model
Post/Pre	.01472	.01433	.01680	.00944
Nextpre/Pre	.04750	.04362	.05403	.03030
Ratio of the two estimates of total absorption	.310	.328	.311	.312

3.3.2 Analysis With Correction for Diurnal Cycles of Creatinine Excretion

As it happens, there is considerable evidence that there are diurnal cycles in the urinary excretion of creatinine, and a host of other renal functions. Some observations of Lakatua et al. (1982) are shown in Figure 3.1. Creatinine excretion is relatively low in the early morning hours just after waking (when the "preshift" urine is accumulating) and relatively high in evening hours.

Lakatua et al. (1982) fit a cosine function to their data. Numerical evaluation of this function (Table 3.3) indicates that the rate of urinary creatinine excretion from 7:00 - 9:00 A.M. averages about 85.6% of the overall mean*, whereas from 3:00 - 5:00 P. M. creatinine excretion averages about 103.4% of the overall mean. This requires us to make two different kinds of corrections to the calculations described in Section 3.2:

(1) The predicted postshift urine concentration in mg EAA/g creatinine should be multiplied by 72.07/87.03 = .8281. As the rate of creatinine excretion rises during the day from the preshift to the postshift urine collection, a constant rate of EAA excretion in mg/hour will translate into a lower rate of excretion when expressed in mg/g creatinine. The multipliers previously given at the top of page 45 for predicting postshift urine concentrations from preshift readings in the absence of further exposure therefore become:

Comparison	Best Estimate Simplest Model	Alternative Simplest Model	Less Simple Model	70-Hr Model
Post/Pre	.6937	.6705	.704	.7621

(2) In the formulas for the final calculation of daily absorption, the previously assumed daily rate of creatinine excretion (1.7 g/day) should be multiplied by the .8559 and 1.034 factors for the preshift and postshift collections, respectively. The conversion factors for translating the excess of observed over predicted urinary mg/g creatinine excretion into moles of EE absorbed (previously given at the top of page 46) therefore become:

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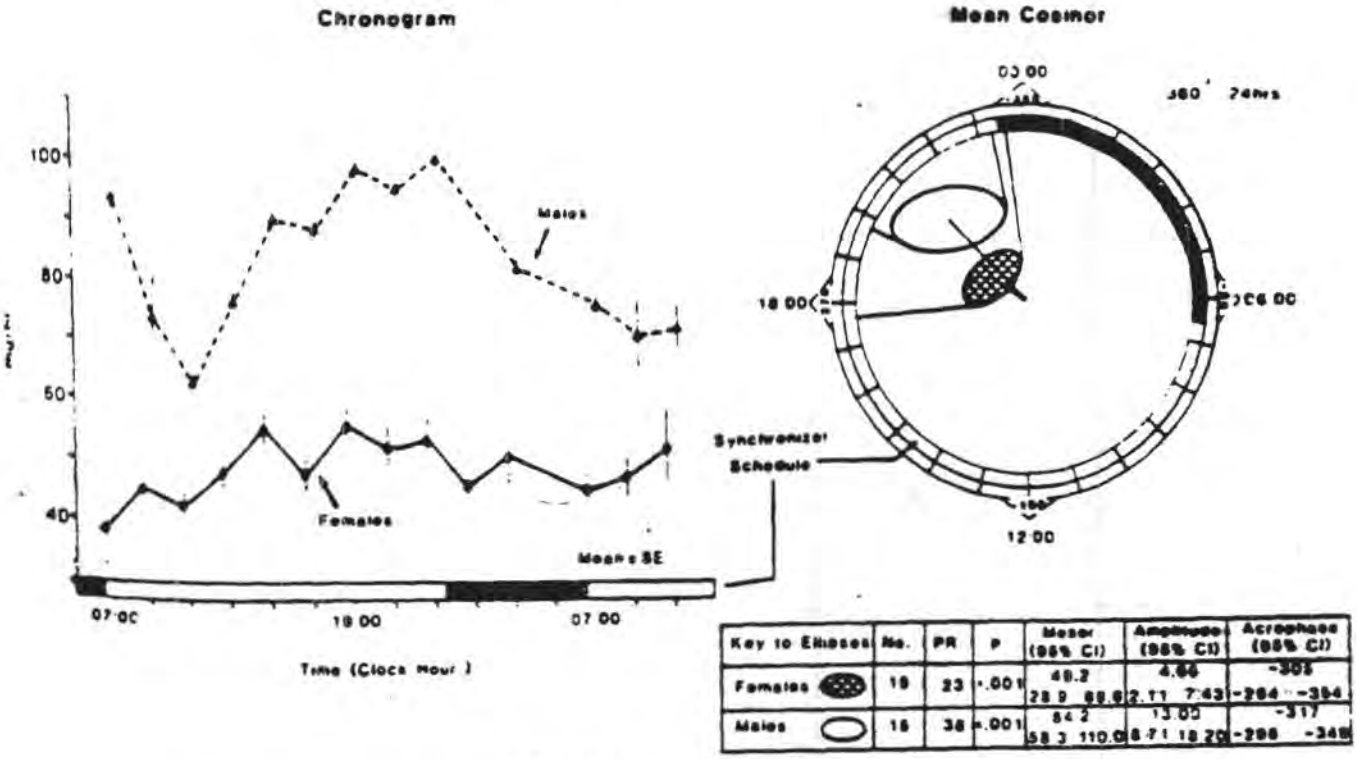
* 72.07 /84.2 = .8559

Figure 3.1
Lakatua et al., 1982--Circadian Rhythm in Urinary Creatinine Excretion



Key to Ellipses	No.	PR	P	Mesor (95% CI)	Amplitude (95% CI)	Acrophase (95% CI)
Females	19	23	<.001	48.2 28.9 67.6	4.66 2.11 7.43	-305 -284 -354
Males	15	38	<.001	84.2 58.3 110.0	13.05 8.71 18.20	-317 -298 -348

*19 Females and 15 Males

Chronogram or display of means and standard errors as a function of clockhour (left). Statistical quatification of the same data by mean cosinor (right, where the mesor is the rhythm adjustated overall mean and the amplitude is half the total predictable change all expressed in actual measured units. The acrophase is the crest time of the cosine curve, best fitting to the data, expressed in negative degrees, with 360⁰ equal to 24 hours (15⁰ = 1 hour) and -360⁰ is equal to local midnight (00:00).

Source: Lakatua et al., (1982)

TABLE 3.3
Numerical Evaluation of the Lakatua et al. (1982) Cosine Fuction for Male Subjects

MG/HR CREATININE EXCRETION = 84.2 + 13.00 COS θ
Where θ is the clock degrees plus 43°

Clock Time	Clock Degrees	θ	Cos θ	Mg/hr Creatinine Excret.	
12:00 midnite	0	43	.731	93.7	
1:00 am	15	58	.530	91.1	
2:00	30	73	.292	88.0	
3:00	45	88	.035	84.6	
4:00	60	103	-.225	81.3	
5:00	75	118	-.469	78.1	
6:00	90	133	-.682	75.3	
7:00	105	148	-.848	73.2	7:00 - 9:00 A.M.
8:00	120	163	-.956	71.8	Average is 72.07 mg
9:00	135	178	-.999	71.2	Creatinine per hour
10:00	150	193	-.974	71.5	
11:00	165	208	-.883	72.7	
12:00 noon	180	223	-.731	74.7	
1:00 pm	195	238	-.530	77.3	
2:00	210	253	-.292	80.4	
3:00	225	268	-.035	83.7	3:00 - 5:00 P.M.
4:00	240	283	.225	87.1	Average is 87.03 mg
5:00	255	298	.469	90.3	Creatinine per hour
6:00	270	313	.682	93.1	
7:00	285	328	.848	95.2	
8:00	300	343	.956	96.6	
9:00	315	358	.999	97.2	
10:00	330	13	.974	96.9	
11:00	345	28	.883	95.7	

Comparison	Best Estimate Simplest Model	Alternative Simplest Model	Less Simple Model	70-Hr Model
Post/Pre	8.82×10^{-5}	7.28×10^{-5}	10.93×10^{-5}	11.95×10^{-5}
Nextpre/Pre	8.07×10^{-5}	6.60×10^{-5}	9.61×10^{-5}	11.04×10^{-5}

With these corrections for diurnal changes in creatinine excretion, Table 3.4 shows the aggregate moles of EE absorbed for the 77 worker-days with complete information, as evaluated by the four models. Clearly, there is now much better correspondence for all the models between the two methods for estimating each day's absorption. By this criterion, the 70-hour model comes closest to reconciling the data, followed by the "less simple" model.*

---

* We should note that for the calculations in Table 3.4, we have assumed that the same diurnal corrections should be applied to wokers employed on the day shift as on the night shift. (We reasoned that night-shift workers would tend to adapt their sleep patterns and other diurnal rhythms so that, like day-shift workers, they would awaken a couple of hours before they were due at work.) If we segregate the 37 day-shift worker-days in Table 3.4 from the 39 night-shift worker-days, we find:

Comparison	Best Estimate Simplest Model	Alternative Simplest Model	Less Simple Model	70-Hr Model
Day-Shift Workers:				
Post/Pre	.02156	.01913	.02585	.02286
Nextpre/Pre	.02774	.02558	.03150	.01718
Ratio of the two estimates of total absorption	.777	.748	.821	1.331
Night-Shift Workers:				
Post/Pre	.00764	.00685	.00910	.00772
Nextpre/Pre	.01291	.01291	.01474	.00875
Ratio of the two estimates of total absorption	.592	.531	.617	.882

It can be seen that restricting the analysis to the day-shift worker-days produces results that are somewhat more favorable for the first three models, and adverse to the 70-hour model. Overall, however, the differences are not large enough to invalidate use of the information for the night-shift worker-days.

Table 3.4
Total Absorption Evaluated by the Different Models With Correction for Diurnal Changes in Creatinine Excretion

Moles of EE Absorbed by the Entire Population, Based on 77 Person-Days of Observation, Where Preshift, Postshift, and Next-Day's Preshift Urinary EAA Levels Were All Available

Comparison	Best Estimate Simplest Model	Alternative Simplest Model	Less Simple Model	70-Hr Model
Post/Pre	.02919	.02598	.03496	.03058
Nextpre/Pre	.04065	.03733	.04624	.02594
Ratio of the two estimates of total absorption	.718	.696	.756	1.179

3.4 Comparison of Model Performance Using Criterion#2: Strength of Association Between Air Concentration Measurements and Total Calculated Absorption

A second criterion we can use to compare the performance of the models is the correlation of the moles of EE estimated to be absorbed with the measured air concentration of EE. Other things being equal, models that suggest a relatively strong correlation (and one that is consistent for pre/post and pre/next-pre calculation methods) are more likely to be closer to the truth than models for which the correlation is weaker and/or inconsistent. For this purpose we performed parallel multiple regression analyses between each of the models' calculated daily absorption amounts and two variables representing exposure:

> "ADJAIR"--The air concentration adjusted for activity level (for days on which the activity level was rated as "2", the air concentration was multiplied by 1.5; for days in whcih the activity level was rated as "3", the air concentration was multiplied by 2.) As we shall see in Section 4.1 below, this adjusted air concentration shows a better correlation with measures of absorption than an unadjusted air concentration.
>
> "ANYSKIN"--This is a "dummy" variable that is set equal to 1 if there was either "some" or "much" skin exposure (SKINEX = 1 or 2 in Table 3.1).*

The results of these regression analyses are presented in Table 3.5. In this table, "N" is the number of worker-days of observation with analyzable data. The "R^2" numbers provide an overall index of the proportion of the variance of the dependent variable (moles absorbed as estimated by the model

---

* We tried a number of multple regression analyses distinguishing between the 2 and 3 ratings of skin exposure, and found that all of the evidence for a positive influence of skin exposure on EE absoption was attributed to the "2" or "someseskin" rating. As it happened, there were only 7 qualifying worker-days with the "3" rating (vs. 31 with the "2" rating) and this small amount of data was evidently insufficient to reveal a signigicant effect. In the light of this result, for purposes of our analysis there is thus no advantage in preserving the "2" vs "3" distinction.

Table 3.5

Regression Analyses Using as the Dependent Variable, the "Moles Absorbed" As Calculated by the Different Models for Individual Workers on Specific Days

A. Observations on Days Where No Respirator Was Worn

Comparison Used For Calculating Moles Absorbed	N	R^2	T_{adjair}	$T_{anyskin}$	Intercept (x10-4)	AdjAir Coeff. ($x10^{-5}$)	Skin Coeff. ($x10^{-4}$)
BEST ESTIMATE SIMPLEST MODEL							
Post/Pre	63	.313	4.82	1.70	0.90	2.55	2.38
Nextpre/Pre	62	.191	3.64	0.53	3.03	2.43	0.95
Ave, Both Above	57	.308	4.75	1.08	1.96	2.49	1.56
ALTERNATIVE SIMPLEST MODEL							
Post/Pre	63	.323	4.91	1.77	0.92	2.16	2.06
Nextpre/Pre	62	.194	3.66	0.62	2.90	2.10	0.97
Ave, Both Above	57	.314	4.78	1.17	1.88	2.14	1.44
LESS SIMPLE MODEL							
Post/Pre	63	.308	4.77	1.66	1.01	3.12	2.88
Nextpre/Pre	62	.189	3.63	0.49	3.39	2.83	1.03
Ave, Both Above	57	.307	4.74	1.05	2.20	2.98	1.82
SEVENTY HOUR MODEL							
Post/Pre	63	.274	4.42	1.44	0.38	3.19	2.75
Nextpre/Pre	62	.145	3.15	0.07	1.39	2.18	0.13
Ave, Both Above	57	.260	4.27	0.70	0.97	2.67	1.21

Table 3.5, Continued

Regression Analyses Using as the Dependent Variable, the "Moles Absorbed" As Calculated by the Different Models for Individual Workers on Specific Days

B. Observations on Days Where A Respirator Was Worn

Comparison Used For Calculating Moles Absorbed	N	R^2	T_{adjair}	$T_{anyskin}$	Intercept ($\times 10^{-4}$)	AdjAir Coeff. ($\times 10^{-5}$)	Skin Coeff. ($\times 10^{-4}$)
BEST ESTIMATE SIMPLEST MODEL							
Post/Pre	20	.180	1.31	-0.98	2.70	0.56	-2.04
Nextpre/Pre	20	.444	3.67	1.04	-0.89	2.04	3.86
Ave, Both Above	19	.368	3.03	0.46	0.62	1.41	1.08
ALTERNATIVE SIMPLEST MODEL							
Post/Pre	20	.186	1.36	-0.98	2.34	0.47	-1.66
Nextpre/Pre	20	.430	3.57	1.03	-0.51	1.68	3.23
Ave, Both Above	19	.362	2.99	0.47	0.68	1.17	0.94
LESS SIMPLE MODEL							
Post/Pre	20	.177	1.30	-0.98	3.28	0.79	-2.55
Nextpre/Pre	20	.449	3.70	1.04	-1.18	2.42	4.55
Ave, Both Above	19	.369	3.02	0.43	0.71	1.69	1.21
SEVENTY HOUR MODEL							
Post/Pre	20	.162	1.18	-0.98	3.14	0.71	-2.91
Nextpre/Pre	20	.488	4.00	1.06	-2.12	2.25	3.99
Ave, Both Above	19	.363	2.96	0.28	0.18	1.60	0.76

in question) that is related by the regression equation to variation in the two independent variables (ADJAIR and ANYSKIN). Higher values for R^2 indicate stronger correlations between the dependent and independent variables. "Tadjair" and "Tanyskin" are the ratios of the ADJAIR and ANYSKIN regression coefficients to their respective standard errors (T values greater than 1.64 indicate that the coefficient is statistically significantly different from zero at $P < .05$ in a one-tailed test*). The final three columns give the absolute values of the regression coefficients themselves. For example, the regression equation for the first line in Table 3.5A is

$$\text{Moles EE absorbed/worker (post/pre comparison)} = .90 \times 10^{-4} + 2.44 \times 10^{-5}\ \text{ADJAIR} + 2.38 \times 10^{-4}\ \text{ANYSKIN}$$

Where ADJAIR is in mg EE/m^3 (multiplied by the activity level) and ANYSKIN is 1 or 0 as discussed earlier. For each model, data are given using as dependent variables (1) the moles absorbed as calculated from a comparison of postshift urine concentrations with preshift, (2) moles absorbed calculated from a comparison of the preshift EAA concentration with the next day's preshift, and (3) the average of (1) and (2) for each worker-day where urinary EAA excretion data were available for all three relevant readings, and air exposure data and skin ratings were also available for the day when exposure took place.

It can be seen in Table 3.5A (without respirators) that all of the models show strong and highly statistically significant relationships between adjusted air concentrations and the estimates of worker absorption. Moreover, the ADJAIR coefficients as estimated by the models for the post/pre and nextpre/pre comparisons are generally consistent with each other. The seventy-hour model performs a little less well in both of these respects than the other models, but the differences are not dramatic.

As might be expected, the data for the smaller number of worker-days where respirators were used (Table 3.5B) show somewhat weaker and less consistent relationships between air exposure and absorbed ethoxyethanol, but the relationships are still significant enough to provide meaningful

---

* A one-tailed test is appropriate here because we have a strong theoretical expectation that there should be a positive correlation between measures of exposure and ethoxyethanol absorption.

information. The ratio of the ADJAIR regression coefficients with and without respirators can give us some indication of the factor by which respirator use appears to reduce exposure via the air route:

Comparison	Best Estimate Simplest Model	Alternative Simplest Model	Less Simple Model	70-Hr Model
Average of post/pre and nextpre/pre	.57	.55	.66	.60

The overall protection factor of a little less than two-fold is at the lower end of the range of results that have been observed in previous studies of the field efficacy of respirator use.*

Curiously enough, if we do a similar calculation to assess the apparent effect of respirator use on absorption associated with visible skin exposure we find:

Comparison	Best Estimate Simplest Model	Alternative Simplest Model	Less Simple Model	70-Hr Model
Average of post/pre and nextpre/pre	.69	.65	.66	.63

The implication is that respirator use may provide nearly as much protection from our measure of "skin" absorption than from exposure associated with the air route. One possible explanation for this is that the workers who showed visible contamination of their hands and arms may also have spattered some paint on their faces, but that the facial contamination was reduced for those who wore respirators.

In the light of the effect of respirators in reducing absorption via the air route, in order to be able to use all of the data in subsequent analyses, we define a second adjusted air concentration (ADJ2AIR) in which the value of

---

* Studies with cadmium particles have indicated an average protection factor of about 4 (Smith, et al., 1980). For coal dust, average protection factors for different groups of workers ranged between 3 and 9 (Harris et al., 1974). Calculations we did based on information on blood lead air lead relationships and measured average air and blood lead concentrations in primary lead smelting, secondary lead smelting, and battery manufacute suggested average protection factors of 2-12 (Goble et al., 1983).

ADJAIR is multiplied by 0.6 when respirators are used. Multiple regression results using this independent variable are shown in Table 3.6.

3.5 Conclusions on Model Performance

Overall, the various comparisons we have made produced no clear "winners" or "losers" among our different model variants. The "70-hour" model on the whole performed somewhat more poorly than the others in correlating calculated exposure with air concentrations of EE (with or without adjustments for activity and respirator use). However in our judgment, the performance was not so drastically worse as to warrant excluding it from further consideration. Because the 70-hour model results in a greater conversion of EE to activated ethoxyacetaldyde and EAA metabolites, and also for a greater persistence of EAA in the body, it may serve in later work to provide a plausible high estimate of internal body exposure to testicular toxins.

If we had to pick a single "best" model based on all the data, on balance we would choose the "less simple" model. This is because:

- It incorporates plausible features used in full physiologically-based pharmacokinetic models (blood flows and organ sizes) and is therefore inherently somewhat preferable.

- It fits no worse to the primary Groseneken et al. (1986b) urinary EAA excretion data than the "best estimate-simplest" model, and somewhat better than the "alternative-simplest" model using the logarithmic least-squares criterion.

- It shows a later peak of urinary EAA excretion than the two "simplest" models, which is more in keeping with the peak times observed by Groseneken et al. (1986b and 1987b).

- It perfoms slightly better than the two "simplest" models in reconciling the moles EE absorbed as calculated by the two methods explored in Section 3.3 (comparing post-shift with preshift urinary EAA vs. comparing next-day's preshift urinary EAA with preshift EAA.)

Table 3.6
Regression Analyses Using "ADJ2AIR" (60% Correction of Air Levels for Use of Respirators)

Comparison Used For Calculating Moles Absorbed	N	R^2	Tadj2air	Tanyskin	Intercept (x10-4)	Adj2Air Coeff. (x10-5)	Skin Coeff. (x10-4)
BEST ESTIMATE SIMPLEST MODEL							
Ave, Both Post/Pre and Nextpre/Pre	76	.313	5.71	1.10	1.671	2.45	1.33
ALTERNATIVE SIMPLEST MODEL							
Ave, Both Post/Pre and Nextpre/Pre	76	.313	5.70	1.18	1.622	2.09	1.22
LESS SIMPLE MODEL							
Ave, Both Post/Pre and Nextpre/Pre	76	.313	5.71	1.06	1.876	2.93	1.54
SEVENTY HOUR MODEL							
Ave, Both Post/Pre and Nextpre/Pre	76	.279	5.29	.715	.799	2.67	1.02

4. INFERENCES FROM THE MODELS AND THE SHIPYARD DATA

4.1 The Effects of Activity Levels on EE Absorption Via Air and Dermal Routes

Table 4.1 shows regression analyses analogous to those in Table 3.6, separated by activity level. There were 44 qualifying worker-days at activity level 1, 30 at activity level 2, and 2 at activity level 3. It can be seen that the ADJ2AIR regression coefficients are much larger for the "2" and "3" group than for the "1" group. This suggests that at higher activity levels the workers are absorbing even more EE than we provided for with the 1.5X and 2X assumptions for increased alveolar ventilation built into the definition of the ADJAIR and ADJ2AIR variables. It can also be seen that the modest suggested effect of the "ANYSKIN" variable is stronger for the group rated at higher activity levels.

We are reluctant to increase our assumption about relative ventilation rates at the different activity levels as much as would be required to accommodate these observations. It seems implausible that the "moderate" activity people could be taking in as much as 4-5 times more air than the "sedate" activity people. Pending confirmation, we simply draw the conclusions that adjustment for activity levels seems to be helpful in achieving overall fits of the models to the data, and that our "Adjusted" air level calculations do not seem to be overstating the effect of activity on EE absorption (they may in fact be somewhat understating it).

4.2 Relative Importance of Inhalation vs Dermal Routes of Exposure

Given the total absorption of EE as calculated from our different models, what can we say about inhalation vs. dermal absorption in the group of shipyard painters we have been studying? Based on the Groseneken et al. (1986a) data and an assumption of 11.4 l/minute alveolar ventilation

Table 4.1
Regression Analyses For Worker-Days At Different Activity Levels

Comparison Used For Calculating Moles Absorbed	N	R^2	$T_{adj2air}$	$T_{anyskin}$	Intercept (x10-4)	Adj2Air Coeff. ($x10^{-5}$)	Skin Coeff. ($x10^{-4}$)
44 Worker-Days At a Relatively Low Activity Level (1="Sedate"):							
			BEST ESTIMATE SIMPLEST MODEL				
Ave, Both Post/Pre and Nextpre/Pre	44	.147	2.56	-.54	3.095	1.17	-.73
			ALTERNATIVE SIMPLEST MODEL				
Ave, Both Post/Pre and Nextpre/Pre	44	.150	2.63	-.39	2.805	1.04	-.47
			LESS SIMPLE MODEL				
Ave, Both Post/Pre and Nextpre/Pre	44	.144	2.51	-.57	3.604	1.36	-.93
			SEVENTY HOUR MODEL				
Ave, Both Post/Pre and Nextpre/Pre	44	.106	1.93	-.91	2.530	1.00	-1.41
32 Worker-Days At Higher Activity Levels ("2" or "3"):							
			BEST ESTIMATE SIMPLEST MODEL				
Ave, Both Post/Pre and Nextpre/Pre	32	.550	5.84	1.30	-.499	4.09	3.01
			ALTERNATIVE SIMPLEST MODEL				
Ave, Both Post/Pre and Nextpre/Pre	32	.541	5.71	1.36	-.244	3.41	2.68
			LESS SIMPLE MODEL				
Ave, Both Post/Pre and Nextpre/Pre	32	.556	5.91	1.28	-.729	4.93	3.53
			SEVENTY HOUR MODEL				
Ave, Both Post/Pre and Nextpre/Pre	76	.552	5.91	.994	-1.575	4.80	2.67

during light work (Brugnone et al., 1980), we implicitly built into all of our models a relationship between moles of EE absorbed and 8-hour TWA exposure in mg/m^3 of:

$$\frac{1.211 \times 10^{-3} \text{ Moles Absorbed}}{20 \text{ mg EE}/m^3 \text{ (8 hour TWA)}} = 6.06 \times 10^{-5} \text{ moles abs}/(mg/m^3)$$

Comparing this with the ADJ2AIR coefficients in Table 3.6, it can be seen that the actual regression relationships derived from the data are weaker than this by 2-3 fold. The difference probably results in part from inaccuracies in the measured levels of the independent variables relative to real exposure.*

We can use the theoretically-defined 6.06×10^{-5} coefficient to evaluate how much of the total absorption indicated by the models for the worker-days studied could have been accounted for by direct air inhalation, and how much therefore must remain to be accounted for by dermal absorption. The results of this calculation for the four model variants are shown in the second line of numbers in Table 4.2. It can be seen that using this assumption, for all of the models, all of the absorbed EE can be accounted for (and then some) by inhalation, and we are not absolutely compelled by the data to attribute any of the absorption to the dermal route.

If we do use the low-biased air regression coefficients in the same kind of calculation, we can arrive at a more conservative estimate of the EE absorption attributable to direct air inhaltion (third line of numbers in Table 4.2). It can be seen that in all cases on the order of half to two thirds of the total moles absorbed (given in the first line) must be attributed to the air route.

Our best estimate of the relative importance of the air and dermal routes comes from comparing the conservative regression-calculated average air absorption in the third line, with a similar conservative regression-calculated figure for the average dermal absorption in the last line of Table 4.2. It can be seen that in all cases, the data suggest that the air route accounts for 3-5 times as much of the estimated EE absorption as the dermal route.

---

* In regression analyses, inaccuracies in the measurement of the dependent variable do not bias the regression equation, but inaccuracies in measuring the independent variables bias the result to larger values of the intercept and smaller values of the coefficients of the independent variables. The positive intercepts in Table 3.6 (when the actual values should be zero) provide other evidence of this kind of bias.

Table 4.2

Moles of EE Absorption Due to Inhalation Vs Other Routes of Exposure in the Shipyard Painter Group

(Based on 76 Worker-Days with Complete Urinary Excretion and Air Exposure Data--All Data Are Moles Absorbed X 10^{-4})

	Best Estimate Simplest Model	Alternative Simplest Model	Less Simple Model	70-Hr Model
Total Moles Absorbed Per Worker-Day	4.53	4.10	5.27	3.70
Moles Absobed Potentially Attributable to Direct Air Inhalation*	5.43	5.43	5.43	5.43
Minimum Moles Absorbed Attributable to Direct Air Inhalation **	2.19	1.87	2.62	2.39
Moles EE Absorption Absorption Remaining to be Accounted for By Dermal Absorption	-.90 to 2.34	-1.33 to 2.23	-.16 to 2.64	-1.73 to 1.31
Estimate of Dermal Absorption from ANYSKIN Regression Coefficient***	.67	.61	.77	.51

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* This calculation uses the theoretical relationship between air inhaltion and moles EE absorbed that was built into the models (assuming complete absorption of EE from alveolar air and an alveolar ventilation rate during light work of 11.4 liters/minute). The average adjusted air exposure level (ADJ2AIR) for the 76 worker-days was 8.96 mg/m^3. Assuming 6.06 X 10^{-5} moles abs/(mg/m^3), this leads to an expectation of an average of 5.43 X 10^{-4} moles absorbed EE potentially attributable to direct air inhalation.

** Calculated using each model's ADJ2AIR regression coefficient and the average ADJ2AIR value of 8.96 mg/m^3. As discussed in the text, this is a minimum estimate because uncertainties in the measurement of air concentrations tend to bias the regression coefficient to lower values.

*** This conservative value is calculated by multiplying the dermal absorption regression coefficient by the average value of ANYSKIN for the 76 worker-days--.5. It is a conservative estimate for the same reason as the analogous set of estimates for absorption by the inhaltion route, and because the qualitative ascertainment of dermal exposure by examining the hands and arms for paint spots is clearly more uncertain, quantitatively, than the measurement of air concentrations. On the other hand, it should be noted that for none of the models was the ANYSKIN statistically significantly different than 0 at the 5% level.

4.3 The Possible Effect of Ambient Temparature on EE Absorption

In doing some sensitivity analyses with our data, one other result appeared for which we do not have a ready explanation. For 12 of the 76 worker-days with complete information covered in Tables 3.6, 4.1 and 4.2, the industrial hygienists recorded relatively low temperatures (in the range of 35-45 ^{o}F.--in contrast to the 70-90 ^{o}F recorded in other cases). The low temperature cases evidently correspond to work outdoors during the December period of the study. Because the low ambient temperatures may have affected the amount of skin area left uncovered and other work practices, we decided to do a set of analyses excluding the 12 low-temperature worker days from the data set (Tables 4.3 and 4.4).

Comparing the regression results in Table 4.3 with those for the full data set in Table 3.6 it can be seen that excluding the low temperature worker-days has improved the correlations as measured by the R values, and the indicated statistical significance of the ADJ2AIR coefficients. If anything, however, the statistical correlation with the ANYSKIN variable has been weakened.

In keeping with this, when we compare the analysis of air-vs-dermal absorption in Table 4.4 with that originally presented in Table 4.2, we now find that our best estimate of the contribution of the dermal route to overall absorption has declined to only about an eighth of the contribution of the direct air route (the third vs. the fifth line of numbers).

4.4 Recommendations for the Use of Urinary Metabolite Measurements to Infer Overall Exposure in Working Populations

The relatively long half-life of EAA in the body (26-70 hours for our various models) means that the use of urinary EAA concentrations to judge ongoing worker exposure is more complex than it ordinarily would be.

Table 4.3
Regression Analyses Excluding 12 Worker-Days at Low Temperatures

Comparison Used For Calculating Moles Absorbed	N	R^2	$T_{adj2air}$	$T_{anyskin}$	Intercept ($\times 10^{-4}$)	Adj2Air Coeff. ($\times 10^{-5}$)	Skin Coeff. ($\times 10^{-4}$)
BEST ESTIMATE SIMPLEST MODEL							
Ave, Both Post/Pre and Nextpre/Pre	64	.418	6.50	.66	1.548	2.75	.787
ALTERNATIVE SIMPLEST MODEL							
Ave, Both Post/Pre and Nextpre/Pre	64	.431	6.68	.66	1.502	2.37	.664
LESS SIMPLE MODEL							
Ave, Both Post/Pre and Nextpre/Pre	64	.412	6.42	.66	1.741	3.26	.951
SEVENTY HOUR MODEL							
Ave, Both Post/Pre and Nextpre/Pre	64	.337	5.46	.63	.752	2.81	.917

Table 4.4

Moles of EE Absorption Due to Inhalation Vs Other Routes of Exposure in the Shipyard Painter Group--Excluding Low-Temperature Data Points

(Based on 64 Worker-Days--All Data Are Moles Absorbed X 10^{-4})

	Best Estimate Simplest Model	Alternative Simplest Model	Less Simple Model	70-Hr Model
Total Moles Absorbed Per Worker-Day	4.48	4.02	5.22	3.80
Moles Absobed Potentially Attributable to Direct Air Inhalation *	5.72	5.72	5.72	5.72
Minimum Moles Absorbed Attributable to Direct Air Inhalation **	2.62	2.26	3.11	2.68
Moles EE Absorption Absorption Remaining to be Accounted for By Dermal Absorption	-1.24 to 1.86	-1.70 to 1.76	-.50 to 2.11	-1.92 to 1.12
Estimate of Dermal Absorption from ANYSKIN Regression Coefficient***	.33	.28	.40	.39

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* This calculation uses the theoretical relationship between air inhaltion and moles EE absorbed that was built into the models (assuming complete absorption of EE from alveolar air and an alveolar ventilation rate during light work of 11.4 liters/minute). The average adjusted air exposure level (ADJ2AIR) for the 76 worker-days was 9.45 mg/m^3. Assuming 6.06 X 10^{-5} moles abs/(mg/m^3), this leads to an expectation of an average of 5.43 X 10^{-4} moles absorbed EE potentially attributable to direct air inhalation.

** Calculated using each model's ADJ2AIR regression coefficient and the average ADJ2AIR value of 8.96 mg/m^3. As discussed in the text, this is a minimum estimate because uncertainties in the measurement of air concentrations tend to bias the regression coefficient to lower values.

*** This conservative value is calculated by multiplying the dermal absorption regression coefficient by the average value of ANYSKIN for the 76 worker-days--.422. It is a conservative estimate for the same reason as the analogous set of estimates for absorption by the inhaltion route, and because the qualitative ascertainment of dermal exposure by examining the hands and arms for paint spots is clearly more uncertain, quantitatively, than the measurement of air concentrations. On the other hand, it should be noted that for none of the models was the ANYSKIN statistically significantly different than 0 at the 5% level.

There is appreciable carryover of EAA from day to day,* and it can be expected that EAA excretion rates build up in the course of a work-week with constant 8-hour exposure on each day. Table 4.5 shows this day to day buildup, and the effects of expressing EAA excretion in ug/min vs mg/g creatinine, given the diurnal changes in creatinine excretion.

The data in Table 4.5 can be used to make estimates of the equivalent 8-hour TWA air exposure for workers exposed to EE and its derivatives by both air dermal routes, even if one only has a single measured value of EAA in the urine for each worker. For example if one has a pre-shift measurement of urinary EAA in mg/g creatinine taken on the third day of the workers' work-week (Wednesday), then the estimated average mg/m^3 EE exposure on the previous two days under our best-estimate ("less simple") model would be:

(urinary mg/g creatinine)*(20 mg/m3 in air)/(20.17 mg/g creatinine)
= .992 * measured urinary mg/g creatinine

Other things being equal, of course, it is better to base estimates of individual daily worker EE exposure on comparisons of urinary EAA output per g of creatinine before and after a particular workshift. To avoid possible complications from inaccuracies in our formulas for diurnal changes in urinary creatinine output (and possibly EE excretion), and to reduce the effects of different patterns of exposure during an 8-hour workshift,** [1] we recommend basing such calculations on preshift urine collections taken 24 hours apart. Given such data, the calculation can be done in two steps:

(1) Predict the second day's preshift urine concentration in the absence of any exposure during the shift in question--for our preferred "less simple" model, multiply by .608.*** Subtract the result from the observed urinary EAA concentration for the second day's preshift collection.

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* See Table 2.9 on page 36 for the pattern of excretion expected after a single day's exposure. Also see Figures 1.2 and 1.3 for the original observations of Groseneken et al. (1986b and 1987b).

** E.g. high peak exposures at the biginning or the end of a work shift, vs a more continuos pattern of exposure.

[1]

*** For the 70-hour model, the factor would be .788--see p. 45 above.

Table 4.5
Predicted Urinary Excretion Of Ethoxyacetic Acid at Various Times During Successive Daily 8-Hour Occupational Exposure to 5.65 ppm Ethoxyethanol (20 mg/m^3)

Time After Start of Exposure (min.)	"Less Simple Model" Predictions (Best Estimate Model). (ug EAA/min. excreted)	(mg EAA/g creatinine*)	"70-Hr Model Predictions (Plausible Upper Bound) (ug EAA/min. excreted)	(mg EAA/g creatinine)
Day 1 Post-shift (420 min)**	15.73	12.52	12.39	9.86
Day 2 Pre-shift (1380 min)***	12.67	12.54	13.27	13.14
Day 2 Post-shift (1860 min)	24.33	19.37	24.65	19.62
Day 3 Pre-shift (2820 min)	20.37	20.17	23.72	23.48
Day 3 Post-shift (3300 min)	30.88	24.58	34.32	27.32
Day 4 Pre-shift (4260 min)	25.04	24.79	31.96	31.64
Day 4 Post-shift (4740 min)	34.85	27.75	41.93	33.38
Day 5 Pre-shift (5700 min)	27.88	27.60	38.46	38.08
Day 5 Post-shift (6180 min)	37.27	29.67	47.93	38.16
4 Day Ave Pre-shift	21.49	21.28	26.85	26.59
5 Day Ave Post-shift	28.61	22.78	32.24	25.67

* Assuming 1.7 g per day of overall creatinine excretion, and diurnal changes in creatinine excretion as given by Lakatua et al. (1982)--See Table 3.3 on p. 50. This results in expected creatinine excretion rates of (.8559*1700 mg/day)/1440 min/day = 1.01 mg/min for the two hours preceeding a 9:00 A.M. "preshift" collection, and (1.034*1700)/1440 = 1.256 mg/min for the two hours preceeding a 5:00 P.M. "postshift" collection.

** The data given here are the expected instantaneous rates of delivery of ethoxyacetic acid to the bladder. The 420 minute point is approximately the average rate that might be seen in a urine collection after an 8 hour shift, assuming that the urine has accumulated in the bladder between the 6- and 8-hour time points after the start of the workday.

*** By the same reasoning as given for the post-shift time points, the pre-shift urine samples are assumed to represent a two-hour accumulation of urine that was delivered to the bladder on average 23 hours after the start of the previous day's workshift.

(2) Calculate the equivalent 8-hour TWA EE air level in mg/m^3 by multiplying the "excess" urinary mg EAA/g creatinine by 20 mg/m^3 /12.54 mg EAA/g creatinine = 1.59 mg/m^3 per mg EAA/g creatinine.*

It should be stressed that because of likely differences among individuals in absorption, alveolar ventilation rates,** the fraction of absorbed EE that is metabolized via ethoxyacetaldehyde to EAA, EAA excretion rates, and other factors,*** the "equivalent air absorption" estimates calculated in this way may often differ appreciably from measured air exposure levels. We believe, however, that for many of these sources of variability**** the "equivalent air absorption" estimates may better reflect the toxicologically relevant internal dosage of EAA.

4.5 Opportunities for Further Work

The modeling we have done with the information available to date has left many unanswered questions about the pharmacokinetics of ethoxyethanol and related compounds. For the construction of full physiologcially-based pharmacokinetic models it would be desirable to have:

(1) Measurements of relevant blood/air and tissue/air partition coefficents for EE, ethoxyacetaldehyde, and EAA.

(2) In clinical settings such as those used by Grosenekent et al. (1986a,b; 1987a,b), measurements of blood concentrations of

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* The analogous multiplyier for the 70 hour model can be derived from the day 2 preshift data in Table 4.5. For other models see the second footnote on p. 45 above.

** The formulas for "equivalent air concentration" assume complete absorption from alveolar air, with an alveolar ventilation rate of 11.38 liters/minute during light work. Increased physical exertion during exposure, as well as skin absorption, will be reflected in higher estimated "equivalent air concentrations".

*** Including any dermal absorption that may be present.

**** With the possible exception of differences in EAA excretion rates. If an individual were to excrete EAA more slowly than usual (or expected with our models) the absorbed dose might well be underestimated, when in fact that individual would be expected to be more susceptible to long term internal buildup of EAA than others (compare the effects of more rapid excretion with the "less simple" model with the slower excretion by the "70-hour" model in Table 4.5.

ethoxyacetaldehyde and EAA. This might allow more definitive estimation of

(a) rates of the two steps of metabolism for the aldehyde dehydrogenase pathway (from EE to ethoxyacetaldeyde, and from ethoxyacetaldehyde to EAA),

(b) the fraction of EE that is metabolized via the aldehyde dehydrogenase vs "other" pathway(s)

(c) rates of tissue storage and release of ethoxyacetaldehyde, and return from storage. (Some aspects of the Groseneken et al. 1986a,b results suggest that the usual pharmacokinetic modeling assumption of equilibration between tissue levels of EE, ethoxyacetaldehyde, and EAA, and the levels in venous blood exiting the tissues may be leading to inaccuracies.)

(3) Analogous pharmacokinetic studies in animal systems where male and female reproductive effects have been measured.

(4) Observations in human workers of the decline in urinary EAA excretion rates over several days of no exposure (including diurnal fluctuations in excretion). This would both allow resolution of some important uncertainties in the construction of human pharmacokinetic models, and assessment of human interinidividual variability in EAA excretion.

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