DRAFT

MEETING OF API/CMA BENZENE TOXICOLOGY TASK FORCE

TUXEDO, NEW YORK - JUNE 13, 1983

Present: C. Ward, Chairman (Gulf)
C. E. Holdsworth (API)
F. B. Thomas (Shell)
G. S. Simon (Exxon)
M. Kaplan (duPont)
C. Stack (API)
R. Albert (NYU)
C. Snyder (NYU)
K. Baarson (NYU)
C. Rosen (NYU)

1.0 In the earlier API-sponsored 2-year inhalation study on benzene NYU gathered but did not publish the following information concerning the production of solid tumors in male Sprague-Dawley rats exposed to 100 ppm of benzene.

1.1 Solid tumors were seen in 11 out of the 40 male rats exposed to benzene. Of these 11 tumors, 8 were malignant and 3 were benign. The control rats had 3 tumors in 40 animals. Of these 2 were malignant and 1 was benign. The solid tumors included carcinomas of the Zymbal gland and hepatomas.

1.2 Chronic myleogenous leukemia was seen in 1 out of 40 male rats in the treated group. NYU is not aware of any historical incidence of CML in Sprague-Dawley rats.

1.3 The RF mouse has a 15% incidence of granulocytic leukemia.

1.4 These data are being prepared for publication.

2.0 In other studies, the CD-1 mouse was exposed to benzene 6 hours/day for 5 days at concentrations between 9.9 - 4800 ppm. The results included a significant drop in CFUs beginning at 100 ppm and plateauing at 300 ppm. The response was approximately the same over all dose levels from 300 up to 4800 ppm.

2.1 The control response is between 5500 - 6500 CFUs per femur in mice 8-12 weeks old.

3.0 The C57 mouse was used in these investigations because in earlier benzene studies this strain developed granulocytic leukemia. The C57 mouse has been used for immunological studies because it is an inbred strain.

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4.0 In another study the CFUc per femur decreased following exposure to 100 ppm benzene with a maximum response occurring at 300 ppm. These were 5-day exposures to benzene with bone marrow samples taken on the last day of exposure. C. Snyder (NYU) does not think there is any biological significance between the 100 and 300 ppm effect even though in several similar studies there was an apparent increased effect at 300 ppm.

5.0 In NYU's experience, the CF-1 mouse responds to benzene exposure by exhibiting leukopenia at concentrations of 100 ppm and above.

6.0 For most of the above studies, blood samples were taken from the tail vein of the mouse in volumes of 20 ul every 2-4 weeks.

7.0 In another study, C57 mice were exposed to 10 ppm of benzene for 6 months. Chamber concentrations of benzene were monitored using both IR and UV techniques. The mean benzene concentration for 6 months was 10.1 $\pm$ 0.3 ppm. The animals were monitored at 30, 66 and 180 days. The study showed a decrease in white blood cell count due to a decrease in lymphocyte count beginning at 30 days. Red blood cell counts also began to decrease at 30 days. 7-10 animals were used per point. There was no rebleeding in this particular study. The data from all animals bled for peripheral blood studies were included in the means; the report contains peripheral blood data for all 10. Only 5 animals from the 7-10 dosed whose peripheral blood counts clearly surrounded the mean were chosen for evaluation of BFU-e and CFU-e. The means for the peripheral blood counts were similar for the groups of 5 and the groups of 10.

8.0 Bone marrow CFU-e decreased at 60 days with exposure to benzene concentrations of 10 ppm and this decline continued as exposure continued. Peripheral blood counts, on the other hand, tended to plateau.

9.0 Responsiveness of the bone marrow CFU-e and BFU-e to benzene may be due to a change in responsiveness rather than cell death.

10.0 NYU is in the process of completing an intermittent exposure study in which C57 mice, CD-1 mice and Sprague-Dawley rats were exposed to 300 and 900 ppm of benzene 6 hrs/day, 5 days/week, 1 week on and 2 weeks off. No effects on mortality were seen. There was no apparent difference in peripheral blood counts between the groups exposed to 300 and 900 ppm of benzene. In a similar but different study peripheral blood counts returned to normal within 10 days following cessation of benzene exposures.

11.0 BFU-e and CFU-e are clinical techniques used for the diagnoses of various hematological diseases, including leukemia.

12.0 In immunology studies being conducted by NYU in the C57 mouse, B and T cells were measured in animals exposed to 10, 30, 100 and 300 ppm of benzene. These animals exhibited a decrease in lymphocyte counts after 6 days of exposure. IgM+ cells were decreased at both 100 and 300 ppm. The ability of B cells to divide was reduced by about one-third following exposure.

13.0 Administration of ethanol potentiates the effect of benzene on peripheral blood and CFU-e at concentrations of 300 ppm in the C57 mouse. This study has been published.

14.0 NYU is conducting a pulse-dose study in which animals are exposed to 1200 ppm of benzene daily for 50 days. Preliminary data show that peripheral blood cell counts recover after exposures are stopped.

15.0 C. Snyder characterized the peripheral blood count response to benzene as follows:

15.1 Lymphocytes are the most sensitive indicator of benzene toxicity. They decline first and to the largest degree.

15.2 Red blood cells decrease next.

15.3 Generally granulocytes increase.

16.0 NYU has blocks of 9 tissues per animal from the API-sponsored 2-year inhalation study on benzene.

* 16.1 API will have a conference call with TRTG to discuss re-cutting and re-examining these tissues histopathologically.

17.0 NYU suggested that future benzene work will likely include suiciding and kinetics of downstream cell lines for an explanation of changes in benzene sensitivity.

18.0 NYU has received funding from NIEHS to conduct a dose-response, a recovery, and a 3-year chronic inhalation study with benzene.

19.0 NYU would like funding to evaluate the role of immunosuppression in the carcinogenic effects of benzene.

20.0 NYU can run bone marrow cell cultures from the C57 mouse and human using the Dexter culture system.

21.0 C. Ward and C. E. Holdsworth (API) reviewed the API-sponsored toxicology studies on benzene.

*ACTION ITEM:

1. API will have a conference call with TRTG to discuss re-cutting and re-examining these tissues histopathologically.

C. Ward

Charles O. Ward

CW:am

cc: H. N. MacFarland
J. H. Butala
C. R. Hopper
D. E. Strother
R. L. Gibson, M.D.