8-413

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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

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) Pharmacodynamics 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-O-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 cell 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 showed, 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 Mehir 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.