

M I N U T E S
MEETING OF PVC/VCM PRODUCERS
THE SOCIETY OF THE PLASTICS INDUSTRY
AND
ASSOCIATION OF AMERICAN RAILROADS

Keller & Heckman Offices
Washington, D. C.

11 August 1976
1:30 p.m.

Present:

Conoco Chemicals: John F. Pinkman
Dow Chemical: Charles O. Hutchenreuther
Ethyl Corp.: Claude Catania
B. F. Goodrich Chemical: Thomas H. Smith
PPG Industries: Michael Petrucci
Shell Chemical: D. Frank McMillan
Stauffer Chemical: George A. Coffenberg
Union Carbide: M. M. Anderson

Association of American Railroads: R. M. Graziano; Mac McCullough

Martin W. Bercovici, Keller & Heckman
Juliette Lang Cahn, SPI

The meeting reconvened at 1:30 p.m. Mr. Coffenberg welcomed Messrs. Graziano and McCullough and invited Mr. Graziano to discuss his views regarding a requested response system.

Mr. Graziano stated that

- his objective was to obtain attention for a VCM incident as soon as possible;
- he wants to rely on someone located close to the incident;

SPI-08284

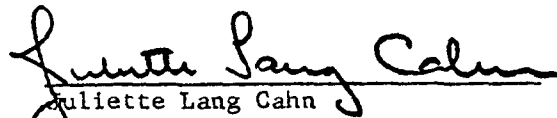
D. A. Kunze of MCA joined the meeting at this point. He was updated on the proceedings of the meeting and the preliminary proposal regarding PVC/VCM mutual response. Mr. Kunze stated that insofar as he could determine, the plan appeared to be feasible and compatible with the existing Chemtrec system.

The Staff Director was requested to send the minutes of this meeting to the PVC/VCM Producers Group and to those present today with a request that each producer study the proposal as set forth on page 2 of the minutes and make a decision as to the company's willingness to participate.

A meeting will be held on September 2nd for the purpose of further discussion and development of the program.

There being no further business, the meeting was adjourned at 4:00.

Respectfully submitted 8/13/76,


Juliette Lang Cahn
Staff Director

SPI-08286

M I N U T E S

VCM/PVC PRODUCERS GROUP

THE SOCIETY OF THE PLASTICS INDUSTRY

SPI Offices
New York City

2 September 1976
9:30 a.m.

Present:

CHAIRMAN: George A. Coffenberg, Stauffer Chemical Co.

Borden Chemical Co.: Ronald Cosey
Conoco Chemical: John F. Pinkman
Diamond Shamrock: George B. Shaw
Dow Chemical Co.: Charles O. Hutchenreuther
General Tire & Rubber Co.: Robert Laundrie
B. F. Goodrich Chemical: Thomas H. Smith
Goodyear Tire & Rubber: Waveland D. Davis; Michael E. Evelsizer
Great American Chemical: O. Paul Cohen
Hooker Chemical & Plastics: Mark N. Soble
PPG Industries: Michael Petruccelli
Shell Chemical Co.: D. Frank McMillan

Dewey A. Kunze, Manufacturing Chemists Association
Martin W. Bercovici, Keller & Heckman
Juliette Lang Cahn, SPI
John R. Lawrence, SPI

Opening of Meeting

Chairman George Coffenberg called the meeting to order at 9:45 a.m. He read a letter from the Staff Director, Julie Cahn, stating that Dr. Ross Adams had requested that Mr. Coffenberg serve as Chairman of this Committee.

For the benefit of those who had not been present at the last meeting, he gave a brief review of the request by the Association of American Railroads for an Emergency Response System for accidents involving VCM.

(more)

Participation

Mr. Coffenberg asked that each company present indicate whether or not it was prepared to participate in a VCM Voluntary Emergency Response Program as proposed in the amended minutes. Mr. Coffenberg called the roll of company attendance and acceptance of the proposed system was unanimous.

Participants - 2 September 1976

Borden Chemical Co.	Goodyear Tire & Rubber Co.
Conoco Chemicals	Great American Chemical Co.
Diamond Shamrock Chemical Co.	Hooker Chemical & Plastics Co.
Dow Chemical Co.	PPG Industries, Inc.
General Tire & Rubber Co.	Shell Chemical Co.
B. F. Goodrich Chemical Co.	Stauffer Chemical Co.

Mrs. Cahn was requested to notify VCM/PVC Producers who are not represented at this meeting and to request them to indicate by ballot whether or not they will participate in the program.

Chemtrec Data Sheet for VCM

The Chemtrec Data Sheet for VCM currently in use was reviewed. Mr. Kunze pointed out that this was drafted some time ago and was in need of revision.

After considerable discussion, agreement was reached as to the text of the Data Sheet. The document was reviewed and approved by Robert Landrie, Chairman of the Technical Committee of the VCM/PVC Producers Group. Mrs. Cahn was requested to prepare the revised form, indicating the amendments made at this meeting and enclose with the minutes of this meeting (Appendix 1).

The Data Sheet will also be forwarded to

- those producers who were not present at this meeting
- the Technical Committee of the VCM/PVC Producers Group via Robert Landrie.

Mr. Kunze **pointed** out that it will require final approval by MCA, the utilizing agent.

Letter of Participation

Mrs. Cahn and Mr. Bercovici were requested to prepare a letter to be signed by participating producers and sent to Chemtrec, with copy to Mrs. Cahn, stating their willingness to participate in the VCM Voluntary Emergency Response Program, listing their geographical locations and authorizing Chemtrec to call them when local assistance is required (Appendix 2). Participating members will be requested to send the letter to Chemtrec by September 30th.

Appendix 1.

Revised 9/2/76

CHEMTREC DATA SHEET

VINYL CHLORIDE

(Interlining denotes deletion; additions are underlined)

1.2, 1.3, 1.4, 1.5 and notations in right hand column - NO CHANGE.

1.6 Shipping or B/L Description: Vinyl Chloride, Flammable Compressed Gas

COMMUNICATOR: READ NOTE ON REVERSE ONLY IF CALLER ASKS ABOUT
POSSIBLE CANCER INVOLVEMENT DUE TO EXPOSURE.

Nature of Product: Extremely flammable, compressed gas that has
~~little or no immediate health hazards.~~ There
may be liquefied gas in the container. Fire
and explosion are the predominant dangers in
any accident involving Vinyl Chloride. Cancer
suspect agent.

HAZARDS

FIRE: Extremely flammable gas transported as a liquid under pressure. It
can be ignited by heat, sparks or open flame. Fire may cause violent
rupture of the tank.

EXPOSURE: MAY EXPLODE IF INVOLVED IN FIRE. Vapor from the burning material
is harmful. It is mostly Hydrogen Chloride. There is little
likelihood of Phosgene being present. Although chronic long term
exposure may cause cancer in humans, nothing has been observed to
indicate any carcinogenic effect for acute short term exposures.
As with any chemical material, minimum exposure is recommended.

IN CASE OF ACCIDENT

SPILL If there is a leak but no fire, DO NOT ignite the gas. Use self
OR contained breathing apparatus and protective clothing. Clear the
LEAK: area, keep upwind and use water spray to disperse vapor and protect
men attempting to shut off leak. Keep low behind the spray and
avoid entering vapor area as it may ignite and flash back to source.
If leak cannot be shut off, it would be best to consult shipper
prior to taking any further steps.

(over)

SPI-08291

Appendix 2.

Please send by September 30, 1976 to:

Mr. Dcwey A. Kunze
CHEMTREC
Manufacturing Chemists Association
1825 Connecticut Avenue N.W.
Washington, D. C. 20009

This is to advise you that _____ will
(company)
assist shippers of vinyl chloride in the event of an emergency involving this
product, and you may release our name, telephone numbers, and the locations of
our response teams to such other shippers. We understand that Chemtrec will
contact the shipper of the tank car involved in the emergency and that it will
be this shipper who will contact our company should it be judged that personnel
are needed on the scene immediately and our company's response personnel are in
a geographic position to render aid quickly. Additionally, you may contact us
in the event you cannot identify or locate the shipper whose product may be
involved in a transportation emergency.

For the Chemtrec Data Sheet, our company number(s) for 24-hour contact
is (are) _____.

Our response team locations are as follows:

We agree to the revised Chemtrec Data Sheet for Vinyl Chloride Monomer as
submitted by the SPI VCM/PVC Producers Group and dated 9/2/76.

cc: Juliette Lang Cahn, SPI

SPI-08293

VCM-PVC COMMUNICATIONS COMMITTEE

Hill & Knowlton, Inc.
633 Third Avenue
New York, N.Y. 10017

September 2, 1976
10 a.m.

Present for the Committee:

Ed Ackerman, Diamond Shamrock
Chemical Co.
M. C. Carpenter, Dow Chemical
Robert B. Downey, B. F. Goodrich
Chemical Co.
Ray Kozakewicz, Ethyl Corporation
Richard Savage, B. F. Goodrich
Chemical Co.

Present for Keller & Heckman:

Joseph Hadley

Present for Hill & Knowlton:

William Daniel Burleson
Robert L. Ferrante

Present for SPI:

E. S. Nuspliger

1. Chairman Ed Ackerman called the meeting to order to 10 a.m.
2. The Minutes of the last meeting were approved.
3. Discussion of an advance press release preparation prior to the FDA announcement on standards was held. Mr. Hadley pointed out that this was extremely difficult under the circumstances since there was no way to tell when the announcement would be made or enough about what it would say to make the previously prepared release meaningful. On the other hand, the EPA announcement on its standard which has a target date of October 2 for the final regulation was prepared and

continued

minutes



VCM/PVC PRODUCERS GROUP EPA TECHNICAL COMMITTEE

EPA - Emission Standards
& Engineering Division
Durham, North Carolina

Wednesday, September 8, 1976 - 6:30 PM
Thursday, September 9, 1976 - 8:30 AM

ATTENDANCE:

For Industry:

G. Baise, Beveridge, Fairbanks & Diamond
F. C. Dehn, PPG Industries
W. C. Holbrook, B. F. Goodrich
J. R. Lawrence, SPI
C. Loechelt, Ethyl Corp.
W. W. Madden, Firestone
J. P. Sandstedt, Tenneco
R. N. Wheeler, Union Carbide

For EPA:

Jack Farmer
Don Goodwin
Susan Wyatt

1. The EPA Technical Committee met on the evening of September 8, to review its position on R&D facilities with respect to EPA's Proposed Standard on Vinyl Chloride. It was agreed that the position stated in the letter on SPI stationery (copy attached) should be submitted. However, several members urged that the proposed change in the regulation be presented as an alternative to the language in the most current Draft Standard.
2. In meeting with Mr. Goodwin and his staff on September 9, the industry's position as presented in the SPI letter was presented with the recommendation SPI's suggested language be considered as an alternative to EPA's most recent version of the Standard.

Mr. Goodwin explained that his work on the Standard is basically completed and that there would be difficulties to make any changes or delay its issuance as it now reads. He indicated that he did understand the concepts of the problem but he would like to have more information on the specific facilities having such problems and the costs involved in conforming to the Standard as it now reads.

Mr. Goodwin indicated that if sufficient information can be supplied rapidly, he would consider introducing some language into the preamble of the Standard when it is published indicating some late information on R&D facilities is being reviewed that may require certain changes to be made in that area of the Standard. He emphasized that this is an unusual procedure and that he would need to have supporting facts

THE SOCIETY OF THE PLASTICS INDUSTRY, INC.

355 Lexington Avenue • New York, N.Y. 10017

(212) 573-9400

SPI-08296

**The Society of the
Plastics Industry, Inc.**



355 Lexington Avenue
New York, New York 10017
(212) 573 9400

September 7, 1976

Mr. Don R. Goodwin
Emission Standards & Engineering Division
Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dear Mr. Goodwin:

After reviewing the proposed EPA Vinyl Chloride Standard, members of SPI have raised an issue regarding the portion of the Proposed Standard relating to the Laboratory and Research and Development facilities.

In SPI's initial comments to EPA on the Proposed Standard for Vinyl Chloride we proposed that polymerization reactors of 500 gal. or less capacity be exempt from the standard. After reviewing current and complete industry data, the SPI now agrees with the EPA that 50 gal. is the appropriate cut-off point for exemption, based on examination of the data presented in Exhibits A and B; however, SPI respectfully requests that EPA reconsider its requirements for reactors between 50 and 1100 gallons capacity.

The difficulties created in meeting the current proposal by EPA, in paragraph 61.64 go beyond the fact that costs far outweigh the benefits derived. It is true that larger reactors tend to be installed near production facilities for convenience of monomer supply; however, please be advised that several are at research facilities. Other research reactors are at a sufficient distance from the production equipment that their interconnection is not feasible. Long runs of vacuum or slurry lines are not practical, especially in climates where sub-freezing conditions are experienced. Line plugging, burning of resin, and excessive pressure drops will make these lines inoperative. There are also problems with synchronization of remote operations and availability of equipment.

In the short time we have focused on this issue, we have had confirmation from Air Products, Conoco, Firestone, Goodrich, Tenneco and Union Carbide that they will experience some or all of the problems raised above.

Two of the major purposes for which pilot-scale equipment is used are development of improved products and processes, and the solution of plant production problems. In the first case, it is often impossible to obtain adequate scale-up data from a 50 gal. reactor. This is becoming more important as reactor size increases in modern plants. In the second case, it is necessary that equipment be available

SPI-08298

Continued

September 7, 1976

immediately to resolve production problems, and that the polymerizer be as similar to production equipment as possible.

Another problem arises when the research facilities are using **different** comonomers from those in use at the production plant, which is a frequent occurrence. Common use of a single recovery/abatement facility is not possible under these circumstances.

The spirit of the Proposed Standard calls for the use of the best available technology, to encourage innovations and to minimize potential losses by encouraging research and providing means for performing **needed** studies on the smallest practical scale. Any regulation that discourages the use of research equipment will limit innovation and improvement in the industry, and will lead to more developmental work being done in production equipment, where the potential for major releases is increased. We believe the present wording of the standard will inhibit use of research facilities, not only because of the cost of compliance, but because of restrictions on the flexibility of operations. For example, in several installations the interconnection of research and production equipment would take the operation of the research equipment out of the hands of trained engineers and put it under the jurisdiction of production labor because of the wording of union contracts. As another example, the rate and timing of the termination and recovery of unreacted monomer at the end of a batch can affect the properties of the product, and to depend on a product-oriented facility for this important service is not realistic.

We, therefore, request that 61.60(b) and (c) be amended to read as follows:

(b) Research and development equipment of 50 gal. or smaller capacity shall be exempt from this subpart. Equipment larger than 50 gal. but no greater than 1100 gal, shall be exempt, except that total combined emissions from all sources shall be no more than 0.05 lb. vinyl chloride per lb. of vinyl chloride charged to the reactor. Each operator of such facilities shall submit a standard operating procedure to the agency for approval of its plan to meet this requirement.

The attached data in Exhibit B show that eight companies would reduce their emissions substantially in complying with the SPI proposal, while **company** G is already in compliance. The resulting total emissions would be about 68,000 lbs, per year, less than that emitted by reactors of 50 gal. or less, and less than 25% of current emissions. These 9 companies represent 45% of industry capacity, and include many of the major producers.

Finally, we want to address the cost-benefit issue raised by the proposed Research and Development Regulation. The Agency has declared it does not want to require a technology when it will create costs which are grossly disproportionate to the benefits derived. SPI believes the proposed Research and Development Regulation creates a problem which to date EPA has sought to avoid--namely grossly disproportionate costs for the removal of small amounts of monomer. For example the cost of compliance with

SPI-08299

EXHIBIT A

EMISSIONS DATA ON
LABORATORY AND PILOT FACILITIES
(≤ 50 GAL. SIZE)
UTILIZING VINYL CHLORIDE

<u>Company Code</u>	<u>Reactor Size</u>	<u>Number of Reactors</u>	<u>PVC Produced #/yr</u>	<u>Emissions # VCM/# PVC</u>	<u>Emissions # VCM/yr</u>
A	50 gal.	2	30,000	.013	400
B	0.4	6	1,084	.082	89
B	3.25	1	987	.101	100
C	50	1	17,000	.165	2,800
D	.5	1	192	.25	48
D	.8	4	2,112	.33	697
D	.8	2	696	.104	910
D	15	6	23,100	.25	5,775
D	30	1	960	.25	240
D	30	2	28,800	.43	12,384
E	5	3	400	15.1	6,075
E	10	1	100	30.38	3,038
F	.5	1	380	.066	25
F	10	2	27,338	.058	1,600
F	50	2	136,687	.079	10,800
G	.5 to 2	11	16,000	.014	225
H	15	1	5,468	.17	928
H	10	1	608	.164	100
I	.5	7	2,245	.049	110
I	50	7	75,634	.063	4,870
J	5	4	76	.105	8
J	30	1	5,285	.061	321
K	2.5	1	1,823	.055	100
K	10	1	606	.05	30
L	12.5	4	15,480	.1	1,548
M	30	2	34,172	.011	375
N	10	2	66,582	.329	21,920
N	30	1	24,698	.111	2,740
O	.05	1	1,200	1.41	1,700
O	1	7	1,063	.329	350
O	10	2	304	.164	50
			521,080		80,355

SPI-08301

**The Society of the
Plastics Industry, Inc.**



355 Lexington Avenue
New York, New York 10017
(212) 573 9400

September 13, 1976

Mr. Don R. Goodwin
Emission Standards & Engineering Division
Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dear Mr. Goodwin:

Following up on our meeting with you on September 9, we want to be sure that you understand that the proposed paragraph (b) included in my letter of September 7 is to be considered as an alternative to be added to the language of paragraph 61.60 of the proposed Standard.

We understand the problems that might be posed by the enforcement of such an alternative without a specific understanding of the measuring and record keeping procedures that would be used to verify compliance. Therefore, as you suggested, I am asking that our PVC Producers Group contact you with information on the operating procedures they would follow to show conformance with the suggested alternative that total combined emissions from all sources in existing 0.05 lbs of vinyl chloride per lb vinyl chloride charged to the reactor.

In addition, I am asking that those companies interested in using this alternative supply you with the following:

- . Description of the R&D facilities identifying where they are located with respect to production equipment and the type of neighborhood surrounding the facility.
- . Information on the technical problems relating to compliance with the Standard as it now reads versus the proposed alternative.
- . Information on the cost of compliance with the plan as it now reads versus the proposed alternative.

We appreciate having had the opportunity to meet with you to discuss this important matter to our industry.

Very truly yours,

A handwritten signature in cursive script that reads "John R. Lawrence".

John R. Lawrence
Technical Director

SPI-08303

JRL:gm

VCM AND PVC PRODUCERS GROUP
STEERING COMMITTEE

SPI Conference Room
New York, New York

Tuesday, September 28, 1976
10:30 A.M.

Attendees:

Dr. A. Ross Adams, Air Products & Chemicals, Allentown, Pa. 18105
Lynn W. Babcock, Diamond Shamrock Corp., 1100 Superior Avenue, Cleveland, Ohio
Gary H. Baise, Beveridge, Fairbanks & Diamond, One Farragut Sq. Wash. D.C. 20006
Robert S. Brookman, Firestone Plastics Co. Box 699, Pottstown, Pa. 19464
G. E. Disch, Tenneco Chemicals, Inc. Box 365, Piscataway, N. J. 08664
Daniel S. Dixler, Keller & Heckman, 1150 17th St. Washington, D. C. 20036
R. B. Downey, B. F. Goodrich Chemical Co. 1600 Oak Tree Blvd. Cleveland, Ohio
Robert L. Ferrante, Hill & Knowlton, 633 Third Avenue, New York City 10017
Ralph L. Harding, Jr. SPI, 355 Lexington Avenue, New York City 10017
Jerome H. Heckman, Keller & Heckman, 1150 17th Street, Washington, D.C. 20036
Harold Himmelman, Beveridge, Fairbanks & Diamond, One Farragut Sq. Wash. D. C.
Karl A. Hochschwender, American Hoechst Corp. Route 202-206 North,
Somerville, N. J. 08876
Bob Laundrie, General Tire & Rubber Co., One General St. Akron, Ohio 44329
John R. Lawrence, SPI, 355 Lexington Avenue, New York City 10017
D. C. Nuechterlein, Dow Chemical, 2020 Dow Center, Midland, Michigan 48640
Dick Savage, B. F. Goodrich Chemical Co., 6100 Oak Tree Blvd. Cleveland, Ohio
Matt Swetonic, Hill & Knowlton, 633 Third Avenue, New York City 10017
J. E. Zimmerman, Diamond Shamrock, 100 Superior Avenue, Cleveland, Ohio 44114

ACTION SUMMARY

1. Steering Committee recommends Group's activities be continued with affirmation to be obtained from full membership.
2. Dr. Maltoni's latest interim report reviewed; action taken to forward it to U.S. government agencies.
3. Proposed that Group advise CEFIC of interest in cooperating with human dose response studies; U. S. protocol to be developed.
4. Task force appointed to study what should be done to develop industry position on PVC's involvement in fires.
5. Recommended that "Action Program" be continued.
6. Tentative date for full Producers Group meeting set for November 30, 1976.

1. Chairman Ross Adams opened the meeting with self introductions and called attention to the agenda listing the items to be covered in the day's meeting.
2. Attention was called to audit of the Group's expenditures for the fiscal year ending May 31, 1976 (copy attached). Dr. Adams noted that the expenditures broke down into the following major categories:

Legal	-	\$308,472.49	-	55.92%
Public Relations	-	227,794.19	-	41.30
Meeting Expenses	-	10,543.69	-	1.91
Office Supplies & Expenses	-	4,076.91	-	.74
Telephone & Telegraph	-	698.38	-	.13
TOTAL	-	<u>\$551,585.66</u>	-	<u>100.00%</u>

Mr. Lawrence reported that the open assessments as of May 31 have all been paid or accounted for. The Group's funds balance as of SPI's August 31, 1976 statement was \$15,934.

NOTE: Although the breakdown of income and expenditures since May 31 were not reported at the meeting, a subsequent review shows them to be as follows:

<u>INCOME</u>	
Balance as of May 31, 1976	\$40,430.37
Income - Assessments	35,100.00
Literature Sales	93.60
	<u>\$75,623.97</u>
 <u>EXPENDITURES</u>	
Legal	\$19,893.90
Public Relations	36,488.33
Meeting Expenses	- 0 -
Office Supplies & Expenses	3.20
Telephone & Telegraph	4.00
	<u>\$59,689.43</u>
TOTAL	-
 <u>Balance as of August 31, 1976</u>	 \$15,934.54

3. Dr. Adams initiated a general discussion on the future status of the Group's activities and posed questions relating to the scope of future activity; organizational apparatus and mandate from the full committee. He proposed that a letter be sent to member companies to get their thinking on these questions and that a full meeting be held to provide future direction.

NOTE: Karl Hochschwender passed these questions along to his CEFIC contact and was advised that it would not be possible for American representatives to meet with Dr. Maltoni to review his research at this time. However, the European sponsors of Dr. Maltoni's studies have many of the same questions as those raised by Dow and they will review these points with Dr. Maltoni at an appropriate time.

After further discussion it was agreed that copies of the latest report on Dr. Maltoni's work should be forwarded to representatives in government agencies that have been directly involved with the toxic hazards of vinyl chloride.

Subsequently, a letter forwarding the Maltoni Report and the CEFIC Statement over Ralph L. Harding's signature was sent to representatives in EPA, NIH and FDA as indicated (copy attached).

- (b) Dr. Adams reviewed the plan that is developing within CEFIC to prepare a dose response curve for humans exposed to vinyl chloride and suggested that the U.S. PVC industry offer to cooperate with the European program. It was agreed that Dr. Adams would advise his CEFIC contacts of our interest in cooperating with this program.

After additional discussion, it was moved that steps be taken to investigate the feasibility of developing a protocol for understanding retrospective human dosage of vinyl chloride.

- 5. Mr. Richard Savage presented a detailed review of the issues relating to the burning of PVC. An outline of his comments are attached to these Minutes. He emphasized the importance of developing specific industry positions on the significance of PVC's involvement in fires. After considerable discussion, it was agreed that an invitation should be sent to PVC producers to appoint appropriate technical representatives to meet, discuss and explore what might be done. Mr. Dan Kent of B. F. Goodrich was nominated to chair this task group.
- 6. Dr. Karl Hochschwender reviewed his activities directed toward establishing better liaison with European developments on VCM and PVC issues. He is maintaining contact and attending CEFIC meetings where he is attempting to keep them informed on U.S. Standards and Regulations as well as keeping abreast of European activities. Evidence of his success in these endeavors are reflected elsewhere in these Minutes.

7.

REDACTED

SPI-08307

DRAFT

RISK-BENEFIT ANALYSIS FOR VINYL CHLORIDE

Richard Wilson
Harvard University
Cambridge, Massachusetts 02138

Written for the Society of the Plastics Industry and read in an abbreviated version at the centennial meeting of the American Chemical Society, Sept. 1, 1976.

SPI-08309

Introduction

The scourge of cancer afflicts one quarter of all Americans in their lifetime, and 18% of Americans eventually die from the disease. Massive efforts have been made to discover the causes of cancer and to effect a cure. About \$25,000 per patient is spent trying to cure cancer.

In the last year, there have been several reassessments of the direction of this attack. For example, the prestigious public interest lobbying organization, the Federation of American Scientists, has summarized a part of the issue in a recent public interest report (May 1976).⁽¹⁾ In the last 15 years, there has been very little improvement in the cure rate for cancer. This is shown dramatically in Figure 1 where it is shown that the survival rate has been only slightly improved.

The trends in cancer mortality rates are shown in Figure 2. These are adjusted by age. This is necessary, because cancer afflicts old people more than young people, and as other causes of death are removed in our society, a larger proportion will die of cancer. For some cancers, mortality has dramatically increased.

Attempts to find a universal cancer virus which causes cancer have so far failed. If a virus were found, a vaccine against cancer would be possible. Therefore, a vaccine against cancer does not seem likely in the near future. Accordingly society is left with two immediate choices--accept cancer and try to cure it by surgery, radiation or chemotherapy, or try to remove causes of cancer.

It has been widely stated that between 50% and 90% of all cancers

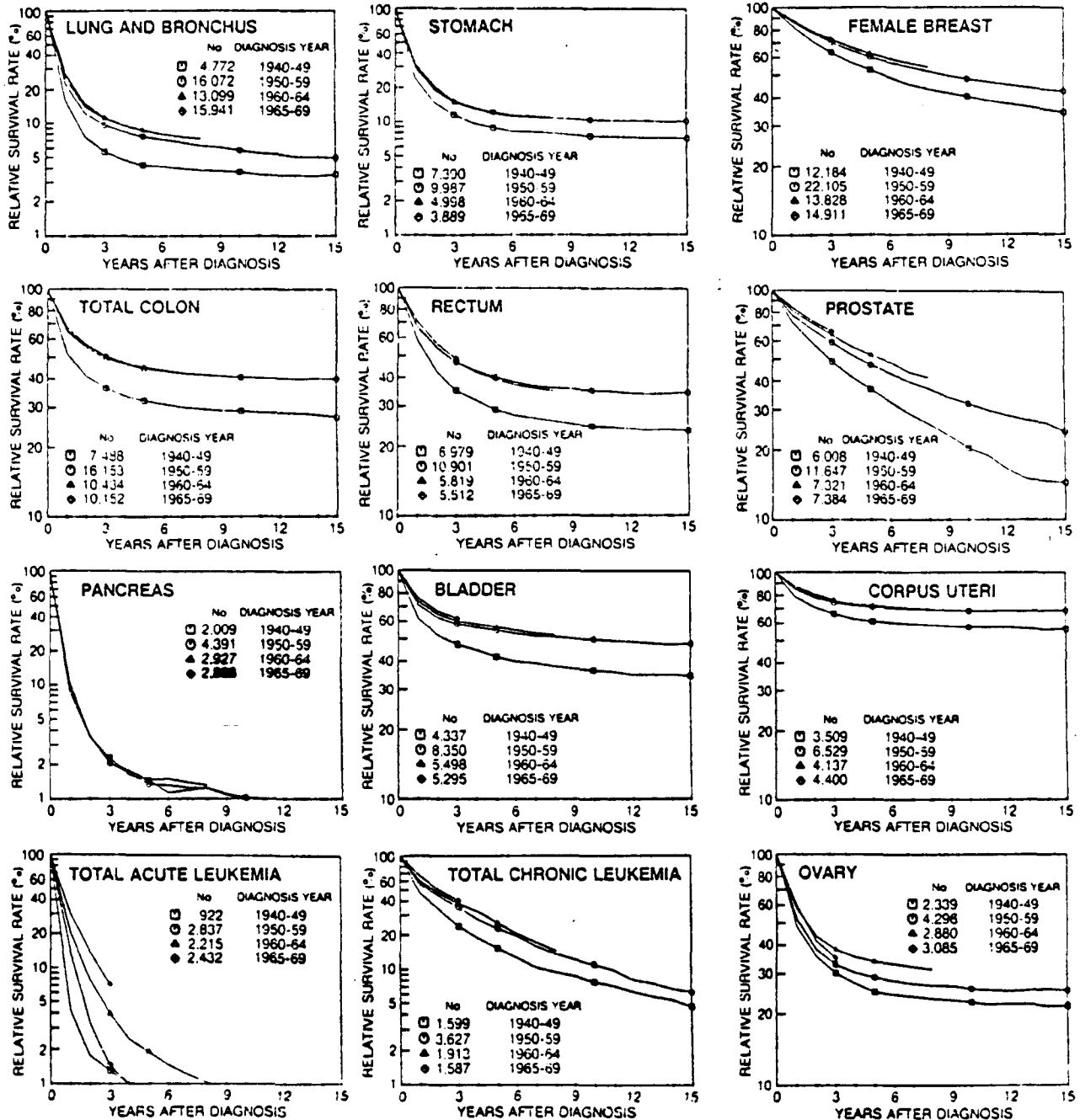
Figure 1

LITTLE RECENT PROGRESS IN CURES

The lower curve on each of the adjoining graphs reflects the survival for patients diagnosed in the forties. If this curve is ignored, one discovers, in virtually all of these cancers, that there has been essentially no difference in the ability to cure or control cancer diagnosed in the sixties as opposed to those of the fifties. Evidently we learned in the fifties how to keep patients alive longer but — since then — very little indeed. In fact, what minor differences exist may only reflect differences in diagnostic ability: finding cancers earlier, diagnosing some illnesses as cancer which were not (and curing them), etc.

SPI-08312

RELATIVE SURVIVAL FOR CANCER OF SELECTED SITES. BY YEAR OF DIAGNOSIS.



Accordingly, society has demanded an unprecedented attack on this problem to determine what chemicals might cause cancer, to control their use, and ban hazardous uses, even in cases of doubt. As with all major challenges, there are problems and opportunities. There are many different interests and lobbying groups. This paper discusses part of an approach to this problem.

It is important to realize that the attempt to prevent cancer by isolating and controlling the causative carcinogens will involve the best intellect that man can muster. There will be no direct evidence that we are successful and no immediate evidence that we have failed^{and we will never be 100% successful.} We will have to use indirect evidence and theory. Moreover this theory of how cancers are formed is incomplete. We seem to be far from a complete theory of carcinogenesis, so any use of theories will be full of uncertainty. Nonetheless, action is necessary, but in deciding on the action, there will be much discussion and argument. Deciding on a correct procedure for resolving the argument is an important part of what politicians call "the war on cancer."

Society demands, correctly and legitimately, that anyone putting a chemical, whether manmade or natural, into food or the human environment shall only do so if he can establish that the risk is low. How is this to be done?

SPI-08314

(from Hiroshima, Nagasaki, and incorrect use of x-rays) are examples. Even if we accept the idea that one species is a surrogate for another, we still have a problem. We want to test a chemical suitable for use by 200,000,000 people. If we are to test at the dose level which we are interested in using, and want to be sure that not more than one person gets a cancer in a generation, we need 200,000,000 mice. Typical mice experiments use 100 mice in each batch! We are forced to use such extrapolations of dose-response curves because we cannot afford to do tests with 200 million mice for every cancer agent (to establish no cancer threat for 200 million people). In addition, the presence of background cancers due to other causes makes definitive testing of particular agents difficult.

Therefore we must test with ^{rats or} mice at a higher level than that we wish to use and find some way of extrapolating the result down to the low dose levels where we wish to apply our results. It is in this extrapolation procedure that the uncertainties arise. This extrapolation is the nub of the problem and must be clearly discussed.

It should preferably be based on a discussion of the theory of the formation of the disease, but we know too little about cancer. Numerical work in the last 20 years has improved our understanding a lot (a brief discussion is in an appendix).

Twenty years ago it used to be argued that there was a threshold dose for every natural and artificial chemical below which no harm occurs. Contrary to common belief, this was not a view

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Vinyl Chloride

In this report I will consider only one set of carcinogens and potential carcinogens, those which break down into non-carcinogenic materials and can be controlled, and how we might decide on reasonable conditions for their use. As a specific example I will take vinyl chloride. This chemical was at one time used as an anaesthetic at high concentrations, but its principal use at the present time is in the manufacture of polyvinyl-chloride plastic (PVC).

The manufacture of vinyl chloride monomer is a closed process and there are few leaks at this stage. But at the process of polymerization to form the plastic, workers ^{used to} enter the reactors to clean them and there they ^{were often} heavily exposed to vinyl chloride gas. There can also be leaks outside the factory buildings and it is here that we find a source of vinyl chloride for a community exposure by inhalation. A small amount of vinyl chloride monomer stays in the plastic due to incomplete polymerization and can enter food and drink. Here there is a small but widespread hazard of ingestion. Fortunately, vinyl chloride breaks down in the air (light) with a six hour half life.

For many years, few restrictions were placed upon the use of vinyl chloride. Concentrations had to be below the explosive limit and the limit of anaesthesia (~10% in air). Workers in the plastics factories where the vinyl chloride was polymerized to PVC were often exposed to concentrations of 0.1%-0.2% (1000-2000 parts per million) in the air. In retrospect this showed lack of caution but many elements of society shared in this attitude with respect to potential chemical hazards.

After some years, some tests on rats at high concentration disclosed some cancers. A little later, in January 1974, a few cases of a rare form of cancer, angiosarcoma of the liver, appeared. Since then about 50 cases of liver angiosarcoma have been diagnosed among PVC workers throughout the world, and because of the latent period, perhaps another 50 will contract the disease from existing exposure. Two steps were soon taken. An extensive series of tests on animals were performed and occupational exposures were reduced. In this paper I will discuss the procedure for establishing a sensible balance (trade-off) between risks and benefits.

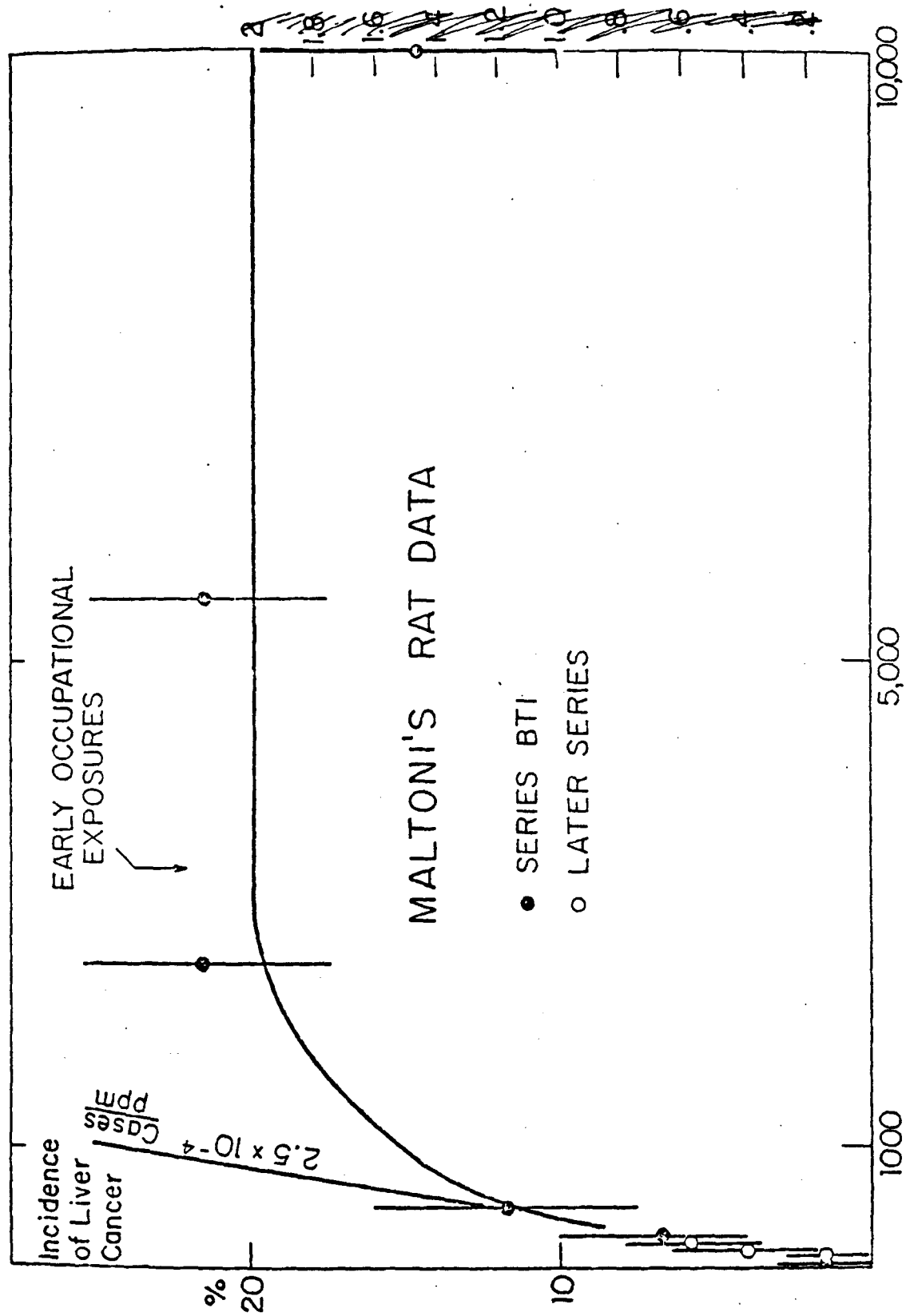


Fig. 3

uptake of vinyl chloride per unit weight. The straight line is the EPA "best fit." The probability of liver cancer = 2.5×10^{-4} multiplied by the concentration in parts per million (ppm). If there is a community exposure, we must increase this for the 24 hour day and 7 day week to calculate a risk increased by a factor of 3.4 or 8.5×10^{-4} liver cancers per part per million.

The adjustment between rats and people is hard. The assumption is made that the same number of cancers would be induced in people over their lifetimes as are induced in rats over their lifetimes. This is consistent with all we know about cancer. With this assumption the one year exposure of rats is equivalent to a 30 year exposure in people. Thus the animal rate of liver cancer should be the above rates divided by 30, or

8×10^{-6} per ppm per year (occupational exposure)

3×10^{-5} per ppm per year (community exposure)

Human data exists for the occupational exposure of vinyl chloride workers to vinyl chloride at high concentrations. Since the exposure was unintentional, establishment of the dose they received is uncertain. However, for EPA Kuzmack and McGaughy⁽⁵⁾ estimate that the effects are about 1.7 times less than calculated above from the rat data. In what follows I will use, as did EPA, the Maltoni rat data, using the human data as an overall, general check on the numbers suggesting that rats may be a little more sensitive than humans, and that to use the rat data in this was is conservative.

As I previously noted, the liver cancers are small in number and is not the dominant cause of death even for vinyl chloride workers. The cancers stand out because this liver cancer is a

Exposures and Risks

To complete the risk assessment we must estimate the exposures to which people are now exposed. In this section the report for the EPA is based on early studies and is more pessimistic than need be.

Table 1

Occupational Hazard in Selected Occupations

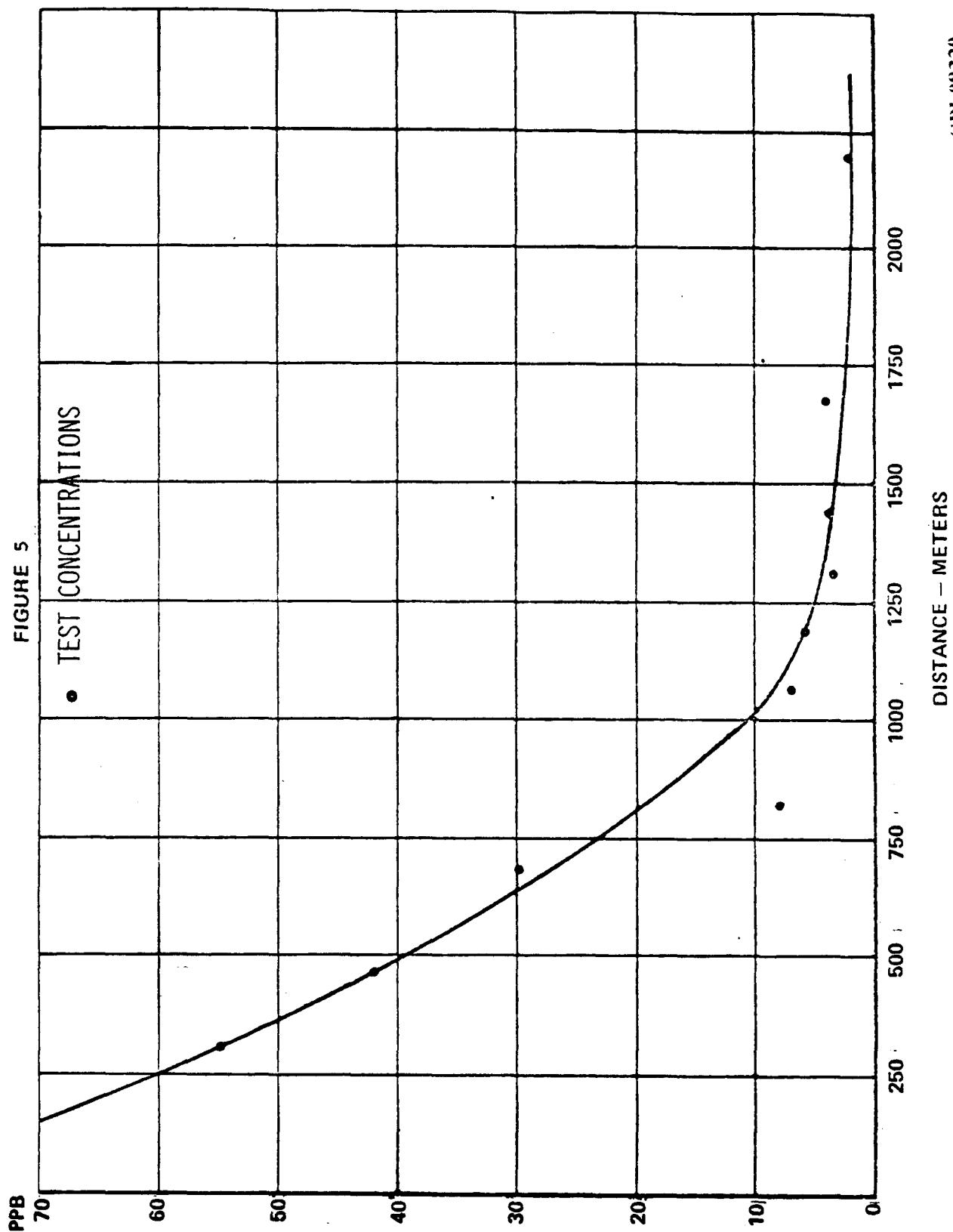
	<u>Lifetime Risk</u>	<u>Annual Risk</u>
Coal mining:		
black lung disease	0.25	0.01
accidents	0.08	0.003
Commercial airline pilot (accident only)	0.006	0.0002
Fire fighters	0.03	0.001
Steel Worker	0.005	0.0006
Railroad worker (accident risk)	0.012	0.004
Vinyl chloride workers: (1 ppm max exposure, .5 ppm aver.)		
liver cancer	0.00001	0.000004
all cancers	0.0003	0.00001
morbidity*	0.0035	0.00012

Data mostly from Statistical Abstract of the U.S. and Mortality Tables.

*the linear extrapolation is extremely pessimistic for morbidity and this is a very conservative limit.

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FIGURE 5



levels should we expect it. It would not have been possible to detect a risk of the size we estimate here. It is for this reason that our main reliance must be on calculation.

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detection limit of 300 parts per billion; even if on rare occasion this were exceeded, this would not matter from a realistic point of view provided that the long term average, which is what counts in the pessimistic linear calculation, is kept low. The occasional bottle with a higher level is only important in contributing to the average.

The vinyl chloride monomer may escape from the package into the food chain; this might particularly be expected in bottles containing liquid such as mineral water. Tests show that an average 20% of the residual monomer does escape after half a year. We can conservatively assume that this applies to solid food packages too and find the total amount added to food. In the U.K., for example, 16,000 tons of PVC/year are used for bottles and for packaging, containing an average of 300×10^{-9} x 16,000 tons vinyl chloride monomer = 500 grams. Of this about 100 grams/year may find its way into the food chain. Assuming a 50 million population, and a 60 kg body weight, we get

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$$\begin{aligned} \frac{\text{Ingestion}}{\text{person, kg body weight}} &= 0.00000003/\text{gm/kg pa} \\ &= 3 \times 10^{-8} / \text{gm/kg pa} \\ &\approx 10^{-6.5} \text{ parts per million} \end{aligned}$$

Assuming this applies to the U.S. we find an average probability of cancer incidence (all cancers) of 7×10^{-10} /year, of morbidity 9×10^{-10} /year, or one cancer in 60 years and ^{two} one case of morbidity ^{per} in ~~four~~ years. Thus the dose through ingestion is 30 times less than that through community exposure--which is already small.*

Maltoni's rat data included some samples where vinyl chloride was ingested. It compares well with data where the vinyl chloride

X the amount of vinyl chloride in packaging is being reduced a factor of 10 below this leading to a further reduction in hazard

Comparing Risk and Benefit

I will go through the comparison of risk and benefit in two ways. Firstly, I will ask what is the benefit of having vinyl chloride (and in particular polyvinyl chloride, the manufacture of which gives the problem). We ask "is the risk worthwhile to society or to individual workers?" Secondly, at what cost can we reduce the risk further and is this worthwhile. (Of course we could also consider increasing the risk further for some corresponding increase in benefit.)

A risk benefit calculation is also recommended by other people. For example, the Federation of American Scientists in their report say: ⁽¹⁾

"There is needed some simple measure of cost and benefit that would make widely different risk situations comparable so as to attempt to maintain, in different areas, roughly similar standards for spending government and industrial funds to save lives. Without such a standard, as economists will sense immediately, cancer-avoiding expenditures cannot be spent efficiently. And, in addition, the public will have the greatest difficulty distinguishing minimal risks from large ones.

One possible approach is to evaluate risks in terms of life-shortening: so many lives likely to be shortened by so many years. The costs of avoiding a year's loss of life can then be compared in one area with another. This has the benefit of being able to encompass not only the risks of getting cancer but the concomitant risks of many other occupationally or environmentally related illnesses. And it provides, at the same time, perhaps the best possible means of driving home, to the individuals at risk, the nature of the risk they are accepting."

Risk/benefit analysis by itself is moderately straightforward. There are scientific uncertainties in evaluating the risk, but no ethical ones. It is possible to stop here, to state the risk in terms of lives shortened or working days lost and compare it to a financial benefit.

discussion of when the fatality occurs and therefore of the life-shortening and I will omit any economic discounting of costs and future benefits. These effects can be included, but will change the figures by at most factors of 2 or 3. I claim it is unnecessary to include them and because they are complex it is desirable to include them only if the risk/benefit inequality is almost equal which is not the case under discussion.

The official EPA view was stated by the administrator Russell Train in May 1976⁽⁷⁾

"It is important to emphasize the two step nature of the decision making process with regard to the regulation of a potential carcinogen...the first decision--whether a particular substance causes a cancer risk [but] detailed and independent risk and economic assessments form the basis for the second decision, namely what, if any, regulatory action to take."

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Benefit--Occupational Exposure

The benefits of vinyl chloride should be easy to calculate, but in fact they have been less well presented than the risks! For a worker in any industry, the benefit of exposure to the hazards of the industry is obvious--he has a job. The benefit of the job is his salary, and in unusually hazardous cases he may get hazard pay.

We can use the techniques of risk/benefit analysis to establish a reasonable level of hazard pay. Theoretically and ideally, this might be related to the hazard in the actual plant so that the employer always has the incentive to reduce the hazard.

In Table 1 I showed a list of hazards in selected occupations. The larger hazards in the table are those which are known to occur; the vinyl chloride ones are calculated conservative limits.

Presently an average charge for cancer treatment is \$25,000. It is an old saying that prevention is better than cure so that we can reasonably ask to spend \$1,000,000 to prevent a cancer case. We might imagine that this amount is paid into an insurance pool for better medical care for those who bear the increased risk. Many other ways are suggested in the literature for deriving a number here. These vary from \$50,000 to \$500,000 per life. In what follows, I will take \$1,000,000 per life as a good round number.

Then in the vinyl chloride industry with an exposed workforce of 20,000 we might get 0.2 cancer cases of all sorts per year. The industry should be willing, according to this reasoning, to pay \$200,000/year to reduce the risk to zero. Alternatively, each

far from certain because the effects are small even at high doses and within the fluctuations of the ordinary incidence of the disease. These various conditions did not show up markedly among vinyl chloride workers at the high concentrations where cancer was discovered; they are likely to vary more with dose rate than the cancers and therefore with the present 1000 fold reduction in dose must now be considered insignificant. Most of them are included in the morbidity estimate in the body of the report.

If some condition is now found among vinyl chloride workers, it is almost certain therefore that it is not due to vinyl chloride exposure, but to some other occupational hazard. It is very important that the history of cancers caused by vinyl chloride not dull our logical thoughts. If such a hypothetical condition were incorrectly attributed to vinyl chloride itself the wrong cure would be suggested. Then not only would money be unnecessarily wasted, but there would be a delay in finding the correct source of a (hypothetical) health condition.

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Appendix II

A Discussion of Uncertainties

The risk analysis which the EPA used and that I outlined above is uncertain because no data exist for the small risks with which we are concerned and uncertain extrapolations are necessary. It is my contention that these extrapolations are conservative and are on the side of overestimating the risk--and should therefore be labelled conservative or pessimistic.

In this Appendix I will note some features of this conservatism. I have already noted that I assume a linear relation between cancer incidence and dose. This, as shown in Appendix I, might be true for a model of cancer incidence where vinyl chloride causes only one of several mutations necessary for a cancer. If two mutations are caused by the vinyl chloride, the incidence will be proportional to the square of the dose. Since the data is "fitted" at a high dose, 1000 times the dose now being considered for workers in the vinyl chloride industry, this means that occupational risks could easily be 1000 times less than calculated here--and risks to the public lower by an even greater factor. The existing experimental data cannot distinguish these possibilities and the risk, assuming the linear extrapolation, is already so low that it is unnecessary to consider the matter further.

The data on cancer incidence in rats which were used to establish the risk were made with an exposure over a time shorter than the lifetime of the rat. This was deliberately done to approximate the fraction of the life of a vinyl chloride worker in which he is exposed to the risk. Yet the cancer incidence formula of Doll and Armitage, discussed in Appendix I has a dependence of

mutation 2 by radiation. Then the probability of cancer is proportional to the product of the probabilities p_1 and p_2 and hence the product of the concentrations, not to the sum of the concentrations. In this theory it is natural to think that each mutation stays until the next insult and mutation. But there do exist repair enzymes to repair cells after mutations and it has been widely suggested that these repair mechanisms will produce a threshold below which no cancer will occur. However, a moment's thought shows that if the repair mechanism is proportional to the number of cells needing repair, the effect will merely be a reduction in the mutation probability, p_t . It is then natural to assume no threshold. This concept is consistent with a linear increase of cancer with dose concentration.

If there were some saturation of the repair mechanism, the amount of repair enzymes might be limited and not be enough to repair large numbers of mutations, thus producing a threshold above which the probability of a surviving mutation increases rapidly with concentration.

There is so much cancer around that it seems likely that there are already enough background pollutants to be above the threshold for most cancers.⁽¹¹⁾ But liver cancers are produced rarely; only rare chemicals, including arsenic and thorast, seem to produce it. It might be that most low vinyl chloride concentrations are below such a threshold. It might also be that two mutations caused by vinyl chloride are necessary to cause liver cancers, giving a quadratic dose-response curve. These concepts are unproven. But it is likely that enough other chemicals exist in the environment

Conclusion

A risk/benefit analysis for vinyl chloride is an easy task and need not be performed accurately to be useful. It clearly shows that occupational, community, and public risks from inhalation and ingestion are now small compared with other hazards in life and are small compared to the benefits of vinyl chloride use.

This might not be true of other chemicals--particularly those that do not break down into innocuous chemicals on exposure to the environment. For these other chemicals refinements may be necessary.

The essence of risk/benefit analyses is not to make decisions, but to present the data in a form whereby the decision makers--the general public and their elected and appointed representatives--can make decisions most easily and reliably. Ease of understanding must have precedence over precision in most cases and the lack of precision should be made up by conservatism in our estimates of risks and benefits.

Step 2. For each of the suspect carcinogens the Ames test or a similar test for mutagenesis must be carried out. If the test shows a mutagenesis strength which is very low the chemical can be cleared for use with reasonable assurance of safety. A comparison can be made with other known carcinogens and mutagens and the strength (λ and k in the equation of the Appendix) determined. Even if λ is found to be zero, it can only be found to be zero within a certain statistical error and the next step can never be completely avoided.

Step 3. The first, simple risk/benefit, or cost/benefit analysis can then be carried out. Care must be taken not to understate the risk or overstate the benefit. If the risk is measured to be zero, the upper limit of the error bar must be taken. If the risk comes out to be less than 0.1% of the benefit, the chemical might be cleared for provisional careful use. Steps might be taken to reduce the exposure and hence the risk.

Step 4. If the risk is more than 0.1% of the benefit, and cannot easily be reduced, more studies would seem to be in order to reduce the uncertainty in the risk/benefit analysis and increase the confidence in the decision. At this stage, rat or mice tests, such as those of Maltoni for vinyl chloride, would seem to be in order. Animal tests should also be done anyway if the chemical is an "obvious" carcinogen as we must now consider many monomers.

Step 5. When the results from the rat or mice tests come in, the risk/benefit analysis can be refined and then the decision made. In principle we can then clear the chemical if the benefit

Societal Benefits

The benefits of vinyl chloride in the packaging industry are great, but a little hard to define. Alternative ways of putting an estimated cost on the benefit are:

1. Society puts a value on PVC by buying it. The total value of PVC sold nationwide is (\$6000 million/yr)
2. 10% of value of food that is packaged because it prevents spoilage (\$100 million/yr)
3. plumbing for new houses; at a cost saving over copper pipes of perhaps \$100/house, approximately 1,000,000 houses/year (\$100 million/yr)

One benefit is a direct improvement in safety. It is possible to make electrically conducting PVC and to use it in conveyer belts to replace rubber. This reduces the probability of a spark and accident in coal mines. This alone might, for example, be 10 lives saved per year.

There are other benefits which are probably smaller; when used for soft drink packaging, the benefit could be a reduction of the (few) cases of exploding glass bottles. There is a hypothetical hazard of abolishing packaging of foodstuffs; the extra handling of the food could add trace carcinogens. Thus the societal benefit of the existence of PVC is roughly \$6000 million/year.

3. Should we reduce exposures--particularly occupational ones--another factor of 10?
4. If a leak is detected, should the plant be instantly shut down? Similarly, if a PVC plant violates rules, how much time should be allowed to come into conformity standards?
5. Should we have an intermittent control system--like those for sulphur dioxide--to only allow operation in times of great dispersion, so that concentrations in the surrounding community will always remain low?
6. Should polymerization and PVC fabrication plants be in buildings with reduced air pressure and high stacks to disperse leaky vinyl chloride? (Such precautions are taken in nuclear reactor buildings.)
7. How much should industry spend in an attempt to prove that there is a threshold for vinyl chloride exposure, or that the Mantel-Bryan extrapolation is valid?

The cost data to resolve all these questions are not known to the writer at this time; but preliminary answers may quickly be given subject to verification in any given case. The first question is hard to answer, but note the comment earlier that dose measurement is preferable to emission controls and is probably cheaper. To answer the second and third questions I note the industry claim that \$500 million capital cost and \$100 million per year operating cost has been and will be spent to meet present regulations. Perhaps only half this would have sufficed to reduce occupational exposures to 10 ppm.

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large compared to the reduction in risk. The answer to question 6 is again no; it would mean rebuilding every factor and even if it were only applied to all new factories, as they are built, it would cost over \$100,000,000 for the industry or with 20% amortization, \$20,000,000/year.

For merely reducing the risk of vinyl chloride the answer to question 7 is that industry should probably not pay anything since the gain to the vinyl chloride industry would be very small. This would be the conclusion of a simple application of the arguments in this paper. But further study may help considerably in a general understanding of cancer, and the pay-off to society would be tremendous. This is particularly true since the vinyl chloride dose can probably be estimated and the background of liver angiosarcoma is small. Some suggestions are in Appendix III.

smoking. If asbestos and radiation are any guide, and this should certainly be checked before proceeding further, the total hazard could be reduced by a factor of 5-50 if only non-smokers were allowed to be vinyl chloride workers just as companies now tend only to hire uranium miners who do not smoke.

The risk in vinyl chloride operations is already so low that this does not seem a worthwhile restriction (we see this at once by noting that a fair hazard pay is \$10/year, and a smoker will spend far more than that on his habit). But for other chemicals it may be worthwhile.

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in the act; either a chemical is carcinogenic or it isn't and either it is present in the foodstuff or it is not. There is no room for the grey area in which we live. The only eventual solution is a risk/benefit analysis, although in some cases, the result of such an analysis is sufficiently clear that there is no problem in making definite distinctions.

For unintentional, low concentration additives there is a particularly good case for modifying the Delaney Clause, to avoid this confusion. The clause could well call upon a risk/benefit analysis to be approved by the FDA. This would have the concomitant advantage of having procedures for foodstuffs similar to the procedures already suggested by EPA.

There are those who argue that the Delaney Clause will be tested in the courts and that if the case is properly presented the courts will exercise common sense and rule along the lines suggested here. Others argue that modifying the legislation is the correct course to follow. Without entering into the argument on this particular question I note that in each case the risk/benefit analysis seems necessary to convince judges or legislators.

Appendix III

Prognosis and Suggestions for Study

The 50 liver cancers which have been diagnosed among vinyl chloride workers have been attributed within 2-3 years. If we allow for the fact that some of these were diagnosed earlier, we find a rate of about 10 per year.

The studies of cancer among cigarette smokers of Doll noted in Appendix I suggest that this risk may stay constant even if all exposure has now ceased. Thus we expect 10 more cases per year to be diagnosed decreasing slowly as the workers die from other causes. Another 100 to 200 cases might yet appear. It is important to be prepared for this, otherwise vinyl chloride workers may lose confidence in the effect of the presently improved working conditions.

Of course this number might be much smaller if a repair mechanism exists for the latent cancer. But such a repair mechanism was not found in Doll's study and the data is consistent with none. If, however, less than 100 cases of liver angiosarcoma were to appear in the next several years among former vinyl chloride workers, we would have strong evidence for a repair mechanism.

This suggests that as we have done in many other cases society can learn a lot from mistakes. The almost unique feature of liver angiosarcomas caused by vinyl chloride suggests that we must have a concerted effort to continue a study of vinyl chloride workers.

At the moment, there is very little information available about the exposure history of the 50 unfortunate victims. If even crude information were available, it might be possible to establish

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review article

SPI-08365

Short term screening tests for carcinogens

Bryn A. Bridges*

There are now short term tests with a high predictive value for mammalian carcinogens. Many of them are based on the ability to detect damage to DNA in bacteria or mammalian cells after metabolic activation by microsomal enzymes. Their introduction will enable provisional safety assessments to be made for the many thousands of industrial and environmental chemicals for which long-term animal testing cannot at present be considered.

It has been estimated¹ that if one could totally abolish human cancer it would add a mere two years to the average lifespan. Most cancer sufferers are past retiring age so that industrial production would be little affected by the abolition of cancer. The fight against cancer must instead be justified in terms of the cost of hospital services and of basic humanity; treatment of cancer, even when it is successful, is a miserable process. When it fails, as it so often does, one feels guilty of a double offence, not only the loss of the patient, but the imposition of heroic measures that themselves may cause considerable physical and mental suffering.

The International Agency for Research on Cancer holds it as a rule of thumb that around 80% of cancer has an environmental cause^{2,3}; others would give a higher figure⁴. The evidence is indirect, being based on differences in tumour incidence between genetically similar populations in different environments^{2,3,5}. Even if this estimate is only approximately correct it leads ineluctably to the conclusion that a substantial proportion of cancers, possibly a majority, are in principle preventable. In past decades those responsible for the disbursement of cancer research funds have tended either to look for a breakthrough in the area of curative treatments or to make a long term investment in basic biology in an attempt to understand the disease (or more properly diseases since "cancer" is but a general term for hundreds of different malignant conditions). Recently, however, these two essential approaches have been complemented by a third, the search for the specific environmental factors involved in carcinogenesis.

The nature of these environmental factors is not known in detail, but it seems likely that many of them are man-made or natural chemicals. Even factors such as diet or stress may act indirectly by altering the metabolism of chemicals in the gut or in the body itself. Of course, identification of environmental carcinogens does not necessarily lead to their removal but it does open the way to control so that the risk that they present is no more than is necessary when weighed against any benefits that they may give.

The most direct method of identifying environmental carcinogens for man is based on population studies, but unfortunately it is expensive and seems to have rather low resolving power. Only a handful of chemicals are known to be carcinogenic to man and most of these have been detected following the study of workers occupationally

exposed to chemicals capable of giving rise to specific and rather rare neoplasms. The classic case is soot which has been known for 200 years to produce scrotal cancer in young chimney sweeps⁶. More recent examples are 2-naphthylamine, vinyl chloride and asbestos which produce, respectively, rare cancers of the bladder, angiosarcomas of the liver, and mesotheliomas of the lung cavity. The problems involved in identifying two populations differing only in their exposure to one chemical are formidable and are further compounded if the chemical gives rise not to specific and otherwise rare tumours, but to a variety of common cancers. Population studies are thus likely to be of limited value in identifying environmental (as distinct from occupational) carcinogens but they will be indispensable in providing the basis for risk evaluation, particularly where dose-response data can be obtained.

The alternative is to screen chemicals to which man is exposed. The generally accepted method of doing this is to carry out long term carcinogenicity tests with laboratory mammals. Not only are those tests very demanding of resources but any extension of animal testing on such a wide scale would be vigorously opposed by a number of animal welfare lobbies. In practice, it is inconceivable that resources could be made available (either men, money or mice) on the necessary scale to screen all the tens of thousands of substances to which humans are exposed. Of necessity, therefore, testing with whole mammals will be restricted to certain groups of suspect substances, for example those suspect but already in use on a large scale, or those substances which it is proposed to administer on a large scale, as food additives or cosmetics, for instance.

If one is to screen for carcinogenic chemicals, therefore, one must use short term tests with a high predictive value. I propose to review a number of possible systems which have been suggested in recent years. As will become apparent, many of them are in fact systems for the detection of agents causing damage to DNA. Damage to DNA leading to heritable changes may be important to man not only because of carcinogenicity but because it may cause hereditary disease⁷⁻⁹. Moreover, DNA damage may conceivably be involved in ageing and diseases associated with ageing¹. I take it as self-evident that any agent likely to damage the DNA of man, whether in somatic or germ cells, is potentially hazardous.

Screening systems

The induction of cancer is but one aspect of long term toxicity and for the evaluation of such hazards a three-tier

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animal carcinogenicity and bacterial mutagenicity with and without metabolic activation (from McCann *et al.*³⁴)

Group of compounds	Carcinogens detected as bacterial mutagens	Non-carcinogens not mutagenic to bacteria	Compounds of uncertain carcinogenicity detected as mutagens
Aromatic amines etc.	23/25	10/12	5/7
Alkaloids, etc.	17/20	1/3	1/1
Polycyclic aromatics	26/27	7/9	1/1
Esters, epoxides, carbamates, etc.	13/18	5/9	0/1
Nitro aromatics and heterocycles	28/28	1/4	0/2
Miscellaneous organics	1/6	13/13	0/1
Nitrosamines	20/21	2/2	1/1
Fungal toxins and antibiotics	8/9	5/5	-
Mixtures (cigarette smoke condensate)	1/1	-	-
Miscellaneous heterocycles	1/4	7/7	-
Miscellaneous nitrogen compounds	7/9	2/4	-
Azo dyes and diazo compounds	11/11	2/3	3/3
Common laboratory biochemicals	-	46/46	-
Total	157/178	101/117	11/17

tion is only as good as the confidence one has in the reliability of both parameters. Whereas positive and negative mutagenicity results can be both unambiguous and reproducible, the same is not true of carcinogenicity results where, as will be discussed below, there are several factors which could result in a failure to detect relatively weak carcinogens. As discussed by McCann and Ames³⁴, there is good reason to believe that many of the "false" positive chemicals will eventually be shown to be carcinogenic. This has already happened with the food additive furyl furamide which had been used for many years in Japan and had given negative results in two carcinogenicity trials³⁵. After positive results had been obtained in *Bacillus subtilis* and *E. coli* systems for detecting DNA damage, it was re-examined and shown to produce a low but significant yield for tumours when given to foetal and young mice³⁶. There is also the real possibility that some of the "false" negatives are genuine, that metabolism *in vivo* is different from that with isolated microsome preparations. Only further studies in depth can resolve this.

It is worth analysing the data of McCann *et al.*, further to see whether there is any particular type of mutational event (as detected by the *Salmonella*) that is correlated with carcinogenicity. It has been postulated³⁷ that carcinogenicity is associated with the ability to produce specific types of frameshift mutation. This hypothesis does not hold up in any general application. As can be seen from Table 2, whereas most members of some groups of carcinogens (for example, aromatic amines, polycyclic aromatics and nitroaromatics) gave rise to both frameshifts and base-pair substitutions, others (for example, esters, epoxides and carbamates, nitrosamines, miscellaneous nitrogen compounds) gave rise exclusively to base-pair substitutions. There was no group that gave rise exclusively to frameshifts. Taken together, 45.2% of mutagenic carcinogens gave rise solely to base-pair substitutions, 14.8% solely to frameshifts, and 40% gave rise to both.

Rosenkranz (cited in ref. 62) using a Pol⁻ strain of *E. coli* together with the *Salmonella* set without plasmids, has obtained results as encouraging as those of McCann *et al.* with the plasmid-containing salmonellas. Of about 100 compounds tested, 85% of the known carcinogens were detected (91% of direct acting carcinogens, 72% of procarcinogens). The proportion of non-carcinogens detected as positive was rather high, 30%, but the figure is not comparable with the lower value derived from the data of McCann *et al.*³⁴ since it did not include the 46 common laboratory biochemicals tested by the latter workers, none of which was positive.

A comparison of the efficiency of various microbial systems for detecting DNA damaging agents has been carried out by Shirasu *et al.*⁴¹. They found that the hypersensitivity of repair-deficient bacteria (Rec⁻ *B. subtilis*) was the most sensitive. Of 166 pesticides studied, 23 were posi-

tive in the Rec-assay (carried out without microsomal activation). Of the 143 negatives, none proved to be positive when tested with *E. coli* or *Salmonella* reverse mutation systems. Of the 23 positives 9 were positive in reverse mutation systems, and of these 9, 1 was not detected by the *E. coli* strains and 1 by the *Salmonella* strains. As far as base-pair substitution mutations are concerned, the non-plasmid *E. coli* strains were found to be preferable to the non-plasmid *Salmonella* strains at least with some groups such as nitrofurans. With other groups such as the organic phosphates a similar small proportion of mutagens was missed by both *S. typhimurium* and *E. coli* strains⁴².

The only study in which a single laboratory has compared a number of different tests for predicting carcinogenicity appears to have been carried out by the Central Toxicology Laboratory of ICI (D. Anderson *et al.*, unpublished). The preliminary results with 120 chemicals point to the value of the bacterial mutation tests when metabolic activation is incorporated. The carcinogenicity, or non-carcinogenicity was accurately predicted for 90% of the chemicals by this test. Cell transformation *in vitro* came close with 83% accuracy. Rather less accurate was degranulation of endoplasmic reticulum, 72%, and morphological changes following subcutaneous implantation, 70% correctly predicted. Sebaceous gland suppression⁴³ was good for polycyclic hydrocarbons (90%) but little better than random for other substances (52-62%). Tetrazolium reduction in mouse skin was also poor (62% overall). The authors conclude that some of these rapid tests are capable of distinguishing between carcinogens and non-carcinogens with sufficient accuracy to enable them to be used for selecting potential carcinogens. They also make the point that figures for successful prediction must be treated with

Table 2 Number of carcinogens detected as bacterial mutagens (with or without metabolic activation) classified as to type of mutation induced.

	Base-pair substitutions only	Frameshifts only	Both base-pair substitution and frameshift mutations
A	1	9	13
B	14	2	1
C*	7	5	14
D	13	0	0
E	5	0	23
F	1	0	0
G*	19	0	0
H	0	3	5
I	0	1	0
J	0	1	0
K	7	0	0
L	3	2	6
M	0	0	0
Total	70	23	62

* Data not available for one member.

Key for chemical groups as for Table 1. (From McCann *et al.*³⁴)

some caution since they can be manipulated within wide limits by the choice of substances tested. As their substances include a large number of non-carcinogenic chemicals closely related to known carcinogens they feel that their results give a reasonably good indication of the likely value of the tests in practice.

DNA damage and human cancer

The correlation between mutagenicity and carcinogenicity is satisfying to those who believe in the somatic mutation theory of cancer²² and distressing to those who do not²³. I think the correlation can be more correctly described as being between DNA damaging ability and carcinogenicity. Gene mutation is but one consequence of DNA damage; others such as chromosomal structural rearrangements, virus integration and excision, and changes in gene expression, may well be important in the carcinogenic process. Non-genetic effects are also probably involved.

One could argue that detecting DNA damage is merely a very sensitive way of detecting electrophilic reagents, and that the actual target(s) may well be in other molecules as well as or instead of DNA. This is quite possible; but there is other evidence strongly implicating DNA damage as the rate-limiting step in many carcinogenic processes.

In man, for example, mutations in five complementation groups are known to reduce or abolish the ability of cells to remove ultraviolet photoproducts from their DNA²⁴. In all cases they enormously increase sensitivity to the carcinogenic effect of sunlight (resulting in the hereditary disease xeroderma pigmentosum). A further mutation causing the same symptoms has been shown to be associated with a deficiency in another DNA repair pathway active on newly synthesised DNA²⁵. Another human mutation responsible for the disease ataxia telangiectasia has been shown to block repair of ionising radiation damage²⁶ and also results in proneness to develop malignant disease²⁷. Thus, the human data strengthen our confidence in the reality of the observed correlation between DNA damaging ability and carcinogenicity. It must be emphasised, however, that even an empirical "litmus paper test", with no known theoretical basis, which gave an 80 to 90% predictiveness for carcinogenicity would be a powerful tool in the screening of chemicals for human toxicity.

The place of tests with mammals

No single test is adequate for a first-tier (sub-mammalian) screen; most authorities agree that a battery of tests must be used as false negatives may occur with any one test. The results of these tests would be used to assign priorities for further testing using mammalian systems. At one extreme, a substance with no apparent effect on sub-mammalian systems might be given a priority so low that no further tests would be considered unless a large human population exposure were to occur or be contemplated. At the other extreme a strongly active substance might well be regarded as hazardous without further testing if the population exposed were small. If it were, say, an industrial chemical, then production workers and users ought to treat it as if it were a known toxic agent or carcinogen, at least until such time as it became possible to carry out full scale animal tests.

The greatest problem in testing for carcinogenicity or mutagenicity with mammals is the insensitivity of most of the tests. This has led, for example, to difficulties in validating microbial carcinogenicity screening systems since many of the "false" positives obtained with these are based on animal experiments that may be inadequate²⁸. There have been, and still are, too many carcinogenicity tests with 20 or 30 animals per group.

Provided that the number of animals in each group is kept small, even a large increase in the frequency of neo-

plasms can fail to be statistically significant and enable a conclusion of "non-carcinogenic" to be drawn (see for example a recent study on the carcinogenicity of hair dyes²⁹). As long ago as 1954, Barnes and Denz³⁰ pointed out that to detect with a probability of 0.01 an effect occurring in 1% of the animals, one would need a group of at least 455 animals. If the effect also occurred spontaneously then the number of animals per group would have to be increased manyfold. Today, notwithstanding, carcinogenicity experiments with 100 animals per group are often regarded as "good" and those with 200 animals per group are extremely rare. But although "kilomouse" experiments are theoretically attractive there may be little to be gained from them in practice. Logistical problems dictate that such experiments be phased over many weeks and involve slightly varying conditions. "Spontaneous" rates of tumour occurrence unfortunately often vary in time and place, perhaps reflecting slight differences in diet, and it is often difficult to run an adequate control group. Errors in handling are also more likely in very large experiments.

Whereas a significant reproducible positive result in a mammalian test may be taken as indicating the existence of a potential hazard for man, a negative result taken should not necessarily be taken to indicate the absence of hazard, particularly if the human population to be exposed is very large, and the number of animals in the test small. We may take some comfort where the disparity in dose between the animal and human exposure is great. This is not always so. Anaesthetic gases, for example, are given to an appreciable fraction of the population in Western society at concentrations which are not far from the lethal level. One might well feel that a negative result in a screening test with a few dozen mice would be of little value.

It can be seen that mammalian tests are not wholly appropriate for the validation of sub-mammalian tests, and it is perhaps remarkable that they should show such good agreement. Validation of one type of test against another must not blind one to the real objective, which is to predict long term toxic effects in man. There are few proven human carcinogens and most of these can be detected by both mammalian and sub-mammalian tests. In man, carcinogens tend to be recognised only when the tumour is of a rare type and there is a sufficient cluster of cases to enable association with a particular occupation to be seen by an alert clinician. Genetic effects in man are even harder to detect retrospectively. There are several examples of somatic chromosome damage in lymphocytes of persons exposed to known mutagenic and carcinogenic substances (for example, vinyl chloride³¹, ozone³², benzene³³, toluene³⁴, cadmium^{35,36} and methyl mercury³⁷). Recent evidence for the possibility of dominant lethal damage in man by vinyl chloride (P. Infante, unpublished) and anaesthetic gases³⁸ is ominous but needs closer examination.

Ultimately quantitative risk assessments must be attempted, for we must face the unpalatable fact that man will almost certainly have to be exposed to some carcinogens and mutagens whose benefits cannot be dispensed with and others which it is impracticable to eliminate from the environment. Risk evaluations at the present time almost always require information which is not available, such as the nature of the dose-effect response at low doses. Nevertheless, approaches must be found that will lead eventually to risk-benefit evaluations based less on guesswork and more upon knowledge. In the meantime the use of short term tests would enable potentially carcinogenic substances to be identified among the many thousands for which long term animal testing cannot at present be contemplated. This in turn would open the door to provisional regulatory action to minimise human exposure. Taken seriously and on a large enough scale, there is good reason to believe that this approach would ultimately result in a reduction in the incidence of chemically induced cancer.

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Institutional Interactions in Problems of Occupational Health:

An Industry View on the Lessons from Vinyl Chloride

by

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

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

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

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

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

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

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

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

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

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

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

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

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

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

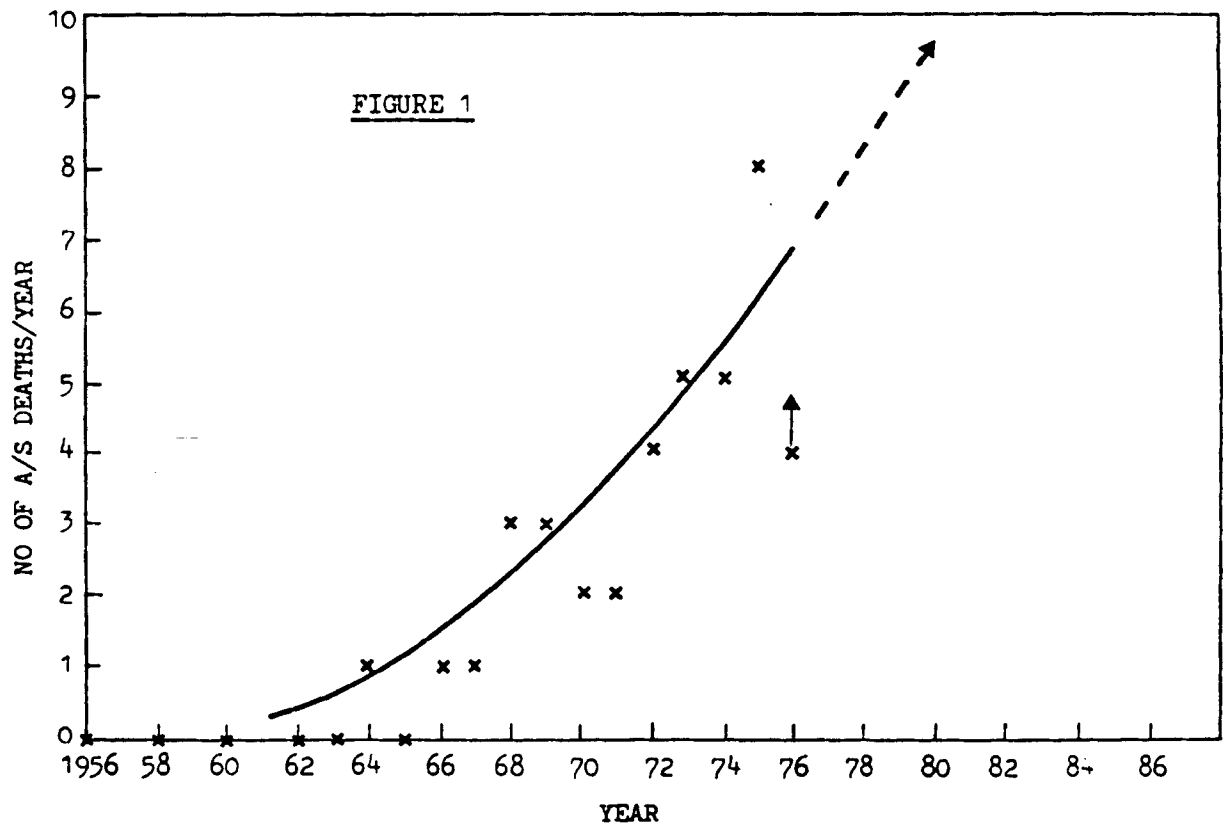
SPI-08377

TABLE 3

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

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

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



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