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THE VC-PVC CRISIS: A SYSTEMATIC APPROACH TO TOXICOLOGICAL PROBLEMS

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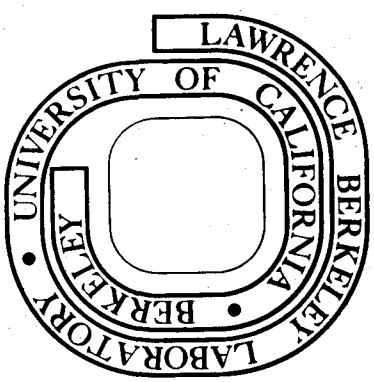

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THE VC-PVC CRISIS: A SYSTEMATIC APPROACH TO TOXICOLOGICAL PROBLEMS

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ABSTRACT

The report released by Goodrich Chemical, relating a high incidence of the rare liver angiosarcoma in workers exposed to vinyl chloride (VC), triggered a series of reactions from industry, government and labor. In April an Emergency Temporary Standard of 50 ppm was announced by OSHA, to be followed (Jan. 1) by a 1 ppm limit (TWA, 8 hr.). Goodyear cut PVC output by 50%, calling the new standard infeasible (Plastics Technol. Dec. 1974). SPI and 8 PVC manufacturers won a temporary stay of the permanent standard but their appeal to review the standard was denied in a U.S. Court of Appeals (C & En 2/10/75).

VC developments come as no surprise to cancer researchers (Job Safety & Health, Jan/75). VC has also been related to acro-osteolysis (J. Occup. Med., Nov/73), 'meat wrapper's asthma' (J. Am. Med. Assn., Mar/74) and to other forms of cancer.

This paper examines the limitations of the "crisis" approach to environmental problems, using VC as an example. In 1973, over 20,000 toxic industrial chemicals were in use (TOXIC SUBSTANCES LIST, NIOSH), but standards were available for only 500 of these. With the introduction of ca. 3,000 new products/year, logistics precluded closing this gap at an acceptable rate.

The need for a viable, more systematic approach is evident. By the application of certain general molecular-chemical principles to toxicological problems, it is possible to expedite their solution. This approach may be applied in industrial decision-making processes involving the elimination and/or monitoring of toxic chemicals and in the development of suitable substitutes.

THE PROBLEM

We seem to be living in an era of recurrent crises---not all of them artifacts engineered by the media or by one or another of the many pressure groups in our society. Let us make no mistake about it--we do have some hard decisions to face in the very near future with respect to the three E's: Economics, Energy, Environment...

In this paper I would like to deal with a so-called "crisis" situation culled from the field of chemical technology in the hope that, by analysis of this relatively microcosmic problem, we can gain some insights into the broader environmental problem of which it is an integral part.

The vinyl chloride dilemma, as it has been called, is neither new nor very different from many which have preceded it--let me just recall the thalidomide and antibiotics scenarios of the past two decades, and the current toxicity and persistence problems of a number of pesticides, leading either to their banning or limited use.

The question is: How can we continue to take advantage of the benefits of potentially useful developments in drugs and pharmaceuticals, plastics and food technology, while at the same time avoiding the health risks and periodic economic and societal disruptions they now entail?

I believe the answer lies in a more rational approach--a systematic examination of potentially toxic chemicals at the molecular level *before they ever get to the commercial development stage*, for by that time it's often too late and too costly to abandon a project.

VINYL CHLORIDE

First, let us explore briefly the historical development of vinyl chloride (VC) polyvinyl chloride (PVC) technology. What is VC? It is a halogenated alkene which was first prepared by Regnault in 1835 by the alkaline ethanolic dehydrohalogenation of dichloroethane in a sealed tube.

Slide 1 shows some typical reactions of VC, starting with its polymerization in the presence of light. Regnault had observed the formation of a white solid in the reaction mixture on exposure to sunlight, but in the state of chemical knowledge of his day, he did not recognize the solid as a polymer, merely noting that the formula weight was C_2H_3Cl.

Other reactions shown on this slide are, from top to bottom: A catalytic bimolecular condensation, with HCl elimination, to chloroprene--another

important chlorinated alkene monomer recently in the news as "cancer suspect"; this is followed by three 1,2-addition reactions: of a halogen, of sulfuryl chloride, and of HCl. What is apparent in all of these reactions is the essential lability of the VC double bond.

Slide 2 is a model of the VC molecule, showing the two centers of potential reactivity: the C-Cl bond (lower left) and the Π-bond. It is well-known rule of thumb in organic chemistry that the C-halogen bond adjacent to a double bond is much less reactive--i.e., more resistant to solvolytic and exchange reactions than the C-halogen bond of an alkyl halide, and this, in turn, is more stable than, say the allyl chloride C-Cl bond, the latter being a well-known lachrymator. These relationships are illustrated on Slide 3. Thus it is the Π-bond which is the reactive center of the VC molecule. On the other hand, the chlorovinyl group (C=C-X) *per se* may well be of particular significance where the long-term toxic or oncologic effects are concerned.

The next five slides show some chlorinated hydrocarbon pesticides which have been the subject of considerable controversy between ecologists and oncologists on the one hand, and the users and producers of pesticides on the other.

Potentially active centers of the chlorovinyl (C=C-X) and chloroalkyl (C-C-X) categories are bracketed by dotted lines. Slides 4 and 5 (DDT and DDD) show the vinyl chloride structure for comparison; on Slide 6 (DDE), the vinylidene chloride structure and toxicity data are included, and the recently banned pesticides Aldrin and Dieldrin are similarly illustrated on the following two slides (7 and 8).

Polyvinyl chloride is now one of the three major polymers manufactured, second only to the polyethylenes. The most important uses of the VC monomer are in the manufacture of PVC resins and copolymers, of which over 7 billion pounds were produced in the U.S. alone in 1974. The monomer is also an intermediate in pharmaceutical manufacturing (e.g., chloral hydrate, sulfa drugs, etc.), in the manufacture of the synthetic rubber monomer chloroprene, and has been used as a refrigerant, extraction solvent, and an aerosol propellant. The latter use has recently been discountinued as a result of the cancer alarm.

PVC is weather-resistant, chemically inert, heat and flame resistant. Its high electrical resistivity and chemical inertness, coupled with ease of fabrication, make it the leading plastic for cable insulation and PVC pipe, and its versatility has made it virtually ubiquitous, since it appears in

about 55% of the fabricated plastics. Quoting from "Job Safety and Health" (Jan/75):

> "Chances are you ride to work on a vinyl seat, walk across vinyl tiled floors on shoe soles of PVC, eat sandwiches wrapped in PVC film from a vinyl tablecloth, and relax to the sound of PVC records. The week-old infant...is likely to suck on a PVC pacifier. It its early days, during World War II, vinyl chloride gas was even used for a brief time as an anaesthetic in surgery."

Let me review briefly with you the vinyl chloride chronology:

1958-9 Dow researchers find "liver problems" in rats and rabbits inhaling VCM at 100 ppm (parts per million). Dow sets its exposure limit at 50 ppm.

1962 The American Conference of Governmental Industrial Hygienists (ACGIH), relying on other data, recommends a time weighted average (TWA) of 500 ppm--primarily aimed at avoiding nausea!

1970 Dr. P.L. Viola, Regina Elena Institute of Cancer Research (Rome) finds tumors of the skin, lung and bones while studying acro-osteolysis in rats.

1971 The ACGIH-recommended 500 ppm limit is adopted by OSHA, then a newly created agency. Publication of Dr. Viola's findings. (Cancer Res. 31(5) 516-22 [1971]).

May 6: Manufacturing Chemists Association (MCA) Occupational Health Committee recommends animal exposure and epidemiological studies.

November 18: Meeting (Washington, D.C.) of representatives from the U.S., Canada, and European firms. Solvay et Cie. report... further studies are "just beginning". Prof. Cesare Maltoni (Instituto Di Oncologia, Bologna) demonstrates induced angio-sarcoma in rats as low as 250 ppm in a study sponsored by the European plastics industry.

1972 17 U.S. firms agree to support VC studies (March 30).

1973 MCA contracts for animal studies with Industrial Bio-Test Laboratories, and for an epidemiologic study of VC workers with Tabershaw-Cooper Associates.

1974 Jan. 22: Goodrich Chemical reports four deaths from angiosarcoma of the liver within five years. To date there have been 16 identified cases among VC workers in the U.S., and 26 world-wide. Angiosarcoma is rare: Only about 100 cases have been reported altogether.

April 5: Emergency Temporary Standard (ETS): 50 ppm ceiling is announced by OSHA.

April 15: Biotest Laboratories (Northbrooke, Ill.) reports studies sponsored by the MCA: Liver angiosarcoma was found in 2/200 mice exposed to VC(50 ppm), 7 hours/day, 5 days/week for 7 months.

May 10: OSHA proposes its standard: "no detectable level" as measured by a sampling and analytical method sensitive to one ppm ± 50%. The standard is based on the finding of carcinogenicity in three species and "substantial probability" that VC is a causal agent in man; also on Maltoni's finding of dose dependence and of no threshold.

October 4: The permanent OSHA VC standard is promulgated (Slide 9). It allows 1 ppm/8Hr. TWA, and a 5 ppm ceiling. Requires respirators the first year for over 25 ppm exposure. The standard applies to the "manufacture, reaction, packaging, storage, handling or use" of VC and PVC but not to the use or handling of finished products. The standard requires:

- Regulated areas and rosters
- Training in safe practices and risks
- Medical surveillance, including blood tests
- Signs and labelling: "Cancer-Suspect Agent"
- Record keeping for at least 30 years, and
- Insures the *employee's right* to his medical records: This latter provision is a first, and a precedent.

Slide 10 summarizes some of the evidence for the carcinogenic effect of VC in man. The basis for this summary will be discussed briefly in the following section.

Table I summarizes a study of 930 white male employees by Dr. Joseph K. Wagoner, NIOSH Division of Field Studies and Clinical Investigations, Center for Disease Control (CDC). Attempts at employee follow-up subsequent to their

termination of employment dates up to December 31, 1973 were not altogether successful, and 285 members of the group were lost to observation. Since all of these individuals were assumed to be alive, any finding of increased mortality of the study cohort would err on the conservative side.

The total of 109 deaths found is just slightly greater than expected. However, *Cancer was the one category where a large increase of mortality over that expected was observed.*

When this was broken down further (Table II), it was found that cancers of the respiratory tract, of blood-forming tissues, and of the brain and central nervous system (CNS) were all in excess, but liver cancer deaths were almost 12 times the expected number. The majority of these cancers exhibited the long latent periods typical of occupational cancers, occurring 15 or more years after onset of exposure.

A similar study by Dr. Irving Selikoff of the Mt. Sinai School of Medicine at the Goodyear Niagara Falls PVC plant showed similar results. Dr. Maltoni's findings of multiple organ involvement were also corroborated by Wagoner's study.

The next table (III) furnishes worldwide data on liver angiosarcoma identified as of August 21/74 by the NIOSH-CDC surveillance network. Of the 14 U.S. cases reported, Number 8 is of particular interest (Table IV): This individual worked at the Goodrich VC polymerization plant between 1951-1954. Although this was his sole known exposure to VC, he died of liver angiosarcoma 18 years later, at age 41. This, according to Dr. Wagoner, suggests that the carcinogenic process, once induced, is irreversible.

Slide 11 summarizes the estimated exposure ranges of VC workers in monomer, polymer, and fabrication plants. Clearly the most serious exposure problem is in the PVC polymerization plants with estimates of 500-1600 ppm for reactor cleaners. However, because of the much larger number of employees engaged in fabrication, and the lack of a demonstrable threshold in the induction of cancer by VC, estimated fabrication plant VC levels of 10-100 ppm are also a cause for concern, particularly since "we now believe that cancer may not result from the cumulative build-up of a substance over a period of time, but that it may be activated by a single instance of exposure" (Dr. William Lloyd, head of the NIOSH Office of Health Surveillance and Biometrics; quoted in Supervisory Management, May 1975).

Slide 12 lists some of the structurally related unsaturated hydrocarbons containing the chlorovinyl potentiator moitié. All are either known carcinogens or "cancer suspect" agents. Heptachlor and chlordane have been banned by the EPA, along with the pesticides DDT, Aldrin, and Dieldrin.

THE NEED FOR A SYSTEMATIC APPROACH

Where do we go from here? We know that chlorinated hydrocarbons as a class have long been suspect. National Cancer Institute (NCI) has recently issued an alert on *trichloroethylene (TCE)*. This was preceded last October by an alert on *ethylene dibromide*, and subsequent alerts on *chlordane* and *heptachlor*, all three alerts sustained by later findings. The question of synergistic toxic effects remains largely unanswered. With over 20,000 chemicals and some 3000 new products introduced per year, it would take more than 200 years to develop standards for existing substances only (Stellman)!, and these standards would at best be questionable, since it is a logistic impossibility to test all of the deleterious synergisms possible.

In short, the time is long past due for a more systematic approach to environmental toxicants. The remainder of this paper will attempt to indicate some possible directions.

THE SOLUTION: A LOOK AT SOME FUNDAMENTAL PRINCIPLES

A. Metabolic Processes

The metabolism of toxic substances is usually an enzymic process which appears to occur in two phases:

1. A Biochemical Process--e.g., oxidation, reduction, hydrolysis-- to form such groups as -OH, $-NH_2$, -COOH, -SH, followed by
2. Conjugation ("Synthesis").

Benzene is an example of a compound which must undergo such a two-step detoxification: a) oxidation to phenol, and b) conjugagtion to the glucuronic acid derivative, as shown (Slide 13). An example of *single step* detoxification is the CN^- ion: this forms the less toxic CNS^- by direct conjugation. Ethanol, on the other hand, appears to be metabolized by a phase I process through acetaldehyde and acetic acid intermediates to CO_2, via acetyl coenzyme A.

Phase I products may be more or less toxic than their precursors. If more toxic, then a high rate of metabolism will mean a greater toxic effect on the organism. If less toxic, then the higher the rate of its formation, the less toxic will be the effect of a given dose of the toxic precursor.

It should be noted, however, that not all substances undergo metabolic change in the body. Some of the more important detoxification enzymes and their functions are listed on Slide 14. Metabolism of toxic substances takes place principally in those organs which provide entrance to, and exit from, the body: lungs, intestines, kidneys, and skin.

A large number of foreign compounds are metabolized in the liver by the so-called microsomal mixed function oxidases by a phase I (oxidation) process. These enzymes contain the Haeme-protein P-450 and require the reduced NADPH, or nicotinamide-adenine dinucleotide and molecular oxygen. Incidently, P-450 is inhibited by carbon monoxide, a common environmental pollutant. The function of the mixed oxidases is to introduce oxygen into foreign compounds (also into lipids and steroids). This hydroxylates aromatics, alicyclics and alkyl side chains, removes alkyl groups from secondary and tertiary amines and ethers, and oxidizes sulfides to sulfoxides and sulfones.

Other enzymes concerned with the metabolism of foreign substances are also found in the hepatic endoplasmic reticulum -- e.g., glucuronyl transferases--enzymes that catalyze the synthesis of glucuronic acid conjugates (a phase II reaction). Cytochrome P-450 also occurs in the kidneys, along with several other enzymes, and in the GI tract. Blood plasma contains a number of phase I enzymes (esterases).

Aromatic amines, sulfonamides and hydrazides are acetylated in Phase II reactions in the liver, spleen, and gastrointestinal mucosa. Foreign compounds are also metabolized in the GI tract by gut microflora. Often these reactions are reductive--e.g., the reductive scission of azo food dyes to toxic amines.

A third process of foreign compounds may produce lethal syntheses (Slide 15): here the compound or its phase I metabolite may mimic a natural intermediary metabolite--e.g., fluoracetate mimics acetate, ultimately blocking this path in the tricarboxylic acid cycle. Again, dimethylnitrosamine is oxidatively converted to an active methylating agent, which reacts with nucleic acids. These may in turn bear a relationship to cancer induction (Craddock and Magee, 1966).

The use of insecticide *synergists* such as methylenedioxynaphthyl compounds is based on their ability to inhibit the enzymes which deactivate the insecticides; thus, they *potentiate* toxicity and insecticidal activity.

It is clear that synergism of chemicals present in the environment and their effect on the metabolism of toxic compounds should be investigated much more thoroughly. As yet we have no clear understanding of what potentiates the chlorovinyl (C=C-Cl) moitié. We do know, however, that the affinity of its double bond *could conceivably enable it to function as an effective inhibitor of important enzyme systems by addition across RSH or* RNH_2 in these systems. It is thus not surprising that liver function tests on workers exposed to VC show a high incidence of anomalies. Certainly, the study of appropriate *in vitro* enzyme systems should have been carried out long ago, in parallel with the animal studies.

Let me cite just one interesting example from the antidote therapy for Lewisite poisoning. Lewisite is betachlorovinyl dichlorarsine--a VC derivative of trichlorarsine (Slide 16). Lewisite was found (Stockton and Thompson, 1946) to combine with two -SH groups in kerateine the reduced form of keratin. This led to the inference that it might be forming a stable ring with two vicinal -SH groups. On the basis of this reasoning, a number of compounds with vicinal -SH groups were tested, and 2,3-dimercaptopropanol (last formula on Slide 16) was successful as an antidote for Lewisite (Peters, 1948). Six years later (1954) Gunsalus found that the pyruvate oxidase system contained lipoic acid, which is 6,8- dithio-octanoic acid, shown on Slide 16.

B. Charge Transfer Phenomena

I wish to examine briefly another approach to the toxicity problem which requires further exploration, at least insofar as the haloalkenes are concerned; namely, the formation of *charge transfer complexes*.

All molecules interact, but normally the intermolecular (Van Der Waals) forces are small compared with interatomic forces. While not being amenable to description in terms of classical chemical bonding, these forces may sometimes be sufficiently strong or unique in some features to defy explanation in the usual van der Waals terms (e.g., dispersion, dipole-dipole interaction, dipole-induced dipole, etc.,). Charge-transfer or electron-donor-acceptor complexes fit into this category. Their observed electronic absorption spectra are best explained by so-called charge-transfer transitions--weak interactions between electron donors and electron acceptors of the order of a few kcal/mole.

Donors fall into three main classes shown on Slide 17:

n-Donors include amines, amine oxides, ethers, phosphines, alcohols, iodides, etc.

σ-Donors, such as the aliphatic hydrocarbons and small cycloparaffin rings show generally weak interactions.

Π-Donors include aromatics and aryl polycyclics with electron-releasing groups such as $-CH_3$ and may show strong interactions with acceptor molecules. *There is relatively little known about the aliphatic Π-donors* such as VC, since the greatest interest here has centered on their radical-induced polymerization properties. The correlation, if any, between the ease of free radical formation of these compounds, their photosensitivity, and their carcinogenicity remains to be investigated. In view of the economic importance and ubiquity of some of these compounds (e.g., VC), it is astonishing that such a potentially fertile approach to the cancer problem has not been seriously addressed.

Acceptors of interest may be of the σ and Π type (Slide 18). σ-Acceptors include the halogens and mixed halogens such as ICl and ICN, HCl and the weakly accepting alkyl halides. Π-Acceptors are the most common organic acceptors and include aromatics containing electron-withdrawing groups such as nitro-, cyano-, halo-, acid anhydrides, chlorides and quinones.

The terms 'donor' and 'acceptor' are relative, and it is quite possible for a single species to show both properties, depending on the molecular environment. For the ideal case of 1:1-complexing, the equation for donor-acceptor complex formation is shown on the next slide:

$$K_C^{AD} = \frac{[AD]}{[D][A]} = \frac{[AD]}{([D]_o - [AD])([A]_o - [AD])}$$

The figure on the slide is a Benesi-Hildebrand plot of A_o/A versus the reciprocal of D_o for a series of 1, 2-dichloroethane solutions of hexamethybenzene (donor) and tetracyanoethylene (acceptor).

SUMMARY AND CONCLUSION

The need for inquiry into the relationship, if any, between the ultraviolet sensitivity and ease of free-radical formation of compounds like vinyl chloride and their carcinogenicity has already been stressed. An attempt to further correlate these characteristics with donor-acceptor properties should also be made, since all of the characteristics may relate to the interaction of these substances with critical sites in biological systems.

Cancer is not a single disease: Rather it is a blanket term covering a range of conditions involving cell malignancies. Chemical carcinogens include aromatic hydrocarbons and amines, urethanes, N-mustards, CCl_4 and a number of inorganic substances. Thus the term "chemical carcinogenesis" is really an expression of our ignorance--for cancer almost certainly occurs by a number of biochemical mechanisms. In the alkylating agents, true covalent bond formation very likely occurs. In the aromatics, there are no apparent reactive sites, and attempts have been made to correlate C-T complex formation with ionization potential, with excited-state interactions of protein-hydrocarbon complexes via energy transfer, with varying success. Actual protein binding with and without carcinogenicity has been demonstrated for the polycyclic aromatics and certain N-heterocyclic polyaromatics.

In my initial statement of purpose, I suggested that a re-examination of the VC problem from a rational chemical point of view might be helpful in anticipating future problems and avoiding future crises. The approaches which would appear to me to hold the greatest promise in dealing with potential toxicants such as VC are:

1) Examination of their chemical reactivity toward important biochemical groupings such as -SH, $-NH_2$, -COOH, purine and pyrimidine derivatives; etc., known to be critical components of biological systems;

2) Inhibition and potentiation studies with critical enzyme systems;

3) Charge-transfer and protein binding studies using relatively simple and inexpensive spectrometric techniques.

If these methods are routinely employed during the initial research stages, most crisis situations could in all probability be avoided from the outset by utilizing appropriate decision-making processes: these may involve the cancellation of a project, the concommitant development of adequate safety monitoring techniques, or the decision to use or develop a substitute--all before the investment of time and capital renders viable alternatives less feasible.

It cannot be stressed enough that we scientists are human. It is not easy to drop an interesting and promising project. For this reason evaluations related to toxicity should be made independently by a qualified agency *in no way involved in the original research*--or better yet--by an outside laboratory, before the final decision is made to develop a product commercially. Thank you for your attention.

TABLE 1

OBSERVED AND EXPECTED DEATHS AMONG SELECTED EMPLOYEES OF TWO VINYL CHLORIDE POLYMERIZATION FACILITIES

1950 - 1973

CAUSES OF DEATH	OBSERVED	EXPECTED	STANDARD MORTALITY RATIO
TUBERCULOSIS	0	.74	
CANCER	31	19.74	157[†]
VASCULAR LESIONS AFFECTING CNS	6	6.45	93
DISEASES OF HEART	43	46.12	93
NON-MALIGNANT RESPIRATORY DISEASE	6	5.12	117
CIRRHOSIS OF LIVER	2	3.21	62
VIOLENT DEATHS	8	11.00	73
ALL OTHER KNOWN CAUSES	12	13.04	92
UNKNOWN CAUSES			
TOTAL	109	105.42	102

[†]SIGNIFICANT AT $p < 0.05$

TABLE 2

EXPECTED AND OBSERVED DEATHS FROM VARIOUS CANCER CAUSES
1950 – 1973

YEARS SINCE ONSET OF EXPOSURE IN THE SELECTED DEPARTMENTS	PERSON YEARS AT RISK	ALL CANCER		LIVER CANCER		BRAIN CANCER		RESPIRATORY SYSTEM CANCER		LYMPHOMA & LEUKEMIA		RESIDUAL CANCER	
		EXP.	OBS.	EXP.	OBS.	EXP.	OBS.	EXP.	OBS.	EXP.	OBS.	EXP.	OBS.
10 - 14.9		4.91	6	.12	0	.22	0	1.50	3	.61	1	2.46	2
15 - 19.9		6.30	11	.17	3*	.25	1	2.08	3	.67	2	3.13	2
20 - 24.9		5.81	11	.15	3*	.20	2*	1.99	4	.55	1	2.92	2
> 25		2.72	3	.07	0	.06	1	.92	0	.24	0	1.43	1
TOTAL	9731	19.74	31*	.51	6**	.73	4*	6.49	10	2.07	4	9.94	7
STANDARD MORTALITY RATIO		157		1,176		548		154		193		70	

* SIGNIFICANT AT $P < 0.05$

** SIGNIFICANT AT $P < 0.01$

TABLE 3

LIVER ANGIOSARCOMA CASES AMONG
VC POLYMERIZATION WORKERS

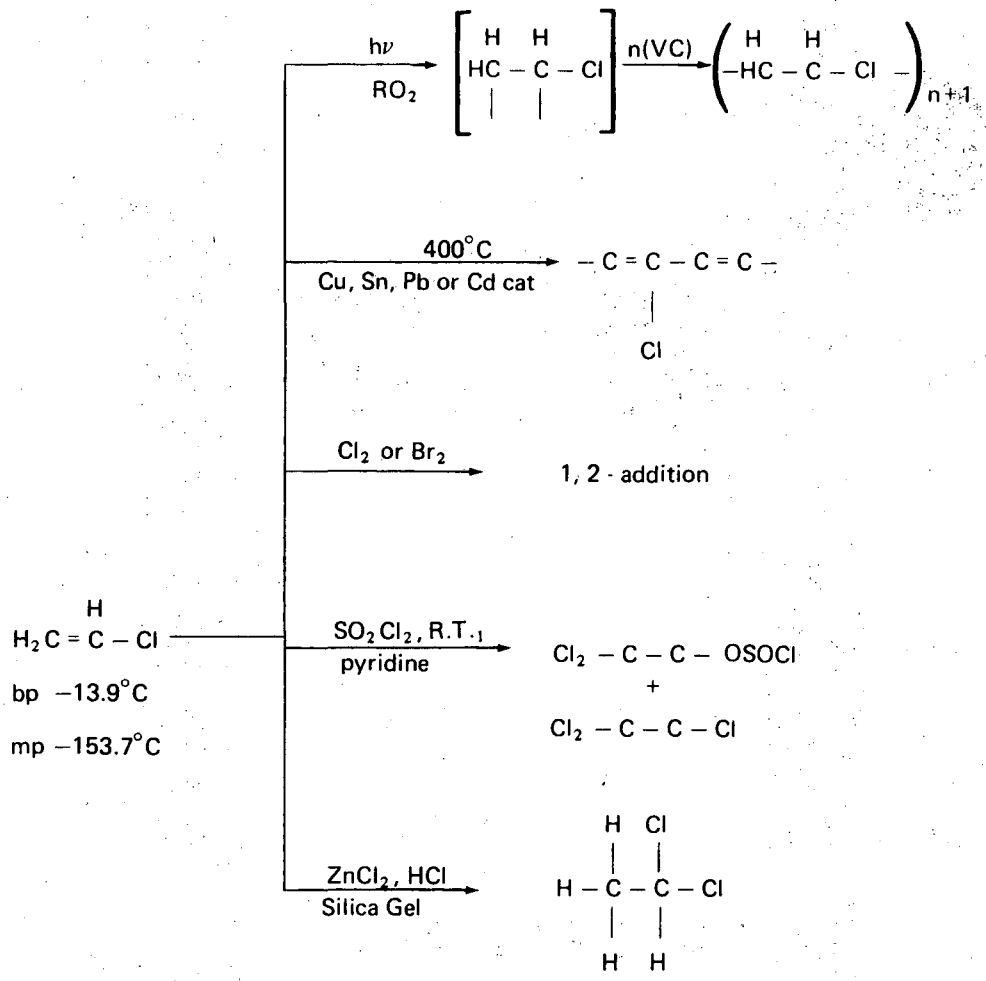
CASE NO.	COUNTRY	DATE OF DEATH	YEARS AFTER EXPOSURE	YEARS OF EXPOSURE	AGE AT DIAGNOSIS
1	WEST GERMANY	1969	11	11	39
2	UNITED STATES	ALIVE	12	12	45
3	UNITED STATES	1971	14	13	37
4	WEST GERMANY	1971	14	14	40
5	UNITED STATES	1968	15	15	44
6	UNITED STATES	1961	15	15	41
7	UNITED STATES	1968	17	17	54
8	UNITED STATES	1969	18	4	41
9	SWEDEN	1970	19	18	43
10	UNITED STATES	1969	20	15	50
11	UNITED STATES	1964	20	18	52
12	UNITED STATES	1973	22	16	51
13	NORWAY	1972	22	21	56
14	UNITED STATES	1970	23	23	60
15	UNITED STATES	1968	24	18	45
16	UNITED KINGDOM	1972	26	20	71
17	UNITED STATES	1973	28	28	59
18	UNITED STATES	ALIVE	29	17	43
19	UNITED STATES	1974	30	30	52
20	CZECHOSLOVAKIA		AWAITING DETAILS		
21	CZECHOSLOVAKIA		AWAITING DETAILS		

CASE NUMBER 8

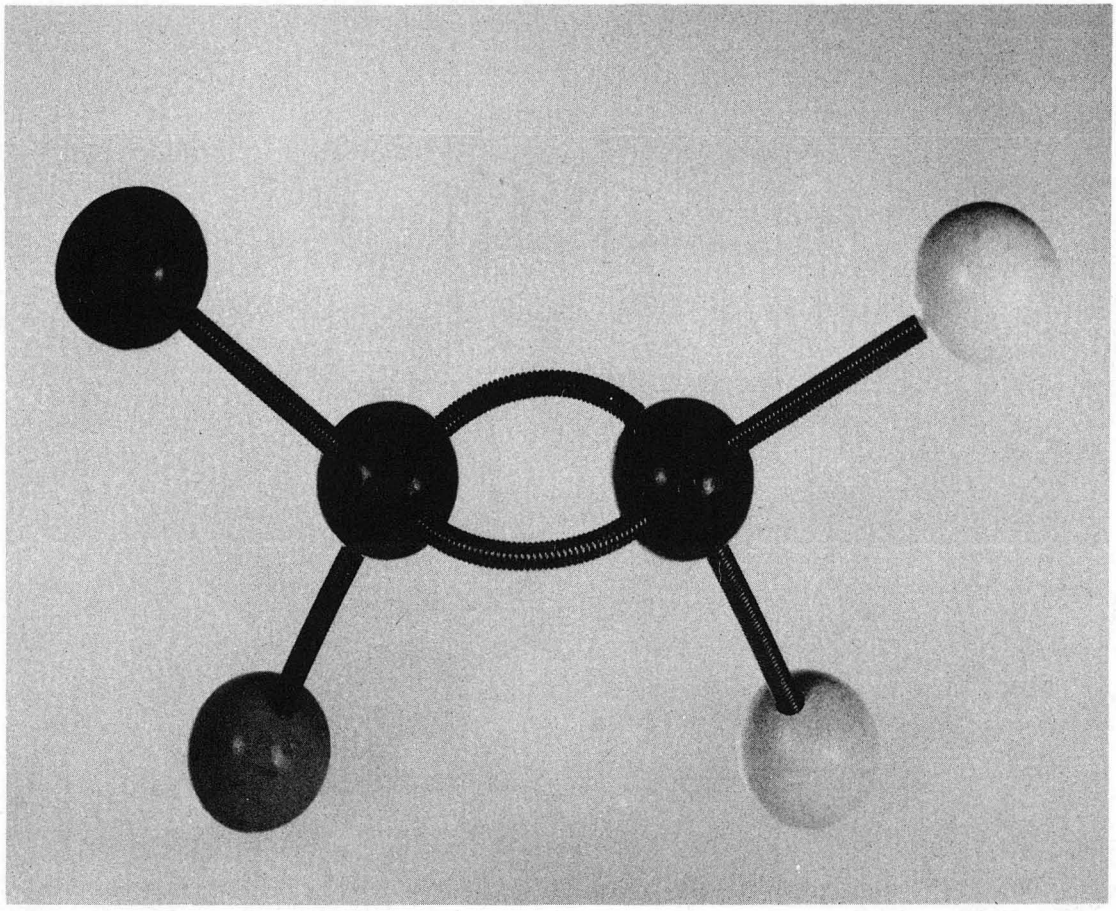
TABLE 4

EMPLOYMENT HISTORY

DATE	OCCUPATION
2/14/46 - 3/7/47	MILITARY
3/7/47 - 4/16/48	UNKNOWN
4/16/48 - 4/6/50	MILITARY
11/11/51 - 11/12/52	CHEMICAL HELPER AT A VINYL CHLORIDE POLYMERIZATION PLANT
11/12/52 - 7/1/53	CHEMICAL OPERATOR AT A VINYL CHLORIDE POLYMERIZATION PLANT
7/53 - 3/7/54	CHEMICAL HELPER AT A VINYL CHLORIDE POLYMERIZATION PLANT
3/7/54 - 6/13/54	CHEMICAL OPERATOR AT A VINYL CHLORIDE POLYMERIZATION PLANT
6/13/54 - 7/14/55	UNKNOWN
7/14/55 - 6/30/63	MILITARY
6/30/63 - 8/1/63	UNKNOWN
8/1/63 - 2/17/67	MILITARY
2/17/67 - 3/27/69	UNKNOWN
3/27/69	DECEASED



Slide 1



(CBB 756-4116)

CHLOROETHENE

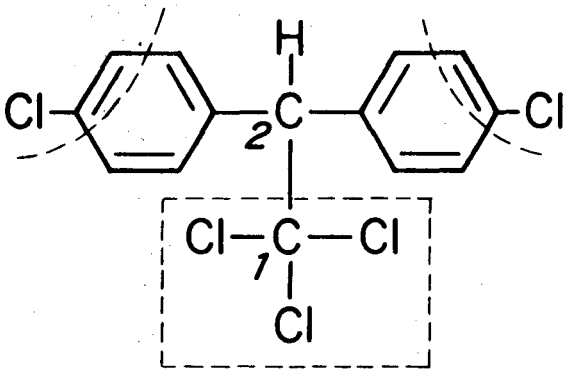
Slide 2

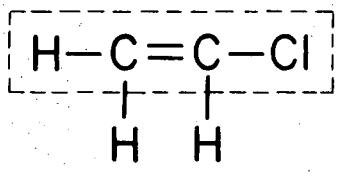
$$C = C - C - X \gg - C - C - X \gg C = C - X$$

$$X = \text{HALOGEN}$$

Slide 3. Relative reactivities of the C – X bond adjacent to allyl, alkyl and vinyl moities.

DDT





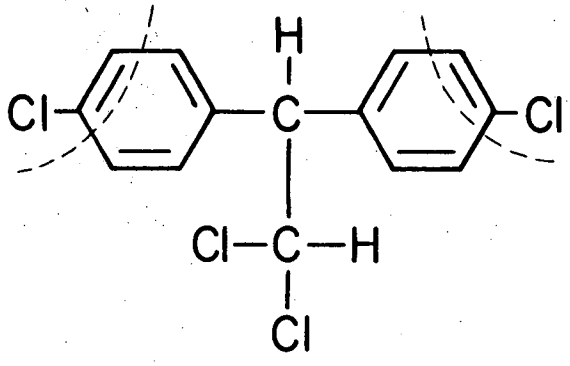
2,2-bis (p-chlorophenyl)-1, 1, 1-trichloroethane

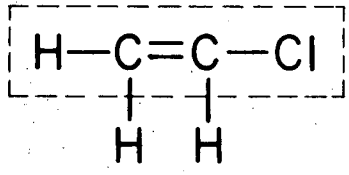
TXDS: orl-hmn TDL_0: 16 mg/kg TFX:CNS
orl-(rat) LDL_0: 150 mg/kg USOS:SKIN

XBL 756-3108

Slide 4

DDD, TDE





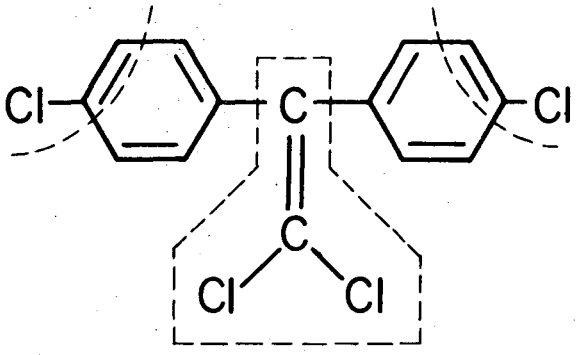
2, 2-bis(p-chlorophenyl-1, 1-dichloroethane

TDS: orl-hmn LDL_0 5000 mg/kg
orl-rat LD_{50} 3400 mg/kg

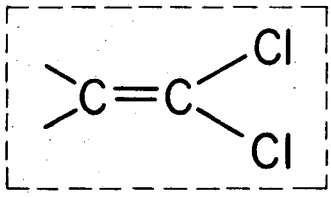
XBL 756-3107

Slide 5

DDE



2,2-bis-(p-chlorophenyl)-1, 1-dichloroethene.



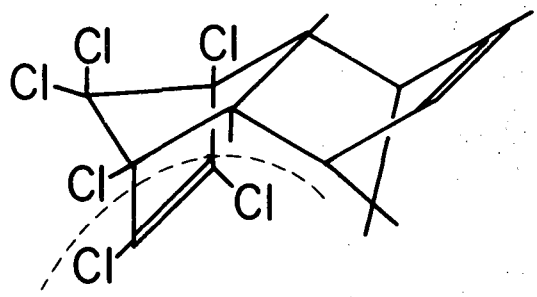
Vinylidene chloride TXDS:

orl-rat LDL_0 400 mg/kg
ihl-rat LDL_0 500 ppm/4H

XBL 756-3106

Slide 6

Aldrin



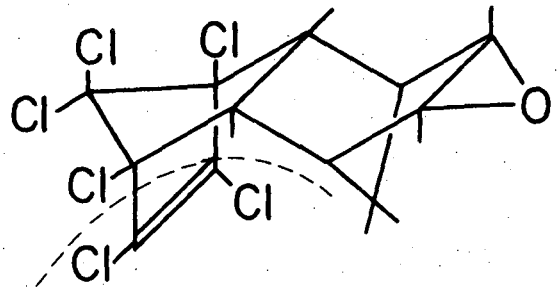
1,2,3,4,10,10-hexachloro-1,4-4a,5,8,8a-hexahydro-1,4-*endo-exo*-5,8-dimethanonaphthalene.....

TXDS orl-rat LD50: 55 mg/kg
skn-rbt LDL_0: 15 mg)kg

XBL 756-3105

Slide 7

Dieldrin



Dieldrin

1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4-*endo-exo*-5,8-dimethanonaphthalene.....

TXDS: orl-rat LD50: 46 mg/kg
orl-rat TDL_0: 1800 mg/kg/2YC TFX:NEO
skn-rat LD 50:90 mg/kg
oral-Mus TDL_0: 870 mg/kg/2YC TFX:NEO

XBL 756-3104

Slide 8

OSHA Standards for Vinyl Chloride

- Assume "no safe limit"
- Limit VC exposures to 1 p p m, TWA (8 hr) with 5 ppm ceiling in any 15 minute period.
- Respirators required over 25 ppm until Jan 1/76.
- "Regulated areas": over 1ppm
- Employee training: safe work practices; risks of of exposure; proper use of rspirators.
- Medical surveillance: exams every 6 months for employees over 10 years.
- Signs and labelling: "cancer suspect agent."
- Record-keeping: maintained at least 30 years. "Employee Rights" provision.

Slide 9

VC: Evidence for Carcinogenic Effect

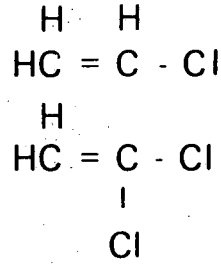
- Deaths from Angiosarcoma of the liver occur far more frequently than expected among VC workers.
- An excess of cancers is also found in other parts of the body.
- Incidence of cancer rises sharply with years of exposure.

Slide 10

Estimates of Employee Exposure to VCM in U.S. Plants

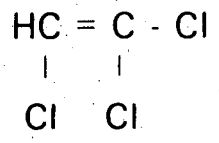
	Plants	No. Employed	Exposure Range p(ppm)
VC Monomer	15	940	up to 200 (Tank Car Loaders)
PVC Polymer	36	5600	500-1600 (Reactor Cleaners)
Fabrication	7500	350,000	10-100 (During melting, extrusion, etc.)

Slide 11

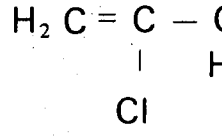


Chlorethene (VCM)

1,1-dichlorethene
(vinylidene chloride)



1,1,2-trichloroethene
(trichloroethylene)



2 - chloro-1,3-butadiene
(Chloroprene)

Pesticides — "Heptachlor", "Chlordane"

Potentiator group: C = C - X

Slide 12. Chlorinated organic compounds containing the C = C – Cl Potentiator group.

DETOXIFICATION

2 STEP: BENZENE

I $C_6H_6 \xrightarrow{oxid} C_6H_5OH$

II $C_6H_5OH \xrightarrow[RCOOH\ HSO_4^-]{Conj'n} C_6H_5-\overset{\overset{O}{\|}}{OC}-R + C_6H_5HSO_4$

---

1 STEP: II $CN^- \xrightarrow{[S]} CNS^-$

I $CH_3CH_2OH \longrightarrow [CH_3CHO] \longrightarrow |CH_3COOH|$

Coenzyme A

$CO_2 \longleftarrow |Acetyl\ CoA|$

Slide 13

DETOXIFICATION ENZYMES

Microsomal Mixed Function Oxidases:

a) Contain the Haeme Protein P–450 (Inhibited by CO)

b) Hydroxyl at aromatics and aliphatics

c) Dealkylate Amines and Ethers

d) Oxidize Sulfides

Other Enzymes

Glucuronyl transferases

Esterases

Gut Microflora

Reductive detoxification

Slide 14

Lethal Synthesis

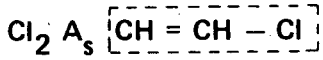
a) Fluoroacetate/Acetate Inhibition

b) Dimethyinitrosamine

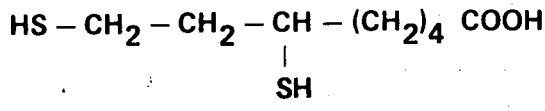
Synergesis/Potentiation

Ex. Methylenedioxynaphthyl compounds inhibit the enzymes which deactivate insecticides; therefore enhance insecticidal activity.

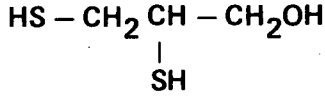
Slide 15



β – Chlorovinyl Dichlorarsine
(Lewisite)



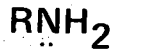
6, 8 – dithio-octanoic acid
(Lipoic Acid)

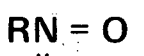


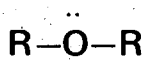
2, 3 – dimercaptopropanol

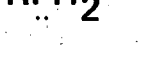
Slide 16

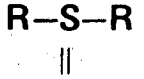
n – DONORS

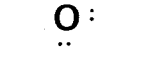












σ – DONORS (Weak)

hydrocarbons

π – DONORS (Strong)

Aromatics

Polycyclic Aromatics

MIXED DONORS

Aromatic Amines

Aza-aromatics

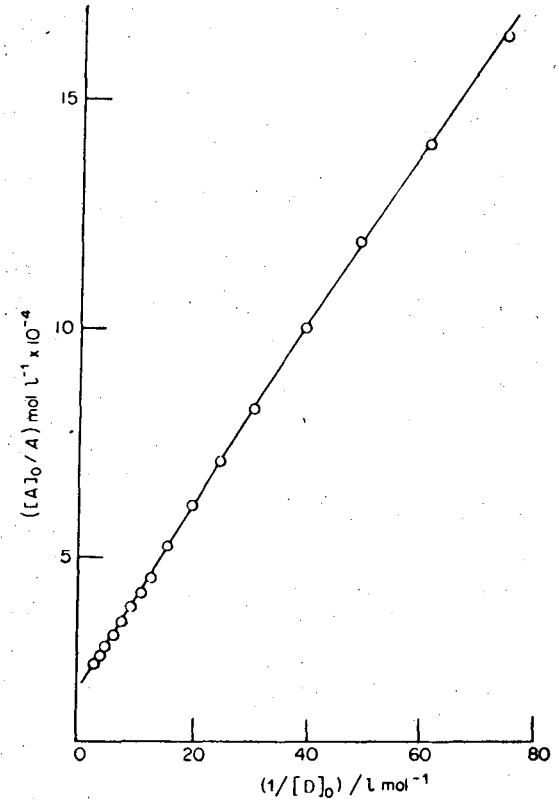
Slide 17

σ – Acceptors	π – Acceptors
RX	Nitro } aromatics
I_2	Cyano } aromatics
Br_2	Halo } aromatics
ICN	Benzoquinone
Mixed	Chloranil Picric Acid
(unpaired electron)	
$I\bullet$, O_2	
DPPH	
Polycylic Aromatics	

Slide 18

BENESI–HILDEBRAND PLOT.

ORGANIC CHARGE-TRANSFER COMPLEXES



$$K_C^{AD} = \frac{[AD]}{[D]\ [A]} = \frac{[AD]}{([D]_0 - [AD])\ ([A]_0 - [AD])}$$

Slide 19

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