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CASWELL FILE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUL 26 1993

010640

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Co. Response - New Histopathological Information Supplemental to Two-year Oncogenic Feeding Study with Bayleton in CF1-W74 Mice (MRID No. 99912).

HED Project No: 1-0725
MRID No: 417797-01
PC No.: 109901
Record No: S391294
Caswell No.: 862AA
DP Barcode No: 161606

TO: Susan Lewis/James Stone, PM 21
Registration Division (H7505C)

for THRU: Roger Gardner, Section Head Pamela M. Hurley 7/22/93
Review Section 1
Toxicology Branch
Health Effects Division (H7509C)

FROM: Nguyen Bich Thoa, Ph.D NT 11/26/92
KB 7/23/93
Review Section 1
Toxicology Branch I
Health Effects Division (H7509C)

Registrant: Mobay Corporation

ACTIONS REQUESTED:

Review Pathology Report from Experimental Pathological Laboratories, Inc., RTP, NC., entitled "Bayleton Chronic Oncogenicity Study in Mice; Study No. T3013775, Pathology No. 2730, Mobay Report No. 68960; Reevaluation of Liver Tissues from Male and Female Mice (MRID No. 417797-01), submitted by Registrant in response to a request from Science Analysis and Coordination Branch (SACB) (Memo Ghali to Lewis dated 04/26/90).

CONCLUSIONS:

The following conclusions are quoted from the Pathology Report:

" The results of this reevaluation of liver sections from male and female mice given 0, 50, 300, and 1800 ppm of Bayleton in a

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Chronic Oncogenicity Study in Mice indicate that several of the lesions diagnosed as hyperplastic or regenerative nodules by the study pathologist were considered to be either hapatocellular adenomas or hepatocellular carcinomas during this review. Since all livers were not available for microscopic evaluation, it is not possible to draw conclusions concerning possible treatment-related differences in the incidence of proliferative hepatocellular changes between control and treated groups".

The Toxicology Branch (TB-I) agrees with the conclusions stated in the Pathology Report. Too few slides were available for an adequate reevaluation of the liver lesions in this study. However, TB-I notes a replacement mouse carcinogenicity study (MRID Nos. 40752101 and 40865101) was submitted to the Agency in 1988.

BACKGROUND:

SACB requested histopatological reevaluation of the liver slides from a carcinogenicity study conducted with CF1-W74 mice by Bayer AG Institute for Toxicology in April, 1978.

In response to SACB's request, the registrant had asked Experimental Pathological Laboratories (EPL), Inc., of RTP, NC, to reevaluate liver slides from the oncogenicity feeding study in mice cited above. Due to unusual circumstances (the laboratory which originally conducted the mice study, Consultox, UK, went out of business), only a very small number of the slides (Males = 6 controls, 8 LDs, 7 MDs, and 13 HDs; Females = 0 controls, 3 LDs, 1 MDs, and 2 HDs) were available for reexamination.

The following criteria were used by the EPL pathologist to differentiate between various hepatocellular proliferative lesions:

Foci of Cellular Alteration:

- '"Localized lesions with tinctorial variation from surrounding hepatic parenchyma,
- Range from less than a hepatic lobule to up to 3 or 4 lobules,
- Merge with adjacent parenchyma without producing notable compression".

Hepatocellular Adenomas:

- "Usually a discrete lesion that compresses adjacent parenchyma,
- Composed of well differentiated cells,
- Absence of normal hepatic lobular architecture within an adenoma".

Hepatocellular Carcinomas:

- "Distinct trabecular or adenoid pattern,
- Cells may be poorly differentiated or anaplastic,
- May be histologic evidence of local invasion or metastasis".

The microscopic findings of the original laboratory (study pathologist) differed from those of EPL. Both sets of results are summarized below:

	MALE MICE								FEMALE MICE							
	Study Pathologist				EPL Pathologist				Study Pathologist				EPL Pathologist			
ppm in Diet	0	50	300	1000	0	50	300	1000	0	50	300	1000	0	50	300	1000
No. Liver Samples Examined	6	8	7	13	6	8	7	13	0	3	1	2	0	3	1	2
Hepatocellular (H) Adenomas	-	2	1	2	3	3	2	3	-	1	-	-	-	-	-	2
H Adenomas Multiple	-	-	-	-	-	-	1	5	-	-	-	-	-	-	1	-
H Carcinomas	-	-	-	-	1	4	4	4	-	-	-	-	-	1	-	-
Focus of Cellular Alteration	-	-	-	-	1	1	-	2								
Regenerative/Hyperplastic Nodule	6	7	7	12	-	1	-	-	-	2	1	2	-	-	-	-
Infarted Lobe	-	-	-	-	-	-	-	-								
No Proliferative Lesion	-	-	-	-	1	-	-	-	-	-	-	-				
Autolysis Precludes Diagnosis									-	-	-	-	-	1	-	1

The results showed that several lesions which were originally classified as hyperplastic or regenerative nodules were reclassified by EPL as either hepatocellular adenomas or carcinomas. The registrant attributed the different findings to the fact that the original laboratory had used a different diagnostic classification. Because of the very small number of samples available for reexamination, the results of this reexamination are inconclusive. The registrant noted that the finding of hepatocellular neoplasia in mice exposed to Bayleton is not new and that a newer mice oncogenic study conducted with NMRI mice (MRID No. 407521-01) was positive for hepatocellular adenomas in both sexes.