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August 10, 1995

Mr. Steven H. Wodka
PO Box 66
Little Silver, New Jersey 07739-0066

Re: William R. Smith, deceased.

Dear Mr. Wodka,

I. OPINIONS

1. Prior to 1956 there was wide acceptance in the cancer research community that long term (life-time) experiments were necessary in order to accurately evaluate the potential for carcinogenic (cancer-causing) effects from exposure to any particular substance or compound.

2. By the late 1950's the technology was available **even at Dow Chemical** to perform experiments essentially similar to those performed by Maltoni beginning in 1971 to identify the cancer risk from low level exposures to vinyl chloride monomer.

3. By the late 1950's, a prudent approach by a major manufacturer of vinyl chloride should have lead to the performance of long term chronic exposure tests similar in content to those performed later by Viola (1968-1970) (Viola, et. al., 1971) and Maltoni (1971-1973) (Maltoni, et. al. 1975, 1977, 1981, 1988).

4. The study by Torkelson, et. al. for Dow Chemical reported in Am. Ind. Hyg. Jr. 22, 354-361(1961) was limited when, in fact the data in this study suggested the necessity for long term testing, and/or longer term follow up of the exposed animal test groups. The published article does not expressly justify or advance the reasons for the termination of the experiment at 4.5 and 6 months of exposure. Most cancer researchers in 1961 would have considered this study to be an inadequate followup in the rodent species (and others) utilized after their chronic exposure, if the objective, in any way, was to eliminate the possibility of carcinogenesis by vinyl chloride monomer.

5. An extended study (2 year) should have been done with the rat strain used because this was (1)suggested by the data, as published, (2)would have discovered the cancer risk, and (3)given both the wide production and use of the chemical by that date and the exposure levels in the work place, especially in particular job categories. The results in animals would have lead to reduction of exposures and the reduction of cancer incidence , prior to Mr. Smith beginning his employment in November, 1973.

II. BASIS FOR OPINIONS EXPRESSED.

1. Prior to 1956 there was wide acceptance in the cancer research community that long term (life-time) experiments were necessary in order to accurately evaluate the potential for carcinogenic (cancer-causing) effects from exposure to any particular substance or compound.

The history of experimental cancer research goes back well into the late 1800's, and had been reviewed frequently since the 1930's. This research work had laid a large empirical foundation on which were solidly based the conclusions that determining cancer risk from exposure to a particular chemical requires (1) near life time studies, (2)comprehensive pathology analysis of all deaths during the study, and, (3) comprehensive pathology on end term sacrificed survivors. In rats the term of study should have been at least two years, and this was largely agreed on throughout the cancer research community prior to 1956. Articles describing the process of chemically induced carcinogenesis as requiring much more than a 6 month chronicity study, was well accepted in the 1950's, prior to the Torkelson study. Key references supporting this observation in the 1950's include Foulds (1954), Shubik and Sice' (1956), Bett (1957) and Peacock (1957). All of these support the above 3 requirements.

That these recommendations were generally agreed upon is presented in the article by Boyland in the British Medical Bulletin(1958), and more detailed conclusions supporting the above are summarized in the World Health Organization Technical Report Series No.220 (1961)based on their consensus meeting of December, 1960.

It should be noted that the report of the WHO International Agency for Research on Cancer(IARC) on Long-Term and Short Term Screening Assays for Carcinogens: A Critical Appraisal: IARC Monographs, Supplement 2" (1980) reporting on their consensus meeting of 1979 In Hanover, Germany , states at the opening of the section on Long Term Testing (p. 24), that "The essence of long-term testing is to observe test animals for a major portion of their lifespan for the development of neoplastic lesions after or during exposure to various doses of a test substance by an appropriate route. ....These requirements are well known and have not undergone any serious changes during the last few decades."

Furthermore, even within the toxicology profession, it was widely understood by 1962 that long term testing should be utilized to determine the risk of carcinogenesis...and that there should be more testing done for the risk of carcinogenesis than was often done (Paget, 1963, 1968).

2. By the late 1950's the technology was available even at Dow Chemical to perform experiments essentially similar to those performed by Maltoni b ginning in 1971 to identify the cancer risk from low level exposures to vinyl chloride monomer.

Dow's toxicology group had developed exposure chambers and measuring devices to accurately expose laboratory animals to vaporous and reactive chemicals such as ethylene dichloride (to levels as low as 300 ppm)(Spencer, 1951), trichloroethylene(to 100ppm) (Adams, 1951), and allyl chloride (8ppm) (Torkelson, 1959). Although these exposures were for relatively short term studies, extension using identical protocols was not limited by any technical reason apparent to me. By the early 1960's, the technology for the Rochester Chambers for analyzing exposure even to something as difficult to control as Radon was published (Wilson, 1961; Fultyn, 1961).

3. **By the late 1950's, a prudent approach by a major manufacturer of vinyl chloride should have lead to the performance of long term chronic exposure tests similar in content to those performed later by Viola (1968-1970)(Viola, et. al., 1971) and Maltoni (1971-1973)(Maltoni, et. al. 1975, 1977, 1981, 1988).**

In July,1970, Viola and colleagues submitted their paper to Cancer Research (Viola, et. al., 1971), which reported the results of exposing 26 rats for 12 months at 30,000 ppm to vinyl chloride vapor. Almost every animal developed tumors of the skin and lungs. Dr. Viola, at that time, alerted the chemical industry to his results, and more extensive studies were begun by Maltoni (described in 1975 reference), in which rats, mice, and hamsters were exposed to vinyl chloride vapor at doses from 10,000 ppm to 50 ppm. Of especial relevance to this case is that this report (1975) yielded brain neuroblastomas at a level of 2500 ppm in 135 week studies, as well as tumors at even lower doses in numbers to be statistically significant. Maltoni subsequently extended and published studies outlining a high risk for a large number of different sorts of tumors in different species from exposure to levels as low as 50ppm.
As indicated by the history of carcinogenesis, and reviewed not only in the works indicated in opinion 1, but also, in Wagoner and Infante (1977) for example, animal test results indicating the potential for carcinogenesis can only be ignored at human peril. In those cases where animal studies were ignored (DES, mustard gas, 4-aminobiphenyl, cadmium, vinyl chloride), there has emerged a number of chemically caused human cancer cases. As Paget observed in 1963:

> "However, carcinogenic action may involve long latent periods between applications of the agent and appearance of its effects, and if a new drug were an active carcinogen and were widely distributed, it might be 10 years of more before suspicion were raised from clinical findings. By this time the numbers of patients involved might be such as to make all preceding pharmaceutical catastrophies look trivial."

The same can be said to apply to industrial exposure to agents that are widely used in the range at which they can initiate carcinogenesis. Vinyl chloride and asbestos both unfortunately fall in those categories.

4. The study by Torkelson, et. al. for Dow Chemical reported in Am. Ind. Hyg. Jr. 22, 354-361(1961) was limited when, in fact the data in this study suggested the necessity for long term testing, and/or longer term follow up of the exposed animal test groups. The published article does not expressly justify or advance the reasons for the termination of the xp riment at 4.5 and 6 months of exposure. Most cancer researchers in 1961 would have considered this study to be an inadequate followup in the rodent species (and others) utilized after their chronic exposure, if the objective, in any way, was to eliminate the possibility of carcinogenesis by vinyl chloride monomer.

It is striking that the Dow Chemical Co. Study carried out by Torkelson at their Biochemiocal Research Laboratory in Midland Michigan (Torkelson, et. Al., 1961) demonstrate that the livers of male and female rats exposed to 500 ppm of vinyl chloride vapor 7 hours/day ,5 days/week for 4.5 months manifested microscopically detectable pathological changes. At 200 ppm, rabbits at 6 months showed similar changes, and there was a statistically significant increase in the average weight of rat livers at this level. There were even slight changes in the weights of rat livers at 100 ppm. These findings were warning bells to the investigators and Dow to extend these studies to ascertain if there were indeed long term risks such as those manifesting as tumors. Certainly no statement could have been made out of these studies that vinyl chloride at 100, or 200 ppm does not pose a risk of human cancer.
Arguments have been made about the relative costs of extending studies (e.g. Gehring, 1973) to lifetime. But given the wide use of the chemical, and its conditions of use (including high exposure levels of reactor cleaners) and the profitability (even as of 1961), the cost of more extensive testing would not have been prohibitive.

5. **An extended study (2 year) should have been done with the rat strain us d by Dow because this was (1)suggested by the data, as published by Torkelson (1961) ,(2)would have discovered the cancer risk(as indicated by Maltoni's studies), and (3)given both the wide production and use of the chemical by that date, and the exposure levels in the work place, specially in particular job categories. The results in animals would have lead to reduction of exposures and the reduction of cancer incidence , prior to Mr. Smith beginning his employment in November, 1973.**

The results of this failure to conduct a lifetime rat study by the late 1950's has certainly lead to excess cancers, particularly angiosarcoma of the liver, and brain cancers as indicated by Wong (1991) among others. Had a prudent manufacturer discovered these tumors at the appropriate time, it should have warned its customers and other users of the results. This action would have led to the development of safer procedures for handling this chemical and ultimately to the prevention of cancers among those with potential exposure, such as William R Smith.

III. REFERENCES USED (EXHIBITS)

1.Adams, EM, HC Spencer, VK Rowe, DD McCollister, DD Irish (1951), "Vapor Toxicity of Trichloroethylene Determined by Experiments on Laboratory Animals" A.M.A. Archives of Industrial Hygiene and Occupational Medicine **4**, 469-481

2. Bett,WR (1957) "Historical Aspects of Cancer" in Cancer,**I**, Part 1, Research into Causation. Ed. RW Raven, Butterworth & Co., London. Pp.1-5

3. Boyland, E (1958) "The Biological Examination of Carcinogenic Substances" British Medical Bulletin **1 4** ,93-98

4. Foulds, L. (1954) "The Experimental Study of Tumor Progression: A Review , Cancer Research **1 4**, 327-339

5. Fultyn, RV (1961) "Contaminant Generators for Continuous Exposure Inhalation Chambers" Am. Industrial Hygiene Assoc. Jr. 22 49-53

6. Gehring, PJ , VK Rowe, SB McCollister(1973) "Toxciology: Cost/Time" , Fd. Cosmet. Toxicol. **1 1** 1097-1110

7. Maltoni C and G. Lefemine (1975) "Carcinogenicity Bioassays of Vinyl Chloride: Current Results" Ann. NY Acad. Sci.**2 4 6**, 195-218.

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9. Maltoni, C, G. Lefemine, A Ciliberti, G. Cotti, D. Carretti (1981) "Carcinogenicity Bioassays of Vinyl Chloride Monomer: A Model of Risk Assessment on an Experimental Basis" Environ. Health Perspec. **4 1** 3-29

10. Maltoni, C. And G. Cotti (1988) "Carcinogenicity of Vinyl Chloride in Sprague-Dawley Rats after Prenatal and Postnatal Exposure" Ann. NY Acad. Sci. **5 3 4**, 145-159

11. Paget, GE (1963) "Standards for the Laboratory Evaluation of the Toxicity of A Drug" in Proceedings of the European Society for the Study of Drug Toxicity. **II,** Intl. Congress Series #73, Excerpta Medica Foundation, Amsterdam. Pp. 7-12

12. Paget, GE (1968) "Drug Safety" Chapter 11 in Modern Trends in Toxicology **IT,** ed. E. Boyland and R. Gould, Butterworth, London, 1968,

13. Peacock, PR (1957) "Carcinogenesis" in Cancer,**I,** Part 1, Research into Causation. Ed. RW Raven, Butterworth & Co., London. Pp. 32-75

14. Shubik, P and J. Sice' (1956) "Chemical Carcinogenesis as a Chronic Toxicity Test: A Review" Cancer Res. **1 6**, 728-742.

15. Spencer, HC, VK Rowe, EM Adams, DD McCollister, and DD Irish (1951) "Vapor Toxicity of Ethylene Dichloride Determined by Experiments on Laboratory Animals" A.M.A. Archives of Industrial Hygiene and Occupational Medicine **4**, 482-493

16. Torkelson, TR, MA Wolf, F Oyen, and VK Rowe (1959) "Vapor Toxicity of Allyl Chloride as Determined on Laboratory Animals" Am. Ind. Hyg. Assoc. Jr. **2 0**, 217-223

17. Torkelson, TR, F Oyen, VK Rowe (1961) "The Toxicity of Vinyl Chloride as Determined by Repeated Exposure of Laboratory Animals" Am. Ind. Hyg. Assoc. Jr. **2 2**. 354-361.

18. Viola, PL, A. Bigotti, and A. Caputo (1971) "Oncogenic Response of Rat Skin, Lungs, and Bones to Vinyl Chloride" Cancer Res. **31**, 516-522

19. Wagoner, JK and PF Infante (1977) "Vinyl Chloride: A Case for the Use of Laboratory Bioassay in the Regulatory Control Procedure" in Origins of Human Cancer **C**,edited by HH Hiatt, JD Watson, and JA Winsten, Cold Spring Harbor Conferences on Cell Proliferation **IV**, pp. 1797-1805

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21. WHO, International Agency for Research on Cancer (1980) Long-Term and Short-Term Screening Assays for Carcinogenes: A Critical Appraisal IARC Monographs, Supplement 2, IARC, Lyon, pp. 23-83.

22. Wilson, R.H. (1961) "Design of a Radon Exposure System" Am. Ind. Hyg. Assoc. Jr. **2 2** 409-415.

23. Wong, O, MD Whorton, DE Foliart, and D. Ragland (1991) "An INdustry-Industry-Wide Epidemiological Study of Vinyl Chloride Workers, 1942-1982" Am. J. Ind. Med. **2 0** 317-334.

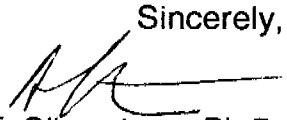
IV. My reimbursement rate is

$125/hour for literature review and preparation time.

$250/Hour, including travel time for deposition and testimony.

V. I have testified as an expert witness in Paternity Testing in the case of "Great Plains Child Support vs. Larry Curtis Roach" U-0238-93, testifying before the Honorable William F. O'Brien III, in the Madison County Courthouse in Wampsville, NY, January 25, 1995. I was testifying for the respondent at the request of his court appointed attorney, Mr. Peter Hedglon of Nemeti, McDermott, Eppolito, and Hedglon, Oneida, NY.

Sincerely,



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