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File VCM

01-vcl PVC-Tx

April 2, 1980

R. J. Reynolds
D. K. Spencer

In a recent memo, I summarized the paper given by Maltoni at the March 20-21 VCM/PVC conference sponsored by OSHA/NIOSH/NIEHS.

Attached for your information is a synopsis of Maltoni's work prepared by the European sponsors of this research.

Attachment

cc: R. E. Joyner, M.D. ✓
C. E. Ross, D.O.

Jerry.

J. E. BERGER

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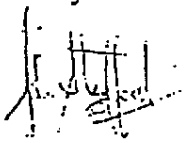
	JS/SEW/DSO-16	3162	3 March 1980

VCM – MALTONI

The Maltoni VCM sponsors have agreed to the attached statement being sent today to national governments, unions, EEC and via APME to the SPI in the USA and to the Japanese PVC Association. This is not a general press release but it is information which should be shared with relevant employees at your next round of consultative meetings.

The key to the communication is in para 4. In its early years, Maltoni's work led us to the discovery of ASL in men highly exposed to VCM over a long period. Maltoni's later work is of interest mainly to the scientific community who will be discussing it for years. There is a limit to the amount of useful information which can be derived from animal studies and in the case of VCM we seem to have passed this limit some years ago. The only relevant and important studies now are those on men.



J Stafford

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AGREED STATEMENT BY THE MALTONI SPONSORS ON THE SEVEN BASIC VCM EXPERIMENTS (BT1, 2, 6, 9, 15, 11 & 27)

1 Introduction

The long term project by Professor C Maltoni on the carcinogenicity assessment of VCM has comprised a series of integrated experiments to study the effects of VCM administered by different routes, at different concentrations and for different periods on animals of various species, strain and age. This work was initiated and sponsored by Solvay, Rhone-Poulenc, Montedison and ICI.

The laboratory work was started in 1971 and ended in 1977. Since 1977, Professor Maltoni has been processing and analysing the vast amount of histological material derived from these experiments and, in cooperation with a team of statisticians from the four sponsoring companies, has been classifying and codifying all the identified pathological lesions to make the data amenable to computer treatment. The data thus derived have been analysed statistically in a rigorous manner.

The results of this work were presented in extenso with all the methodological, biological and statistical details in a meeting held by the Chemical Carcinogenesis Club (Club de Cancerogenese Chimique) at the Curie Foundation (Fondation Curie) in Paris on 10 November 1979. The proceedings of the meeting will be published in full at the earliest possible moment.

2 Biological Assessment of the Results

In Professor Maltoni's opinion regarding these animal experiments "the following tumours should be given proper attention viz, extrahepatic angiosarcomas, hepatomas, Zymbal gland carcinomas, liver angiosarcomas, neuroblastomas, nephroblastomas, forestomach papillomas and mammary carcinomas.

In oncological terms, the meaning of the results at the lowest doses may be better evaluated by considering, not separately, but together, the tumours found to be VCM dependent. Thus the following results should be considered:-

at 25 ppm - In 120 animals, 5 liver angiosarcomas, 4 Zymbal gland carcinomas and 1 nephroblastoma.

at 10 ppm - In 120 animals, 1 liver angiosarcoma, 2 extra-hepatic angiosarcomas and 2 Zymbal gland carcinomas.

at 1mg/kg - In 150 animals, 3 liver angiosarcomas, 1 extra-hepatic angiosarcoma, 1 hepatoma and 5 Zymbal gland carcinomas.

at 0.3mg/kg-In 150 animals, 1 liver angiosarcoma and 1 hepatoma."

In addition, it is worthwhile emphasising that none of the previously cited tumours have been observed at 5ppm by inhalation and 0.03mg/kg by ingestion.

3 Statistical Assessment of the Results

A multi-disciplinary working group was set up by the sponsors for the in-depth quantitative analysis of the data.

A statistical evaluation of all the available results from the above seven animal experiments has led to the conclusion that VCM induces a carcinogenic response in the following organs viz, the Zymbal gland, liver, kidneys, brain and perhaps the mammary gland in females. The survival of the rats decreased as a function of VCM concentration. A clear correlation could be established

between excess mortality and tumorigenic power of VCM but the excess mortality cannot be explained only by the development of cancers at the higher dose levels. Correspondence analysis between tumours and doses showed that two major opposing factors may explain tumour distribution viz:

(i) the differential susceptibility of the target organs to the carcinogenic effect of VCM

(ii) an antagonistic factor (early mortality) which at too high a dose inhibits the manifestation of certain tumours.

Several models of dose-effect relationships fit the experimental data. This study also illustrated the problems of extrapolating to untested doses and from species to species.

4 In conclusion

The publication of the proceedings of the 10/11/79 Paris meeting and other related papers will no doubt lead during the course of the next few years to the comprehensive discussion and comparative assessment by the scientific community of the Maltoni and other animal studies on VCM. The Maltoni animal studies have provided much useful information especially in the early years; the later experiments have highlighted the problems of evaluating low dose animal experiments.

26 February 1980