CHEMICAL MANUFACTURERS ASSOCIATION

August 15, 1994

Dear Vinyl Chloride Health Committee Members:

The American Cancer Society's response to our August 1, 1994 letter is enclosed. The response is very favorable and you may want to consider sharing it with your legal departments. Dr. Heath's opinion as the Vice President of the Epidemiology and Statistics Department of the American Cancer Society would add considerable weight to the industry position.

I am looking forward to speaking with you on September 9 at 3:00 p.m., EDT. If you have any questions, please call me at (202) 887-1192.

Sincerely,

Has Shah

Hasmukh C. Shah, Ph.D.
Manager, Vinyl Chloride Panel

Enclosure

R&S147547

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AMERICAN CANCER SOCIETY®
NATIONAL HOME OFFICE

CLARK W. HEATH, JR., MD
Vice President
Epidemiology and Statistics
August 4, 1994

Hasmukh C. Shah, Ph.D.
Manager, Vinyl Chloride Panel
Chemical Manufacturers Association
2501 M Street, N.W.
Washington, DC 20037

Dear Dr. Shah:

Thank you for your recent letter. The Time magazine chart is certainly misleading. It may well be that the American Cancer Society source they are citing is *Cancer Facts and Figures 1994,* in which case it is unfortunate that they ignore the word "possible". *Cancer Facts and Figures* is widely quoted and not infrequently quotations are not entirely accurate.

We review the *Cancer Facts and Figures* text and update the numbers each year and shall certainly take your comments into consideration. There are, of course, many degrees of "possible" when considering risk factors, and in the instance of lymphoma I would think there is a distinctively lower possibility for vinyl chloride than for herbicides, neither being proven. The document is not meant, of course, to be an exhaustive treatise on all possible cause factors at each cancer site, but to provide brief overviews of major points. For no site other than liver (angiosarcoma) is vinyl chloride evidence conclusive, and even there it concerns only high, repeated, occupational exposures to vinyl chloride monomer (ideally, we should distinguish between monomer and polymer).

Again, thanks for your letter and its attachments.

Sincerely,

Clark W. Heath, Jr., M.D.

cc: S. Montgomery
A. Stone
J. Laszlo, M.D.

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CHEMICAL MANUFACTURERS ASSOCIATION

August 1, 1994

Clark Heath Jr., M.D.
Vice-President for Epidemiology
and Surveillance
American Cancer Society
1599 Clifton Rd. NE
Atlanta, GA 30329-4251

Dear Dr. Heath:

I am writing this letter on behalf of the Chemical Manufacturers Association Vinyl Chloride Panel to express our concerns regarding a statement in the first full sentence of page fifteen of the ACS publication *Cancer Facts and Figures 1994* (as well as in earlier issues). Referring to the risk factors associated with malignant lymphoma, this statement reads as follows:

> "Other possible risk factors include exposures to herbicides, industrial solvents, and vinyl chloride."

We believe that a misunderstanding of this statement may have lead to the association of vinyl chloride exposure with risk of lymphoma in an article by J. Madeleine Nash in the April 25, 1994 issue of *TIME* magazine (page 60). A copy of this page is enclosed. The description in the table entitled "The Big Killers" implies, we believe, that vinyl chloride is a "proven" rather than a "possible" risk factor for malignant lymphoma. We are concerned that others may similarly misinterpret the statement appearing in *Cancer Facts and Figures 1994*.

A large number of epidemiologic studies have been conducted on well-defined occupational cohorts with potential exposure to vinyl chloride. In some of these studies an elevation in lymphoma mortality was observed, but not in others. The largest and most recent such study, published by Wong et al. in 1991, did not observe any excess of lymphatic or hematopoietic cancer deaths, even among workers who were first exposed prior to 1950. In contrast, mortality due to cancer of the liver, with which vinyl chloride exposure is certainly causally associated, was most elevated in the subcohort of workers exposed prior to 1950. We believe that the epidemiologic evidence does not lead to an inference of a causal association between vinyl chloride exposure and malignant lymphoma.

Our view is consistent with that of Sir Richard Doll, who reviewed the evidence in 1988. We note that Doll refers to the studies by Tabershaw and Gaffey (1974) and Waxweiler et al. (1976) as having raised the possibility of an association between vinyl chloride and lymphoma. We hasten to point out that these were early studies conducted on workers who were eventually included in the much larger cohort studies by Wong et al. and referred to in this letter.

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We respectfully request that the statement in *Cancer Facts and Figures 1994* be amended to better reflect the current state of knowledge about the suspected association of vinyl chloride exposure with lymphoma. The suggested wording to be added is (underlined and in italics):

> "Other possible risk factors include exposures to herbicides, industrial solvents, and vinyl chloride, *although the evidence supporting an association with vinyl chloride exposure is limited.*"

An alternative to this change of wording would be to remove the specific reference to vinyl chloride from the statement. We note that vinyl chloride is not mentioned specifically as a possible risk factor for cancer of the lung, although there is also equivocal epidemiologic evidence for an association between vinyl chloride exposure and this type of malignancy.

We feel that our suggestion encompasses the current state of the evidence concerning vinyl chloride and lymphoma and would minimize the possibility for the kind of misinterpretation we observed in the *TIME* magazine article. At the same time, we wish to point out that this letter was intended solely to address possible misinterpretations with respect to lymphoma and vinyl chloride. In no way do we acknowledge the existence of any association between exposure to herbicides or industrial solvents and the occurrence of malignant lymphoma.

We trust that this letter and the attachments will serve to provide you with a comprehensive view of the evidence concerning the health effects of vinyl chloride exposure in humans. If you have any questions or would like more information, please contact me at (202) 887-1192.

Sincerely,

Has Shah

Hasmukh C. Shah, Ph.D.
Manager, Vinyl Chloride Panel

Enclosures

R&S147550

References Cited and Enclosed:

American Cancer Society. Cancer Facts and Figures, 1994; 1-28.

Doll R. Effects of exposure to vinyl chloride. An assessment of the evidence. Scand J Work Environ Health 1988;14:61-78.

Nash JM. Stopping Cancer in its Tracks. TIME Magazine 1994; April 25: 54-61.

Tabershaw IR and Gaffey WR. Mortality study of workers in the manufacture of vinyl chloride and its polymers. J Occup Med 1974;16:509-18.

Waxweiler RJ et al. Neoplastic risk among workers exposed to vinyl chloride. Ann NY Acad Sci 1976;271:40-48.

Wong O et al. An industry-wide epidemiologic study of vinyl chloride workers, 1942-1982. Am J Ind Med 1991;20:317-34.

R&S147551

"It was like a shot for measles or mumps. I do not expect any side effects, except to feel better."

JACK SWEPSTON, 48. Pancreatic Cancer. On March 31 this Dallas dentist traveled to the National Cancer Institute in Bethesda, Maryland, to receive a new type of anticancer vaccine. Prepared by a team of researchers, including Drs. David Carbone and John Minna of the University of Texas Southwestern Medical Center, the vaccine was a synthetic version of a mutant protein fragment found in Swepston's tumor. The hope is that the immune system will learn to recognize this target and destroy the cells that make it. "I haven't felt a significant improvement yet," he says, "but the doctors are tremendously excited."

enues of escape. Not all the myriad cells shed by tumors survive the turbulent voyage through the bloodstream, notes experimental oncologist Ann Chambers of the London Regional Cancer Centre in Ontario. But those that do eventually slip through blood-vessel walls with ease. Using a video camera attached to a microscopic lens, Chambers has watched in wonder as melanoma and breast-cancer cells, injected into mice, become lodged in capillary walls, then crawl out into the liver. Three days later, her camera resolves the spidery shapes of tiny metastatic growths. The lesson, Chambers believes, is depressingly clear. Cancer cells zip in and out of blood vessels so readily that, once angiogenesis occurs, they should be presumed to have already spread around the body.

Metastasis is an event of awesome complexity, one that requires multiple genes to cooperate as closely as musicians in an orchestra. Some of these genes code for chemical solvents that enable the advancing cell to dissolve surrounding tissue. Others order up the production of adhesion molecules that, like treads under a tank, move the cell forward. Why would genes do that? The answer, notes Patricia Steeg of the National Cancer Institute, is that while the genes important to metastasis are abnormally turned on, they are not necessarily abnormal themselves. A cancer cell, in many ways, is not that different from an embryonic cell on its way to becoming a patch of skin or a bundle of nerves. Both embryonic and cancer cells divide and form ill-defined clumps. Both get up and move around. Both migrate and populate new areas. But while an embryonic cell stops proliferating and matures into adult tissue, the cancer cells just keep dividing.

One reason for the difference may lie in a gene known as nm23, first identified by Steeg in 1988. It seems to help mature cells stop dividing and arrange themselves in an orderly fashion. Steeg's research suggests that in cancer cells this crucial gene often malfunctions. When she introduced a normal nm23 gene (nm stands for nonmetastatic) into highly malignant human breast cells, then injected these cells into mice, their tendency to form metastases dropped as much as 90%.

GUARDING THE MASTER SWITCH Until last week, p53, the subject of some 1,000 scientific papers in 1993 alone, was considered the most important cancer gene. The journal *Science* even named it Molecule of the Year. But now there is a new contender for notoriety—MTS1, as Alexander Kamb and his colleagues refer to the multiple tumor-suppressor gene they have just discovered. "Multiple" refers to the fact that defects in this gene can cause many kinds of cancer, including melanoma, lung, breast and brain tumors. In fact, functional copies of MTS1 may be missing in more than 50% of all human cancers.

What makes MTS1 so significant is its clear role in the cell-division cycle. A cell divides not at will but in response to specific signals, such as growth factors produced by white blood cells rushing to repair a wound. These signals are picked up by receptors on the membrane of the cell and passed along—like batons in a high-speed relay—through the interior, all the way to a master "on" switch positioned deep in the nucleus. Not surprisingly, many oncogenes, including one called ras, the first human cancer gene ever identified, are involved in this type of signaling pathway. But there are other molecules that determine whether the cell should heed these signals. And the small protein produced by

THE BIG KILLERS

Estimates in the U.S., 1994

Cancer		Deaths	New cases	Five-year survival rate	Risk Factors
Lung		153,000	172,000	13%	Cigarette smoking; exposure to asbestos, chemicals, radiation, radon
Colon/Rectum		56,000	149,000	58%	Family history; high-fat, low-fiber diet
Female Breast		46,000	182,000	79%	Age; family history; no pregnancies; late menopause; early menarche
Prostate		38,000	200,000	77%	Age; family history, possibly fat intake
Pancreas		25,900	27,000	3%	Age; smoking; fat intake
Lymphoma	Hodgkin's Non-Hodgkin's	22,750	52,900	78% 52%	Reduced immune function; exposure to herbicides, solvents, vinyl chloride
Leukemia		19,100	28,600	38%	Genetic abnormalities; exposure to ionizing radiation, chemicals; viruses
Ovary		13,600	24,000	39%	Age, family history, genetic disorders, no pregnancies
Kidney		11,300	27,600	55%	Smoking
Bladder		10,600	51,200	79%	Smoking
Uterus	Cervical Endometrial	10,500	46,000	67% 83%	Intercourse at an early age; multiple sex partners; smoking Early menarche; late menopause; obesity
Oral		7,925	29,600	53%	Smoking; excessive use of alcohol
Skin Melanoma		6,900	32,000	84%	Sunburn; fair complexion; exposure to coal tar, pitch, creosote, arsenic, radium

Source: American Cancer Society

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