

Epidemiology of Hepatic Angiosarcoma in the United States: 1964-1974

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A nationwide survey of hepatic angiosarcoma (HAS) in the United States during the years 1964 through 1974 identified 168 cases. Of these, 42 cases (25%) were associated with known etiologic factors, such as vinyl chloride monomer exposure during preparation of poly(vinyl chloride), use of Thorotrast in angiography, exposure to inorganic arsenic, and treatment with androgenic-anabolic steroids; 126 cases (75%) are of uncertain etiology. HAS most often affects males (ratio of approximately 3:1), peaks in the sixth and seventh decades of life (somewhat earlier than other sarcomas of the liver) and appears to occur more often in the industrialized Northeast and Midwest (although reporting artifact may be a factor). There is an extraordinary relative risk for poly(vinyl chloride) polymerization workers; there may also be other chemical-industrial associations that require further investigation. Prospective epidemiologic studies of HAS should be considered as a means of identifying other causative factors (e.g., chemicals or drugs) related to HAS.

Introduction

This report is an overview of the nationwide hepatic angiosarcoma (HAS) case-finding study for the years 1964-1974 conducted by the Centers for Disease Control (CDC).

At the start of this study, three causative factors had been identified for HAS: vinyl chloride monomer (VCM) (1, 2), Thorotrast (3), and inorganic arsenic (4). The recently discovered association between VCM and HAS has served as a stimulus for this investigation, and multiple epidemiologic studies of polyvinyl chloride (PVC) polymerization

workers exposed to VCM have since demonstrated very high relative risks for the development of HAS (5, 6). Thorotrast is a colloidal suspension of thorium dioxide, a radioactive alpha-emitter with markedly prolonged radiologic and biologic half-lives, which was used for carotid angiography and liver-spleen scans in the period 1930-1955. The thorium dioxide is sequestered by the reticuloendothelial system, primarily in the Kupffer cells of the liver; radiation injury to adjacent cells is the presumed carcinogenic mechanism. Epidemiologic studies of Thorotrast recipients have shown very high relative risks for the development of HAS as well as hepatocellular tumors (7, 8). The association between arsenic and HAS is based on data from several small autopsy series in German vintners in the 1940s and 1950s (4, 9), which demonstrated an increased incidence of liver disease, including HAS. These workers were exposed to inorganic arsenical pesticides during application of the pesticide and also by drinking beverages prepared from the skins of the sprayed grapes. Subsequently, HAS cases were reported following long-term ingestion of Fowler's solution (potassium arsenite) (10, 11) and

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arsenic-contaminated well water (12). Individual cases suggesting associations between HAS and hemochromatosis (13) and copper exposure (14) have also been reported.

Earlier reports from this study reviewed cases associated with single causative factors (15-18), including androgenic-anabolic steroids which we feel are implicated as a fourth cause of HAS (19). In this paper, we present an overview of the case-finding effort, placing the known causative factors and cases of idiopathic origin in perspective.

Methods

Information relating to cases of HAS occurring in the United States during the years 1964 through 1974 was solicited by CDC in a variety of ways: (1) announcements were placed in seven medical journals; (2) a mailing was sent to all pathologists in the country; (3) separate mailings were sent to all state epidemiologists, major tumor referral centers, and statewide tumor registries; (4) a death certificate review for International Classification of Diseases (ICD), Eighth Revision, Code 197.8 (liver tumors, unspecified primary or secondary) for the period 1966-1973 was conducted with the assistance of the National Center for Health Statistics (NCHS) and the 50 state health departments (Code 155.0, primary liver tumors, was not reviewed because it would have been impractical to obtain the much larger number of certificates in this category and because it was felt that the majority of cases of HAS listed as such on the death certificate would have been coded as 197.8); (5) arrangements were made with the Armed Forces Institute of Pathology (AFIP) to include cases in their files (1943-1975) in the review; (6) a number of cases were identified from industrial surveys of PVC polymerization workers and others potentially exposed to VCM; and (7) permission was requested to include the previously published cases of HAS occurring in 1964-1974.

The evaluation procedure for each identified case was as follows: Initially, permission was requested to review the appropriate pathologic specimens (all submitted non-AFIP case material was reviewed at the National Cancer Institute's Laboratory of Pathology by H. P. and L. B. T.). Following confirmation of the diagnosis, the local physician was notified, and, with his permission, the nearest of kin was identified and contacted. Consent was obtained to review medical records, and a questionnaire was administered by telephone to obtain detailed occupational, residential, and chemical exposure histories. In selected instances, friends, employers, previous physicians or others were also interviewed.

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In all, approximately 350 submitted cases were reviewed by the pathology review group, some outside our requested time period of 1964-1974. Pathologic specimens were obtained for review in approximately 95% of cases, many of which were considered by our pathology panel not to be HAS. Since survival after diagnosis is very brief and many cases were only diagnosed at autopsy, we have included all 168 confirmed cases with death during 1964-1974 in the study group.

The above effort is essentially a case review. Subsequently, the 22,432 death certificates obtained from the review of Code 197.8 were used to carry out a case-control study of occupation as recorded on the death certificate in the following manner. Death certificates were sought for all 168 confirmed HAS cases; 166 were available. Controls were sought from among the 22,432 death certificates in ICD Eighth Revision Code 197.8 (liver tumor, unspecified primary or secondary) that had been obtained in the HAS case-finding effort (see above); certificates of confirmed HAS cases were excluded from the control selection process. Although deaths in Code 197.8 might not represent the ideal control group, the rationale was that these deaths resulted from a broad variety of tumors of multiple sites metastatic to the liver or represented cases which were diagnostically uncertain; it was therefore unlikely that any single diagnostic category would predominate or that the occupational listings would be heavily biased by any single group of cases.

Up to four controls (as many as were available) were matched to each case ≥ 30 years of age on the basis of the following criteria: age (± 6 years), sex, race, county of residence, and year of death (± 3 years). One hundred thirty-five cases were successfully matched (79 of these had 4 matched controls; the overall ratio of controls to cases was approximately 3:1). Individuals who could not be matched were primarily young females and residents of sparsely populated counties.

A combined occupation and industry coding scheme was developed to accommodate all listings recorded on the certificates and to group listings on the basis of potential hazardous exposures. The data were analyzed by Rothman's method for matched groups with multiple controls per case (20).

Results

Our study identified 168 deaths from confirmed HAS during the years 1964 through 1974. For this rare tumor, the best sources of case identification were the pathologists, with the largest number of cases identified through the single mailing to all pathologists and the second largest number of cases

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identified through pathology referral centers (particularly the AFIP).

Table 1 summarizes the results of the death certificate review portion of the case-finding effort and points up some of the inadequacies of using this method in epidemiologic studies of uncommon tumors. Only 42% of the cases initially identified on the death certificate as HAS were confirmed as such on pathologic review; 50% of the cases were confirmed not to be HAS. Furthermore, only 23% of all the total cases in our study during the years 1966-1973 would have been identified by the death certificate search alone. It can be seen that an epidemiologic study based only on a death certificate search of Code 197.8 would have been quite inadequate.

Figure 1 compares age, race and sex data for the confirmed HAS cases in our study with 131 cases of non-angio hepatic sarcoma identified in the death

certificate survey (these latter cases were not confirmed by pathologic review). HAS has a striking male preponderance of approximately 3:1; this is not true for other hepatic sarcomas. HAS also appears to occur more often in younger age groups.

The higher proportion of males than females with HAS first appears in the 40- to 49-year-old group (Fig. 2) and is associated with a younger peak age for males than females, although the mean age for female HAS cases (50.1 years) is lower than that for males (57.9 years). These findings are not solely related to the VCM-induced cases among polymerization workers. The male preponderance is also present in the Thorotrast, arsenic, and androgenic-anabolic steroid associated cases, as well as in the idiopathic cases (Table 2). Cases with known etiology, however, have a younger age distribution than idiopathic cases (Table 3), with a mean age of 51.0 years compared to 57.6 years for the idiopathic cases.

Table 4 presents the 168 cases of HAS by year of death and etiologic status. The VCM-, Thorotrast- and androgenic-anabolic steroid-associated cases were more common during the latter part of the study

Table 1. HAS cases, CDC survey: death certificate review—code 197.8 (8th revision ICD), 1966-1973

Length of review	
7.5 years (1966-1971, 1973, 1/2 of 1972)	
Total number of death certificates reviewed	22,432
Sarcomas of the liver, death certificate diagnoses:	
Angiosarcoma (HAS)	74 (36.1%)
Leiomyosarcoma	24 (11.7%)
Fibrosarcoma	14 (6.8%)
Sarcoma (type unspecified)	64 (31.2%)
Sarcoma (other types)	29 (14.1%)
Total	205
Final pathologic diagnoses of 74 cases identified on death certificate as HAS	
Confirmed HAS	31 (42%)
Confirmed not HAS	37 (50%)
No pathology available	6 (8%)

Table 2. HAS cases, CDC survey, 1964-1974: sex ratios, etiologic categories.

	Male	Female	Ratio
Vinyl chloride	12	0	(12 : 0)
Thorotrast	15	5	(3 : 1)
Arsenic	4	2	(2 : 1)
Androgenic-anabolic steroids	3	1	(3 : 1)
Subtotal	34	8	(4.3 : 1)
Idiopathic	93	33	(2.8 : 1)

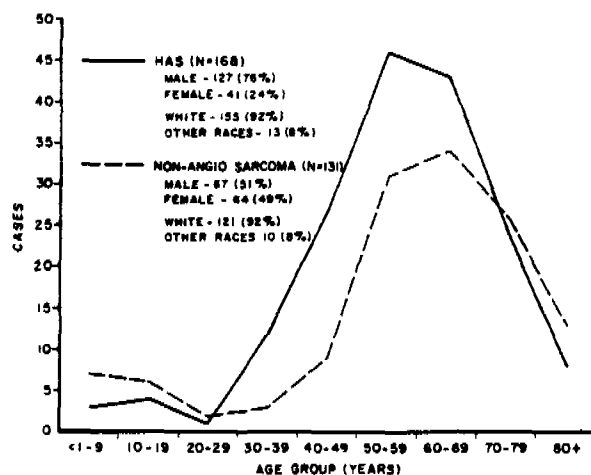


FIGURE 1. Hepatic angiosarcoma (HAS) cases compared with non-angio hepatic sarcoma cases, by age group: U.S., 1964-1974.

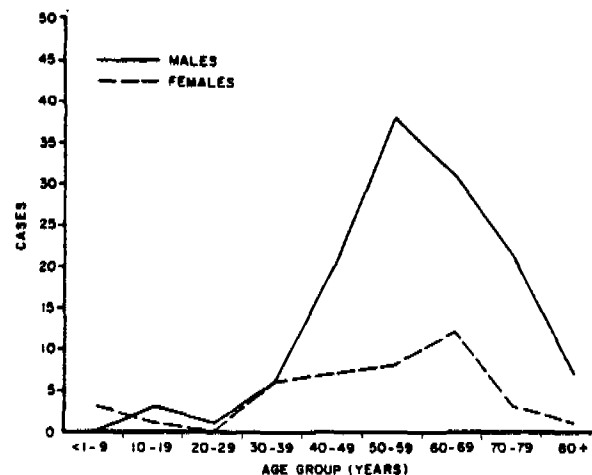


FIGURE 2. Hepatic angiosarcoma cases, by age group and sex: U.S., 1964-1974

Table 3. HAS cases, CDC survey, 1964-1974: age distribution for cases of known cause and for idiopathic cases.

Age, yr	Known etiology No. %	Idiopathic No. %
0-9	1 (2)	2 (2)
10-19	0 (-)	4 (3)
20-29	0 (-)	1 (1)
30-39	4 (10)	8 (6)
40-49	8 (19)	19 (15)
50-59	22 (52)	24 (19)
60-69	4 (10)	39 (31)
70-79	3 (7)	21 (17)
≥80	0 (-)	8 (6)
Total	42	126

period. For the VCM- and androgenic-anabolic steroid-associated cases, this is due to the relatively recent introduction of these causative agents. For the Thorotrast-induced cases, however, this pattern was an unexpected finding. Based on the originally calculated latent period of approximately 20 years (21), the general impression was that such cases would be diminishing by 1975. However, the number of cases appeared to still be increasing as of 1974, apparently due to an increase in cases having relatively low-dose angiographic procedures and prolonged latent periods (16). The arsenic-associated

cases (including five adults with a history of prolonged use of Fowler's solution and one child with environmental exposure) occurred primarily during the earlier years of the study and may represent the tail end of a larger problem in previous years. The number of idiopathic cases was low during the first few years of the study (perhaps related to poor recall by pathologists, and to the fact that the death certificate search started with 1966). Case numbers, however, remained steady for most of the study period except for a spurt in 1974. The latter occurred right after the original report and the attendant publicity of the first cases of VCM-induced HAS (January 1974) and may be related to improved diagnostic evaluation. Review of the idiopathic cases occurring in 1974 demonstrated a large number of elderly cases with no evidence of clustering in a particular exposure setting.

The HAS mortality rate for the entire United States during the study period was 0.75 cases per 10⁷ population per year. Crude mortality rates by region, based on county of residence at time of diagnosis (Table 5), suggest a somewhat higher incidence in the Northeast and in the industrial portions of the Midwest. There was also an increase in the mountain region, although this is based on a very small number of cases. The rates were low in farming states and in the South; however, since

Table 4. HAS cases, CDC survey, 1964-1974: distribution by causative factors and year of death.

	1964	1965	1966	1967	1968	1969	1970	1971	1972	1973	1974	Total
Idiopathic	4	10	9	13	12	13	11	12	13	11	18	126
Vinyl chloride	1	-	-	-	3	2	1	1	-	3	1	12
Arsenic	1	-	1	2	1	-	-	-	-	1	-	6
Thorotrast	-	-	-	1	2	2	3	2	4	1	5	20
Androgenic-anabolic steroids	-	-	-	1	-	-	-	1	-	1	1	4
Total	6	10	10	17	18	17	15	16	17	17	25	168

Table 5. HAS cases, CDC survey, 1964-1974: distribution by region.

Region	States	Pop. 1970	No. of cases (HAS/10 ⁷ /yr.)	No. of idiopathic cases (idiopathic HAS/10 ⁷ /yr.)
1. New England	ME, NH, VT, MA, RI, CT	11,847,186	12 (0.92)	9 (0.69)
2. Mid-Atlantic	NY, NJ, PA	37,152,813	38 (0.93)	28 (0.69)
3. E.N. Central	OH, IN, IL, MI, WI	40,252,678	35 (0.79)	30 (0.68)
4. W.N. Central	MN, LA, MO, ND, SD, NB, KS	16,324,389	10 (0.56)	9 (0.50)
5. S. Atlantic	DE, MD, DC, VA, WV, NC, SC, GA, FL	30,671,337	23 (0.68)	15 (0.44)
6. E.S. Central	KY, TN, AL, MS	12,804,552	7 (0.50)	1 (0.07)
7. W.S. Central	AR, LA, OK, TX	19,322,458	12 (0.56)	10 (0.47)
8. Mountain	MT, ID, WY, CO, NM, AZ, UT, NV	8,283,585	10 (1.10)	7 (0.77)
9. Pacific	WA, OR, CA, AK, HI	26,525,744	21 (0.72)	17 (0.58)
Total		203,184,742	168 (0.75)	126 (0.56)

many cases are diagnosed only after referral to major hospital and tumor centers, it is possible that low rural rates could be artifactual.

To summarize this portion of the study, it is apparent that HAS has a strong male preponderance, that it appears to occur more often in younger age groups than other sarcomas of the liver, and that there may be geographic differences which are unrelated simply to the distribution of VCM associated cases (the largest number of which were in Kentucky and West Virginia). As part of the follow-up effort we looked at occupation in the death certificate case-control study. Table 6 shows that the case-control ratios were elevated only for the last two occupational categories. The first of these (#7) shows a highly significant difference for chemical workers that is entirely related to exposure to VCM; all 10 cases were PVC polymerization workers. The last category (#8) combined a large number of laboring groups with potential exposure to a variety of chemicals; included are laborers, machinists, maintenance workers and others. The association of this heterogeneous grouping of occupations with HAS is not statistically significant, nor in reviewing the individual occupational data from the interviews with family members were we able to identify a specific chemical, plant, or process as a causative factor. Nevertheless, taken together with the earlier findings, this association suggests that some chemical exposure or industrial factors may be related to a portion of the idiopathic cases. Such an association would not be unreasonable; machinists, e.g., are potentially exposed to trichloroethylene (an experimental hepatocarcinogen that is structurally related to vinyl chloride), inorganic arsenic and nitrosamines (which have been identified in cutting fluids and are a known cause of HAS in animals) (22, 23).

Discussion

A particularly intriguing feature of HAS is that there are now four probable causes of this tumor, and yet about 75% of the cases are of uncertain etiology. Given that the HAS cases associated with the four quite distinct etiologic factors (VCM, Thorotrast, arsenic, and androgenic-anabolic steroids) share a common morphologic progression to HAS which is indistinguishable from that of idiopathic cases (24), it is likely that additional causal factors are (or will be) associated with HAS. In this study, the male preponderance, the younger age distribution, the possible geographic relationship with industrial portions of the country, and the suggestion from the death certificate case-control

study that groups with chemical exposure may be at higher risk, raise the possibility that some of the idiopathic cases may be related to presently unidentified environmental or occupational exposures.

This study and that of Baxter et al. (25) confirm the limited diagnostic reliability of death certificate diagnosis of HAS and the need to assess a variety of

Table 6. Occupation as recorded on death certificate, case-control study, CDC HAS survey, 1964-1974.

Occupation	Cases (N = 135)	Control (N = 421)
Professional, technical, engineers	16	40
Managers, administrators	5	23
Sales, wholesale/retail trade	3	29
Clerical	9	13
Communications	1	5
Finance, insurance, real estate	2	4
Business, store owners, proprietors	5	11
Service workers	8	36
Housewife, homemaker	18	58
Military, government	2	3
Unlisted, retired, disabled	5	12
	74 (55%)	234 (56%)
Agricultural (farming, stock, feed, fisherman)	4 (3%)	23 (5%)
Mining	1 (1%)	8 (2%)
Transport	4 (3%)	21 (5%)
Carpenters, craftsmen	2 (1%)	9 (2%)
Manufacturing (unspecified, untitled, other)	2	13
Lumber, logging, wood products	0	3
Metal, steel	0	5
Food, beverages, tobacco, packing	2	6
Textiles	3	9
Paper, printing	1	5
Rubber/plastics	1	2
Automobile	0	3
	9 (7%)	46 (11%)
Chemical	10 (7%)	1 (0%) ^a
		$p = 4.29 \times 10^{-12}$
Machinist-metal cutter	7	14
Machine operators	0	8
Forgers, molders, casters	1	3
Painters	1	4
Sanitation, water works, power	3	2
Maintenance, custodians	5	9
Laborers	8	20
Construction	1	2
Heavy equipment operators	2	6
Repair services	1	5
Mechanics	2	6
	31 (23%)	79 (19%)
		$p = 0.11^a$

^aStatistical analysis for case-control study with multiple matches (20).

sources of data in order to identify cases for studies of rare tumors such as HAS.

The Thorotrast data are instructive because the initial estimate of the latency period has lengthened with time; recent cases have been in individuals who had relatively low-dose procedures but prolonged latent periods (16). This accentuates the need to continue evaluation of VCM exposed groups for the possible appearance of a similar pattern. The time frame covered by our study is perhaps too early to detect a sizable number of cases with relatively low VCM exposure either in occupational or environmental settings. In addition, Thorotrast-induced HAS was noted approximately 10 years before Thorotrast-induced hepatocellular tumors were recognized; given the identical morphologic appearance after VCM exposure, involving mixed hyperplasia of sinusoidal cells and hepatocytes, and the occurrence of hepatocellular tumors in experimental animals exposed to VCM (26), we need to continue to follow-up VCM-exposed cohorts for the possible appearance of hepatocellular tumors.

Cases of HAS associated with various factors have previously been reported (14, 27, 28); individual cases associated with hemochromatosis, prior radiotherapy, chloroprene exposure and chemotherapy with urethane were also noted in this study, but we have not discussed them in detail here.

It would appear valuable to continue epidemiologic studies of this rare tumor. This might enable early detection of additional etiologic factors for this disease, such as the various structural analogs of vinyl chloride (e.g., vinyl bromide and vinylidene chloride) which have had industrial use. However, because of the difficulty and time involved in establishing adequate surveillance for rare tumors such as HAS or mesothelioma, it would be best to establish a single framework for studying a number of rare tumors or marker illnesses at once. One would then be able, e.g., to survey pathologists or other groups at a single time to obtain information on a variety of such conditions.

HAS is a rare tumor with at least four probable causes and undoubtedly others that have not yet been identified. Ascertainment of the range of causative agents for HAS, as well as for more common tumors, presents a challenge to epidemiologists.

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J. R. Venable

SUBJECT: ALBERTA AMBIENT AIR STANDARDS FOR VINYL CHLORIDE

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I have reviewed the two articles you provided that form the basis for Alberta's assessment of ambient air standards for vinyl chloride [Falk et al. (1981)] and Kuz'mack and McCaughy (1975)].

The Falk et al. article appears to be a well-balanced account of the epidemiology of hepatic angiosarcoma (HAS) in the United States. What is lacking is an assessment of VCM exposure intensities associated with VCM induced cases of HAS. Furthermore, there is no indication of whether or not HAS cases were associated with proximity to VCM emission sources. Apparently this was not the case, since it would have been pertinent to report such an association. A cautionary note was sounded in that for thorotrast-induced HAS cases, lower exposure was associated with longer latency. However unlike VCM, thorotrast is persistent in the body. I have enclosed a similar article on the epidemiology of HAS in Great Britain (Baxter et al.). That study did not include controls when assessing risk factors, used occupation

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as shown on the death certificates rather than as obtained through interview and therefore is a much less reliable assessment of HAS epidemiology. Even so, there is only the possibility of one case linked to geographic proximity to a PVC facility (no risk ratio provided) and several possible cases linked to low level VCM exposure at work.

The following are areas of difficulty I see with the Kuzamack paper:

- (1) assessment of the consistency of the animal risk assessment models with human epidemiologic data across the dose-response curve,
- (2) the problem of discrimination between the alternative mathematical models (e.g., linear versus probit) based on existing data,
- (3) consistency of the mathematical models with biologic knowledge (e.g., knowledge about the metabolic activation requirements of VCM),
- (4) the assertion that HAS accounts for only one half the VCM induced cancers and,
- (5) applicability of the United States risk assessment to a situation in which the potential target population is much smaller.

The validity of the extrapolation of rat data to humans (Kuzamack and McCaughy) is based on crude estimates of HAS risk from existing positive human occupational studies of highly-exposed VCM employees. Clearly, there is a correspondence in that both man and rodents evidence increased HAS risk with exposure. The validation, however, is performed at only one point on the dose-response curve, and therefore, does not validate the correspondence at lower exposures (see Gehring et al. article for an alternative approach to the extrapolation issue). There are now much more extensive human data than were available either to Kuzamack and McCaughy or Gehring et al.

Internationally, the number of VCM-related cases now exceeds 100. What has been remarkable is that most of the cases worked as autoclave cleaners at one time or another and that cases tended to cluster in certain plants. This would suggest that higher TWA exposures were experienced by the cases than the 350 ppm TWA assumed by Kuzamack and McCaughy.

It may also be that there is a steep slope in the dose-response curve. The issue facing the Alberta government is that of the nature of the dose-response curve at very low exposure intensities. Currently, there is no evidence in man that exposures below 1 ppm lead to HAS cases. Gehring et al. have shown that the number of predicted cases based on extrapolation to low level

exposure depends greatly on the model assumed (e.g., linear versus probit). Unfortunately, it is difficult to distinguish between alternative models based on experimental data because sample sizes at low doses may be inadequate. The only test of a model can come from a comparison of predictions with actual human experience at lower exposure intensities. This has not been formally done to my knowledge.

I have included articles by Tamburro, Watanabe et al., and Guengerich and Watanabe concerning the mechanism of action of VCM. It is evident that metabolic activation plays a role and that alternative metabolic pathways are available. The mathematical models proposed by Kuzamack and McCaughy simply do not consider these biologic issues.

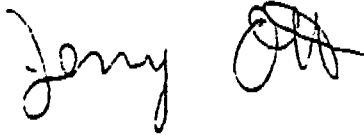
Recent articles by Theriault do not support the contention HAS accounts for only one half of the cancers induced by VCM.

An important component of risk assessment is knowing the size of the population possibly at risk. In the United States, this was estimated to be in excess of 4 million people within a 5 mile radius of VCM or PVC plants. The number of people possibly at risk in Alberta must be much smaller than 4 million. This should be considered in the risk assessment.

In summary, to my knowledge, epidemiologic evidence that people exposed to less than 1 ppm VCM are at increased risk of

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developing HAS is lacking. Yet because of the signal tumor nature of HAS, such evidence would be relatively easily to develop. The regulatory actions are being contemplated based on extrapolation of animal data via mathematical models to low level exposures rather than based on direct human evidence. While the objective is clearly to prevent any cases of VCM-induced HAS from occurring, it is unclear whether or not a more stringent ambient air standard will impact on the likelihood of such cases.



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