Vinyl Chloride

FATE OF ^{14}C-VINYL CHLORIDE FOLLOWING INHALATION EXPOSURE IN RATS

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SUMMARY

Inhalation exposure to vinyl chloride (VC) has been shown to be carcinogenic in rats and man. It is important in assessing the toxicological potential of inhaled VC to understand the disposition of VC in the body. Therefore, the objective of the present study was to determine the fate of inhaled ^{14}C-VC at different exposure concentrations in rats.

Male rats were exposed to 10 or 1000 ppm ^{14}C-VC for 6 hours and the routes and rates of elimination of ^{14}C-activity were followed for 72 hours after termination of exposure. Following exposure to 10 ppm VC, urinary ^{14}C-activity and expired VC comprised 68% and 2% respectively of the recovered radioactivity. After exposure to 1000 ppm VC, the proportion of the radioactivity in the urine decreased while that expired as VC increased representing 56% and 12% respectively.

The pattern of pulmonary elimination of VC *per se* was described by similar apparent first order kinetics following 10 or 1000 ppm with respective half-lives of 20.4 and 22.4

minutes. The elimination of ^{14}C-activity in the urine occurred in accordance with a two exponential equation; the half-lives for the initial phase of excretion were 4.6 and 4.1 hours following 10 and 1000 ppm respectively. The percent of the recovered ^{14}C-activity remaining in the carcass after 72 hours was 14% and 15% at the respective low and high exposure level. VC per se was not found in tissues.

The urinary ^{14}C-activity was separated by high pressure liquid chromatography into 3 major metabolites corresponding to N-acetyl-S-(2-hydroxyethyl)cysteine, thiodiglycolic acid and a third unidentified metabolite. The proportions of the urinary metabolites were not markedly influenced by the exposure magnitude.

The fate of inhaled ^{14}C-VC was shown to be dose dependent, and this is consistent with previous studies on the fate of VC following ingestion as well as inhalation. The relation of the present work to other recently reported studies on VC is discussed.

INTRODUCTION

Inhalation exposure to vinyl chloride (VC) has been shown to be carcinogenic in rats (Maltoni and Lefemine, 1975) and in man (Creech and Johnson, 1974; Tabershaw and Cooper, 1974). Preliminary studies on the fate of inhaled VC (Hefner, et al., 1975) indicated that VC was metabolized in part to polar products which were excreted in the urine. By using kinetic parameters and inhibitors of drug metabolism it was shown that the fate of VC was dependent on the magnitude of exposure. Also, the data led to the hypothesis that VC may be metabolized to a reactive metabolite which may ultimately be responsible for the carcinogenic activity. The important aspect of these results is that the toxicity of VC may increase disproportionately with increasing exposure or that the mechanisms for detoxification of VC per se or its reactive products may become saturated at high levels of exposure.

Two of the three major urinary metabolites of VC in rats have been identified as N-acetyl-S-(2-hydroxyethyl)cysteine and thiodiglycolic acid (McGowan et al., 1975). Thus it appears that the primary detoxification mechanism of VC or its reactive metabolites involves conjugation with hepatic glutathione. The glutathione conjugates are subject to

hydrolysis resulting in excretion of cysteine conjugates in the urine. This is also consistent with the observed depression of hepatic non-protein sulfhydryl groups in rats exposed to VC (Hefner et al., 1975).

Several studies on the fate of ingested ^{14}C labeled VC have been completed recently (Green and Hathway, 1975; Watanabe et al., 1975). Results from the latter study show that as the oral dose of ^{14}C-VC was increased from 1 to 100 mg/kg the proportion of the administered dose expired by the lungs as VC per se markedly increased from 2 to 67%. Conversely, with increasing doses of ^{14}C-VC, the percent of the dose metabolized and eliminated via the urine decreased. Since the rate of urinary excretion was not altered by the dose level, it was concluded that the dose dependent fate of ingested VC was due to saturation of metabolism.

Since the previous work on the fate of inhaled VC in rats (Hefner et al., 1975) was conducted primarily with non-labeled VC, it was not possible to thoroughly investigate the metabolism or the elimination kinetics following inhalation exposure. The objective of the present study was

to characterize the pharmacokinetics and metabolism of ^{14}C VC in rats following a single inhalation exposure to different concentrations.

METHODS

Test Material. 1,2-^{14}C-vinyl chloride (^{14}C-VC) was synthesized directly from 1,2-dichloroethane (1,2-^{14}C, lot #819-021, 3.4 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. The ^{14}C-VC was synthesized immediately prior to each experiment. Non-labeled VC (Matheson Gas Products) of 99.9% minimum purity was mixed with the ^{14}C material to obtain the desired specific activity. Typically 40 ml of the ^{14}C-VC, helium gas mixture (about 20,000 ppm VC) was injected into a 5 liter SARAN bag (Anspec Inc) containing the desired quantity of 100% non-labeled VC.

Exposure. Groups of 4 rats were exposed to 10 or 1000 ppm ^{14}C-VC for 6 hours. The exposure chambers consisted of two glass Roth type metabolism cages (each approximately 5 liters). Two rats were placed in each chamber and room air was drawn by vacuum through the chambers connected in parallel at a rate of 1 liter/minute. The ^{14}C-VC in the SARAN bag was metered into the system with a glass dual syringe pump at the appropriate rate to maintain the correct atmospheric concentration. The VC concentration entering the inhalation chambers was monitored continuously by an infrared spectrophotometer (Wilks) sat at 10.6 μ. Samples (1 ml) of the atmosphere in each of the inhalation chambers was analyzed by gas chromatography (Watanabe et al., 1975) at 1 hour intervals throughout the exposure. At corresponding intervals, the ^{14}C-activity was determined by bubbling 1 ml aliquots of the chamber atmosphere into a scintillation vial containing CONCIFLUOR (Mallinckrodt Chemical Works), 2-methoxyethanol, toluene (6:11:83) and subsequent counting in a Nuclear Chicago Mark II liquid scintillation spectrometer. The specific activities were 4848 and 68 DPM/μg VC for the 10 and 1000 ppm VC exposures, respectively.

The inhalation chambers were operated in laboratory fume hoods to minimize contamination of the working environment. After transit through the inhalation chambers the ^{14}C-VC was trapped by bubbling through a trap containing 500 ml of toluene, 2-methoxyethanol (80:20). This trap was changed hourly and the ^{14}C-VC disposed of as liquid radioactive waste according to standard regulations.

Animals and Sample Collection. Male Sprague-Dawley (Spartan substrain) rats weighing from 235-260 g purchased from Spartan Research were used in all studies. Food and water was available ad libitum except during exposure. Immediately after exposure, individual rats were placed in separate glass Roth-type metabolism chambers for the collection of urine, feces and expired air. Room air was drawn by vacuum through the chambers at 400-500 ml/min. The exiting air was passed through a series of traps to collect the expired ^{14}C-VC and $^{14}CO_2$. The air exiting the chamber was first passed through a glass tube containing about 40g 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.

Samples of excreta were collected for 72 hours after termination of exposure. Expired VC was collected at 0.5 hour intervals for 4 hours; the CO_2 trap and urine receptacle (immersed in dry-ice bath) were changed at 12 hour intervals for 72 hours; and feces were collected every 24 hours. At the termination of the study (72 hours) the animals were decapitated, exsanguanated and samples of tissue (fat, kidney, liver, lung, muscle, plasma) were collected for analysis of ^{14}C-activity. The remaining carcass was skinned and homogenized (50% w/v) in distilled water and analyzed for ^{14}C-activity.

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, tissues and the remaining carcass 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.

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. After separation from the methanol extracts by high pressure liquid chromatography (McGowan et al., 1975), the ^{14}C-containing urinary metabolites were quantitated by counting sequential fractions from the chromatographic column by liquid scintillation spectrometry.

RESULTS

Excretion of ^{14}C-activity within 72 hours after exposure to 10 or 1000 ppm ^{14}C-VC is shown in Table 1. The percent of ^{14}C-activity eliminated or retained in the body was calculated from the total recovered radioactivity. A slightly greater percentage of the ^{14}C-activity was metabolized and eliminated in the urine in rats exposed to 10 ppm than those exposed to 1000 ppm. In contrast, the percentage of the ^{14}C-activity expired by the lungs as VC per se was 2% and 12% following exposure to 10 and 1000 ppm ^{14}C-VC, respectively. Although more VC was expired via the lungs following exposure to 1000 ppm, it is noteworthy that the proportion of radioactivity remaining in the carcass and tissue was essentially equivalent following both levels of exposure suggesting that a greater fraction is being sequestered by tissue at the high level of exposure.

The pattern of pulmonary elimination of ^{14}C-VC following exposure to 10 or 1000 ppm were similar (Figure 1). Although VC was collected for 4 hours after terminating exposure, ^{14}C-activity in the VC traps could be detected for only 2 hours at both levels of exposure. The curves were fit by linear regression analysis of the logarithmically transformed data. The apparent first order rate constants for pulmonary elimination of VC were 0.034±0.002 and 0.031±0.001 (±S.D.) hrs^{-1} following exposure to 10 and 1000 ppm ^{14}C-VC. These rate constants correspond to half-lives of 20.4 and 22.4 minutes respectively.

The elimination of ^{14}C-activity (metabolites of VC) in the urine as a function of time is shown in Figure 2. A similar biphasic elimination was evident following 10 and 1000 ppm exposure levels. The initial linear portions of the excretion curves from 12-36 hr were fit by regression analysis of the logarithmically transformed data. Estimates of the respective apparent first order rate constants for the initial phase of elimination were 0.151±0.009 and 0.168±0.001 (±S.D.) hr^{-1}. These correspond to half-lives of 4.6 and 4.1 hours. The data for the slow phase of the urinary

excretion curves were extremely variable and since this phase accounted for less than 3% of the total urinary radioactivity, no attempt was made to estimate the rate constants.

Although unlikely, VC per se may accumulate in some tissues; therefore, at autopsy duplicate samples of tissue were obtained. One set of tissues was processed at -196°C to insure detection of VC or other volatiles. These samples were frozen immediately by immersion in liquid N_2 (-196°C) and then pulverized at this temperature in a Spex freezer mill (Spex Ind. Inc.). Aliquots of the powdered tissue were placed directly in scintillation vials containing AQUASOL (New England Nuclear) and a thixotropic gel was prepared for counting. The tissue ^{14}C-activity determined by this procedure was not significantly different than that determined by conventional combustion techniques using a biological material oxidizer (refer to methods section). Since there were no apparent differences between the two methods and since larger aliquots could be processed using the combustion technique giving greater accuracy, the values in Table 2 represent those determined from the combustion analysis. ^{14}C-activity found in the tissues represents non-volatile metabolites of VC. Therefore the tissue data (Table 2) is

expressed both as the percent of total ^{14}C-activity recovered per g tissue and as the percent of metabolized ^{14}C-activity per g tissue. The latter parameter was calculated by dividing the ^{14}C-activity per g tissue by the total ^{14}C-activity recovered minus the ^{14}C-activity contributed from expired VC *per se*. This calculation normalizes the tissue radioactivity to the VC which was metabolized. The liver and skin contained the highest concentrations of ^{14}C-activity after 72 hr at both exposure levels. When normalized for metabolized VC, the ^{14}C-activity in liver and skin appeared to increase between the 10 and 1000 ppm exposures. Although not statistically significant, this apparent increase suggests that at the high level of exposure a greater proportion of the metabolized VC has been sequestered by these tissues.

Carbon-14 activity in the urine was separated into three major metabolites by high pressure liquid chromatography (McGowan *et al.*, 1975). The urinary metabolites following inhalation exposure showed the same chromatographic characteristics when compared to those after oral ingestion (Watanabe *et al.*, 1975). This indicated that the same metabolites were formed following both routes of administration. Two of the three major metabolites have been identified previously as *N*-acetyl-*S*-(2-hydroxyethyl)cysteine and

thiodiglycolic acid (McGowan et al., 1975). Identification of the third metabolite is currently under investigation. In the present study, the proportions of radioactivity determined by the three metabolites were not markedly influenced by exposure concentration (Table 3). The 3 metabolites represented 96-97% of the total radioactivity excreted in the urine.

DISCUSSION

The fate of ^{14}C-VC in rats following exposure to 10 and 1000 ppm for 6 hours was shown to be dose dependent. The predominant route of excretion for metabolized VC following either level of exposure was via the urine. Since ^{14}C-activity in the urine represented non-volatile metabolites of VC, this further substantiated the previous conclusion (Hefner, et al., 1975) that VC is readily metabolized to polar products. The present results are also consistent with the dose dependent fate of VC following single oral administration in rats (Watanabe et al., 1975; Green and Hathway, 1975).

If the absorption, distribution, metabolism and elimination of a chemical can be described by first order processes over a specified range of doses (linear pharmacokinetics) then

1) the rate of elimination by a given route, and 2) the proportion of ^{14}C-activity eliminated by the various routes of excretion will not be altered over the dose range tested. It also follows that the body burden (total µg equivalents) following various exposure levels should increase proportionately with the increase in exposure. Since it is evident that the criteria stated above are not applicable to the fate of inhaled VC, the question is raised as to what parameter may be responsible for the dose dependent fate of VC. The rate of elimination of VC per se from the lungs or ^{14}C-activity in the urine was not different in rats exposed to 10 or 1000 ppm VC. This implies that the dose dependent fate was not due to saturated routes of excretion of VC. However, the results are consistent with the hypothesis that the metabolism of VC is saturated at high exposure levels.

In previous studies on inhaled VC (Hefner, et al, 1975) the rate of VC metabolism appeared to be more rapid in rats exposed to 100 ppm or less than in rats exposed to 220 ppm or greater. The rate of metabolism at levels above 220 ppm was about 33% of the rate when compared to exposure levels below 100 ppm. Since the body burden (µg equivalents VC) following inhalation exposure consists primarily of metabolites of VC, it might be expected that the body burden

values should reflect the degree of metabolism of VC. The body burden increased 27 fold as the exposure was increased 100 fold (from 10 to 1000 ppm). The increase in body burden coincides well with the reduced rate of metabolism at exposure concentrations >220 ppm as observed in the previous study. The 27 fold increase in body burden following a 100 fold increase in exposure concentration further suggests that the metabolism of VC is saturated in rats when exposed to 1000 ppm VC.

Although a greater proportion of the ^{14}C-activity was expired as VC per se following exposure to 1000 ppm than 10 ppm, it is significant that the proportion of radioactivity remaining in the carcass and tissues following 1000 ppm was still equivalent to that after 10 ppm. The highest levels of tissue radioactivity (expressed on a per g basis) were detected in liver and skin. When these values were normalized for that portion of VC which was metabolized, an increase appears to have occurred in those rats exposed to 1000 ppm. The data suggest that a greater proportion of the metabolized VC remained in the tissues following the 1000 ppm exposure, and this appears to be a result of the dose dependent metabolism of VC. If the carcass and tissues were assayed at an earlier time after exposure rather than 72 hr, it is very likely that the magnitude of the increase in tissue residues between the 10 and 1000 ppm levels would be more pronounced.

VC is a lipophilic molecule and therefore may accumulate in fat or fatty tissue. In fact it has been reported that VC was detected in fat biopsy samples obtained from industrial workers (Selikoff, 1974). However, in rats 72 hours after a single exposure to 10 ppm ^{14}C-VC, fat samples contained the least amount of ^{14}C-activity when compared to other tissue. Interestingly, the ^{14}C-activity detected at the 10 ppm exposure appeared to be comprised of non-volatile metabolites rather than VC per se. In exposure of rats to 1000 ppm VC no ^{14}C-activity was detected at a detection limit of 3 µg VC equivalents per g fat. The absence of detection following exposure to 1000 ppm versus finding trace amounts following exposure to 10 ppm is likely a reflection of the higher specific activity used in the latter exposure. It is concluded that VC per se will not accumulate in fat. The propensity of a lipophilic molecule such as VC to accumulate in fat is very likely counteracted by its rapid metabolism and pulmonary elimination.

Two of the three major urinary metabolites of VC identified from rats treated orally with ^{14}C-VC were N-acetyl-S(2-hydroxyethyl)cysteine and thiodiglycolic acid (McGowan et al., 1975). The three major urinary metabolites in rats

following inhalation exposure showed an identical chromatographic profile as those isolated after oral administration. This establishes that the metabolites are the same in both the oral and inhalation studies.

It appears that the metabolism of VC is mediated by several pathways. The metabolic uptake of VC in rats has been shown to be blocked by ethanol (Hefner et al., 1975) and inhibitors of microsomal drug metabolizing enzymes (Bolt et al., 1975a). Furthermore, Kappus et al. (1975) demonstrated the essential requirement of NADPH for the covalent binding of VC metabolites to rat liver microsomes and an additional study showed that a xanthine oxidase-hypoxanthine system also caused covalent binding of VC metabolites to albumin. These data suggest that the metabolism of VC may be mediated by both soluble and particulate enzymes.

Although evidence has been presented which suggests that the dose dependent fate of ^{14}C-VC following oral (Watanabe et al., 1975) and inhalation administration is due to metabolic saturation, the urinary metabolites have not shown any qualitative or striking quantitative differences over the dose or exposure ranges tested. Although this may appear inconsistent, it is conceivable that the several pathways

responsible for the metabolism of VC produce the same end products. It must be emphasized that the urinary metabolites of VC represent metabolic end products and do not necessarily indicate formation of similar metabolic intermediates.

From a conceptual standpoint it is important to consider how the present results relate to previous studies as well as recently published studies on VC. The fate of VC following inhalation exposure was shown to be dose dependent. This observation is consistent with the theory that the metabolism of VC becomes saturated at high exposure levels. The urinary metabolites appear to be primarily conjugates of cysteine indicating that VC or its reactive metabolites are detoxified primarily by covalent binding with hepatic glutathione. Evidence that the toxicity of VC is mediated by the production of reactive metabolites is mounting. Numerous studies have shown an enhanced positive mutagenic response in certain strains of Salmonlla typhimurium and E. coli if fortified liver homogenates or microsomal enzymes are present (Bartsch et al., 1975; Malaveille et al., 1975; Rannug et al., 1975; Greim et al., 1975).

Since non-protein sulfhydryl groups (primarily glutathione, GSH, in the liver) are decreased upon treatment with VC

(Hefner et al., 1975), as hepatic GSH is reduced, VC or reactive metabolites may be free to react with other intracellular macromolecules including DNA, RNA, protein, lipids (Watanabe et al., 1975). Recent reports have demonstrated that in the presence of fortified microsomal preparations VC covalently binds to rat liver microsomes (Kappus et al., 1975), protein sulfhydryl groups and RNA (Bolt et al., 1975b). In the study reported herein, preliminary evidence has been obtained which indicates that in rats exposed to 1000 ppm for 6 hours, there is a disproportionate increase in the ^{14}C activity in the liver and skin 72 hrs postexposure when compared to rats exposed to 10 ppm. This finding suggests that upon exposure to the higher level, a larger fraction of the reactive metabolites are binding to macromolecules (DNA, RNA, protein and lipids) of these tissue rather than to GSH. If substantiated in studies underway, such results will be consistent with predicting a disproportionate increase in toxicity including cancer, as the exposure level is increased.

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LEGENDS

Figure 1 — Expired vinyl chloride expressed as percent of the recovered radioactivity versus hour following a 6 hr exposure to 10 and 1000 ppm VC. Each point represents the mean ± standard error of the mean of four rats. The curves were fit by linear regression analysis.

Figure 2 — ^{14}C-activity excreted in the urine expressed as percent of the recovered radioactivity versus hour following a 6-hour exposure to 10 and 1000 ppm VC. Each point represents the mean ± standard error of the mean for four rats. The initial log linear phase of the curves (12-36 hours) were fit by linear regression analysis.

TABLE 1

Percent ^{14}C-Activity Eliminated During 72 Hr Following Inhalation Exposure to ^{14}C-Vinyl Chloride for 6 Hr[a]

	Percent ^{14}C-Activity			
Exposure Concentration:	10 ppm		1000 ppm	
Expired:				
As VC	1.61±0.16[b]	(4)[c]	12.26±0.96[b]	(814)[c]
As CO_2	12.09±0.43	(30)	12.30±0.63	(817)
Urine	67.97±1.71	(169)	56.29±1.96	(3739)
Feces	4.45±0.22	(11)	4.21±1.05	(280)
Carcass and Tissues	13.84±1.16	(34)	14.48±0.52	(977)
Cage Wash[d]	0.15±0.08	(<1)	0.23±0.09	(15)
Total µg equivalents VC recovered		(248)		(6642)

[a]Expressed as percent of the total ^{14}C-activity recovered.

[b]Mean ± standard error from 4 rats.

[c]Microgram equivalents vinyl chloride

[d]Water, acetone wash of the metabolism cage at termination of the experiment.

TABLE 2

Percent of ^{14}C-Activity Per Gram Tissue 72 Hr Following an Inhalation Exposure to ^{14}C-Vinyl Chloride for 6 Hr

Tissue	Exposure Concentration:	Percent ^{14}C-Activity 10 ppm		1000 ppm	
Liver		0.139±0.009[a]	(0.35)[c]	0.145±0.008[a]	(9.63)[c]
		0.141±0.009[b]		0.165±0.009[b]	
Skin		0.072±0.004	(0.18)	0.115±0.010	(7.64)
		0.073±0.004		0.131±0.011	
Carcass		0.048±0.004	(0.12)	0.049±0.004	(3.26)
		0.049±0.004		0.056±0.005	
Plasma		0.051±0.001	(0.13)	ND[d]	
		0.052±0.001			
Muscle		0.052±0.005	(0.13)	0.038±0.003	(2.52)
		0.053±0.005		0.043±0.003	
Lung		0.065±0.007	(0.16)	0.046±0.001	(3.06)
		0.066±0.007		0.052±0.001	
Fat		0.026±0.006	(0.07)	ND[d]	
		0.026±0.006			
Kidney		0.079±0.003	(0.20)	0.057±0.005	(3.79)
		0.080±0.003		0.065±0.006	

[a] Expressed as percent of total ^{14}C-activity per g tissue. Uncorrected for expired VC: $\frac{\text{DPM per g tissue}}{\text{total DPM recovered}}$

Mean ± standard error from 4 rats.

[b] Expressed as percent of metabolized ^{14}C-activity per g tissue. Corrected for expired VC:

$$\frac{\text{DPM per g tissue}}{\text{total DPM recovered minus DPM of expired VC}}$$

Mean ± standard error from 4 rats.

[c] Microgram equivalents vinyl chloride per g tissue

[d] Not detectable, detection limit for plasma and fat was 3 µg/g tissue (3 ppm).

TABLE 3

Separation of ^{14}C-Containing Urinary Metabolites Excreted by Rats During the First 24 Hr Following Exposure to Vinyl Chloride for 6 Hr

Metabolite	10 ppm	1000 ppm
A) N-acetyl-S-(2-hydroxyethyl)-cysteine	40.6±3.9[a]	39.0±2.4
B) Thiodiglycolic acid	25.9±3.6	17.6±2.1
C) Unidentified	30.4±2.2	39.4±1.2
TOTAL	96.9	96.0

[a]percent of total urinary ^{14}C-activity (mean ± standard error from 4 rats).

FIGURE 1

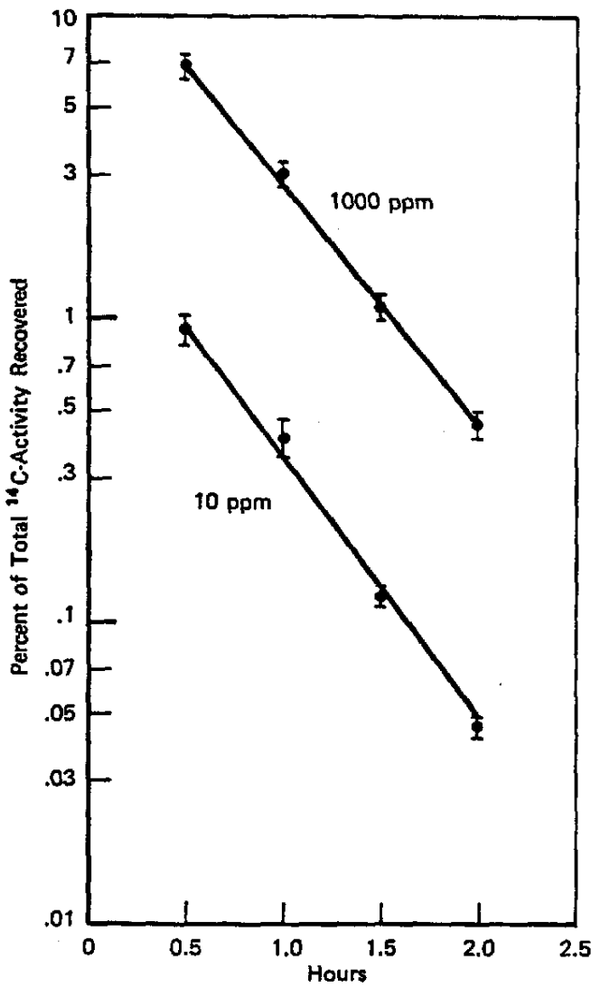

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FIGURE 2