



INTERNAL CORRESPONDENCE

CHEMICALS AND PLASTICS

SOUTH CHARLESTON PLANT P. O. BOX 8004, SOUTH CHARLESTON, W. VA. 25303

To (Name)	Dr. W. R. Manning, 511	Date	June 13, 1974
Division	Dr. A. B. Steele, NYO-28		
Location	Dr. J. W. Whittlesey, NYO-46	Originating Dept.	
	Dr. E. Q. Hull, 511	Answering letter date	
Copy to		Subject	

PERSONAL & CONFIDENTIAL

These notes were received, in confidence, from
Dr. Mayo Smith of Air Products and Chemicals. Please use for
your own personal information only.

R. N. Wheeler, Jr.
R. N. Wheeler, Jr.

RNWJr/ra

Attachments (2)

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COMPANY CONFIDENTIAL

INTEROFFICE MEMORANDUM

Date 6 June 1974

Subject Closed Meeting - Vinyl Chloride
Monomer Health Problem, New York
City, 5 June 1974

To Richard Fleming

Valley Forge

(Location, Organization, or Department)

From W. Mayo Smith

T-Town

(Location, Organization, or Department)

cc: A. Ross Adams
W. L. Ball
J. T. Barr
T. L. Carey/H.L. Watson/J.C. Novak

E. Donley
G. J. Mantell
E. M. Spurlock
Dr. Paul Kotin (via. R. Fleming)

The writer received an invitation from Ethyl Corporation's Dr. William E. Rinehart to attend this small meeting which Ethyl had arranged with Prof. Maltoni.

Attendees: Ethyl Corporation

Dr. William E. Rinehart
Toxicologist

Mitchell R. Zavon, M.D.

Dr. Bernard Sobel
Mathematician

Mr. Bergin
Operations Manager, Manufacturing

Mr. Raymond Wilkins
Product Manager--Business

B. F. Goodrich

M. N. Johnson, M.D.

Union Carbide Corporation

Kenneth Lane, M.D.

Dow Chemical Company

Dr. Theodore Torkelson
Toxicologist

Uniroyal

Dr. Walter Harris
Toxicologist

Shell Oil Company

Howard L. Kusnetz
Manager Industrial Hygiene
Occupational Safety & Health

Prof. Cesare Maltoni, M. D.
Istituto di Oncologia, Bologna, Italy

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Solvay & Cie

Auguste Gosselin
Direction Centrale Petrochimie
Brussels, Belgium

Air Products & Chemicals Mayo Smith

Dr. Rinehart opened the meeting by stating that Ethyl had arranged for Prof. Maltoni to provide any additional information he might have concerning cancer and laboratory animals since his report at the New York Academy of Sciences, 10-11 May 1974. Dr. Rinehart emphasized that he had invited a select group and with deliberate intent SPI and MCA should receive no word which would transpire during the course of the day. Similarly, Dr. Rinehart stated that we were not at liberty to give any notes to other monomer and polymer producers not specifically present at this meeting. Dr. Lane of Union Carbide will see that their Mr. R. N. Wheeler will be advised and Dr. Rinehart will possibly advise Dr. Zeb Bell of PPG Industries who was unable to attend.

The following information will be given in the order of its presentation. In this informal meeting Mr. Gosselin of Solvay & Cie spoke first relating the experiences of his company. He stated that Solvay has the largest investment in monomer and PVC production in the world. He made mention of the AOL (acroosteolysis) problem which Solvay first discovered in 1962 in Belgium. In mid 1965 Solvay made contacts in Europe and the United States describing this problem confined to reactor cleaning personnel who suffered bone degeneration in the fingers. By 1968 Solvay had discovered 12 cases of this disease in eight PVC plants. In separate PVC plants of Solvay's in Germany and in Austria no cases of AOL have ever been detected. All 12 AOL cases in Solvay's history have involved reactor cleaner personnel. Since 1968, no entrance to autoclave is made for cleaning purposes but for maintenance only. Solvay expects no further cases of AOL.

In 1967 Solvay engaged Prof. Viola, Regina Elena Institute for Cancer Research, Rome, Italy, to study rodents to see if he could produce AOL in animals exposed to vinyl chloride vapor.

Prof. Viola's AOL experiments were with rats and monkeys but the latter had to be destroyed because of the occurrence of another unknown disease to Mr. Gosselin.

Mr. Gosselin did make reference which we have known for some long period of time that Viola's animal exposures were 3% monomer in air and this level was chosen to be the maximum which would be below explosive limits of monomer in air. Mr. Gosselin further reviewed what we know and has been published that Viola's work, although not resulting in AOL in rats, did produce the various malignant tumors which were later substantiated by Prof. Maltoni but in a much more scientific manner and much more careful biopsy and pathology to the incidence of primary cancer versus metastasis and more importantly, the primary cancers of liver angiosarcoma. Dr. Viola presented his results in a paper in Tokyo in September 1969 and later at Houston, Texas in May, 1970 followed by publication in the Journal of Cancer Research in 1971.

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Mr. Gosselin said that Prof. Viola's laboratory for exposure of animals as well as his staff is relatively small. Because of Viola's cancer findings, in November, 1970, Montedison, Rhone Progil, ICI and Solvay sought excellent facilities anywhere in Europe to extend the work of Prof. Viola. Prof. Maltoni's laboratory at Bologna was judged by all standards to be the best for such study in all of Europe, and these four companies commissioned him which began experimentation at Bologna in July, 1971. At this time Prof. Maltoni stated to his sponsors that this work would require 2½ to three years of a confidential program which he hoped to publish without any release except to the funders at the International Cancer Conference in Florence, Italy, in 1974 (believed late this month). In June, 1973, Prof. Maltoni was convinced that there is a distinct relationship between vinyl chloride exposure in rodents and that which would occur as cancer in man. Note that this statement precedes any knowledge of angiosarcoma liver findings until Goodrich's announcement in January, 1974. In the fall of 1972 at the request of MCA Task Group on Vinyl Chloride Research Dr. Dinman of the University of Michigan was asked to contact Prof. Maltoni. Dr. Dinman, who interpreted the AOL X-rays for the U.S. PVC industry, was in Europe on other business for the University of Michigan. Dr. Dinman could obtain no data whatsoever from Prof. Maltoni and later this was duly reported by Dr. Dinman to the MCA Task Group.

Mr. Gosselin said that his three associated companies in Prof. Maltoni's rodent studies agreed in 1972 at the request of the MCA Task Group to exchange information completely with the MCA Group but that secrecy must be held until agreement by the European group had been granted for release or publication by the MCA Task Group. (All recipients know that due to advice from Mr. Richard Gray, APCI and this writer did not make such an agreement to hold secret but we have not been denied access to any findings of the European Group.) Further, Mr. Gosselin said that in early 1973 a U.S. delegation of the Task Group visited Prof. Maltoni at Bologna and received complete information he had developed to that point. (In October, 1972, Dr. Walter Harris had visited Prof. Maltoni but had received only the protocol; no findings of cancer.) Mr. Gosselin said that they were informed by the MCA Task Group in mid 1973 that the U.S. industry had started an epidemiology survey. At this same time, the European Group invited American participation in funding Dr. Maltoni's work. Subsequently, as I have reported, this was rejected by the MCA Task Group primarily because of the firm opinion of Mr. William McCormick of B. F. Goodrich that animal studies must be made in the U.S. for credibility.

Mr. Gosselin said that in June, 1973, the MCA requested of the European Group that permission be given by them to disclose their findings to various United States governmental agencies. Mr. Gosselin said that with some reluctance they agreed to do so but requested 15 days extension so that individual European sponsoring companies of Maltoni's studies could contact their own governmental institutions. ICI contacted its ministry and revealed the full story at this time. In Belgium, France, and Italy only regional medical offices in charge of medical surveillance in the plant manufacturing areas were contacted and not high governmental health officials in those countries. Despite no financial aid to the rodent studies of Maltoni, German monomer and polymer industry was informed of the cancer findings.

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These West German monomer and PVC producers said they had no problems at all involving health and they would not contact German authorities. At this point Prof. Maltoni injected that in Belgium, Italy and France, health is still provincial districts which were developed during Napoleonic era and that only local M.D.'s where there is an industrial health problem are generally informed.

Mr. Gosselin reported their concern when ICI reported its first case of a retired 71 year old worker. This ex-ICI employee had 20 years experience in PVC and from his first exposure to death in December, 1972, of angiosarcoma of the liver totaled 26 years. Mr. Gosselin said that the British press is the least militant of any in Europe on the vinyl chloride health problem. Similarly, the British unions have taken in stride the one case in Great Britain and have no desire to impose standards which will close this industry in their country. England's industry is concerned, however, that if levels are set by U. S. Governmental agencies at a level lower than they can obtain, such may also be imposed upon them by their government. Mr. Gosselin said that the worst situation regarding labor and industry is Holland where the unions have requested immediate cessation of all VCM and PVC manufacture as well as its use in water piping, food wraps, etc. Despite this adversity in Holland, industry and the Dutch government remain sympathetic and on good relations primarily lead by Royal Dutch Shell. The situation in Belgium is such that there is a new government with insufficient majority to impose too strict regulations today. There has been no reaction from authorities in this country regarding the health situation and vinyl chloride. In France, industry has made contact of the Ministry of Health but no reaction has occurred.

Prof. Maltoni said that in March, 1974, the Italian Ministry of Health summoned him to appear before a committee of government workers, labor unions and industry. This single meeting has been organized into a small group which has subsequently met once to determine what should follow regarding health problems. This meeting is set for 14 June 1974. Maltoni said that Solvay in Tuscany has dealt with local government officials and will make an epidemiology survey inside and outside of the plant for vinyl chloride monomer only which is expected to include non-workers in an adjacent town. Not yet released or prepared for release is a complete study by Solvay at this location and no concern regarding health was expressed. Coincidentally, Prof. Viola is the medical doctor of this particular plant. Prof. Maltoni said that death findings in Italy are particularly vague because autopsy from any circumstance is unlikely.

Mr. Gosselin in speaking of the German industry said that the situation at Dynamit Nobel is incredibly bad. This small 45 metric ton per year PVC plant employs 120 people with 78 known cases of AOL and many (but not quantified) workers with enlarged liver and spleen. One of the U.S. medical doctors present asked if the medical study of the Dynamit Nobel workers was of high quality. Prof. Maltoni answered that it was excellent and as we know was conducted by highly qualified physicians at the University of Bonn. Prof. Maltoni said that he thought Bonn had published these findings in Germany. Further to Dynamit Nobel, Mr. Gosselin said he had never entered a plant manufacturing PVC where the odor of monomer was so high. He said recently he was confident that this level was certainly in excess of 1,000 parts per million. He did mention, as we have heard, that Dynamit Nobel will probably close this facility as they were discussing such seven years ago because at that time it was uneconomical.

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Prof. Maltoni said that Dynamit Nobel workers who show fibrosis of the liver have not shown regression after they have been removed from the VCM environment. These data have been collected by the University of Bonn. Dr. Maltoni said that liver fibrosis from VCM biopsy is easily recognized by pathology experts and he believed Dr. Harold Stewart in the U.S. is particularly expert in this regard. There will be a meeting in Bologna in November of a few medical experts to evaluate on a scientific basis medical tests and all aspects of health due to vinyl chloride monomer exposure. Prof. Maltoni said he still has to learn whether fibrosis is present in all liver angiosarcomas. He also does not know whether this particular fibrosis of the liver is different from other fibrosis caused by carcinogens of aromatic and other structures. Further to this, Prof. Maltoni posed if fibrosis is not related to angio, a test for early fibrosis of the liver would of course be of no value.

Mr. Gosselin then stated that in Sweden official state action has set vinyl chloride worker exposure at a 20 ppm TWA level with a maximum excursion to 50 ppm.

Some of European industry have formed a Confederation of European Federal Industrial Chemistry (CEFIC). This committee will be composed of one representative from each company according to Mr. Gosselin. It would be represented by Rhone Progil, Dutch Shell in Holland, Solvay in Belgium, Montedison in Italy, ICI in England, and possibly a German company known as VKE. None of us, including Mr. Gosselin could decipher who this German company is.

Ethyl Corporation stated that there will be a meeting in Europe in June of the International Labor Organization (ILO). US labor representatives plus those from the Soviet Union will meet in Geneva at this annual meeting which will also have representatives from industry present. Although this is a regularly scheduled meeting, Dr. Maltoni said that vinyl chloride will be a prominent item for discussion. Dr. Mastramato, a Canadian, will be in charge of this meeting.

Dr. Maltoni said that immature neurogenous tumors (neuroblastomas) of the brain have increased in the rats which he has had exposed to vinyl chloride with greater frequency than his control rodents.

Dr. Johnson of Goodrich said that Harvard University has been conducting a study for Goodrich and Armstrong Tire Company. In this study, Goodrich's Louisville plant will report cancer of all kinds. Dr. Johnson summarized this as the ratio of observed tumors/expected in the U.S. population as a whole.

Prior to 1965 Observed/Expected	0.8
1965 to 1970 Observed/Expected	1.5
After 1970 Observed/Expected	2.1

Dr. Johnson stated further that at the University of North Carolina all rubber companies except B. F. Goodrich are involved in a health study.

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Dr. Torkelson spoke vaguely that Dow Chemical data showed that VCM TWA levels of 200-300 ppm increased the number of tumors over those expected from non-exposed personnel but that this greater incidence was considered statistically unimportant.

Prof. Maltoni said that currently a questionnaire has been sent to all Montedison employees which will ultimately lead to an epidemiology survey of this company and VCM. Maltoni again made reference to the cytology of sputum and urine in medical studies for bladder tumors at Montedison. He said these cytology tests were conclusive for aromatic chemicals which is causing them to do similar work to those exposed to vinyl chloride monomer. He does not believe nephroblastomas in urine are as likely for VCM as has been shown for aromatic hydrocarbons. Maltoni did say that there is a clear cut abnormality in sputum of workers who have had long exposure at Montedison to vinyl chloride monomer, but these changes in the cellular structure are not neoplastic.

Mr. Gosselin of Solvay said that his company in concert with ICI estimate vinyl chloride worker exposures in the period 1945-1955 to have been at least 1,000 ppm. He said that their concern in those days was only to stay well below the limits of explosion (3.6% monomer in air). (This certainly parallels this writer's experience as it was well known that American PVC industry had frequent nausea among its polymer operators and unconsciousness on occasion with poly cleaners.) Mr. Gosselin continued stating that Solvay using the Drager instrument measured values in the period of 1950-1960 which after process improvement for economic reasons showed 400-500 ppm in the worker environment; 1960-1970 more precise measurements showed the TWA to be less than 200 in 1970. Because of Prof. Maltoni's findings of extensive cancer in rats, Solvay in 1973 had lowered the TWA value for monomer to 150 ppm by not opening autoclaves at the end of polymerization and also much improved stripping procedures of the monomer. These have resulted in today's TWA levels of approximately 50 ppm in Solvay's eight PVC plants. Mr. Gosselin was of the opinion that in 1-2 years Solvay can reach 25 TWA and in 4-5 years a TWA level of 10 but certainly not lower than 10 TWA. (Because of Solvay's reputation and larger production than any company in the free world, this statement of 10 TWA limit by Mr. Gosselin is considered to be important. Personally, this writer believes that many companies are making statements that they can achieve certain levels with these achievements based, at least in some cases, on wishful thinking rather than engineering knowledge. If unachievable monomer levels are widely stated at the coming hearings beginning 25 June, ultimate repercussions could result to our industry.) Mr. Gosselin agreed to the writer's statement and said that European industry and his company as well fear that levels of VCM exposure set by American governmental authorities which are unattainable may well be imposed by European governments as well. Mr. Gosselin will consider making a presentation at the 25 June hearings.

Dr. Torkelson said Dow will probably present skin absorption data at these hearings also.

Mr. Kusnetz of Shell, a former high ranking official in the U. S. Public Health Service, stated that the 10 May proposed standards regarding self-contained air were totally unreasonable and should be fought by the industry. He said such carried by each worker would be burdensome and would require

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frequent changes.

Limited discussion on whether additional evidence could be presented after the conclusion of the 25 June hearings was inconclusive in regard to whether additional data could be presented after the formal closing of this hearing. Opinion was expressed that it was quite probable that either unions or individual monomer and polymer producers would appeal the decision. (Unifroyal) Mr. Gosselin said his European associated companies would do extensive metabolic and other studies which will be referred to later.

Prof. Maltoni had tabular data which he had presented at the New York Academy of Sciences meeting 10-11 May 1974. Maltoni stressed that these data had been given to no American company nor to any government or other medical personnel in the U.S. It was exceedingly difficult to follow these charts as none of us had such and Maltoni was speaking from them without projection. He has revised them to include up-to-date data and such revisions plus the New York Academy of Sciences presentation tabular data are to be received by Dr. Rinehart who has promised to send this writer a copy. Maltoni is being pressed by Dr. Selikoff of Mt. Siani Hospital in New York and others including U.S. governmental agencies to present his data at the 25 June hearings. Maltoni stated despite pressure from Dr. Selikoff to send him immediately the presentation Prof. Maltoni made at the New York Academy of Sciences, he will do so not before some 15 days have elapsed and at this same time will give copies to United States industry. Dr. Maltoni stated whatever he presented at the hearings would only include those data given in New York and will not include his current findings post this meeting in New York on 10-11 May. Dr. Maltoni said he has found it physically impossible to visit all of the companies who have asked him to do such in various parts of the world and prepare proper presentation of a technical paper on an interim basis. Dr. Maltoni wishes to complete some additional phases of his work before he will make written presentation in its entirety. The writer is not at all certain that that which follows and given by Prof. Maltoni is entirely accurate but it should be corrected when the tabular data are received from Dr. Rinehart. Maltoni reported three cancers at 50 ppm in rats after 145 weeks of exposure. These were one liver angio, one peritoneal angio, and one nephroblastoma. Eleven cancers in all have been found at 50 ppm with ten animals having 11 types of carcinoma. In six rats he has found ten tumors in his control group but none are angiosarcoma. Prof. Maltoni reported the following data in mice and the incidence of various malignancies:

10,000 ppm	28
6,000 ppm	27
2,500 ppm	13
500 ppm	17
250 ppm	15
50 ppm	8
(Control 1)	

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At this point Prof. Maltoni said the data to be presented 25 June will be done by him in person or by manuscript and not by Dr. Selikoff or a representative of the United States industry.

Again, Maltoni's hurried verbal presentation was most difficult to understand. He had reported previously two malignant tumors in the offspring of 60 rats exposed at 6,000 and 10,000 ppm (30 rats each group). He has now revealed that carcinomas are being observed in the mother rats who were exposed to the above monomer concentrations from the 12th to the 18th day of pregnancy for 6 days per week. There was confusion among us after Prof. Maltoni had left for he made the statement that no tumors have been found in the pregnant Wistar rats so it must be assumed that tumors in the pregnant rodents were in mice.

Prof. Maltoni stated he hopes to reach "practical exposure" where no cancer occurs. He himself defined practical exposure as one that could be met by the monomer-polymer industry. He then stated that he thought the medical profession was overlooking hazards of VCM exposure other than cancer and here he mentioned enlarged liver and spleen with or without fibrosis but not cancer.

The Ethyl Corporation mathematician had plotted Maltoni's data and reported these data on semi-log scale can be shown to show zero frequency at 35 ppm VCM exposure in regard to liver angiosarcoma.

Prof. Maltoni was asked whether he thought those additional animal experiments not yet defined precisely to be run at Industrial Bio-Test were practical. His response was that he believes future animal studies are most essential on high but intermittent exposures which would be characteristic of actual plant experience and that he would choose either rats or guinea pigs for the study.

At this time (mid-afternoon) Prof. Maltoni became very angry and said that someone had given his data presented to the MCA group under secrecy agreement with the European to a United States Government official. Maltoni said he had seen such data in the governmental official's hands in July, 1973. He said these data had been given to the government agency prior to release from the confidentiality agreement by the four European sponsors of his research. Dr. Maltoni would not identify the U.S. agency but inadvertently slipped and named NIH. Mr. Kusnetz through his many contacts when he was in government service will attempt to determine who gave these data to NIH. An Ethyl Corporation representative said asbestos producers who manufactured PVC pipe knew of Maltoni's findings before they were made public and he mentioned Certain-Teed, Flintkote, Capco and Johns Manville specifically.

At this point Prof. Maltoni said that when NIH spoke to him in the summer of 1973 they stated they had been prepared to fund an extensive study of VCM in rodent exposure but now that they were aware of Maltoni's work they saw no reason to do so. This, in part, contributed to Maltoni's ire.

Mr. Gosselin stated that the CEFIC Group referred to earlier will in the near future start further most extensive studies. Animal exposures and certain pathology will be done by Prof. Maltoni at Bologna, Italy. Additional studies

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will be performed at the Institute of Negri, Milan, Italy, with Prof. Garattini in charge of the research. Among the items to be studied by this European group are:

1. development of a sensitive method to determine metabolites in body fluids and in tissues using Carbon 14 versus onset of tumors;
2. vinyl chloride levels in excretion and changes in the animals so exposed;
3. identification of specific metabolites or foreign bodies produced;
4. significance of #3 relative to the onset of cancer (this seems to be similar to item 1);
5. chronic toxicity other than tumor formation by (a) animal behavior studies, (b) analyses of all organs including electron microscopy, (c) changes in blood and urine of rats and monkeys, (d) effect on liver functionality of mouse, rat, guinea pig and dogs for detection of lesions, (e) synthesis of biological important macromolecules, (f) effect of metabolite formation on the coagulation of blood and vascular function, (g) microhepatic induced hemolytic anemia, (h) effect of exposure on nucleolates on lipid metabolites, (i) reproductive function in mice of three different strains and at three exposure levels for three generations, (j) effect of vinyl chloride monomer on functionality of immune systems.

There were other laboratory experiments to be made which were spoken too rapidly for me to note. I did ask Mr. Gosselin if their group required additional funding to do these studies and he replied they had more than enough money to conduct these.

Dr. Rinehart of Ethyl Corporation had received a similar letter from Mr. Werner Freiesleben of Wacker Chemie to Dr. Adams of 30 May 1974. Dr. Rinehart asked the writer to discuss this and its technical feasibility. Such was done and the statement made that literature references show the decomposition upon cleavage of vinyl peroxide into the components as shown in Mr. Freiesleben's letter. I was unable to comment on Dr. Sabel's statement that formaldehyde and HCl is formed from vinyl chloride and oxygen in the presence of liver in an aqueous medium at 400C. There have been frequent discussions in the past that vinyl chloride may not be the actual carcinogen but the intermediate whether by metabolism or other routes to synthesis of a carcinogen which is the active agent in producing cancer. Dr. Maltoni was extremely dubious about these data which also were previously known to him and apparently to Mr. Gosselin as well. Dr. Maltoni stated that vinyl chloride is an alkalating agent and their future work as well as work in prospect at Dow Chemical would seem much more plausible than the formation of bis-chloromethyl ether. It was Maltoni's opinion that he hopes that this ether is not the carcinogen because he knows of no conceivable route that it might be blocked and prevented in acting as a human carcinogen. Dr. Maltoni is of the opinion that if vinyl chloride per se is not in itself

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a carcinogen of potency, he believes it possible that metabolites produced by alteration of the liver induced by vinyl chloride may be the causative agent. Such work as this is underway at present at the Dow Laboratories.

Dr. Maltoni in addition to the attached article has published Occupational Carcinogenesis at the International Congress, Series No. 322, Volume 2, Bologna, Italy, April 9-12, 1973. This concerns cancer detection and prevention and is published in English. Dr. Maltoni said he would provide each of us with a reprint of this article.

The last statement made was by Dr. Torkelson who said that Dow Chemical will bring their epidemiology study to date and would present this during the forthcoming hearings. (I did learn that evening that Dr. Selikoff who conducted physical examinations on Dow employees at Midland, Michigan, the past weekend, reportedly has found some medical findings which possibly Dow had not previously observed.)



WNS:clw

Attachment - Translation -- Academia dei Luce - 3 March 1974
by Prof. Cesare Maltoni
Istituto di Oncologia, Bologna, Italy

Accademia dei Luce - 3 March 1974

by Cesare Maltoni
Istituto di Oncologia, Bologna, Italy

In these last decades the number and quantity of oncogenic agents produced and dispersed in the working environment have increased and are increasing in a disturbing manner. From plants oncogenic agents are introduced into the general environment thereby becoming an ecological problem.

As a consequence of this situation an increase has been registered in occupational tumors and in latent ambient exogenic agents.

Most of the oncogenic agents present in the human environment have been identified through retrospective epidemiological survey. The need for epidemiological proof should be avoided. It would be preferable that all new products be subjected to systematic experimental tests to predict this ultimate oncogenic potential.

Such tests have not been made in a systematic way essentially for two reasons. The first consists of the lack of a norm. The second is that, since frequently the design and conduct of the experiments are inadequate and their result hence not translatable to man, a certain skepticism has been raised about them.

In our opinion however the experimental test, if properly planned and executed, has a high predictive value.

We refer now to an example. To our knowledge it is the first time whereby means of an experimental test the oncogenic risk can be accurately predicted, its amount and the target tissue.

The present observations refer to tests of the carcinogens of vinylchloride (VC).

This monomer is of great industrial import. It is used in the production of polyvinylchloride (PVC) as a copolymer in the production of saran and other plastics, as a solvent and chemical intermediate. For a short time it was also used as an anesthetic. VC production is about 12 million tons per yr.

The following are subject to risk of exposure of this product:

- 1) workers in PVC production and in other resins in which it is a component, in the production of VC and other industrial uses of VC;
- 2) workers using PVC;
- 3) residents of areas surrounding plants which produce VC and PVC; and
- 4) even if a minor extent, those who use or come in contact with plastic based ^{to} on VC or materials packaged in it.

The program to test the oncogenic potential was a result of the preliminary findings of the pioneering work of Prof. Viola, presented at the X Int. Congress on Cancer (Houston 1970) which was subsequently published in Cancer Research in 1971 (Viola et al 1971).

Prof. Viola's results indicated that exposure to 30000 ppm VC, 4 hr per day, 5 days per week, for 10 months produced tumors in rats. In Prof. Viola's interpretation these tumors arose on the skin, lungs and bones.

Immediately after the presentation in Houston we contacted Prof. Viola who kindly made available to us the histological sections of his tumors and his expanded paper still in publication.

On the basis of this work we concluded the following:

- 1) Under the experimental conditions used by Prof. Viola, VC showed a carcinogenic effect on rats;
- 2) 30,000 ppm VC was an extremely high dose;
- 3) The tumors described as cutaneous arose from the Zymbal glands, which are sensitive to a large spectrum of carcinogenic agents (2-acetylaminofluorene, benzidene, polycyclichydrocarbon, aminostilbene, urethane, etc);
4. Tumors described as pulmonary were in reality metastatic from the Zymbalgland cancers. The neoplastic pulmonary cases were all found in animals which showed Zymbal gland tumors and were identical to those tumors.

It became urgent to undertake systematic research to clarify the type and degree of carcinogenic effect of VC with particular concern regarding those experimental factors such as mode of administration, concentration, duration, etc. which could give more exact indications of the risk under the conditions of the working environment.

For this purpose because the Institute of Oncology and the Tumor Center of Bologna have particularly specialized in the prevention and control of tumors, Montedison, the major Italian VC producer, turned to us to implement our program of tests on the biological effects of VC. Montedison was in order joined ICI (Great Britian), Solvay (Belgium) and Rhone-Progil (France) (European Cooperative Group for the Study of the Biological Effects of VC).

Before beginning the operational phase of this research it was necessary to establish proper conditions for exposure by inhalations.

The study and construction of an apparatus for the program and controlled exposure required several months. Control was through gas chromatography. Such an apparatus enables exposure to concentrations from 30000 to 50 ppm and the simultaneous treatment of 1200 experimental animals. The equipment is essentially made of stainless steel and glass.

VC was furnished by Montedison. Each lot was analyzed prior to use to determine impurities. The VC we used contained negligible amounts of impurities.

The experiments were conducted primarily on Sprague - Dawley rats; Wistar rats, Swiss mice and hamsters were also used. All animals except hamsters were raised in our Institute for many years and regardless of their use they were subjected to complete autopsy, hence we know their current pathology.

Fourteen experiments in sequence were begun. Some of these were programmed from the beginning. Others, however were deemed to be necessary subsequently on the basis of initial experimental results.

The plan of the experiments and the actual data are given in Table 1.

Essentially, we wanted to verify the action of VC in relation to various facts: The manner of administration, dosage, duration, and the time and rhythm of the treatment, the type of test animal, and the age of the animal.

Further, we want to test the eventual possibility of the transplacental action of the compound.

All the animals were kept under observation up to spontaneous death. At death

each animal was subjected to a complete autopsy. Examined histologically were: The Zymbal glands, the interscapular fat, the salivary glands, the tongue, the lungs, the liver, kidneys, spleen, the stomach, various sections of the intestines, the veins, the brain, and the leg bones and any other tissue with pathological lesions. All the animals were exposed to very high dosages, 30,000 and 10,000 parts per million, with or without tumor, they were examined radiologically during treatment and/or at death to verify the onset of eventual acrosteolitic lesions.

Those animals exposed to lower levels were also examined radiologically when they bore tumors.

In Tables 2 - 6 are given preliminary data pertaining to experiments BT-1, BT-3, BT-6, BT-5, BT-4. The other experiments are still incomplete. Results are still being awaited.

From what was presented in the tables and from the histological study the following points emerge:

1. VC is oncogenic and under the experimental conditions we tested it: it produces cancer of the zymbal glands (Figure 1), nephroblastomas (Figure 2) and angiosarcoma of the liver (Figure 3 and 4) and in other tissues and organs (Figure 5 and 6) and pulmonary adenoma-adenocancers, mammarian cancers, hepatic angiosarcomas in the mouse;
2. There is a relation between dosage and response
3. The nephroblastomas and the tumors of the zymbal glands may be bilateral
4. The liver angiosarcomas are polycentric.
5. In the treated animals, whether or not they have angiosarcomas, there are frequently diffuse vascular changes present in various tissues and organs, consisting of a simple endothelial proliferation, distipical and frequently atypical. The oncogenic action is however, maintained to be a systemic effect on the vessels.

6. The observation of three ossifying angiosarcomas suggest new approaches to a different pathogenic interpretation of the acrosteolysis in workers exposed to action of VC.
7. Up to now in the rats we treated, we did not observe any acrosteolytic lesion.

Cancers of the zymal glands, hepatic and extra hepatic angiosarcoma and nephroblastomas have never been observed in untreated animals of our strain of Sprague-Dawley rats. The three known cases of cancer of the Zymal glands in rats which were not treated, were encountered by Tannenbaum and colleagues in 1962; these were Sprague-Dawley rats.

To our knowledge, spontaneous nephroblastomas and hepatic angiosarcomas in rats have never been reported.

Nephroblastomas have never been induced experimentally. Hepatic angiosarcomas were never experimentally induced in rats with diethylnitrosoamine (Reuberphic, 1968 Hadjolor 1972).

In rats hepatic and extrahepatic angiosarcomas were induced with o-aminoazotoluene (Andervont and co-workers 1942, Andervont 1950) and with p-trimethylaminobenzene, 1-azo, 2-naphthalene (Mulay and Saxen 1953) and with other agents among which were urethane, diethylnitrosoamine, dimethyl nitrosoamine and dimethylhydrazine.

In the rabbit angiosarcomas were induced with thorotrast (Zeithlhofer and Speiser 1954).

In man, angiosarcomas are rare. Handells in 1958, discussing the situation of angiosarcomas in the literature gathered 117 cases of which only 21 were hepatic

They are, however, seemingly increasing in recent days.

In the literature, there are references in man of one case of hepatic angiosarcoma from radium (Ross 1932) and many cases of hepatic angiosarcomas from thorotrast (McMahon and co-workers 1947; Luden 1953, Silva Horta and co-workers 1965) and from Arsenic (Roth 1957).

As soon as it appeared clear to us about a year and a half ago that vinyl chloride showed carcinogenicity as referred above, we immediately communicated the fact not only to the societies of the cooperative European group but also to the other major producing societies of the world.

Our data has directed clinical observations and an epidemiological study.

At the end of December 1973 one worker in an American PVC factory died from hepatopathy.

The autopsy revealed that we were dealing with hepatic angiosarcoma.

The retrospective survey conducted these last weeks has brought forth eight analogous cases (7 in the United States and 1 in Great Britian) of hepatic angiosarcoma which were in the past were neither correctly diagnosed or not corrolated however to working exposure (Figure 7 and 8). This number is bound to increase.

In the United States and in Germany several employees exposed to VC with suspect liver ailments have now been subjected to constant observation.

In conclusion, we want to proposed that experimental tests of cancerogenity became a prime rule before approval of the admission of new reagents, so that one works more or less in the manner of a scholarly discussion (frequently in the form of a Congress and committee) of the validity and extrapolation to man of experimental results for which only too frequently there is lacking sufficient evidence.

(NOTE FROM WMS - Professor Maltoni's unpublished paper was translated crudely from the Italian by Shell Oil Company. No tabular data were given by Professor Maltoni.)