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Texas City JUN 16 1983

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To (Name)
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D. H. Glenn, MD
H. L. Greenberg
T. E. Lawrence
T. A. Lincoln, MD
F. S. Provenzano
A. R. Schnatter
~~██████████~~
A. P. Yalcinkaya

Date June 16, 1983

Originating Dept. HS & EA

Area Epidemiology

Subject Critiques of NIOSH Case-Control Study

Attached are critiques of the NIOSH case-control study of brain tumors at Texas City from Drs. Enterline and MacMahon. It is interesting that they are in such close agreement and they draw attention to the misleading abstract summary which we have already requested NIOSH to change.

Sincerely,

SG Austin

Susan G. Austin, Sc.D.
Corporate Director of Epidemiology

SGA/rjk
Attachments

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HARVARD UNIVERSITY
SCHOOL OF PUBLIC HEALTH
DEPARTMENT OF EPIDEMIOLOGY

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JUN 14 1983

S. G. AUSTIN, Sc.D.

677 Huntington Avenue
Boston, Massachusetts 02115
(617) 732-1050

June 10, 1983

Susan G. Austin, Sc.D.
Corporate Director of Epidemiology
Union Carbide Corporation
Old Ridgebury Road
Danbury, CT 06817

Dear Dr. Austin,

I have reviewed the manuscript describing the NIOSH case-control study of brain tumor cases in the Union Carbide Texas City plant.

The study seems to have been undertaken with great care and attention to detail and one gets the impression that the investigators are competent and thorough. With respect to the study and analysis itself, I have only one point to make. This is that in limiting analysis to those chemicals to which four or more cases were exposed the investigators are, in a sense, stacking the cards. They have selected those chemical associations which by chance alone are likely to have proportionally more exposed cases than controls. This is a legitimate thing to do, since the objective is to explain an observed excess of tumors. However, it should be discussed as another reason (in addition to the multiple test issue) why some things might be found to be "significantly" associated when they are in fact not. It might have been instructive to identify one control in each matched set, select those chemicals to which at least one of the identified controls were exposed and see whether there were as many exposures that appeared to be protective as there are that appear to be positively associated in the present analysis. This would have given a more balanced view than the present one which is geared solely to detecting positive associations. Since, in my view, the question of whether there is a real increase in risk of CNS tumors in this plant is still open, I think the balanced approach would be more appropriate.

Apart from the analysis itself, I have a few problems with the manuscript. Specifically:

(1) The summary. Insofar as occupational chemical exposures are concerned I interpret the findings as essentially negative, and the authors' own Discussion also leaves that impression. This is not, however, the impression

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Susan G. Austin, Sc.D.
June 10, 1983
Page 2

that is left by the Summary. The reader who reads only the Summary - and they are probably in the majority - will get the impression that all the chemicals listed there were found to be associated with risk. The Summary does not state that only for carbon dioxide is the association statistically significant by both methods of analysis (including and excluding maintenance workers) and even there the results are inconsistent with respect to time of exposure. The last sentence of the Summary is particularly misleading because, although it is true, it implies that the associations referred to earlier were statistically significant.

(2) On page 5, the first sentence of the third paragraph is not true. In fact, duration of exposure is assessed in Table V for all the chemicals listed in Tables III and IV - regardless of whether they were "significantly associated with brain tumors" in the analyses of frequency of exposure.

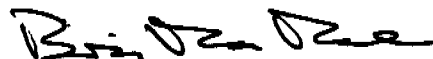
(3) On page 11, it hardly seems appropriate to refer to the chemical exposures as "risk factors" (line 2) when they have not been shown to be associated with increased risk.

(4) On page 13, line 6, this sentence should end after the word "chemical". The rest is gratuitous; it is always true and it suggests that the authors do not believe their own findings.

(5) On the same page, paragraph 2, the first sentence is a very strange summarization of the findings. Far from being conclusive, the evidence for carcinogenicity is not even suggestive.

I hope these comments will be useful to you.

Sincerely,



BM:dc

Brian MacMahon, M.D.
Professor

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University of Pittsburgh

GRADUATE SCHOOL OF PUBLIC HEALTH
Department of Biostatistics

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JUN 13 1983

S. G. AUSTIN, Sc.D.

June 8, 1983

Dr. Susan G. Austin
Corporate Director of Epidemiology
Health, Safety and Environmental Affairs
Union Carbide Corporation
Old Ridgebury Road
Danbury, CT 06817

Dear Susan:

I have had a chance to read the paper by Leffingwell et al on the Texas City brain cancers. Generally, I think this is a very nice piece of work. I particularly like the fact that residence was examined as a co-variate. There is, however, some additional information that would have made the paper more useful. For one thing it is never stated how many chemical exposure groups there were in which 4 or more cases were present. The only thing shown are the 9 chemicals with 4 or more cases and which showed the strongest positive association plus vinyl chloride. Some of the 9 are not very interesting. It is also strange that there is no strong relationship with time since first exposure for any chemical. Probably most interesting is diethyl sulfate, since this appears to be a carcinogen for upper respiratory cancers among workers producing ethanol and isopropanol.

One thing that bothers me is a requirement that to be studied a particular chemical must have been associated with at least 4 of the brain tumors. I think this is the same rule used in earlier papers and it seems to introduce some bias. I wonder what would have happened if there had been a requirement that at least 24 controls be exposed to a particular chemical.

I also have the feeling that there was some overmatching since not only were dates of hire controlled for but only the work experience of controls were examined which corresponded with the time of work experience for the cases. This, of course, rules out any discovery of time related exposures. If it is clear that such exposures didn't occur, this of course isn't important.

It is curious that the odds ratio for maintenance department workers was .32. I assume this means there was a shortage of brain tumors among maintenance department employees. Generally these employees are thought to have the most opportunities for exposure and this could be commented on.

I am concerned about the summary. Something is needed here to indicate how many chemicals were examined and what the range of odds ratios actually was. The statement in the summary, "no significant

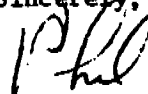
Dr. Susan G. Austin
June 8, 1983
Page 2.

association was found between exposure to VCM and brain tumors in this study" sort of implies there was a significant association found for the 9 other chemicals listed. It should be noted in the summary that the only significant association from a statistical standpoint was with carbon dioxide. The summary should also indicate that there was in no case an association with latency.

Incidentally Reference 22 can't be right; I did not have any co-authors on the paper in the Annals of the New York Academy of Sciences. Also I don't know of any cancers associated with isopropanol exposures (page 12, line 18). To my knowledge all of the positive reports have related to exposures in the production of isopropanol.

Somehow I think diethyl sulfate should have been dealt with more fully. The Alderson and Rattan paper is a good reference and a paper by Lynch et al (JOM, May 1979) should be looked at also.

Sincerely,



Philip E. Enterline
Professor and Chairman

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UNION CARBIDE CORPORATION OLD RIDGEBURY ROAD, DANBURY, CT 06817
Corporate Health, Safety and Environmental Affairs Department

May 25, 1983

Sanford S. Leffingwell, M.D., M.P.H.
Centers for Disease Control
NIOSH
Robt. A. Taft Laboratories
4676 Columbia Parkway
Cincinnati, Ohio 45226

Dear Dr. Leffingwell,

I am writing to you in response to the draft of the final report of the NIOSH/OSHA case-control study of brain tumors among workers at the Union Carbide Texas City, Texas plant. Thank you for the opportunity to comment.

I found the study well designed, thorough, thoughtfully and carefully interpreted, and the report well written. It is also pleasing that the results of your study correspond so well with ours.

I do have one suggestion, however. Although the summary accurately reflects the findings of the study, it does not clearly state or imply that the study was primarily designed for hypothesis generation. Therefore, I would amend the second paragraph of the summary to read as follows (the underscored words are my additions):

To investigate the etiology of this excess, we carried out a nested case-control study to examine possible associations between brain tumor and job title, departmental employment history, chemical exposure history, geographic location within plant, dates of employment, and residence. Among the 33 chemicals to which four or more cases were exposed, the greatest apparent risks were associated with exposure to carbon dioxide, diethyl sulfate, diethylene glycol, ethanol, ethylene, isopropanol, methane, tetraethylene glycol, and vinyl acetate. However, no significant differences between cases and controls were apparent in duration of exposure to any chemical. A suggestion of elevated risk was also associated with first employment in the 1940's or early 1950's and with residence in La Marque, Texas. Although vinyl chloride monomer (VCM) has been implicated in the etiology of brain tumors before, and was produced and used at this plant for many years, no significant association was found between exposure to VCM and brain tumors in this study. Caution must be used in interpreting results which appear to be statistically significant in this analysis, since multiple tests of significance were used.

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I look forward to the publication of the report. Please call me if I can be of any assistance.

Sincerely,

Susan G Austin

Susan G. Austin, Sc.D. *sl*
Corporate Director of Epidemiology

SGA/pmb

cc: Mr. J. B. Browning
Dr. D. H. Glenn
Dr. T. A. Lincoln
Mr. F. S. Provenzano

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