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March 31, 1975

Mr. John Stender.
Occupational Safety & Health
Administration
Department of Labor
Washington, D. C. 20210

Re: Standard for Exposure
to Vinyl Chloride; Request
for Interpretation and
Other Relief

Dear Mr. Stender:

The purpose of this letter is to follow-up on a meeting held Thursday, March 20, of Messrs. Flowers and McClure and Mrs. Ryer of the Staff of the Occupational Safety and Health Administration and Messrs. Thomas Smith, B. F. Goodrich Chemical Company; Grant Arnold, Ethyl Corporation; Philip Cupertino, Stauffer Chemical Company, and the undersigned on behalf of the Committee on Distribution of the Society of the Plastics Industry, Inc. The subject of this meeting was the implementation of the OSHA Standard for Exposure to Vinyl Chloride 1/ with respect to labeling and other transportation related functions.

As we are certain you are aware, the Society of the Plastics Industry (SPI) is the national trade association of the industry and represents approximately 99 percent of the production of vinyl chloride (VCM) and polyvinyl chloride (PVC) in this country. The Committee on Distribution is a service committee within SPI and is charged with the responsibility to study and work toward

1/ 29 C.F.R. §1910.93g.

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improvement of the function of physical distribution of materials and products. The Standard for Exposure to Vinyl Chloride is accordingly of extreme importance to the Committee on Distribution due to its impact upon materials handling, transportation equipment, packaging and labeling.

LABELING

The Committee on Distribution has adopted a program for the labeling of transportation equipment and packaged materials relative to the requirements for container labeling of subsection (1) of the Standard. We respectfully request your concurrence with our interpretation that this program fulfills those requirements, and we further request that OSHA field personnel be advised that the labeling program described herein satisfies compliance responsibilities of those employers whose employees may be handling VCM and PVC materials.

The industry believes that a uniform approach to marking and labeling is desirable in order, first, that transportation companies and carrier employees will become accustomed to recognizing the prescribed warnings irrespective of the company making shipment. In this regard, carriers are accustomed to standardization in hazardous materials regulations; and a uniform industry approach would thereby facilitate not only industry but also common carrier compliance obligations. Secondly, a uniform approach would be effective in warning employees of the fabricator segment of the industry who will become accustomed to seeing the warnings in similar fashion and location irrespective of the producer or plant wherein the shipment originates. Finally, uniformity will enable OSHA inspectors to impartially judge compliance and effect uniform enforcement, thereby assuring that all producers are treated in a similar manner, and further assuring that the same standard of compliance will be applied to a shipment at origin by one inspector as at destination by another.

The provisions of subparagraph (1) of the Standard simply require that containers of vinyl chloride and polyvinyl chloride shall be "legibly labeled" with the

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warning statements designated therein. In formulating the program described below, the Committee on Distribution has considered the intent of the Standard that employees handling vinyl chloride and polyvinyl chloride materials shall be reasonably apprised of the warnings prescribed by the Standard in view of the handling and exposure at all levels, e.g., producer, fabricator, carrier and warehouseman; and the Committee's deliberations further took into account the specific characteristics pertaining to each "container" for marking purposes.

Vinyl Chloride

Vinyl chloride may be packaged for transportation in bulk in tank cars, in bulk in tank trucks, or in cylinders. 2/ The practices and requirements of transportation for each mode mandate specific consideration. With respect to tank car movements, the industry has elected to employ option (ii) of subsection (1)(5) of the Standard to mark "Cancer-Suspect Agent" in conjunction with the DOT placard requirement. Associated with this letter and identified as Exhibit "A" is a DOT placard utilized for VCM movements as amended to reflect the OSHA-prescribed warning. Modification of the placard to accommodate the OSHA warning has been assented to by the Federal Railroad Administration of the Department of Transportation. 3/ This approach presents all transportation safety information in one location, and railroad employees are accustomed to looking to the placard for such information. Moreover, this approach appears to fulfill the intent of the Standard as described in the preamble, as follows:

Since labeling or placarding that is in compliance with the U.S. Department of

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- 2/ For waterborne movement, the carcinogenic hazard of VCM will be regulated by the Department of Transportation. See, CGD 74-167, 39 Fed. Reg. 26752.
- 3/ Letter dated November 21, 1974, from Mr. W. F. Hall for Mac E. Rogers, Associate Administrator, Office of Safety, Federal Railroad Administration of the Department of Transportation, addressed to Mr. S. Kuzma, Allied Chemical Corporation.

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Transportation regulations (49 CFR Part 173, Subpart H) already warns of the fire hazard, only a statement concerning the carcinogenic hazard need be *added to* the Department of Transportation labels. 4/

The movement of vinyl chloride by tank truck is currently very limited in scope, involving one VCM producer and a single motor carrier. It is the position of the Committee on Distribution, and of the parties particularly involved in this movement, that option (i) of subparagraph (1)(5) is preferable. It is intended that the full warning statement 5/ will be applied by a label, stencil or tag, as illustrated by Exhibit "B" to this letter, in the vicinity of all hatches and all outlets. The producer and customer personnel handling the material at both origin and destination will, of course, be familiar with and trained in the handling requirements of vinyl chloride. Additionally, a single driver is responsible for the truck during the entire transportation movement. Accordingly, it is believed that this system of notification will serve to adequately warn all employees who may be anticipated to be within working distance of the vehicle during transportation of the health hazard involved. 6/

4/ 39 Fed. Reg. 35890, 35895 (Emphasis added).

5/ It is understood that the shipper involved intends to petition for a variance to use the phraseology "Flammable Compressed Gas" in lieu of "Extremely Flammable Gas Under Pressure" in order to correlate to DOT hazardous materials terminology.

6/ Exhibit "B-1" hereto is a DOT placard used for truck movement of vinyl chloride. The nature of this placard, and its failure to identify the material in the vehicle, do not accommodate modification to include the OSHA-prescribed warning as readily as does the rail placard. This distinction, and also differences in the manner of handling tank cars and tank trucks, has caused the Committee on Distribution to select the labeling of hatches and outlets so to give particular warning to those actually handling the product.

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With respect to cylinders, which move comparatively infrequently in transportation, it is intended to utilize the "Cancer-Suspect Agent" legend, in lettering one-half the size of the "Flammable Gas" lettering of the DOT required label, near the DOT label on the cylinder. A sample DOT label is associated herewith as Exhibit "C".

Polyvinyl Chloride

Polyvinyl chloride may be in either powder, pellet or liquid form. PVC is moved in bulk in hopper cars, tank cars, hopper trucks and tank trucks; and PVC is packaged in bags, bulk boxes and drums. With respect to bulk equipment, whether rail or motor carrier, the Committee on Distribution program calls for warning with the legend prescribed in subsection (1)(4) of the Standard by label, stencil or tag in the vicinity of all hatches and all outlets, in the form of Exhibit "D" to this letter. Such a label will serve to give notice of the potential health hazard prior to handling the PVC material.

Exhibit "E" to this letter is a label to be utilized on packaged material. This label will be applied to bags on the sides or ends, to boxes on each side which bears the product identification, and to drums on the front, i.e., near the product identification. This application of the warning is intended to be visible when the packages, particularly bags, are palletized, and so may be seen by warehouse personnel and also by employees or fabricators who may be called upon to remove the bags from the pallets for usage.

Waste Material Contaminated with Vinyl Chloride

It is intended to label waste materials contaminated with vinyl chloride, which move very occasionally in bulk in trucks, with the labeling prescribed by subsection (1)(3) of the Standard in similar fashion to the label identified as Exhibit "D" to this letter.

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It is respectfully submitted that the foregoing labeling program complies with the requirements and intent of the Standard insofar as the responsibility of all employers, e.g., producer, fabricator, warehouseman and transportation company, is concerned with respect to the movement of vinyl chloride and polyvinyl chloride materials; and we request your concurrence in this interpretation.

TRANSITION

As the direct result of the present state of the economy, many, if not all, PVC producers find themselves with substantial inventories of packaged materials. As of December 31, 1974 these inventories amounted to approximately 300 million pounds. ^{7/} Such inventories are held at public as well as company warehouse facilities. The provision of the Standard requiring that containers of polyvinyl chloride must be labeled effective April 1 apparently applies to existing inventories as well as to newly packaged materials; however, whereas newly packaged PVC materials will be labeled in accordance with the program described above, the labeling of each individual package in inventory may be highly impractical.

By and large, PVC materials are packaged in bags containing 40 or 50 pounds of material; and it is common industry practice that such packages are palletized, 50 bags to a pallet. Within each pallet, the bags are glued or banded together to maintain stability and facilitate handling of the palletized unit. In consideration of the unitized nature of packaged PVC materials or pallets, it is our interpretation that each palletized unit may be considered to be a container, and accordingly that the requirement of subsection (1) of the Standard may be satisfied by the labeling of each palletized unit itself.

^{7/} Source: SPI Committee on Resin Statistics, as compiled by Ernst & Ernst.

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To otherwise interpret the Standard may require that each pallet load be broken down, thereby resulting in a weakening of the individual packages as the outer ply of paper, glued to the next package, tears as the bags are separated from one another so that labels may be individually applied.

While the PVC producers do not have a single approach to the labeling of packages during this transition period, it is generally intended that labels will be placed on each palletized load in such fashion as to be conspicuous to warehouse and transportation employees who will be handling the material. Additionally, the labels will be so located that the warning will be apparent to employees of fabricators as the bags are removed from the palletized load for use, until the last package has been severed from the pallet.

It is respectfully submitted that the foregoing approach to labeling during the transition period, and until present inventories are depleted, will serve to fulfill the requirement of subsection (1) of the Standard at all levels of handling; and we further request your concurrence in this interpretation.

EXPORT

Members of SPI's Committee on Distribution have been advised that materials bearing the "Cancer-Suspect Agent" label will not be accepted for handling by certain stevedoring companies. Moreover, some foreign customers have indicated that they will not accept products bearing this label since they can purchase PVC materials from producers in other countries which are not labeled in this fashion.

SPI's statistics show that the export of PVC, amounting to approximately 300 million pounds in 1974, accounts for 21% of all plastic materials exported. 8/

8/ Source: SPI Committee on Resin Statistics, as compiled by Ernst & Ernst.

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SPI is aware that the B. F. Goodrich Chemical Company has filed a request for an interpretation concerning this matter. Considering that (1) the warning is primarily intended for the benefit of employees actually working with the PVC material in the fabrication process, and that foreign employees are not within the purview of the OSH Act, (2) that producer and transportation employees will be trained in the handling of PVC materials, and (3) that longshoremen and other dock personnel have only occasional and limited exposure in an open air environment to packages of PVC material, the SPI Committee on Distribution supports the B. F. Goodrich Chemical Company request that the Standard be interpreted as not requiring the labeling of PVC materials in export movement.

SAMPLES

It is common practice within the industry for PVC producers to ship samples of materials to customers, such samples ranging in amount from 5 pounds to one bag consisting of 40 or 50 pounds of product. Such samples may be sent by United Parcel Service, parcel post or air freight and are appropriately packaged in outer containers sufficient to withstand the rigors of handling. As presently constituted, the provisions of the Standard, most particularly the monitoring, training, labeling and record retention requirements, would apply to the handling of these shipments in equal force as they do to the transportation of a 40,000 pound consignment. Obviously, the burdens of compliance with the Standard would make the handling of such sample shipments economically infeasible for the postal system, UPS or the airlines. In view of the negligible exposure and health hazard presented by the handling of such sample shipments, it is respectfully requested that the Secretary either interpret the Standard so to exclude such transportation from the scope of subsection (a)(3), or alternatively that the Secretary amend the Standard to exempt from its scope the transportation of PVC in quantities not exceeding 50 pounds. Should such an amendment be required, it is submitted that it would constitute a minor amendment within the context of Section 1911.5 of

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the Regulations.

Your attention to the foregoing request is very much appreciated. Should there be any questions concerning the foregoing matters or should any further information be desired, please feel free to communicate with the undersigned.

Very truly yours,

Martin W. Becovic
Assistant General Counsel To:
THE SOCIETY OF THE PLASTICS
INDUSTRY, INC.

Enclosures

cc: Mr. Barry White
Mr. Grover Wrenn
Mr. Charles Ray McClure

The Value of Predictive Experimental Bioassays Environmental Carcinogenesis

An Example: Vinyl Chloride

BY CESARE MALTONI

The vinyl chloride story demonstrates the need for experimental carcinogenicity testing of chemical compounds before they are released into the occupational and general environment.

It is increasingly demonstrated and accepted that the high and rising incidence of tumors, especially in particular sites (lung, urinary tract, hemopoietic tissues), is due to the extensive and growing diffusion of oncogenic agents in the environment.

Furthermore it is assumed that 80 to 90 percent of tumors depend on causes which are, or may be identified as being, part of the human environment. Recognition of such causes and protection from their effects could significantly reduce tumor morbidity and mortality.

This increasing diffusion of environmental oncogenic agents is a phenomenon particularly correlated to the growth of industrialization, and especially to those industries producing and manufacturing new synthetic compounds. In modern times, from 100 000 to 200 000 new chemical compounds are produced annually, and we know very little about their effects on man.

There is a strict correlation between occupational and general environmental carcinogenesis. Potential carcinogenic agents spread in fact throughout the general environment from the factories where they are produced, thus rapidly creating an ecological problem. Hence, results of studies in the field of occupational oncogenesis, directed towards identifying oncogenic industrial agents and assessing protective measures for workers, can be extrapolated easily to general environmental oncogenesis.

Environmental and occupational carcinogenesis are, therefore, socially important. As regards occupational carcinogenesis, it is one of the most interesting, tragic and difficult

fields in oncology: it is interesting from a scientific standpoint because it represents, dramatically, an experiment on human beings which has taught us much about the natural history of tumors; tragic because work, which is, *per se*, a natural necessity of life, should not cause cancer, and difficult because the care of workers' health often conflicts with the productive goals of industry and with major economic and political interests.

NEED FOR PREDICTIVE CARCINOGENICITY BIOASSAYS

Most of the oncogenic occupational and environmental agents have been identified when the incidence of a particular type of tumor in an exposed population has been outstanding, or on the basis of retrospective epidemiological studies.

Progress in these areas of oncology should facilitate systematic experimental carcinogenicity testing of agents which are, or will be, released in the general and occupational environment. These testing should be carried out before the exposure of humans to potentially oncogenic agents takes place (since the specific effects on tissues produced by carcinogens are irreversible) and before economical, political and social interests are well established (as then they can not easily be changed).

Carcinogenicity experimental bioassays are surprisingly few as compared with the need. This is due to several factors: scepticism concerning the validity of testing, the vast amount

of agents to be tested, lack of experience. Let us briefly and

Scepticism. Too frequent occupational agents whose results could not be experimental testing has often carcinogenic risks. critical of the validity critically evaluate the

Vast amount of agents. Vast amount of agents which priorities for the widely diffused.

Complications in perfect experimental tests on human exposure, the to be examined should in degree of precise expose the more danger

Lack of experimental a number of oncological carcinogenicity bioassays; those centers or agencies promoting public relations coordinated. Moreover the large number and mental and intergovernmental promoting such studies. proper protective measures commission, together with, should: 1) plan the an international level a experimental units, and decide on proper prevention

In sharp contrast to mental carcinogenicity there are numerous pre-effect on experimental agents which are already. These studies, of course oncology, but they have occupational and environmental

Furthermore, medical phasis. In our opinion, mainly to determine the epidemiological data. In its own experience have shown on a broad range of widely the target organ

Experimental Bioassays in Occupational and Environmental Health

of agents to be tested, complications in performing elaborate tests, lack of experimental units and conflict of responsibilities. Let us briefly and critically review these points:

Scepticism. Too frequently in the past, environmental and occupational agents have been tested improperly so that the results could not be extrapolated to man. Consequently, experimental testing has often been considered obsolete for predicting carcinogenic risks. In our opinion, one should not be sceptical of the validity of carcinogenicity bioassays, but rather critically evaluate the methods of testing.

Vast amount of agents. Since this is a reality, one must establish priorities for the products which are, or will be, most widely diffused.

Complications in performing elaborate testings. The more experimental tests on animals reproduce the conditions of human exposure, the more relevant they are to man. Agents to be examined should follow a pattern of tests which progress in degree of preciseness and scrutiny, so as to filter out and expose the more dangerous compounds.

Lack of experimental units and conflict of responsibilities. The number of oncological units throughout the world performing carcinogenicity bioassays is indeed low (if one does not include those centers or agencies whose activity is devoted mainly to promoting public relations in this field) and are not sufficiently coordinated. Moreover it is often difficult to assess (because of the large number and lack of correlation between governmental and intergovernmental agencies) who is responsible for promoting such studies, verifying the results and undertaking proper protective measures. A permanent intergovernmental commission, together with representatives from interested parties, should: 1) plan the programs and priorities, 2) promote at an international level an adequate and integrative network of experimental units, and 3) critically evaluate the results and decide on proper preventive programs.

In sharp contrast to the insufficient attention given experimental carcinogenicity bioassays for predicting potential risks, there are numerous projects which study the carcinogenic effect on experimental animals and the metabolic patterns of agents which are already known to be carcinogenic for man. These studies, of course, may be of some interest for basic oncology, but they have little bearing on the prevention of occupational and environmental tumors.

Furthermore, medical controls have been given great emphasis. In our opinion, the value of medical examinations is mainly to determine the risk; that is, they may provide epidemiological data. In fact, as collective information and our own experience have shown, the carcinogens exert their effects on a broad range of organs in exposed humans and affect widely the target organs, and the tumors which arise are

potentially multicentric. Consequently very little can be done after the tumors have arisen.

The major value of experimental testing in the prevention of occupational and environmental oncogenesis is demonstrated clearly by the story of vinyl chloride carcinogenicity.

VINYL CHLORIDE CARCINOGENESIS

Vinyl Chloride (VC) has been produced in many countries for more than 30 years. It is the constituent of polyvinyl chloride (PVC) which today is the plastic industrial material most often used and diffused throughout the world. Moreover, it is used as a copolymer in Saran and other plastics, as a chemical intermediate, as a solvent, and as a propellant. In the past, for only a short period, it was also used as an anaesthetic. VC at present is produced at a rate of almost 12 million tons per year.

The following population groups may be exposed to VC: 1) workers engaged in the production of PVC and VC, and in the use of VC for other industrial purposes; 2) workers manufacturing PVC; 3) residents in areas neighboring factories producing PVC and VC; and to a much lesser extent 4) people consuming products containing VC, as some propellant sprays; 5) people having contact with resins made with VC and with materials containing these resins; and 6) populations consuming food contained in plastic made by VC.

Valuable bioassays on the long term effects of VC were not available until 1970. This situation reflects the scarce consideration which has been given until now to experimental bioassays in predicting the oncogenic effects of environmental and occupational agents on man.

At the end of 1970 we planned a project of correlated investigations to clarify the type and degree of carcinogenic risk from VC.

This project included a series of experiments, which were started in sequence. They were designed to study the effects of VC, administered through different routes (inhalation, ingestion, peritoneal and subcutaneous injection), at different concentrations (by inhalation: 30 000, 10 000, 6000, 2500, 500, 250, 200, 150, 100, 50, 25, 10, 5, 1 ppm), for varying periods of time (by inhalation: from 52 weeks to 1 week), by continuous or intermittent treatment, on animals of different species (rats, mice, hamsters), strains (Sprague-Dawley and Wistar rats), sex and age (adults, newborn, embryos).

The planning of the program and the preparation of suitable experimental conditions, particularly the building of an apparatus for inhalatory exposure, took until May 1971. In July 1971 we started experimenting. The exposure by inhalation was generally performed 4 hours daily, five days per week.

The chambers of exposure, basically built of stainless steel and glass, have been designed to deliver concentrations of gaseous agents varying from 30 000 ppm to 1 ppm of VC. The VC concentration in the chambers is controlled by gas chrom-

on a scientific standpoint an experiment on human at the natural history of 1 is, *per se*, a natural cer, and difficult because flicts with the productive onomic and political in-

GENICITY BIOASSAYS and environmental agents ce of a particular type of been outstanding, or on cal studies.

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says are surprisingly few i due to several factors: testing, the vast amount

Treatment (a)	mg/ml	µg
1	10000	10000
2	5000	5000
3	2500	2500
4	1250	1250
5	625	625
6	312.5	312.5
7	156.25	156.25
8	78.125	78.125
9	39.0625	39.0625
10	19.53125	19.53125
11	9.765625	9.765625
12	4.8828125	4.8828125
13	2.44140625	2.44140625
14	1.220703125	1.220703125
15	0.6103515625	0.6103515625
16	0.30517578125	0.30517578125
17	0.152587890625	0.152587890625
18	0.0762939453125	0.0762939453125
19	0.03814697265625	0.03814697265625
20	0.019073486328125	0.019073486328125
21	0.0095367431640625	0.0095367431640625
22	0.00476837158203125	0.00476837158203125
23	0.002384185791015625	0.002384185791015625
24	0.0011920928955078125	0.0011920928955078125
25	0.00059604644775390625	0.00059604644775390625
26	0.000298023223876953125	0.000298023223876953125
27	0.0001490116119384765625	0.0001490116119384765625
28	0.00007450580596923828125	0.00007450580596923828125
29	0.000037252902984619140625	0.000037252902984619140625
30	0.0000186264514923095703125	0.0000186264514923095703125
31	0.00000931322574615478515625	0.00000931322574615478515625
32	0.000004656612873077392578125	0.000004656612873077392578125
33	0.0000023283064365386962890625	0.0000023283064365386962890625
34	0.00000116415321826934814453125	0.00000116415321826934814453125
35	0.000000582076609134674072265625	0.000000582076609134674072265625
36	0.0000002910383045673370361328125	0.0000002910383045673370361328125
37	0.00000014551915228366851806640625	0.00000014551915228366851806640625
38	0.000000072759576141834259033203125	0.000000072759576141834259033203125
39	0.0000000363797880709171295166015625	0.0000000363797880709171295166015625
40	0.00000001818989403545856475830078125	0.00000001818989403545856475830078125
41	0.000000009094947017729282379150390625	0.000000009094947017729282379150390625
42	0.0000000045474735088646411895751953125	0.0000000045474735088646411895751953125
43	0.00000000227373675443232059478759765625	0.00000000227373675443232059478759765625
44	0.000000001136868377216160297393798828125	0.000000001136868377216160297393798828125
45	0.0000000005684341886080801486968994140625	0.0000000005684341886080801486968994140625
46	0.00000000028421709430404007434844970703125	0.00000000028421709430404007434844970703125
47	0.000000000142108547152020037174224853515625	0.000000000142108547152020037174224853515625
48	0.0000000000710542735760100185871124267578125	0.0000000000710542735760100185871124267578125
49	0.00000000003552713678800500929355621337890625	0.00000000003552713678800500929355621337890625
50	0.000000000017763568394002504646778106689453125	0.000000000017763568394002504646778106689453125
51	0.0000000000088817841970012523233890533447265625	0.0000000000088817841970012523233890533447265625
52	0.00000000000444089209850062616169452667236328125	0.00000000000444089209850062616169452667236328125
53	0.000000000002220446049250313080847263336181640625	0.000000000002220446049250313080847263336181640625
54	0.0000000000011	

TABLE 2. Experiment 5B

	(a)	(b)	(c)	(d)	(e)
The animals were used	for 17 weeks.	All weeks.	Different cases of pregnancy (generally abdominal)†	In different animals with 2 or 3 subsequent angles.	
No treatment					
VC 80 ppm					
VC 120 ppm					
VC 600 ppm					
VC 1500 ppm					
VC 3000 ppm					
VC 6000 ppm					
Total					

[illegible]

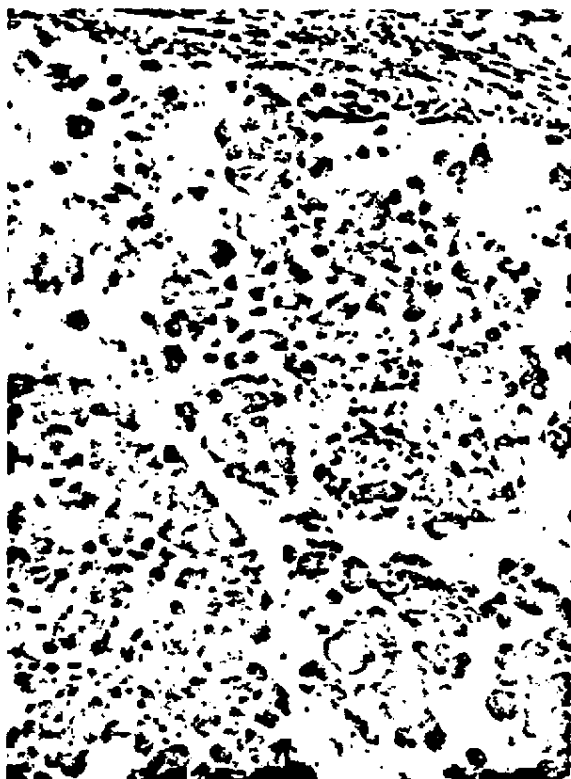
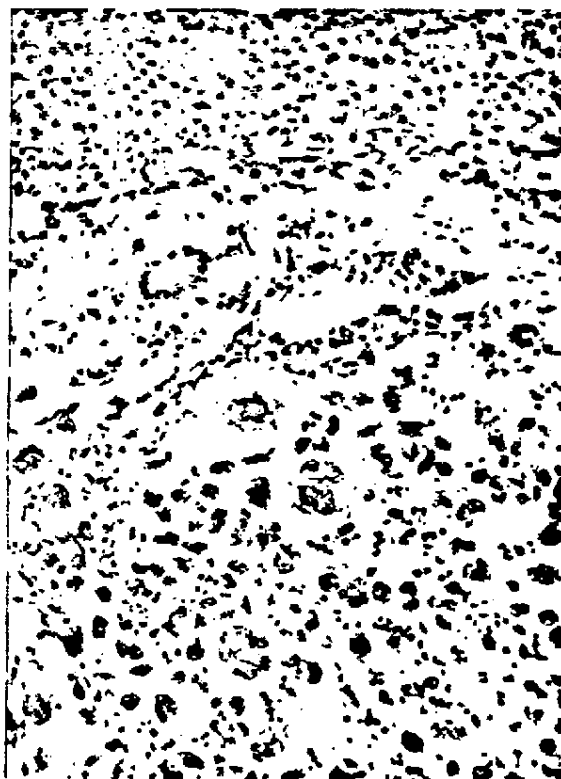
Animal Treatment (Group)	(a)
Total	57
VC 1000 ppm	46
VC 400 ppm	25
VC 200 ppm	17
VC 100 ppm	14
VC 50 ppm	34
VC 25 ppm	27
VC 12.5 ppm	27
VC 6.25 ppm	27
VC 3.125 ppm	27
VC 1.5625 ppm	27
VC 0.78125 ppm	27
VC 0.390625 ppm	27
VC 0.1953125 ppm	27
VC 0.09765625 ppm	27
VC 0.048828125 ppm	27
VC 0.0244140625 ppm	27
VC 0.01220703125 ppm	27
VC 0.006103515625 ppm	27
VC 0.0030517578125 ppm	27
VC 0.00152587890625 ppm	27
VC 0.000762939453125 ppm	27
VC 0.0003814697265625 ppm	27
VC 0.00019073486328125 ppm	27
VC 0.000095367431640625 ppm	27
VC 0.0000476837158203125 ppm	27
VC 0.00002384185791015625 ppm	27
VC 0.000011920928955078125 ppm	27
VC 0.0000059604644775390625 ppm	27
VC 0.00000298023223876953125 ppm	27
VC 0.000001490116119384765625 ppm	27
VC 0.0000007450580596923828125 ppm	27
VC 0.00000037252902984619140625 ppm	27
VC 0.000000186264514923095703125 ppm	27
VC 0.0000000931322574615478515625 ppm	27
VC 0.00000004656612873077392578125 ppm	27
VC 0.000000023283064365386962890625 ppm	27
VC 0.0000000116415321826934814453125 ppm	27
VC 0.00000000582076609134674072265625 ppm	27
VC 0.000000002910383045673370361328125 ppm	27
VC 0.0000000014551915228366851806640625 ppm	27
VC 0.00000000072759576141834259033203125 ppm	27
VC 0.000000000363797880709171295166015625 ppm	27
VC 0.0000000001818989403545856475830078125 ppm	27
VC 0.00000000009094947017729282379150390625 ppm	27
VC 0.000000000045474735088646411895751953125 ppm	27
VC 0.0000000000227373675443232059478759765625 ppm	27
VC 0.00000000001136868377216160297393798828125 ppm	27
VC 0.000000000005684341886080301486968994140625 ppm	27
VC 0.000000000002842170943040150743484497072265625 ppm	27
VC 0.00000000000142108547152007537174224985390625 ppm	27
VC 0.0000000000007105427357600376858711244298828125 ppm	27
VC 0.000000000000355271367880018842935562214546875 ppm	27
VC 0.0000000000001776356839400094214677811072729375 ppm	27
VC 0.00000000000008881784197000471073389055363646875 ppm	27
VC 0.000000000000044408920985002355366945276818234375 ppm	27
VC 0.0000000000000222044604925011776834726384091171875 ppm	27
VC 0.00000000000001110223024625058884173631920455884375 ppm	27
VC 0.00000000000000555111512312529442086815960227919375 ppm	27
VC 0.000000000000002775557561562514721043440798011395875 ppm	27
VC 0.0000000000000013877787807812573605217203990056979375 ppm	27
VC 0.00000000000000069388939039062536826086019950284896875 ppm	27
VC 0.000000000000000346944695195312518413043009975142484375 ppm	27
VC 0.0000000000000001734723475976562509206520498755712121875 ppm	27
VC 0.00000000000000008673617379882812504603260249377856109375 ppm	27
VC 0.000000000000000043368086899414073016301249689439280546875 ppm	27
VC 0.0000000000000000216840434497072365081506248447196402734375 ppm	27
VC 0.0000000000000000108420217248536172540753124223598201171875 ppm	27
VC 0.00000000000000000542101086242680862703765621117991005884375 ppm	27
VC 0.00000000000000000271050543121340431351878105589950294421875 ppm	27
VC 0.00000000000000000135525271560670216593939052794975122109375 ppm	27
VC 0.0000000000000000006776263578033510829696952639748756110546875 ppm	27
VC 0.0000000000000000003388131789016755414848476319874378055734375 ppm	

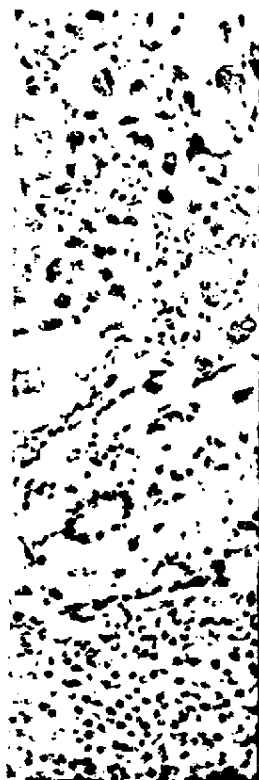
Table 1. Experiment 3B

Nephroblastomas (in rats) are often bilateral. Their histological picture reminds us of an embryonal kidney. Hyperplasia of nephroblastem-like tissue is often observed in the kidney of treated rats, with or without nephroblastomatous angiosarcomas and angiosmas (in rats, mice, hamsters) they are often polyanteric. Hepatic (Figure 1) and extrahepatic angiosarcomas are more or less differentiated. Blood vessel ectasias, endothelial hyperplasia, associated or not associated with collagen dysplasia, are treated animals, with or without local or distant angiosarcomas or angiosmas. Therefore, the effect of VC on blood vessels and endothelia should be considered systematic.

The current results up to September 10 of several experiments are shown in Tables 1-6. Among 60 Sprague-Dawley rats exposed by inhalation to 50 000 ppm of VC for 52 weeks (BT5) in the same way as the animals of experiment BT1, within 51 weeks from the beginning of the experiment Zymba gland carcinomas have been found in 30

Figure 1. Liver angiosarcoma in a rat treated with VC. H-E, X 125.





exposed to VC, M-E, X 125.

13 animals. For the latter table. Different types of animal may be bilateral. Histology to a certain extent, the ad, but often they present ic and polymorphous pat-

in bilateral. Their histological kidney. Hyperplasia observed in the kidney of dastoma. rats, mice, hamsters) may same animal. In the liver Figure 1) and extrahepatic regulated. hyperplasia, associated or are often observed in the in treated animals, with or as or angiomata. Therefore, and endothelia should be

Table 1. Experiment BT1: Results after 135 weeks (end of the experiment)

Treatment (a)	Animals (Sprague-Dawley rats)		Zymbal gland carcinomas (c)		Nephroblastomas (d)		Animals with tumors										Total (h)	
	Total	Corrected number (b)	No.	1/2 (d)	Average latency time (weeks)	No.	1/2 (d)	Average latency time (weeks)	Angiosarcomas		Subcutaneous angiosarcomas	Sialocarcinomas	Hepatomas	Brain neuroblastomas	Other type and/or sites (g)			
									Liver (f)	Other sites						No.		No.
VC 10000 ppm	69	61	18	26	50	5	4	36	9	15	64	3 (i)	4	3	1	7	7 (o)	38
VC 6000 ppm	72	60	7	12	51	4	7	85	13	22	70	3 (j)	3	1	1	3	8 (p)	31
VC 2500 ppm	74	59	2	3	53	6	10	74	13	22	76	3 (k)	3	1	2	9	4 (q)	32
VC 500 ppm	67	56	4	7	78	4	7	83	7	12	81	2 (l)	1	1	3	—	4 (r)	22
VC 250 ppm	67	59	—	—	—	6	10	60	4	7	78	2 (m)	—	4	—	—	3 (s)	16
VC 50 ppm	64	59	—	—	—	1	2	135	1	2	135	1 (n)	1	1	—	—	9 (t)	10
No treatment	64	58	—	—	—	—	—	—	—	—	—	—	—	—	—	—	10 (u)	6
Total	577	464	28	—	—	26	—	—	47	—	—	14	12	11	7	15	45	155

- (a) The animals were treated by inhalation for 4 hours daily, 5 days weekly, for 62 weeks.
 (b) Animals alive after 26 weeks, when the first tumor (a Zymbal gland carcinoma) was observed. The percentages are referred to the corrected number.
 (c) Metastases to lung.
 (d) Percentage of corrected number.
 (e) Metastases to liver, lung, spleen and brain.
 (f) Metastases to lung.
 (g) Several cases of breast fibroadenomas, adrenal and pituitary tumors (generally adenomas) have not been considered, since their distribution in the different groups does not vary.
 (h) Several animals with 2 or more tumors.
 (i) 1 angiosarcoma of the lips; 1 angiosarcoma of the nose; 1 intra-abdominal angiosarcoma (next to liver).
 (j) 1 angiosarcoma in subcutaneous fibrosarcoma; 1 ossifying paravisceral angiosarcoma; 1 intra-abdominal angiosarcoma (next to liver).
 (k) 2 intra-abdominal angiosarcomas (1 next to spleen and 1 next to ovary); 1 ossifying angiosarcoma of the neck.
 (l) 1 pulmonary angiosarcoma; 1 angiosarcoma of the uterus.
 (m) 1 intra-abdominal angiosarcoma (next to spleen); 1 intrathoracic ossifying angiosarcoma.
 (n) 1 intra-abdominal diffuse angiosarcoma.
 (o) 2 Zymbal gland adenomas; 3 mammary carcinomas; 1 neurilemmoma; 1 ovarian cystadenocarcinoma.
 (p) 4 Zymbal gland adenomas; 1 salivary gland adenocarcinoma; 2 hepatic and 1 peritoneal angiomata.
 (q) 1 Zymbal gland adenoma; 1 mammary carcinoma; 2 endometriomas.
 (r) 1 mammary carcinoma; 2 lymphomas; 1 pulmonary fibrosarcoma.
 (s) 1 Zymbal gland adenoma; 1 mammary carcinoma; 1 lymphoma.
 (t) 3 Zymbal gland adenomas; 2 mammary carcinomas; 1 subcutaneous angiosarcoma; 3 uterine adenocarcinomas (1 with sarcomatous component).
 (u) 1 invasive squamous carcinoma of Zymbal gland; 1 subcutaneous fibrosarcoma; 2 peritoneal fibrosarcomas; 2 uterine adenocarcinomas (1 with sarcomatous component); 1 uterine leiomyosarcoma; 1 ovarian fibrosarcoma; 1 pulmonary rhabdomyosarcoma; 1 lymphoma.

Table 2. Experiment BT6: Results after 86 weeks

Treatment (a)	Number of animals (Sprague-Dawley rats)		Number of animals with tumors (b)							Total (d)
	Total	Survivors	Zymbal gland carcinomas	Nephroblastomas	Angiosarcomas		Brain neuroblastomas	Other type and/or site (c)		
					Liver	Other sites				
VC 10000 ppm	80	6	4 (10)	— (0)	— (0)	1 (0) (3)	6 (7)	3 (2) (13)	16 (40)	
VC 6000 ppm	80	16	4 (5)	— (0)	— (1)	— (3)	2 (3)	7 (13) (9)	10 (27)	
VC 2500 ppm	80	37	1 (2)	2 (4)	— (0)	— (3)	2 (2)	— (7)	5 (23)	
VC 500 ppm	80	37	— (0)	— (0)	— (3)	— (2)	—	2 (1) (7)	2 (13)	
VC 250 ppm	80	18	—	1 (4)	— (2)	— (1)	—	2 (1) (5)	3 (8)	
VC 50 ppm	80	18	—	—	—	1 (5)	—	— (3)	1 (5)	
No treatment	180	128	—	—	—	—	—	3 (K) (3)	3 (8)	
Total	590	256	11 (27)	3 (10)	— (34)	2 (12)	10 (12)	17 (46)	38 (117)	

- (a) The animals were treated by inhalation 4 hours daily, 5 hours weekly, for 17 weeks.
 (b) Between brackets are recorded the tumors found in experiment BT1 after 86 weeks.
 (c) Several cases of breast fibroadenomas, adrenal and pituitary tumors (generally adenomas) have not been considered, since their distribution in the different groups does not vary.
 (d) Several animals with 1 or more tumors.
 (e) 1 subcutaneous angiosarcoma.
 (f) 1 orbital angiosarcoma.
 (g) 1 paravisceral fibrosarcoma; 1 nasal papilloma; 1 renal adenoma.
 (h) 2 Zymbal gland fibrosarcomas; 2 skin carcinomas; 1 subcutaneous angiosarcoma; 1 mammary carcinoma; 1 forestomach papilloma; 1 cranial osteoma.
 (i) 2 lymphomas.
 (j) 1 Zymbal gland adenoma; 1 retrobulbar fibroma.
 (k) 1 Zymbal gland adenoma; 2 lymphomas.

Table 2. Experiment BT7: Results after 81 weeks

Treatment (a)	Number of animals (Wistar rats)		Number of animals with tumors (b)								Total
	Total	Survivors	Zymbal gland carcinomas	Nephroblastomas	Angiosarcomas		Brain neuroblastomas	Other type and/or site			
					Liver	Other sites					
VC 10000 ppm	30	6	— (7)	1 (3)	2 (3)	— (1)	1 (2)	2 (c) (7)	6 (18)		
VC 6000 ppm	30	13	— (1)	— (1)	— (2)	— (1)	— (1)	— (1)	— (5)		
VC 2500 ppm	30	6	— (1)	— (1)	— (1)	— (1)	— (1)	— (1)	— (5)		
VC 500 ppm	30	16	—	—	—	—	—	—	— (1)		
VC 250 ppm	30	16	—	—	—	—	—	—	— (1)		
VC 50 ppm	30	22	—	—	—	—	—	—	—		
No treatment	40	34	—	—	—	—	—	—	—		
Total	220	117	— (10)	1 (9)	3 (6)	— (4)	1 (3)	3 (9)	7 (30)		

- (a) The animals were treated by inhalation for 4 hours daily, 6 days weekly, for 32 weeks.
 (b) Between brackets are recorded the tumors found in male Sprague-Dawley rats of the experiment BT1, after 71 weeks.
 (c) 2 Zymbal gland adenomas.
 (d) 1 angiosarcoma of the caecum.

Treatment (a)	Number of animals (Sprague-Dawley rats)		Number of animals with tumors					Total	
	Total	Survivors	Zymal gland adenomas	Nephro- blastomas	Angiosarcomas		Other type and/or site		
					Liver	Other sites			
VG 10000 ppm Breeders	30	8	—	—	—	—	—	—	
VG 1000 ppm Breeders	30	2	—	—	—	—	—	—	
VG 10000 ppm Offspring	54	31	1	—	—	1 (b)	—	3	
VG 1000 ppm Offspring	32	13	—	—	—	1 (c)	—	1	
Total	148	58	1	—	—	2	—	3	

Table 6. Experiment 3T4: Results after 21 weeks

Treatment (A)	Animals (Swiss mice)										Animals with tumors										
	Total		Corrected number (B)				Survivors				Pulmonary tumors (C)			Mammary carcinomas (D)			Liver angio-sarcomas	Vascular tumors of other type and/or site	Epithelial tumors of the skin	Other type and/or site	Total (E)
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	No.	%	Average latency time (weeks)	No.	%	Average latency time (weeks)	No.	No.	No.	No.	No.
VC 18000 ppm	30	30	40	23	26	40	—	—	—	—	36	70	36	13	47	31	8	8 (7)	3 (1)	2 (0)	26
VC 1800 ppm	30	30	40	26	24	34	—	—	—	—	36	70	38	8	26	5	6 (9)	4 (0)	4 (0)	4 (0)	38
VC 2100 ppm	30	30	40	23	30	43	—	—	—	—	30	67	43	9	30	30	11	12 (3)	3 (0)	1 (0)	31
VC 1500 ppm	30	30	40	26	26	44	—	—	—	—	30	66	41	7	24	37	11	16 (1)	1 (0)	1 (0)	35
VC 150 ppm	30	30	40	28	29	54	3	3	1	4	51	43	43	11	32	39	14 (1)	—	—	—	36
VC 150 ppm	30	30	40	27	30	57	1	8	10	1	3	64	10	—	—	37	1	17 (5)	—	—	18
No treatment	30	70	150	74	87	141	24	34	64	4	3	53	—	—	—	—	—	—	—	1 (0)	6
Total	240	240	320	200	241	431	26	44	74	172	—	—	—	48	—	—	27	23	19	14	207

(a) The animals were treated by inhalation for 4 hours daily, 5 days weekly, for 3 weeks.	(j) 8 liver angiosarcomas; 6 liver fibrosarcomas; 2 intra-abdominal angiosarcomas; 1 pulmonary angiosarcoma; 1 scrotal angiosarcoma.
(b) Animals alive after 16 weeks, when the first tumor (a mammary carcinogen) was observed. The percentages are related to the corrected number.	(k) 2 liver angiosarcomas; 2 liver fibrosarcomas; 1 subcutaneous angiosarcoma; 2 subcutaneous angiosarcomas; 1 subcutaneous fibrosarcoma; 1 intra-abdominal angiosarcoma; 1 intrathoracic fibrosarcoma; 1 angiosarcoma of the inter-scapular fat pad.
(c) A total of some of which undergoing malignant transformation.	(l) 2 squamous carcinomas; 1 invasive sarcoma.
(d) Several cases with 2 or more tumors.	(m) 1 squamous carcinoma; 2 sarcomas.
(e) 1 liver fibrosarcoma; 3 subcutaneous angiosarcomas; 1 heart fibrosarcoma;	(n) 1 squamous carcinoma; 2 sarcomas.
(f) 1 testicular fibrosarcoma; 1 sarcoma.	(o) 1 sarcoma.
(g) 4 liver angiosarcomas; 2 liver fibrosarcomas; 1 subcutaneous angiosarcoma;	(p) 2 zymal gland adenomas; 1 forestomach papilloma.
(h) 1 renal fibrosarcoma; 1 thymic angiosarcoma.	(q) 1 lymphoma; 1 parotid gland adenoma; 1 forestomach papilloma;
(i) 1 liver angiosarcoma; 1 subcutaneous angiosarcoma; 1 subcutaneous pulmonary angiosarcoma; 1 subcutaneous angiosarcoma; 1 subcutaneous angiosarcoma; 1 intra-abdominal angiosarcoma; 2 renal angiosarcomas; 1 pulmonary angiosarcoma.	(r) 1 forestomach papilloma; 1 parotid gland mixed tumor.
(j) 1 liver angiosarcoma; 3 liver fibrosarcomas; 2 subcutaneous angiosarcomas;	(s) 2 zymal gland adenomas.
(k) 1 subcutaneous angiosarcoma; 1 subcutaneous fibrosarcoma; 1 intra-abdominal fibrosarcoma; 3 intra-abdominal angiosarcomas; 1 angiosarcoma of the oesophagus; 1 renal angiosarcoma; 1 pulmonary fibrosarcoma; 1 testicular fibrosarcoma.	(t) 1 zymal gland adenoma; 1 lymphoma; 1 Leydig cell tumor.
	(u) 1 parotid gland adenocarcinoma.
	(v) 1 lymphoma.

Table 6. Experiment 2B: Results after 48 weeks

Treatment (a)	Number of animals (Golden hamsters)		Number of animals with tumors					Total (c)
	Total	Survivors	Liver angiosarcomas	Skin trichosporiomas (b)	Melanomas	Lymphomas	Foraneurine papillomas and acanthomas	Other type and/or site
VC 10000 ppm	33	9	—	3	—	—	—	3
VC 1000 ppm	32	8	—	2	1	1	—	4
VC 2500 ppm	33	11	—	1	—	—	4	4
VC 500 ppm	33	13	1	1	—	1	1	4
VC 150 ppm	32	6	—	1	—	—	—	2
VC 50 ppm	33	11	—	3	1	1	—	5
No treatment	70	30	—	2	—	—	—	2
Total	264	86	1	13	2	2	5	16

(a) The animals were treated by inhalation for 4 hours daily, 5 days weekly, for 30 weeks.
(b) Several cases with scanthosis and some undergoing malignant transformation.
(c) Several animals with 2 or more tumors.
(d) 1 hepatocarcinoma.
(e) 1 subcutaneous angioma.

Table 7. Tumors presently correlated to VC exposure (by inhalation) on experimental rodents and man.

Species	TUMORS										
	Angiosarcoma of liver	Tumors of brain	Tumors of lung	Lymphomas and leukemias	Angiosarcomas and angiosarcomas of other sites	Nephroblastomas	Sebaceous carcinomas	Squamous tumors of epidermis	Mammary carcinomas	Hepatomas	Forestomach epitheliomas and carcinomas
Rat	+	+			+	+	+	+	(+)	+	
Mouse	+		+		+						
Hamster	+			+	(+)				+		
Man	+	(+)	(+)	(+)							+

Angioblastic proliferation of the liver and in other fibroplasia. From the local changes in the appears to be as follows: atypias of endothelial glomas, angiosarcoma. Fibro-angioblastic frequently observed in Skin carcinomas arising from sebaceous glands. extent the morphological Hepatomas observed differentiated. Metastases Brain neuroblastoma medulloblastoma.

Lung adenomas (L number is higher in a of these tumors appear

Mammary carcinoma
They are usually well circumscribed, monomorphous or polimorphous. A distinct feature of these present areas of squamous metaplasia is the presence of large, hyperchromatic, pleomorphic nuclei, which are arranged in a disorganized manner. The cells are arranged in a disorganized manner, and the nuclei are large, hyperchromatic, and pleomorphic. The cells are arranged in a disorganized manner, and the nuclei are large, hyperchromatic, and pleomorphic.

Several of the tumors were exceptional. To our knowledge, the blastomas and neuroblastomas, which spontaneously occur in sarcomas have been in experimental rodents (rats, Maltoni and Lefemine, 1967) in time in which nephroblastomas have been experimentally reproduced.

SUMMARY OF FINDINGS

1. Under our experimental conditions, the three animals

2. The range of incidence of species to species. With rats, Zymbal gland carcinomas and angiosarcomas, hepatomas and adenomas, mammary sarcomas and angioendothelial tumors; in hamsters, evidence seems to suggest forestomach papillomas and angiosarcomas.

3. In the BT1 and E
ogenic effect at 50 ppm

4. From the BTI exposure dose-response relationships, comas and nephroblastomas ranges: i.e. from 500 ppm from 250 ppm to 50 ppm

5. A comparison of moment in rats exposed BT3 experiments) show particularly as far as an

6. The comparison of different strains, *ie* Spi at the present moment, considerably affects the

7. The onset of two thyroid gland carcinomas during pregnancy for a central effect of VC.

Our data have been for companies which have been able to attract all interested parties.

Before the end of 1970 VC was inducing in rats nephroblastomas and it also made known to the tion (MCA). This infor

312 0000.
312 100000.

2 intra-abdominal angiosarcoma;
subcutaneous angiosarcoma;
fibroangioma; 1 intra-abdo-
ma; 1 angioma of the inter-

piloma.
 no; 1 forestomach papilloma;
 and tumor.
 with nail tumor.

Other type and/or site	Total (e)
—	3
1 (d)	6
—	4
1 (e)	4
—	2
—	3
—	3
3	23

ry Hepa- Forstomach
rues tomas papillomas and
carcinomas

Several of the tumors produced by VC are quite rare or exceptional. To our knowledge liver angiosarcomas, nephroblastomas and neuroblastomas have never been described as spontaneously occurring in rats. Liver and extrahepatic angiosarcomas have been induced only in a few instances in experimental rodents (rats, hamsters and mice) [for references see Maltoni and Lefemine (1)]. As far as we know, this is the first time in which nephroblastomas and neuroblastomas have been experimentally reproduced.

Before the end of 1972, a short time after it was known that VC was inducing in rats not only Zymbal gland tumors, but also nephroblastomas and liver angiosarcomas, these results were also made known to the US Manufacturing Chemists Association (MCA). This information promoted the clinical observa-

It is our hope that the story of VC carcinogenicity may serve as a convincing example to urgently promote experimental bioassays for all new industrial compounds, and for those compounds which are already produced and widespread, but whose effect we still ignore.

1. C. Nakoni, G. Lafemine, *Environmental Research*, **7**, 327 (1974).

Professor Doctor Cesare Maltoni, MD, Professor of General Pathology and of Experimental Oncology, has been Director of the Bologna Center for Prevention and Detection of Tumors and Oncological Research since the Celsi's foundation. He has been Director of Istituto di Oncologia in Bologna since 1964. He is present President of the Italian Society for Prevention and Diagnosis of Tumors, Vice-President of the Italian Society for Therapy of Tumors, and member of the Executive Board of the International Study Group for Cancer Prevention and Detection (De P. Ca), and is past-president of the European Coordinating Committee on Human Tumors Investigation (1971-1973). Among his many professional activities, he is Editor of a new series entitled *Advances in Tumor Prevention, Detection and Characterization* published by *Excerpta Medica*, and is co-editor of *Acta Oncologica* (Italian Journal of oncology). The results of his research and scientific activities have been reported in 132 publications. His address: Istituto di Oncologia "Felice Adorni", Ospedale di Bologna, Enia Ospedaliere Regionale, Viale Ercolani 4/2, 40138 Bologna, Italy.

Recent Perspectives in Occupational Cancer

BY IRVING J SELIKOFF

In recent years, many previously unsuspected carcinogenic agents have been identified and new perspectives established for the evaluation of the increasing numbers of chemical substances introduced into the environment.

Attention is sometimes called to the fact that the first neoplasms for which etiological factors could be established, were occupational cancers. The report 200 years ago by Percivall Pott of cancer of the scrotum in individuals who had been employed as chimney sweeps (1), or that of chemical carcinogenesis in humans first described 80 years ago as "aniline cancer" (2), or that radiation-induced cancer had an occupational starting point among miners in Schneeberg and Joachimsthal almost 90 years ago (3), are cited. These claims are true, yet it is equally true that each was an isolated descriptive observation, of muffled impact in its time.

Accelerated development of a connecting mature body of knowledge, the discipline of occupational cancer, has rather been a matter of the past two decades. Although it was related to what went before by the continuing productive studies of the effects of carcinogenic aromatic amines (2), if one event can be said to be the origin of this new phase, it may be the brilliant description in 1955 by Richard Doll of the association between occupational exposure to asbestos and an important risk of death of lung cancer (4). Doll's demonstration of the applicability of chronic disease epidemiology provided an important example for future research. Many of the concepts we now take for granted in the evaluation of occupational carcinogenicity, as, the need for long periods of observation (5), the utility of cohort studies (6), the possibility of co-existence of cancer and other biological toxicity (7), were inherent in his classic report. Similar approaches have guided the best of experimental studies and have increased their relevance to human disease (8).

With this background, a good deal has been learned about occupational cancer in recent years. This has included identification of carcinogenic agents previously unsuspected of such effects and the establishment of a number of perspectives which are now available for the evaluation of other materials used in industry and/or agriculture or which may be introduced in the future (9). The latter achievement is perhaps more important, since the number and complexity of new or recently introduced agents has attracted much attention, and little is known concerning their carcinogenic potential.

LATENT PERIOD

The above term is perhaps inexact since we do not actually know what is happening in tissues between the time of first exposure and initial evidence of clinical disease. Changes may be under way, albeit not detectable with current techniques. Perhaps "period of clinical latency" or "lapsed period" would be more exact (10). In any case, each of these terms describes an important phenomenon—that a considerable time must usually elapse between onset of exposure to an occupational carcinogen and the first evidence of resulting cancer. Generally, this period is 20–35 years, although as little as 10–15 years may suffice, or 35–50 or more years will pass. The time sequence can be affected by a number of variables touched on below, but it is remarkable how their influences operate within relatively narrow constraints.

Understanding this, two conclusions become evident. First, it would have been difficult or impossible to establish the carcinogenicity of substances widely introduced only in the

past 30–50 years, and not be able, with prehumans of recently three decades (11), from other disciplines must elapse before designed to correct is effective. This has been smelter workers (12).

The importance of has nowhere been associated with occupational Laboratory, we have sulation workers, e Union of such work January 1, 1967 (5). had died, almost 46 were 275 deaths of anticipated. Analysis cated that the excc workers who had ac their work (Tables 1).

The risk of lung asbestos could easily drawn, if studies ar serve a sufficient nu from onset of work tained in studies of l refineries (14) and v cancers are seen af β -chloromethylether intense exposure or f

MULTIPLE FACTOR

Investigations of oc generally seek to iso able. Nevertheless, t carcinogenic agents complex work envi substances of unstu personal and social possibility of interac known in the expe shown for occupatio found among asbest. risk was not signific not also have a hist. had much more lung Asbestos exposure t risk of cigarette an asbestos worker whc of death of lung ca same age who neith The powerful multi; agents can be appr asbestos insulation v established, the smol was recorded; 9590 h a history of pipe anc ing, and 1437 had experience, with p detailed in Table 3. one lung cancer was cember 31, 1972. Th only one lung cance 179 lung cancer deat smoking, although o This, despite the fac: same trade, with eq to asbestos.

The significance r action has many ram First, some substanc genic effect: in com Such influence may l there could also be a substances now deen new circumstances; c there may be many

past 30–50 years, until the last decade or so. Second, we will not be able, with present knowledge, to identify cancer risk in humans of recently introduced agents for another two or even three decades (11), and epidemiology must look to assistance from other disciplines. Parenthetically, a similarly long period must elapse before it can be ascertained whether measures designed to correct an occupational cancer hazard are actually effective. This has been the case, for example, among nickel smelter workers (12).

The importance of the principle of clinical latency has perhaps nowhere been better demonstrated than with lung cancer associated with occupational exposure to asbestos. In our Laboratory, we have been following a cohort of asbestos insulation workers, composed of all 17 800 members of the Union of such workers in the United States and Canada on January 1, 1967 (5). By December 31, 1972, 1356 of these men had died, almost 400 more than had been expected. There were 275 deaths of lung cancer, whereas only 56 had been anticipated. Analysis of the work history of these men indicated that the excess deaths were largely limited to those workers who had achieved more than 20 years from onset of their work (Tables 1 and 2).

The risk of lung cancer with occupational exposure to asbestos could easily be missed, and inaccurate conclusions drawn, if studies are made without the opportunity to observe a sufficient number of individuals 20–30 or more years from onset of work exposure. Similar results have been obtained in studies of uranium miners (13) and workers in nickel refineries (14) and with other agents; indeed, when many lung cancers are seen after significantly shorter periods, as with β -chloromethylether (15), one might justifiably suspect rather intense exposure or particularly virulent agents.

MULTIPLE FACTOR ETIOLOGY

Investigations of occupational exposures for carcinogenicity generally seek to isolate the suspect materials. This is reasonable. Nevertheless, this approach is in a sense artificial, since carcinogenic agents are infrequently used singly, but rather in complex work environments, often with a variety of other substances of unstudied potential, and by individuals whose personal and social environments are equally varied. The possibility of interaction of two or more agents has long been known in the experimental setting; since 1968 it has been shown for occupational cancer in humans as well (16). It was found among asbestos workers, for example, that lung cancer risk was not significantly increased among those men who did not also have a history of cigarette smoking. Those who did, had much more lung cancer than cigarette smokers in general. Asbestos exposure thus markedly increased the lung cancer risk of cigarette smoking; it has been calculated that an asbestos worker who smokes cigarettes has 92 times the risk of death of lung cancer compared with an individual of the same age who neither smokes nor works with asbestos (16). The powerful multiplying effect of the combination of two agents can be appreciated by examining the experience of asbestos insulation workers cited above. When the cohort was established, the smoking habits of the majority of the workers was recorded: 9590 had a history of cigarette smoking, 609 had a history of pipe and/or cigar smoking but no cigarette smoking, and 1457 had never smoked at all. Their mortality experience, with particular reference to lung cancer, is detailed in Table 3. Among those who never smoked, only one lung cancer was seen from January 1, 1967 through December 31, 1972. The pipe and cigar smoking group also had only one lung cancer death. On the other hand, there were 179 lung cancer deaths among those with a history of cigarette smoking, although only 32 such deaths were expected to occur. This, despite the fact that all of these men had worked in the same trade, with equal opportunity for occupational exposure to asbestos.

The significance of the principle of multiple factor interaction has many ramifications. Two are of immediate interest. First, some substances, by themselves, may have no carcinogenic effect; in concert with others, malignancy may occur. Such influence may be additive or multiplicative (theoretically, there could also be a protective effect, as well). As a corollary, substances now deemed innocuous may change their habit in new circumstances; our vigilance must be constant. Too, since there may be many more substances of limited carcinogenic

potential than those individually capable of inducing malignancy, and since at least some working environments now tend to become more complex, this may turn out to be of considerable practical importance in the future.

Second, animal studies generally are directed to the investigation of one agent; negative results may therefore be misleading insofar as actual work risk is concerned. (To compensate, one should hasten to add, dosages can be far greater than those which occur in industry, and carcinogenicity enhanced).

SIGNAL CANCERS

Most occupational cancers are identified as occurring as increased numbers of common malignancies. Thus, increased rates (taking age, year and sex into account) of lung cancer occur, for example, with occupational exposure to talc, chromates, arsenic, nickel carbonyl, uranium mining, fluor spar mining, hematite, β -chloromethylether and asbestos; of blad-

Table 1. Expected and observed deaths among 17 800 asbestos insulation workers in the United States and Canada January 1, 1967–December 31, 1972.

	Duration from onset of exposure			
	Less than 20 years		More than 20 years	
	Expected*	Observed	Expected*	Observed
Total deaths—all causes	203.80	248	758.12	1108
Cancer all sites	30.42	64	146.15	211
Lung cancer	8.40	26	47.47	247
Asbestosis	—	7	—	84
All other causes	173.49	178	610.66	904
Number of persons	12 001		5119	

* Expected rates are based upon age-specific white male death rate data of the US National Office of Vital Statistics. Rates for 1972 were extrapolated from rates from 1967–1971.

** US rates are not available, but these are rare causes of death in the general population.

Table 2. Deaths from lung cancer among 17 800 asbestos insulation workers in the US and Canada, January 1, 1967–December 31, 1972; relation to elapsed period from onset of work exposure.

Years from onset	Lung cancer		
	Expected deaths*	Observed deaths	Ratio
<10	0.58	0	—
10–14	1.97	5	2.6
15–19	3.87	23	5.9
20–24	8.95	34	3.8
25–29	10.70	56	5.2
30–34	8.20	60	7.3
35–39	6.88	29	4.2
40–44	4.84	27	5.6
45–49	4.51	18	4.0
50+	4.97	22	4.4
Total	58.87	278	4.8

* Expected deaths are based upon age-specific white male death rate data of the US National Office of Vital Statistics. Rates for 1972 were extrapolated from data from 1967–1971.

Table 3. Expected and observed deaths of lung cancer among 17 800 US and Canada asbestos insulation workers, January 1, 1967–December 31, 1972; relation to cigarette smoking.

	No. of persons	Deaths from lung cancer		
		Expected*	Observed	Ratio
Smoking habits not known	6164	16.78	84	5.0
History of cigarette smoking	9590	31.80	179	5.7
No history of cigarette smoking	2098	7.51	2	0.3
Never smoked	1457	4.40	1	0.2
History of pipe and/or cigar only	609	3.11	1	0.3

* Expected deaths based upon age-specific US mortality rates for white males disregarding smoking. Lung cancer estimates based upon US rates for cancer of lung, pleura, bronchus and trachea, categories 162 and 163 of the International Classification of Diseases and Causes of Death, 7th Revision.

it has been learned about This has included identifi- cally unsuspected of such number of perspectives luation of other materials or which may be intro- silevement is perhaps more complexity of new or re- ted much attention, and inogenic potential.

since we do not actually between the time of first ical disease. Changes may with current techniques, or "lapsed period" would h of these terms describes considerable time must suture to an occupational resulting cancer. General- ough as little as 10–15 : years will pass. The time er of variables touched on r influences operate with-

ms become evident. First, possible to establish the y introduced only in the

der cancer with β -naphthylamine and benzidine; of leukemia with benzene and radiation. To find the effect of such substances, appropriate population studies are necessary to see if the expected background rates are increased. Sometimes, especially if less common tumors are being considered, as brain or adrenal or kidney or lymphoma, extensive observations are necessary, if not of moderate sized groups over long periods of time (after the 20 year point), then of very large groups for shorter periods (to achieve an adequate number of "person-years" of observation).

In a number of instances, unusual tumors have been observed in considerable numbers for which the usual expected ratios are almost superfluous. When cancer of the scrotum occurred among Pott's chimney sweeps the absence of biostatistical calculations did not prevent recognition of the unusual situation. Sinus tumors among woodworkers may be looked at in somewhat the same light (17).

Two neoplasms, infrequent in general but common with industrial exposure, have demonstrated that such "signal" tumors can be important factors in identifying occupational carcinogenesis. One, hemangiosarcoma of the liver, has assumed such a role recently and will be discussed below. The second, mesothelioma, has a longer history. First reported in the pleural cavity of an asbestos worker in 1953 (18) and in the peritoneum of another the next year (19), its link to asbestos was firmly established in 1960 (20) when, in a series of 47 cases in one laboratory in South Africa, over a five year period, 45 were shown to have had opportunity for asbestos exposure of one or another type, decades before. The impact of this finding can be gauged by appreciation that, in general, approximately one in a thousand deaths in the general population had been known to be caused by these previously uncommon tumors. With occupational asbestos exposure, these tumors have proven common (21). In some cohorts of asbestos workers, approximately five or six percent of deaths have been due to pleural and peritoneal mesothelioma (5). In others, the percentage is lower; it has been reported, for example, that this neoplasm is less frequent among Quebec chrysotile asbestos miners (22). When found in family contacts, it led to the understanding of the danger of bringing dust from the factory to the home (23), when found amid residents in the neighborhoods about asbestos plants, it bespoke uncontrolled asbestos air pollution in the past. In South Africa's large series of cases, with adequate history, only approximately fifteen percent have been judged not to have had some known asbestos contact (24). Thus, wherever mesothelioma is found, asbestos is sought. In this way, otherwise unsuspected occupational exposures to asbestos have been identified—in shipyards, especially (25).

ENVIRONMENTAL CANCERS FROM OCCUPATIONAL SOURCES

An important dimension was added to occupational cancer with the discovery that neoplasms might occur with the dissemination of the agent beyond the factory gate, either by its release during the manufacturing process or from resulting waste, or by contamination of households with the offending material being brought home on workers' clothes. Although instances of such disease had been known before (20), the full import of the problem was not appreciated until Newhouse's report in 1965 (23) when she demonstrated that, of 76 confirmed cases of mesothelioma in the files of the London Hospital, of the 45 not known to have had occupational exposure to asbestos, nine had simply lived in the households of asbestos workers ("conjugal disease") and 11 had neither worked with the material nor lived with someone who had been so employed, but had resided, many years before, within one half mile of an asbestos plant in London. This finding was soon confirmed (26), and the principle of carcinogenic risk derived from occupational sources is an important factor in current evaluation of control of environmental cancer, whether it be from radiation-producing power sources, agricultural use of pesticides, air and water pollution from petrochemical industry operations, carcinogenic mineral dust, or other substances or processes (11). These considerations are separate from those involving cancer risk with end-product use, either during further industrial manipulation of materials or in utilization of consumer products.

PETROCHEMICAL INDUSTRY CANCER

There was a curious discrepancy during the first half of this century between continued concern regarding the potential for occupational cancer in the burgeoning petrochemical industry and reliable evidence that this was occurring with any frequency. In considerable part, the contradiction remains. On the one hand, the industry deals with a very large number of chemicals which either have been shown to have carcinogenic potential in laboratory animals, or are related to these chemicals, belonging to such suspect groups as the polycyclic aromatic hydrocarbons or some of the halogenated hydrocarbons; in several instances, as benzo(a)pyrene or β -naphthylamine, occupational cancers in humans have been clearly established. On the other hand, the number of chemical agents so incriminated has remained comparatively small and the number of workers involved, limited.

With the recent identification of vinyl chloride induced cancer (27, 28), the situation has changed somewhat. It is still not known whether a good many of the petrochemical industry's materials will turn out to be carcinogenic—in large part, an adequate "latent period" has yet to run its course, to allow for proper evaluation. Still, to find that a key chemical in the giant plastic industry was clearly carcinogenic has been disconcerting. Further, it was sobering to realize that if vinyl chloride's carcinogenicity had been expressed in increased risk of cancer of lung or colon, elevated rates of neoplasms of these sites among the affected workers might not have been identified for some years, at the earliest. The fact that it was an unusual tumor, hemangiosarcoma of the liver, otherwise rare in the general population (perhaps one in 10,000—40,000 deaths), which occurred, attracted attention.

Three cases in one plant, the B F Goodrich Company in Louisville, Kentucky, were sufficient to establish a strong suspicion of the risk (29) and the suspicion became a virtual certainty when the same neoplasm was found in other vinyl-chloride polymerization plants, making vinyl chloride the likely offender, rather than other coexisting chemicals, as special additives or process chemicals, peculiar to the Louisville plant's operation. At the same time, the fact that only a dozen and a half cases came to notice in the first five months after discovery of the condition did little to allay concern, since these cases, when analyzed, had begun work, on the average, approximately 20 years before death, at a time when the vinyl chloride-polyvinyl chloride industry was limited in size and still employed relatively few workers. Of the 19 cases recorded by mid-June, 1974, 15 had begun work 1944—1952, with an overall average of 20.4 years from onset for the group as a whole. Since the great majority of workers in vinyl chloride-polyvinyl chloride plants were first employed during the 1950s and 1960s, it was evident that the full impact of vinyl chloride tumors would not be known for another two decades. Limited data so far available suggests that, at least for polyvinylchloride polymerization workers, the incidence of occupational cancer will be significant. We have examined the mortality experience of a cohort of workers employed at a large polyvinylchloride polymerization facility in the United States. The plant opened in 1946 and from that year to 1963, 257 individuals were employed in the production process for five years or more. While exposures began in 1946, relatively few individuals were employed prior to 1951, when a significant increase in the work force took place. Thus, the majority of the cohort has had a bare 20 years or less from onset of exposure.

An initial report of the experience of these men has been made (30). We have traced each of the 257 individuals to December 31, 1973. Twenty-five were found to have died, of all causes. Three of the deaths, each confirmed at autopsy, were due to hemangiosarcoma of the liver (Table 4). Ages at death were 41, 54, 60. Elapsed time from onset of first exposure to death was 14, 17, 23 years.

DOSE-DISEASE RESPONSE RELATIONSHIPS

Discussion of this thorny question, with social, ethical and economic implications co-mingled with scientific perspectives, was stimulated and made much more acute in the evaluation of regulatory measures necessary for the control of vinyl chloride cancer. While it has been generally agreed that the risk of malignancy increases with intensity and duration of exposure, there has been much less concordance in the evalu-

Table 4. Causes of death for 5 or more years.

Cancers of all sites
Hemangiosarcoma of liver
Neoplasms of lymphatic
Brain (Glioblastoma)
Pancreas
Colon
Bone
Cirrhosis (with esophagus)
Post-operative bleeding
Cardiovascular disease

ation of whether it would not occur. The this aspect of the question be that such data are meager, to be convincing numbers of animals large numbers of v longed periods of time the monomer. Even would always be only conceivably could show would seem to indicate threshold limit for regulations for the vinyl chloride in the United States from this point of view been proposed (32) might be considered allows for inevitable occur in the industry of practical problems of the work environment

PRETESTING OF NE

Recognition of the onset of exposure to and their carcinogenicity raised the corollary question of evaluation and short-term. Much attention is recently, however, to Although structural occasion a high level necessarily follow structural known. Further, while with biological activity with toxic effects on them, without concomitant

Experiences with suggests, however, that for at least some age were able to establish stance which was late 33). It is not known whether other labor studies, will extend to hoped for and much information on the question for selection of agents include such considerations other biological activity exposed. For substance could apply, with the studies should be suggested workers whose exposure

DER

ing the first half of this regarding the potential for g petrochemical industry occurring with any fre- in contradiction remains. On a very large number of own to have carcinogenic e related to these chemi- as the polycyclic aroma- genated hydrocarbons; in 3-naphthylamine, occupa- learily established. On the gents so incriminated has the number of workers

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e of these men has been of the 257 individuals to e found to have died, of h confirmed at autopsy, e liver (Table 4). Ages at from onset of first expo-

RELATIONSHIPS

with social, ethical and ith scientific perspectives, e acute in the evaluation for the control of vinyl generally agreed that the intensity and duration of concordance in the evalu-

Table 4. Causes of death among 26 workers exposed to vinyl chloride for 5 or more years.

Cancers of all sites	9
Hemangiosarcoma of liver	3
Neoplasms of lymphatic and hematopoietic tissues	2
Brain (Glioblastoma)	1
Pancreas	1
Colon	1
Bone	1
Cirrhosis (with esophageal varices)	1
Post-operative bleeding (Cholelithiasis)	1
Cardiovascular diseases, other	14

ation of whether a lower threshold existed below which cancer would not occur. There have been few data bearing directly on this aspect of the question and, in the nature of things, it might be that such data are unlikely to appear. "Negative" experiments, to be convincing, would have to involve very large numbers of animals and, more important, observation of very large numbers of vinyl chloride workers exposed for prolonged periods of time at measured low levels of exposure to the monomer. Even if these data should be obtained, they would always be only an approximation, since further study conceivably could show exceptions. Theoretical considerations would seem to indicate that there is no identifiable lower threshold limit for carcinogenic agents (31). The proposed regulations for the control of occupational exposure to vinyl chloride in the United States seem to approach the problem from this point of view; a level of one part per million has been proposed (32) which, interpreted in practical terms, might be considered a "no threshold" level but one which allows for inevitable mistakes and accidents which might occur in the industrial environment, as well as recognition of practical problems concerned with instrumental monitoring of the work environment.

PRETESTING OF NEW MATERIALS

Recognition of the long period of clinical latency between onset of exposure to materials in the occupational environment and their carcinogenic effect, if this is to occur, has recently raised the corollary question whether we might anticipate such evaluation and shorten, or eliminate, this period of uncertainty. Much attention is now being paid to this possibility. Until recently, however, expectation and desire exceeded promise. Although structural similarity to known carcinogens might occasion a high level of suspicion, cancer potential does not necessarily follow structural resemblance; many exceptions are known. Further, while suspicion could be directed to agents with biological activity other than cancer, many are known with toxic effects on kidney, liver, lung, central nervous system, without concomitant recognized cancer potential.

Experiences with vinyl chloride and β -chloromethylether suggests, however, that laboratory screening might be feasible, for at least some agents. In each instance, laboratory studies were able to establish the carcinogenicity of a chemical substance which was later shown to be carcinogenic in man (28, 33). It is not known whether such experimental screening approaches will be equally productive with other agents, nor whether other laboratory techniques, including mutagenic studies, will extend their utility (34). Certainly, this is to be hoped for and much work is being initiated to provide information on the question. Guidelines that would point priorities for selection of agents to be tested are also being discussed, and include such considerations as chemical structure, evidence of other biological activity, number of workers likely to be exposed. For substances already in use, similar considerations could apply, with the added dimension that epidemiological studies should be suggested when there are available groups of workers whose exposures began 10—15 or more years ago.

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Air Product and Chemicals

*vc m Shipping
fc*

From:

7 April 1975

Gerald J. Mantell

Route cc: M. H. Danzig

C. A. Heiberger

E. H. Hollister

W. W. Stawasz

Note page 2 re samples.

Route CC: ~~J. T. Chang~~

~~M. Langsam~~

~~G. H. Worman~~

~~R. E. Grandin~~

~~R. K. St. Clair~~ - see page 4

G. J. Mantell - last

AP00005708

cc JPB
mhd
GJM
RC
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fig

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APR 2 1975

J. M. D.

cc memo to Mx
on 77
PRC Study & apm.

Date 1 April 1975

INTEROFFICE
MEMORANDUM

To C. E. Bowman
W. F. Smith

From R. C. Danziger

Subject Labelling Requirements to Meet

OSHA Standards

Pace

Calvert City

(Location, Organization, or Department)

Valley Forge

(Location, Organization, or Department)

cc: A. R. Adams
J. T. Barr
W. W. Brand
S. F. Burke
T. L. Carey
J. M. Davidson
R. Fleming
R. E. Jones

J. D. Kramer
J. C. Novak
H. A. Quigley
J. T. Sebastiane
W. M. Smith
G. B. H. Speed
H. L. Watson

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AIR PRODUCTS & CHEMICALS INC.

APR 4 1975

R & D

Confirming my telephone conversation of 31 March 1975, the following is a breakdown of labelling and marking requirements necessary to comply with OSHA standards.

Hopper Cars

Should be stencilled on or in the vicinity of all hatches and all outlets in 3/8 inch lettering.

Bulk PVC Trucks

Should be tagged with tags already provided on or in the vicinity of all hatches and outlets.

Bags

All bags should be labelled or stamped on one side or on one end.

Gaylords or Bulk Boxes

Should be labelled or stamped on the side or sides which bear the product identification.

Box Cars, Vans and Containers

Outsides of these units should not be labelled, since bags or boxes inside are labelled and it is not necessary to label a secondary container.