CMA

CHEMICAL MANUFACTURERS ASSOCIATION

Vinyl Chloride Panel
Health Committee
Fax
October 20, 1994

TO:			
	James Barter	PPG	412/434-2137
	Ed Beeler	GEON	216/447-6459
	Ron Gilbert	Westlake	713/963-1540
	Mark Gruenwald	Borden	614/431-6611
	James Knaak	OxyChem	716/286-3141
	Patrick Logue	Georgia Gulf	504/687-0294
	Dave Penney	Vista	512/331-2387
	David Pun	Formosa	201/716-7283
	Jonathan Ramlow	Dow	517/636-1875

FROM: Has Shah

RE: Conference Call Reminder

A letter from James Swenberg regarding the Committee's visit to EPA is enclosed for your review prior to our conference call on Monday, October 24, at 9:30 a.m. If you have any questions, please call me at (202) 887-1192. Thanks.

PAGES: 3 (including cover)

SENDER: Kim Reed

PHONE: (202) 887-1191

SL 107728

2501 M Street, NW, Washington, DC 20037 Telephone 202-887-1100 Fax 202-887-1237

Responsible Care® A Public Commitment

THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

The School of Public Health
Department of
Environmental Sciences and Engineering

The University of North Carolina at Chapel Hill
CB# 7400, Rosenau Hall
Chapel Hill, N.C. 27599-7400

October 19, 1994

Dr. Hasmukh C. Shah
Manager, Vinyl Chloride Panel
Chemical Manufacturers Association
2501 M Street, NW
Washington, D.C. 20037

Dear Dr. Shah:

I enjoyed seeing you at the CIIT Open House last week. This letter is a follow up to our conversation regarding the discussions that the Vinyl Chloride Panel held following our visit to the EPA. I would be interested in working with you on some of the issues that are still of concern such as determining the $T_{1/2}$ of the ethenoguanine DNA adduct (EG), and quantitating the amount of the methyl purine DNA glycosylase (MPG) and P450 2E1 in tissues of humans of different ages.

We discussed the approach that I would use to determine the $T_{1/2}$ of EG. This would require the synthesis of [$^{13}C_2$]-vinyl chloride. I would then expose groups of 3-4 rats using the closed chamber technique to the stable isotope and sacrifice them at different times (0, 4, 12, and 24 hours) after a 6 hour exposure to ~1000 ppm VC. This would be repeated several times to determine the average $T_{1/2}$ of EG using our GC/ high resolution MS methodology. Dr. Johannes Filser will visit me next week and I plan on discussing the details of the animal exposure with him, as he is an expert in the closed chamber technique.

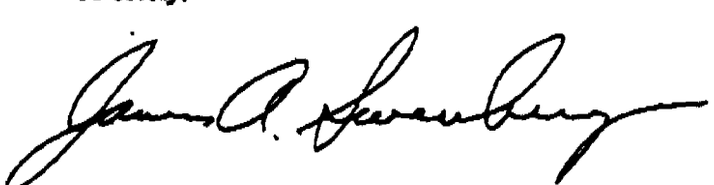
We are just setting up a quantitative polymerase chain reaction (PCR) method for measuring the expression of the MPG DNA repair protein. We plan to evaluate age differences in rats and mice under our Superfund Basic Research Program proposal, providing it gets funded. What I hadn't considered until I met with the VC Panel was doing this in human tissues of different ages. This may require slight adjustments in methodology and the synthesis of different primers. I believe that I can obtain human tissues from various tissue banks such as Vanderbilt University and the University of

Maryland. It may also be possible to get them from UNC and Duke. You indicated a desire to also examine P450 2E1 expression in similar tissue. I would probably ask Dr. Fred Guengerich to collaborate on this aspect. He has all of the methods in place and could use the same tissue specimens that we use for MPG.

These studies would be modest in size and scope, but should provide very important information relevant to human risks associated with vinyl chloride exposure. The direct cost of this research would be ~ $50,000 per year for two years, with half of this for the DNA adduct studies, 35% for the MPG determinations and 15% for the P450 2E1 studies. If this is handled as a grant to the university, there would be 44.5% overhead charged on the direct costs. If it is provided as a gift, there is no overhead. If a grant is desired, I will need to submit a research proposal and budget for university approval.

I hope this provides enough information for your next year's budget meeting. We can obviously increase or decrease the effort if this is deemed to little or to great. Please let me know what the Panel decides. Thank you again for your interest in our research.

Sincerely,



James A. Swenberg, D.V.M., Ph.D.
Director, Curriculum in Toxicology
Professor, Environmental Sciences and
Engineering, and Pathology

SL 107730

Carlo H. Tamburro, M.D., M.P.H.
Chief, Division of Occupational Toxicology
Director, Liver Research Center

School of Medicine, 119A
University of Louisville
Louisville, Kentucky 40292
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UNIVERSITY of LOUISVILLE

October 27, 1994

Hasmukh Shaw, M.D.
Chemical Manufacturers Association
2501 M. Street, N.W.
Washington, D.C. 20037

RE: Study of Brain Cancer in Vinyl Chloride Exposed Workers

Dear Dr. Shaw:

As per Mr. Michael Sweeney's request, I am submitting our time and cost estimate for the rapid completion of our study of brain cancer occurrence in vinyl chloride exposed workers. Enclosed you will find a summary of the budgetary assistance needed for us to complete the updating and publication of this brain cancer and vinyl chloride exposure study. The need to update is due in part to the recent reorganization of the B.F. Goodrich Company. Although all the original workers are still physically present in the original B.F. Goodrich Company Bells Lane plant, that site is now split into three different corporate structures: B.F. Goodrich, Geon, and Zeon Kentucky. As I indicated to Mr. Sweeney during their recent visit, we are now reestablishing a working network with all three companies that will provide for scientific information to be made available. This updating, based on part-time effort, was expected to proceed to completion over the next two years and one-half years.

We are prepared to proceed at a more rapid rate to complete the brain study with a 20-year prospective follow-up. This update would also provide a 25-year combined retrospective evaluation of the relationship of vinyl chloride to brain cancer. Each brain cancer case will be paired with all available matched controls and be analyzed by rank ordered analysis (reference Greenburg and Tamburro, JOM 1981). By this approach, each case will become an individual causal study. Each additional case will add further confirmation to the absence or presence of an identifiable relationship between any of 22 or more chemicals studied. In this manner we expect to revalidate our first observation, that no causal relationship exists between vinyl chloride exposure and brain cancer.

The assistance we require, in the form of a grant to the University, would allow us to analyze workers exposed to vinyl chloride both by rank order and environmental levels. The study hypotheses to be confirmed are based on our initial observation. That:

1. Vinyl chloride exposure is not associated, clinically or histologically with brain cancer development, based on 20-years of prospective and 25-years of retrospective study.

2. There is an environmental vinyl chloride level or biological threshold (minimum environmental level) at which no association with any brain disease has been found.

3. The biological threshold for disease development for humans exposed to vinyl chloride is 50ppm (parts per million) or less TWA (time weighted average) exposure for less than 3 years.

We feel, scientifically, that the complete updated analysis will reconfirm these initial observations.

Our time estimate regarding updating, verifying, analyzing, and preparing the report for submission to a recognized national peer reviewed journal would be completion in 7-9 months. Enclosed is a summary of the work and services required to update the B.F. Goodrich study database in this time frame.

If I can provide any further clarification or information, please do not hesitate to give me a call. I look forward to hearing your response at your earliest convenience.

Sincerely,

Carlo H. Tamburro, M.D., M.P.H.
Professor of Medicine
Director of Liver Research Center & Lab
Professor of Pharmacology & Toxicology
Chief, Division of Occupational Toxicology

CHT:sam
Enclosures

BUDGET FOR CMA

PERSONNEL NAME	TIME ON PROJECT	ROLE ON PROJECT	SUMMARY COST
Carlo H. Tamburro, MD, MPH	10%	Principle Investigator	13,000.
H. Philip Fortwengler, MS	75%	Occupational Data Manager	33,066.
Lark Reynolds, BS	75%	Data Coordinator	15,190.
Mary Heck, MT	25%	Histological Procurement	7,420.
Stephen W. Looney, PhD	20%	Biostatistician	18,130.
SUBTOTAL			86,806.
EMPLOYEE CONSULTATIVE COSTS[1]			2,140.
SUPPLIES, EQUIPMENT[2]			1,900.
TRAVEL[3]			200.
SUBTOTAL			4,240.
TOTAL (DIRECT COSTS)			91,046.
INDIRECT COSTS (25% S&W)			21,702.
GRAND TOTAL			112,748.

1. Consultative cost for past and present key employee needed to work with U of L staff in work and environmental record data collection and verification, also cost for external independent biostatistical and epidemiology review.

2. Includes special computer updated software to increase speed and efficiency of large data set analysis, use of university main frame (computer time), telephone, mailing and support services cost.

3. Costs that will be encountered to check all regional hospitals for tissue verification of tumor diagnosis, especially the 100 not having complete cause of death data.

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PROPOSAL AND OUTLINE
LABOR AND SUPPLIES NEEDED
FOR RAPID UPDATING OF
THE 20 YEAR PROSPECTIVE/45 YEAR RETROSPECTIVE
BRAIN CANCER STUDY ON VINYL CHLORIDE EXPOSURE

INFORMATION NEEDED:

1. **Contiguous Work Histories.** Updating of the contiguous industrial work histories will need to be completed and verified on all employees from the original B.F. Goodrich Company and the two offspring companies, Zeon and Geon. Some employees have been continually employed, others are new hires, retired, or have died since the last update. A reasonable estimate is 600-700 employees per year from 1979-1993 need updating or verification.

2. **Job Title Listings by Industry, Plant, Building, and Year.** Review and updating of all past (before 1980) and new job titles (after 1980). New plant construction, renovations, and manufacturing location changes, which have occurred in recent years necessitate this step. In addition, there have been physical plant areas segregated into offspring companies. These job title listings will be used to produce a table of updated exposure ranking for all employees for all of the 1980's and 1990's.

3. **Exposure Rankings.** Exposure ranking updates are required on the cohort as described above. Updated ratings (ranking) will be given to all new job titles and old job titles used in the old and new sections of the plant(s) from 1979-1994. Participation of experienced employees will be needed and used for rating processes.

4. **Chemical History.** Updated documentation/verification of the continuous use of the 22 chemicals originally identified is needed. The area and personal monitoring data, where available, for these chemicals under evaluation will also be updated. This will be used for quantitative confirmation of rank order. The years and the buildings in which any of the 22 chemicals under study were used will also be reconfirmed.

5. **Death Confirmation Data.** Death certificate data is available on 484 vinyl monomer workers. Forty-six have incomplete data or need updating for cause of deaths. Retired, and separated employees data needs to be completed and reverified.

6. **Cancer Records.** The histology, where and when ever available, will be examined for all brain cancer cases. This will be done for verification and confirmation of the histological tissue type. There will also be a follow-up conducted by phone or mail for retired former employees living outside the greater Louisville area if contact information is available.

LABOR EXPENDITURES REQUIRED:

Where needed, employees from B.F. Goodrich, Zeon, and Geon, paid by and working for the U of L staff, will be used to assist in gathering all pertinent work records and documents. The U of L staff will supervise the acquisition of all employee work records and the transfer of data via computer into the occupational interrelational data bank.

RECORDS GENERATED:

1. **Employee-Year Records.** An estimated 600-700 employees per year for 15 years yields approximately 9,750 employee-years of work histories.

2. **Maximum Estimated Cancer Cases.** Brain cancer cases (all types) from 1945-1993 is estimated (based on all Kentucky cancer deaths 200/100,000) at no greater than 5-7/1,000. This estimate includes non-death cancer cases. At this point, we have identified 136 cancer cases (all types) and 10 brain cancer cases in the 484 deaths.

3. **Analysis.** Analysis regarding exposure and cancer by site and tissue type will be analyzed by nonparametic statistics. These methods are used and validated in the publication: Greenburg RA, Tamburro CH, Exposure indices for epidemiological surveillance of carcinogenic agents in an industrial chemical environment. *Journal of Occupational Medicine* 1981; 23(5):353-358.

SL 107736

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

Richard A. Greenberg, Ph.D., M.P.H., and Carlo H. Tamburro, M.D.

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]

From the University of Louisville, Dept of Community Health (Dr. Greenberg) and Dept. of Medicine (Dr. Tamburro), P.O. Box 35260, Louisville, KY 40232.

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

Reprinted from Journal of Occupational Medicine
May, 1981, Volume 23, No. 5
pp. 353-359

VCM PANEL

Tomburo Request

- 10 brain cancer deaths in BFG workforce to date

1) • Have tissues from cases sent to Army/Air Force Inst of Pathology to determine if primary cancer site or secondary.

2) Evaluate exposure of primary brain cancers to 22 of cases NESTED CASE CONTROL STUDY

PROPOSE: Bring Tomburo to CMA Mtg to discuss this in early Jan '95

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FILING INSTRUCTIONS:
ASSOCIATIONS
CMA
VINYL CHLORIDE PANEL

SL 107738