

W. J. Nolan

KINETICS AND METABOLISM OF INHALED METHYL CHLOROFORM⁷⁴
(1,1,1-TRICHLOROETHANE) IN HUMAN VOLUNTEERS

By

R. J. Nolan, N. L. Freshour, D. L. Rick
L. P. McCarty and J. H. Saunders

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The Dow Chemical Company
H&ES, Toxicology Research Laboratory
Biomedical Research Lab
607 Building
Midland, Michigan 48640

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SUMMARY

The kinetics of inhaled methyl chloroform (MC) and its principal metabolites, trichloroethanol (TCE) and trichloroacetic acid (TCA), were defined in 6 healthy male volunteers following single 6 hr exposures of 350 and 35 ppm. Blood and expired air MC concentrations were proportional to the exposure concentration and indicated about 25% of the MC inhaled during the 6 hr exposure was absorbed. Elimination of MC was tri-exponential with half-lives estimated as 44 min, 5.7 hr, and 53 hr for the initial, intermediate and terminal phases. Over 91% of the absorbed MC was excreted unchanged via the lungs, 5-6% was metabolized and excreted as TCE and TCA, and less than 1% remained in the body after 9 days. Urinary TCE and TCA excretion were extremely variable and indicated that urinary TCE and TCA measurements provide at best only a rough estimate of the exposure. These data suggest that the kinetics of MC in man are essentially first-order at or below the current TLV of 350 ppm. Based on a comparison of the blood MC levels and amounts of MC metabolized, the rat is a better model than the mouse to predict the toxicity of MC in man.

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INTRODUCTION

Methyl chloroform (MC; 1,1,1-trichloroethane; CAS Registry No. 71-55-6) is a colorless, non-flammable¹ liquid used primarily as an industrial metal degreasing solvent. It is also used as a solvent for adhesives, inks and coatings, and as an aerosol propellant. Due to the use pattern and vapor pressure (127 torr at 25°C) inhalation is thought to be the major route for human exposure.

The current exposure guideline (TLV®-TWA) recommended by the American Conference of Governmental Industrial Hygienists (1982) for 5 day a week 8 hour occupational exposures to MC is 350 ppm (1900 mg/m³ air). The principal manifestation of excessive acute or chronic MC exposure is depression of the central nervous system (Stewart, 1968; Torkelson and Rowe, 1981). Even at concentrations which were frankly anesthetic it had a low potential to produce systemic organ damage (Gehring, 1968) but at concentrations required for surgical anesthesia it can sensitize the myocardium to adrenergic stimuli (Dornette and Jones, 1960).

The purpose of the present study was to define the fate of inhaled MC and its metabolites in man. The kinetics of MC and its metabolites have been described in previous reports but interpretation of the human data are complicated by the fact that: (1) measurements were limited to the first 24 hr post-exposure, (2) an ambiguous method was used to quantitate urinary metabolites, or (3) exercise and other regimens were included in the experimental design.

EXPERIMENTAL

Volunteers. Volunteers were obtained by public advertisement and screened by a physician with no other involvement in the study. Those found to be in good general health were briefed and admitted to the

¹Non-flammable by conventional tests.

study after giving written informed consent. The six male Caucasians who participated in this study ranged from 26 to 54 years of age (mean = 43) and weighed between 77 and 106 kg (mean = 85). None was taking any medication on a chronic basis or had known recent exposure to chlorinated solvents. One volunteer smoked cigarettes and two were pipe smokers, but no smoking was permitted during the 6 hour exposure periods. The volunteers were also asked to abstain from all medication including aspirin, mega-vitamins and alcohol, and from vigorous exercise during the period samples were collected.

On the morning of the exposure, the volunteers arrived at the laboratory between 7:00 and 7:30 AM and were given a standard breakfast. A venous cannula (Butterfly infusion® set) was placed in a lower arm vein and maintained with a heparin lock (25 units/ml of normal saline). They entered the test atmosphere at 10 min intervals starting at about 9:00 AM and exited precisely 6 hours later. Throughout the exposure, the volunteers were allowed to move about at will but spend most of their time at sedentary activities. A lunch was provided at about 12:00 PM in the test room and the volunteers were asked to drink at least 12 fluid ounces during the exposure. An evening meal was provided about 2 hours after exiting the test atmosphere. The volunteers left the laboratory at about 9:00 PM and returned at specified times for subsequent specimen collections.

Test Material. The MC used was CHLOROTHENE* VG*; this is a stabilized commercial formulation which contained 95% MC. Gas chromatographic and infrared analysis confirmed that the test material was MC and within current product specifications.

Exposures. The volunteers were exposed as a group for 6 hr to 350 and 35 ppm of MC in air. Three weeks separated the exposures which were conducted in a 70 cubic meter chamber (6 x 5 x 2.3 m). The test atmosphere was generated by metering liquid MC through two glass atomizers into a heated flask (200°C). Nitrogen was used to drive the atomizers and sweep the resultant vapors into the chamber

*Trademark of The Dow Chemical Company.

inlet where they were mixed and diluted with filtered tempered air (70°F and 50% relative humidity). Exhaust fans maintained the airflow through the chamber at about 32 m³/min and the pressure slightly below ambient atmospheric pressure. Temperature and humidity were continuously recorded on a Serdex® recorder. Samples of the test atmosphere were collected for analysis via a stainless steel line from the normal breathing zone in the center of the test room. The concentration of MC in the chamber air was monitored at 15 min intervals with a gas chromatograph (GC) equipped with a flame ionization detector (FID; GC column was 1.8 m by 2 mm i.d. packed with 7.5% Oronite and 2.5% Carbowax 20 on 80/100 mesh Supelcoport and maintained at 104°C) and continuously by infrared spectrometry (wavelength = 9.3 microns). The GC analysis was used to calculate the time weighted average concentrations and the infrared spectrometer was used to back-up and confirm the GC analysis. These instruments were calibrated with standards prepared by adding known amounts of MC to Saran bags filled with 100 liters of dry filtered air.

Sample Collection and Analysis. Blood specimens (5 ml each) were collected prior to entering the chamber and at pre-selected intervals during and following the exposures. Venous cannulae were used to draw the specimens on the day of the exposure. Subsequent specimens were obtained by venipuncture. The blood was collected in Glasspak® syringes and 2 ml transferred immediately to a tared, sealed 10-ml reaction vial (Wheaton Scientific, Milville, NJ). The vial headspace was sampled and injected onto the GC column (1.5 m by 2 mm i.d. packed with 0.1% SP-1000 on 80/100 mesh Carbopack C and maintained at 100°C) with a 5-ml gas sample loop. Blood MC concentrations above 0.1 mg/liter were quantified with a FID and those below 0.1 mg/liter with a ⁶³Ni electron capture (EC) detector. Then chilled concentrated H₂SO₄ (1 ml) and dimethyl sulfate (100 µl) were added to the vial to convert trichloroacetic acid (TCA) to its methyl ester, and the vial was placed in a 60°C temperature bath for 4 hr. The 5-ml gas sample loop was again used to withdraw a sample of the vial headspace and inject it onto the GC column (1.5 m by 2 mm i.d. packed 90%/10% by length with 1% SP-1240 DA on 100/120 mesh Supelcoport and 0.1% SP-1000 on 80/100 mesh Carbopack C maintained at

85°C). Blood trichloroethanol (TCE) and TCA concentrations were determined using an EC detector.

An expired air specimen was collected each time a blood specimen was drawn. These specimens were collected by having the volunteers inhale nasally and exhale orally into a 10 liter Saran bag for 1 min. Samples of expired air were injected using a 5-ml gas sample loop onto a 1.5 m by 2 mm i.d. GC column packed with 2.5% Oronite NIW on 60/80 mesh Carbopack B and maintained at 135°C. Expired air samples containing over 3 µg/liter of MC were quantified using FID and those containing less than 3 µg/liter with an EC detector. The concentration of TCE in expired air was quantified only when the sample contained less than 3 µg/liter of MC and could be analyzed using an EC detector.

The following urine specimens were collected: (1) The first urine voided on the morning of the exposure, (2) all urine voided during the 6 hr exposure, (3) all urine voided between the end of the exposure and retiring for the evening, (4) the first urine voided on the morning of the first, second, fifth, seventh, and ninth post-exposure days, and (5) all urine voided between the first voiding and retiring for the evening of the first post-exposure day. To collect first morning voided urine, the volunteers voided before retiring for the evening, discarded the urine and recorded the time. In the morning the entire volume of urine in the first voiding was collected in a glass bottle and the time of voiding recorded. The length of each urine collection was calculated from the times recorded by the volunteers, and the volume and creatinine concentration of the collection were measured. The concentrations of TCE and TCA in urine were determined using a GC headspace method. Two-milliliter aliquots of urine were placed in 10-ml reaction vials along with chilled concentrated H_2SO_4 (1 ml) and 5 drops of 10% formalin (to reduce phenolic interferences). The vials were sealed and dimethyl sulfate (100 µl) added to derivatize the TCA for analysis. The samples were mixed and placed in a 60°C temperature bath for at least 2 hr. A 1-ml gas sample loop was used to withdraw a sample of the vial headspace and inject it onto a 3.4 m by 2 mm i.d. column packed 50%/50% by length with 1% SP-1240 DA on 100/120 mesh Supelcoport and 3% OV-17 on

100/120 mesh Gas Chrom Q and maintained at 87°C. Urinary TCE and TCA were quantified using an EC detector.

Data Analysis. The variation for both blood and expired air MC concentrations between the individual volunteers was small; thus, the geometric means rather than the individual volunteers' data were used in the kinetic analysis. Half-lives and area under the curve (AUC) were obtained by stripping and the trapezoidal rule (Gibaldi and Perrier, 1975). A physiological kinetic model was also developed to simultaneously describe the absorption, distribution, metabolism and elimination of MC and its principal metabolites, TCE and TCA (Figure 1).

This model was similar to that described by Caperos et al. (1982) in that the tissues and organs were grouped into three compartments based on their relative blood flow. Standard values for respiratory minute ventilation (RMV), cardiac output (CO), and the compartmental volumes (V_i) and blood flows (Q_i) were taken from Davis and Mapleson (1981). The blood and expired air MC data were used to estimate the blood/air partition coefficient (BAP), tissue/blood partition coefficients (P_i), and the first-order rate constant describing the metabolism of MC to TCE (k_m). The blood, urine and expired air TCE and TCA data were then used to estimate the volume of distribution for TCE (V_{TCE}) and TCA (V_{TCA}), the first-order rate constants describing the metabolism of TCE to TCA (k_m) and urinary excretion of TCE (k_{TCE}) and TCA (k_{TCA}), and the blood/air partition coefficient for TCE (BAP'). Optimum estimates for these parameters were obtained using DACSL: modified version of Advanced Continuous Simulation Language (Mitchell and Gauthies, Accs., Concord, MA) which contains numerical integration and optimization routines (Agin and Blau, 1981).

RESULTS

The time weighted average concentration (± 1 S.D.) of MC per se in the chamber during the 350 and 35 ppm exposures were 350 ± 8 and 33.3 ± 0.7 ppm, respectively. Continuous infrared analysis indicated that the chamber concentration ranged from 342 to 359 ppm during the 350 ppm

exposure, and from 36 to 38 ppm during the 35 ppm exposure. Chamber airflow was maintained at $32 \text{ m}^3/\text{min}$, and temperature and relative humidity within 70 to 76°F and 60 to 70%.

The odor of MC was very evident on entering the 350 ppm test atmosphere, but became less noticeable within 30 minutes. No adverse effects were experienced by the volunteers at these exposure concentrations.

Blood and expired air MC concentrations exhibited the same temporal pattern and were roughly proportional to the exposure concentration (Figures 2 and 3). The concentration of MC in the blood increased rapidly during the initial portion of the exposure and by 1.5 hr equaled 90% of the mean concentration observed after 6 hr, i.e., 1752 ± 90 and $153 \pm 27 \text{ } \mu\text{g/liter}$ after 6 hr exposure to 350 and 35 ppm, respectively. The mean concentration of MC in the expired air also increased rapidly and equaled 71% of the inhaled concentration after 1.5 hr versus 78% after 6 hr of exposure. Following both exposures, blood and expired air MC concentrations decreased in a tri-exponential manner. The half-lives for the initial, intermediate and terminal phases were estimated as 44 min, 5.7 hr and 53 hr. Blood MC concentrations 1.5, 16 and 40 hr post-exposure were about 59%, 7% and 3%, respectively, of the concentration observed at the end of the exposure.

The concentration time profile of MC in the blood and expired air (Figures 1 and 2) were well described by the three compartment physiological model depicted in Figure 1a. The disposition of inhaled MC predicted by the model is summarized in Table 1. The volunteers retained an average of 1005 and 101.6 mg of MC during 6 hr exposures at 350 and 35 ppm, respectively; this represents about 25% of the MC inhaled. The lungs were the principal route of excretion with over 91% of the absorbed MC eliminated unchanged in the expired air. By contrast, only 5-6% of the absorbed MC was metabolized, and less than 1% remained in the body after 9 days.

Blood TCE concentrations and urinary excretion rates peaked during the first 6 hr post-exposure, and then declined with a mean half-life of 27

hr (Figures 4 and 5). The concentration of TCE in the blood and its excretion via the urine were extremely variable as evidenced by the large standard deviations, and the mean blood TCE concentrations were clearly not proportional to the exposure concentrations. For example, there was only a 4.2-fold increase in the area under the blood TCE concentration time curve 0-11 hr for a 10-fold increase in exposure concentration. The total amount of TCE excreted in the urine following the 35 and 350 ppm exposures equaled 1.9 and 12.7 mg, respectively.

Concentrations of TCE in the expired air could not be quantified following the 35 ppm exposure and were extremely low following the 350 ppm exposure (<60 ng/liter; data not shown). Based on the area under the curve (4.87 mg.hr/liter) and assuming a respiratory minute ventilation of 6 liters/min, 1.8 mg of TCE was excreted via the lungs following the 350 ppm exposure.

Blood TCA concentrations and urinary excretion rates peaked 30-40 hr post-exposure and then declined with an average half-life of 76 hr (Figures 6 and 7). Although the blood TCA concentrations and urinary excretion rates were more variable than for TCE, the mean blood TCA concentrations and urinary excretion rates were nearly proportional to the exposure concentration. The area under the blood TCA concentration time curve 0-9 days post-exposure increased 8.9 fold as the exposure concentration increased 10-fold, and total urinary TCA excretion following the 35 and 350 ppm exposures equaled 3.2 and 24.4 mg, respectively.

The time course of TCE and TCA in the blood and urine (Figure 4-7) were well described by the simple kinetic model depicted in Figure 1b. The model parameters listed in Figure 1, except for V_{TCE} , represent the average estimate obtained when the 35 and 350 ppm data were fit separately. The apparent volume of distribution for TCE (V_{TCE}) had to be varied to account for the disproportionality in the blood TCE concentrations. The need to vary V_{TCE} might be due to dose-dependent binding of TCE to blood proteins which has been demonstrated for TCE in the dog (Garrett and Lambert, 1973). The total amount of TCE and TCA excreted following the 35 and 350 ppm exposures represented 4.32 and

32.86 mg equivalents of MC. If the TCE and TCA remaining in the body after 210 hr were included, recovered TCE and TCA would represent 77% of the MC metabolized as calculated from the blood and expired air MC data (Table 1). The excellent overall agreement between the calculated amount of MC metabolized and that actually recovered indicates that all major metabolites of MC were quantified.

DISCUSSION

These data indicate that about 25% of the MC inhaled during a continuous 6 hr exposure was retained. Over 91% of the absorbed MC was eliminated unchanged via the lungs, 5-6% was metabolized and excreted as TCE and TCA, and less than 1% remained in the body after 9 days. The disposition of inhaled MC was similar to that described by previous investigators. Humbert and Fernandez (1977) found that the concentration of MC exhaled after 4 hr of exposure equaled 72% of the inspired concentration (versus 78% in our study). They also found that over 90% of the absorbed MC was eliminated unchanged via the lungs and 6% was excreted as TCE and TCA. Monster et al. (1979) reported that the concentration of MC in air expired after 4 hr of exposure equaled 70% of the inspired concentration. Following the exposure they reported that 70-80% of the absorbed MC was excreted unchanged via the lungs and another 3% was excreted as TCE and TCA. However, air leaking around the mouthpiece through which their volunteers were exposed may explain the somewhat higher absorption and lower post-exposure recovery of MC reported by Monster et al. (1979).

In agreement with previous reports, the highest blood concentrations and urinary excretion rates for TCE occurred within 6 hr post-exposure, whereas peak blood concentrations and urinary excretion rates for TCA were observed 30-40 hr post-exposure. Although we found that twice as much TCA as TCE was excreted in the urine, others have reported more TCE than TCA was excreted. This discrepancy may in part be due to differences in analytical methods. Monster et al. (1979), Seki et al. (1975) and Ikeda and Ohstuji (1972) used the Fujiwara reaction to quantify urinary TCE and TCA; this is a non-specific method based on a colored

product formed when organic halides are heated with pyridine and NaOH which Reith et al. (1974) concluded should not be used for quantitative purposes. The explanation for the discrepancy between our data and that of Humbert and Fernandez (1977) is uncertain since in both studies a GC method was used to quantify urinary TCE and TCA. However, Muller et al. (1974) reported more TCA than TCE was excreted by volunteers who ingested TCE, and the volumes of distribution and half-lives for elimination estimated from their data for TCE (300 liters and 13 hr) and TCA (8.4 liters and 51 hr) are in reasonable agreement with ours.

The model depicted in Figure 1 is similar to that described by Caperos et al. (1982), and is based on a realistic description of the body and the physical properties of MC. The blood/air partition coefficient (1.6) was within the range of in vitro estimates (1.4-7.0; Astrand, 1975, and Morgan et al. 1972), and the fat/blood partition coefficient (108) was similar to the olive oil/blood partition coefficient (103; Sato and Nakajima, 1979). This model can predict the effects of different exposure conditions, and can explain what otherwise might be considered discrepancies between studies. For example, Stewart et al. (1969) found that expired air MC concentrations increased very little on a day-to-day basis when volunteers were exposed 6.5-7 hr per day for 5 consecutive days to 507 ppm of MC. Although the apparent absence of accumulation seems in conflict with the 53 hr terminal half-life for the elimination of MC, simulations based on the model in Figure 1 indicated that at the end of the fifth daily exposure expired air and blood MC concentrations will be within 4 and 8%, respectively, of the concentrations observed after a single 8 hr exposure. These same simulations indicated that after the fifth exposure there will be 1.8 times more MC in the body than following a single exposure. Furthermore 12 daily exposures (4.5 half-lives) are required for the amount of MC in the body to reach 95% of steady state. When steady state is reached, the body will contain only 3.6 times more MC than after a single 8 hr exposure and about 70% of this will be in the fat.

Previous investigators have suggested that concentrations of MC in expired air (Stewart et al., 1969) or urinary excretion of TCE and TCA

(Caperos et al., 1982; Monster et al., 1979; Seki et al., 1975; and Ikeda and Ohtsuji, 1972) could be used to monitor MC exposures. Expired MC concentrations are highly dependent on the time the specimens are collected. Collecting the samples more than 6 hr post-exposure will reduce the time dependency but reliable information on the exposure and post-exposure history are still needed to interpret these data. Urinary TCE and TCA excretion also depend on when the specimen was collected, but a more serious problem is that these are common metabolites of other chlorinated solvents (e.g. trichloroethylene) and chloral hydrate (a frequently prescribed sedative). Because the quantity of TCE and TCA formed from the sources is potentially much greater than from MC, urinary TCE and TCA excretion should not be used to monitor MC exposures unless other sources of these metabolites can be excluded. Even then urinary TCE and TCA provide only a rough estimate of the exposures, since large differences in urinary TCE and TCA excretion were observed between identically exposed individuals.

Comparative pharmacokinetic analysis provides a rational basis for extrapolation of animal toxicity data to man (Ramsey and Gehring, 1980). Although the same metabolites of MC were found in man and laboratory animals, important species differences were observed in the pharmacokinetics of MC that should be considered when interpreting the animal toxicity data. For example the blood of mice and rats exposed for 6 hr at 150 ppm contained 12.6 and 2.6 $\mu\text{g CH}_3\text{CCl}_3/\text{g}$, respectively (Schumann et al., 1982). When normalized for differences in exposure concentration these levels were 17.3 and 3.5 times larger than those found in our volunteers. Differences were also observed in the amount of MC absorbed and metabolized. During a 6 hr exposure mice and rats absorbed an average of 1.2 and 1.0 $\mu\text{mol CH}_3\text{CCl}_3/\text{kg/ppm exposure concentration}$ (Schumann et al., 1982), whereas our volunteers absorbed an average of 0.4 $\mu\text{mol/kg/ppm exposure concentration}$. Following a 6 hr 150 ppm exposure, mice metabolized 0.16 and rats 0.06 $\mu\text{mol CH}_3\text{CCl}_3/\text{kg/ppm exposure concentration}$ and our volunteers metabolized an average of 0.014 $\mu\text{mol/kg/ppm exposure concentration}$. The difference in blood concentrations and absorption of MC indicate that mice and rats will be more sensitive than man to effects which are due to MC per se.

The differences in the amounts of MC metabolized suggest that mice and rats will also be more sensitive than man to effects which are due to metabolism of MC. This conclusion is based on the demonstration that when toxicity is mediated via a reactive metabolite differences in species sensitivity are directly proportional to the amount of chemical metabolized (Schumann et al., 1980; Reitz et al., 1982; Stott et al., 1982). Thus, species differences in the pharmacokinetics of MC indicate that the rat is a much better model than the mouse to evaluate potential human health effects of MC.

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Table 1
Absorption and Elimination of Inhaled MC

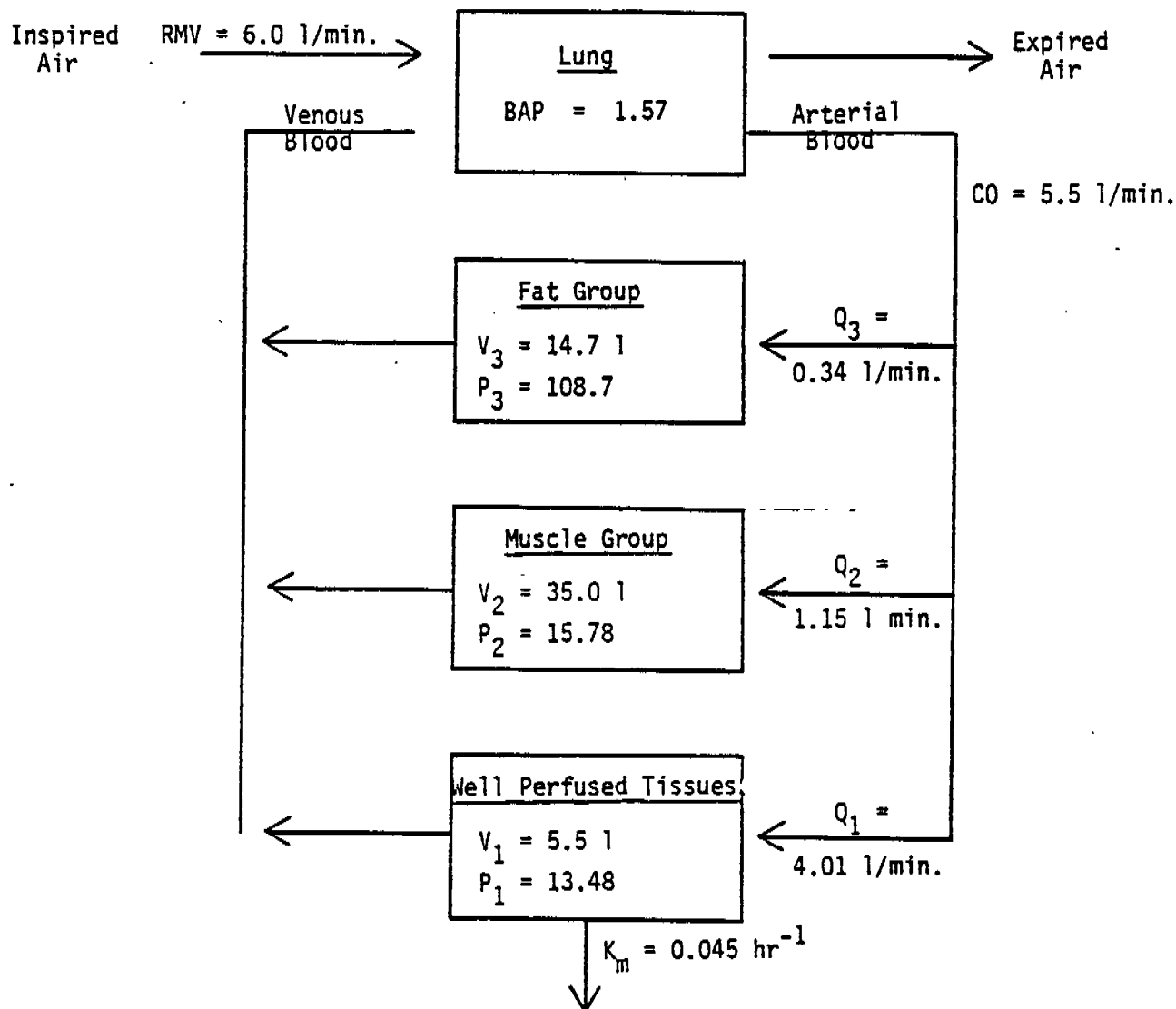
	Disposition of Inhaled MC			
	350 ppm Exposure		35 ppm Exposure	
	<u>mg</u>	<u>%</u>	<u>mg</u>	<u>%</u>
MC Absorbed	1005.	--	101.6	--
MC Expired	924.	91.9	92.8	91.3
MC Metabolized	49.	4.9	6.1	6.0
MC in Body 9 days Post-exposure	7.9	0.8	0.6	0.6

Values represent model predictions expressed in mg and as % of the MC absorbed during and following 6 hr exposures to MC.

FIGURE LEGENDS

- Figure 1. Kinetic model used to describe the fate of MC (1a) and its metabolites (1b). Cardiac output (CO) and respiratory minute ventilation (RMV) were set at 5.5 and 6.0 liters/min., respectively. Alveolar ventilation was assumed to equal 75% of RMV. Compartmental volumes (V_i) and blood flows (Q_i) were taken from Davis and Mapleson,¹1981. The blood/air¹(BAP) and tissue/blood (P_i) partition coefficients, volumes of distribution for metabolites (V_{TCE} and V_{TCA}), and first order rate constants (k_i) for the metabolism and elimination processes represent the average estimates obtained when the 35 and 350 ppm data were fit separately.
- Figure 2. Expired air MC concentrations during and following a 6 hr inhalation exposure at 35 and 350 ppm. Data represent geometric means $\pm$ 1 S.D. for 6 volunteers. The lines indicate the model predicted concentrations.
- Figure 3. Blood MC concentrations during and following a 6 hr inhalation exposure at 35 and 350 ppm. Data represent geometric means $\pm$ 1 S.D. for 6 volunteers. The lines indicate the model predicted concentrations.
- Figure 4. Blood TCE concentrations during and following a 6 hr inhalation exposure to 35 and 350 ppm of MC. Data represent geometric means $\pm$ 1 S.D. for 6 volunteers. The lines indicate the model predicted concentrations.
- Figure 5. Urinary TCE excretion rates during and following a 6 hr inhalation exposure to 35 and 350 ppm of MC. Data represent geometric means $\pm$ 1 S.D. for 6 volunteers. The lines indicate the model predicted excretion rates.
- Figure 6. Blood TCA concentrations during and following a 6 hr inhalation exposure to 35 and 350 ppm of MC. Data represent geometric means $\pm$ 1 S.D. for 6 volunteers. The lines indicate the model predicted concentrations.
- Figure 7. Urinary TCA excretion rates during and following a 6 hr inhalation exposure to 35 and 350 ppm of MC. Data represent geometric means $\pm$ 1 S.D. for 6 volunteers. The lines indicate the model predicted excretion rates.

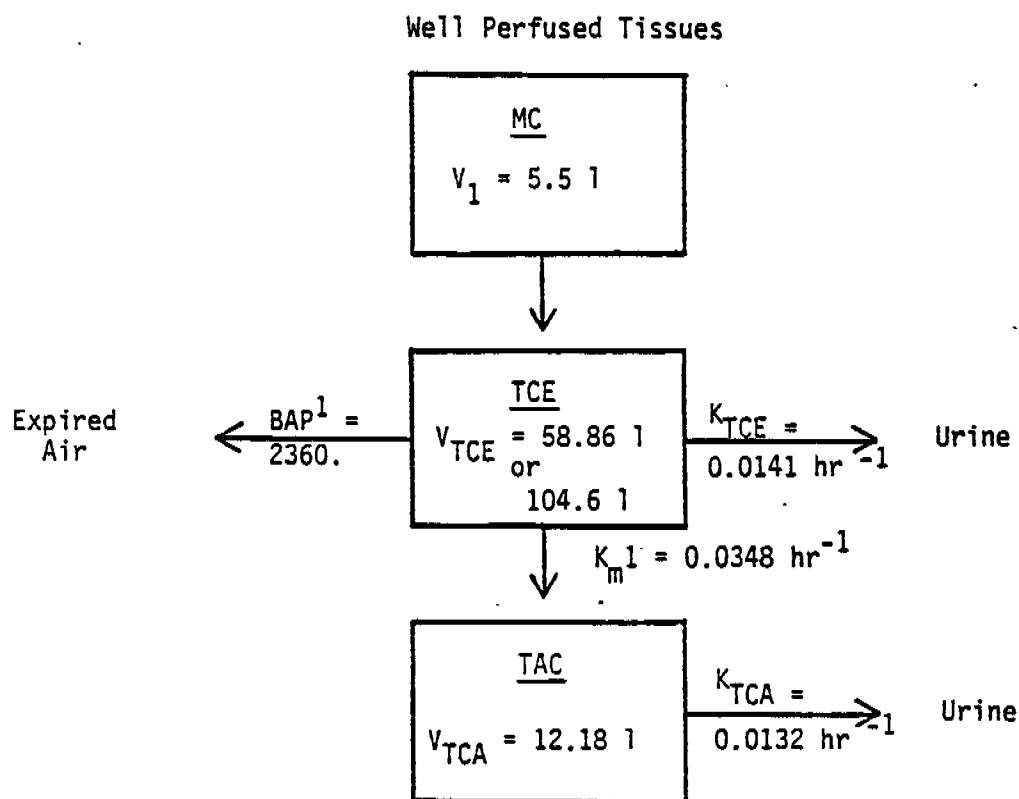
Figure 1a



DOW CONFIDENTIAL

SL 036577

Figure 1b



DOW CONFIDENTIAL

SL 036578

DOW CONFIDENTIAL

Figure 2

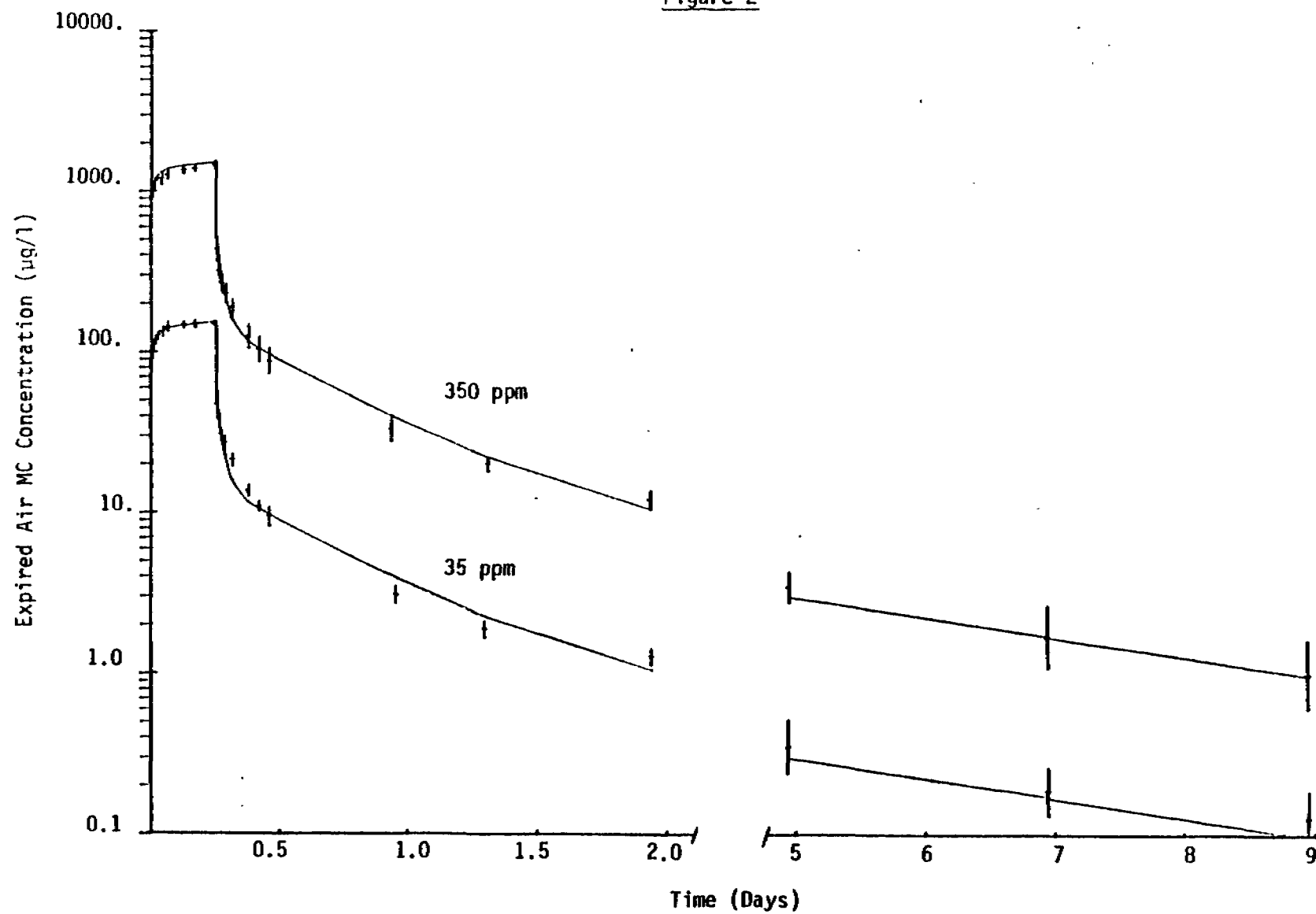
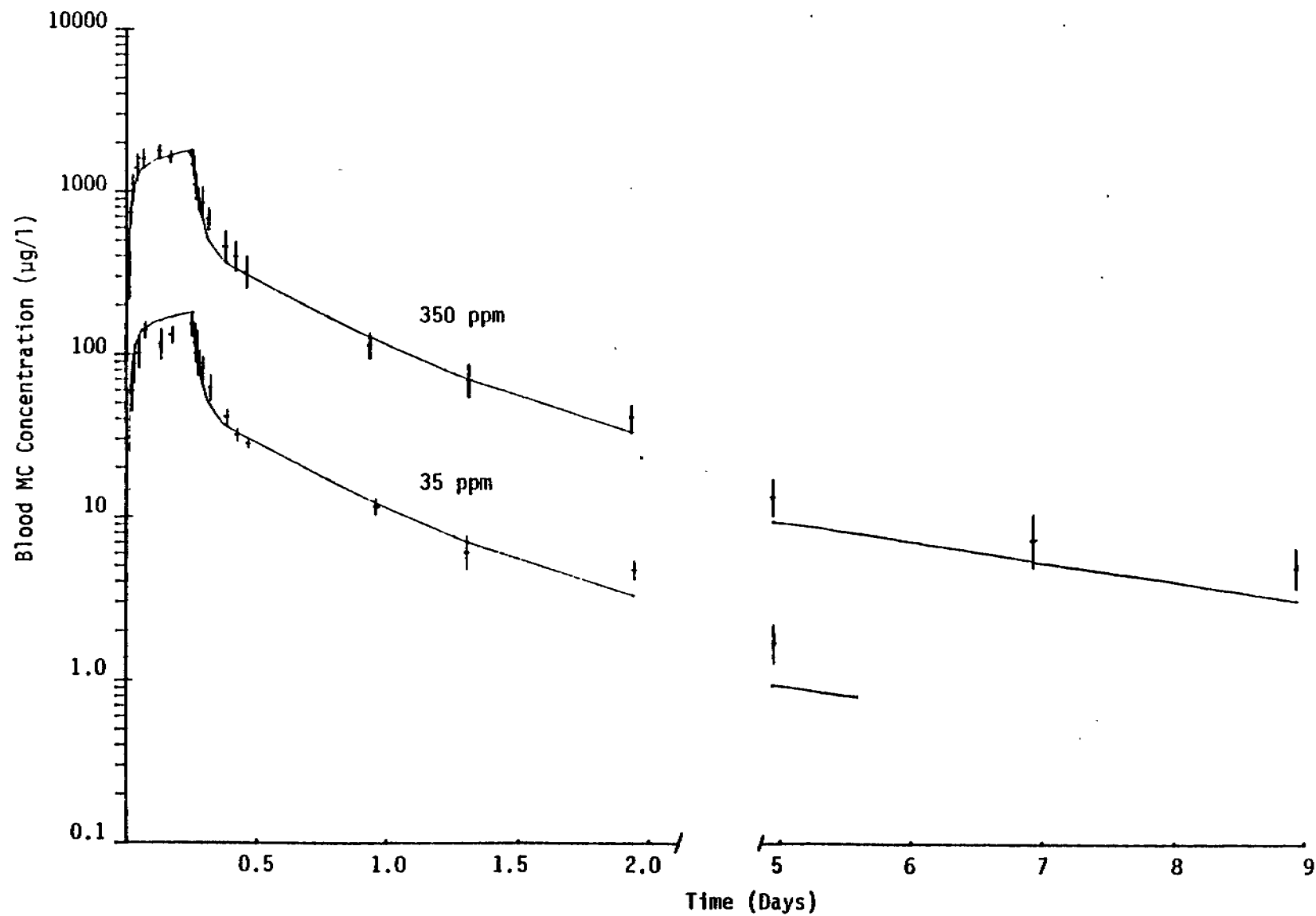


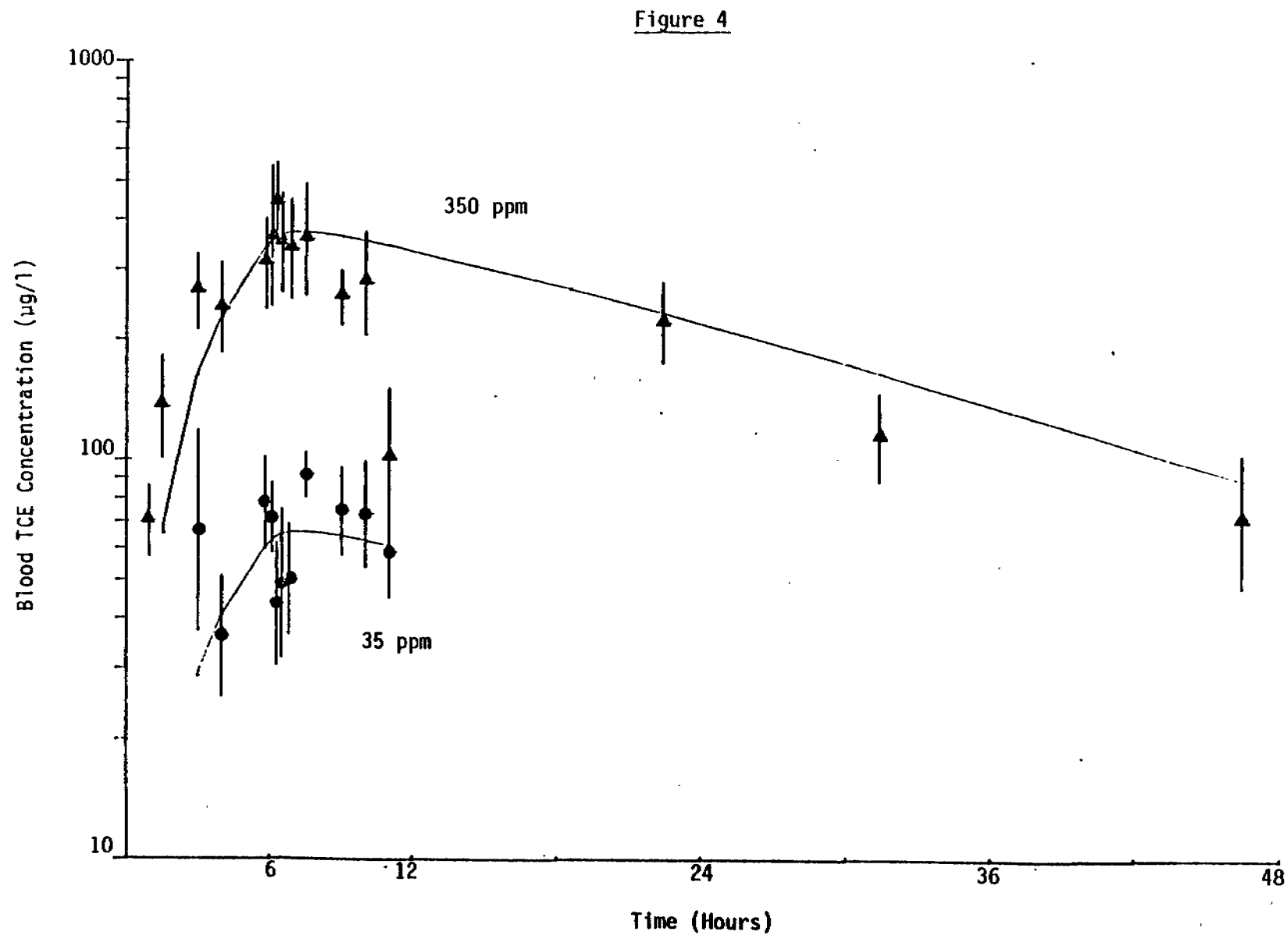
Figure 3



DOW CONFIDENTIAL

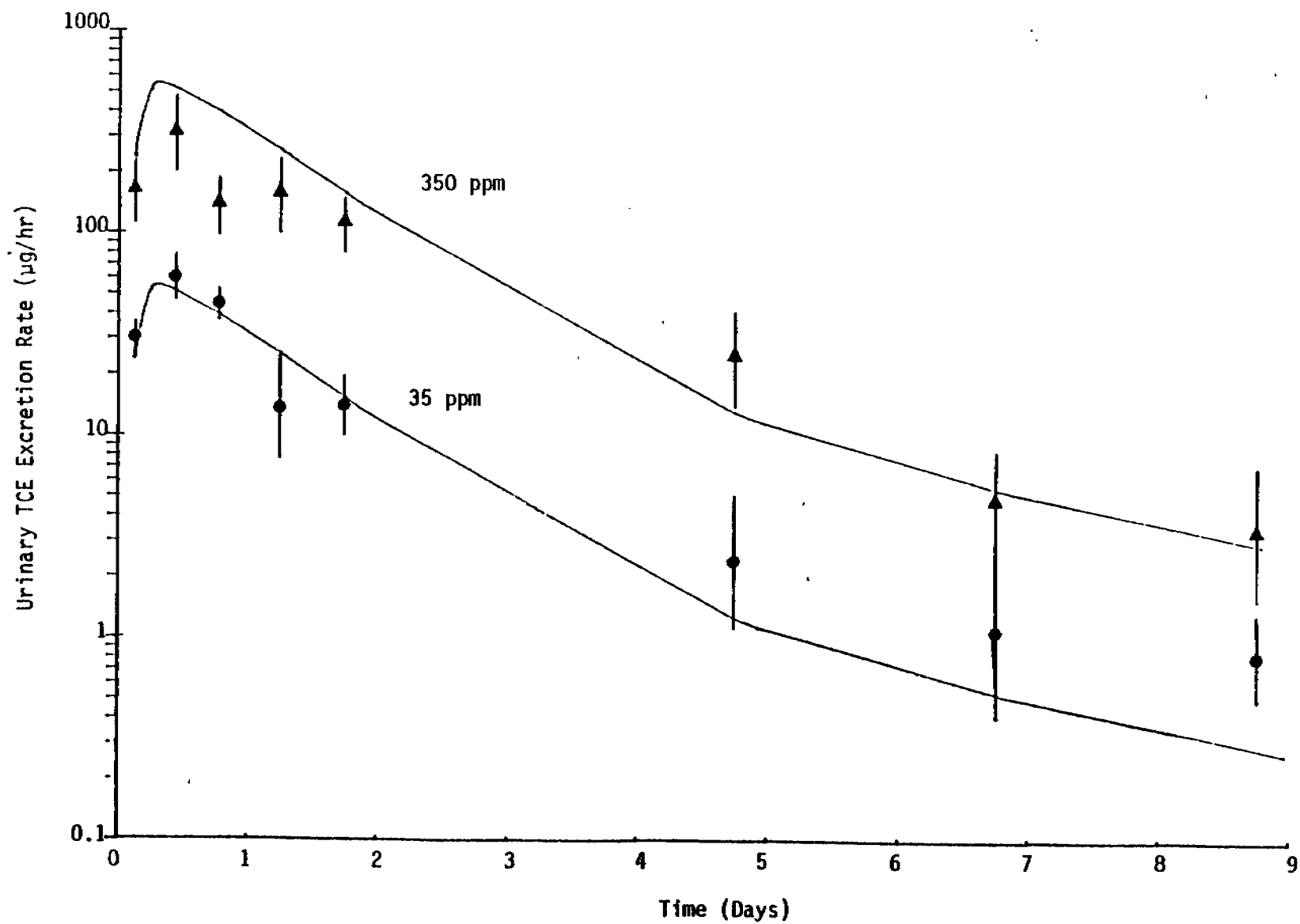
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DOW CONFIDENTIAL

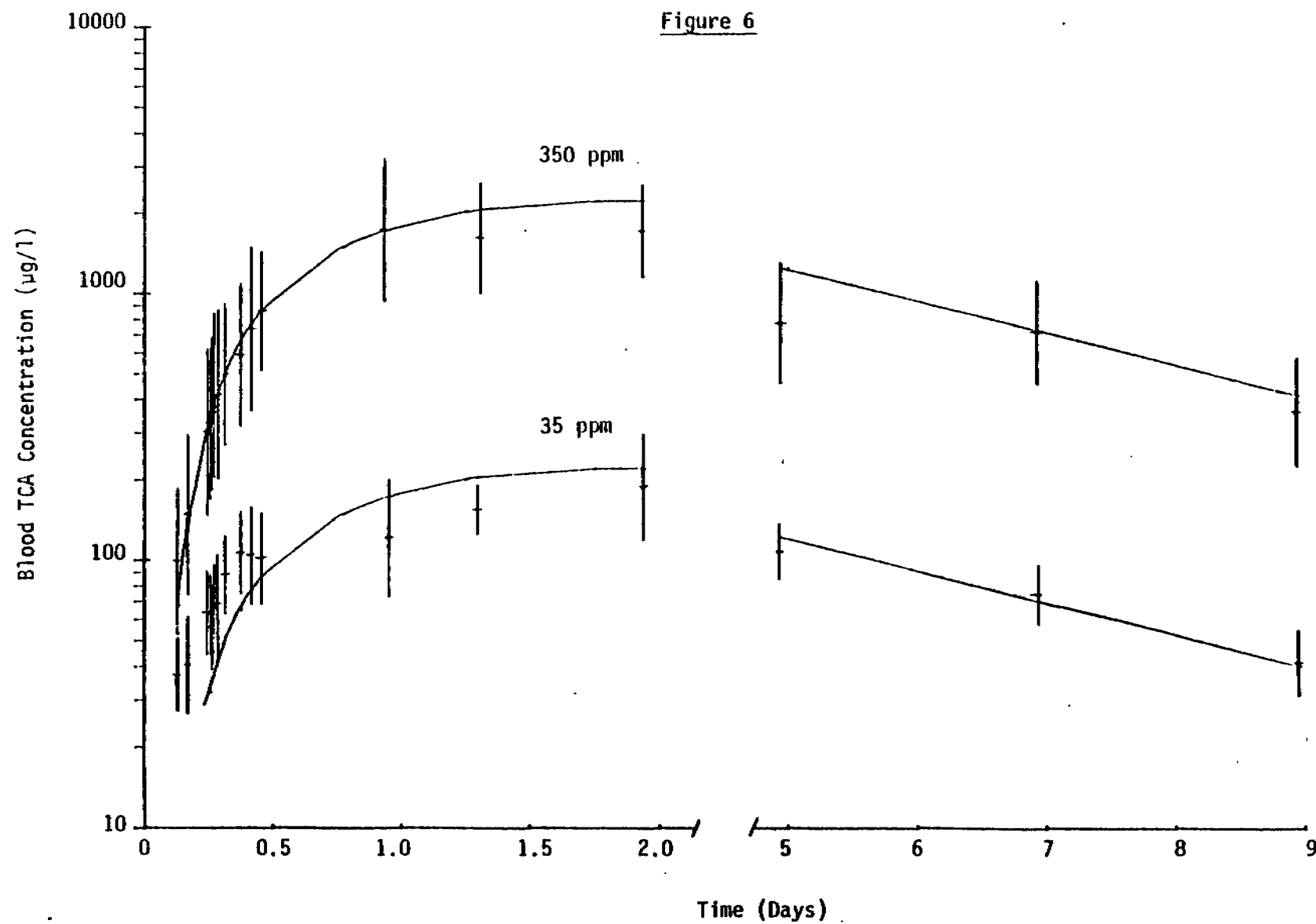


DOW CONFIDENTIAL

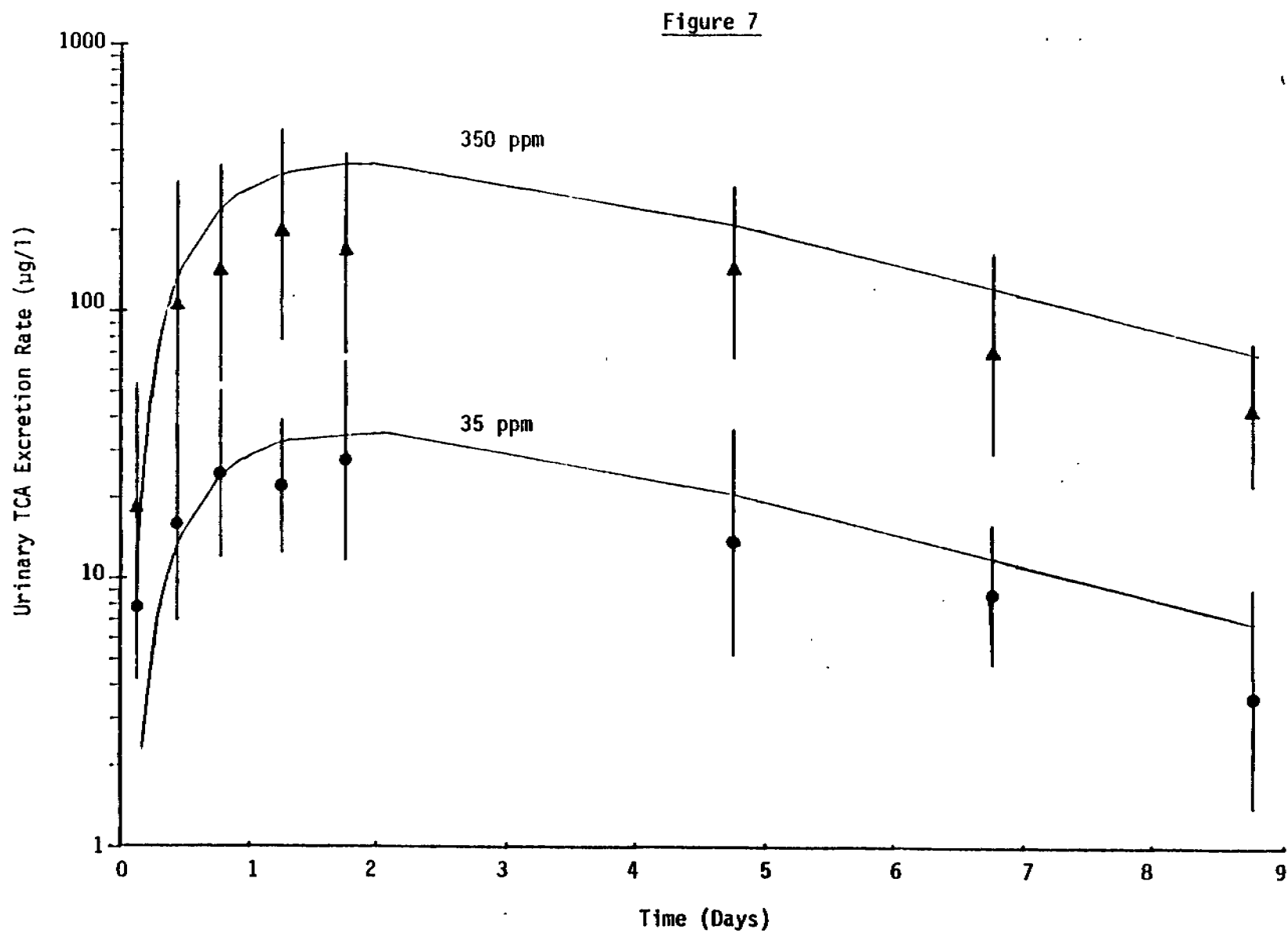
Figure 5



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appears that such use exposes vulnerable neonates to potential hexachlorophene toxicity.*

Two to 11 vaginal examinations were performed in each of 28 full-term women during active labor using approximately $\frac{1}{2}$ teaspoon of PhisoHex per examination. Within a half hour after delivery, ten of the 14 women whose labor had exceeded 4 hours (71.4%) had serum hexachlorophene levels ranging from 224-942 ng/ml. In contrast, only 2 of 14 women whose labor lasted less than 4 hours had detectable serum hexachlorophene levels (100 ng/ml or more). At delivery, 9 neonates had hexachlorophene in their cord serum (up to 617 ng/ml); 6 of them were born of mothers whose labor had exceeded 4 hours. No neonatal morbidity from hexachlorophene was reported.*

CLINICAL IMPLICATIONS: Hexachlorophene is neurotoxic. Neonates weighing less than 1200 g and those with a gestational age of less than 35 weeks are particularly susceptible to this toxicity. Daily bathing of infants with 3% hexachlorophene has caused toxicity in some newborns. Since hexachlorophene enters the fetal circulation following vaginal absorption, surgical soaps containing 3% hexachlorophene should probably not be used for routine vaginal examinations during labor. The risk of fetal exposure is greater when hexachlorophene is used during active labor that lasts for more than 4 hours. Signs of acute hexachlorophene neurotoxicity include cerebral irritability, confusion, diplopia, lethargy, twitching and seizures.

*Strickland D, et al: Vaginal absorption of hexachlorophene during labor. American Journal of Obstetrics and Gynecology 147:769-772, 1983.

Physicians' Drug Alert, June 1984.

ACETAMINOPHEN OVERDOSE

In contrast to the adolescent and adult population, there have been only a few reports of the hepatotoxic effects of acetaminophen in young children, even when the young child achieves a plasma level clearly within the toxic range on the acetaminophen nomogram. The reasons for this are unclear. The authors report 417 young children who had ingested a potentially serious amount of the drug and who were examined and treated in a national multicenter study. Fifty-five had plasma levels in the potentially toxic range and 43 had a full course of acetylcysteine treatment. Three of the 417 patients had SGOT values consistent with a hepatotoxic reaction. The children who had also ingested alcohol had significantly lower SGOT levels than those who had not ingested alcohol. The incidence of transient hepatotoxic effects is significantly lower in children with potentially toxic plasma levels than in adults with similar toxic plasma levels. There were no deaths in this series of children.

Rumack BH. Am J Dis Child 138:428-433, May 1984)

TREATMENT OF BARBITURATE OVERDOSE

Old standard therapy: consisted of gastric lavage, charcoal, and analeptic therapy; associated with 20-40% mortality.

Newer approach (Scandinavian approach): consists of supportive therapy only (ventilatory support; fluid therapy; good nursing care); associated with 1-2% mortality.

Specific measures: correct life-threatening symptoms; treat respiratory depression with endotracheal

intubation and mechanical ventilation; treat shock with fluid resuscitation; vasopressors contraindicated.

Methods for removing drug: forced diuresis should be reserved for severe cases involving long-acting barbiturates only (has limited role in severe barbiturate overdoses); alkaline diuresis safer form of therapy for phenobarbital toxicity.

Patient with shock: attempt to alkalinize urine by giving sodium bicarbonate, attempting to increase urine pH above 8.

Peritoneal dialysis: no more effective than alkaline diuresis for treating barbiturate overdoses.

Hemodialysis: nine times more effective than alkaline diuresis in removing long-acting barbiturates, but not very effective in removing short-acting barbiturates; indicated when standard therapy ineffective in life-threatening situation, or when patient has extremely high drug blood levels and failure of metabolizing organ (kidneys for long-acting barbiturates; liver for short-acting barbiturates).

From: Audio Digest-Family Practice, Feb. 6, 1984, Vol. 32, No. 6.

EDITOR'S COMMENT: Any responses to the "Scandinavian Approach"?

ABUSE OF TYPEWRITER CORRECTION FLUID BY ADOLESCENTS

A current report describes a widespread outbreak of substance abuse that involves the inhalation of fumes from typewriter correction fluids (Liquid Paper, Wite-Out, Snopake, etc). Adolescent boys inhale the fluid either directly from its small container or they place it in a bag, from which it is then inhaled. This practice, known as getting "whited out", is said to induce almost immediate euphoria, followed by a "pleasant" form of drowsiness. "None of those interviewed had any awareness that the inhalation of these products was potentially harmful other than that they might have 'passed out' during particularly heavy abuse."

This pattern of abuse usually begins in preteen years, peaks at about age 15, and then tapers off in favor of other substance abuse (marijuana, alcohol). One of the main reasons for using typewriter correction fluid is its easy availability--such fluids are ubiquitous in offices (including those in schools and hospitals), and they are also available on open shelves in stores, where they are inexpensive and easy to steal and conceal. They can be used quickly (such as between classes) and no detectable odor lingers. Typewriter correction fluids contain three main chlorinated solvents (trichloroethane, trichloroethylene, and perchloroethylene), and their abuse has been associated with sudden death from cardiac arrhythmias or respiratory arrest. In addition, they can cause respiratory depression, massive hepatic necrosis, and renal failure; CNS effects, in addition to the intended euphoria, include seizures, loss of consciousness, incoordination, and CNS depression.

To reduce this form of abuse, the author suggests that the manufacturers place a warning label on their products (at least one product, Liquid Paper, now has such a warning); that retail stores, schools, offices, and the general public be made aware of the problem, in the hope they will restrict their easy availability; and that drug education programs include information on the hazards of abuse of typewriter correction fluids.

Greer JE: South Med J 77:297-298, 301, Mar 1984.