XC R.N Wheeler -> (41)

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8 May 1980

Docket Officer
Docket H-034
Room 56212
U.S. Department of Labor, OSHA
200 Constitution Avenue, N.W.
Washington, DC 20210

Sir:

Air Products and Chemicals submits herewith its response to the request for information on vinyl chloride and polyvinyl chloride by The Department on 18 December 1979 (44FR74928 and 45FR6668).

This submittal consists of two parts:

I. A bibliography of articles on these substances, selected to include those articles published since the 1974 rulemaking procedure on vinyl chloride which are not included in the preliminary bibliography transmitted by R. Appledorf to J. Hadley with a letter of 10 January 1980, and not presented or discussed at the joint conference in Bethesda on March 20-21, 1980. These articles therefore are presumably new information for OSHA. You are urged to study each document, but for your convenience a brief author abstract, if available, or other summary is included.

II. Comments on the paper and discussions of the Bethesda conference (45FR12560).

Please address any questions relating to this submittal to the undersigned.

Sincerely,

J. T. Barr
Regulatory Response

JTB/rw
699-N-3
Attachment

bcc: R. Fleming
J. E. Hadley - Keller and Heckman
R. H. Schenck
H. J. Smith
L. B. Tepper

UCC
021713

Part I

Additional Literature Submitted for the Record and for the Consideration of the Secretary.

For the convenience of the reader, this bibliography is divided into sections by subject. Author abstracts are provided where available, otherwise short summaries are given. The reviewer is urged to consult the original document for complete details.

A. Analytical Studies

B. Angiosarcoma Surveys

C. Animal Studies Metabolism

D. Birth Defects, Mutagenicity

E. Chromosomal Effects

F. Dust Studies

G. Environmental Studies

H. Morbidity Studies

I. Mortality Studies

A. Analytical Studies

Hoffmann, D. et al., (1976) Chromatographic Determination of Vinyl Chloride in Tobacco Smoke. Analytical Chemistry 48 47-50

A chemical-analytical method has been developed for the quantitative determination of vinyl chloride (VC) in tobacco smoke. VC from the mainstream smoke is trapped on charcoal, extracted, and subsequently converted to 1,2-dibromo-1-chloroethane (DB-VC). The latter is enriched by column chromatography and determined by gas liquid chromatography using an electron capture detector with a high sensitivity for DB-VC. From the mainstream smoke of a popular 85-mm cigarette without filter tip, we isolated 12.2 ng of VC per cigarette. The VC content in the smoke of some domestic and foreign cigarettes and little cigars ranged from 5 to 27 ng, and that of a marijuana cigarette was 5.4 ng. The analytical data suggest that the total inorganic chloride in tobacco is a determining factor for the amount of VC in the smoke. VC may also be released into our respiratory environment during the burning of other chlorine-containing organic matter.

B. Angiosarcoma Surveys

Baxter, P. J. and Fox, A. J. (1976) Angiosarcoma of the Liver in PVC Fabricators. Lancet, 245.

A review of 707 deaths among fabricator workers in 1970-72 found no angiosarcoma and no excess of deaths from cancer at other sites.

Dalderup, L. M., et al., (1976) Angiosarcoma of the Liver. Lancet, 246.

A review of all angiosarcoma deaths in Holland since 1950 found none which had "any traceable contact with vinyl chloride".

Barr, J. T., (1976) Letter to J. T. Smith, EPA, April 6.

Reference to EPA statements that there were no known cases of "neighborhood" angiosarcoma found by the Agency searches (entire document attached).

Barnes, A. W. (1976) "Institutional Interactions in Problems of Occupational Health: An Industry View on the Lessons from Vinyl Chloride". Medichem 4th International Conference, HAIFA.

A review of data on angiosarcoma cases (entire document attached).

Saric, M. et al., (1976) "Malignant Tumors of the Liver and Lungs in an Area with a PVC Industry". Environmental Health Perspectives, 17 189.

The incidence of malignant tumors of the lung and bronchus and of cytologically confirmed primary malignant tumor of the liver was analyzed for a four-year period in a city with several factories, including a PVC industry. Prior to the study two cases of angiosarcoma of the liver were diagnosed in workers employed in PVC production.

The total incidence of analyzed tumors was only slightly higher than predicted. The tumors of the liver recorded did not show any dependence on place of work or residence. During the period of observation, malignant tumors of the bronchus (lung) were not recorded in the PVC industry. Their rate in the area in which the PVC industry is situated was approximately the same as that for the entire city area.

The study does not indicate that the occurrence of malignant tumors other than angiosarcoma is associated with exposure to vinyl chloride.

Baxter, P. et al., (1977) "Angiosarcoma of the Liver in Great Britain, 1963-1973 Preliminary Study". British Medical Journal, 2, 919.

Deaths attributed to primary angiosarcoma of the liver (ASL) in Great Britain between 1963-73 were reviewed by submitting available histological material to a panel of histopathologists and by obtaining full occupational and residential histories for the cases agreed as ASL by the panel. On average four recorded cases of ASL occurred a year, but in only one-third of the cases submitted did the panel agree with the original diagnosis. Only one of the agreed cases could be confidently associated with exposure to vinyl chloride.

International Plastics News (1978). Britain's OSHA has Second Thoughts About VCM. Plastics World, 42 (entire article attached).

Gehring, P. J., et al., (1979) Risk of Angiosarcoma in Workers Exposed to Vinyl Chloride as Predicted from Studies in Rats. Toxicology and Applied Pharmacology 49, 15-21.

Dose-response data for the induction of angiosarcoma in rats exposed to various levels of vinyl chloride (VC) together with attendant biotransformation data were used to estimate the risk of developing angiosarcoma in persons exposed to VC. Since a biotransformation product of VC, not VC per se, is responsible for the induction of angiosarcoma, the body surface area of people relative to rats was used to estimate the dose of the carcinogen biotransformed from VC by the former. Four models were used to extrapolate the data. Using a probit model, 10 hepatic angiosarcomas were predicted to occur in a recently reported epidemiological cohort of 9677 workers whereas five have occurred. Linear models and that based on the equation, Risk = $1 - e^{-x}$, where x = dose, do not appear as reliable. For an eight-hour day, five days/week, 35-year time-weighted, average exposure of 1 ppm, the predicted incidence of hepatic angiosarcoma using the probit model is 1.5×10^{-3}.

C. Animal Studies - Metabolism

Kappus, et al., (1975) Rat Liver Microsomes Catalyse Covalent Binding of ^{14}C-Vinyl Chloride to Macromolecules. Nature 257 134.

The authors find covalent binding of VC metabolites provides additional support for an active intermediate as the actual carcinogen.

Bolt, et al., (1975) Metabolism of Vinyl Chloride. Lancet 1425.

Results similar to Kappus, et al.

Green, T. and Hathway, D. (1975) The Biological Fate in Rats of Vinyl Chloride in Relation to its Oncogenicty. Chem-Biol. Interactions. 11 545.

The main eliminative route for [^{14}C] vinyl chloride after oral, i.v. or i.p. administration to rats is pulmonary; both unchanged vinyl chloride and vinyl chloride-related CO_2 are excreted by that route and the other [^{14}C] metabolites via the kidneys. After intragastric administration, pulmonary output of unchanged vinyl chloride is proportional to the logarithm of reciprocal dose. Excretion patterns after i.v. and i.p. injections are predictable from the characteristics of excretion following oral administration. Pulmonary excretion of unchanged vinyl chloride after oral dosing is complete within 3-4 h, but pulmonary elimination of CO_2 and renal excretion of metabolites occupies 3 days. In comparison, 99% of a small i.v. dose is excreted unchanged within 1 h of injection; 80% within 2 min.

The rate of elimination of single oral doses of [^{14}C] vinyl chloride is uninfluenced by up to 60 days' chronic dosing with the unlabeled substance.

The distribution volume of vinyl chloride as displayed by whole-animal autoradiography agrees with deductions from excretion data. Small localization of ^{14}C in the para-auricular region of appropriate sections occurs in sectioned tubules, belonging possibly to the Zymbal glands.

Biotransformation of vinyl chloride into S-(2-chloroethyl) cysteine and N-acetyl-S-(2-chloroethyl) cysteine occurs through addition of cysteine, and biotransformation into: (i) chloroacetic acid, thiodiglycollic acid and glutamic acid, and (ii) into formaldehyde (methionine, serine), CO_2 and urea is explicable in terms of an associative reaction with molecular O_2 involving a singlet oxygen bonded transition state in dynamic equilibrium with a cyclic peroxide ground state. There is no evidence for chloroethylene oxide formation.

Thiodiglycollic acid is the major metabolite of chloroacetic acid in rats; more than 60% of the dose.

The interaction of vinyl chloride and of its primary metabolites with the intermediates of mammalian metabolism is discussed in relation to the oncogenicity of that substance.

Reynolds, E. S., et al., (1975) Hepatatoxicity of Vinyl Chloride and 1,1-dichloroethylene: Role of Mixed Function Oxidases. Presented at the 59th Annual Meeting of the Federation of American Societies for Experimental Biology, Atlantic City, New Jersey, April 15.

Vinyl chloride, an occupational carcinogen, produces acute liver injury in rats pretreated with phenobarbital or Aroclor 1254. Injury appears related to morphologic changes in the endoplasmic reticulum. Degree of injury as indicated by elevation of serum enzymes derived from the liver correlates with magnitude of induction of cytochrome P-450 and its reduction by NADPH. Hepatic injury following 1,1-dichloroethylene differs strikingly and appears to involve plasma membranes, mitochondria and chromatin, sparing endoplasmic reticulum. In contrast to vinyl chloride, induction of cytochrome P-450 appears to protect against 1,1-dichloroethylene.

Withey, J. R. (1976) Pharmocodynamics and Uptake of Vinyl Chloride Monomer Administered by Various Routes to Rats, J. of Toxicology and Environ. Health, 1 381.

To assess the hazard presented by the oral ingestion of vinyl chloride monomer, rats that had been surgically prepared with an indwelling jugular cannula were dosed by intragastric intubation with aqueous solutions containing up to 2.0 mg/ml vinyl chloride. Time-concentration curves were obtained from sequential samples of blood. The uptake of vinyl chloride by this route was found to be extremely rapid; peak concentrations were achieved less than 10 min after administration of the dose. Elimination from the blood compartment appeared to be biexponential.

Studies with the same animal model in a single restraint cage that allowed a "head only" exposure to concentration of vinyl chloride up to 7,000 ppm in the gas phase have shown a similar rapid uptake followed by a plateau blood concentration during several hours of exposure. On removal from the vinyl chloride atmosphere, blood levels fell rapidly to barely detectable concentrations after 2 hr.

The precise kinetic coefficients that describe the distribution and elimination rates of vinyl chloride from the blood compartment were also determined from the blood concentration data after the administration of an intravenous dose of aqueous or vegetable oil solution.

Guengerich, F. P. and Strickland, T. W. (1977) Metabolism of Vinyl Chloride Destruction of the Heme of Highly Purified Liver Microsomal Cytochrome P-450 by a Metabolite. Molecular Pharmacology, 13 993.

The NADPH-dependent, vinyl chloride-mediated destruction of cytochrome P-450 was demonstrated in rat liver microsomes and in highly purified reconstituted enzyme systems containing NADPH-cytochrome P-450 reductase (NADPH:ferricytochrome oxidoreductase, EC 1.6.2.4) and cytochrome P-450. This loss of cytochrome P-450 could be attributed to heme destruction, but not to lipid peroxidation or binding of electrophiles to free sulfhydryl groups. The system required all components necessary for mixed-function oxidation, including molecular oxygen, and was inhibited by carbon monoxide, suggesting strongly that oxidative metabolism of vinyl

chloride by cytochrome P-450 is necessary for the observed destruction. The NADPH-cytochrome P-450 reductase-catalyzed destruction of free and cytochrome P-450-bound heme was also observed in reconstituted systems in the absence of vinyl chloride. Inhibition experiments with carbon monoxide 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 and 2-chloroacetaldehyde, 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 examined by EPR spectroscopy or when attempts were made to inhibit cytochrome P-450 destruction with radical-trapping agents.

Hathway, D. (1977) Comparative Mammalian Metabolism of Vinyl Chloride and Vinylidene Chloride in Relation to Oncogenic Potential. Environ. Health Perspectives. 21 55.

Elucidation of the role of vinyl chloride metabolites in the various reaction sequences which comprise the metabolic pathway, including the interaction of reactive metabolites with some purine and pyrimidine residues of target-organ DNA, provides some explanation for the (oncogenic) properties associated with the original substance. Comparative investigation of the biological fate of vinylidene chloride reveals an agent of low oncogenic potential which is likely to be damaging only under special curcumstances, and species differences which suggest that the mouse is more susceptible than the rat towards vinylidene chloride oncogenicity.

Green, T. and Hathway, D. (1977) The Chemistry and Biogenesis of the S. Containing Metabolites of Vinyl Chloride in Rats. Chem. Biol. Interact. 17 137.

In order to determine whether vinyl chloride yields chloroethylene oxide in vivo, the biogenesis of the various urinary S-containing metabolites in rats has been investigated.

N-Acetyl-S-(2-hydroxyethyl) cysteine is a major vinyl chloride metabolite in rats, but according to the method of protective esterification that is used, so either N-acetyl-S-(2-chloroethyl) cysteine or N-acetyl-S-(2-hydroxyethyl)-cysteine may be isolated from the body fluids. N-Acetyl-S-vinylcysteine is a second related metabolite. These S-containing vinyl chloride metabolites are not mutagenic in S. typhimurium. Neutral methanol methylates N-acetyl-S-(2-hydroxyethyl)cysteine. N-Acetyl-S-(2-methoxyethyl)cysteine plus N-acetyl-S-vinylcysteine degrade to give the volatile S-(2-methoxyethyl)(prop-1 or 2-enyl)sulphide.

Administration of several vinyl chloride metabolites and closely related compounds to rats shows that chloroacetaldehyde and S-(carboxymethyl)-cysteine, but not chloroacetic acid, lie on a pathway or pathways connecting vinyl chloride with thiodiglycollic acid. The fact (a) that chloroacetaldehyde affords both thiodiglycollic acid and N-acetyl-S-(2-hydroxyethyl)cysteine in the animal and (b) that S-(carboxymethyl) cysteine has been identified amongst the hydrolytic products from an hepatic extract prepared from vinyl chloride-treated animals is consistent with the formation of chloroacetaldehyde, and with the reaction of chloroethylene oxide or chloroacetaldehyde with glutathione in the presence of a glutathione S-epoxide transferase to give the identified S-containing metabolites.

Buchter, Bolt, et al., (1978) Pharmacokinectics and Carcinogenesis of VC. Verh Deutsch Ges. Arbeitsmed. 18 111.

A discussion of the relative metabolism, enzyme saturation, and clearance mechanisms of vinyl chloride in humans and rodents.

Vainio, H. (1978) Vinyl Chloride and Styrene - Metabolism, Mutagenicity and Carcinogenicity. Chem. Biol. Interacts. 22 17.

Vinyl chloride and vinyl benzene (styrene) are mutagenic in microbial tests, in Drosophila, in yeast, and in mammalian cells. Reports from various countries have shown an excess of chromosomal aberrations in the lymphocytes of workers exposed to vinyl chloride monomer when the workers were compared with controls. Workers occupationally exposed to styrene also revealed a clear increase in the rate of chromosome aberrations in their lymphocytes. Both chloroethylene oxide and styrene oxide, the primary biotransformation products of vinyl chloride and styrene respectively, bind covalently to cellular macromolecules. Vinyl chloride is a carcinogen in both animals and man. Styrene is currently being tested in animals. These findings, the demonstration of mutagenic response via microbial and other test systems and with observations of significant excesses of chromosomal aberrations among workers exposed to these agents, raise scientific and health-oriented concern about the possible genetic risks of vinyl chloride and styrene to man.

Green, T. and Hathway, D. (1978) Interactions of Vinyl Chloride with Rat Liver DNA in vivo. Chem. Biol. Interact. 22 (2-3) 211.

Vinyl chloride-derived chloroethylene oxide and/or chloroacetaldehyde behaves as a bifunctional alkylating agent towards deoxyadenosine and deoxycytidine residues of DNA. The separation of DNAs and the 2 ethenodeoxyribosylnucleosides by liq. chromatog., and the mass spectra of ethenodeoxyadenosine and ethenodeoxycytidine and of their O-bis(trimethylsilyl) derivs. are described. In the animal expt. (ii), the resulting proportion of ethenodeoxyadenosine was small compared with that of ethenodeoxycytidine. Ethenoadenine (imidazo [2,1-i]purine was identified: (a) in the supernatant after sedimentation of the modified DNA in the model expt. (i), and (b) in the product resulting from the reaction between chloroacetaldehyde and deoxyadenosine. The effect on the structure of DNA of the imidazo cyclization of deoxyadenosine and deoxycytidine residues and of the depurination of ethenodeoxyadenosine residues is discussed in relation to vinyl chloride oncogenicity.

Winell, M., Holmberg, B., Kronevi, T. (1977) A possible correlation between biochemical changes and pathological findings in VCM - exposed mice and hamsters. Int. Symp. Control Air Pollut. Part 1., p. 152.

Mice and hamsters were exposed by inhalation to 50 and/or 500 ppm vinyl chloride during 6-18 mo. Blood samples were taken at regular intervals during the exposure for anal. of plasma enzymes indicative of liver damage or early malignancy. Some animals were sacrificed for histopathol. examns. after 6 mo. and the rest were examd. when dead or moribund. Alk. phosphatase and total lactate dehydrogenase (LDH) activities were elevated

in VCM exposed mice. There was also a shift towards cathodic isoenzymes of LDH. The transaminases were not significantly elevated. No changes in plasma enzymes were found in exposed hamsters. Pathol. examn. of VCM-exposed mice showed the presence of hemangiosarcomas in fat tissue, histol. benign alveologenic lung adenomas as well as a few benign and malignant tumors at various sites. Only one liver hemangiosarcoma was noted.

No liver fibrosis was seen. All mice exposed to 50 ppm VCM for 76 mo. developed tumors. Tumor incidence was high also in the hamsters. Enzyme changes occurred late in the study, subsequent to tumor appearance. The value of enzyme changes as a diagnostic criterion on tissue injury or early malignancy caused by VCM was discussed.

Stockle, G., Laib, Filser, Bolt (1979) Vinylidene Fluoride: Metabolism and Induction of Preneoplastic Hepatic Foci in Relation to Vinyl Chloride. Tox Letters 3 337.

The velocity (Vmax) of metabolic elimination of vinylidene fluoride from the rat is 1/100 that of vinyl chloride. In the light of the current concept of metabolic activation of halogenated ethylenes, this may explain the much lesser ability of vinylidene fluoride, compared with vinyl chloride, to induce pre-neoplastic "ATPase"-deficient hepatic foci in newborn rats.

Laib, Stockle, Bolt, Kunz (1979) Vinyl Chloride and Trichloroethylene. Comparison of Alkylating Effects of Metabolites. J. Cancer Res. Clin. Oncol. 94 139.

[1,2-^{14}C] Vinyl chloride and [1,2-^{14}C] trichloroethylene were incubated with rat liver microsomes, NADPH and RNA (from yeast). Whereas trichloroethylene metabolites were irreversibly bound to proteins in microsomal incubations to a higher extent than vinyl chloride metabolites, irreversible binding to RNA was lower for trichloroethylene metabolites. Hydrolysis of the RNA which was reisolated from microsomal incubations with ^{14}C-vinyl chloride or ^{14}C-trichloroethylene and separation of the nucleosides showed different alkylation products arising from vinyl chloride and from trichloroethylene, characteristic for vinyl chloride being formation of 1,N^6-ethenoadenosine and 3,N^4-ethenocytidine. The different reactivities of metabolites of vinyl chloride and of trichloroethylene prompted a comparison of the oncogenic effects of both compounds against the rat liver cell. Newborn rats were exposed for 10 weeks to 2000 ppm vinyl chloride or trichloroethylene (8 h/day; 5 days/week). After this period livers of the animals were stained for nucleoside-5-triphosphatase. Whereas the vinyl chloride-exposed rats showed focal hepatocellular deficiencies in this enzyme, which are supposed to represent an early sign of malignancy, no such changes were induced by trichloroethylene exposure. The data therefore suggest differences between the hepatocarcinogenic activity of vinyl chloride and possible effects of trichloroethylene on the liver.

Zajdela, F. et al., (1980), Carcinogenicity of Chloroethylene Oxide. Cancer Research 40 352.

Repeated s.c. administration of chloroethylene oxide, a reactive metabolite of the carcinogen vinyl chloride, induced local tumors in mice, with an incidence comparable to that of bis(chloromethyl)ether, a structurally related human and animal carcinogen, when both compounds were applied at maximum tolerated chronically toxic doses; no tumors distant from the injection site were produced. Bis(chloromethyl)ether, chloroethylene oxide, and its rearrangement product chloroacetaldehyde, a highly toxic compound, were further tested in an initiation-promotion experiment. Application to the skin of a single dose of either bis(chloromethyl)ether of chloroethylene oxide, followed by 3-times-weekly applications of 12-0-n-tetradecanoylphorbol-13-acetate for 42 weeks, produced skin tumors in mice; chloroacetaldehyde under comparable conditions produced no increase in benign or malignant tumors. A good correlation between the chemical reactivity, on the basis of hydrolysis constants in aqueous media, and the carcinogenicity of the three compounds was noted. Our results support the hypothesis that epoxidation of the ethylenic double bond in vinyl chloride yields an ultimate carcinogenic metabolite, chloroethylene oxide, a highly reactive compound which appears also to be largely responsible for the known genetic changes caused by the parent compound.

D. Birth Defects, Mutagenicity

Speros, J.: (1974) Telegraph Survey Indicates No Link to PVC. Defects Painsville, OH, Telegraph, Sept. 11.

Entire article attached.

Center for Disease Control: (1975) Vinyl Chloride and Congenital Malformations-Ohio. Morbidity and Mortality Weekly Report 24 245.

A follow-up story on reported CNS malformations in Ohio "could not establish any association between cases and vinyl chloride exposure".

Edmonds, L. D., Falk, H. and Nissim, J.: (1975) Congenital Malformations and Vinyl Chloride. Lancet, 1098.

"No association was found with vinyl chloride exposure".

Purchase, I. F., Richardson, C. R., Anderson, D.: (1975) Chromosomal and Dominant Lethal Effects of Vinyl Chloride. Lancet, 410.

Because of reported elevated chromosomal breaks in exposed humans, a dominant lethal test was carried out on mice, which was negative. The authors conclude that VC does not affect the stem cells.

Paddle, G. M.: (1976) Genetic Risks of Vinyl Chloride. Lancet. May 15.

A criticism of the Infante paper on fetal wastage in wives of exposed workers.

Edmonds, L: (1976) Birth Defects and Vinyl Chloride: Prac. Conf. on Women and the Workplace, Washington, D.C., p. 114.

A review of the above papers on the Ohio and West Virginia studies. No connection was found with vinyl chloride and birth defects.

Edmonds, et al., (1976) Congenital Central Nervous System Malformations, Kanawha County, W. Va., Public Health Service EPI-76-60-2, Atlanta, July 26.

Data available through the Birth Defects Monitoring Program (BDMP) revealed that from 1970 through 1974, Kanawha County, West Virginia--where 1 of the 40 polyvinyl chloride production plants in the United States is located--had rates of congenital central nervous system defects that were significantly higher than national BDMP rates for those years.

In February 1976 an investigation was undertaken because of the possibility that these higher than expected rates may have been related to parents' occupational or residential exposure to vinyl chloride. The study confirmed that an increase in CNS defect rates had occurred in Kanawha County, and cases clustered primarily in the area east of the plant; however, no relationship between infants with malformations and parents' exposure to vinyl chloride could be established.

Downs, Stallones, Frankowski, Laberthe: (1977) Vinyl Chloride. Birth Defects and Fetal Wastage - A Critical Review. Prepared for the Society of the Plastic Industries, Inc. Unpublished.

We have reviewed the available pertinent literature on vinyl chloride and birth defects and fetal wastage. Individual studies in a particular area have been assessed for the strength and validity of their conclusions, and the several studies in each area synthesized, accordingly, by taking into account the consistency, strength, specificity, temporal patterns and coherence of the study results.

In summary, we have concluded that, to date, (A) there is some evidence of an association between vinyl chloride and chromosome aberrations in lymphocyte cells of vinyl chloride workers, (B) there is no evidence of an association between vinyl chloride and excess fetal wastage in wives of VC workers, and (C) there is no evidence of an association between vinyl chloride and excess birth defects in communities with PVC production facilities.

The task of collating the existing literature on vinyl chloride and birth defects, and arriving at general conclusions therefrom, has not been an easy one. The difficulties have been enhanced by the poor quality of many of the study designs, and by inappropriate and misleading statistical methods. The methods of selecting control groups for the epidemiologic studies has been, to say the least, very disturbing. We fervently hope greater efforts will be devoted in future studies to improvement of study methodologies and designs.

Henschler, D. and G. Bonse (1977) Metabolic Activation of Chlorinated Ethylenes: Dependence of Mutagenic Effect on Electrophilic Reactivity of the Metabolically Formed Epoxides. Arch. Toxicology. 39 7-12.

In chlorinated ethylenes, the chlorine substitution exerts, by its electron withdrawal effect, a stabilization of the molecule which increases with the number of chlorine residues. All chlorinated ethylenes are metabolically transformed, in a first step reaction, to epoxides which may rearrange to aldehydes or acyl chlorides, respectively, undergo hydrolysis to diols, conjugate with glutathione, or react, by alkylation, with cellular macromolecules. The electrophilicity of the epoxides is high with those having an unsymmetric chlorine substitution, and comparatively low with the others bearing symmetric chlorine residues. According to in vitro mutagenicity testing in a modified Ames system, the following rule on structure/activity-relationship has been worked out: mutagenic potential is bound to unsymmetric substitution and high chemical reactivity (as with vinyl chloride, vinylidene chloride, and trichloroethylene), symmetric substitution results in lower chemical reactivity and non-mutagenicity. So far, the rule is substantiated by positive carcinogenic effects in animal experiments with vinyl chloride, vinylidene chloride and trichloroethylene.

Hopkins, J. (1979) Vinyl Chloride - Part 2: Mutagenicity, Fd Cosmet. Toxicol., 17 (5) 542.

A review.

Peter, S., and G. Ungwary, Lack of Mutagenic Effect of Vinyl Chloride Monomer in the Mammalian Spot Test. Mut. Res., 77 193 (1980).

The authors conclude that, although vinyl chloride has been shown to cause point mutation in bacteria, their tests with color-coat mosaic reversions in mice at 4,600 ppm "provides no evidence that VCM induces somatic gene mutation."

E. Chromosomal Effects

Picciano, D. J., Flake, R. E., Gay, P. C., Kilian, D. J., Vinyl Chloride (1977) Cytogenetics. Journal of Occupational Medicine, 19 527-530.

This report presents cytogenetic findings from a group of 209 workers employed for up to 28 years in the manufacture of vinyl chloride monomer at the Texas Division of Dow Chemical U.S.A. Cytogenetic evaluation results from this group were compared to results found in examination of individuals being considered for employment. Statistical analyses were performed on a group basis for chromatid aberrations, chromosome aberrations and proportion of abnormal cells; no statistical difference of significance was found between the two groups. Comparison of these results with reported studies suggests that the level of cytogenetic aberrations in vinyl chloride workers is probably related to the length and level of exposure, and that risk of adverse genetic effect can be avoided in controlled, minimal-exposure environments.

MacMahon, B., Vinyl Chloride and Reproduction. A literature review, prepared for the Society of the Plastics Industry, Inc., and submitted to the Environmental Protection Agency in response to the Proposed Amendment to the National Emission Standard for Vinyl Chloride, August 11, 1977.

In short, until more and better studies are available, vinyl chloride monomer must be regarded as potentially mutagenic to man, and at leaast in high doses potentially teratogenic. However, except for the evidence of chromosome breakage in heavily exposed workers - evidence which itself cannot be regarded as definitive - the literature to date contains no credible evidence that vinyl chloride has actually caused mutations, fetal abnormalties, or fetal death in humans.

Fleig, I., Thiess, A. M. (1978) Seminar in Occupational Medicine. Mutagenicity of Vinyl Chloride J. Occup. Med., 20 557-562.

A review. Published data show no conformity of results.

Hansteen, I-L, et al., (1978) Effects of VC in Man: A Cytogenetic follow-up study. Mutation Research 78 271.

Cytogenetic studies were performed on 39 workers from a PVC plant in 1974. Sixteen healthy men without any connection with the plant were chosen as controls. The cytogenetic study was repeated for 37 of the 39 workers 2-2 1/2 years later. During this time interval the workers had only had a minimal exposure to VCM. This repeated study was performed with 32 matched controls from the office employees in the factory.

Breaks, gaps and stable rearrangements were scored in 100 metaphases per person from 48 hour lymphocyte cultures.

The mean chromosome breakage frequency for the workers (3.41 per cent) was significantly higher than for the controls (1.79 per cent) in the first investigation. In the repeated study no difference was found in mean chromosome breakage frequency between the workers and their matched

controls. Neither was there any difference between these breakage frequencies and the breakage frequency for the previous control group. These results might indicate a relationship between the reduction in exposure to VCM and the normalized chromosome breakage frequency. Sister chromatid exchanges were studied for 16 workers with matched controls in the repeated study. A mean of 7.6 SCE's per call were found for both workers and controls.

F. Dust Studies

Waxweiller, R., Smith, A., Tyroler, H., Falk, H.: (1978) An Epidemiologic Investigation of an Excess Lung Cancer Risk in a Synthetic Chemicals Plant. 19th Inter. Conf. on Health. Dubrovnic. Yugo.

The authors find that lung cancer rates are not related to VC exposure, and hypothesize that dust may be a factor, although several possible confounding agents, including smoking, were not controlled. They conclude that more studies are needed to confirm the eitological agent.

NIOSH (1977) Exposure of Rats, Guinea Pigs and Monkey to PVC dust. May, unpublished.

Rats, guinea pigs, and monkeys were exposed to 10 mg/m^3 respirable PVC dust for 6 hrs/day, 5 days/week for 22 months for monkeys and 12 months for rats and guinea pigs. No lung or liver damage was found, either acute or chronic, nor was any carcinogenicity observed.

Johnson, W. and R. E. Schmidt, Effects of PVC Ingestion by Dogs. Am. J. Vet. Res. 38 1891 (1977)

With the exception of occasional soft feces, abnormal clinical signs were not seen. The test material was observed to pass through the digestive system of all animals unchanged. Results of hematologic examination, blood chemical analyses, and urinalyses were within normal values in all dogs throughout the testing periods. Gross and microscopic lesions attributable to the test material were not seen.

Wakeman, I. and Johnson, H. (1978) Vinyl Chloride Formation from the Thermal Degradation of PVC. Polymer Eng. Science, 18 404.

The volatile products from the thermal degradation of poly(vinyl chloride) (PVC) resins and compounds are shown to contain trace amounts of vinyl chloride. Data presented show the effect of temperature and resin type on the amount of vinyl chloride formed. At the maximum temperatures involved in PVC processing which may reach 210°C, vinyl chloride monomer (VCM) evolution amounts to less than 1 ppm (resin basis). A technique employing a thermogravimetric balance and charcoal adsorption of volatiles is described for studying thermal degradation of PVC. The volatiles are analyzed for vinyl chloride by gas chromatography. Peak identity was confirmed by mass spectrometry.

Richards, R. J. et al., (1975) Biological reactivity of PVC dust. Nature 256 664.

From these preliminary findings we conclude that certain forms of PVC dust exhibits a high haemolytic potential because of the presence of a readily soluble, surface associated agent.

Costa, V., and Frongia, N. (1978) Historical and Ultrastructural observations on the peritoneal changes induced by the endoabdominal inoculation of a single dose of polyvinyl chloride powder (PVC) in rats, Sard Medical Review, 81, 217-226.

The inoculation into the abdominal cavity of rats of a single dose of PVC powder caused a granulomatous non-inflamatory reaction of the peritoneum that histologically and ultrastructurally appears fairly typical, and perhaps exclusive, for this substance.

Furthermore, it is pointed out that after seven months from the inocluation no changes even ultrastructural indicative of a possible neoplastic evolution were observed in the examined rats.

G. Environmental Studies

Hill, J., (1976) Dynamic Behavior of Vinyl Chloride in Aquatic Ecosystems. Environmental Research Laboratory, Athens, GA, January, PB-249-302.

VC is not absorbed or converted by several common components of ecosystems, nor is there evidence for bioaccumulation. Escape from these systems is rapid because of the high vapor pressure.

H. Morbidity Studies

Maricq, H. R. et al., (1976) Capillary Abnormalities in Polyvinyl Chloride Production Workers. JAMA 236 1368.

Examination by wide-field capillary microscopy of the hands of 152 workers in vinyl chloride (VC) polymerization plants demonstrated scattered, scleroderma-like microvascular abnormalities in 21 workers and isolated capillary abnormalities in 27, as compared with only three isolated abnormalities in 50 manual workers not exposed to vinyl chloride. Thirteen of 17 VC workers with objective evidence of VC-associated abnormalities (angiosarcoma or fibrosis of liver, acroosteolysis, or scleroderma-like skin lesions) were observed to have microvascular abnormalities.

If prospective studies confirm the implications of this study, capillary microscopy may become a useful mass-screening procedure in the early detection and prevention of VC-associated disease.

Gamble, J. et al., (1976) Effect of Occupational and Nonoccupational Factors on the Respiratory System of Vinyl Chloride and other Workers, Journal of Occupational Medicine, 18 659.

There are suggestions in the literature that vinyl chloride (VC) acts as a lung irritant. Respiratory questionnaires and lung function tests were administered to 174 chemical (VC) workers, 81 polyvinyl chloride (PVC) workers, 72 former VC workers, and 136 rubber workers, and 68 maintenance workers with exposure to VC, PVC, and rubber. Except for small airways obstruction associated with rubber, increased respiratory symptoms and decreased pulmonary function were not associated with working in chemicals, plastics, or rubber. Some increases in baseline pulmonary function were associated with VC exposure. Acute reductions in pulmonary function were observed in smokers working in chemicals, plastics, and rubber. Heavier cigarette smokers over 40 years of age had the most adversely affected respiratory system.

Work was not associated with chronic respiratory effects, but all exposure groups experienced some acute respiratory insult.

I. Mortality Studies

Duck, B. Carter, J., (1975) Coombes, E.: Mortality Study of Workers in a Polyvinyl Chloride Production Plant. Lancet, 1197.

Age-standardized mortality rates for a population of 2100 male workers exposed to vinyl chloride for periods of up to 27 years do not show any excess of total or cause-specific mortality. One case of angiosarcoma of the liver was identified just outside the study period. There was no suggestion of an increased frequency of deaths from the more common malignant diseases.

Wagoner, J., Infante, P. and Saracci, R. Vinyl Chloride and Mortality Lancet. 194 (1975).

Berry, G., Rossiter, C., also Fox, A. (1976) Vinyl Chloride and Mortality Lancet. 416, 417.

Polemics on the Duck article. Berry and Fox conclude that no effect from exposure is found.

Frentzel-Beyme, R., Schmitz, T., Thiess, A. M.: (1978) Mortality Studies of VC/PVC worker of BASF plant. Arb. Socialmed. Practicat., 131.

The results of the prospective mortality study of 1,618 VC-PVC exposed persons will be given conclusionally as a supplement to an earlier report in this journal. Proceedings and analysis were based on the usual international methods, which makes a comparison with other studies possible.

As it was not possible to offer reliable details with regard to the degree of exposure, the mortality of the VC-cohort was investigated by considering VC-exposure periods of 5, 10, 15 years and more than 15 years, with a minimum observation period of 5, 10, 15 years accordingly. The total VC-cohort was further subdivided into groups comprising those who had been exposed before 1960 and those who had their first exposure between 1960 and the deadline of the study.

Reference mortality figures from:

-- Ludwigshafen (180,000 inhabitants)

-- Rhinehessia-Palatinate (3,6 million inhabitants)

-- Styrene-cohort consisting of 1,960 workers, as an internal control group were taken as a comparison to the VC group.

The follow-up of all German employees was 95.5% successful. However, in the case of the foreign workers, all exposed after 1960, the follow-up was only 60% successful.

The study revealed the following results:

-- angiosarcoma deaths could not be registered

-- cirrhosis of the liver and myocardial infarctions were less than expected

-- the expected number of natural causes of death (ICD 0-796) was higher than the number of 61 observed cases

-- the unnatural causes of death (ICD 800-999) were nearly as frequently observed as expected

The following diseases were more frequently observed than expected:

-- tuberculosis of the lung

-- malignant tumors of the colon and the stomach

-- hypertrophy of the prostate

They significantly exceeded the expectancy rate although these events only occurred in a few cases.

The division of the cohort in groups with exposure beginning before or after 1960, showed after a minimum observation period of 5 or 10 years resp., a higher observed than expected mortality rate for natural deaths if exposure started before 1960.

The duration of exposure had no recognizable influence on an increased rate of mortality after long exposure periods.

Observations of other studies were not confirmed that lung cancer, brain tumors and tumors of the liver were observed more frequently after VC exposure, or that VC may be a specific risk to these tumors. The deviations from other published risk-predilections could perhaps be due to a dose-response effect, as the VC exposure level within the BASF has always been comparatively low.

Peto, R. Distorting the epidemiology of cancer: The need for a more balanced overview. Nature 284 297 (1980).

The author presented criticism of the recent Epstein book "The Politics of Cancer", and of the NIEHS/NIOSH "Estimates" paper which stated that upwards of 20% of cancer was occupationally-related. Of the letter document he says "it shows how a group of reasonable men can collectively generate an unreasonable report." A plea is presented for less misrepresentation in the regulatory arena.

PART II

Comments on the Bethesda Symposium
March 20-21, 1980

I. Introduction

Both the procedures used at the Symposium and the papers presented were extremely disappointing because of the lack of a scientific approach in the organization and execution of the symposium. The interval between the call for papers and the symposium was too short to permit the preparation of any new or original work, so that what was presented consisted primarily of repetition of published data. The schedule was so crowded that there was inadequate time for a reasonable exchange of questions and answers between the speakers and the attendees, and in the case of the late afternoon session of the first day, an opportunity to discuss the papers was not provided until the next morning, when it was most ineffective. This crowded schedule also required that several proffered papers be refused. Several of the speakers strained very hard to reinterpret the old data, to the extent of near misinterpretation in some cases. The situation is exacerbated by the fact that the results will be published in a non-peer-reviewed journal, thus helping to perpetuate these errors of interpretation.

The end result is that the Symposium fell far short of a sound or balanced scientific colloquium, and little useful or new information was presented. However, as stated above, many incorrect interpretations of fact were allowed to stand uncorrected. These comments will review a number of such cases, and discuss several other points of interest which were presented.

II. Animal Studies - Vinyl Chloride

A. Professor Maltoni, in the first paper, reviewed the data from his feeding and inhalation studies which he had presented last November in Paris. His data showed a clear no-effect level at 10 ppm and lower exposaves in the lifetime feeding and inhalation and gavage experiments (see pages 35-38 of the transcript, and again at page 43).

B. In paper 2, Suzuki reported that vinyl chloride induced a non-malignant, non-metastasizing alveolar cell tumor in mice.

C. Paper 3, by Groth, reported that the incidence of angiosarcoma increased and the latency decreased with age in mice when exposed to 948 ppm of vinyl chloride for about 24 weeks at various starting ages. It would appear from these results that the repair mechanism is not as effective in older animals as it is in the younger. (However, these results are contrary to those reported by Stutman (J. Nat. Cancer Inst. 62, 353 (1979), who found a decreased incidence and increased latency period when mice were injected with 3-methyl-cholanthrene at ages from 30 to 360 days.) There were no significant blood chemistry signals observed in the test animals. There were no angiosarcomas in the two youngest age groups, and lung cancer was not reported.

D. Radike snowed, in paper 4, that ethanol alone is a powerful carcinogen in rats, and that it greatly enhances the potency of vinyl chloride when animals are exposed to both substances simultaneously. Again, there were no significant findings in blood chemistry differences between exposed and control groups.

E. Paper 5 by Hehir showed that rats and mice exposed to up to 50,000 ppm of vinyl chloride gave no neoplastic response. Mice showed a dose-dependent response in benign adenomas, but no significant progression to carcinoma. He supported Maltoni's conclusion of a no-effect level. He also reported no deleterious effects on reproductive performance or on subsequent generations from the exposures of his study.

III. Animal Studies - Polyvinyl Chloride

A. Paper 6 by Groth described the response of monkeys, rats and guinea pigs to dispersion resin dust at 13 mg/m^3 of essentially totally respirable dimensions. He found a benign simple pneumoconiosis with no lung function changes in the monkeys after 22.5 months exposure, and even less obvious cellular responses in the rodents after 12 months. Identifiable microphage aggregates were seen in all test animals, but to a smaller degree in the rodents. There was no progression of the aggregations to other lesions.

B. Wagner found a similar "minor interstitial response" in various organs with no increase with time in various organs as the result of intraplural injections of a very fine polymer. A few animals in the first experiment developed tumors that were not physically connected with the aggregates, but the experience could not be repeated. Human pathological material also showed dust retention in macrophages. In the discussion Tamburo and Popper both pointed out the lack of relationship between the macrophages and subsequent malignancies (transcript, pps 128-130). Wagner also emphasized that he did not find classical pneumoconiosis, permanent damage to the lung, or fibrosis, but "we've only got very minor tissue reaction...," (transcript, p.134).

IV. Human Studies - Vinyl Chloride

A. Maltoni described in paper 8 the results of sputum cytology studies in 6,780 workers from monomer and polymer plants in Italy. He found a higher dysplasia in the "plastics industry" than some others, that was variable according to the geographical location of the plant, and which was not affected by the smoking history of the worker. He concluded that "much remains to be done to qualify the part played by the monomer and the polymer in determining the lesion of respiratory tract material among VC/PVC workers."

B. Infante presented a list of 9 human epidemiology studies in paper 9. He concluded that, although none of these gave statistically significant results associated with vinyl chloride for anything other than angiosarcoma, the preponderance of the evidence for so many studies must be considered conclusive. A critical factor which the speaker failed to mention but which was partially acknowledged by Beaumont (tr. p. 174), is that all of the six United States studies of workers are the same general cohort. The Tabershaw and Cooper 1974 study is an earlier version of the more complete Equitable Environmental Health study of 1978, which was presented separately as paper 11. The Waxweiler, Manson, Buffler and Ott studies all were of subsets of the EEH cohort, some of which duplicated each other to some degree, and several of which were carefully selected to include those few plants where there were angiosarcoma cases, omitting all the other plants.

Further, the 1975 Duck study is a major subset of the 1977 Fox and Collier cohort. Thus, there are but three studies which are comparable as separate cohorts, the EEH study of the entire United States, the Byren study of two plants in Sweden, and the Fox and Collier study of Great Britain. None of these three comprehensive national studies gave a significant elevation of cancer at sites other than the liver. It is not scientifically sound to attempt to draw separate conclusions from subsets of cohorts, particularly when they were so carefully selected. The Waxweiller study itself points out that if one of its plants were not considered, there would be no elevated incidences. Further, considerable liberties were taken with the data in the Tabershaw, Cooper and Ott subsets in mathematically manipulating the brain case data to obtain an "estimated" excess incidence. The speaker also overlooked the fact that the supposed excesses of cancer at other sites consisted of many different types of cancers, which violates the rule of specificity which is widely accepted. Another failing in the support for the conclusion was the absence of any dose response effect for the other sites. Therefore, the speaker strained credulity and science in drawing the stated conclusions.

C. Weber gave as paper 10 a study of West German workers through 1974 which showed elevated SMR values for lymphatic and digestive cancers. This is the only study which suggests an increase in lymphatic neoplasia. He did not see the brain cancer elevation suggested by others. As Radike pointed out in the later discussion (tr. p. 181), the elevations found in Germany and not in the other countries may be due to differences in lifestyle.

D. Cooper presented the results of the CMA-sponsored EEH study for the VC/PVC workers. He reported a suggestive increase in brain tumors that was not dose dependent, and it should be noted that this cohort also contains the group from the Waxweiler study which, if eliminated, would not produce even a suggestive increase in incidence. This fact points more toward a local situation than to a VC-associated cause. See also Landrigan's comments on this point at p. 185 of the transcript, and further discussion by Cooper on pages 188-191, and Tassignon on pages 191-192, who agree that there is no basis for association between VC exposure and cancer at other sites.

E. Beaumont analyzed the statistical power of some of the human epidemiological studies in paper 12. He pointed out that the two largest studies, with the greatest power, were negative for other sites.

F. Paper 13, by Falk, described a detailed search by the CDC for all U.S. angiosarcoma cases over the 10-year period ending in 1974. None were found which could be traceable to exposure from living near VC/PVC operations or working in fabrication plants. Because of the tremendous publicity attendent upon angiosarcoma, it is certain that any cases since 1974 would have been announced, thus we now have a 16-year period in which no neighborhood cases have been seen.

G. Baxter reported in paper 14 a similar study in Great Britain with similar results. The only liver cancer deaths associated with vinyl chloride are those of PVC production workers.

H. Chiazze presented a follow-up on the ORC-sponsored study of fabricator workers as paper 19. Further examination of the original data has confirmed that there have been no angiosarcoma cases among the fabricator employees, and that there is no significant elevation of relative risk for tumors at other sites. An original suspicion of elevated mammary cancer in females was investigated by a case control study and found not to be related to exposure.

I. Paper 20 by Molina was a mortality study of Swedish fabricator workers. He, too, found no statistically significant elevation of deaths from any causes among this cohort.

J. Tamburo discussed a prospective clinical study of 1200 exposed workers in paper 16. He found that, of all the many blood and functional tests being performed, only the GGT, SGPT, and ICD clearance tests had adequate sensitivity and specificity to be of practical value in determining early liver damage. The other tests now in use are either too insensitive or have too high a false positive rate to be useful.

V. Human Studies, Polyvinyl Chloride

A. Seaton presented, as paper 21, the results of a study in Great Britain of a selected group of workers who had experienced long, high exposures to PVC dust, primarily those from dispersion resin operations, which have high respirable size fractions. One of three X-ray readers found a slightly higher proportion of small opacities which correlated with exposure in 50 of the 818 film. There was some correlation of loss of FEV-1 with exposure, but less than that which was due to smoking, or age alone. There were no frank clinical effects found in the study group.

His conclusion was that dust exposures cause "pneumoconiosis in the sense that there are very minor changes in the chest X-ray in relation to the dust exposure, and that there is also a minor effect on lung function..."

B. Arnaud related the case history of one man in paper 22. The patient had bagged an undisclosed type of PVC for 23 years, and suffered from bronchitis related to smoking. His studies showed an accumulation of PVC granules in phagocyte clusters, and the disease was therefore diagnosed as PVC-pneumoconiosis. Studies of 60 other "strongly" exposed workers showed no abnormalaties.

C. Paper 23 by Mostrangelo discussed the examination of 731 workers exposed to undefined PVC dusts, generally well above the OSHA limits, and 485 exposed to monomer. Twenty workers, 16 of whom were smokers, had noticeable X-ray changes, classified as at least one perfusion. In 388 subjects an ILO classification of 0-1 was found, the lowest positive reading. Statistical analysis showed that 32% of these cases were explained by age, and 6% by exposure if age were held constant. Similarly, smoking could explain 70% and dust 9%, if smoking were held constant. Monomer exposure was not a factor. The author concluded that the "changes are mainly related to age and smoking habits, and the rate of exposure (to dusts) is minor."

D. Waxweiler discussed in paper 24 a study of the plant mentioned above in the comments on the Cooper paper which had an excess of lung and brain cancers. The lung cancer excess was primarily of the undifferentiated large cell type. He found no relationship for these cases to exposure to specific substances, and in fact observed that many of the cases were in workers with very short job histories, and therefore very low exposures. He stated that for the lung cancer cases, chemical exposure "almost looked like a protective effect." He then speculated that the cause of the lung cancer could be PVC dust, but could not establish highly significant correlations with exposure levels or times.

In the subsequent discussion period, Greenberg (tr. p. 337-342) updated this study from its end in 1974. The exposure estimates were revised and strengthened, and the case histories for various tumors were compared again to exposure with the following results:

1) There was a positive correlation between angiosarcoma cases and exposure to vinyl chloride, and also some of the catalysts used in the plant.

2) There was no correlation between the large cell lung cancer and chemical or dust exposures.

E. Lillis reviewed some earlier papers on lung studies in workers on paper 25. In one study a preliminary review of the X-ray film of workers in two plants showed some 1/0 or 0/1 levels (ILO classification) of opacities that tended to increase with exposure. A third plant with lower exposures (VC and PVC were not differentiated) did not show this relationship. As Cooper pointed out in the subsequent discussion (tr. p. 343-3), this low level classification indicates very minor changes, such as found by Seaton. Lillis found age to be at least as important a factor as exposure.

In the second study Lillis found that smoking history was much more influential than exposure; and the mechanism of the observed changes was "not at all clear."

A survey of other literature on the subject of the effect of VC on the lung was prefaced by the statement that "the evidence in this respect is less striking, I'd say. There are a number of studies which point to the possibility rather than actually demonstrate a specific sequence of events."

F. Wheeler, in paper 16, discussed the differences in the various processes for producing PVC, and emphasized the large differences in the respirable dust fractions. Resin made by the dispersion or emulsion process is the only product that produces a significant proportion of respirable particles.

In summary, there was no evidence presented that could lead to the conclusion that PVC does not still meet the conditions outlined by the ACGIH for "nuisance" dusts, e.g., no changes in the architecture of the air spaces, no collagen or scar tissue formation, and a reversible tissue reaction (see p. 5 of the 1979 edition of the TLV booklet by ACGIH).

VI. Reproductive Effects of Vinyl Chloride

A. Johns presented her 1977 data in paper 26 which indicated that vinyl chloride may have a slight fetotoxic effect at very high concentrations such as 2500 ppm in rabbits and mice, but displays no significant teratogenic effect, and reviewed several other papers in general agreement with this finding, including the fact that ethanol enhances the fetotoxic effect.

B. Rice presented a literature review as paper 27, with no new data. He reviewed the differences between fetotoxins, teratogens, and transplacental carcinogens, and cautioned about too literal extrapolation from reproductive effects observed in rodents to the higher mammals. He then concluded that the Maltoni data showed vinyl chloride to be a transplacental carcinogen in the rat. He also cautioned that, in those cases where a material may be a prenatal carcinogen, the danger period to the mother may well be before she is aware of pregnancy.

C. The entire presentation by Fabricant in paper 28 on mutagenic effects appeard to be based on a misunderstanding of the subject. Her principal theme was that, because vinyl chloride is mutagenic in in vitro bacterial tests, it is a human mutagen. This, of course, does not follow. The bacterial tests are screening tests for potential carcinogenicity, about which there is no doubt for vinyl chloride. Such tests have no relationship at all, necessarily, for the development of inheritable genetic changes, which is the definition of mutagenicity. Many experiments, discussed in this symposium and elsewhere, have failed to produce any evidence of the mutagenicity of vinyl chloride in mammals. Similarly, chromosomal breakage or exchange in somatic cells is not related to mutagenicity, per se. Damage must be done to the stem cells or to the ova or sperm themselves to affect the next generation. Therefore, this paper offered no facts on its putative subject.

D. Hatch explored the statistical power of various studies on reproductive effects. She found that the Infante Ohio CNS study was deficient in power, but that the negative CDC recheck of this report had adequate power to detect a significant effect, as did the CDC study in West Virginia, which also was negative. Similarly, the Infante Firestone worker study on abortions and miscarriages had design deficiencies that prevented its results from being accurate, while the similar negative Buffer study did have adequate power. Therefore, there are no acceptable studies which show a human reproductive effect from vinyl chloride.

VII. Incidence of Angiosarcoma

Several statements were made by the final panelists which were incorrect. In particular, both Nicolson (transcript, p. 490) and Wagoner (transcript pages 495-496) stated that the incidence of angiosarcoma was increasing. The fact is that the incidence in the United States has been decreasing since a peak was reached in 1975-76, and that there have been no new cases reported since 1978. The attached table gives a chronology of the reported deaths from angiosarcoma for this country, and had Dr. Stafford of ICI been permitted to present his proffered paper on his worldwide angiosarcoma registry, these facts would have been presented to the symposium.

It is important to recognize that all of these deaths have occurred in persons heavily exposed occupationally; there have been none in fabricator workers or in the general population. Wagoner's incorrect interpretation of the Brady report has been discussed above.

The two peaks of 1968-69 and 1975-76 correspond to the recognized latency period since the two major expansion periods of the PVC industry that occurred just after World War II and in the late 1950's, when several new companies entered the industry. There has been no comparable influx of new cohorts or workers into the existing cohorts since that time, and thus, with the concentrated effort to reduce exposure which the industry undertook in the 1960's as the result of the discovery of the acroosteolysis problem, we can have confidence that the majority of the cases are behind us.

Deaths from Angiosarcoma in the U.S.

VC/PVC Workers

Year of Death	Number of Deaths
1961	1
1962	0
1963	0
1964	1
1965	0
1966	0
1967	0
1968	3
1969	2
1970	1
1971	1
1972	0
1973	2
1974	1
1975	4
1976	4
1977	3
1978	2
1979	0
1980 (thus far)	0
Total	25

VIII. Conclusions

The results of this symposium confirm, if any confirmation is needed, the carcinogenicity of vinyl chloride in humans to produce angiosarcoma of the liver. Insofar as carcinogenesis at other sites, or activity as a teratogen or mutagenicity are concerned, results are negative.

Evidence was added that there is a no effect level in animals and humans, from the work of Maltoni, Hehir, Chiazze, Falk, Baxter, and Molina.

PVC dust has been shown to accumulate in the lungs, and to produce a "benign" effect on lung capacity that is less than the normal effects of aging, and far less than smoking. It meets the conditions established by ACGIH for nuisance dusts.

There were no new data presented, nor any evidence that the present limits on vinyl chloride or polyvinyl chloride dust are not protecting adequately the health of the exposed workers, and therefore, the general populace.

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747

April 6, 1976

Mr. J. R. Smith
Special Studies Staff
Environmental Protection Agency
National Environmental Research Center
Research Triangle Park, North Carolina 27711

Dear Mr. Smith:

This will furnish you further information on the subject of reported non-polymerization worker cases of angiosarcoma which we discussed by telephone on March 31 and April 2.

Some confusion seems to have arisen over the nomenclature applied to the reported cases of angiosarcoma in Connecticut. They have been variously called "community cases" or "neighborhood cases" in the media, in EPA documents (STAR Document, p. 1), and in the EPA hearing (cross-examination of Barry Castleman by Dr. William Marcus, hearing transcript p. 42, copy attached), "non-polymerization cases" by NIOSH, and "non-occupational cases" by CDC and in other places. Unfortunately, we seem to have added to the confusion by using both "non-occupational" and "non-polymerization" on page 19 of the Air Products' submittal to Dr. Goodwin, dated February 23, 1976.

I will hereinafter use the NIOSH designation of "non-polymerization" for employees not working in PVC plants and "non-occupational" for persons not employed in any part of the PVC industry.

The cases with which we are concerned are therefore "non-polymerization" cases. NIOSH does list these in "Table II" which they maintain. The latest listing of these cases is dated September 12, 1976, and is attached. It has not been distributed routinely with Table I over the last few months, and Drs. Adams and Smith of this company were informed earlier this year by Dr. Lloyd that it had been discontinued. This led to the statement in the submittals by Air Products and the Society for the Plastics Industry that these cases had been dropped. In a conversation today with Dr. Pierre Decaufle of NIOSH, he confirmed that this list is not normally distributed now, but that it is still in existance and will be maintained.

The burden of proof is on NIOSH to substantiate their listing of these cases, and to show their relationship to vinyl chloride. No one presently exercises this responsibility. Angiosarcomas do occur in populations not exposed to vinyl chloride. The CDC has recently published a survey of ten cases in Wisconsin which have no vinyl chloride relationship whatsoever (copy attached). The Connecticut cases would seem to fall into a similar classification except for the very casual relationship to fabrication operations. This type of correspondence is expected to occur on a statistical basis from time to time.

Regarding the foreign cases listed in NIOSH Table II, Germany 03 filled aerosol cans where the exposure from leakage was reported to be high. We have no more information than NIOSH on Germany 07, or Great Britian 02. Italy 01 did not have primary liver angiosarcoma. Sweden 02 worked in an obsolete acetylene-process vinyl chloride plant where the exposure was high.

The two U. S. (Connecticut) cases are discussed by you in the footnotes to Table 6-19 of the STAR Document, where you quote Dr. L. B. Thomas of the National Cancer Institute. He states that both cases are uncertain. Furthermore, EPA has stated that their measurements of vinyl chloride around fabrication plants show it to be "almost negligible" (Preamble to Standard 40 FR 59534). The highest found was 6 ppb, and none was found at 3 of the 5 plants tested. Thus, these "non-polymerization" cases are doubtful in relationship to vinyl chloride, and do not support any concern for harm at "levels of exposure as low as 1-10 ppm" (STAR Document, p. 1).

The exchange between Mr. Castleman and Dr. Marcus at the EPA hearing indicates that the EPA has reached the same conclusion. This is supported by the statement in Appendix E, page 5, of the Risk Assessment Document by A. M. Kusmak and R. E. McGaughy that, "This survey has produced no evidence that living around vinyl chloride plants is a risk factor in the occurrence of liver angiosarcoma."

Thus, we stand on our position that there is no demonstrated risk to persons not exposed to high concentrations of vinyl chloride for long periods of time, and therefore the proposed standard is unnecessary.

I hope that this clarification is of help to you, and apologize for any confusion to which we may have contributed. We will be happy to discuss any other part of our comments with you whenever you may wish.

Very truly yours,

AIR PRODUCTS AND CHEMICALS, INC.

John T. Barr
Technical Manager

JTB:mjv

Attachments

cc: Mr. G. Baise, Ruckelshaus, Beveridge, Fairbanks & Diamond, Wash., DC
Dr. D. R. Goodwin, EPA, Research Triangle Park, NC
Mr. J. Hadley, Keller & Heckman, Wash, DC
Mr. R. Harding, SPI, New York, NY

bcc: A. R. Adams
R. Fleming
R. H. Schenck
W. M. Smith
L. B. Tepper

DR. MARCUS: Do you know of any evidence of the increased risk in the general population, other than the studies that have been done in work?

MR. CASTLEMAN: Aside from the fact that there were apparently two neighborhood cases with no known occupational exposure, no I don't.

DR. MARCUS: I would like to say that EPA investigated very carefully those cases, and we consulted with our expert doctor, Hans Popper of Mount Sinai, and it was his expert opinion that these people did have angiosarcoma that was of a different type than that caused by vinyl chloride monomer, and I must say, to date we do not have any evidence that angiosarcoma has been produced by vinyl chloride monomer in the general population.

MR. CASTLEMAN: I think it is important to realize that only about one-fourth of the present PVC plants were operating 20 years ago. The latency of this disease is 20 years or more, and of these ten plants, at least one-fourth of the present level of plants, which is about ten, the total production rate is one-tenth of the rate it is today. The population may also have been thinner around the plants than it is today.

So, if you look at the present situation in terms of how many people lived near the plants of a certain size, it bears little resemblence to the situation 20

years ago.

The mortality experience that we observe today started 20 years ago. I don't think the absence of cases is any proof of anything. Wouldn't you agree with that?

DR. MARCUS: In general I would say that is a very cogent comment. The only thing here is that vinyl chloride happens to offer us a unique opportunity to see an extremely rare cancer, which we can say is maybe due to the substance in question, rather than an increased rate of cancer, which is a very difficult thing to assess.

That is why I say, I was hoping somebody would have some information about VCM induced angiosarcoma in the general public, because we have not been able to find it as yet.

MR. CASTLEMAN: I talk to the same people you do

CHAIRMAN DENNEY: Dr. McGaughy.

DR. MC GAUGHY: I just have one short question.

We are interested in getting as accurate a picture as we can as to what the risk is to the population due to vinyl chloride exposure. You mentioned there were two or three factors that we have not considered.

Mainly the carcinogicity of vinyl chloride and other chemicals and the transplacental effects that might caused to expectant mothers.

NIOSH
September 12, 1975

TABLE II

REPORTED CASES OF ANGIOSARCOMA OF THE LIVER AMONG
NON-POLYMERIZATION WORKERS EXPOSED TO VINYL CHLORIDE

COUNTRY	CASE #	BIRTH DATE	1st VC or PVC EXPOSURE	DX ANGIO-SARCOMA	AGE AT DX	YRS 1st EXP TO DX	TOT YRS EXP	DATE OF DEATH	
Fed. Rep. Germany	03*	07-16-30	06-09-52	03-00-73	43	21	14	10-10-73	Note 6
Fed. Rep. Germany	07*	05-09-36	00-00-60	00-00-74	38	14	03	12-16-74	Note 9
Great Britain	02*	09-08-14	00-00-46	02-00-70	55	24	11	12-00-70	Note 1
Italy	01	06-15-34	00-00-65	04-19-71	36	6	3	04-16-71	Note 2 & 7
Sweden	02*	11-27-11	00-00-45	05-15-72	61	27	23	08-16-72	Note 3
United States	14	00-00-13	08-18-38	06-00-73	60	36	00	07-03-73	Note 4 & 8
United States	15*	00-00-25	00-00-00	07-00-72	47	00	00	02-15-73	Note 5

Note 1 Pouring PVC oil mixture onto fabric bases
Note 2 Production of PVC sacks
Note 3 Production of Vinyl Chloride
Note 4 Machine operator covering electrical wire with PVC plastic insulation
Note 5 Accountant at plant making PVC fabric
Note 6 Loading pesticide cans with VC propellant

Note 7 Angiosarcoma involving liver, lung, and pericardium. Although difficult to determine, primary site seems to be pericardium.
Note 8 Diagnosis: Sarcoma (possibly "angiosarcoma"), liver. Possibility of generalized neoplasm of the reticuloendothelial cell system cannot be ruled out.
Note 9 Assistant Factory Chemist

* Indicates microscopically confirmed angiosarcoma of the liver.

"00" Indicates unknown data.

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Institutional Interactions in Problems of Occupational Health: An Industry View on the Lessons from Vinyl Chloride

by

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Institutional Interactions in Problems of Occupational Health: An Industry View on the Lessons from Vinyl Chloride

A W Barnes

I have been asked to speak this morning about "Institutional interactions in problems of occupational health". The views I want to express are personal ones: they derive solely from my personal experiences over the past 2½ years when I was closely involved with the vinyl chloride problem. My involvement, and that of my colleagues in the general management of the European PVC industry, was in part as a layman in a highly specialised field where the initial contributions had to be made by experts and professional people from universities, government and research associations. As industrial general managers, and with our trade union colleagues, our prime responsibility was to see that all possible steps were taken at the maximum speed to ensure the safety of the plant workers: ultimately though I believe we also made some contribution through our experience in bringing together the views of experts in different specialist fields, because, as generalists, the critical appraisal and pulling together of expert opinion is part of our normal daily jobs. Once our colleagues outside industry had found that our objective was precisely similar to theirs - i.e. the full safety of our workers - the result was an enormously fruitful co-operative effort involving everyone who could help. Indeed, if it were not for the personal tragedies which preceded and initiated all this effort, we would have good reason for feeling entirely pleased with the way groups of people from different disciplines and countries, from different institutions and with different responsibilities, came together to solve an immensely difficult problem.

Of course we had our difficulties in the early days. Industry seems nowadays automatically to be cast in the role of the villain of the piece by much of the media, and a suspicion that this might be true exists in the minds even of reasonable people. Our first task therefore was to convince people that we were just as concerned as they - perhaps more so - to see that our staff worked under safe conditions: but this was not too difficult since the statement was true, and the people we were involved with in government, universities and trade unions were willing to listen, and then to observe that our actions confirmed our words.

Another difficulty initially was the belief that this was a medical problem and that only doctors therefore could speak with authority, even when it came to framing legislation. But a doctor is not a lawyer nor yet an engineer: nor is he an expert on industrial control processes or analytical techniques; and rarely do we find, in any one doctor, an expert epidemiologist, toxicologist, oncologist, clinician and statistician combined! Yet all these and many other disciplines were necessary for the definition of the problem and for its resolution; and some of these resources industry could provide. The barriers between the medical profession and industry were real and potent because they prevented, initially, the dialogue which alone could lead to a full understanding of the situation: but with goodwill they were broken down and have led, I believe, to enhanced mutual respect and indeed to many lasting friendships.

One of the bigger problems, which persisted throughout the period, was the effect of reports and comment from American sources. The character of some of these came as a total surprise and one of the major lessons many of us learnt from the vinyl chloride problem was that American information had to be treated with extreme care. America is enormously important because of its resources, and its influence throughout the world; but its method of debating matters of public concern is very different from the custom in Europe. The glare of publicity which attends these debates certainly seems to encourage some scientists to speak out with a certainty that is hardly justified by the quality of their information. Whatever the reasons, many American reports were of doubtful validity because they frequently gave information which was incomplete or unconfirmed or simply inadequately analysed. Their impact nevertheless was major: by heightening the feeling of alarm, they increased the pressure on European institutions to take up extreme positions, as in the USA, and this, if it had happened, would have made co-operation and rational analysis extremely difficult. Fortunately it didn't happen: medical institutes, government departments, trade unions and industry realised that, while taking full note of US information and comment, their proper task was to develop a European response, independently, to the problem. In this context it is interesting to note a remark by Dr Marcus Key, who was director of NIOSH at the height of the vinyl chloride crisis. Speaking at the Royal Society of Medicine Conference in September 1975 he commented that in Europe we seemed to have reached roughly the same end point as the USA without the tensions and trauma surrounding the generation of the OSHA regulations.

How did we achieve this, first nationally and then internationally in Europe; and how did representatives of institutions from many different nationalities and with widely different interests and experience learn to work together? At the national level, I can speak more knowledgeably of the UK, although similar processes, I know, developed in the rest of Europe.

At an early stage in the UK, the government set up a Tripartite Working Group composed of senior representatives from government, the trade unions and industry. It is important to note that, at no point, did this become a negotiating body made up of three factions. From the beginning, it was one group with a single common purpose: it owned the problem as a group and it was committed, as a group, to the solutions it developed. This attitude is well exemplified by one of its actions: a smaller tripartite group was formed from the main committee to visit all the UK PVC plants. The purpose of this was not to check that management was doing the right things - though we had the opportunity of seeing this too - but to allow everyone on the plant, from works manager to plant operator, the opportunity of checking that we, who ultimately had to recommend standards and codes of practice, were doing our job properly. On each visit an open forum was held to allow the works staff to fire questions at us so that they could determine to their own satisfaction that we knew what we were talking about. The standard of debate and of information throughout was at an extremely high level: and a very important result of the visits, was that the tripartite group and the workforce throughout the industry were very firmly united in a common endeavour.

Internationally, the European PVC industry formed a series of vinyl chloride committees under the auspices of CEFIC (the European Council of Chemical Manufacturers Federations); and within these committees a great deal of co-operative work was done in both the technical and medical fields. As a

result of this, representatives of the main committee were able to speak with authority for the whole of Europe whenever a contribution from industry was required. This was no mean achievement, for Badische and ICI and Solvay and Montedison are just as much institutions in their own right as is the University of Louvain or the University of Wurzburg or the Mario Negri Institute.

But one of the most constructive of European moves was the invitation to CEFIC from Directorate General V of the Commission to join with their Ad-Hoc Committee on MAK values in considering and advising on a possible Commission directive. This committee was composed largely of distinguished medical academics and the meetings provided the first opportunity for a dialogue between European industry and the European medical establishment as well as with the Commission itself. Of course there were some misunderstandings initially, for industry was talking the language of science and technology while our colleagues were talking the language of medicine. As an example may I quote the initial belief among our medical and commission colleagues that if a directive were to lay down a maximum of, say, 10 ppm (averaged over any 8-hour period) then industry would be able to operate at a constant level of 9.5 ppm. They had not appreciated that the products of industrial processes are rarely constant day in and day out, and that there is always a variation about a mean. Because of this, for 10 ppm never to be exceeded, plants must be operated, on average, well below 5 ppm and will frequently be producing results of 1 or 2 ppm! So a legal requirement for 10 ppm not to be exceeded, is very close to a medical requirement that average exposure should be below 5 ppm!

Fundamental difficulties of this type were relatively quickly sorted out however because of the willingness of members of the committee to meet and discuss the problems on an individual basis. For instance, Professor Maltoni from Italy and Professor Lauwerys from Belgium paid day-long visits to ICI's plants in the UK and Professor Foa arranged for one of his Italian colleagues to visit us also. Similar exchanges occurred in the other countries of Europe and, quite soon, we were all talking a common scientific language and progress was rapid.

Within DGVI of the Commission initial progress was not quite so positive. This Directorate-General, which was concerned with the control of PVC for packaging foodstuffs, also remitted the problem to its scientific advisory committee but unlike DGV made no formal invitation to industry, or other interested parties, to contribute. The committee, composed largely of toxicologists, had the impossible task of proposing control levels for vinyl chloride in foodstuffs, where the human exposure levels were already a million times lower than any level at which carcinogenic effects had been observed. Not surprisingly, their conclusions could owe little to toxicological data; and in an understandable effort to ensure the absolute maximum in safety while still, they believed, supplying a practicable solution, their first proposal was that "vinyl chloride should not be detectable in food or potable water by an agreed method. Attempts should be made to develop generally applicable analytical methods with a sensitivity of the order of 0.001-0.002 mg/kg."

An obvious philosophical objection to this early proposal was that it related the control level simply to the state of advancement of analytical science which of course is in no way related to the question of hazard from vinyl chloride. Of even more concern to industry, though, was that

it was a totally impracticable solution since the problem of variation of results about a mean had again been overlooked; and the problem here was complicated further since vinyl chloride reaches a foodstuff by a slow diffusion process. In addition to the normal variation in any industrial process, which is to a degree controllable, a further factor therefore is the period of storage of the product, which is not. To ensure a non-detectable amount in any foodstuff at any time, it would be necessary to control at the factory or packing station at a level say of 1/10th of non-detectable! A moment's reflection will make it clear that this is somewhat difficult to measure! - and therefore impossible to ensure. Effective control of an industrial process demands the facility to measure key parameters of the system while they are still within specification, so that any trend away from the norm and towards the specification limit can be detected and then corrected.

Our concern, within industry, was such that the CEFIC committee produced a discussion paper which some of you may have seen. It is the only document I know which attempts to bring together, in an orderly fashion, all the facts and factors relevant to a particular aspect of the vinyl chloride story. Its purpose was to encourage debate on matters of judgement and, if necessary, to allow argument in areas of disagreement - but always disciplined by facts and figures. I believe it has proved of some value and that in this part of the vinyl chloride problem - as in that concerned with worker protection - real progress became possible once we had found a way for medical experts, government representatives and industry, to challenge and to educate one another in rational debate.

These are but a few examples of how, in Europe, we learnt to work together. In all they add up to a story of some considerable success: but before we get too complacent I think we have to ask the question "Did we do - have we done - all we could?". I'd like to spend the rest of this paper in explaining, as a layman in a medical field, why I believe we have not.

It seems to me that vinyl chloride is almost unique among known human carcinogens. Our knowledge of its effects on animals, through the distinguished researches of Professor Maltoni, is more extensive than for many, perhaps most, other carcinogens; and our knowledge of its effect on humans, because of the rarity of angiosarcoma of the liver, is in almost all cases precise and unambiguous. It must be rare to find so clear-cut an effect on a human population in conjunction with such thorough animal experimentation. I would have expected that the data on vinyl chloride would have been seized upon to see what more it could teach us about carcinogenisis in general. But what we have had is a flood of papers on epidemiology by epidemiologists, on toxicity by toxicologists and on metabolism, clinical treatment, immunology, chromosome aberration, etc. Any attempt at analysis of the human data on a world scale has been minimal and most references to Professor Maltoni's work have been limited to a superficial treatment of the results from his experiment BT1. It is indeed startling to observe that, from all of Professor Maltoni's massive research, the only conclusion that has actually been used in the field of industrial hygiene is the conclusion that vinyl chloride is a carcinogen. As an employee of one of the companies who sponsored Maltoni's work, I feel bound to ask whether the cost and effort, on our part and on his, was worthwhile if this is the only useful information we can extract.

Why has the yield been so poor? Could it be that the medical profession itself is getting a little over-specialised and that vinyl chloride has been seized upon by the specialist as a useful vehicle for testing out theories and advancing knowledge in his own specialism? Is it possible that rather more interaction is required within the medical profession and that we need the interest of one or two good medical "generalists" who can pull together all the data and begin to answer some of the outstanding questions? Only you can say whether these are foolish questions or whether they are worthy of some consideration. But the fact remains that there are questions still to be answered.

General to the whole problem of carcinogenesis and toxicity is the relationship between the results of animal testing and the effect of the toxic substance on humans. How many times in the past 2½ years have I heard the remark that we don't know how to relate the one to the other; and while we remain in this ignorance the value of work like Professor Maltoni's is diminished. I cannot help feeling some surprise that there has been so little effort to analyse the human data on vinyl chloride and to relate this to Professor Maltoni's comprehensive findings. Of course any relationship we find for vinyl chloride will not provide the key for all future problems but it would at least be one more step along the road of understanding.

There remain two major questions, specific to vinyl chloride, which demand more application by all of us. The first asks whether there remains any risk to the consumer from food, wrapped in PVC, at the infinitesimally small levels of vinyl chloride which can still be detected: and if so, what the level of risk is. The problem for toxicologists is that there is no experimental animal data on vinyl chloride at the minute exposure levels we are talking about: but even if there could be, they would still be faced with the problem of relating rats to humans and this is a permanently insoluble problem if we confine our studies to evidence from ingestion. There would be no possibility of obtaining convincing human ingestion data even if the risk were a significant one - which is of course completely contrary to our belief. Yet, tantalisingly, there exists a great deal of data on the effect of inhaled vinyl chloride, on both rats and humans, which, as I've already indicated, could give us some pointers to the relative sensitivities of the two species. The need is to achieve some definition, albeit imprecise, of a risk; for in matters of public concern qualitative generalities have little - or too much - impact depending on the speaker. The problem is to find some way of bringing all the results together to bear upon the question.

Within industry, we were greatly indebted to my colleague Dr K S Williamson who pointed out that all known results, inhalation, ingestion, human and animal, could be examined in one table by defining exposures in mgm/kgm of body weight; and that, when this was done, a degree of consistency could be observed across all the results. Starting from these unified results, and with the help of published work by Schneiderman, Mantel and Bryan and the late Dr Leo Friedman (this last incidentally in a very relevant WHO report which has received surprisingly little attention) the CEFIC discussion document was able to suggest a value for the maximum residual risk from foodstuffs of the order of 1×10^{-10}, or some 80,000 times lower than the risk, calculated by Friedman, arising from the consumption of 70 gms of "charcoal-broiled" steak daily. The analysis we have done is an elementary and quite unsophisticated one: our answer is certainly imprecise - how could it be otherwise at these levels? - but wherever we

have had to make assumptions of our own, rather than drawing on the published work of specialists in the field, we have tried always to be conservative. What is disturbing to me is that I know of no other published attempt to determine the order of magnitude of the risk. I recognise the immense difficulty of being able to speak with certainty when results have to be extrapolated over at least six orders of magnitude. But where the need is great, some effort should be made: in its absence the discussion is left wide open for pure speculation undisciplined by any facts.

So far I have discussed two problems which require us to apply much more thought to the relationship between Maltoni's animal results and the known human data. A third problem exists which is, for industry, much more important than the previous two and which concentrates our attention exclusively on better analysis of human information.

Throughout the past 2½ years one group of people has shown a maturity and a sense of responsibility and of determination which is an example to the rest of us. This is the industrial workforce actually engaged on producing PVC. Clearly all of us - medicals, engineers, chemists, legislators - had to establish conditions which were safe for work, but, with that achieved, our obligation to the work people is not yet fully discharged. We, and they, know that, in the future, there will be further cases of angiosarcoma of the liver among vinyl chloride workers, deriving from the higher exposures of earlier years. When these occur, there will be an inevitable diminution in their sense of security; and doubts will naturally arise, for them and their wives and families, about the effectiveness of the new safety measures. If this happens, we who helped to devise the regulations will not have done our duty if we can only reproduce the same qualitative reassurances that we were using in 1973 and 1974. With the finalising of regulations around the world the job - for doctors, administrators, statisticians and general managers - is not finished. We must be in a position to reassure those most directly concerned that we have done our job well; and this requires us to pursue our research and our analyses further and further towards a quantitative conclusion.

What, you may ask, can be done? I'd like to devote the last section of this paper, to a brief review of what has been done on data analysis and then to suggest a scheme for further work. These latter proposals derive from many discussions I have had with my colleagues Dr Williamson and Dr Paddle of ICI who would be much better equipped to present them today: I must present them in simple layman's terms for that is the only way I know.

Until early 1976, the only formal document which surveyed the world data on the effect of vinyl chloride on humans was the NIOSH list of angiosarcoma cases among vinyl chloride workers. But this was only a list; no analysis of any kind was attempted.

In April 1976, the CEFIC document, to which I have already referred, made a first step in classifying the human data. It listed the cases according to the particular plant on which they occurred; and it summarised its findings in the following (up-dated) table.

TABLE 1

Number of A/S Deaths/Plant	Number of Plants	Location of Plant
10	1	USA
9	1	Canada
3 each	2	USA
2 each	6	Germany, Sweden, France + E Europe
1 each	13	USA + Europe
50	23	
No cases reported	~20 plants with >20 years life	

Many of us believe that this rather puzzling distribution can only be explained on the basis of differing exposure levels, many years ago, from one plant to another and that this is the first indication that some sort of dose-response relationship might be deduced for man. If it does - and Maltoni has certainly demonstrated one for rats - then we should be doing all we can to determine it. Before considering how this might be done, let us see whether the crude data can tell us anything else.

If the deaths are tabulated, by year of death (where we know this) we get the following information.

TABLE 2

Years of Deaths	Numbers of Deaths in Period	Average Number of Deaths/Year
Before 1961	0	0
1961-65	2	0.4
1966-70	10	2.0
1971-75	24	4.8
1976 so far	4	⩾4.0
	40	

At first sight this is alarming since the number of deaths/year appear to be on a rapidly ascending curve; but before we proceed, it is worth looking at another classification, which I have not seen published elsewhere. If we group the deaths according to the year of first exposure, we get results which I have summarised in Table 3.

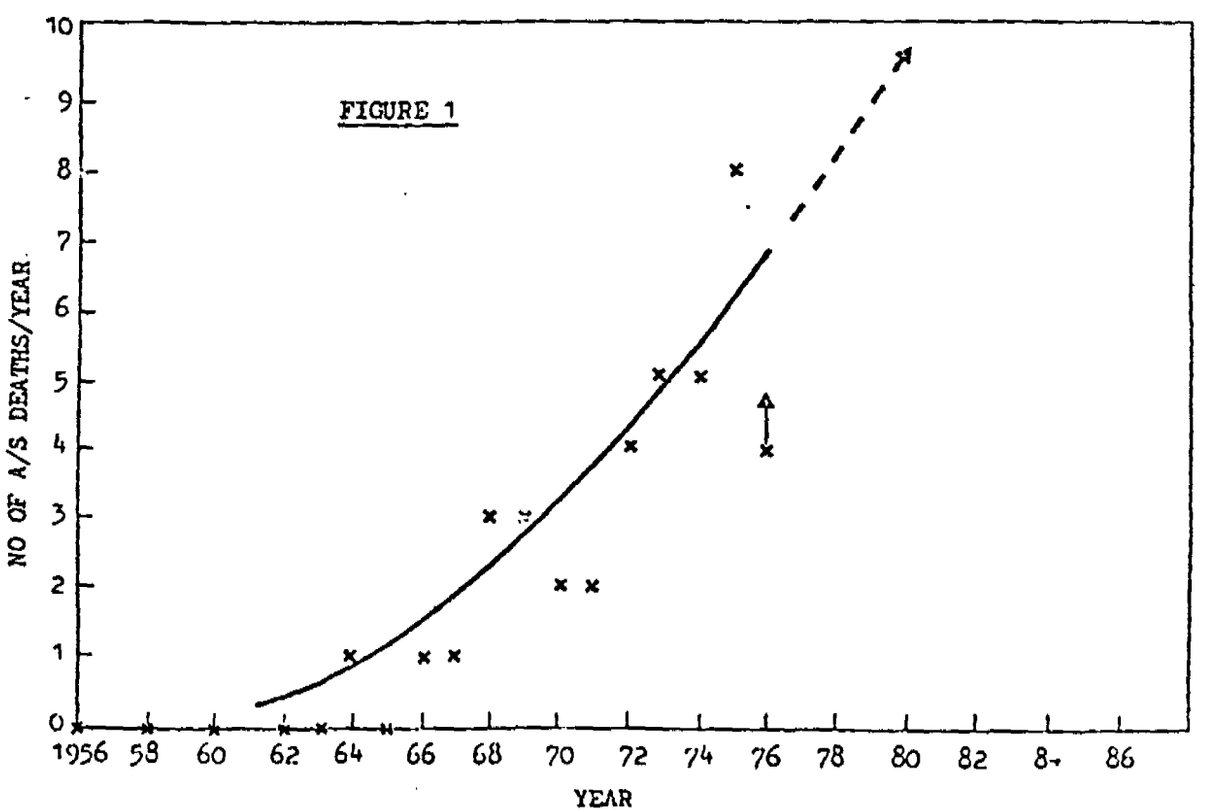
TABLE 3

Years of First Exposure	Number of Cases	Latency Period from First Exposure	
		(a) Range (years)	(b) Number of Cases With <15 Years Latency
1943-54	28	15->32	0
1955-66	14	9-20	8

In the second of the two 12-year periods the fact that we have no latency periods > 20 years is not of course surprising. The elapsed time has not yet been sufficient for longer latencies to appear; and regrettably we must expect further cases to arise. What is interesting, however, is that 8 out of the 14 cases in this period have latencies less than 15 years whereas, in the first period, no latencies as short as this have been reported. It seems difficult to believe they did not exist: indeed this analysis seems to provide the clearest evidence yet in support of the suggestion that, prior to 1961 and possibly later, deaths from angiosarcoma were under-recorded.

We can best see where this takes us by looking at some simplified graphs. If we plot actual numbers of deaths per year against the year, we get the following picture (Figure 1), which is disturbing if true.

FIGURE 1



However, we have seen that early deaths are probably under-recorded, so the real line has, almost certainly, a lower slope than this. Further, the industry, and the numbers of people becoming at risk each year, grew rapidly in the 1950's and 1960's so that if we were to plot the incidence of deaths, i.e. the number of deaths each year as a proportion of the population at risk, say 20 years earlier, then we would expect the righthand side of the graph - and its extrapolation - to decrease relative to the earlier years. A further factor still is that exposure levels have steadily decreased over the past 20-30 years, from values of possibly 1000 ppm in the 40's and 50's to values below 200 ppm in 1973, immediately before the recognition of vinyl chloride as a human carcinogen. Since we believe there is a dose-response relationship, these changes should result in a decreasing incidence by the late 1970's. By 1985, the effect of the latest standards should be quite marked; we must expect, still, some 30 year latencies dating from 1955 (but what about Maltoni's BT3 results?) but there ought to be no 12 year latencies dating from 1973, and I hope there will be few 20 year latencies dating from 1965.

Figure 2 shows the original line of Figure 1 with arrows suggesting likely changes because of the factors listed above. A very notional revision is indicated by the dotted line.

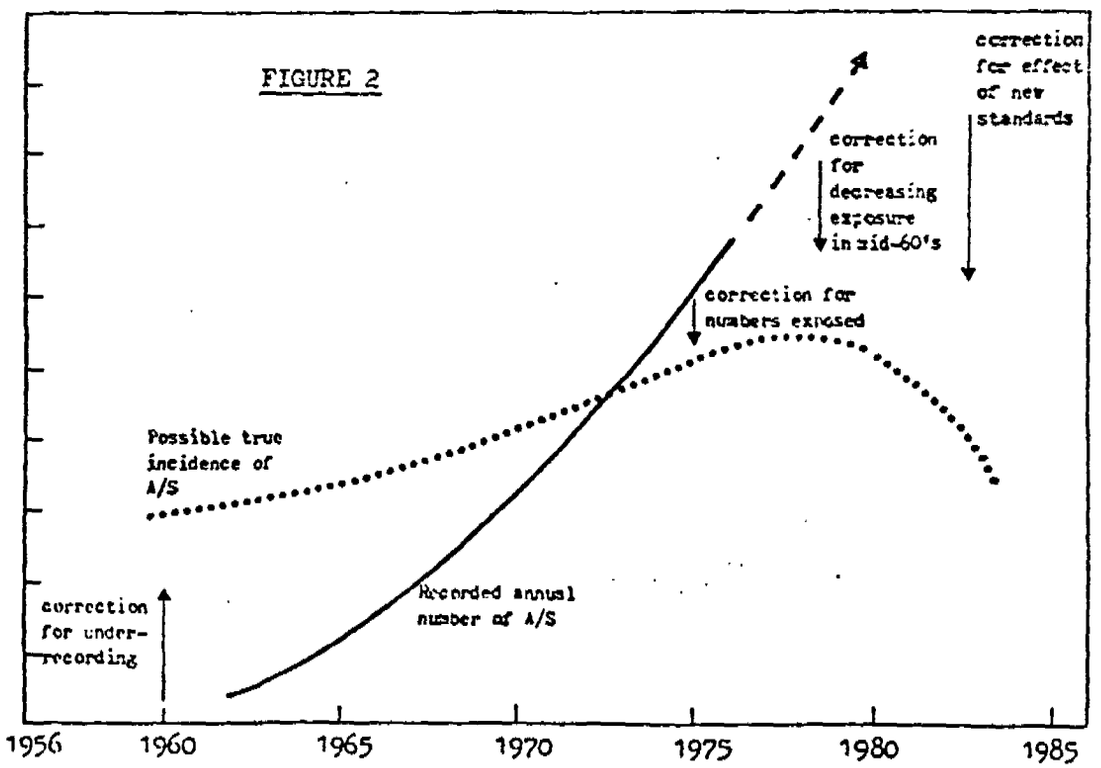


FIGURE 2

Can we get a better idea of where this new line really is? As an amateur who doesn't therefore see the difficulties may I suggest

(a) that our statisticians might be able to give some estimate of the number of missing cases in the early years and

(b) that industry, with some difficulty, ought to be able to estimate the yearly populations at risk.

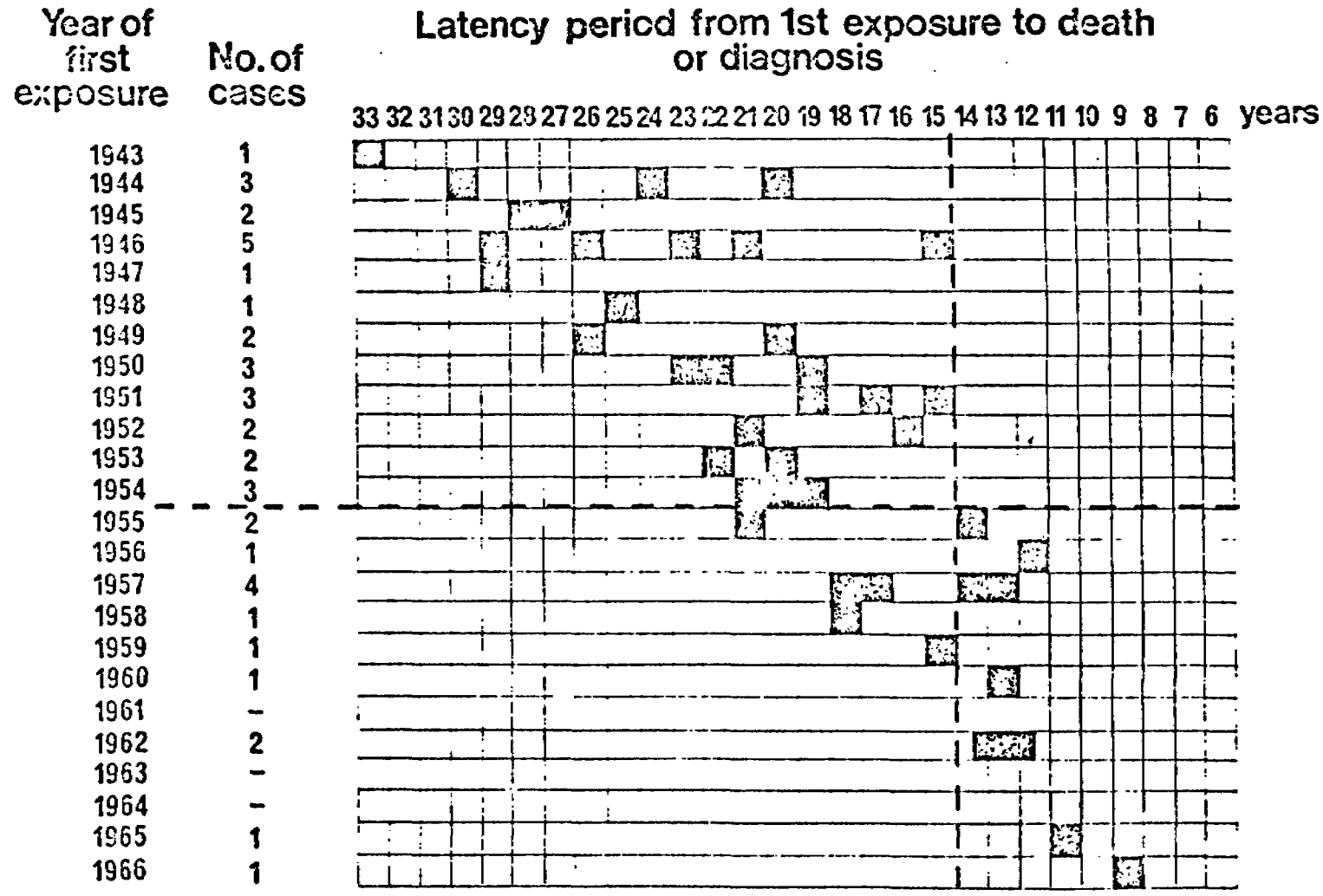
To estimate the effect of reduced exposures, we need to know what the exposures have been over the whole period and we need to know the dose-response effect for humans. These are much the most difficult problems; but indications of exposures have been given by industry spokesmen and some refinement of these must be possible. With these available, the human mortality data may be susceptible to analysis. In addition, we need a detailed development of a dose-response relationship for rats, from Maltoni's data. At best this relationship may be cohesive with and supportive of any tenuous relation we develop from human information: at worst we may have to use it alone, possibly with arbitrary factors applied, since the crude data does seem to suggest that rats may be more sensitive than man to vinyl chloride.

A dose-response relationship is essential for the last correction which requires the calculation of the risk of getting angiosarcoma in 1985 after exposure to only a few ppm of vinyl chloride. This may be difficult, but we have a duty to the people in the industry to attempt it. Perhaps we do not have to be overprecise, for if we are correct in believing our new standards to give a large margin of safety, the calculation of extremely low risk at these exposures may not be too sensitive to errors in the extrapolation.

All this then needs to be done. What is being done? Within ICI, my colleagues Dr Williamson and Dr Paddle are working on the problem, but it is difficult within one company to achieve everything, for the data available to us in ICI may not be representative of the world situation. Nevertheless I believe they will be able to publish some preliminary observations shortly, and I know they would welcome comment, suggestions, or involvement with them, on the subject.

The word "involvement" brings me back to my subject of "interactions". When the task - of devising safe operations - was clear, many institutions in Europe interacted well and achieved much. I've tried to show that much remains to be done: so let interaction, co-operation and contribution flourish still. As another of my colleagues, Dr John Stafford, has put it "the sooner we address and apply ourselves ... unreservedly to ... the task ..., the sooner we shall have really well-founded data to satisfy ourselves, our neighbours, customers, critics etc that the VCM health problem has not only been satisfactorily contained but finally solved."

AWB/JJG
September 1976


Year of first exposure
No. of cases
Latency period from 1st exposure to death or diagnosis
33 32 31 30 29 28 27 26 25 24 23 22 21 20 19 18 17 16 15 14 13 12 11 10 9 8 7 6 years
1943 1
1944 3
1945 2
1946 5
1947 1
1948 1
1949 2
1950 3
1951 3
1952 2
1953 2
1954 3
1955 2
1956 1
1957 4
1958 1
1959 1
1960 1
1961 –
1962 2
1963 –
1964 –
1965 1
1966 1

[illegible] indicates no link to PVC, defects

By JIM SPEROS
Telegraph Staff Reporter

A survey by The Telegraph indicates [illegible] between the occupation of parents of children born in Painesville in 1973 and the abnormally high rate of birth defects in the area for that year.

The Ohio Department of Health reported in August that it was investigating reports that three northeastern Ohio communities, including Painesville, had double the statewide average of birth defects for 1973. The reports linked the defect rate to the use of vinyl chloride in industrial plants in Avon Lake, Ashtabula, and Painesville.

Painesville had 826 births in 1973 with 23 born with birth defects or congenital malformations. This gave the city a rate of 27.8 defects per thousand as compared with a statewide average of 11.2 defects per thousand births. Reports from the AFL-CIO Industrial Union Committee had indicated that the defects in several communities might be related to the use of the chemical, used to make polyvinyl chloride, the most common form of plastic.

The Telegraph survey found that of the 23 children born in 1973 with defects, [illegible] working at either Uniroyal or Robintech, the two area plants that use vinyl chloride. In the control group of parents of children born normally that year, one also worked at a vinyl chloride plant prior to his child's birth.

Similarities also existed between groups of parents who worked in chemical plants where vinyl chloride was not used, and also between groups of parents who worked in plants or careers in which volatile chemicals were not used at all.

No correlation could be found between the type of defect in the child, or residence of the parent, and occupation. A cross tabulation of those variables produced only random patterns. Hyaline membrane disease (a disease that prevents air from entering the bloodstream in the lungs) was the most common defect, and Painesville, Madison, and North Madison were the communities with the highest concentration of births in both groups.

Dec 11, 1974

[illegible] investigation [illegible] polling

The Telegraph survey on possible effects of the use of vinyl chloride in two area plants and the abnormally high rate of birth defects in the area was done using scientific polling techniques.

Each certificate of birth at the Painesville City Health Department is numbered consecutively. The certificates also show whether the baby was born with any kind of birth defect and the name and address of the parents.

Each birth certificate that noted a baby born with a defect was made part of the sample called the "experimental" group. The name and address of the 23 children born with defects in 1973 was taken as the basis for polling.

To select a "control" group, or group that accurately represented the entire population of babies born in Painesville in 1973, a random selection process was used. A number between one and 35 was selected at random, and the certificate with that number made part of the control sample. Each subsequent 35th certificate after that was also made part of the sample to make a control sample of 25, approximately the same number as in the experimental sample. Because the first certificate was chosen at random, each birth had an equal chance of being included in the control sample. In three cases, the 35th subsequent certificate could not be included in the control sample, either because it was one included in the experimental sample, or because the baby was adopted and the identity of its parents could not be determined. In each of the three cases, the next certificate was taken, and the selection of subsequent respondents taken based upon the original numbering system.

selected in both groups by telephone and told each respondent that [illegible] been selected to participate in an occupational survey." The respondents were then asked the occupation of both parents, the company they worked for, and the length of time with that company. When either parent had worked for his or her present employer for less than five years, the respondents were asked the name of the former employer and the dates worked in an attempt to determine the employer just prior to the time the baby was born.

If the respondents could not be reached by phone, either because there was no current listing or because there was no answer after repeated attempts, the occupation of the respondent was determined by using various directories for 1972 and 1973. In two cases in the experimental and 12 cases in the control group, the respondents could not be reached and had no listing in the directories, and their names were discarded from the sample.

The answers from the respondents were then placed into four categories.

The first category included those who had worked at either Uniroyal or Robintech just prior to the birth of their child in 1973.

The second category included those who had worked at either a plant in which PVC or other volatile chemical was used, or worked as a laboratory technician where the worker was in contact with chemicals of various nature throughout the working day.

The third category was used for respondents who worked in plants or jobs that had no connection with the VC or PVC industry or had no contact with chemicals.

The fourth category was used for those who gave the interviewer insufficient information with which to place that respondent in any of the first three categories. The results of the categories can be found in the tables.