Environmental Health Perspectives
Vol. 17, pp. 217–219, 1976

Studies on the Metabolism of Vinyl Chloride

by H. Antweiler*

Vinyl chloride (VCM) is not carcinogenic by itself, it is bioactivated to the highly reactive alkylating oxirane chloroethylene oxide. Further metabolism, apparently, leads via an interaction of the primary alkylating metabolites with glutathion to *S*-(2-carboxymethyl)-cysteine and thiodiacetic acid which are eliminated with the urine. Up to now, it has not been ascertained whether the oxirane alone is the essential carcinogenic factor or whether other metabolites are also involved in carcinogenicity. Likewise, it is still unknown whether the metabolites excreted in the urine might be used as biological criteria for exposure to VCM, because these metabolites probably can originate from a series of substances other than VCM. This problem could stimulate investigations on the possible carcinogenic activity of these substances.

Studies on the pathway of the carcinogenic and mutagenic activity of vinyl chloride (VC) are not only of interest in relation to this special substance. Such studies also allow further insight into the possibly carcinogenic and mutagenic mechanism of chemically related substances which are suspected to be dangerous in occupational exposure. Furthermore, the knowledge of carcinogenic metabolites may furnish us with biochemical criteria to judge the dimension of risk in exposure to potentially carcinogenic and mutagenic substances.

Moreover research into the carcinogenic activity of VC becomes more and more interesting when we just learn that also tobacco smoke contains about 30 ppb of VC, a concentration which may not be important *per se*, but which could assume increased importance in connection with the other carcinogenic substances contained in the smoke (*1*).

I want to report briefly some investigations which were performed in our country quite recently by Norpoth and co-workers in a working group in Munster in the Department of Occupational Medicine and the hypothesis derived from the results of these experiments.

In 1966 Grigoresen and Toba (*2*) had found chloroacetic acid as a metabolite of VC. This was confirmed in 1971 by Hefner and co-workers (*3*) and in 1975 by Radwan and Henschler (*4*).

Bartsch and colleagues (*5*) then supposed that the presumed intermediary metabolite, chloroethylene oxide, would be really the active alkylating substance because this substance proved to be a strong mutagen as well as VC in the presence of an oxygenating system. Its mutagenic activity in certain sensitive bacteria was superior to the activity of chloroacetaldehyde and chloroacetic acid.

About the same time Green and Hathway (*6*) as well as Norpoth and co-workers (*7*) identified thiodiacetic acid as a conjugated metabolite in the urine of rats which inhaled VC. This finding was in good agreement with the statement of Hefner and colleagues that free SH-groups in the liver, not bound to proteins, are strongly used by VC and its metabolites respectively. Reynolds et al. (*8*), however, were not able to confirm a loss of SH groups. On the contrary, they reported an increase of SH groups. It is not yet clear if this can be explained as a rebound effect.

Hefner et al. supposed *S*-(2-carboxymethyl) cystein to be a further metabolite. This compound has since been confirmed a metabolite of VC by Norpoth and co-workers. Since Ullner (*9, 10*) also found this substance and additionally also thiodiacetic acid to be the main metabolite of chloroacetic acid in experiments

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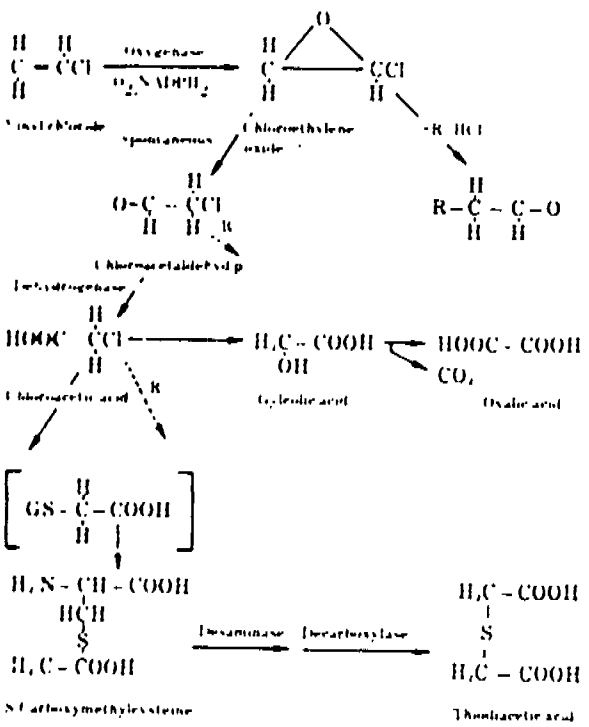
on mice. Norpoth and co-workers were interested in the problem of coincidence of metabolism in mice and men. They analyzed urine samples of patients who were given Ifosfamid, an analog of cyclophosphamide, and stated that a chloroethyl group is cleaved by side-chain oxidation so that choloroacetaldehyde can be produced. Indeed, its metabolites could be identified as thiodiacetic acid and *S*-carboxymethyl cysteine. Estimation of the dechloroethylated products shows about 80% of the value related to these products to analyze as thiodiacetic acid and *S*-(2-carboxymethyl) cystein. Thus, the results in mice and men seem to be in agreement (*11*).

Norpoth and colleagues have found thiodiacetic acid also to be a metabolite of dichlorodiethyl ether. Thus, conversion to chloroacetaldehyde is very probable. Chloroacetaldehyde itself may be a carcinogenic substance. With VC certainly the additional formation of chloroethylene oxide is an important factor.

When we try to get a synopsis of the results in metabolic research of VC as presented in the reaction scheme (*1*), the first oxidation step is followed by a chain of detoxicating reactions, some of which occur spontaneously and some of which are enzyme-catalized. The first three



alkylating substances are of decreasing t
They can have biologically alkylating ac
or they may be detoxicated stepwise, t
acetaldehyde and chloroacetic acid are k
to be toxic substances. New animal experi
by van Duuren (*12*), however, did not j
chloroacetic acid to be a carcinogen.

The results of investigations of Hen
and co-workers (*13*) could be interpret
indicate that all precursors of oxiranes v
are not symmetrically halogen substituted
as trichloroethylene, and also vinylidene
ride, vinyl bromide, vinylidene bromide,
haps also vinyl iodide, may be carcinogen

Regarding the development of biologica
teria for dangerous, carcinogenic, and m
genic exposure, we have still the proble
the specificity of the criterion.

Thiodiacetic acid can probably orig
from: 2-chloroethanol, 2-bromacetic acid, c
roacetic acid, chloroacetaldehyde, br macetal
hyde, 1,2-dichloroethane, 1,2-dibromoethan
and 1,1,2-trichloroethane.

All drugs containing oxidatively cleava
chloroethyl side chains, such as cyclophosph
mide, for instance, are supposed to cause de
opment of thiodiacetic acid.

These hypotheses likewise might be discus
for *S*-(2-carboxymethyl)cysteine which has
been shown to be a naturally occurring
stance in the intermediary metabolism.

Most of these investigations have been
cluded *in vitro* tests in mutagenicity. As the
exists a close correlation between carcinogen
and mutagenic effects of chemical substa
I feel that at present there exists no better p
sibility to learn about the metabolic activa
of carcinogenic substances in a reasonable
short time. It should be considered also th
there are some difficulties in the interpretati
of such experiments, as, for example, in t
case of English research workers who re
recently were not able to find a mutagenic eff
in mice with the dominant lethal test wh
they exposed the animals to concentrations
to 30,000 ppm of VC.

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R&S 134715

K-1711-(100) 1977

Chemosphere No. 6, pp 309 - 325, 1977. Pergamon Press. Printed in Great Britain.

VINYLCHLORIDE METABOLISM - A REVIEW

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(Received in The Netherlands 29 April 1977; accepted for publication 13 May 1977)

In 1971 vinyl chloride (VC) was shown to be a carcinogenic chemical[46]; rats exposed to vinyl chloride levels as low as 50 ppm developed angiosarcoma, a rare type of liver cancer,[28,29] and approximately 50 human deaths have been attributed to this cancer.[43] A syndrome occurring in VC and polyvinylchloride (PVC) fabrication and production workers was aptly called vinylchloride-disease and is characterized by extensive liver, lung and spleen damage.[25,27,31,35,45] Mortality among VC/PVC workers is extensively increased.[35,43,51] In addition it has been established that in communities surrounding PVC production facilities cancer and congenital anomalies are statistically higher in comparison to similar towns in the same counties[19]. All these effects are connected with VC and its transformation in the body and thus an understanding of the metabolism of VC is essential in understanding the toxicity of this chlorohydrocarbon. This review attempts to discuss and summarize VC metabolism and to interpret seemingly contradictory data which appear in the literature.

VINYLCHLORIDE URINARY METABOLITES

The *in vivo* metabolism of VC has been studied by several groups[14,16,32,48,49] and has led to a diversity of results and conclusions. The major metabolic pathway for the formation of the major urinary metabolites is shown in Figure 1.

VC is metabolised by the liver mixed function oxidase system (MFOS) to chloroethylene oxide which readily rearranges to chloroacetaldehyde. Chloroethylene oxide and chloroacetaldehyde

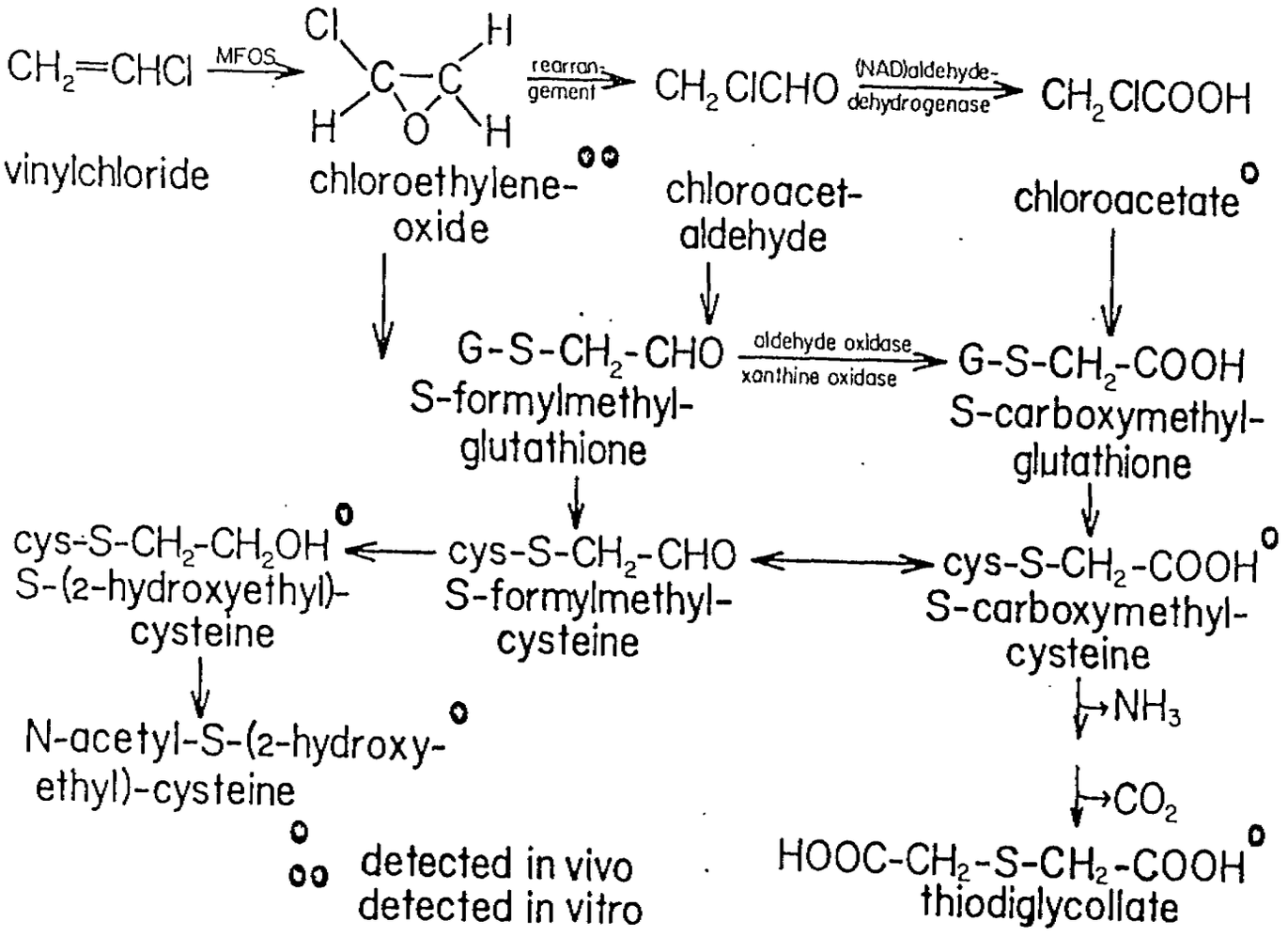
then either bind directly or enzymatically via glutathione-epoxide-transferase[11] or other glutathione transferases[7,38] to glutathione to form S-formylmethylglutathione. Chloroacetaldehyde can also be directly oxidised to chloroacetate presumably by an NAD^+-dependent aldehyde dehydrogenase. Chloroacetate is then either excreted or bound to glutathione to form S-carboxymethylglutathione which can also be formed from S-formylmethylglutathione. S-Carboxymethylglutathione is then hydrolysed to S-carboxymethylcysteine which can be N-acetylated, excreted or deaminated and decarboxylated to thiodiacetate/thiodiglycollate. The latter process undoubtedly involves pyridoxal phosphate and a Schiff base intermediate. Vinylchloride has also been shown to be metabolized by the in vitro MFOS system to chloroethylene oxide. This highly reactive intermediate was not isolated but trapped as its addition product to 4-(4-nitrobenzyl)pyridine and the adduct was similar to the product formed with synthetic chloroethylene oxide.[1] Trapping studies with 3,4-dichlorobenzenethiol point to either chloroethylene oxide or chloroacetaldehyde as the primary in vitro metabolites of VC.[13]

Vinylchloride metabolism in the MFOS is predominantly through the cytochrome P450 system[20, 40,41]. In vivo VC metabolism was shown to be increased after administration of P-450 inducers such as phenobarbital, Aroclor 1254 and hexachlorobenzene[20,40,41] as measured by the extent of liver damage measured by the release of alanine ketoglutarate[40], glutamic oxaloacetic and glutamic pyruvic[41] transaminases into the serum. Increased glutathione levels (due to short-term induction of glutathione?)[40,41] and decreased cytochrome P-450[20,41], b_5[20,41] and c reductase (NADPH/NADH dependent variety) levels were also observed (see Table 1).

Table 1. Effect[a] on cytochromes and cytochrome reductases of MFOS 24 hours after VC

Pretreatment	Exposure[b]	cytochrome		cytochrome c reductase	
		P-450	b_5	NADPH	NADH
		nmoles/mg prot.		nmoles/mg prot. min.	
Vehicle	Air (4)	1.11±.05	1.73±.06	67±3	381±13
Vehicle	VCM (5)	.81±.07[f]	1.57±.05	50±5[e]	377±40
PBT	Air (4)	2.42±.11[d]	1.50±.11	91±5[d]	278±45[c]
PBT	VCM (6)	.82±.08[f]	1.39±.07	98±9	667±95[f]
A-1254	Air (5)	2.53±.09[d]	1.61±.03	87±8[d]	213±26[d]
A-1254	VCM (8)	.97±.07[f]	1.44±.07	83±6	628±44[f]

a mean SEM
b VCM exposure 5% x 6 hr. number in parenthesis is number of animals
c $p<0.05$ compared to animals receiving vehicle
d $p<0.01$ compared to animals receiving vehicle
e $p<0.05$ compared to animals receiving same pretreatment
f $p<0.01$ compared to animals receiving same pretreatment


CH2=CHCl
MFOS
vinylchloride
chloroethylene-oxide
rearran-gement
CH2ClCHO
chloroacet-aldehyde
(NAD)aldehyde-dehydrogenase
CH2ClCOOH
chloroacetate
G-S-CH2-CHO
S-formylmethyl-glutathione
aldehyde oxidase
xanthine oxidase
G-S-CH2-COOH
S-carboxymethyl-glutathione
cys-S-CH2-CH2OH
S-(2-hydroxyethyl)-cysteine
cys-S-CH2-CHO
S-formylmethyl-cysteine
cys-S-CH2-COOH
S-carboxymethyl-cysteine
NH3
CO2
N-acetyl-S-(2-hydroxy-ethyl)-cysteine
detected in vivo
detected in vitro
HOOC-CH2-S-CH2-COOH
thiodiglycollate

Cytochrome P450 (P450) concentrations decrease during the *in vitro*[20]/*in vivo*[41] incubation/exposure of liver homogenates from phenobarbitol and Aroclor 1254 induced rats[20,41] and non-induced rats (Table 2). P450 was broken down to cytochrome "P-420" as indicated by UV spectra and this breakdown was inhibited to some extent (Table 2) by glutathione and by replacing the NADPH in the liver homogenate incubation mixture with $NADP^+$.

Table 2. The effects of incubation in the presence of VC on the levels of hepatic microsomal enzymes from variously induced rats[a,b]

Type of Induction	VC	Cyt P-450 (nmol/mg mic. protein)		% Loss Cyt P-450	% Loss Cyt b_5	% Loss NADPH - Cyt c Reductase
		0 min	15 min.			
None	-	1.25±.08	1.23±.09	2	104	96
	+	1.02±.05	0.92±.08[c]	10	100	99
MC	-	1.50±.10	1.48±.06	1	102	97
	+	1.35±.05	1.24±.02	8	106	91
PB	-	2.36±.05	2.32±.06	2	103	98
	+	2.10±.10	1.43±.10[c]	32	100	94
	+[d]	1.98±.10	1.99±.16	0	-	-
	+[e]	2.04±.03	1.58±.03[c]	22	-	-
	+[f]	2.16±.01	2.01±.02	7	-	-
	+[g]	2.20±.08	1.98±.05	10	-	-

[a] Samples contained microsomal suspension (2 mg protein/ml 0.02 M Tris-HCl, pH 7.4). NADPH generating system and 0.2 mM EDTA. References contained only microsomes. Incubation was at 30° with shaking for 15 min.

[b] Abbreviations used are VC, vinyl chloride (30 mM); cyt, cytochrome; mic., microsomal; MC, 3-methylcholanthrene; PB, phenobarbital.

[c] An absorbance peak centered at 420 nm was observed in these samples.

[d] Minus NADPH generating system.

[e] Plus 5 mM reduced glutathione.

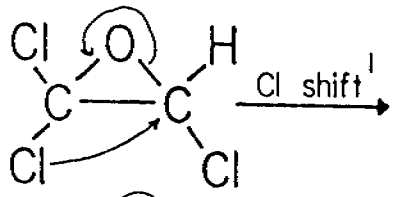
[f] $CO:O_2$ (80:20; v/v) was bubbled through the microsomal suspension after the addition of vinyl chloride.

[g] NADH (0.6 mM) replaced the NADPH generating system.

Induction with 3-methylcholanthrene, a "P448" inducer still gave rise to VC metabolism, although the decrease in "P448" was 25% of the decrease in "P450" of PB induced liver microsomes and 80% of the non-induced P448-P450 decrease[20] (Table 2). Cytochrome b_5 and NADPH cytochrome c reductase were not reduced *in vitro*[20] or *in vivo*[41] and in the latter study it was shown that NADH cytochrome c reductase was increased after VC exposure. MFOS inhibitors had different influences

Trichloroethyleneoxide

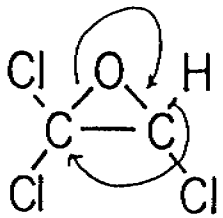
in H_2O



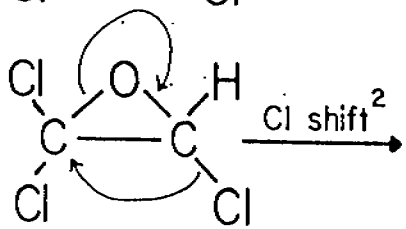
$CHCl_2—COCl$

dichloroacetylchloride

H shift



in vivo



$CCl_3—CHO$

trichloroacetaldehyde

$\longrightarrow$ $CCl_3—COOH$

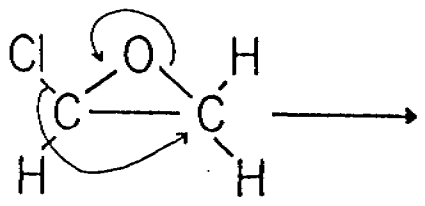
trichloroacetate

$\downarrow$

$CCl_3—CH_2OH$

trichloroethanol

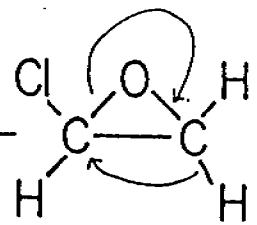
Chloroethyleneoxide



$\longrightarrow$ $CH_2Cl—CHO$

chloroacetaldehyde

$\longleftarrow$



on VC metabolism *in vitro*. SKF-525A inhibited binding to P450 but did not decrease NADPH consumption whereas metyrapone did not inhibit P450 binding but reduced NADPH consumption by 70%[20]. Metyrapone did not inhibit VC metabolism *in vivo* but other MFOS inhibitors did.[3] The inhibitors (dose applied in DMSO, % inhibition) were; 3-bromophenyl-4(5)-imidazole (35 mg/kg, 100%); 6-nitro-1,2,3-benzothiadiazole (50 mg/kg, 76%); SKF-525A (50 mg/kg, 76%; and pyrazole (50 mg/kg, 66%; 100 mg/kg, 100%; 100 mg/kg in H_2O, 71%).

Table 3. The effects of inducing agents on the interaction of vinyl chloride with hepatic microsomal cytochrome P-450 *in vitro*[a].

Pretreatment of Animals	Cyt P-450 (nmol/mg mic. protein)	K_s (mM)	ΔA_{max} ($A_{385}-A_{418}$)	K_m (mM)	V_{max} (nmol NADPH/ min/mg mic. protein)
None	1.1	80±30	0.05±0.01	-	0.4±0.2[b]
MC	1.7	12±6	0.03±0.01	-	0.6±0.2[b]
PB	3.2	8±2	0.08±0.01	5±3	2.3±0.2

[a] Abbreviations used are cyt P-450, total type P-450 cytochromes; mic., microsomal; MC, 3-methylcholanthrene; PB, phenobarbital.

[b] Apparent V_{max} values measured at the highest concentration of vinyl chloride achievable by bubbling (30 mM).

Chloroethylene oxide rearranges to chloroacetaldehyde in aqueous solution[5,15] with a half-life time of 1.6 min[1]. The mechanism of the rearrangement of chloroethylene oxide to chloroacetaldehyde is not clear but by analogy with trichloroethylene oxide the two mechanisms in Figure 2 may compete[5] (i.e.):

(i) in aqueous solution trichloroethylene oxide can rearrange to dichloroacetylchloride (dichloroacetate) by either of the two pathways as shown in Figure 2;

(ii) trichloroethylene oxide rearranges *in vivo* to trichloroacetaldehyde which is further metabolised to trichloroethanol and trichloroacetate.[18] Clearly these metabolites are also formed *via* a 1,2-Cl rearrangement and further studies with isotopically-labelled substrates are required to determine the precise mechanism involved.

Chloroacetaldehyde has been found to bind to glutathione but only in situ[21] and exposure

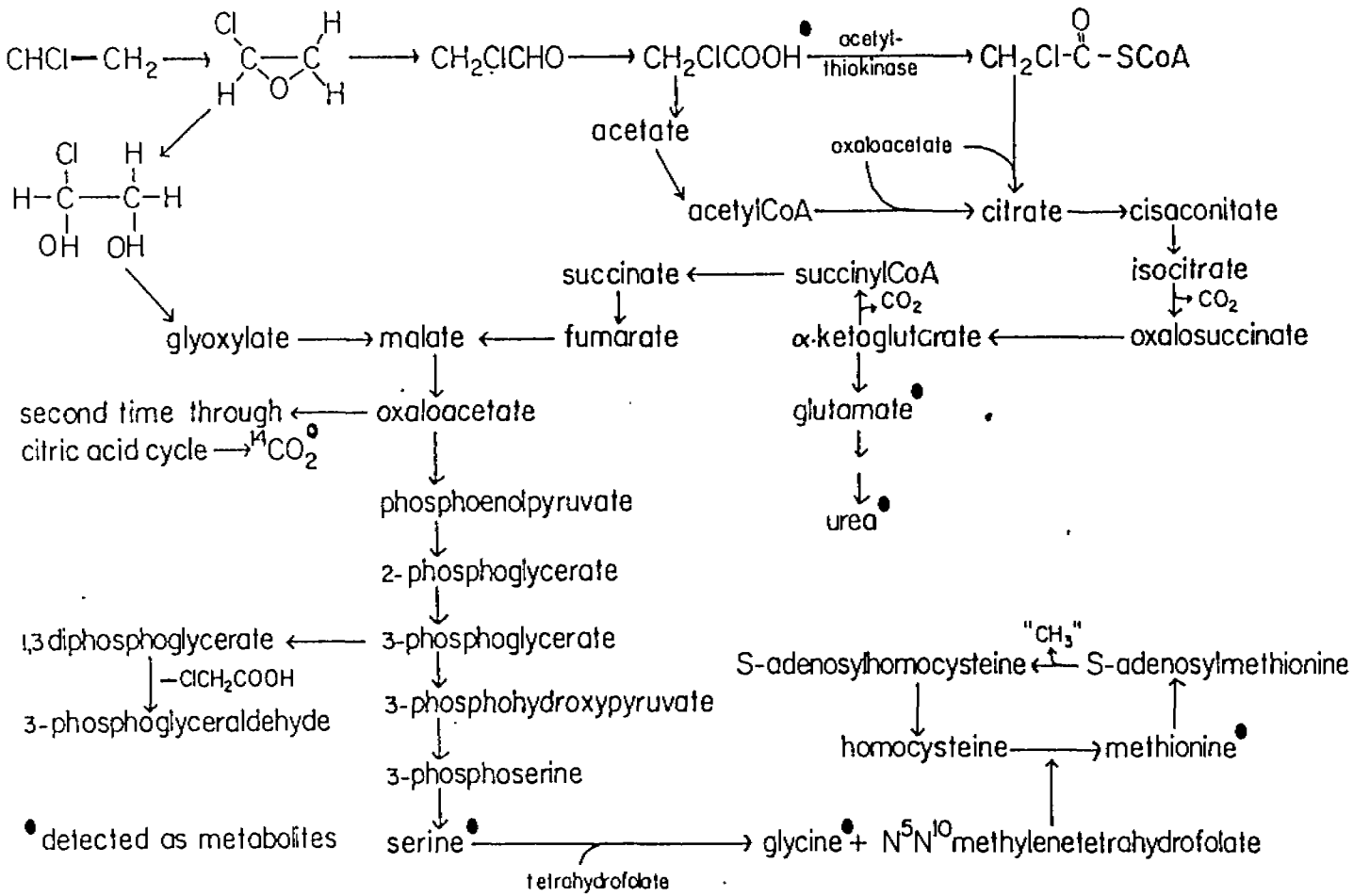
of rats to 2000, 1000, 500, 250, 150 ppm VC for 1-7 hours resulted in a substantial reduction of liver non-protein sulfhydryl (thiol) levels.[50] Exposure to 50 and 10 ppm of VC for 7 hours gave a slight reduction of sulfhydryl levels at the 50 ppm level and no reduction at the 10 ppm level. At the 150, 250 and 1000 ppm level an apparent maximum level of sulfhydryl depression was reached after 4-5 hours giving a 25, 35 and 37% depression respectively. Exposure to 2000 ppm led to a sulfhydryl depression of 33% after 2, 47% after 4 and 62% after 7 hours.

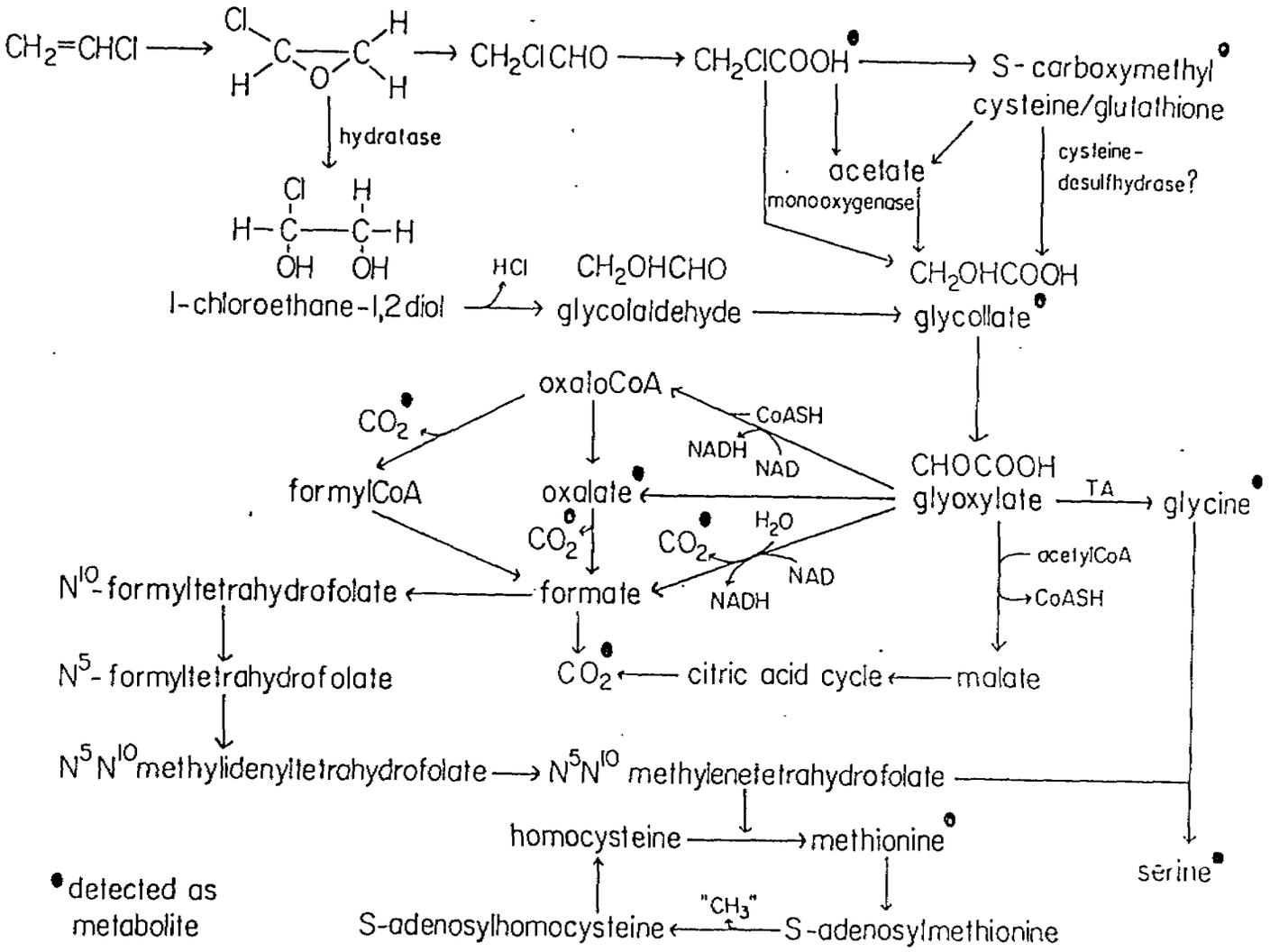
The metabolism of chloroacetaldehyde has not been studied in detail but chloroethanol[21] is metabolized in vivo and in vitro (liver enzymes) to give S-carboxymethylglutathione which can be derived from either S-formylmethylglutathione or chloroacetate. In addition chloroacetate has also been detected as a chloroethanol metabolite[53]. Chloroacetate was metabolized to two major urinary metabolites, S-carboxymethylcysteine and thiodiacetate[52] and small amounts of glycollate were also detected (see below for explanation). S-Carboxymethylcysteine was detected in one study as a VC metabolite together with thiodiacetate[32] which is the product of S-carboxymethyl cysteine metabolism[52]. This latter metabolite was not reported in several VC studies[14,48,49] which did identify thiodiacetate as a metabolic product. N-Acetyl-S-(2-hydroxyethyl)cysteine was shown to be the major metabolite from VC after oral administration and inhalation[48,49]. This could be derived from S-formylmethylcysteine/S-formylmethylglutathione which formerly were presumed either not to be formed or to be further metabolised to S-carboxymethylcysteine.[21] N-Acetyl-S-(2-chloroethyl)-cysteine has also been reported as a VC metabolite[14] but this may be an artifact due to the isolation procedure[12] which involved boiling with HCl. S-(2-chloroethyl)cysteine has been synthesized by heating S-(2-hydroxyethyl)cysteine with conc HCl.[6,9] An unidentified major metabolite (30-40% overall) was also reported and a possible structure could be (N-Acetyl)-S-Carboxymethyl cysteine.[48, 49]

OTHER VINYLCHLORIDE METABOLITES

Administration of [^{14}C]-vinyl chloride resulted in the formation of $^{14}CO_2$ and the following levels were found (based on the amount of VC administered):

inhalation	12.1% (10 ppm) 12.3% (1000 ppm)[49]
oral	9.0% (0.05 mg/kg) 13.3% (1 mg/kg) 2.5% (100 mg/kg)[48]
intragastric	13.5%(250 µg/kg)0.7% (450 mg/kg)[14]
intraperitoneal	11.0% (250 µg/kg) 0.7% (450 mg/kg)[14]


CHCl—CH2
CH2ClCHO
CH2ClCOOH
acetyl-thiokinase
CH2Cl-C(=O)-SCoA
acetate
oxaloacetate
acetylCoA
citrate
cisaconitate
isocitrate
succinate
succinylCoA
CO2
glyoxylate
malate
fumarate
α-ketoglutcrate
oxalosuccinate
second time through citric acid cycle
14CO2
oxaloacetate
glutamate
urea
phosphoenolpyruvate
2-phosphoglycerate
1,3 diphosphoglycerate
3-phosphoglycerate
-ClCH2COOH
3-phosphoglyceraldehyde
3-phosphohydroxypyruvate
3-phosphoserine
"CH3"
S-adenosylhomocysteine
S-adenosylmethionine
homocysteine
methionine
detected as metabolites
serine
glycine + N5N10methylenetetrahydrofolate
tetrahydrofolate


CH2=CHCl
hydratase
CH2ClCHO
CH2ClCOOH
S-carboxymethyl cysteine/glutathione
acetate
monooxygenase
cysteine-desulfhydrase?
1-chloroethane-1,2 diol
HCl
CH2OHCHO
glycolaldehyde
CH2OHCOOH
glycollate
oxaloCoA
CO2
CoASH
NADH
NAD
formylCoA
oxalate
CHOCOOH
glyoxylate
TA
glycine
H2O
acetylCoA
CoASH
N10-formyltetrahydrofolate
formate
N5-formyltetrahydrofolate
CO2
citric acid cycle
malate
N5N10methylidenyltetrahydrofolate
N5N10 methylenetetrahydrofolate
homocysteine
methionine
serine
detected as metabolite
S-adenosylhomocysteine
"CH3"
S-adenosylmethionine

Two pathways can explain the generation of $^{14}CO_2$:

(i) addition/transfer of an (chloro)acetyl group to CoA followed by metabolism in the TCA cycle (Figure 3) or

(ii) the formation of glycollate followed by its oxidation to glyoxylate (Figure 4) after which it enters the C_2 and C_1 pools.

From these two, the glycollate pathway seems to be preferred since by analogy chloroethyleneoxide is hydrated via a hydratase[36] to 1-chloroethane-1,2-diol* and rearranges to glycolaldehyde which is oxidised to glycollate. Another pathway for glycollate formation involves the use of a monooxygenase "hydrolase" to convert chloroacetate to glycollate**[52]. In addition S-carboxymethylcysteine could be enzymatically cleaved to give either glycollate directly or acetate which could be oxidised to glycollate. This is not likely to be a major metabolic pathway since S-carboxymethylcysteine produced very little CO_2 during its metabolism.[52] Glycollate is further oxidised to glyoxylate. Glyoxylate can be transaminated into glycine, a product of chloroacetate metabolism or can be converted into formate, oxalate and oxalo CoA, all of which can yield formate. Formate can either enter the C_1 pool, explaining the occurrence of labelled serine and methionine in urine of rats administered [^{14}C]-VC[14] or it can be oxidised to CO_2. Further metabolites detected in the study[14] were urea, glutamate and chloroacetate, whose occurrence can be rationalized as shown in Figures 3 and 4.

VC BINDING TO PROTEINS

In vitro protein binding of VC (metabolites) was shown to be dependent on the thiol content of proteins[22] and protein binding was NADPH[22,23] and oxygen[23] dependent. Incubation with nitrogen gave ±50% of control metabolism but only 6% of the protein binding (Table 4). Glutathione slightly increased metabolism and decreased protein binding (Table 4)[23].

1,1,1-Trichloropropyleneoxide, an 97% effective hydratase inhibitor[36], increased metabolism by only 10% but effectively doubled protein binding due to the *in vitro* accumulation of chloroethyleneoxide (and therefore chloroacetaldehyde and chloroacetate) which is available for protein binding[23] (Table 4). Generation of superoxide radicals with NADH and phenazinemethosulfate, also gives VC metabolism and protein-binding at approximately 10% of the control level, using a liver

* Hydratase activity is responsible for approximately 40% of VC metabolism *in vitro*[23].

** Chloroacetate autohydrolyses to glycollate very slowly at pH 7 which can not account for its *in vivo* metabolism[52].

microsomal preparation with added NADPH.[4]

Table 4. Uptake and irreversible protein binding of ^{14}C-vinyl chloride by hepatic microsomes of rats

	Uptake[a] (nmol/ml)	Percentage of control	Protein binding[b] (nmol/mg microsomal protein)	Percentage of control
With NADPH (control)	50.8±8.7[c,d] (n=8)	100.0	0.44±0.05[c,d] (n=8)	100.0
Without NADPH	4.1±0.69[c] (n=8)	8.0	<0.001[c] (n=8)	--
With NADPH under nitrogen	27.2±1.8[d] (n=4)	53.5	0.06±0.01[d] (n=4)	13.6
With NADPH under 95% CO/5% O_2	2.4±0.4[d] (n=4)	4.7	0.01±0.002[d] (n=4)	2.3
Without NADPH under 95% CO/5% O_2	0.3±0.09[d] (n=4)	0.6	<0.001[d] (n=4)	—
With NADPH + L-glutathione (1 mM)	60.0±12.2 (n=8)	118.0	0.33±0.03[c] (n=8)	75.0
With NADPH + L-glutathione (1 mM) + cytosol (1 mg protein/ml)	65.8±5.6[c] (n=8)	130.0	0.28 (n=2)	63.6
With NADPH + trichloropropene oxide (10 μM)	56.9±8.1 (n=6)	110.0	0.98±0.06[c] (n=6)	222.5

[a] Uptake is expressed as nanomoles of vinyl chloride taken up per 1.0 ml of incubation mixture.

[b] Protein binding is expressed as nanomoles of vinyl chloride metabolites irreversibly bound per 1.0 mg of microsomal protein. Microsomal protein concentration was 1.0-1.2mg/ml. incubation time 60 min, and partial pressure of vinyl chloride 2.0-4.0 Torr.

[c,d] Differences are statistically significant within both experiments. [c] $p<0.001$ (paired comparison); [d] $p<0.001$ (group Student's t test).

In vivo binding of VC to microsomal proteins has also been reported.[4] Table 5 shows the levels of total metabolites and irreversibly protein bound metabolites directly and 48 hours after the termination of an exposure to 44 ppm VC for 5 hours. Protein-binding is relatively constant on a 48 hour time scale except in the kidney where an approx. 16% decrease in protein bound metabolites occurred over this period. Extractable and total-protein bound metabolites decrease substantially which is understandable as excretion of metabolites is nearly total after 48 hours.[3]

Table 5. Metabolites of ^{14}C-vinyl chloride and irreversible protein binding in different tissues of rats after 5 hours exposure to ^{14}C-vinyl chloride.

Initial concentration of vinyl chloride in atmosphere = 44 ppm
Uptake per rat (200 g) = 6.5 µmol vinyl chloride

	Radioactive Metabolites immediately after Exposure		Radioactive Metabolites 48 hours after beginning of Exposure		
	nmol metabolites/100 mg tissue		nmol metabolites/100 mg tissue		
	Total Metabolites	Irreversibly Protein Bound Metabolites	Total Metabolites	Polar, Extractable Metabolites	Irreversibly Protein Bound Metabolites
Liver	11.45±1.84	1.46±0.47	2.16±0.14	0.38±0.03	1.49±0.06
Spleen	2.25±0.30	0.88±0.02	1.21±0.08	0.33±0.01	0.83±0.06
Kidney	13.15±2.63	1.18±0.14	1.37±0.19	0.40±0.04	0.99±0.07
Lung	n.d.	n.d.	1.01±0.08	0.30±0.11	0.77±0.01
Small Intestine	n.d.	n.d.	1.04±0.08	0.33±0.04	0.72±0.07
Brain	1.05±0.05	0.13±0.04	0.22±0.03	n.d.	n.d.
Adipose Tissue	1.36±0.17	0.26±0.06	0.30±0.03	n.d.	n.d.
Muscle (M.psoas)	1.97±0.44	0.13±0.01	0.32±0.07	n.d.	n.d.

Figures show $\bar{x} \pm$ S.D.; n=3

n.d. = not determined

BINDING OF VC TO RNA AND DNA

VC binds to RNA[22] *in vitro* and to RNA and DNA *in vivo*[4]. DNA binds 3½ times more metabolites than RNA on a molecular basis although the total amount of RNA which reacts is about 3½ times as great as the DNA (Table 6) which reacts, all measured at their peak values. DNA binding reaches its maximum value immediately after exposure and declines rapidly in the next 6 hours probably due to the excission of alkylated bases, most probably ethenoadenosine and ethenocytidine, by DNA repair enzymes.

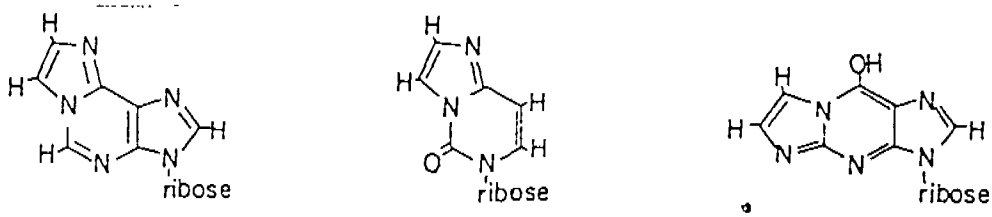
Table 6. Irreversible binding of metabolites of ^{14}C-vinyl chloride to DNA and RNA of liver of rats exposed to ^{14}C-vinyl chloride

Initial concentration of ^{14}C-vinyl chloride in atmosphere = 145 ppm
Time of exposure = 5 hours
Uptake per rat (210 g) = 16.4 µmol vinyl chloride

Time after beginning of exposure	pmol metabolites bound to 1 mg		pmol metabolites bound per g liver (wet weight)	
	DNA	RNA	DNA	RNA
5 hours (immediately after exposure)	132	15.9	102	118
12 hours	55	19.6	46	164
24 hours	61	42.5	43	340
48 hours	37	36.6	22	307

RNA binding levels peak after 24 hours; some of the possible explanations for this delayed peak are a long turnover time, continuous reaction with metabolites and a building-in of excised DNA bases. Chloroacetaldehyde is known to bind to adenosine to form 3-β-D-ribofuranoxylimidazo [2,1-i] purine or 1,N^6-ethenoadenosine[2,24,42]. Cytidine gives a similar reaction to form 5,6-dihydro-5-oxo-6-β-D-ribofuranosylimidazo [1,2-c] pyrinidine or 3,N^4-ethenocytidine. The structures are shown in Figure 5. Guanosine was reported to be unreactive with chloroacetaldehyde[24] but preliminary work in our laboratory has shown the presence of a product with a mass similar to that of 3 (Figure 5).

Both the ethenoadenosine and cytidine derivatives are easily detectable at concentrations below 10^{-8} M[2]. Chloroacetaldehyde also readily reacts with DNA in vitro[26]. Chloroethylene oxide and VC + microsomal preparation produced 1,N^6-ethenoadenosine on incubation with adenosine in vitro[1]. The formation of the ethenoadenosine and cytidine has been proposed as the basis of the carcinogenic action of VC[44].



1 2 3

Figure 5. (Possible) Products of VC reaction of 1,N^6-ethenoadenosine(1),3,N^4-ethenocytidine(2) and 1,N^2-ethenoguanosine(3).

PREPARATION OF VC METABOLITES

CHLOROETHYLENEOXIDE (CEO)

Different methods have been proposed to prepare chloroethyleneoxide. The earliest synthesis used tert-butylhypochlorite and ethylene oxide to yield CEO after irradiation at -10°C [10,47]. Molecular photochlorination of ethyleneoxide was suggested as an alternative[15] to the earlier reaction[47] both of which were not very successful[13]. A modified version, including design of glassware has been published.[39] Extreme care should be taken in handling this compound as it is 10,000 times as reactive a mutagen as methylmethanesulfonate and ethylene oxide[17].

CHLOROACETALDEHYDE (CA)

This compound is commercially available as either 30% or 45% aqueous solutions which are "somewhat" impure. Commercial 45% CA solutions were found to consist of a 40:60 mixture of the monomeric and dimeric hydrates of CA[10]. Synthesis of CA was first reported in 1882[34] and in our laboratory a modified version of this method is used to prepare CA. Chloroacetaldehyde dimethylacetal (20 ml) was refluxed at 70° - 80° with 5% H_2SO_4 (80 ml) until a light brown color developed. The solution is then distilled at 150° and the fraction coming over between 87 and 94° is collected and cooled in a dry ice-acetone mixture. This is presumed to be pure chloroacetaldehyde. Pure CA can also be prepared by cracking the trimer at 100°[10,39]. Synthesis of this trimer from chloroacetaldehyde dimethylacetal[39] and commercial 45% CA[10] has been described.

S-(2-HYDROXYETHYL)CYSTEINE/GLUTATHIONE

S-2 hydroxyethylcysteine/glutathione are prepared by the addition of ethyleneoxide to cysteine/glutathione[21]. An additional synthetic method has also been published.[33]

S-FORMYLCYSTEINE/GLUTATHIONE

S-Formylmethyl glutathione cannot be prepared directly from CA due to polymerisation at pH > 7. However preparation of CA in situ by reduction of 2 chloroethanol by alcohol dehydrogenase at pH 7.8 in the presence of cysteine[21] resulted in the preparation of this metabolite.

S-CARBOXYMETHYLCYSTEINE/GLUTATHIONE

S-Carboxymethylcysteine/glutathione was prepared by the reaction in a basic environment of cysteine/glutathione with either chloro-[52] or iodoacetate[21].

N-ACETYL-S-CARBOXYMETHYLCYSTEINE

The synthesis of N-acetyl-S-carboxymethylcysteine through the acetylation with acetic anhydride of S-carboxymethylcysteine has been described.[37]

THIODIGLYCOLLATE/ACETATE

This compound is commercially available or can be synthesized by the reaction of sodium sulphite with chloracetic acid.

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Data are presented on the levels of all chemical contaminants resulting from environmental pollution which have been found in human tissues including blood, urine, breast milk, and tissue samples obtained at autopsy. Most data results from specific surveys to determine health hazards. The roles of trace elements and recognition of the need to determine baseline levels of chemicals introduced into the environment are factors which have motivated surveys by individual investigators. Thus, most data on chemicals in human tissues record levels of pesticides (e.g., DDT and metabolites), levels of trace metals such as lead, cadmium, and mercury, or levels of nutritionally essential elements such as zinc, copper, manganese, and fluoride. Data available on iron and calcium are not presented as their presence in the environment is generally not considered hazardous. Data on several uncommon chemicals, such as indium and ytterbium, are included basically as items of interest and to further document their presence in healthy individuals. Baseline data were presented where available to provide perspective as to chemical levels which might be expected under conditions where exposure could be considered normal or not directly related to a pollutant source. Nearly 600 cited surveys or investigations, most of which were reported within the past decade, are listed. Ninety-four different chemical contaminants, primarily trace metals and organochlorine pesticides, are reported. It is estimated that over 75% of the data published during the past 30 years on chemical contaminants derived from environmental pollution and found in human tissue in the United States are represented in this report. (ERA citation 04:019820)

—*Highlight*—

Vinyl Chloride: A Review, 1835--1975; an Annotated Literature Collection, 1976--1975; a Literature Compilation, 1976--1977.

H. S. Warren, J. E. Huff, and H. B. Gerstner.
Toxicology Information Response Center, Oak Ridge, TN. Nov 78, 218p
ORNL/TIRC-78/3 Price code: PC E13/MF A01

Vinyl chloride (CH sub 2 CHCl) (VC) is a colorless gas, produced and marketed in large volume primarily as the base for its versatile and relatively inert homopolymer, polyvinyl chloride. The toxicological problem posed by VC has broad ramifications rooted in the long interval between the industrialization of the VC/PVC processes and the first recognition of the potential carcinogenicity of the VC monomer. This time delay represents the latent period of the carcinogen within the human organism and may mean that the VC-associated cancer cases detected to date represent only the beginning of a growing clinical statistic. This report on vinyl chloride consists of three parts: Part I provides a review of vinyl chloride and its health-related aspects as summarized from the literature through 1975; Part II comprises an annotated, keyworded, indexed collection of 555 references (1835--1975) which emphasizes biological effects and includes references concerning analysis and control in both workplace and environment; Part III is an updated collection of references which extends the bibliography through September 1977. This bibliography was compiled from the major scientific abstract literature. Current journals in appropriate disciplines were also scanned. References are arranged alphabetically by first author's name. A permuted title index is appended for easy access to the bibliography. (ERA citation 04:024713)

—*Highlight*—

Methods Development for Assessing Air Pollution Control Benefits. Volume I. Experiments in the Economics of Air Pollution Epidemiology.

Thomas D. Crocker, William D. Schulze, Shaul Ben-Dav and Allen V. Kneese.
Wyoming Univ., Laramie. Feb 79, 177p EPA/600/5-79/001A See also Volume 2, PB-293 616. Also available in set of 5 reports PC E14, PB-293 614-SET.
PB-293 615/1WP Price code: PC A09/MF A01

The volume employs the analytical and empirical methods of economics to develop hypotheses on disease etiologies and to value labor productivity and consumer losses due to air pollution-induced mortality and morbidity. In the mortality work, 1970 city-wide mortality rates for major disease catagories have been statistically associated with aggregate data from sixty U.S. cities on physicians per capita, per capita cigarette consumption, dietary habits, air pollution and other factors. The estimated effect of air pollution on mortality rates is about an order of magnitude lower than some other estimates. Nevertheless, rather small but important associations are found between pneumonia and bronchitis and particulates in air and between early infant disease and sulfur dioxide air pollution. The morbidity work employed data on the generalized health states and the time and budget allocations of a nationwide sample of individual heads of household. For the bulk of the dose-response expressions estimated, air pollution appears to be significantly associated with increased time being spent acutely or chronically ill. Air pollution, in addition, appears to influence labor productivity, where the reduction in productivity is measured by the earnings lost due to reductions in worktime.

Supplementary Data System, Microdata File, Michigan, 1976.

Norman Root, and Wayne Drawdy.
Bureau of Labor Statistics, Washington, DC. Office of Occupational Safety and Health Statistics. 1976, mag tape BLS/DF-79/044 Source tape is in EBCDIC character set. Tapes can be prepared in most standard 7 or 9 track recording modes for one-half inch tape. Identify recording mode desired by specifying character set, track, density, and parity. Call NTIS Computer Products if you have questions. Price includes documentation, PB-288 258.
PB-293 669/8WP Price code: CP T02

Tape contains records of individual occupational injuries and illnesses. Selected injury and illness factors were classified in accordance with standard definitions used in the Supplementary Data System of the Bureau of Labor Statistics. Each case record contains year, month and day of occurrence; nature of injury or illness, part of body affected, type of accident or exposure, and source of injury or illness; and industry, age, and sex, of injured or ill employee. Technical documentation is available: PB-288 258, Supplementary Data System, Microdata Files, User's Guide, 1976-77. Data were compiled by the Michigan Bureau of Safety and Regulations from workers' compensation reports of cases which occurred during 1976 and which resulted in death or seven or more lost workdays. Data include cases arising in private and public employments with these principal exceptions: Those employed by certain nonagricultural employers with less than three employees; those employed by agricultural employers of less than three regular employees; those employed by certain agricultural employers with three or more employees; and

K-1711-(90) Abstracts

88: 32775q **Metabolism of vinyl chloride: destruction of the heme of highly purified liver microsomal cytochrome P-450 by a metabolite.** Guengerich, F. Peter; Strickland, Thomas W. (Cent. Environ. Toxicol., Vanderbilt Univ. Sch. Med., Nashville, Tenn.). *Mol. Pharmacol.* 1977, 13(6), 993-1004 (Eng). The NADPH-dependent, *vinyl chloride* [75-01-4]-mediated destruction of *cytochrome P-450* [9035-51-2] was demonstrated in rat liver microsomes and in highly purified reconstituted enzyme systems contg. *NADPH-cytochrome P-450 reductase* (*NADPH: ferricytochrome oxidoreductase, EC 1.6.2.4*) [9023-03-4] and cytochrome P-450. The loss of cytochrome P-450 could be attributed to *heme* [14875-96-8] destruction, but not to lipid peroxidn. or binding of electrophiles to free sulfhydryl groups. The system required all components necessary for mixed-function oxidn., including mol. O, and was inhibited by CO, suggesting strongly that oxidative metab. of vinyl chloride by cytochrome P-450 is necessary for the obsd. destruction. The NADPH-cytochrome P-450 reductase-catalyzed destruction of free and cytochrome P-450-bound heme was also obsd. in reconstituted systems in the absence of vinyl chloride. Inhibition expts. with Co and catalase suggest that the vinyl chloride-mediated destruction of cytochrome P-450 heme differs from these processes. Two proposed metabolites of vinyl chloride, *vinyl chloride epoxide* [7763-77-1] and *2-chloroacetaldehyde* [107-20-0], do not appear to be responsible for the heme destruction. Evidence for the involvement of free radicals could not be demonstrated when the reaction was examd. by EPR spectroscopy or when attempts were made to inhibit cytochrome P-450 destruction with radical-trapping agents.

K-1711 - (100) PV

R&S 134735

87: 188691z **Safeguarding the health of workers exposed to the harmful effects of vinyl chloride during production of PVC.** Marzec, Jozef; Kaleta, Jerzy (Inst. Ekon. Przem. Chem., Krakow, Pol.). *Polimery (Warsaw)* 1977, 22(2), 67–8 (Pol). A general discussion is given of safety precautions that must be obsd. during the manuf. and handling of vinyl chloride [75-01-4] and its polymers. E. A. Ackermann

Air Pollution, Ind. Hyg.
Vol. 87, 1977