

- INTER-OFFICE MEMO

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FROM F. M. Toca

AT Saddle Brook

COPY TO

SUBJECT Comments: Conference on Occupational Carcinogenesis

During the week of March 24-27, 1975 I attended the Conference on Occupational Carcinogenesis sponsored by the New York Academy of Sciences. My comments and impressions of this meeting follow. I have also included abstracts of those papers of particular interest to TCI.

Special My overall impression about this meeting is that it was very anti-industry. The tone was set with the opening remarks by Dr. Wagener when he said, "No longer can we permit industry to provide policies as to scientific problems... we must place human over economic values..." Thus throughout this meeting it was insinuated that industry only reacted when made to, that industry must be made responsible for worker health, that industry was only concerned with economics, etc.

Despite this overall negative tone, many of the scientific issues raised were valid and many of the papers presented were worthwhile. Issues of interest included:

1. Can screening methods be used to test chemicals for carcinogenicity? A battery of such tests are needed to reduce the time and expense of present methods. But can these methods alone be used to determine whether or not a material should be removed from the marketplace?
2. Is mutagenesis a true test of carcinogenesis? Present studies with bacteria show 75% of known carcinogens cause mutagenesis of certain bacterial strains.
3. How good are epidemiological surveys and biostatistical methods for predetecting carcinogenicity. Many of the papers presented at the meeting were based on the review of death certificates and subsequent prediction of effect based on the observed vs. the expected results.
4. Is there a dose-response relationship for carcinogens? This point was not really debated at this meeting because the predominating belief was that there should be NO, zero, exposure to any carcinogen.
5. Can cytologic monitoring be used as a predictive test for respiratory cancers? Several papers were presented which showed a correlation between the presence of "oat" cells in the sputum and the finding of respiratory track tumors.
6. This meeting dealt with toxicity but did not consider hazard potential. It has been accepted practice that safe systems can be designed for handling even the most toxic of substances, but this was not at all considered.

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Author Abstracts:

"CRITERIA FOR CARCINOGENESIS by Emmanuel Farber, M.D., Ph.D., Fels Research Inst., Temple University, Sch. of Med., Philadelphia, Pa.

Comments: The emphasis of this paper was towards the early detection of cancer by identification of the chemical-chain reaction.

Thus, if the precursors of disease can be identified, preventive action can be taken.

The development of a bacterial test system for the detection of carcinogens and mutagens will be described. The test utilizes specially constructed mutants of Salmonella typhimurium for detection of mutagenic activity and rat (or human) liver microsomes for metabolic conversion of carcinogens to their active mutagenic forms. Chemicals are tested directly on petri plates with the bacterial tester strains and the microsomal activation system. The test is rapid and economical, and is proving extremely efficient in detecting carcinogens. Hundreds of compounds have been tested with our strains and about 75% of the carcinogens can be detected as mutagens and extremely few of the non-carcinogens are mutagenic. We have adapted the method for detection of

mutagenic metabolites in urine. The test is being utilized in detecting potential mutagenic/carcinogenic activity of uncharacterized compounds in complex mixtures, and we have detected mutagenic activity in cigarette smoke condensates, and soot from city air. Recently, new tester strains containing resistance transfer factors have been developed which greatly extend the versatility and sensitivity of the test. A number of compounds of environmental importance, such as vinyl chloride and some metabolic products, can be detected in our system."

Comments: This technique was very strongly debated pro and con at the meeting. Its advantages include savings in time and money. But it does not elevate the need to do more extensive testing. It also remains to be proven that positive findings are synonymous with carcinogenicity.

"DOSE-RESPONSE RELATIONSHIP AND THRESHOLD CONCEPTS by Paul Kotin, M.D., Johns-Manville, Denver, Colorado

Dose-response relationships and threshold (DRRT) are numerical expressions of the effect of the reaction of an agent(s) with the chemical constituents of living organisms. In multicellular hosts a hierarchy of levels of reaction exists which can be categorized in several ways: anatomical--cellular protein to intact host; biochemical--transitory to persistent; functional--physiological to pathological; clinical--reversible to permanent; and teleological--good to bad. For noncarcinogens the concept of DRRT is universally recognized and has been quantified for many agents. The existence of DRRT for interaction of a carcinogen with the cell is controversial. The question of DRRT for a neoplasm as distinguished from a transformed cell is a critical one. The verification of DRRT for cancer production must include traditional pharmacologic criteria as well as additional factors such as repair mechanisms, the relationship of altered cells to the normal cell population in the host, latency, and the normal frequency distribution extant in heterogeneous populations. The biology of carcinogenesis and cancer induction appears to be compatible with DRRT."

Comments: The author's position that DRRT is compatible with carcinogenic agents was not the majority opinion held by the attendants at this conference.

"LABORATORY APPROACHES TO THE IDENTIFICATION OF CARCINOGENS by Richard R. Bates, M.D., NCI Frederick Cancer Research Center, Fort Detrick, Frederick, Maryland.

Occupational cancer results from failure to detect the carcinogenicity of chemicals before human exposure occurs. Chronic exposure of experimental animals is still the only definitive test for carcinogenicity, but high cost and long duration of these tests prevent testing more than a small proportion of environmental chemicals for carcinogenicity. Recommended improvements in bioassay protocols often lead to more definitive results for each chemical tested while decreasing the number of chemicals which can be tested on a limited budget. More consideration is needed of the optimum balance between test refinements and ability to test more chemicals. Short-term prescreening techniques being developed may permit more effective identification of carcinogens by increasing the proportion of them in environmental chemicals selected for chronic animal bioassays. Approaches to prescreening include identification of electrophilic reactants among environmental chemicals and their metabolites, detection of reaction of chemicals with critical molecular targets in cells and their repair, mutagenesis prescreens, and cell culture transformation tests. Use of in vitro systems requires the development of effective metabolic activation

systems to couple with the assays."

Comments: These tests can only be used for screening and are not at present definitive tests for the identification of whether or not a material is carcinogenic. However, they can be effectively used for setting priorities as to which chemicals require further study immediately. The problem is that the government agencies may use these tests to legislate whether a material is or is not safe to use in the marketplace.

"Predictive Values of Carcinogenesis Bioassay, Cesare Maltoni, M.D., Istituto de Oncologia "Felice Addaril," Bologna, Italy"

Date was presented on the production of carcinogenicity of body systems and organs other than the liver in mice exposed to vinyl chloride for 56 weeks showed a total of 7 carcinomas in different parts of the body. The areas most frequently effected were the liver, brain, and the respiratory track.

Comments: This paper did not really present any new research data.

"NEOPLASTIC RISK AMONG VINYL CHLORIDE POLYMERIZATION WORKERS by Richard J. Waxweiler, MSIE, William Stringer, MS, Henry Falk, M.D., Coleman Carter, M.D., James Jones, BSChE, Joseph K. Wagoner, S.D. Hyg., NIOSH, CDC

A retrospective cohort study of mortality among persons working at four separate polyvinyl chloride polymerization facilities was carried out. Study observations were limited to the period following five years of exposure and ten years since onset of exposure to vinyl chloride (VC). This restriction was imposed to avoid bias due to selection or due to insufficient latency for occupationally induced malignancies to become clinically manifest. An environmental profile indicated areas of VC exposure and the limitations of calculating individual estimated cumulative exposure to VC. Death certificates were obtained for all cohort members known to have died. Hospital records, pathology reports and tissues were collected, when available, for review by an expert panel of pathologists to evaluate the primary site and specific histology of malignancies.

When mortality of the cohort was compared with U.S. white males, results demonstrated a close agreement with previous animal bioassay studies and human epidemiological studies in terms of excess risk of cancer and site distribution of those cancers."

Comments: Two of the four facilities studied also made VC monomer. The results showed 136 observed vs. 126 expected tumors of all types. The observed level for liver cancer was 7.0 vs. 0.6 expected and for respiratory cancer 12.0 vs. 7.7 expected. The latency period of 10 years was statistically significant at the 0.05 level. One man in the study was shown to have liver cancer after four years as a reactor cleaner and a latency period of 19 years. (This type of study is becoming more and more prevalent. Many of the papers presented at this meeting were based upon such retrospective studies.)

"ONCOGENIC AND MUTAGENIC RISKS IN COMMUNITIES WITH POLYVINYL CHLORIDE PRODUCTION FACILITIES by Peter F. Infante, DDS, Ohio Department of Health, Columbus, Ohio.

The results of a preliminary investigation indicate that residents of the three Ohio communities with polyvinyl chloride production facilities gave birth to a significantly greater number of children with malformation during the period 1970-73, as compared to the expected, based on occurrence in the entire state. The rate of malformations in the index cities also was significantly greater than the rate in the balance of the counties in which these cities were located, $P < 0.001$. Other county-city combinations of similar size revealed no significant differences in malformation rates. Most notable among specific birth anomalies were those involving the Central Nervous System; 5.62 expected versus 17 observed. These preliminary findings do not link the presence of polyvinyl chloride production facilities with the increased occurrence of malformations, but indicate the need for further study of possible contributing factors."

Comments: There were many gaps in this study, which included: a) No study of the impact of other environmental factors in these communities was made; b) Wind direction and other factors which could relate to exposure were not evaluated; c) The population of one of the communities increased by 30% during the study period; d) No attempts were made to relate these statistics to the families of vinyl chloride workers and their contribution to the statistics.

"CASE STUDY 3. VINYL CHLORIDE - BEST AVAILABLE TECHNOLOGY by Donald V. Lassiter, Ph.D., Occupational Safety and Health Administration, Washington, D.C.

Promulgation of a standard regulating occupational exposure to vinyl chloride (VC) by OSHA on October 4, 1974, marked the initial Federal attempt to regulate occupational exposure to a carcinogen on the basis of available analytical methodology. Demonstration of carcinogenicity of VC had included experimental animal studies performed by separate investigators and a continuing case list of human cancer in workers occupationally exposed to VC. Although various tumors were observed both in experimental animals and in occupationally exposed workers, the finding of angiosarcoma of the liver in both instances revealed a definite correlation between chemical exposure and induction of cancer. The significance of polyvinyl chloride (PVC) production to the Nation's economy rendered impractical even de facto elimination of this important industry through unattainable controls prescribing "zero" employee exposure to VC. Rather, exposure to VC was limited to one ppm as an 8-hour TWA and 5 minutes as a 15-minute TWA. The one ppm exposure limit was based on recommendations made to OSHA by NIOSH and represented the sensitivity of available analytical methodology for determination of compliance."

Comments: OSHA seemed to be on the defensive about its one part per million standard.

"CANCER AMONG BENZOYL CHLORIDE MANUFACTURING WORKERS by Hiroyuki Sakabe, M.D., Hidetsuru Matsushita, Ph.D., and Shigeri Koshi, M.D., Natl. Inst. Ind. Health, Kawasaki, JAPAN.

Three lung cancers (2 dead and 1 alive) and one maxillary malignant lymphoma were found in a small plant which had produced benzoyl chloride from 1954 to 1972. The number of employees had usually been 20. These four workers had engaged in the manufacture of benzoyl chloride in the very bad environmental conditions during 6 to 15 years before the onset of disease. Expected value of lung cancer death among benzoyl chloride manufacturing workers is 0.06 and observed 2 ($p=0.0017$). Benzoyl chloride was manufactured by hydrolysis of benzotrichloride which was prepared by chlorination of toluene. These victims had mainly been exposed to toluene, chlorine, hydrogen chloride, benzotrichloride, and benzoyl chloride. Benzotrichloride and/or benzoyl chloride are suspected to be carcinogenic to humans considering that benzyl chloride which has a similar chemical structure to these was reported to be carcinogenic to rats."

Comments: This paper indicates that TCI could have problems at its Fords plant. My forthcoming Industrial Hygiene survey will consider exposure to each of these materials at that facility.

"TOWARD AN INTEGRATED PROGRAM OF GOVERNMENTAL ACTION by David P. Rall, M.D., Ph.D., Director, National Institute of Environmental Health Sciences; Chairman, DHEW Committee to Coordinate Toxicology and Related Programs, Research Triangle Park, North Carolina.

The elements of a rational program of governmental action on environmental carcinogenesis include: Information - Decision - Action - Followup. I shall concentrate on the first and last. The critical information needs are: What chemical--with what toxic effects (on laboratory animals or man)--at what concentration is in contact with what population? The sources of this information include the private sector, the academic community and governmental laboratories. Before a governmental decision is made, it is critical that all information be collected and evaluated. The DHEW Committee to Coordinate Toxicology and Related Programs is in an excellent position to facilitate information collection, evaluation and dissemination from the academic and governmental sectors. Problems may exist in obtaining timely information from the private sector. Followup of a decision and the resulting action is important and has similar elements, emphasizing clinical and epidemiological studies."

Comments: The important point in this presentation is the mention of obtaining information from the private sector. The proposed "Toxic Substances Act" would make all information about the composition, toxicity, etc., of any product, intermediate, or raw material available to the EPA, regardless of confidentiality.

"LEUKEMIA ASSOCIATED WITH BENZENE EXPOSURE by Enrico C. Vigliani, Clinico del Lavoro "L. Devoto," University of Milan, Italy.

Benzene has been known for more than a century as a bone marrow poison, leading to hyporegenerative or aplastic anemia. However, evidence has been accumulating in the last 40 years that benzene can also cause leukemias. More than 150 cases of benzene leukemia are known at present; in many cases leukemia develops as a terminal stage of a hyporegenerative anemia. It is mostly an acute hemocytoblastic or myeloblastic leukemia, sometimes leukopenic, but other types of leukemia are also said to occur after exposure to benzene. The experience of the Institutes of Occupational Health of Milano and Pavia are recorded, showing that more than 50% of the fatal cases of chronic benzene poisoning died of acute leukemia. There

may be a latent period extending over several years between cessation of exposure to benzene, with more or less pronounced anemia, and the onset of leukemia. In the cases of anemia ending with acute leukemia, the anemic stage can be considered as a pre-leukemic one. Benzene is known to induce chromosomal aberrations and this might be an important factor in the pathogenesis of leukemia."

Comments: The author also presented data on acute anemial exposures, 200-1500 ppm, which showed the production of leukemia after four months of exposure. No comparable chronic exposure data was available.

"SPUTUM CYTOLOGY AMONG ALUMINUM POTROOM WORKERS by David P. Discher, M.D., Bryce D. Breitenstein, M.D., and Abraham I. Schweid, M.D., University of Washington, Seattle, Washington.

In addition to a number of other parameters, the cytopathologic findings in sputum from a sample of aluminum potroom workers in the Pacific Northwest were compared with a group of matched controls. The results of this study were as follows:

Classification	Sample	Controls
Negative	0.58	0.63
Atypical	0.26	0.11
Suspicious	0.006	0.0
Positive	0.002	0.0
Unsatisfactory	0.13	0.21
Unknown	0.02	0.05

The morphologic findings were those typically seen in sputa ranging from regular metaplasia to outspoken squamous cancer. The meaning of the differences between the sample and controls remains doubtful."

Comments: This technique is being used for the diagnosis of lung cancer in many other exposure situations. Including one paper presented at this conference of a cohort study of Bis CME workers by Dr. R. A. Lemen of NIOSH, which indicated that this method could be used to predict lung cancer.

"PREVENTIVE SURVEILLANCE OF OCCUPATIONAL GROUPS AT HIGH RISK OF CANCER by Irving J. Selikoff, M.D., Mount Sinai School of Medicine of the City University of New York, New York, N. Y.

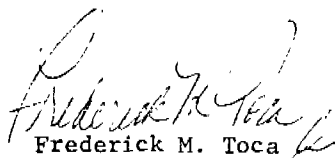
Once occupational cancer is recognized it can be controlled, but it is too late for those workers who have already been exposed. Workers exposed to Vinyl Chloride who showed negative liver function test have died of angiosarcoma six months later. Also, workers who have been exposed to Vinyl Chloride will still show its presence in their body tissues even after the exposure has been stopped for many months. There is no safe level of exposure to carcinogens."

"MORTALITY AMONG WORKERS EXPOSED TO CADMIUM by Jeffrey S. Lee, MPH, NIOSH,
Salt Lake City, Utah

Cadmium has been shown to produce cancer by inhalation in animals, but not by ingestion, after one year of exposure to concentration between 0.05 mg/M³ and 1.0 mg/M³. A cohort of 283 white males exposed to cadmium for at least 3 years between 1940 and 1970 was conducted. The observed incidence of respiratory cancers was 12.0 vs. the expected rate of 4.0. The latency period was 25 or more years."

Summary and Conclusions:

In conclusion, while the tone of this meeting was very negative toward industry, the papers presented give a good indication of what is to come. The use of screening test, epidemiological studies and the push for zero exposure to all carcinogens are all facts of life that we must deal with.


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