01-VC/PVC-1XG 1
06-A-001

Shell Development Company
A Division of Shell Oil Company

Toxicology Laboratory
Westhollow Research Center
P.O. Box 822
Houston, Texas 77001

December 16, 1980

ANITH Attc

John T. Barr
Manager, Regulatory Response
Air Products & Chemicals, Inc.
Box 538
Allentown, PA 18105

Dear Mr. Barr:

Paul Deisler has asked me to comment on your VCM document. It is obvious that a lot of work went into the preparation of the assessment and it serves as a valuable review of the literature.

In my view there are several areas which need to be clarified in future drafts and I would suggest that the individual sections need to be reviewed by appropriate experts at this stage.

Among the points noted were:

1. p. 4, para. 3: The statement on drinking water versus air requires checking. Assuming that VCM is completely retained on inhalation, then the inhalation dose may be bigger than the oral dose by our calculations, using a common exposure period.

2. p. 5, para. 3: I cannot believe that uptake of VCM is blocked by cytochrome P-450 inhibitors, since uptake is a physical process.

3. p. 6, last para: The wording is loose - DNA is not a protein and I don't know whether protein binding per se can lead to genotoxic effects.

4. p. 7 (B): The quotation does not indicate the carrier. If, for instance Schaumann used 50 vol percent in air, then the side effects could easily be due to anoxia. The data on cardiac irregularities in dogs also requires scrutiny since it is easy to induce certain types in dogs by sympathetic stimulation or epinephrine.

5. p. 16: I am not aware that transmissable hereditary defects are necessarily caused by repair mechanism deficiency.

6. p. 17: Chromosome damage is commonly classified with mutogenetic effects rather than reproduction.

1/25/81

SCC
1-1126

7. p. 21: I have serious problems with the use of Maltoni's data for many reasons - apart from the fact that I am not aware he has issued a detailed report on any of his studies with or without quality assurance. The concentrations associated with tumor increases need clarification since Maltoni used a variety of exposure regimes, varying from 1 to 4 hrs per day and 1-5 days per week and from 17 weeks to one year. The cut-offs suggested have to be incorrect, e.g., experiment BT.2 had 10 nephroblastomas out of 120 rats at 100 ppm, while the draft suggests 10,000 ppm as the lowest effect level.

   I also am against selecting the incidence of a specific tumor type such as ASL where there are many different types of tumor, e.g., in Bt1, both zymbal gland carcinomas and nephroblastomas have a shorter latency than ASL, so that unless a relative risk analysis is carried out a falsely low impression of the incidence of ASL is obtained. In other words, many animals did not get ASL because another tumor killed them first.

8. p. 21, 2nd para: I believe 0.952% should be 0.0952%. I think the FDA reference requires checking because without actually seeing it, I get the impression that the quoted rate is for all liver tumors and not ASL.

9. p. 26, last para: I do not believe that there is a threshold for metabolism, i.e., that active metabolites do not escape until glutathione is depleted. The difference is quantitative rather than qualitative.

10. p. 29, para 2: I believe the statement on other tumors to be untrue. Inspection of the data indicates that at least nephroblastomas and zymbal gland carcinomas occur at low doses as well.

11. Maltoni's mouse data is only mentioned in a summary table. Since mice are possibly more sensitive, I believe this omission needs to be discussed.

12. In line with the comments above, Table 6 is misleading since it only quotes ASL and does not mention competition by other tumors. I also am not sure of the equivalent dose calculations. If it is assumed that a rat has a minute volume of 500 ml/kg then in 4 hours the total volume will be 120 l/kg or approximately 0.5 m^3 week of 5 x 4 hr. exposures. 10,000 ppm ≡ 20,000 mg/m^3 so that the weekly dose could be as high as 10 g/kg/week if all the VCM is retained. The calculation of 300 mg/kg/year is not in the same order and the basis for the quoted figures need checking. I don't claim mine are correct!

13. In my opinion a detailed risk assessment will require the individual animal data since it will be important to identify animals with multiple tumors. It is very unfortunate that Maltoni has never, to my knowledge, provided sufficient information to allow a properly conducted statistical evaluation of his work.

If you would like to discuss my comments, please do not hesitate to call. Some of the points which I have raised could lead to considerable debate.

Sincerely,

Donald E. Stevenson
Director
Toxicology Research

DES:sal

cc: P. F. Deisler
D. H. Hughes