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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

TXR NO. 0052033

MEMORANDUM

DATE: July 16, 2003

SUBJECT: PHMB Cancer Peer Review: Pathology Working Group (PWG) Peer Review of Proliferative Vascular Lesions in Male and Female Mice

PC code: 111801

FROM: Jessica Kidwell, Executive Secretary, Cancer Assessment Review Committee
Science Information Management Branch
Health Effects Division (7509C)

Jessica Kidwell

TO: William Burnam, Chair, Cancer Assessment Review Committee
Immediate Office
Health Effects Division (7509C)

Attached please find Dr. Pletcher's memo (dated October 28, 2002) confirming the validity of the PWG peer review (MRID No. 45710802) of proliferative vascular lesions in male and female mice dosed with PHMB.

cc: Jonathan Chen

MEMORANDUM

TO: Joycelyn Stewart
Health Effects Division
Environmental Protection Agency (EPA)

FROM: John M. Pletcher, DVM, MPH, DACVP
EPA Consulting Pathologist
Pathology Associates (PAI), A Charles River Company

DATE: 28 October, 2002

SUBJECT: Pathology Working Group Peer Review of Proliferative Vascular Lesions in Male and Female Mice

I have completed my review of Dr. Peter Mann's report entitled as above and dated June 27, 2002. Dr. Mann served as the PWG's Chairperson and Dr. Chirukandath Gopinath did the Peer Review of all sections containing proliferative vascular lesions from the 440 mice that comprised the four groups of an oncogenicity study of PHMB entitled Polyhexamethylene Biguanide (PHMB): Two Year Oncogenic Study in Mice. The study (CTL Study No. PM0937) was conducted by the Zeneca (now Syngenta) Central Toxicology Laboratory in the United Kingdom. The purpose of the Peer Review/PWG process was to determine the incidence of proliferative vascular neoplasms following currently accepted nomenclature and diagnostic criteria and to discuss the relevance, for purposes of risk assessment, of the vascular neoplasms, which occurred in the study. The PWG was conducted in Research Triangle Park on March 5, 2002.

Six experienced toxicological pathologists were assembled to conduct the PWG including a pathologist representing Syngenta (Dr. Mervyn Robinson), the Review Pathologist (Dr. Gapinath), as well a veterinary pathologist observers. Based on Dr. Mann's report, both the Peer Review and the PWG were conducted in accordance with EPA pesticide Regulation (PR) Notice 94-5 dated August 24, 1994.

The results of the PWG review indicate that there was indeed clear evidence of a treatment-related increase in the incidence of mice with either benign or malignant vascular neoplasms in the high dose group (4000 ppm) of both sexes. This increase was mainly due to the increase in vascular tumors in the liver. It is important to understand that the members of the PWG agreed with the representatives of the Registrant that, because of the multicentric nature of vascular neoplasms, it is more appropriate to consider the number of tumor-bearing mice in each group rather than the total number of tumors. If one accepts this assumption, and I do, the significant increase in tumor bearing mice was only found at the 4000 ppm dose level, and that dose level was, based

on marked decrease in body weight gain and an increase in mortality, determined to be in excess of the Maximum Tolerated Dose (MTD), it cannot be considered for the purposes of carcinogenic risk assessment. The incidence of mice with vascular neoplasm in the Mid Dose (1200 ppm), Low Dose (400 ppm) and Controls was not significantly different and fell within the historical control range for mice.

I cannot find fault with the conduct or constitution of the PWG nor its conclusions and, therefore, I recommend that the finding of this report be considered valid.

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