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DRAFT #4

(4)

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 dost-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 implicity 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 known 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

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 angiosarcome 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 ~~174~~ 1974(?) 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,

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

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~~).

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).

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 seen~~ in the long cases ~~concomitant~~ (continuously) exposure ~~group~~ cases. (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 parnechymal 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 leves (> 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.

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

different pattern of latency in chemically-induced cancer, even though its distribution characteristics are mathematically the same as reported by Doll and Hill[33] and fit the concepts of latency initially illustrated by Sartwell[34] 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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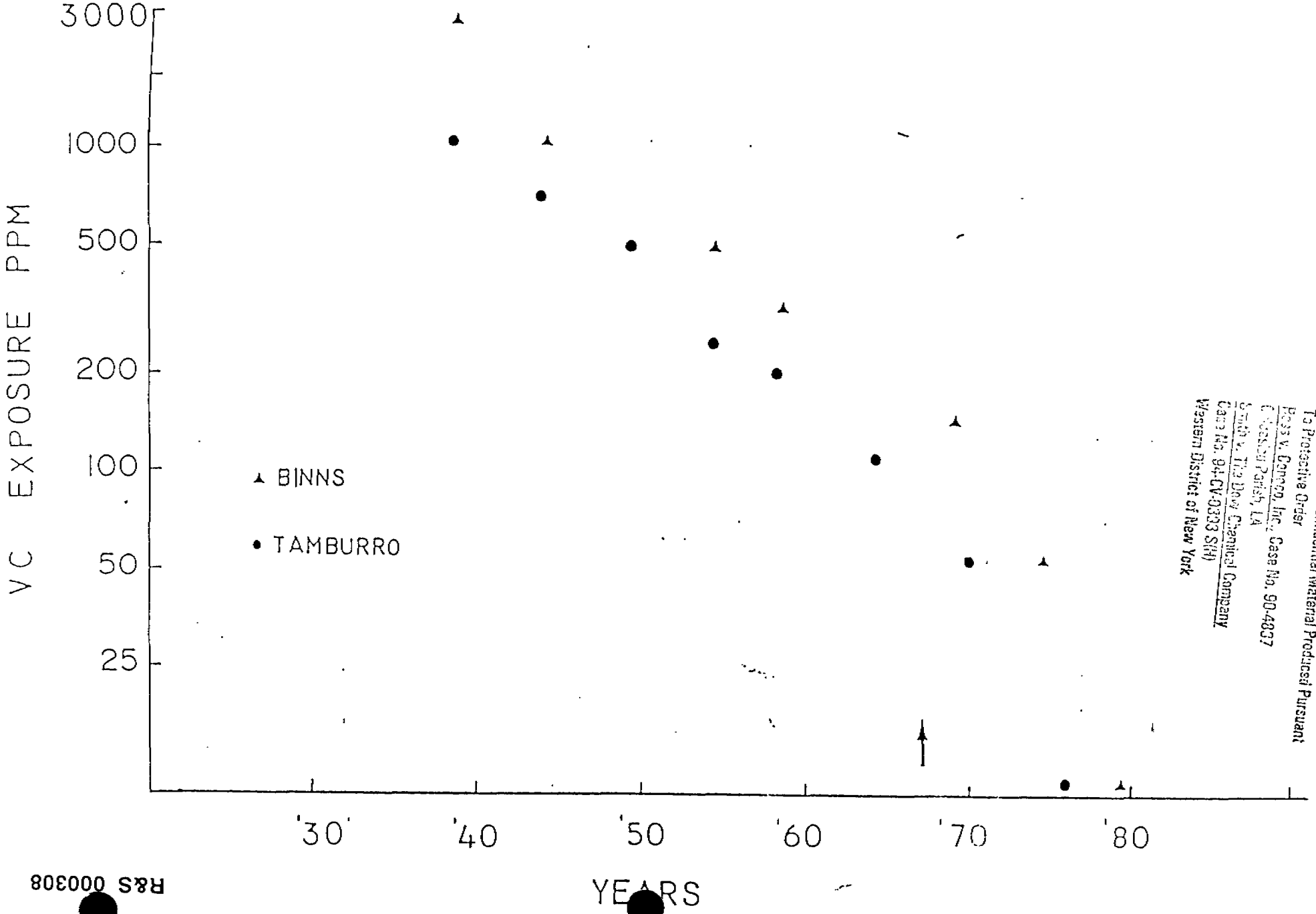
ESTIMATED VINYL CHLORIDE EXPOSURE



Dow Chemical Confidential Material Produced Pursuant To Protective Order
Ross v. Conoco, Inc., Case No. 90-4837
[illegible] Parish, LA
Smith v. The Dow Chemical Company
Case No. 94-CV-0333 S(M)
Western District of New York

R&S 000308

VINYL CHLORIDE ASSOCIATED ANGIOSARCOMA
(BFG Exposure Cases)

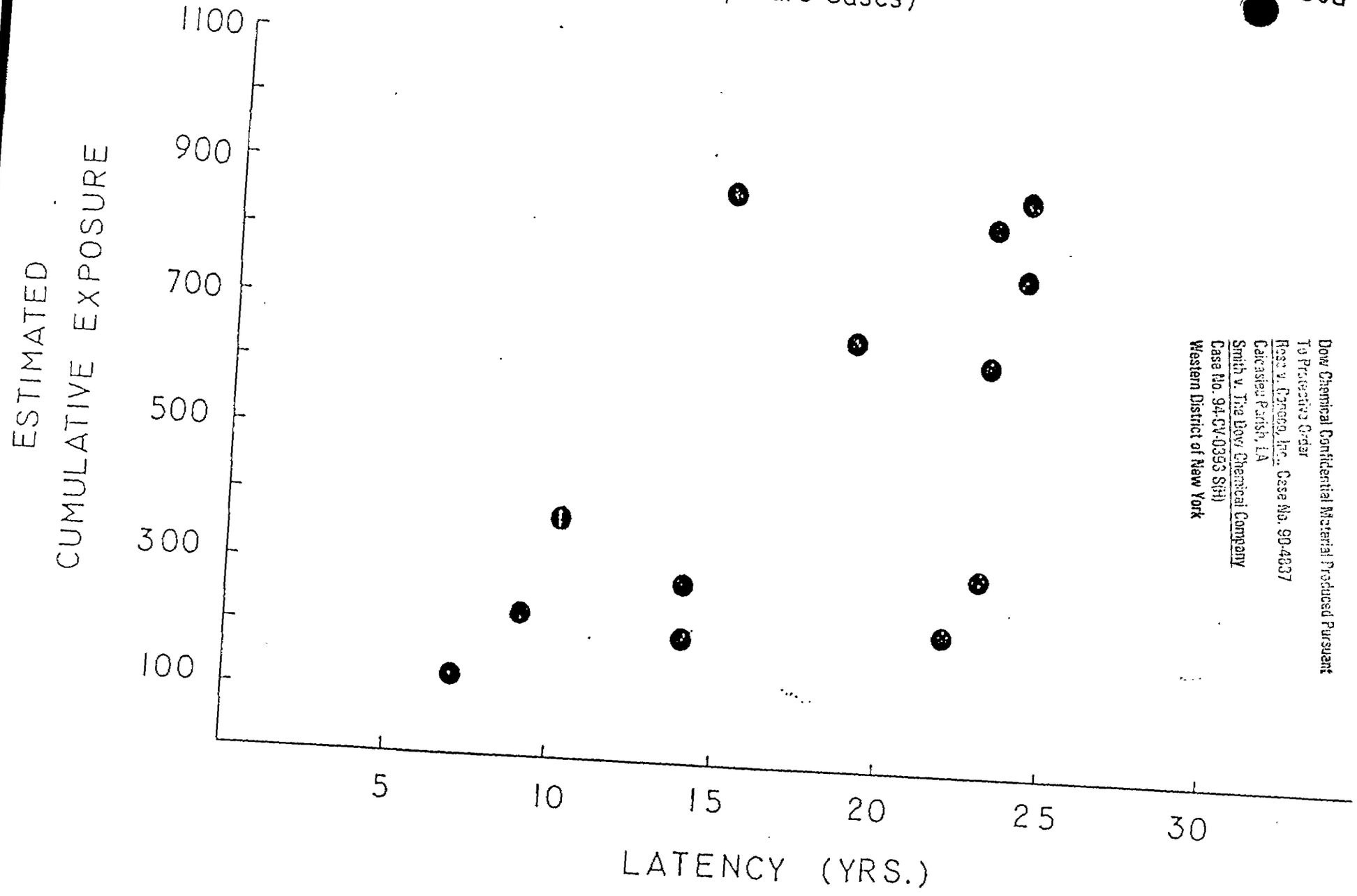


FIGURE 11

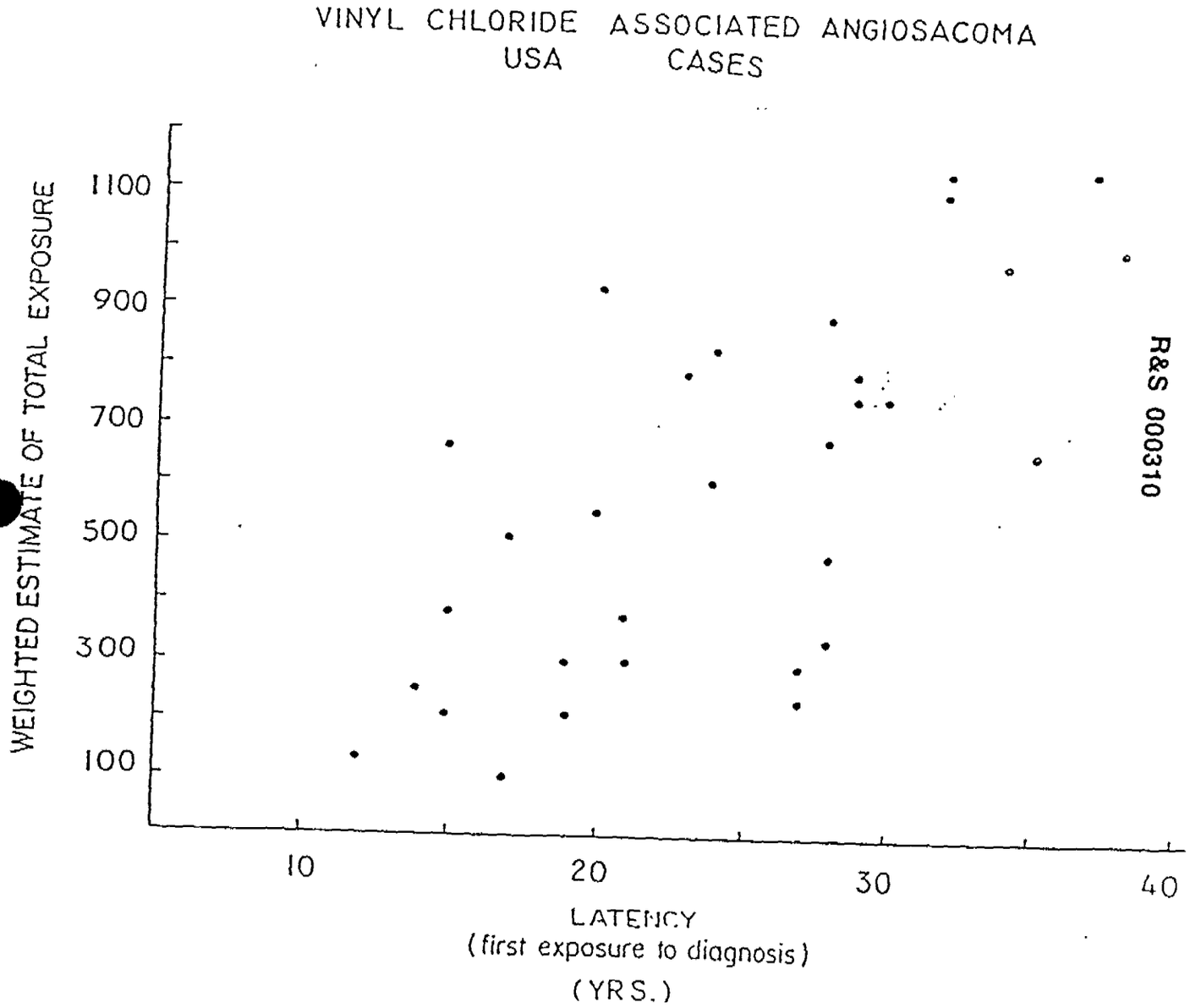


FIGURE 12

R&S 000311

CANADA CASES

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To Protective Order
Rose v. Dow Chemical Co., Case No. 90-4837
Calcasieu Parish, LA
Smith v. The Dow Chemical Company
Case No. 94-CV-0333 S(H)
Western District of New York

14

VINYL CHLORIDE ASSOCIATED ANGIOSARCOMA

(Short Exposure Cases)

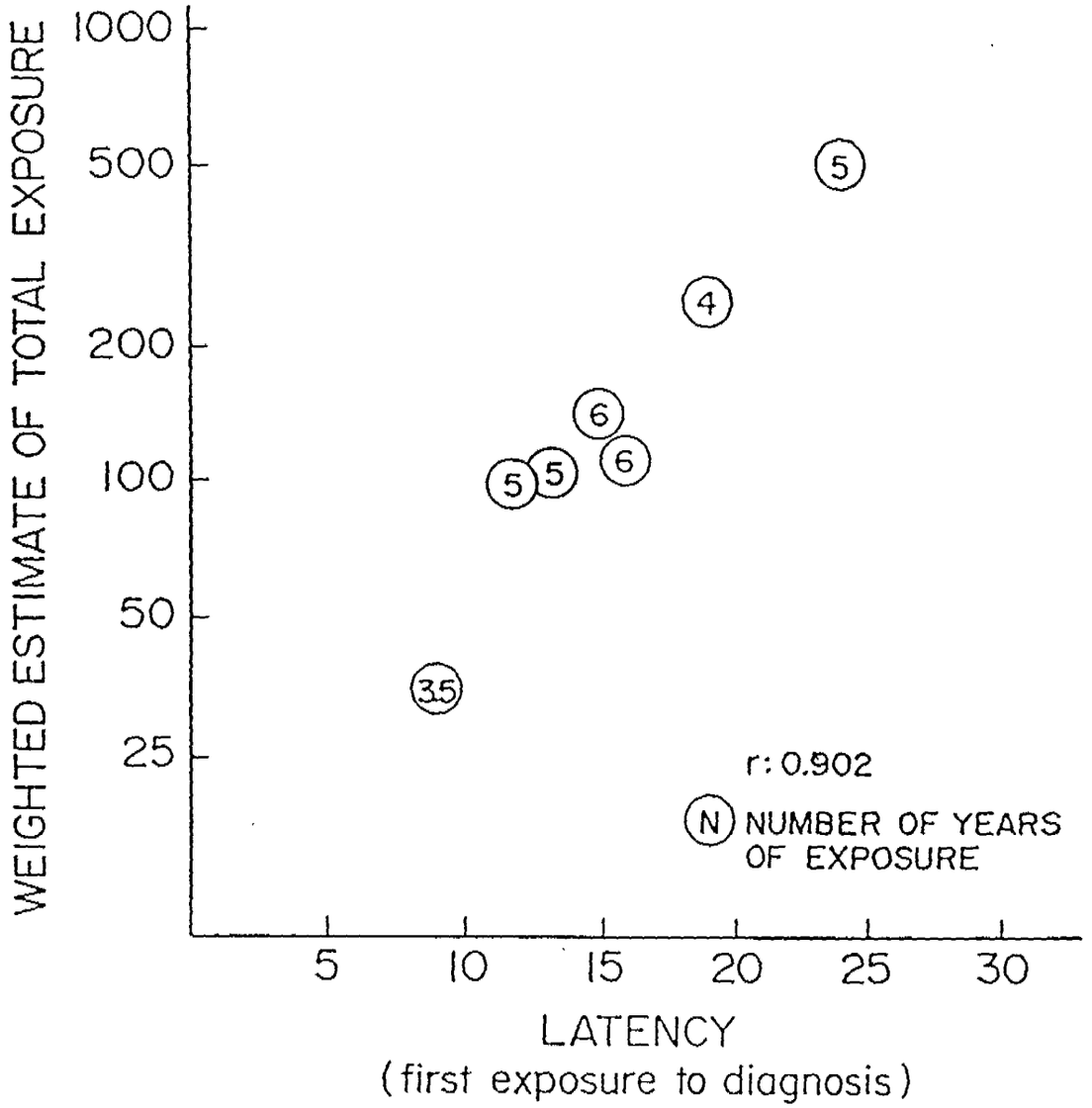

Fig 14

POLYVINYL CHLORIDE PRODUCTION PLANTS

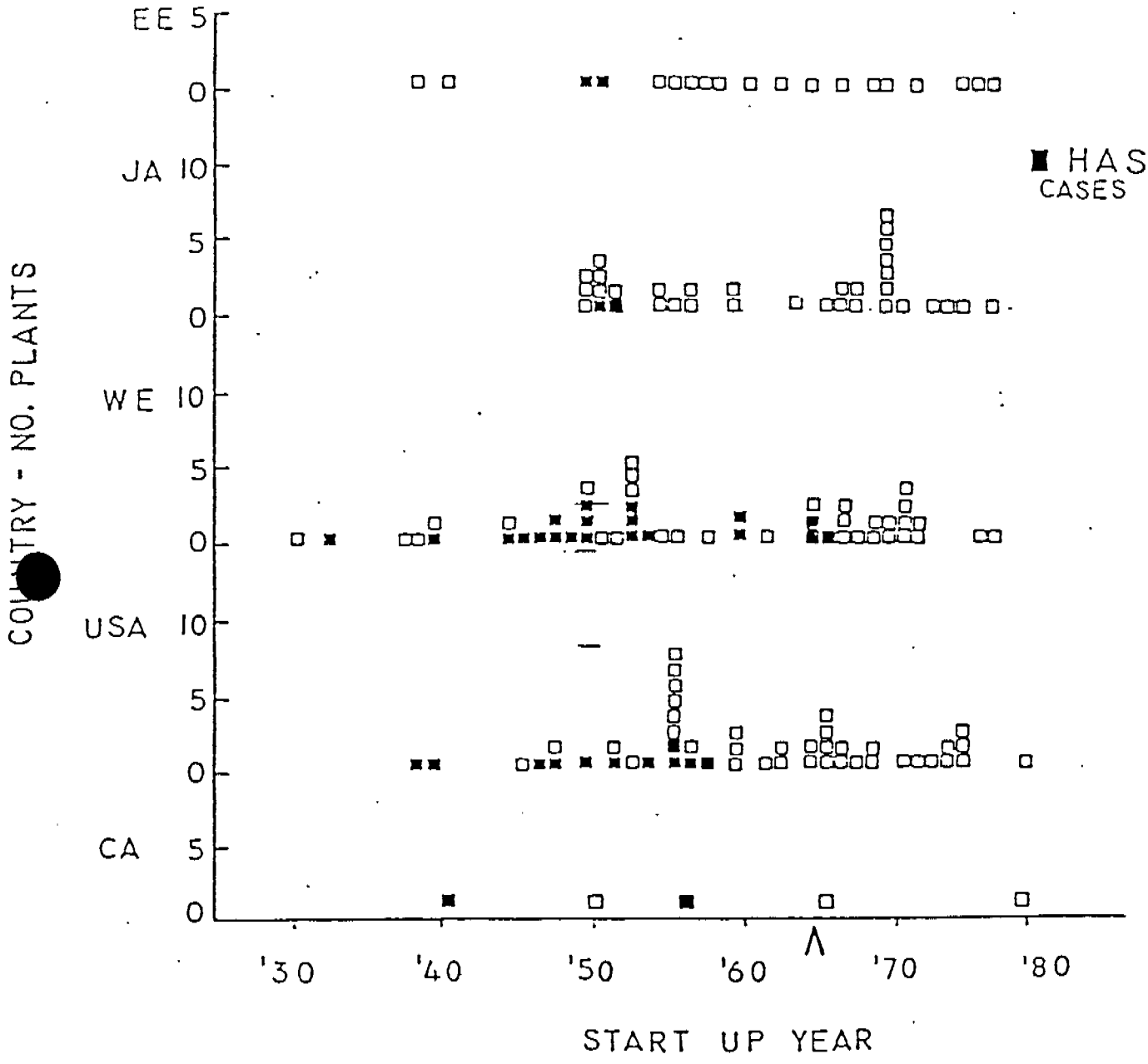

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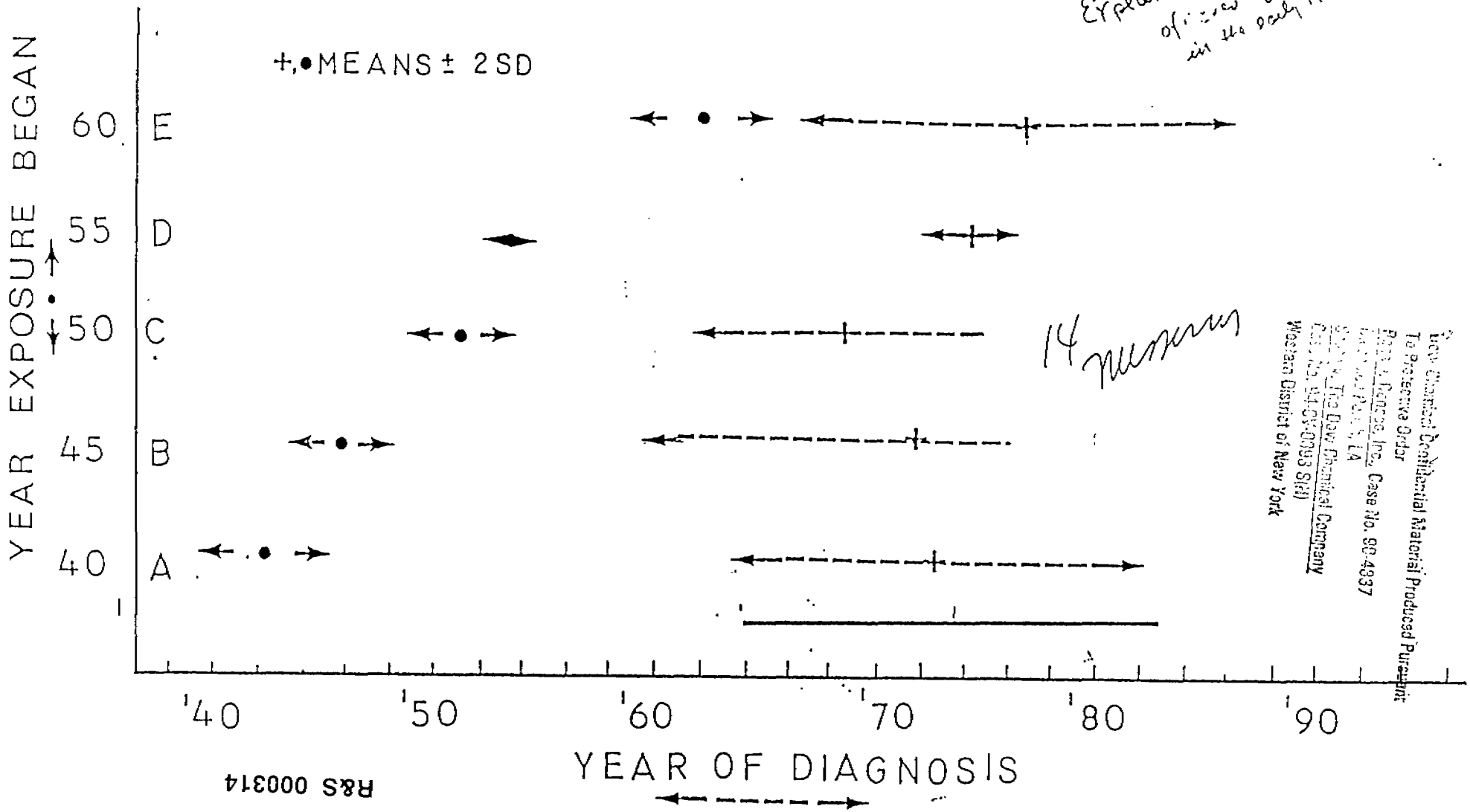
FIGURE 15

VINYL CHLORIDE ANGIOSARCOMA
U.S.A. CASES



Explanation of the number of cases of ASH in the early 1970's

14 persons

Dow Chemical Confidential Material Produced Pursuant To Protective Order
Reese, Inc. Case No. 80-4937
The Dow Chemical Company
Civil No. H-80-0593 (RH)
Western District of New York

RRS 000314

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Figure 10: Two exposure curves illustrating reported exposure levels covering the 1940-74 years.

Figure 11: Latency vs. total cumulative exposure (weighted exposure) in index plant cases.

Figure 12: Latency vs. total cumulative exposure (weighted exposure) in USA cases.

Figure 13: Latency vs. total cumulative exposure (weighted exposure) in Canadian cases.

Figure 14: Latency vs. total cumulative exposure (weighted exposure) in the short exposure group.

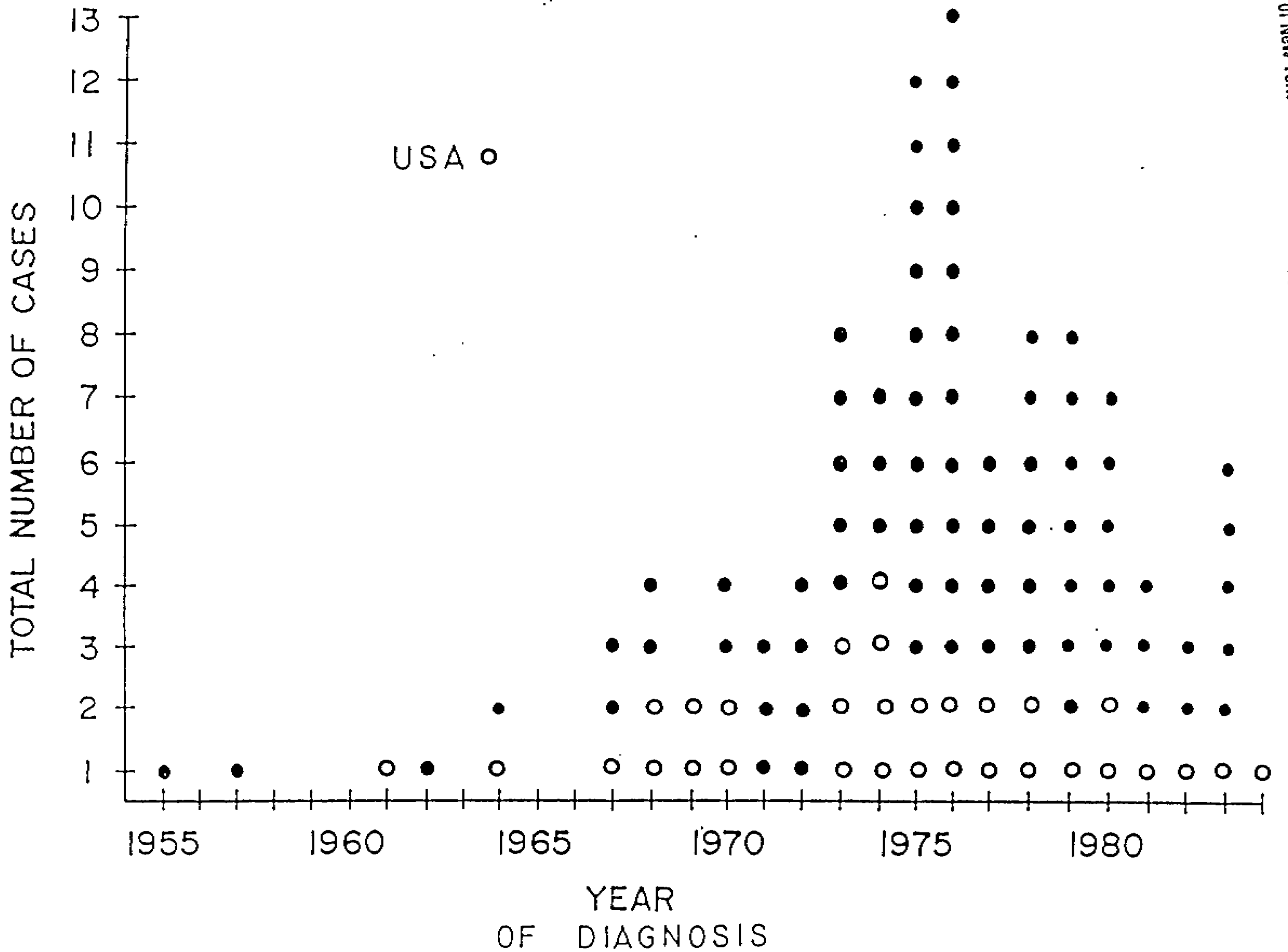
Figure 15: All HAS cases developed in PCB plants whose start-up began before 1967 (in eastern Europe before 1953, in Canada before 1941, in the United States before 1953, and in western Europe all but three plants before 1954).

LIST OF TABLES

Fig 16

~~Table I~~ 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.

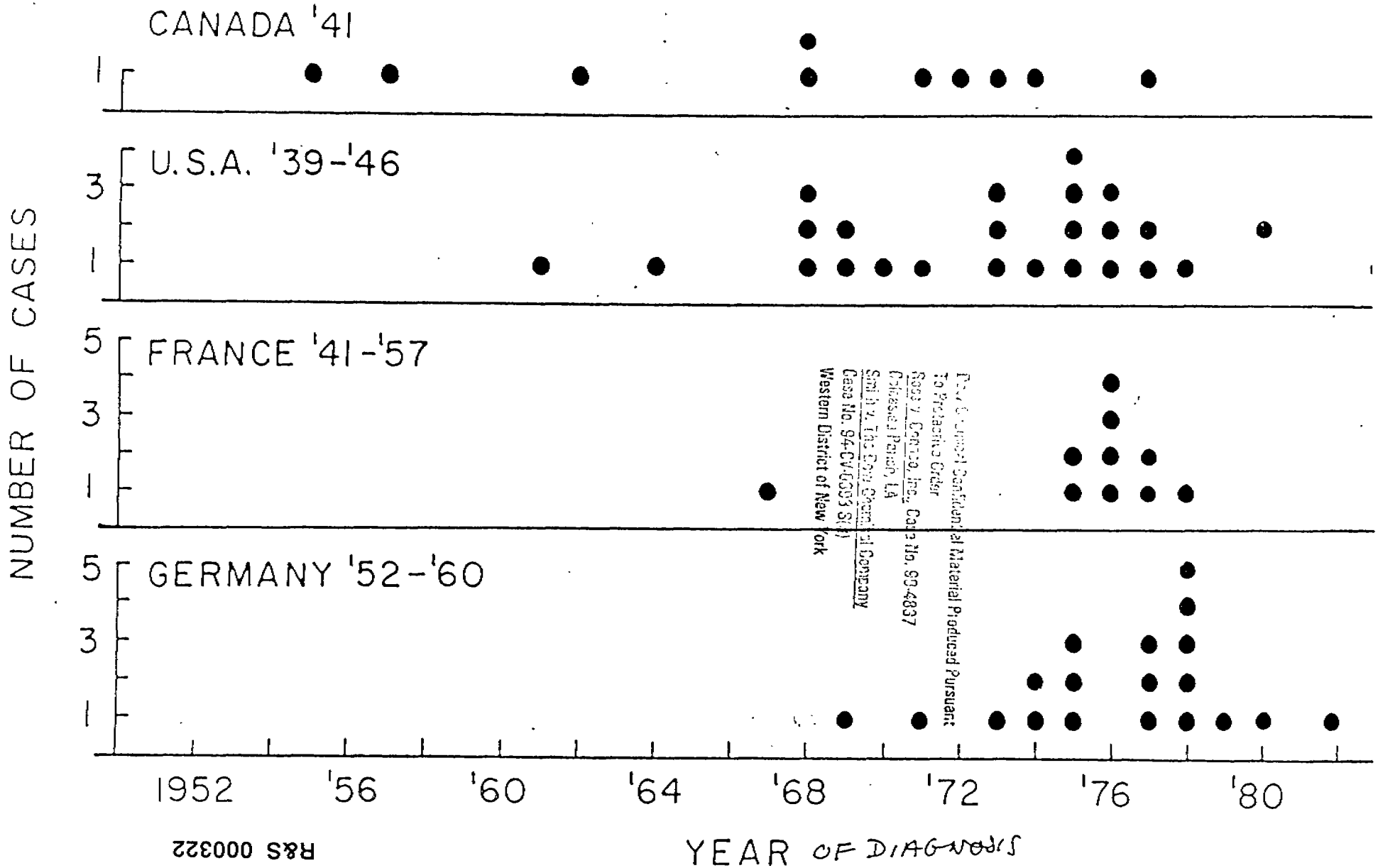
VINYL CHLORIDE ANGIOSARCOMA
CASES WORLD-WIDE



to be updated

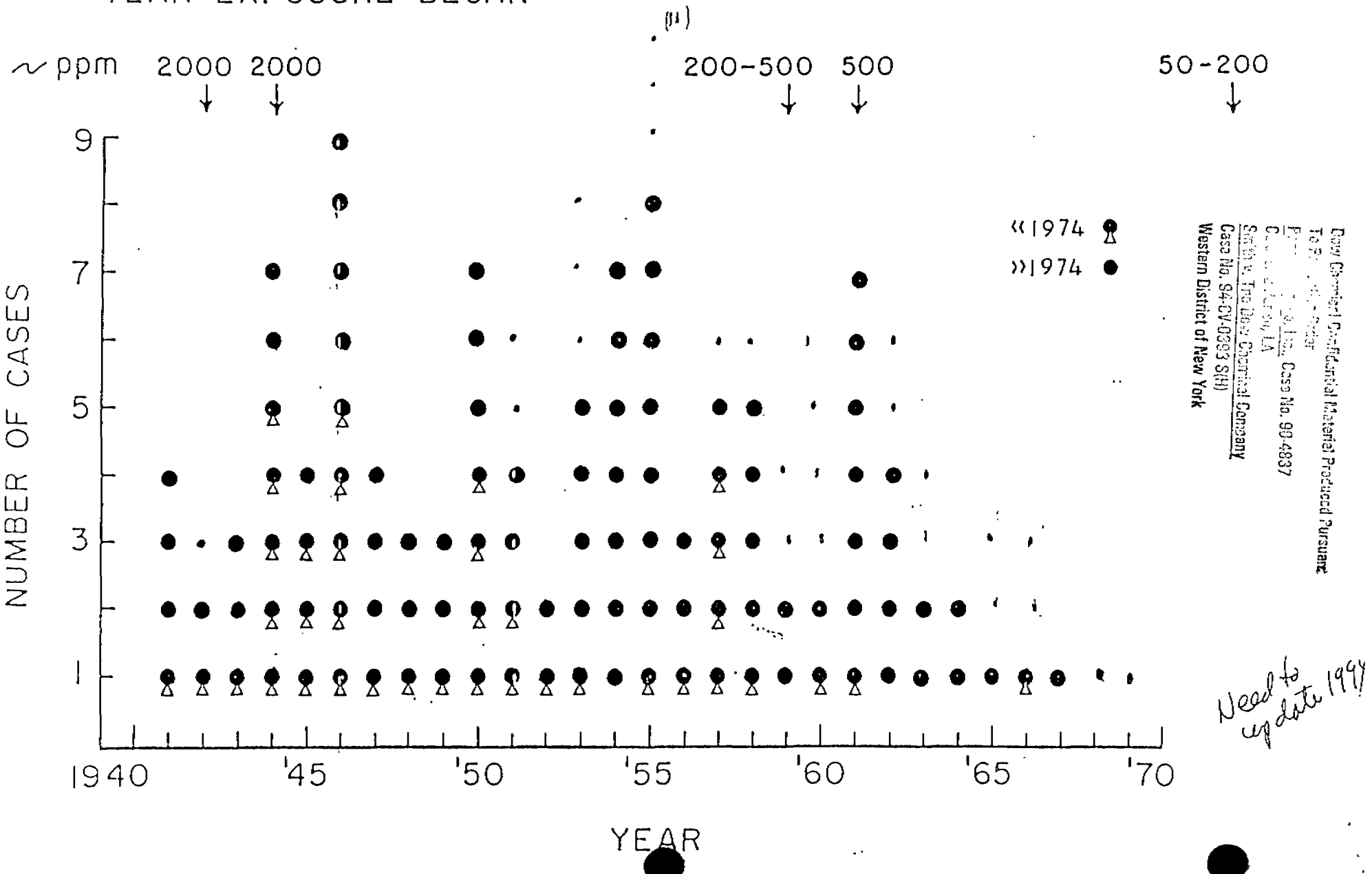
add new Cases
up to 1974

VINYL CHLORIDE ASSOCIATED ANGIOSARCOMA IN VARIOUS COUNTRIES



VINYL CHLORIDE ANGIOSARCOMA

YEAR EXPOSURE BEGAN



Dow Chemical Confidential Material Produced Pursuant
Case No. 90-4837
Case No. 94-CV-0393 S(H)
Western District of New York

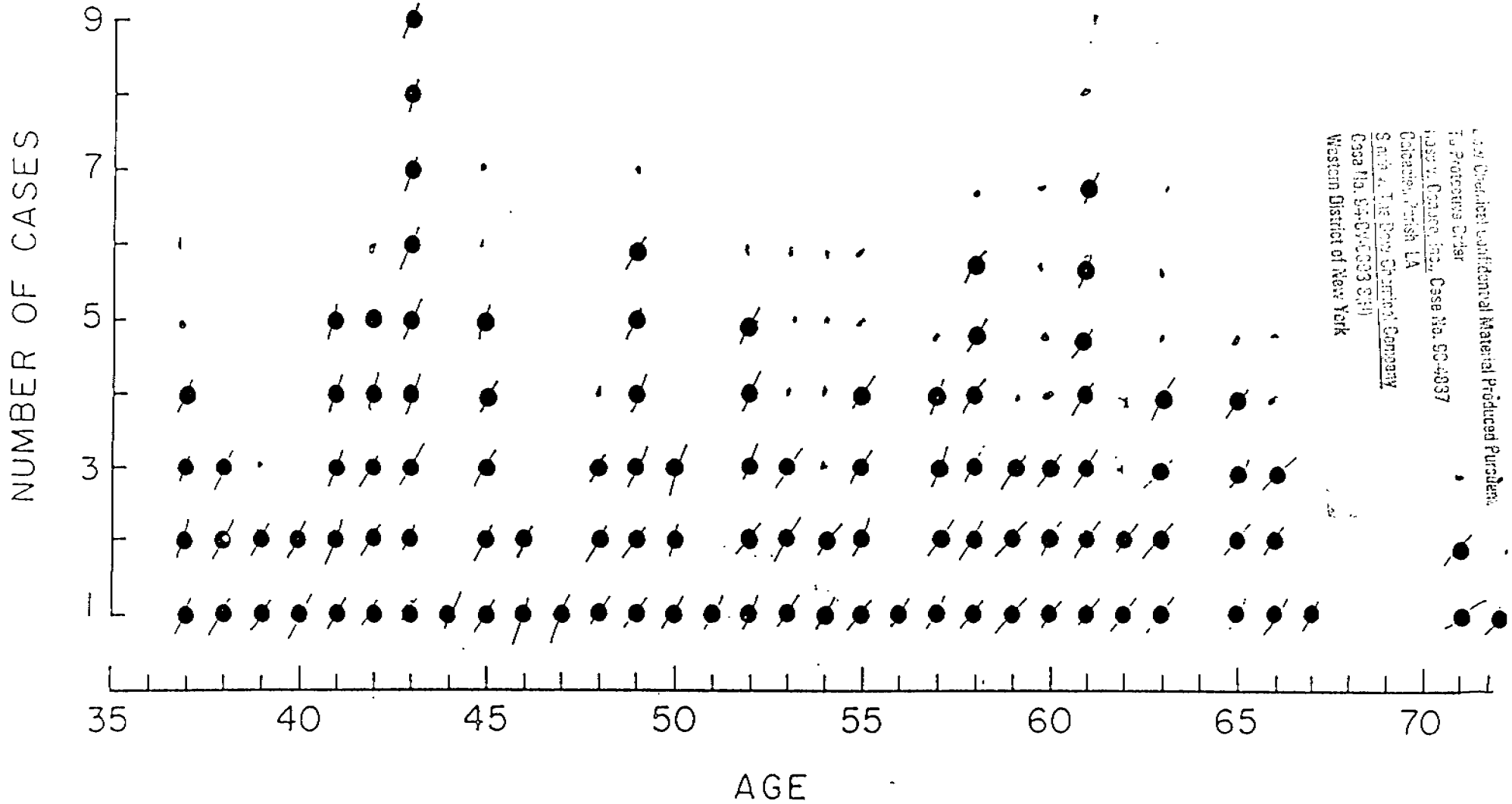
Need to update 1997

1979
1980

VINYL CHLORIDE ANGIOSARCOMA

AGE AT TIME OF DIAGNOSIS

update to 1994



Subject to Confidential Material Produced Pursuant to Protective Order
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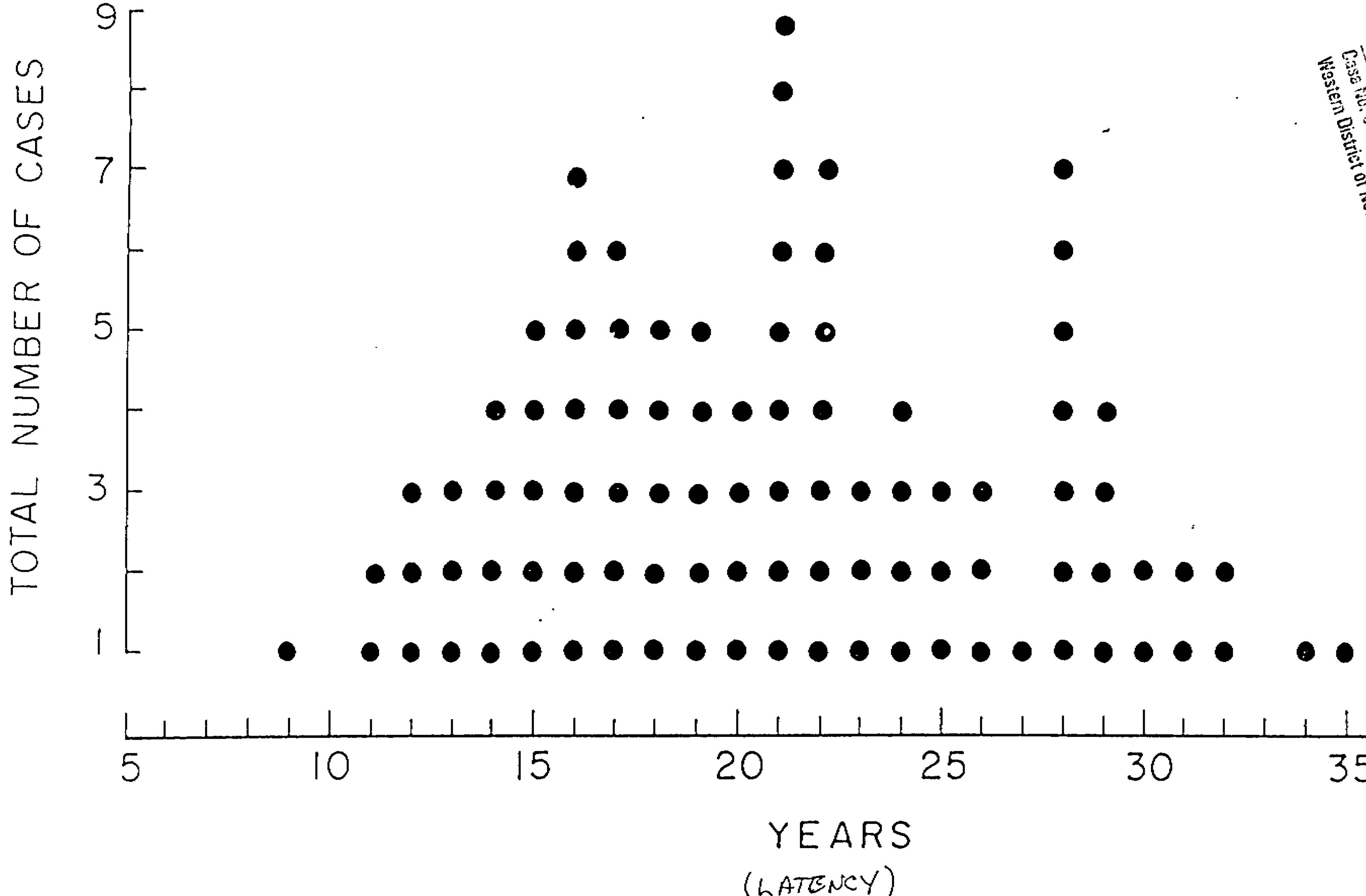
Case No. 94-CV-0033 (LH)
Western District of New York

R&S 000324

VINYL CHLORIDE ANGIOSARCOMA

TIME FROM FIRST EXPOSURE TO DIAGNOSIS



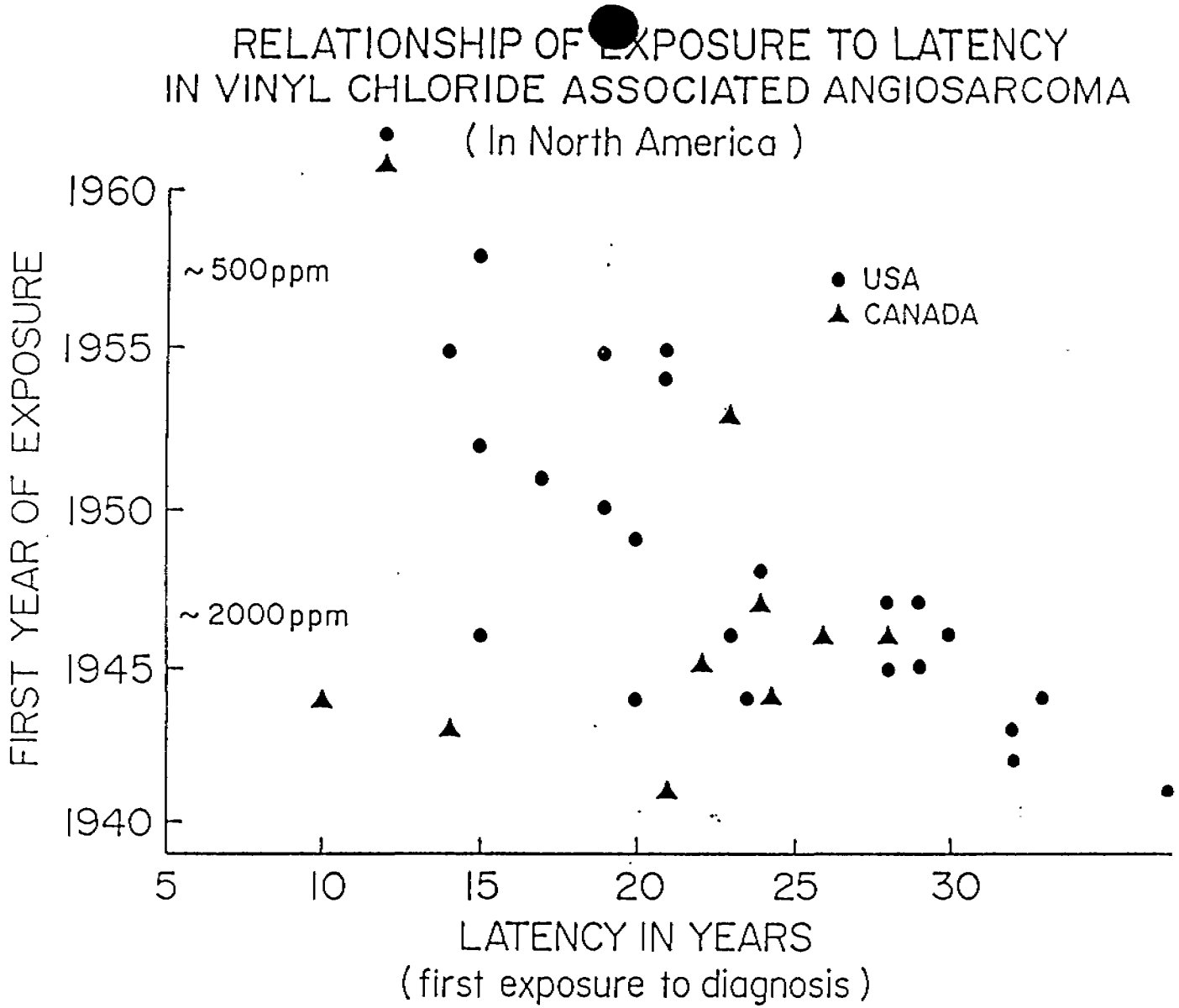


FIGURE 6

RELATIONSHIP OF EXPOSURE TO LATENCY IN VINYL CHLORIDE ASSOCIATED ANGIOSARCOMA

(In Europe)

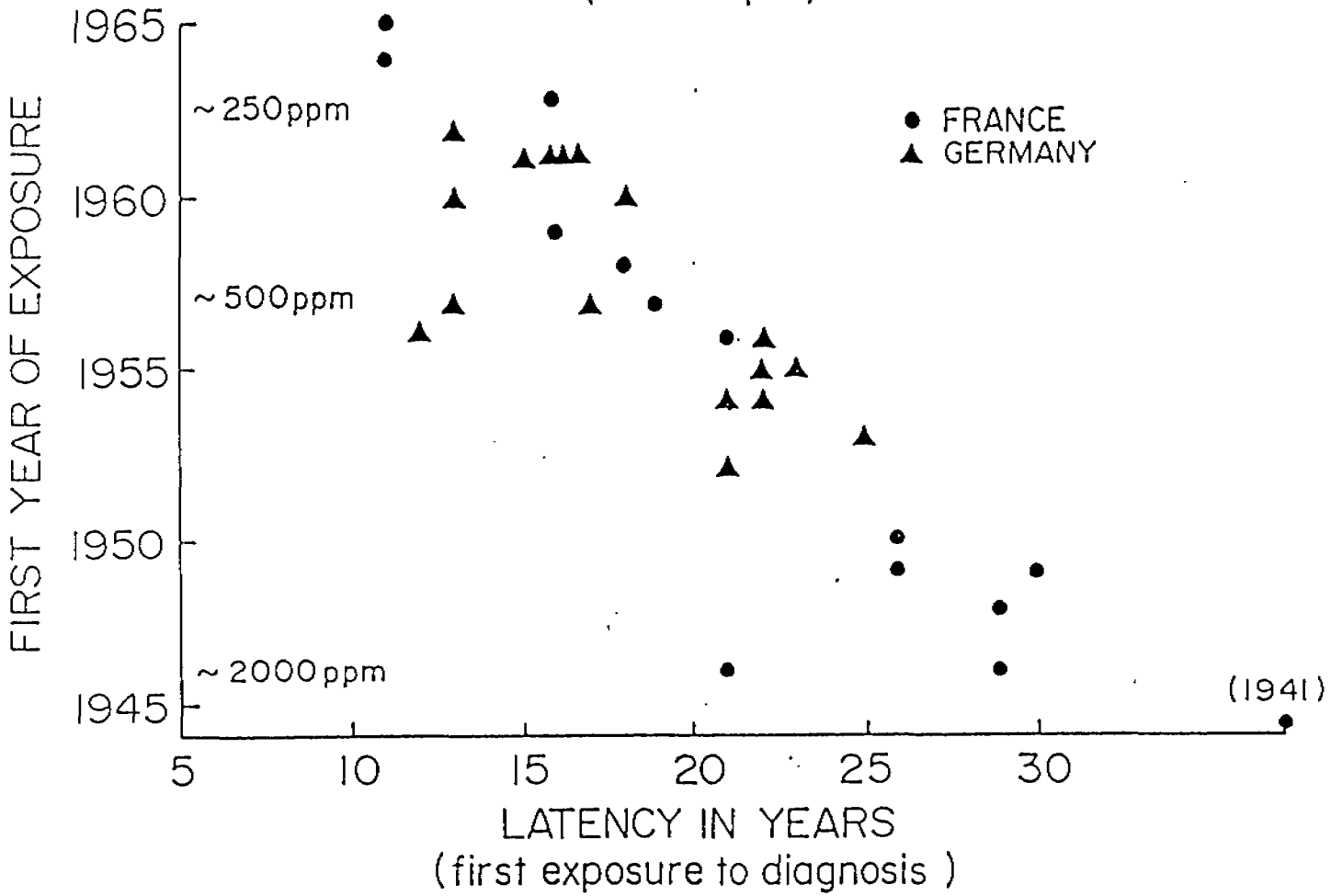
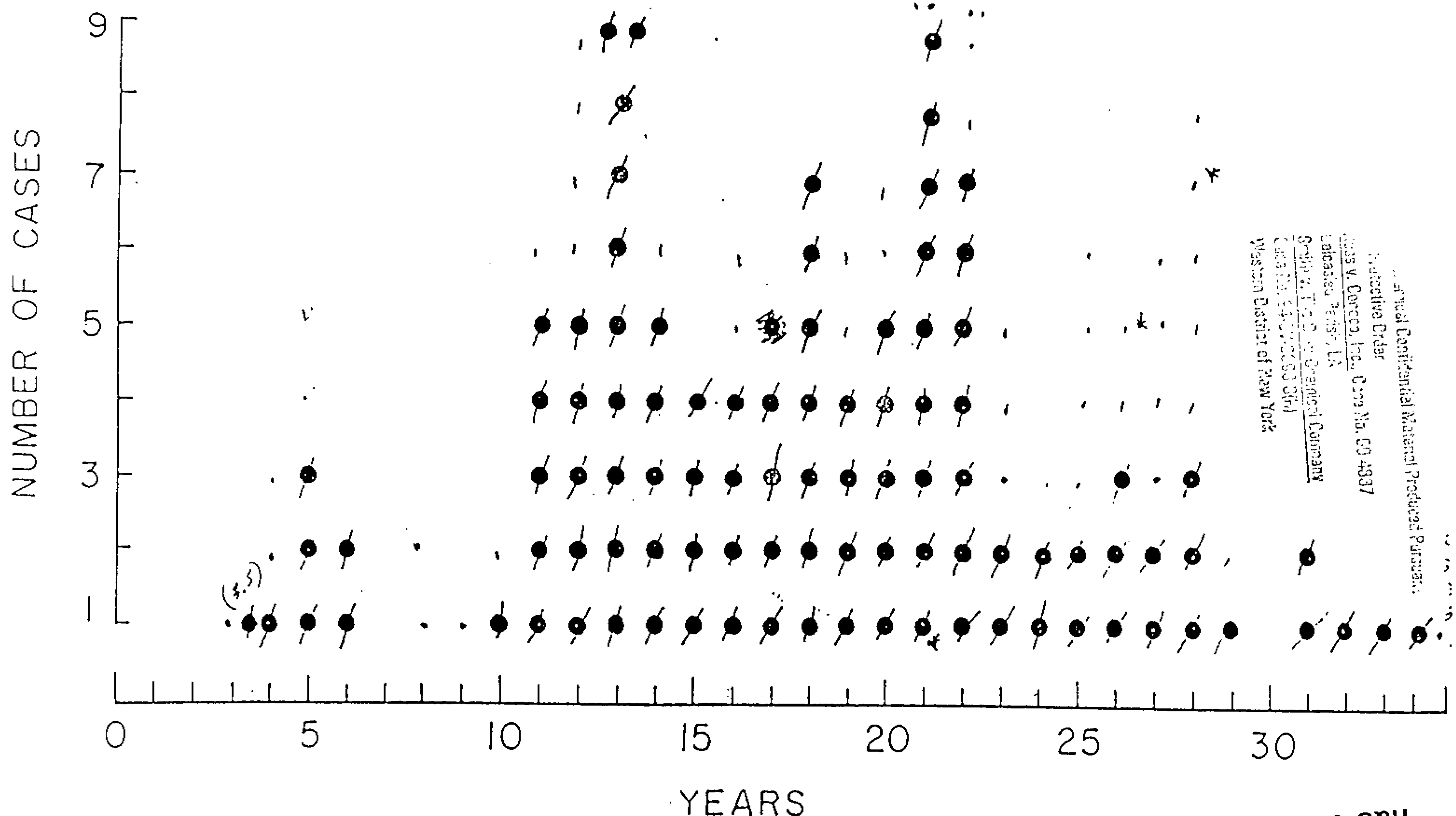


FIGURE 7

TOTAL YEARS OF EXPOSURE IN CASES OF HEPATIC ANGIOSARCOMA IN VINYL CHLORIDE WORKERS



* G07: 12 - 21
USA 24: 24 -26

FIGURE 8

VINYL CHLORIDE ASSOCIATED ANGIOSARCOMA

(Short Exposure Cases)