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FATE OF ^{14}C-VINYL CHLORIDE AFTER SINGLE ORAL ADMINISTRATION IN RATS

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In the production of polyvinyl chloride (PVC) small amounts of unreacted monomer may be retained in the polymer. Because residual monomer may be leached from PVC used in food wrapping and packaging material, it is important to evaluate the toxicological potential of ingested VC. The objective of this study was to assess the fate of orally administered VC in rats.

Male rats were given single oral doses of 1 and 100 mg/kg ^{14}C-VC and the routes and rates of elimination of ^{14}C-activity followed for 72 hours. Following 1 mg/kg VC, excretion in the urine as non-volatile metabolites and as $^{14}CO_2$ in expired air accounted for 59 and 13%, respectively, of the administered dose. Only 2% of the dose was expired by the lungs as VC. Conversely, after 100 mg/kg, 67% of the dose was eliminated by the lungs as VC, while urinary non-volatile metabolites and $^{14}CO_2$ comprised 11 and 3% respectively.

Pulmonary elimination after 100 mg/kg VC showed an apparent biphasic clearance with half-lives ($t_{1/2}$) of 14.4 and 49.5 minutes for the respective fast and slow phases. Following 1 mg/kg the pulmonary clearance of VC was monophasic with a $t_{1/2}$ of 63.0 minutes. The percent of the dose remaining in the carcass after 72 hours was 11 and 2% for the 1 and 100 mg/kg doses, respectively. The urinary radioactivity was separated by thin layer chromatography into three major regions corresponding to S-(2-hydroxyethyl)-N-acetyl cysteine, thiodiglycolic acid, and a third unidentified metabolite. The proportions of the urinary metabolites were not influenced by the dose.

The fate of VC following 1 and 100 mg/kg doses is clearly dose dependent. Consistent with our previous studies on the fate of VC following inhalation exposure in rats, the metabolism of VC appears to be a saturable process. The identification of sulfur containing cysteine conjugates in the urine supports the hypothesis that the carcinogneicity of VC is related to metabolic formation of alkylating metabolites. The presumed conjugation of these metabolites with glutathione appears to be the primary mechanism of detoxification. The relation of the present work to other recently reported studies on VC are discussed.

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FATE OF ^{14}C-VINYL CHLORIDE AFTER SINGLE ORAL ADMINISTRATION IN RATS

INTRODUCTION

The hazard of industrial exposure to vinyl chloride (VC) during the production of polyvinyl chloride and other plastics has received considerable attention. Maltoni and Lefemine (1974) demonstrated the carcinogenic potential of VC in rats exposed daily by inhalation to concentrations ranging from 50-10,000 ppm. Subsequent epidemiologic data obtained from industrial workers with long term exposure to high concentrations of VC demonstrated an association between exposure and various hepatic abnormalities including induction of angiosarcoma (Creech and Johnson, 1974).

The fate of inhaled VC has been previously studied in rats (Hefner, et al., 1975). Although some aspects of the fate of inhaled VC remain to be elucidated, the data indicated that in rats exposed to 50 ppm for 1 hour the inhaled VC was metabolized to polar products which were excreted predominantly in the urine. Using kinetic parameters and inhibitors of drug metabolism, additional evidence indicated that the fate of inhaled VC was concentration dependent and that at least two metabolic pathways were involved in its metabolism. Consideration of these data, led to the speculation that the carcinogenic

activity of VC may be mediated through formation of alkylating metabolites such as chloroacetaldehyde and chloroethylene oxide. Even more important is the fact that the production of carcinogenic metabolites may increase disproportionately with the extent of exposure; or conversely, the capacity to detoxify alkylating metabolites may decrease disproportionately with the extent of exposure. Resolution of these possibilities is critical in assessing the hazard of exposure to low levels of VC.

In the production of polyvinylchloride (PVC) small amounts of unreacted monomer may be retained in the polymer. Because residual monomer may be leached from PVC used in food wrapping and packaging material, it is important to evaluate the toxicological potential of ingested VC. The objective of this study was to assess the fate of orally administered VC in rats.

METHODS

Compound. 1,2-^{14}C-vinyl chloride (^{14}C-VC) was synthesized directly from 1,2-dichloroethane (1,2-^{14}C, lot # 819-021, 4.1 mCi/mmole, New England Nuclear, Corp.) by the method of Wagner and Muelder (1975). The radiochemical purity of a representative sample of ^{14}C-VC from this synthesis has been reported to be 95-96% pure (Wagner et al., 1975). The primary ^{14}C-containing contaminant (4-5%) in the ^{14}C-VC preparation was ^{14}C-acetylene. Non-labeled VC (Matheson Gas Products) of 99.9% minimum purity was mixed with the ^{14}C material to obtain the desired specific activity.

Preparation of Dose. The ^{14}C-VC was synthesized immediately prior to use. Typically, 20 ml of the ^{14}C-VC, helium mixture (approximately 2.6 mCi/mmole) was bubbled directly into 15 g of USP corn oil in a sealed septum vial. An appropriate quantity of non-labeled VC was then bubbled into the corn oil to obtain the desired concentration. One µl of the corn oil dosing solution was subjected to gas chromatography and the final concentration of VC in the corn oil was determined by comparison to standard gas samples. The specific conditions of the analysis were as follows:

Gas Chromatograph	Hewlett Packard (Model 5750)
Column	Porapak Q (80/100 mesh, 6 ' x 1/4" stainless steel)
Column Temperature	180°C
Helium Flow	15 ml/min
Detector	Flame Ionization (250°C)
Injection Temperature	250°C

The radioactivity of the dosing solution was determined by placing aliquots (0.050 - 0.100 g) into pre-filled scintillation vials containing 20 ml scintillant, Concifluor® (Mallinckrodt Chemical Works), 2-methoxyethanol:toluene, 6:11:83. The radioactivity was determined in a Nuclear Chicago Mark II liquid scintillation spectrometer (Searle Inc.). The specific activities for the 1 and 100 mg/kg dose solutions were 20.50 and 0.18 μCi/mg VC respectively. The VC-corn oil solution was administered by oral gavage with a glass syringe and stainless steel dosing needle in a volume not exceeding 5 ml/kg.

Animals and Apparatus. Male albino Sprague-Dawley (Spartan substrain) rats weighing from 180-225 g purchased from Spartan Research were used throughout the studies. All animals were fasted overnight and the VC administered between 8 and 10 AM the following morning.

The rats were housed in glass Roth-type metabolism chambers designed for the separate collection of urine, feces, and expired air. Room air was drawn by vacuum through the chambers at 400-500 ml/minute. The exiting air was passed through a series of traps to collect the expired ^{14}C-VC and $^{14}CO_2$. Initially the routinely used urine and feces traps were replaced by a straight glass tube. This modification reduced the dead space in the chamber and allowed air to be drawn directely through the metabolism chamber. Pilot studies indicated that the majority of the expired VC was eliminated during the first 2 hours after dosing; therefore, the conventional urine and feces traps were used after 4 hours.

The air exiting the chamber was first passed through a glass tube containing about 40 g of Drierite® (W. A. Hammond Drierite Co.) to remove moisture. Subsequent transit through a series of 2 cold finger traps containing 50 ml of toluene, 2-methoxyethanol (80:20) and a single trap containing 120 ml of 5M ethanolamine in 2-methoxyethanol enabled the collection of ^{14}C-VC and $^{14}CO_2$ respectively. The cold finger traps were immersed in 2-methoxyethanol, dry-ice baths throughout the collection periods. The trap for CO_2 was maintained at room temperature.

Experimental Procedure. The animals were placed in the modified metabolism cages immediately after dosing. The VC traps were changed at 30 minute intervals for the first 4 hours. Two subsequent changes at 4 hour intervals (8 and 12 hours) completed the collection of expired VC. The CO_2 trap, urine, and feces, receptacles were changed at 12 hour intervals for 72 hours. The urine trap was immersed in a 2-methoxyethanol, dry-ice bath throughout the collection periods.

At termination of the study the animals were decapitated, exsanguanated, and samples of tissue (liver, lung, perirenal fat, muscle, plasma) were collected for analysis of ^{14}C-activity. The remaining carcass was skinned and homogenized (50%, w/v) in distilled water.

Sample Preparation and Assay. Aliquots of the VC traps (5 ml) were prepared for counting by addition of an equal volume of scintillant containing Concifluor® (Mallinckrodt Chemical Works) 2-methoxyethanol, and toluene (6:11:33).

Five ml samples of the solution from the CO_2 trap were added to 5 ml of 5M ethanolamine in 2-methoxyethanol and 10 ml of the scintillant described above. The urine samples, 250 mg, were prepared by adding 1 ml of distilled water and 12 ml of Aquasol® (New England Nuclear).

Aqueous homogenates (33 or 50%, w/v) of feces and tissues were oxidized to CO_2 and H_2O in a Biological Material Oxidizer (Beckman Instruments). The $^{14}CO_2$ from the combustion was trapped in 8 ml of 5M ethanolamine in 2-methoxyethanol and added to the Concifluor® scintillant as described previously. Samples of skin and fat were combusted without homogenization.

Carbon-14 activity in all samples was determined by counting in a Mark II liquid scintillation spectrometer. External standard channel ratios were used to determine the counting efficiency. The counts per minute were converted to disintegrations per minute using a standard quench curve.

Radiochemical Separation of Urinary Metabolites.

Urine samples from each animal were pooled individually through the 24 hour collection period. Aliquots (10 ml) of

these pooled samples were lyophilized and reconstituted in 15 ml of methanol. The methanol extracts were evaporated under dry N_2 to approximately 1 ml. Five µl of the methanol extract was spotted on a thin layer chromatography plate composed of DOWEX® 50 ion exchange resin (Dow Chemical Co.). The plates were developed in n-propanol, H_2O, NH_4OH (70:21:9). The developed plates were scraped in 0.5 cm segments and the scrapings suspended in an Aquasol® gel (New England Nuclear) for scintillation counting.

RESULTS

Excretion of ^{14}C-activity within 72 hours following a single oral dose of 1 and 100 mg/kg ^{14}C-VC is shown in Table 1. The percentage of the dose expired as VC per se was 2 and 67% respectively. Due to the disproportionate pulmonary elimination of VC, a greater percentage of the dose was metabolized and eliminated in the urine, feces, and as expired $^{14}CO_2$ by rats given 1 mg/kg than by rats given 100 mg/kg. No special precautions were taken to insure detection of volatile compounds when collecting and processing the urine, feces, and carcass. Thus, the ^{14}C-activity in the excreta and carcass represent non-volatile metabolites of ^{14}C-VC. The

overall recovery of ^{14}C-activity was 88.8% and 82.3% at the 1 and 100 mg/kg dose levels, respectively. The primary radiochemical contaminant in the ^{14}C-VC preparation was ^{14}C-labeled acetylene (4-5%). Due to the physicochemical properties of acetylene, the solvent cold traps used for the collection of expired VC would not trap the highly volatile ^{14}C-acetylene. Based on this assumption the total recovery of ^{14}C-activity due solely to VC would be slightly higher than expressed in Table 1.

The characteristic pattern of pulmonary elimination of VC differed greatly between rats given 1 and 100 mg/kg. (Figure 1, Table 2). During the first 4 hours after administration of 100 mg/kg, the pulmonary elimination of VC was biphasic. The two linear portions of the curves were determined by regression analysis of the logarithmically transformed data. The data were feathered by inspection to obtain an approximation of the rate constant for the rapid phase of elimination. The apparent first order rate constants for the rapid and slow phases were 0.043 and 0.014 min^{-1} (95% confidence intervals, ±0.012 and ±0.010, respectively).

These rate constants correspond to half-lives of 14.4 and 49.5 minutes. Following a dose of 1 mg/kg, pulmonary elimination of VC was monophasic with an apparent first order rate constant of 0.011 min^{-1} (95% confidence interval, ±0.001) corresponding to a half-life of 63.0 minutes. To assure that the ^{14}C-activity collected in the cold traps was VC, the trapping solutions were analyzed by gas chromatography. Other than the components of the trapping solution the only compound detected had an identical retention time as a standard gas sample of VC.

The elimination of ^{14}C-activity in the urine as a function of time after 1 and 100 mg/kg ^{14}C-VC is shown in Table 3 and Figure 2. Table 3 also shows the expiration of $^{14}CO_2$ as a function of time. At both doses, the excretion of urinary and expired $^{14}CO_2$ was rapid. Greater than 80% of the total excreted by these routes was eliminated within 24 hours.

In Figure 2 shows the urinary excretion of ^{14}C-containing metabolites of VC (the curves were drawn by inspection). A similar biphasic elimination was evident at both dose levels. For rats given 1 and 100 mg/kg VC

respectively, estimates of the apparent first order rate constants for the initial phase of elimination were 0.134 and 0.153 hours^{-1}. These correspond to half-lives of 5.2 and 4.5 hours. During this initial phase of elimination which lasted through 36 hours, 57 and 11% of the administered ^{14}C-activity had been excreted by rats receiving the low and high dose, respectively.

At both dose levels of ^{14}C-VC the liver contained the highest concentration of ^{14}C-activity after 72 hours (Table 4). The concentration in the liver expressed on a percent dose per gram tissue basis was 3-5 fold greater than muscle lung or fat. Consistent with the proportionally greater metabolism at the 1 mg/kg level, the proportion of the dose remaining in the tissues after 72 hours was considerably higher in rats given 1 mg/kg than those given 100 mg/kg.

Carbon-14 activity in the urine was separated into three regions of radioactivity by thin layer chromatography (Table 5). These three regions represent three ^{14}C-containing polar metabolites of VC. Regions II and III correspond to thiodiglycolic acid and S-(2-hydroxyethyl)-N-acetyl cysteine as identified by McGowan et al. (1975). The proportions

of radioactivity determined in the three regions were not influenced by dose. The 3 regions do not represent one-hundred percent of the ^{14}C-activity since streaking of radioactivity occurred and it was not possible to separate these areas into discreet peaks.

DISCUSSION

The results of the current study establish that the fate of VC following ingestion by rats is dose dependent. Following a dose of 1 mg/kg ^{14}C-VC, most of the ^{14}C activity was excreted in the urine as non-volatile metabolites and as $^{14}CO_2$ in expired air. After 100 mg/kg, the predominant mode of excretion was by expiration of VC. Therefore, it appears that the metabolism of VC is a dose-dependent, saturable process. Similar results on the excretion of ^{14}C-VC following oral ingestion in rats have been reported recently by Green and Hathway (1975).

The fate of VC following oral administration is consistent with its fate after inhalation (Hefner et al., 1975). In those studies, the rate of VC metabolism was more rapid in rats exposed to 100 ppm or less than in rats exposed to 220 ppm or greater. Because of the experimental procedure used by Hefner et al. (1975), evidence was obtained indicating that at least two pathways may be involved in the metabolism of VC and that the degree of their involvement was concentration dependent.

Interestingly, the predominant pathway for the metabolism of VC by rats exposed to 100 ppm or less was inhibited almost completely in rats pre-treated with ethanol. This suggested that the pathway for the metabolism of ethanol, which is also saturable, may be involved in the metabolism of VC. At low blood levels of ethanol, its elimination is solely a function of metabolism. As the blood concentration increases, a greater proportion of ethanol is excreted via the lungs (Lundquist and Wolthers, 1958).

Recently, Withey (1975) reported a biphasic clearance of vinyl chloride from the plasma of rats after cessation of inhalation exposure to concentrations of 500 to 7000 ppm or after intravenous injection of 50 to 75 mg/kg VC. The half-lives of the biphasic process were 4 to 9 min and approximately 40 minutes. These results deviate to some degree from those reported here. In this study the biphasic pulmonary excretion of VC following a dose of 100 mg/kg had half-lives of 14.4 and 49.5 minutes for the two phases. All considered, the half-lives for the slow component, 40 min vs 49.5 min appears equivacol. With regard to the differences for the half-lives of the first phase, 4 to 9 min vs 14.4 min, our value may be somewhat slower because of delayed absorption from the gastrointestinal tract.

In any case, the results of this study and those of Withey (1975) appear compatable for interpretive purposes.

Of paramount importance to assessing the hazard of exposure to VC is the fate of that portion metabolized. In the previous study (Hefner et al., 1975) it was speculated that potential alkylating metabolites such as chloroacetaldehyde and chloroethylene oxide may be formed in vivo from VC. A concurrent analytical chemistry study in this laboratory has identified two of the three polar urinary metabolites of VC as thiodiglycolic acid and S-2-(hydroxyethyl)-N-acetyl cysteine (McGowan et al., 1975). The identification of these metabolites is consistent with the proposed pathways for metabolism of VC. Chloroacetaldehyde and chloroethylene oxide will conjugate with glutathione and cysteine leading ultimately to the metabolites identified in the urine. Göthe (1975) reported recently the trapping of acetaldehyde formed from VC by an in vitro microsomal preparation. This provides additional support for the formation of chloroacetaldehyde.

Finally, work in progress and that reported previously by Hefner et al. (1975) shows that exposure of rats to

VC reduces the non-protein sulfhydryl content of the liver. Thus the metabolites of VC appear to react with and deplete the hepatic non-protein free sulfhydryls *in vivo*.

Green and Hathway (1975) recently reported the identification of 3 major metabolites in rats given 3 doses of 50 mg/kg VC at 3 hr intervals. The major urinary metabolite comprising 47% of all ^{14}C metabolites excreted in the urine was thiodiglycolic acid. In our study, the percentage of the total urinary metabolites identified as thiodiglycolic acid was 15.1±2.0 and 21.5±1.5% for rats given 1 and 100 mg/kg, respectively. Although these results appear inconsistent with those of Green and Hathway, it is likely that more thiodiglycolic acid is produced when repeated metabolically saturating doses of 50 mg/kg are given.

Contrary to our identification of S-(2-hydroxyethyl)-N-acetyl cysteine as a major ^{14}C-metabolite of VC, Green and Hathway (1975) reported S-2-chloroethylcysteine and S-(2-chloroethyl)N-acetyl cysteine as major urinary metabolites. S-2-chloroethylcysteine is a monofunctional sulfur mustard and has been shown to be mutagenic (Fahmy and Fahmy, 1958). Due to its chemical properties this compound would be extremely unstable and has been reported to have a half-life of only 7 minutes in an aqueous solution at 37°C and pH 7 (Ross, 1962). Therefore, it seems unlikely that the S-2-chloroethyl compounds would be stable in the urine. Nachtomi (1970) studying the metabolism of 1,2-dibromoethane (EDB) in vitro demonstrated the enzymatic conjugation of EDB with glutathione (GSH) to form β-bromoethyl-SG and its subsequent spontaneous hydrolysis to produce the isolated hydroxyethyl-SG. This is additional evidence for the instability of halo-ethyl sulfur derivatives.

Since it is possible that S-hydroxyethyl cysteine as identified in the current work is derived from a totally different pathway other than via chloroethyl cysteine, additional studies may be necessary to clarify the

discrepancy between the types of cystein conjugat s excreted in the urine. The metabolic scheme proposed by Green and Hathway (1975) does not include enzymatic processes. Chemical processes such as the free radical mediated mechanisms proposed by Green and Hathway for the metabolism of VC are governed solely by laws of mass action. Therefore, their proposed mechanism is inconsist nt with the saturation phenomena demonstrated in our work and effects of various enzyme inhibitors (pyrazole, ethanol, SKF525A) on VC metabolism as reported previously (Hefner, et al., 1975). The ultimate isolation of the reactive intermediates of VC may require further in vitro studies.

As a final point for discussion, it is important to consider, how the data gathered by this laboratory and others may relate to assessing the hazard of exposure to VC. Such a discussion has been made previously (Hefner et al. 1975). Data gathered since that report continue to support the hypothesis that the carcinogenicity of VC is related to the metabolic formation of alkylating metabolites. Rannug et al. (1974) have reported a positive mutagenic response in Salmonella typhimurium exposed to VC if microsomal enzymes are present but not in their absence.

The metabolites of VC identified in the urine indicate that the primary deactivating mechanism is by conjugation with the non-protein free sulfhydryl compounds, glutathione and cysteine. Studies in progress in this laboratory show that the non-protein free sulfhydryls of the liver are depleted in rats exposed to VC both as a function of concentration and exposure duration. As the levels of non-protein free sulfhydryls are depleted, the alkylating metabolites are more likely to react with protein, DNA, and RNA, eliciting proportionally greater toxicity including carcinogenicity. This phenomena has been demonstrated to markedly influence the toxicity of compounds such as N-acetylaminofluorene, bromobenzene, and furosemide (Gillette 1974a and 1975b). The threshold for the toxicity of these materials coincides with their reaction with tissue protein, DNA, and RNA.

Reactions with these cellular components and discernible toxicity occurs only after the glutathione levels are sufficiently depleted to preclude deactivation of the reactive metabolites of these agents.

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LEGENDS

Figure 1 Expired Vinyl Chloride expressed as % of the dose administered (1 and 100 mg/kg) versus hours. Each point represents the mean ± standard error of the mean of 5 rats. The linear phases of the curves were fit by linear regression analysis.

Figure 2 ^{14}C-activity excreted in the urine expressed as % of the dose administered (1 and 100 mg/kg) versus hours. Each point represents the mean ± standard error of the mean for 5 rats. The curves were drawn by inspection.

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TABLE 1

PERCENT OF ADMINISTERED ^{14}C-ACTIVITY RECOVERED FOLLOWING A SINGLE ORAL DOSE OF VINYL CHLORIDE (VC)[a]

	Dose Level	
	1 mg/kg	100 mg/kg
Expired:		
As VC	2.13±0.22[b]	66.64±0.67
As CO_2	13.26±0.47	2.52±0.13
Urine	59.30±2.75	10.84±0.95
Feces	2.20±0.39	0.47±0.06
Carcass & Tissues	11.10±0.47	1.83±0.14
Cage Wash[c]	0.84±0.45	0
Total Recovery	88.83±1.98	82.32±0.43

[a]Percentage of dose excreted over 72 hours. Only the ^{14}C-activity associated with the expired VC can be attributed to VC per se.

[b]Mean ± standard error of the mean, 5 rats/dose

[c]Distilled water wash of metabolism cage at termination of the study.

FIGURE 1

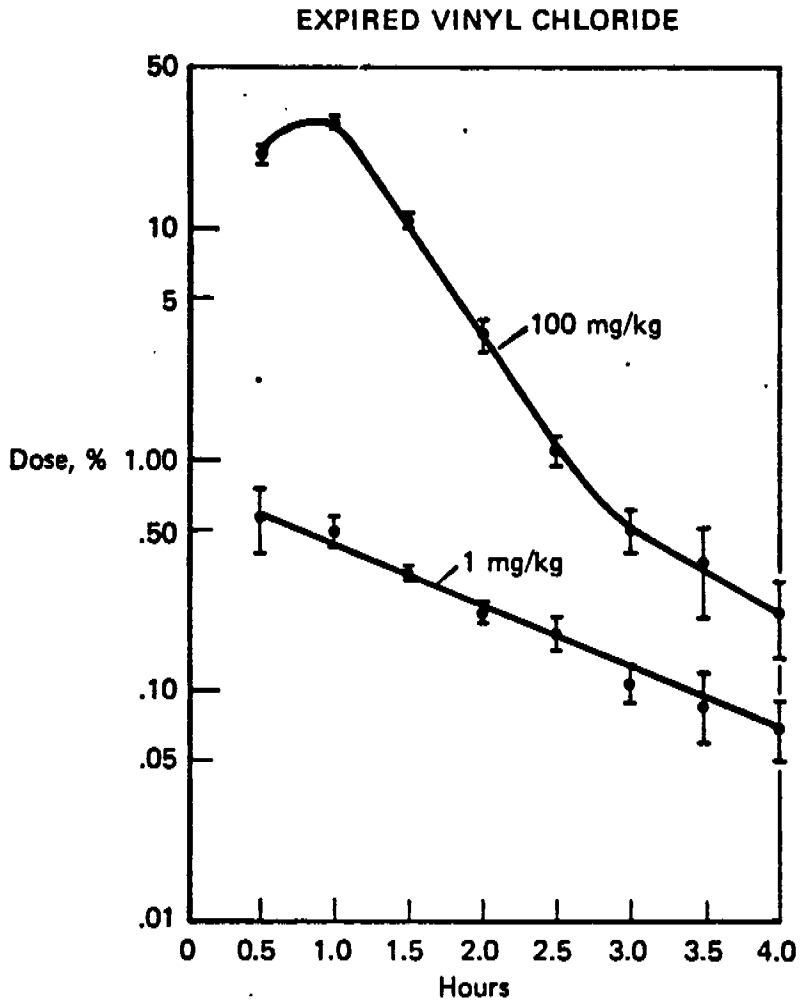

TABLE 2

PERCENT OF ADMINISTERED ^{14}C-VINYL CHLORIDE EXCRETED BY THE LUNGS AS A FUNCTION OF TIME FOLLOWING SINGLE ORAL ADMINISTRATION[a]

Time (hr)	Dose Level	
	1 mg/kg	100 mg/kg
0-0.5	0.58±0.18 [b]	20.90±1.56
0.5-1.0	0.50±0.07	28.93±1.19
1.0-1.5	0.33±0.02	10.96±0.69
1.5-2.0	0.22±0.02	3.46±0.53
2.0-2.5	0.18±0.03	1.10±0.16
2.5-3.0	0.11±0.02	0.51±0.10
3.0-3.5	0.09±0.03	0.36±0.15
3.5-4.0	0.07±0.02	0.22±0.08
4.0-8.0	0.04±0.01	0.18±0.04
8.0-12.0	0.01±0.00	0.02±0.01
Total	2.13±0.22	66.64±0.68

[a]VC in expired air was trapped exclusively of $^{14}CO_2$, see Methods. The ^{14}C VC in the trapping solution was confirmed by gas chromatographic analysis.

[b]Mean ± standard error of the mean, 5 rats/dose

FIGURE 2

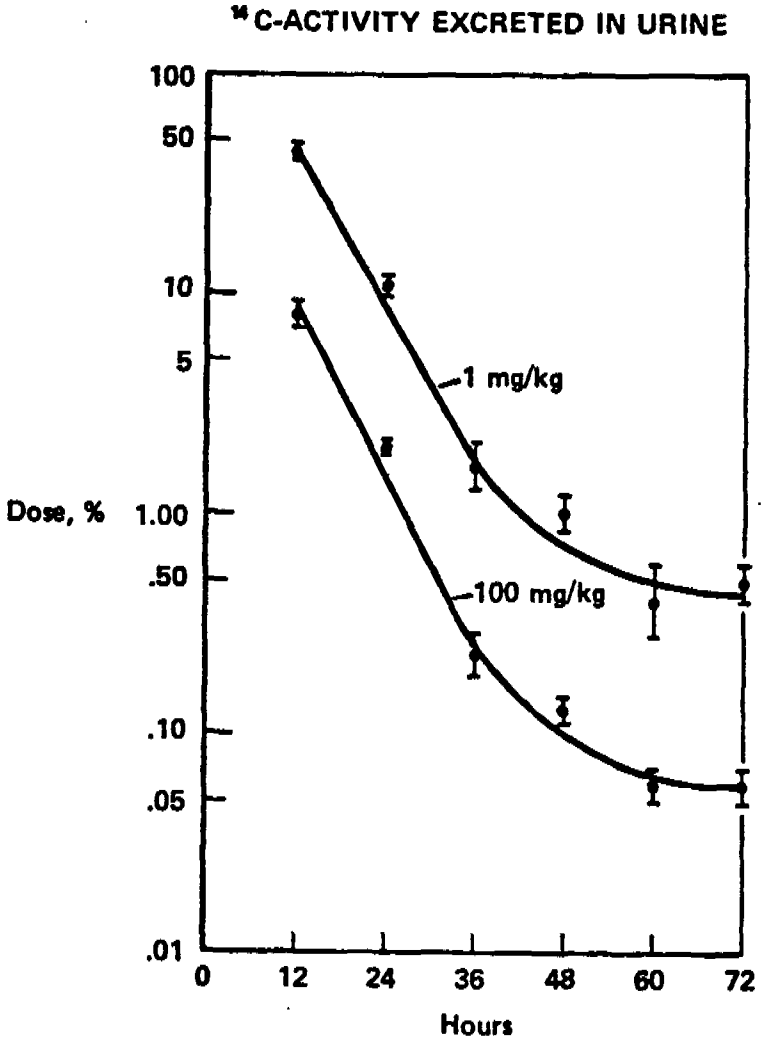
^{14}C-ACTIVITY EXCRETED IN URINE
Dose, %
100
50
10
5
1.00
.50
.10
.05
.01
1 mg/kg
100 mg/kg
0
12
24
36
48
60
72
Hours

TABLE 3

PERCENT OF ADMINISTERED ^{14}C-ACTIVITY EXCRETED IN THE URINE AND AS $^{14}CO_2$ FOLLOWING A SINGLE ORAL DOSE OF ^{14}C-VINYL CHLORIDE

	Dose Level			
	Urine		CO_2	
Time (hr)	1 mg/kg	100 mg/kg	1 mg/kg	100 mg/kg
0-12	44.47±3.19[a]	8.30±0.95	9.21±0.23	1.79±0.11
12-24	11.14±0.92	2.05±0.09	1.63±0.16	0.34±0.02
24-36	1.72±0.40	0.24±0.05	0.94±0.07	0.16±0.02
36-48	1.02±0.17	0.13±0.02	0.59±0.09	0.09±0.01
48-60	0.44±0.16	0.06±0.01	0.54±0.02	0.07±0.01
60-72	0.51±0.09	0.06±0.01	0.35±0.01	0.07±0.01
Total	59.30±2.75	10.84±0.95	13.26±0.47	2.52±0.13

[a]Mean ± standard error of the mean, 5 rats/dose

TABLE 4

PERCENT OF THE ADMINISTERED ^{14}C-ACTIVITY PER GRAM TISSUE AFTER ADMINISTRATION OF ^{14}C-VINYL CHLORIDE[a]

	Dose Level	
Tissue	1 mg/kg	100 mg/kg
Liver	0.182±0.005[b]	0.029±0.002
Skin	0.076±0.010	0.010±0.002
Carcass	0.046±0.002	0.007±0.001
Plasma	0.053±0.007	ND[c]
Muscle	0.031±0.003	0.006±0.001
Lung	0.061±0.003	0.011±0.001
Fat	0.045±0.008	0.006±0.001

[a]Remaining in the body after 72 hours.

[b]Mean ± standard error of the mean, 5 rats/dose

[c]Not detectable above background

TABLE 5

THIN LAYER CHROMATOGRAPHIC SEPARATION OF ^{14}C-CONTAINING METABOLITES IN THE URINE OF RATS GIVEN ^{14}C-VINYL CHLORIDE[a]

	R_f	Dose Level	
		1 mg/kg	100 mg/kg
Region I	0.18	19.1±4.6[b]	17.5±4.4
Region II[c]	0.45	15.1±2.0	21.5±1.5
Region III[d]	0.60	53.4±4.8	47.8±6.8

[a]Percent of total ^{14}C-activity recovered from the chromatography plate. The plates were composed of DOWEX® 50 ion exchange resin and developed in n-propanol, H_2O, NH_4OH (70:21:9).

[b]Mean percent ± S.E., 5 rats/group

[c]Corresponds to thiodiglycolic acid

[d]Corresponds to S-(2-hydroxyethyl)-N-acetyl cysteine