INTERPRETIVE REVIEW OF THE ANIMAL TOXICOLOGIC, PHARMACOKINETIC/METABOLISM, BIOMOLECULAR AND IN-VITRO MUTAGENICITY STUDIES ON VINYLIDENE CHLORIDE AND THE SIGNIFICANCE OF THE FINDINGS FOR MAN

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Introduction

This paper presents an interpretive scientific review of these and other pertinent references concerned with toxicity, pharmacokinetics/metabolism and biomolecular studies on VDC in laboratory animals. The appropriateness of extrapolating findings from the various lab animal species to man and the overall implications of the animal data for man is discussed.

Summary

Pharmacokinetic/metabolism and biomolecular events in rodents exposed to vinylidene chloride (VDC) clearly demonstrate the inherent species differences which contribute to differences in target organ toxicity and in species/strain specific and sex-related tumorigenic response. The target organ toxicity in the rodent species is related to the capacity to biotransform VDC to reactive species with the mouse having a far greater capacity than the rat or man. The tumorigenic response to VDC, was shown to be mediated via a non-genetic mechanism, namely, recurrent tissue damage. Man, by virtue of having a slower rate of oxidative metabolism than either rodent species is likely to be less sensitive to the toxic effects of VDC than the rat and significantly less sensitive than the mouse. Expoure to VDC concentrations not causing cytotoxicity would be unlikely to result in adverse health effects in man.

I. Long-term Studies Demonstrate the Mouse is More Sensitive to the Toxic Effects of Vinylidene Chloride Than the Rat or the Hamster.

The results of several long-term inhalation and ingestion studies on vinylidene chloride (Rampy et al., 1977; Quast et al., 1982; McKenna et al., 1980, Maltoni et al., 1977, 1980; Viola and Caputo, 1977) showed that the mouse is more

were increased, however, the increase which was evident after the 2nd day of exposure to 60 ppm was a fraction of that observed in the mice (Table 1).

TABLE 1

Effect of Vinylidene Chloride Exposure on Serum Enzymes in Male Rats and Mice

Days Exposure	Serum Enzyme	VDC - (ppm) Rats[a] 0	Rats[a] 60	Mice[b] 0	Mice[b] 60
1	SGOT	66±10	74±6	56±8	1946±271
	SGPT	28± 2	44±7	32±6	3043±209
2	SGOT	63± 4	264±33	82±30	751±150
	SGPT	34± 4	198±29	38±4	1112±226
3	SGOT	81± 4	238±47	64±14	no survivors
	SGPT	34± 6	122±29	29±2	

[a]Control and 60 ppm n = 5.

[b]Control n = 4 or 5; 60 ppm day 1 n = 4, day 2 n = 2.

Adapted from Short et al., 1977

The toxicity to the liver of the mice and rats as revealed by the elevation of serum enzyme, was confirmed by histopathologic observations. Examination of kidney tissue of the CD-1 mice showed the kidney also to be a target organ with all the mice exposed to 15, 30 or 60 ppm VDC having severe tubular necrosis after 1 or 2 days of exposure; no kidney toxicity was observed in the rats at 60 ppm.

sensitive than the rat or the hamster to toxic effects of VDC; mice exposed to 25 ppm showed liver and marked kidney changes whereas 25 ppm exposure of hamster was a no-toxic effect concentration and 75 ppm exposure of rats caused only minimal, reversible liver changes. Furthermore, only following exposure of mice to vapor concentrations that were markedly toxic and near the acutely lethal level (Maltoni et al., 1977, 1980) was a tumorigenic response observed. Various shorter term studies also demonstrated significant differences between the rat and mouse in the expression of frank toxicity, an understanding of which is paramount in the evaluation of the animal data prior to assessment of safety for man exposed to VDC at permissible levels in th workplace, or in the ambient environment.

A direct comparison study to delineate the differences between male CD rats and male CD-1 mice following exposure to various vapor concentrations up to 60 ppm continuously for 23 hours/day was conducted by Short et al., 1977. After 2 days of exposure to 60 ppm VDC, mortality differences between the species were dramatic, 80% in the mice and 0% in the rats. VDC was observed to produce more damage, as measured by elevated serum enzymes, in the liver of the mice than in the rats. A dose-related increase in both serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) occurred in mice exposed to VDC for one day. The serum enzymes in the rats

Longer-term exposure via inhalation or ingestion of VDC of Sprague-Dawley, CD and Alderley Park rats likewise revealed the liver to be the target organ in this species. Specifically the results of a 90-day toxicity inhalation study and a two-year toxicity and oncogenicity study involving 18 months of exposure of Sprague-Dawley rats to 25 or 75 ppm VDC, 6 hours/day, 5 days/week, showed a minimal exposure-related effect characterized as a midzonal hepatocellular fatty change after 30 and 90 days of the 90-day study and after 3, 6 and 12 months of the 2-year study (Balmer et al., 1976; McKenna et al., 1980). The non-progressive liver change in the rats was readily reversible on cessation of the exposure after 18 months in the 2-year study. No toxicologically significant exposure-related changes were observed in serum enzymes values in either study.

Lee et al., 1977 reported that the liver of CD rats exposed to 55 ppm VDC, 6 hours/day, 5 days/week for periods up to 12 months, showed marked or severe focal, disseminated vacuolization indicative of fatty change. No persistent change was found in serum enzyme values. Gage, 1970 reported that Wistar-derived Alderley Park rats exposed to 500 ppm VDC, 6 hours/day, 5 days/week for 4 weeks showed liver cell degenerative changes whereas at 200 ppm no liver toxicity was observed. Serum enzymes determinations were not made in this study.

II. The Highest Tolerated Concentration for Survival of Swiss Mice on Oncogenicity Inhalation Studies was Determined to be 25 ppm; Histopathologic Examination, However, Established That 25 ppm in the Mouse and 200 ppm in the Sprague-Dawley Rat Exceeded the Maximum Tolerated Dose.

Oncogenicity studies conducted in Sprague-Dawley rats and Wistar rats revealed the highest level of VDC tolerated by these rats was less than 200 ppm (Maltoni et al., 1977, 1980; Viola and Caputo, 1977). Maltoni et al., 1977, 1980 reported that two sequential daily exposures of 4 hour duration to 200 ppm VDC produced strong toxic effects, fatty degeneration in the liver and early necrotic changes of renal tubuli in the Sprague-Dawley rat and that 150 ppm was the highest "bearable" level for prolonged exposure. Likewise, Viola and Caputo, 1977, reported that the high exposure level in their original oncogenicity study with Wistar rats was lowered from 200 ppm to 100 ppm in the 6th month to avoid toxic reactions from occurring during the remainder of the 12-month study. A second study by these investigators was conducted in the Sprague-Dawley rat at 100 ppm and 75 ppm VDC; the pathologic findings in this study have not as yet been reported.

A study on Swiss mice revealed high mortality and severe toxic effects as a result of exposure, 4 hours/day, to VDC vapor concentrations of 200 or 100 ppm for 2 days, and of 50 ppm for 4 days, and the mice exposed to 25 ppm reportedly

TABLE 3

Mortality in Various Strains of Mice Exposed to 200 ppm Vinylidene Chloride

Mouse Strain	Mortality Rate	
	Male	Female
Ha(ICR)	6/10	4/10
$B_6C_3F_1$	10/10	10/10
CD-1	10/10	0/10
CF-W	10/10	1/10

Gross and histopathologic examination of these strains of mice showed that the male mice at all exposure levels had a marked degree of nephrotoxicity with renal failure accounting for the mortality. Renal toxicity was insignificant in all female mice when compared to the male mice of the same strain. The cause of death in the Ha(ICR) and $B_6C_3F_1$ female mice was reportedly associated with acute hepatotoxicity.

The greater sensitivity of the Swiss mouse, and particularly the male mouse, to the toxic effects of VDC has been correlated with a carcinogenic response after repeated exposure to a concentration of 25 ppm. This concentration, which was near the lethal concentration (50 ppm) for the Swiss mice, produced marked changes in the kidneys of the mice. Exposure to 10 ppm, a concentration producing significantly

less toxicity, did not result in a carcinogenic response. The kidney changes at 25 ppm were confirmed by autopsy of several mice that died within 1-2 months of the start of the study (Maltoni, 1977b). No carcinogenic response was elicited in Balb/c, C_3H, and $C_{57}Bl_6$ mice exposed to VDC in long-term inhalation studies (Maltoni, 1980).

No tumorigenic response was observed in a third species, the Chinese hamster, following inhalation exposure of 25 ppm VDC, 4 hours/day, 4 days/week for 1 year and held for 1 year post-exposure period before termination (Maltoni et al., 1977, 1980). Furthermore, the lack of tumorigenic response following oral administration via gavage of VDC has been demonstrated in bioassays with the rat or the mouse (NCI, 1980; Maltoni et al., 1977, 1980). National Toxicology Program, 1981 reported that no tumorigenic response had been observed in a 2-year study in Fischer 344 rats, at dose levels, 1 or 5 mg/kg/day, nor in $B_6C_3F_1$ mice given 2 or 10 mg/kg daily. Maltoni et al., 1977, 1980 reported no tumorigenic response in Sprague-Dawley rats administered via gavage 20, 10 or 5 mg/kg/day and 0.5 mg/kg/day for 4 or 5 days/week for 1 year and held for 1 year post-exposure period before termination.

A 90-day toxicity study incorporating VDC in the drinking water of Sprague-Dawley rats at concentrations of 60, 100 or 200 ppm (equivalent average doses 6, 10 or 19 mg VDC/kg body

weight/day for male rats and 8, 13 or 26 mg/kg/day for female rats) showed minimal hepatocellular fatty changes in rats ingesting 200 ppm VDC. The changes were not progressive in nature as demonstrated by the results of the 2-year toxicity and oncogenicity drinking water study conducted at the same concentrations (Humiston et al., 1978). The group of male rats ingesting 200 ppm VDC over a 2-year period showed, in addition to minimal hepatocellular changes, had an increased incidence of periportal hepatocellular hypertrophy. The female rats at all dose levels showed minimal hepatocellular fatty change and periportal hepatocellular hypertrophy.

IV. The Toxicity and Tumorigenicity Observed in Mice Exposed to Vinylidene Chloride Correlates With the Greater Capacity of the Mouse to Metabolize Vinylidene Chloride, the Enhanced Production of Reactive Metabolites in the Target Organs, and the Time Course for Covalently Bound ^{14}C-Activity in the Kidney of the Mouse, Relative to that of the Rat.

In an attempt to understand the differences between the mouse and the rat studies were designed to characterize the pharmacokinetics and metabolism in various strains of both rodent species. A comparison of the overall fate of inhaled or ingested VDC in rats and mice showed that the major differences were quantitative rather than qualitative. The

most conspicuous difference was in the greater amount of the parent compound excreted via the pulmonary system by the rat as compared to the mouse following an oral dose of 50 mg/kg (Jones and Hathway, 1978a). Twenty-eight percent (28%) of the administered dose of VDC was excreted unchanged via the lungs of Wistar derived Alderley Park rats whereas in the Alderley Park mice only 6% of the administered dose was thus excreted. McKenna et al., 1978 reported that Sprague-Dawley rats administered the same dose, 50 mg/kg, excreted 19% of the administered dose as unchanged VDC via the pulmonary system.

A major quantitative difference in the metabolism of VDC between the rat and mouse was in the considerably greater amount of N-acetyl-S-cysteinyl acetyl derivative formed by the mouse (Jones and Hathway, 1978a).

The quantitative differences in the metabolism of VDC between the species are attributable to a combination of physiological and biochemical factors. The initial step in the metabolic pathway for VDC in mammals appears to be the epoxidation of VDC catalyzed by microsomal monooxygenases with further biotransformation, via two pathways, one to chloroacetic acid via rearrangement of the metabolite 1,1-dichloroethylene oxide to chloroacetyl chloride, and the other ultimately to the glutathione conjugate, N-

acetyl-S-cysteinyl acetyl derivative catylyzed by glutathione-S-transferases which are thought to have a physiological role in initiating the detoxification of potential alkylating agents (Boyland and Chasseaud, 1969). Specific epoxide-hydrating pathways appear to be of minimal significance in the metabolism of VDC to reactive species (Andersen et al., 1980). Since the mouse possesses high monooxygenase activity relative to the rat (Oesch et al., 1977; Oesch, 1973), a greater proportion of VDC administered to the mouse is metabolized to the reactive metabolite, 1,1-dichloroethylene oxide. The relative proportions of the N-acetyl-S-cysteinyl acetyl derivative arising through the reaction of 1,1-dichloroethylene oxide with glutathione, in the mice and rats paralleł the activities of liver glutathione-S-epoxide transferase in these species (Hayakawa et al., 1974). Sinc the mouse, however, excretes greater than expected amounts of the N-acetyl-S-cysteinyl acetyl derivative, it would appear that the greater production is due to the higher cytochrome P-450 activity which found in the organs of th mouse (Litterst et al., 1975). This observation (Jones and Hathway, 1978a) is consistent with results of a pharmacokinetic comparison study reported by McKenna et al., 1977, 1979, in that not only was metabolism of VDC greater in the Ha(ICR) mouse than in Sprague-Dawley rat exposed to 10 ppm VDC for 6 hours, but the production of the reactive metabolites in the target tissues for VDC-induced toxicity was markedly greater in the mouse. The fact that the enhanced

production of reactive VDC metabolite in the mouse tissue could not be solely attributed to the increased metabolism of VDC over that of the rat was indicated on normalization of the binding data for differences in metabolism. Thus the ratios of covalently bound ^{14}C-activity/gram of protein in the liver and particularly in the kidney of the mouse to the total VDC metabolized by the mouse were increased relative to ratios determined for the rat. The data obtained from this comparison study are summarized below:

TABLE 4

Vinylidene Chloride Metabolism and Covalently Bound ^{14}C-Activity in Male Sprague-Dawley Rats and Ha(ICR) Mice (10 ppm, 6 Hour Exposure)

Animal Species (Strain)	A Metabolized VDC (mg/Eq/kg)	Tissue	B Covalent Binding (µg Eq ^{14}C-VDC/g Protein)	Ratio B/A
Rat (Sprague-Dawley)	2.84±0.26	Liver	5.28±0.14	1.86
		Kidney	13.14±1.25	4.63
Mouse (Ha(ICR))	5.27±0.74	Liver	22.29±3.77	4.23
		Kidney	79.55±19.11	15.09

All values are $\bar{x}$ ± S.E.; n = 4.

Adapted from McKenna et al., 1979

McKenna et al., 1977, 1979 furthermore reported that the time course for the disappearance of covalently bound ^{14}C-

activity from th liver and kidney of Sprague-Dawley rats and the liver of CD-1 mice exposed to 5 ppm or 100 ppm was consistent with those observed for normal protein turnover in rodent tissues, $t_{1/2}$ 51-65 hours (Omura et al., 1967). However, the time course for covalently bound ^{14}C-activity in mouse kidney was exposure-concentration dependent. At a concentration of 100 ppm the ^{14}C-activity was persistent ($t_{1/2}$ >500 hours), whereas at 5 ppm the time course was consistent with normal turnover time. The observed enhanced production in the mouse of covalently bound ^{14}C-activity in the liver (22.29 vs. 5.28 µg Eq ^{14}C-VDC/g protein) and particularly in the kidney (79.55 vs. 13.14 µg Eq ^{14}C-VDC/g protein) and the dose-dependent time course for disappearance of the ^{14}C-activity from the kidney correlate with the reported greater susceptibility of the mouse relative to the rat to the toxic effects of VDC in these target organs and the tumorigenic response in the kidneys of Swiss mice following exposure to concentrations producing marked toxicity.

The transformation of the 1,1-dichloroethylene oxide to chloroacetic acid, via the second pathway, is a potentially saturable process (Hathway, 1977). Therefore since the availability of both 1,1-dichloroethylene oxide and its rearrangement product, chloroacetyl chloride is greater in the mouse than in the rat due to increased cytochrome

P-450 activity in the mouse, th pot ntial of these r - active species to bind with DNA is likewise greater, thus saturation of the chloroacetic acid process is likely to be more significant in the mouse than in the rat (Jones and Hathway, 1978a).

V. The Mechanism Responsible for the Vinylidene Chloride-Induced Tumors in the Mouse is Primarily Non-Genetic.

The potential of VDC to cause DNA alkylation, DNA repair, and/or DNA replication with associated tissue damage in the rodent target organs has been researched in male Sprague-Dawley rats and male CD-1 mice exposed to 10 ppm and 50 ppm for 6 hours (Reitz et al., 1980).

Overall alkylation of DNA by VDC was minimal in both kidney and liver of the rat and mice following exposure to 50 ppm or 10 ppm and DNA repair, measured directly in the mice, showed a slight but significant increase only in the kidneys of mice exposed to 50 ppm VDC (Table 5).

Failure to demonstrate significant genetic effects at tumorigenic doses of VDC confirmed the observation that the tumors in the kidneys of mice did, in fact, arise via a non-genetic mechanism, namely, cytotoxicity.

TABLE 5

DNA Alkylation and DNA Repair in Tissue of Mice and Rats Exposed to Vinylidene Chloride; Ratio of Treated Animals to Controls

Species/Exposure/ Tissue	Alkylations/ Nucleotide ($\times 10^6$)	DNA Repair Ratio[a] (Observed/Expected[b] ± 95% Confidence Limits)
Mouse - 50 ppm		
Kidney	30	1.38±0.090*
Liver	6.1	1.16±0.363
- 10 ppm		
Kidney	11	1.16±0.255
Liver	0.94	0.764±0.222
Rat - 10 ppm		
Kidney	2.0	N.A.
Liver	0.87	N.A.

[a]Repair ratio of 1.0 indicates little or no repair is present; any increase above 1.0 is taken as indication that prior DNA damage has occurred.

[b]Observed hydroxy urea-resistant TdR incorporation to expected using control data.

*Ratio significantly greater than 1.0 ($p<0.05$, t-test).

N.A. - not available.

Adapted from Reitz et al., 1980.

Reitz et al., 1980 reported dose-related tissue damage and increased DNA replication (Table 6) in the kidneys of mice. Effects comparable to those observed in the mouse kidney were not observed in the liver of either species or in the kidneys of the rats.

TABLE 6

DNA Synthesis in Tissues of Vinylidene Chloride Exposed to Rats and/or Mice

	VDC Concentration - ppm		
	Mouse		Rat
	10	50	10
DNA Synthesis[a]			
Kidney	7.72*	24.7*	2.20*
Liver	1.20	2.45	0.88

[a]DNA synthesis was estimated by determining specific radioactivity of DNA following (^{3}H) thymidine ((^{3}H)TdR) injection. (^{3}H)TdR was injected 48 hours after the treatment suspected of causing cytotoxicity. A positive response is indicated by an increased rate of incorporation of (^{3}H) TdR into DNA relative to a control group, resulting in a ratio greater than 1.0.

*Ratio significantly greater than 1.0 ($p<0.05$, t-test).

Adapted from Reitz et al., 1980.

The tissue damage in the kidneys of mice exposed to 50 ppm VDC for 6 hours determined directly after cessation of exposure and at various times up to 192 hours thereafter showed toxic nephrosis immediately after exposure, progressive nephrosis at 8 and 24 hours, and regeneration after 96 hours. At the 10 ppm concentration slight dilation and swelling were observed immediately after exposure with nephrosis evident after 96 hours post-exposure.

VI. In-Vitro Mutagenicity Tests on VDC Comparing Speci s/ Tissues Give Results Consistent with Biomolecular Data in Mice and Rats; Normal Human Liver and Liver of Marmosets Failed to Elicit a Positive Bacterial Mutagenic Response.

In-vitro comparison mutagenicity tests conducted on VDC using tissue extracts from rats and mice have given results consistent with species differences observed in in-vivo studies. Jones and Hathway, 1978b reported that Salmonella typhimurium strain TA1535 or TA100 exposed to VDC gave a weakly mutagenic response in the presence of S-9 mixture from mouse liver or kidney and a strongly mutagenic response in presence of S-9 mixture from Aroclor 1254-induced tissues. In rats, only liver preparation from Aroclor-induc d animals, gave a positive, but weak, bacterial mutagenic response. VDC was also shown to be weakly positive in Salmonella typhimurium mediated by liver S-9 mixture from a human subject who had been on long-term phenobarbitone medication, but no bacterial mutagenic response was observed in the same test systems mediation by liver S-9 mixture from a normal human subject or from normal marmosets.

VII. The Significance of the Pharmacokinetic/Metabolism and Biomolecular Data in the Interpretation of Animal Toxicity and Oncogenicity Data and the Implication in the Assessment of Risk for Man.

The pharmacokinetic/metabolism and biomolecular data on

VDC exposed rats and mice clearly indicate inherent species differences contributed to the observed differences in target organ toxicity, and in the tumorigenic response in the kidney of the mice following exposure to concentrations in excess of a maximum tolerated dose for a long-term study. The capacity to metabolize VDC to the reactive metabolites correlates with the sensitivity to the toxic effects of VDC observed in these species. The mouse which has a greater capacity to metabolize VDC than does the rat, is more sensitive to VDC-caused tissue and tumorigenicity.

For many xenobiotics, including the halogenated hydrocarbons, the rate of oxidative metabolism appears to be roughly related to the body surface area (Weiss et al., 1977; Schmidt-Nielsen, 1970; Pinkel, 1958). Thus in man, the total amount of reactive species formed by the metabolism of VDC would be less than that formed by the laboratory rodents. This observation is consistent with the findings of Reitz et al., 1980 and Jones and Hathway, 1978a, who demonstrated that the rat metabolizes less VDC than the mouse and Walker, 1978 who reported significant metabolic dissimilarities exist between man and the mouse relative to the monooxygenases which catalyze the metabolism of VDC to the reactive species.

The correlation between metabolism and toxicity was confirmed at the macromolecular level. At concentrations causing degenerative/regenerative changes in the kidneys of mice, there was significant binding of the reactive species to cellular macromolecules, and a significant increase in DNA replication, but not in DNA repair. Thus the probable mechanism of the tumor formation was shown to be non-genetic.

The results of these studies indicate that the exposure of man to concentrations which do not produce cytotoxic effects would be unlikely to produce a tumorigenic response. Furthermore, the metabolic differences seen in the rodents and man make it unlikely that organ injury would result from exposure of man to the current TLV of 10 ppm. The lack of adverse health effects reported by Ott et al., 1976 in a health survey study of 138 employees exposed to up to 70 ppm VDC is supportive of the finding that man is less susceptible to VDC than the rat and far less than the mouse.

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