

Exposure Indices for Epidemiological Surveillance of Carcinogenic Agents in an Industrial Chemical Environment

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A prospective system for establishing chemical exposure indices was developed and implemented for 22 chemicals used at a Louisville chemical plant. Validation of the indices was done statistically using industry-related cancer (liver angiosarcoma) and worker-matched controls. A rank ordered system for exposures was used to identify a relationship between the occurrence of disease and the presence of a suspect chemical used in the industrial environment.

A major difficulty in the epidemiology of occupational carcinogenesis is obtaining accurate exposure data, especially if the data must be procured after cancer develops. While epidemiological investigations of outbreaks of disease, infectious or chronic, are always retrospective, the long latent period between exposure to a causative factor and the occurrence of cancer complicates this problem. Routine continuous recording of exposure to possible carcinogens is an ideal goal. Unfortunately, this is not practical for most chemicals in a modern industrial setting. What is eminently practical, however, is a system utilizing rank ordering of exposures for highly suspect chemicals.

The B. F. Goodrich Louisville Chemical plant developed such a system in 1974 in response to the discovery of cases of hepatic angiosarcoma.¹⁻⁵ This system was the basis of the initial reports. It was extensively modified during a prospective medical screening program established by the University of Louisville under contract NO1-CN-55212 with the cancer control program of the National Cancer Institute.^{6,7} The authors are unaware of other similar existing data sets. Occupational studies are usually based on group, rather than individual, exposures. An excellent review of the literature is given by Gamble et al.⁸ A recent discussion of a computerized system is given by Kerr.⁹

The system for establishing exposure indices on an ongoing basis was developed through employee work histories and rank ordered job exposure categories. All jobs are classified uniquely by both area location and work description by means of area-description (A-D) codes which identify employment occurring in a particular building or area, independent of job; in a particular job, independent of building or area; or by both area and description.

The exposure index combines two components, i.e., work history and job exposure category, by utilizing the A-D code. The chemical exposure rating is an ordered, six-category ranking assigned to each A-D number for each calendar year, as follows:

Rating	Level of Exposure
0	<u>Absent from Environment</u> (on leave, furlough, layoff, etc.)
1	<u>Lowest Exposure</u> (includes exposure up to somewhere near one hour per day)
2	<u>Minimal Exposure to Low Levels</u> (chemical in building — not handled; low vapor pressure and dust level; individual probably works on different floor)
3	<u>Moderate Exposure</u> (works around the chemical, but exposure is minimal; individual is frequently exposed to little spills or leaks and infrequently — less than once per month — to large spills or leaks)
4	<u>Works in Area Subject to High Occupational Exposures</u> (normally exposure is minimal, but large spills or leaks occur once per month or more)
5	<u>Works in Areas Where Level is High</u> (exposure levels in area are frequently high; might consider that some risk is involved if the chemical is very toxic)
6	<u>Intimate Contact — Skin or High Inhalation</u> (includes individuals with daily and direct contact with the chemicals, such as poly cleaner in the old days and those who handled slurry)

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Table 2. — Standard Normal Deviates Comparing Exposure Ranks of Angiosarcoma Cases with the Average Exposure of Matched* Controls (by Selected Chemicals).				
Chemical	Group			
	1 (23 Controls)	2 (29 Controls)	3 (36 Controls)	4 (4 Controls)
1	-1.43	2.32	-0.66	-2.20
2	-2.13	-0.93	-2.00	-0.53
3	-3.54	-2.16	-3.16	-1.50
4	-3.31	-1.79	-0.06	-1.76
5	3.97	0.84	5.08	1.11
6	-2.01	-2.58	-1.59	—
7	-2.33	-2.59	-1.93	-1.50
8	0.29	-0.47	1.56	—
9	-3.92	-0.27	6.44	-2.28
10	-0.76	3.64	0.17	-0.71
11	11.27	7.59	0.93	5.08
12	-1.69	-1.35	0.45	-1.00
13	-1.78	-1.41	5.95	0.00
14	-2.41	-2.91	-2.35	-0.85
15	-1.87	-1.63	0.40	-1.21
16	5.13	3.12	5.77	2.55
17	-0.77	-3.43	5.53	-1.50
18	1.55	-1.45	5.68	1.07
19	2.56	-4.36	4.64	-0.83
20	9.11	2.65	3.72	2.60
21	-3.87	-2.39	-2.91	-1.31
22	6.55	2.34	2.36	2.85

*Matched by age, sex, race, year of employment and survival as a B. F. Goodrich employee to January 1, 1974

did not have the A-D numbers that were subsequently developed; these older records referred to many jobs which no longer existed, and to some which were performed in buildings long since torn down. However, a staff of knowledgeable employees matched the jobs listed on these payroll records with current A-D numbers. Final determination for controversial work records was made, wherever possible, by an individual employee's review. The chemical exposure judges, who were assigning ordered rating exposures to A-D numbers for each year, faced these same problems. They used, in addition to their memory, whatever records of chemical processes and procedures that were available. (The company maintains a file on all products ever produced and all processes ever used at the plant.)

This system of determining work exposure data was validated empirically in the following manner: The incidence of hepatic angiosarcoma at the B. F. Goodrich plant since January 1, 1974, presented in four subjects. Each of the four subjects was matched by exact year of birth, by sex and race (white or non-white), by exact year of employment, and by continuing employment at the

B. F. Goodrich plant through January 1, 1974. All matches are included in the subsequent analysis. Each of the angiosarcoma subjects and the corresponding matched group were compared on CERM separately for each calendar year. The results were then ranked within each calendar year and the ranks were summed over the calendar years. If the work histories and the ordered rating exposures were no better than random assignments, one would expect a uniform distribution of ranks within each year and independence from year to year. Otherwise, rank order exposures should demonstrate higher exposure to vinyl chloride in those individuals with hepatic angiosarcoma.

Table 2, which gives standard normal deviates, was calculated from the observed sum of ranks, the expected sum of ranks, and the theoretical standard error (conditional on the observed pattern of tied ranks) of the expected sum of ranks. Sums were over years. The results show a very clear pattern of high exposure to chemical number 16, vinyl chloride. This is to be expected a priori if the work history data and the exposure rank data are valid. A second finding of importance is that all four angio-

Table 3. — Comparison of Frequency of Observed and Expected Excess Exposure to Selected Chemicals.				
Number of Angiosarcomas Showing Excess Exposure	Expected* Proportion	Observed Frequency	Expected Frequency	Contribution to Chi Square
0	1/16	6	1.25	18.05
1	4/16	6	5.00	0.20
2	6/16	2	7.50	4.03
3	4/16	1	5.00	3.20
4	1/16	5	1.25	11.25
Total		20	20.00	36.73 = χ^2 $p < 0.001$

*Calculated from the binomial distribution with $n=4$ and $p=1/2$

ANGIOSARCOMA CASE IV

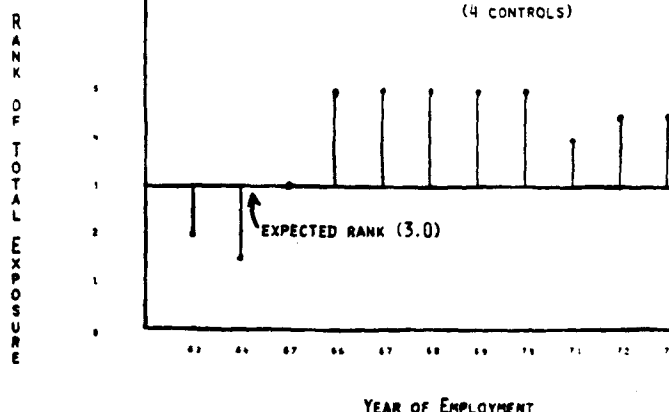


Fig 4. — Observed and expected exposure rank to vinyl chloride for each full year of employment matched by age, sex, race, year of employment and survival as a B. F. Goodrich employee to January 1, 1974.

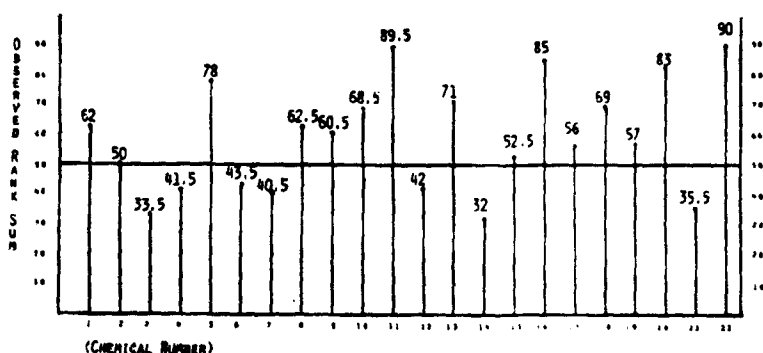


Fig 5. — Observed and expected cumulative exposure rank sums for four angiosarcoma cases compared with matched sets of controls. (Matched by age, sex, race, year of employment and survival as a B. F. Goodrich Chemical Company employee to January 1, 1974. The numbers of controls for the four angiosarcoma patients were 4, 23, 29 and 36. The maximum possible rank sum is 96 and the minimum is 4. Expected rank sum is 50. A rank sum of 80 or more would occur by chance 2.6% of the time. A rank sum of 20 or less would occur 2.6% of the time.)

sarcoma subjects also showed significantly high exposures to chemicals number 20 and 22. Chemical number 20 is a group of catalysts used only with vinyl chloride and chemical number 22 is hexane, used as a solvent for the group of vinyl chloride catalysts. In addition, the data also strongly suggest a high exposure to chemical number 11, diethyl maleate, also a specialized catalyst used only for a specialized process with vinyl chloride.

A clear pattern of exposure is apparent in Table 2. All four angiosarcoma subjects showed excess exposure to 5 of 20 chemicals (numbers 5, 11, 16, 20, 22). By chance, this would be expected to occur for only 1.25 chemicals. All four angiosarcoma subjects also had less than expected exposure to six additional chemicals (numbers 2, 3, 4, 7, 14, 21). The expectation again is only 1.25. When the binomial distribution is inspected (i.e., the distribution of the number of successes in four trials with the probability of success at each trial being one-half), the results are statistically significant ($\chi^2 = 36.7$; $p < 0.001$). These are summarized in Table 3. Once more the null hypothesis of random assignment of exposures is rejected. For chemicals number 6 and 8, the exposure was tied for all members of group 4 and they were not included in the analysis. Figs 1 to 4 show the observed to the expected rank exposure for each employee with angiosarcoma by each full year of exposure. The pattern is one of consistent high exposure

as compared to the matched controls. It is evident that the system does reflect the autocorrelation in jobs over time as well as the exposure to vinyl chloride among the subjects with angiosarcoma.

To remove the assumption of independence from year to year (as would be required in new field studies), the CERM were summed over years for each angiosarcoma subject and the associated controls. These then provided a single ranking for each matched group. The observed independent ranks of the four angiosarcoma subjects were then summed and compared to the expected rank sums in 5. The exact distribution of the rank sums was obtained by direct enumeration. The angiosarcoma subjects again show significantly high exposure to chemicals number 16 (vinyl chloride), number 20 (catalysts), number 22 (hexane used as a catalyst solvent), and number 11 (diethyl maleate). Fig 6 displays the vinyl chloride rank of the angiosarcoma subject in each matched group; this is the chemical through which empirical validation of the procedure is achieved.

Prior knowledge of the etiology of angiosarcoma was used by the authors to validate these exposure indices. It is questionable what the situation would have been if such prior knowledge had not existed. This study would have shown that employees who subsequently developed angiosarcoma had had high exposure as compared to

Questions For Consideration With Respect To The Proposed University of Louisville Brain Cancer/VCM Case-Control Study

Carlo:

1. What is the current status of your relationship with each of the three companies formerly comprising B.F. Goodrich in Louisville? When you met with the CMA panel earlier this year you said something about "re-establishing a working network with all three companies."
2. What data would you need to get from all three units? Do you anticipate any problems obtaining the necessary data? Are there any other sources of the necessary data that could be accessed if needed?
3. You have described the brain cancer study in terms of "20-year prospective follow-up" and "25-year combined retrospective" evaluation. What periods of time do these cover? How are the data alike and/or different between the two periods of time?
4. Do you still have the peer reviewers' comments on your 1981 paper on ASL and vinyl chloride? If so, could you make them available to us? This would help us understand how other researchers have viewed the methodology that you employed for that paper and would employ for the brain cancer study.
5. What is your best estimate of the maximum number of brain cancer cases that could be available for study, assuming 1) that you could only get tissue for Goodrich employee cases that were hospitalized in the Louisville area; and 2) that you could get tissue from Goodrich employees hospitalized outside the Louisville area as well? This is really a question about what the maximum statistical power of the study is likely to be.
6. Can we develop a firm timetable for initiation and completion of the study?
7. Can we develop line-item breakdowns and prepare a more detailed study budget?
8. Would you consider working with someone like Kenneth Mundt as a co-investigator/co-author, to add some additional epidemiologic expertise to the brain cancer study and to take full advantage of the follow-up data that he will be generating in the industry-wide cohort study?

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- Protocol: Outlined as part of the proposal; defined as initial product of the project.
- Impact of any pending AS in operation of
Univ. of Med School & Hospital.

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1990 File for Update

BIOLOGICAL THRESHOLD FOR VINYL CHLORIDE EXPOSURE-INDUCED HEPATIC ANGIOSARCOMA IN HUMANS

Introduction

In most epidemiological studies, it has not been possible to determine the dose of the agents to which humans have been exposed. Occasionally, crude retrospective dose-response curves have been developed. A summary was made by the Meselson Committee regarding the dose levels of several known human carcinogens which appear to be carcinogenic in certain human populations.¹ The characteristics of exposure and the spectrum of effect comes together in a correlated relationship customarily referred to as a dose-response relationship. This relationship is a fundamental and pervasive concept in toxicology. Indeed, an understanding of this relationship and its facile use is the essence of the study of toxic materials. Although a full understanding of the intricacies of both dose and response entails many complexities, only a few assumptions form the skeleton of the relationship. The first is that an implicit assumption of causality is made. To arrive at a quantitative and precise statement of the relationship between a toxic material and an observation effect or response, one must know with reasonable certainty that the relationship is indeed a causal one. This is true for vinyl chloride and angiosarcoma.

In many epidemiological studies, results show an *association* between a response and the disease, and one or more impinging variables. Not infrequently the data are amenable to

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presentation in terms similar to those employed in experimental use of dose response in pharmacology and toxicology. In strict usage, the dose-response relationship is firmly based on the knowledge or a reasonable presumption that the effect is a result of the toxic agent. The second assumption is simply and obviously that the response is, in fact, related to the dose. The simplicity of this assumption is often a source of misunderstanding. This assumption is really a composite of three others that will recur frequently:

- A. There is a molecular or receptor site with which the chemicals interact to produce the response;
- B. The production of response and the degree of response are related to the concentration of the agent at reactive sites;
- C. The concentration at the site is, in turn, related to the administered dose.

Thus, the numerical and graphic dimensions of a dose-response relationship can include the assumptions that: (1) the response is a function of concentration at the site; (2) the concentration at the site is a function of the dose; and (3) the response and dose are causally related.^{2, 3}

In toxicology, when assessing the safety of a substance, it is necessary to have both a quantifiable method of measurement and a variety of criteria in points of toxicity that can be used. The ideal criteria should be closely associated with the molecular events resulting from exposure to the toxic agent. This idea is usually considered unapproachable in clinical

settings, especially with regard to effects with great latency, such as malignancy. Vinyl chloride-induced hepatic angiosarcoma among plastic workers represents such a clinical setting.

The selection of a toxic end-point for measurement is also not always so straightforward. In vinyl chloride exposure, other end points (non-malignant) have been quantitatively demonstrated to be precise indicators of the acute and chronic phases of hepatotoxicity.^{4, 5, 6} In addition, prospective clinical data has been accumulated and developed over the past ten years through extensive screening and medical surveillance of vinyl monomer-exposed workers which fulfill most of the above criteria. This paper provides the clinical and epidemiological evidence for both a dose-response and biological threshold response to an occupational hazard.⁷

Materials and Methods

Vinyl chloride-associated hepatic angiosarcoma (HAS) was studied in two populations. One consisted of 1,200 vinyl chloride polymerization workers from the index plant, i.e., where the original human vinyl chloride-associated HAS observations were made. This index plant also is the single largest contributor of VC-related HAS cases worldwide. This cohort has been followed respectively from 1¹₇₄ to the present via a medical surveillance program. The medical surveillance program consisted of annual medical examinations, clinical laboratory screening on an annual/semi-annual basis which included over 50 biochemical studies of blood and urine, x-ray examinations of the chest, abdomen and hands,

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radioisotopic studies of the liver, spleen and brain, and angiographic-hemodynamic examinations of the portosplenic system. Detailed follow-up clinical investigations were performed on all biochemical, radiological, or clinical abnormalities. Approximately 110 cases of hepatic disease constitute a sub-cohort of this population, 15% of whom have vinyl chloride-associated non-malignant liver injury.^{8, 9}

The second population of cases consisted of all VC-associated HAS cases reported to the *Angiosarcoma of the Liver Registry of the Imperial Chemical Industries Corporation* in England.¹⁰ This Registry contains all histologically-documented VC-associated HAS cases reported in the scientific literature, by government agencies and/or chemical industries, from North America, Europe, South America and Asia.¹¹⁻²³ All cases have been histologically confirmed as liver angiosarcomas. Each case has a date of birth, company or factory of employment, date of clinical diagnosis, age at diagnosis, date of first exposure, years of exposure (i.e., years worked in a vinyl chloride polymerization manufacturing plant), years from first exposure to time of diagnosis (latency), date of death, estimated exposure levels, occupational (job) activities, and some information with regards to prior occupation, nationality or country of origin.

From these two cohorts, 108 histologically-confirmed cases of angiosarcoma constitute this study population group. Each case spent from three to 37 years working in vinyl chloride polymerization production plants in 12 different countries from 1938 through 1984. Forty-three (43) cases of HAS are from North America, 2 from Japan, 6 from

Eastern Europe, and the remaining 57 from Western Europe and the United Kingdom. All cases have been histologically confirmed as liver angiosarcomas. All histological identifications were made or confirmed by internationally-recognized and experienced pathologists before this analysis and independent of this study's author. No histologically-confirmed case has been excluded. Forty (40) cases were retrospectively identified or identified before the beginning of this study in 1975. The remaining 68 cases developed during the 10-year follow-up interval since the beginning of this study.

Data and Results

Worldwide HAS case occurrences demonstrate a poisson-like distribution with the peak occurring about 1976 (Figure 1). The earliest cases identified in North America occurred in 1962 with a peak and median occurrence between 1974-1975. The open circles identify the North American cases, including the index plant first identified in 1967, with the median in 1976 and peak in 1978. The eight remaining cases were identified between 1965-78 with the median and peak occurring in 1973. The annual incidence of HAS by date of diagnosis and geographic location for four leading countries is shown in Figure 2.

The distribution by year of first exposure for the entire cohort begins in 1940 and finishes in 1968 (Figure 3). The initial 38 cases (triangle-based circles) retrospectively identified (between 1955-1974), began their vinyl chloride exposure before 1968. Since 1974, all 68 prospectively identified cases (closed circles) also began their year of first exposure prior to 1968. Figure 4 illustrates the age at which diagnosis was first made among

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the VC-associated HAS. The frequency of HAS latency periods has a skewed distribution, peaking at approximately 20 years (Figure 5). The range of the latency periods is from 9-38 years. The mean latency period for each five-year interval, starting with 1940-44, demonstrates a progressive shortening from 35 to 14.6 years with an overall average latency of 22.6 years (^{Fig 16}~~Table 1~~).

The latency periods point out a discrepancy between the reduction in occupational exposure levels and the sudden decrease in HAS occurrence. On initial observation, the reduction of exposure levels in 1974 appears to have produced a rapid and profound reduction in the incidence of angiosarcoma (Figure 1). Had the reduction in exposure levels instituted in 1974 been a major factor in reducing the occurrence of HAS, its effect would not be expected for at least nine years, i.e., shortest latency. In fact, study of the latency period in other cancers in which the carcinogen, its dose and duration are known, have shown a prolongation of the latency period which a decrease in dosage or duration of exposure.

A review of the index plant cases (13 cases) illustrates a reversed exposure-latency relationship between the total (or first year of) exposure and the onset of disease. This relationship holds for all the North American (United States and Canada) cases and the various European countries (western Germany, France, United Kingdom, Sweden and Yugoslavia). In contrast, these HAS cases' latency periods decrease with shorter duration of exposure (Figures 6 and 7).

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Utilizing this data, each year of exposure was weighted on the basis of the estimated level of exposure. Each case's total exposure was redetermined based on the exact year of exposure. Replotting of the latency versus total cumulative exposure (weighted exposure) continues to demonstrate the same linear relationship in an even more highly correlated manner. This is seen in index plant cases (Figure 11), USA cases (Figure 12), the Canadian cases (Figure 13), and holds true for the European and world-wide cases. It is most dramatically shown in the short-exposure group (Figure 14).

Discussion

These data provide, for the first time, clinical (human) evidence for a biological threshold for VC toxicity including carcinogenicity. The retrospective and prospective demonstration that all cases of VC-associated HAS began their first exposure before 1968 in plants which began operation before 1967 (majority before 1960), indicate that a common pattern of environmental working conditions were present during the induction and subsequent promoting periods. Vinyl chloride's carcinogenic effect is related to a particular time and environment. This pattern is confirmed in seven countries around the world.

If, as traditionally understood, the risk of developing VC-associated HAS is related to the different levels of environmental exposure during the earlier years of employment, then the gradual reduction in exposure levels should be reflected in the changing incidence rates among those workers exposed at different times and durations.²⁵ Exposure during early

The total years of exposure for each of the cases is shown in Figure 8. Ninety-three cases (93%) had 10-43 years of exposure (median 20 years); seven cases (7%) had only 3½-6 years of exposure (median 5 years).

Continued exposure during the latency period could affect the length of latency. Therefore, the relationship between total years of exposure and latency was studied among those with concomitant exposure and latency periods versus the smaller groups with limited short total exposures. This latter group is not significantly affected by continued exposure which might of itself act as a promoter. These eight individuals (short-exposure group [SEG]) had left the chemical industry for other occupations with no or very limited exposure to other known carcinogens. Figure 9 correlates the year of first exposure with latency in SEG. In regards to total years of exposure, the same reverse relationship was found ~~as was~~ ^(continuously) ~~seen~~ in the long cases ^{cases} ~~concomitant~~ exposure ~~group~~. (Fig. 12)

The Effect of Weighted Exposures

A review of the literature and industrial records indicates a progressive linear decrease in exposure levels from 1940 (1-3 ppms) to 1974 (50-250 ppms). Data reported in the literature and extrapolated from the various industrial data were used to construct estimated exposure levels.^{7, 24} Two exposure curves were plotted from these reported exposure levels covering the 1940-74 years (Figure 10).

years (1940-1950) was at a higher intensity. The cytotoxic effect of VC was shown by the severity of the hepatocellular injury seen among workers exposed during those years. In these early workers, far more parenchymal injury, hepatocellular necrosis, fibrosis, and portal hypertension were found, concurrent with clinical development of HAS.^{26, 27} It is highly probable that in these situations the liver and endothelial cells were unable to undergo cancer transformation between the VC cytotoxic injury did not allow the cells to survive. Therefore, fewer total induced cells were available for further transformation by the action of promoters or repeated exposure.²⁸

Those individuals whose exposure occurred in later years (1951-60) were exposed to lower vinyl chloride levels. Although these levels were less cytotoxic, they were still able to induce the carcinogenic effect. Therefore, a larger proportion of surviving cells were initiated and available for the promoting effect of either continuing exposure or other environmental agents. This group had the more rapid induction (shorter latency) of HAS development.

As the environmental levels were further decreased (after 1968), the liver was able to maintain adequate detoxification to prevent both the cytotoxic effect and the carcinogenic induction or initiating phase. This level of exposure appears not to be affected by other promoting agents or continued low-level VC exposure. In support of this hypothesis are the findings in later exposed workers (1960-1975), and evidence of histological hepatocellular adaptation, e.g., focal hepatocellular hyperplasia and mild increase in sinusoidal fibrosis.⁶

These findings reflect the hepatocyte's adaptation and very mild cytotoxic injury to endothelial cells, which in turn stimulates collagen forming cells. The latter scenario is further supported by the fact that after five to ten years of follow-up, these histological lesions (which are highly correlated with the individual's total exposure to vinyl chloride) have shown no evidence of progression even with continued low-level VC exposure (< 10ppm).²⁰ In addition, all biochemical abnormalities initially seen have regressed and the histological picture on subsequent biopsies has been stable and unchanging.^{28, 30}

Therefore, these data support the concept that high levels (> 750ppm) of vinyl chloride produce severe liver cell (hepatic and sinusoidal) injury and reduce or significantly delay the malignant expression or transformation of initiated endothelial cells. At lower levels (or range of levels) which appear to be somewhere between 250-700 ppm, there is a maximal carcinogenic effect with less cytotoxic injury. Whether this latter phase can be totally accounted for by the VC level of exposure and not contributed to by confounding or enacting secondary agents, requires further study. Finally, low levels (1-50 ppm) appear to be within a biological threshold. Neither significant cytotoxic nor carcinogenic effects occur at these exposure levels. In addition, this level also does not appear to act as a promoter nor cause progression of already existing hepatocellular lesions.

The data also suggests that there may be a co-factor or interaction of other chemicals occurring which may play a role in the shorter latency periods and reverse dose-response with regards to malignant transformation.

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Greenberg and Tamburro,^{31, 32} utilizing a rank-order method for estimating chemical exposure, illustrated this method's ability to identify the causal relationship between VC and other chemicals with the development of HAS. Their study suggests that catalysts which biochemically inhibit the liver's major detoxifying mechanism responsible for the removal of active vinyl chloride metabolite might be a confounding or interacting factor. Industrial plants performing different operations might have environments which provided dual exposures. One, like vinyl chloride, which is hepatotoxic and carcinogenic, and another, like diethyl maliete, which might decrease or impede the liver's detoxifying capabilities, thus allowing for a more rapid induction of carcinogenesis -- hence, a shorter latency. In contrast, those plants not utilizing these detoxifying inhibitors may account for the usual and more prolonged course of cancer induction, i.e., increased exposure, decreased latency.

This hypothesis is supported by review of HAS cases in the various countries and their plants' start-up dates. As shown in Figure 15, all HAS cases developed in PCB plants whose start-up began before 1967 -- in eastern Europe before 1953, in Canada before 1941, in the United States before 1953, and in western Europe all but three plants before 1954. This indicates a high probability that either the level of exposure and/or type of exposure during these periods play an important role in type of injury seen and the way in which the tumor developed.

These clinicql data provide a clear demonstration of a biological threshold for a known carcinogenic non-radiation agent in a human population. It demonstrates a uniquely-

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different pattern of latency in chemically-induced cancer, even though its distribution characteristics are mathematically the same as reported by Doll and Hill³³ and fit the concepts of latency initially illustrated by Sartwell³⁴ and later expanded by Armenian and Lilienfeld.³⁵ The reverse dose-response to latency relationship, however, is quite different from that reviewed by Polednak, Cobb and others, and reflects a different mechanism or model for chemical carcinogenesis.³⁶ This study provides carefully-observed human experience data, prospectively acquired, which can be used to guide the development of future environmental policy with regards to vinyl chloride environmental exposure.

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Figure 1: Worldwide HAS case occurrences, with the peak occurring about 1976.

Figure 2: The annual incidence of HAS by date of diagnosis and geographic location for four leading countries.

Figure 3: The distribution by year of first exposure for the entire cohort (1940-68).

Figure 4: Illustrates the age at which diagnosis was first made among the VC-associated HAS.

Figure 5: The frequency of HAS latency periods (skewed distribution), peaking at approximately 20 years.

Figure 6: I. HAS cases' ^(U.S.) latency periods decrease with shorter duration of exposure.

Figure 7: II. HAS cases' ^(Europe) latency periods decrease with shorter duration of exposure.

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Figure 15: All HAS cases developed in PCB plants whose start-up began before 1967 (in eastern Europe before 1953, in Canada before 1941, in the United States before 1953, and in western Europe all but three plants before 1954).

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^{Fig 16}
~~Table 1~~ The range of the latency periods is from 9-38 years. The mean latency period for each five-year interval, starting with 1940-44, demonstrates a progressive shortening from 35 to 14.6 years with an overall average latency of 22.6 years.

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