

SHELL OIL COMPANY

PRIVATE AND CONFIDENTIAL

DATE NOVEMBER 30, 1973

TO SHELL CHEMICAL COMPANY - VINYL CHLORIDE
BUSINESS CENTER - MANAGERFROM MANAGER, INDUSTRIAL HYGIENE -
HEAD OFFICESUBJECT MEETING OF VINYL CHLORIDE
RESEARCH COORDINATORS

The Research Coordinators met on November 28, 1973, at MCA Headquarters in Washington. In addition to the seven-member group the following were present: Dr. David Duffield (ICI), Dr. P. Gehring (Dow), A. B. Lindquist (Stauffer), T. R. Aalto (Tenneco), M. N. Johnson (Goodrich), R. Henderson (Olin), C. A. Johnson (Goodyear), and Ken Johnson and A. C. Clark from MCA. A copy of the final agenda is attached. Highlights of the discussions follow.

On Item No. 3, the Maycock letter on bis-CME, it was pointed out that the tumors seen in Maltoni's work were not the same as that caused by bis-CME. The suggestion was made that each company test its own product for this contaminant. I pointed out, however, that the technique is a rather esoteric one, and I was afraid that chromatographic peaks might be construed as bis-CME but would not really be so. Gehring agreed with the contention. It was recommended, and Torkelson and Gehring agreed, that they will ask Dow which has developed proprietary methods for bis-CME analysis to look into the possible content and report back to the committee.

On Item No. 4, there was no new information from Industrial Bio-Test. Tabershaw-Cooper Associates (TCA) now have 2,000 records on hand with an additional 2,000 being worked on, but the data are not yet fully tabulated. Their attempts to trace terminated employees have been quite successful. It is expected that data on mortality will be available around January 1974, and it was proposed that a meeting of the Research Coordinators with TCA take place in mid-February to review the draft of the report with the final report out in March. This would enable the TCA paper to be submitted for inclusion in the International Cancer Congress which will meet in Florence, Italy next October.

Duffield reported on the current status of Maltoni's work. A table of results is appended. It is apparent that there does seem to be a very definite dose-response relation with a possible threshold somewhere between 50 and 250 ppm. All tumors noted are macroscopic. The tissues slides have not yet been read. The absence of "other" tumors in the controls raised some questions. For example, Sprague-Dawley rats should have had a finite number of mammary tumors. Torkelson raised the question as to whether Maltoni might be working with a highly resistant strain. Duffield will check into this.

On a repeat of the Maltoni test which started in January 1973, exposure was at the same levels for four months and observations made for the eight months to date. As of November 12, one tumor, that of the Zymbal gland at 10,000 ppm was noted.

In a "teratogenic study" by the Italians some fibrosarcomas were noted at 10,000 and 6,000 ppm concentrations. The data are sketchy, and the limited number of offspring in the rats could lead one to believe that VCM at the concentrations given might be highly embryotoxic. Duffield indicated that there was no positive establishment of pregnancy in the rats, and therefore, one could not be sure of embryotoxicity; but this led to the question as to whether the MCA group ought to be doing a teratology study.

For this type of activity Gehring estimated that the costs per study per compound at one level and a control would be \$15-18,000. Dow is already doing studies of this sort and will be reporting soon on MEK, chloroform, vinylidene chloride, and carbon tetrachloride. They are also working on tri- and perchloroethylene and ethyl chloroform and methylene chloride. Dr. Johnson of Goodrich recommended to the committee that they underwrite Dow's work on VCM for the teratology study.

Duffield reported further on additional exposure of animals in Maltoni's laboratory at low levels, namely 200, 150, and 100 ppm. (In this case there are 120 animals per group, 185 controls.) Exposure started in June 1973. Food has remained in the environment. There have been no results to date. They also added a special study in rats at 30,000 ppm. This started in June '73 and was designed to check on Viola's work. So far all animals are still alive, and no tumors have been noted. In order to closer duplicate Viola they have also looked at another species of mice (Wistar) at levels of 10,000 ppm and on down but without vinyl acetate. This started in June '73. There have been no tumors to date. And finally, Maltoni has just started on a third species of mice and with hamsters at the same seven levels and has no data to report on.

The question of concern of the ILO Meeting which was just held in Geneva was a statement in a news release which said, "Vinyl chloride, used to manufacture vinyl plastic, produces emphysema." A query to ILO's Washington, D. C. office resulted in no information as to the source of this statement. Ken Johnson will follow this up as will Duffield in Europe.

With regard to the International Cancer Congress there will be one-half day on occupational cancers; Maltoni will be in the chair. The group discussed the best way of getting VCM onto the program. The consensus was that the presentation follow the lines: a) there is a major interest in occupational cancers generally, b) extensive work really has to be done to define the potential of the problem if any, and c) VCM is an example of an approach that might be taken. In this way VCM would not be highlighted as being something of a special concern with regard to cancer.

We felt that there be a meeting between the U. S. and European technical people on how to present both the epidemiologic papers from this side and the animal work in Europe. Duffield suggested a small subcommittee of representatives from the U. S. and Europe for this discussion.

The question was then raised as to whether we should contact Japanese chemical makers to see if they would be doing epidemiologic activity. I suggested that we not go running off to Japan until the TCA data are in since all this would do would be to lead to implications that there were positive significant data to be found. Once the TCA data have been completed we would be in a better position to see what appropriate action or recommendations should be taken.

The research group thought that it was now appropriate for someone from Bio-Test to visit Maltoni to learn the scope of Maltoni's work and be familiar with the pathologic and histologic techniques being used in Italy. We decided that the most appropriate individual to go would be Dr. Calandra and that this should be done sometime at the end of January or early February.

There was a rather large discussion on the SPI reaction to PVC liquor bottle ban. SPI has submitted a statement to the Food and Drug Administration (October 15) requesting withdrawal of sanctions on PVC liquor bottles. A report of this appears in the Food and Chemical News of October 22, 1973. SPI used a technique of estimating, by calculation, the dietary equivalent of an inhaled amount. While this can be done mathematically, the implications of such a proposal are quite serious. If the FDA adopts this as an appropriate method, then the possibility of expanding the scope of known exposure which would be covered by the Delaney amendment becomes quite great. There was a fair amount of discussion on this point which included the possibility of the MCA group going to FDA with the same story that they had presented to NIOSH. We finally recommended that since SPI was suggesting that the limit for free VCM in liquor be set at no greater than the limit of analytic sensitivity (approximately 50 ppb), we take no further action at this point.

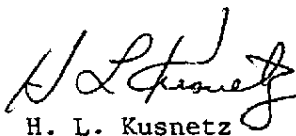
One of the outcomes of the discussion on the plastic bottles was a concern that dietary studies should be started, and that support of the participating companies be sought. Once this was brought up we asked what other types of studies might be needed. In addition to a two-year feeding study, one on teratology, one on metabolism, one on prospective epidemiology, a three-generation reproduction study, and a study on mutagenicity were all possible candidates. The last two were considered of very low priority. The prospective epidemiology study was considered desirable, but we were unable to determine how such one would be run, administered, and funded. Costs of the metabolism study would run about \$50,000-80,000, and comments have already been made on the projected costs of the teratology study. Dr. Rinehart was asked to chair a subcommittee on feasibility costs and

options of the feeding studies, but preliminary estimates were that for the two years of exposure plus perhaps a year of observation the costs would be in the neighborhood of \$120,000.

Dr. Gehring reported on the metabolic studies that were being done at Dow. Basically, the thrust seems to be that vinyl chloride reacts with cysteine and glutathione, both of which are free sulfhydryl contributors in enzyme systems. The implication is that since cysteine is known to have a protective effect against the cancer potential of radiation and against the toxicity of radiation and alkylating agents, a reduction of cysteine (and glutathione) would reduce the protection against any cancer agent, endogenous or exogenous, that might cause tumors. Gehring thinks that this may not be directly dose related. Thus, if the action of VCM is to reduce cysteine content thereby leading to cancer induction, it might be possible to protect against cancers that might be associated with VCM exposure by maintaining workers in cysteine and glutathione levels.

Gehring now thinks that Dow is at a point where it has to fully determine the metabolites using C-14 labeled VCM and that the techniques are such that Dow probably is the only company that can do the work. The proposal was made then to validate the phenomenon in at least one additional animal species and ultimately to do it in man. The committee decided a proposal from Dow asking for up to \$80,000 would go to the full member committee requesting support for the metabolic studies in principle. This recognizes that the management members of the MCA companies concerned would have to give the final approval.

Since the implications of the additional costs are rather large and involved, I thought it best to request a meeting to discuss this so that our Business Center can decide at what point if any, and to what extent if any, we would be willing to support these additional studies.



H. L. Kusnetz

Attachments

cc - Messrs. R. E. Joyner, M.D.
R. L. Maycock
K. W. Wood
R. F. Nelson

REVISED AGENDA
VINYL CHLORIDE RESEARCH COORDINATORS
NOVEMBER 28, 1973

- (1) Early billing by MCA. Request for billing before January 1, 1974, by D. A. Rausch,
- (2) Meat cutters asthma. JAMA. November 5, 1973, Sokol, Aelony and Beall,
- (3) Analysis of vinyl chloride for Bis CME. Letter from R. L. Maycock,
- (4) Review of status of Industrial BIO-TEST Laboratories, Inc. and Tabershaw-Cooper Associates, Inc. projects,
- (5) Drafting of plans for presentation of American industry data at the International Cancer Congress in Florence, Italy, next October,
- (6) ILO meeting November, 1973,
- (7) Proposal that Industrial BIO-TEST pathologist visit Dr. Maltoni,
- (8) Metabolic Studies, Dr. Perry J. Gehring, Dow Chemical,
- (9) Dietary feeding studies,
- (10) SPI action of PVC bottles,
- (11) Review of contents of company bulletins on vinyl chloride monomer handling and recommended industrial hygiene standards. Committee action to date,
- (12) Other items, and
- (13) Next meeting.

CONFIDENTIAL

SUMMARY OF MALTONI DATA TO DATE

Start - May '71 - one-year exposure - one year observation - but continuing to now.

Used Sprague-Dowley rats - 270/group - 96 in group for vinyl acetate (positive controls)

	Inhalation Level, ppm							VA
	10,000	6,000	2,500	500	250	50	0	
Survivors	0	0	0	1	1	8	12	0
Zymbal Gland Ca's	13	5	2	2	0	0	0	0
Liver Ca's Angiosarcoma	6	11	9	7	2	0	0	
Kidney Ca's								
Nephroblastomas	3	3	6	3	5	0	0	
Scattered Tumors (No Pattern)	5	2	3	2	1	0	0	

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October 22, 1973

DA. RAUSEN 2020
KEN BURGESS 2040
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FOOD CHEMICAL NEWS

PVC SANCTION FOR LIQUOR BOTTLES WITH EXTRACTION LIMIT URGED

The Society for the Plastics Industry last week unveiled research showing no detectable migration from alcoholic beverage bottles, and said that this can be analytically checked.

In a comment, SPI endorsed the Food and Drug Administration's proposed prior sanction affirmation for PVC in food packaging, but opposed the proposed ban on use of PVC for packaging alcoholic beverages (See FOOD CHEMICAL NEWS, Oct. 15, Page 2).

"... It is now apparent that polyvinyl chloride compounds for rigid containers can be prepared on commercial equipment which will show no detectable migration of vinyl chloride monomer to distilled alcoholic spirits packaged therein," SPI said, enclosing a report of the scientific studies.

When the problem of possible migration arose, the Society said, "a concentrated effort was made by the major suppliers of such compounds to confirm and then take very possible and practical steps to eliminate the possibility of such unexpected migration."

PVC compounds, the comments said, have been "prepared by new technology to assure a low residual vinyl chloride monomer content," and have been processed into bottles and extracted with water, 3% acetic acid, 50% ethanol, and heptane.

"... It can be stated that for each manufacturer reporting the extraction studies at 120°F. for periods of time up to one month, no vinyl chloride monomer was detected in any of the solvents with methods ranging in sensitivity from 0.5 p.p.m. to at least 0.05 p.p.m.," SPI wrote.

One bottle manufacturer performed extraction tests on bottles made from compounds supplied by two manufacturers, and no vinyl chloride monomers were detected with a method sensitive to at least 0.05 p.p.m., the letter said.

Two firms independently developed gas chromatographic methods for determining vinyl chloride content in the 50% ethanol solvent, SPI said, and it would appear "that either method can be used satisfactorily for the intended purpose."

Tests were made both of bottles made from virgin material and from 40% regrind, SPI said, with no vinyl chloride monomer detected using methods sensitive to 10 p.p.m. "From this it can be concluded that there was no significant increase in residual monomer content as a result of processing and reuse," the letter said. SPI continued:

"... The FDA can now be assured that manufacturers of PVC bottle compounds can provide formulations which, when used for packaging distilled spirits, will not yield detectable vinyl chloride monomer to the contents when tested with analytical methods sensitive to 0.05 p.p.m. In light of the calculated no-effect level of 250 p.p.m. for VCM in the total diet..., a finding of 'none detected' using methods sensitive to 0.05 p.p.m. is eminently suitable by a large safety factor to assure safety of such compounds when used to package distilled alcoholic spirits."

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"Accordingly, it is submitted that the industry has now clearly demonstrated that continuing to accord prior sanctioned status... to polyvinyl chloride resins in such a way as to encompass the use of such resins, when properly formulated, to package distilled alcoholic spirits would be wholly appropriate and consonant with the public interest."

In a separate letter, Dewey and Almy submitted to FDA the results of its extraction tests using PVC gaskets in 8% alcohol, 100% alcohol, and wine which was 12% alcohol. The firm said vinyl chloride monomer in each test was less than 50 p.p.b.

SPI recommended that a limit be placed on "the level of vinyl chloride monomer detectable in an appropriate food-simulating solvent when exposed under suitable test conditions," suggesting that the proposed §121.2009 prior sanction regulation read, as follows:

"Polyvinyl chloride resins ... may be used as a component of food packaging material. As regards rigid containers made from polyvinyl chloride resins and intended for packaging of distilled alcoholic spirits, such containers shall show no detectable extraction (at the level of sensitivity of the method) of vinyl chloride monomer in a 50% solution by volume of ethyl alcohol in water when one pint containers containing such alcohol solutions are stored at 120°F. for 28 days and are tested with a procedure capable of detecting vinyl chloride monomer down to a sensitivity of 0.05 p.p.m. A suitable procedure is available from the Commissioner on request."

The Society said a ban on PVC for packaging alcoholic foods "is neither necessary nor appropriate," and that such a ban "would cause unnecessary hardship and economic loss..." SPI also said consumers "would be denied the choice of a safe and suitable packaging material."

The letter said that "any controls required should be directed not at PVC resins per se but, rather, should be aimed at assuring that the compounds... used for packaging distilled alcoholic spirits are suitable for their intended use."

SPI also asked that FDA not use the phrase "alcoholic foods," noting that since any migration problem pertains only to distilled alcoholic spirits that any limitations should apply to "well identified problem areas." The term "alcoholic foods," the letter said "would be subject to wide variations in interpretation and could only lead to unnecessary and continuing confusion."

The American Conference of Governmental Industrial Hygienists have set a 200 p.p.m. limit for vinyl chloride monomer in air, SPI said, concluding from this that "250 p.p.m. in the total diet is without effect." The organization explained that the ACGIH figure was "based upon chronic exposure in man, not experimental animals, and the assumptions quite 'conservative' on the side of safety..."

October 22, 1973

FOOD CHEMICAL NEWS

SPI also referred to limits on PVC set under two Food Additive Orders, §121.2514 for resinous and polymeric coatings and §121.2550 for sealing gaskets with closures for food containers. Extraction studies were conducted with PVC can liner enamels which have been cleared under the Orders, SPI said and the test results showed "no detection of vinyl chloride monomer in alcoholic beverages such as malt beverages and wine or in the spectrum of food-simulating solvents used to 'clear' other food packaging materials."

Regarding possible environmental effects, SPI recalled that the Bureau of Alcohol, Tobacco and Firearms had filed a favorable Final Environmental Impact Statement, which concluded that "PVC plastic is a suitable material for use in the manufacture of liquor bottles."

The Society endorsed FDA's proposal to affirm the PVC prior sanction, noting that this will be the first one listing a basic polymer "indirect additive." SPI called the affirmation "precedental."

Tracing the history of PVC use for alcoholic beverages, SPI noted that BATF in 1968 permitted experimental use, and said:

"At a very late and critical time when BATF had completed and published a favorable Final Impact Statement on the use of PVC liquor bottles so that it appeared routine commercial use would soon be allowed, it was reported to the FDA, to the surprise of most of those in the plastics and alcoholic beverages industries that vinyl chloride monomer in the range of 10 to 20 p.p.m. was found in some experimentally packaged distilled alcoholic beverages."

SPI said it is "unaware of any contention that the presence of vinyl monomer in foods even at the 10 to 20 p.p.m. range presents a problem to public health or safety," and said it understands that the problem would be one of adulteration under §402 of FDA's law. The Society also noted "that the reports on detection of the presence of monomer in distilled alcoholic spirits came as a surprise to the scientific community because it had been generally assumed that the monomer, being a gas in nature, would most certainly volatilize off during the various manufacturing processes involved in compound and bottle production."

SPI said research was conducted into the "possible migration of vinyl chloride monomer to alcoholic beverages of lower alcohol content packaged in Japan," and that "no sample showed detectable vinyl chloride monomers." The letter added:

"It is recognized that these results are at variance with those alluded to in the preamble of the subject proposed regulation wherein it is stated that vinyl chloride monomer was found in wine packaged in PVC containers. It is believed that any differences probably reflect differences in the vinyl chloride compounds which were used to prepare the bottles. In any case, it is submitted that these Japanese data -- the only information known to us directly relevant to lower alcohol content beverages -- adequately indicate that the distilled spirits situation is unique and should be

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