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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: SAN582H

Caswell No. 195J HED Project No. 2-0227

TO: Jim Stone
Product Team 22
Registration Division (H7505C)

FROM: Deborah L. McCall DLMcCall 12-9-91
HED / Toxicology Branch II / Section III (H7509C)

THROUGH: James Rowe, Ph.D., Section Head James N. Rowe 12/19/91
HED / Toxicology Branch II/ Section III (H7509C)

and

Marcia Van Gemert, Ph.D., Branch Chief MVanGemert 12/20/91
HED / Toxicology Branch II / (H7509C)

The registrant (Sandoz Crop Protection Corporation) submitted a written response (October 9, 1991) to Toxicology Branch II's review of their chronic study in reference to the EUP application and temporary tolerance petition. The Combined Chronic Toxicity/Carcinogenicity Study in rats (MRID # 417068-08) was classified as Supplementary in the initial review (3/26/91). The reviewer indicated that the study may be upgraded if the registrant would submit recent historical control data on relevant tumor incidences from animals given the same type of diet as that used in the study. The registrant has submitted the requested data and the review follows:

Rat Chronic/Onco Historical Control Data (MRID 420301-02): The malignant liver cell tumors (MLCT) in the male rats are just outside of the historical controls values supplied by Sandoz (See Table 1 and Attachment I). The incidence of MLCT observed in the 1500 ppm dose group was 4%, compared to 0-3.6% in the historical control values (same stock diet) and 0-6.0% with different stock diet. [Note: In Attachment I, the registrant has incorrectly listed the 700 ppm group with an incidence of 2% for MLCT - it should be 0%.]

The benign liver cell tumors (BLCT) in male rats are outside of the historical control values. The historical control values with rats on the same diet were 0-1.8%, while the percent of BLCT in the 700

and 1500 ppm groups were 2% and 6%, respectively. These benign liver cell tumors in the male 1500 ppm group appear to indicate a treatment-related effect.

The incidences of female rat ovarian tubular adenomas were 2%, 4%, 12% for 100, 700, and 1500 ppm groups, respectively (see Table 1). The historical control values were 0-5.5% with the same stock diet. The high dose (1500 ppm) was approximately twice that of the historical control values. Therefore, it is the opinion of this reviewer that the rat ovarian tubular ademonas are a treatment-related effect in the highest dose tested.

Conclusion: The data in this study support the conclusion of limited evidence of carcinogenicity for SAN582H, based on the occurrence of increased benign liver cell tumors in males and the female ovarian tubular adenomas in the 1500 ppm dose groups.

NOEL = 100 ppm,
LEL = 700 ppm,
MTD = 1500 ppm (♂ & ♀)

CORE CLASSIFICATION: The study (MRID 417068-08) is upgraded to **Core Minimum**.

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Table 1: Incidence (%) of Neoplastic Lesions in Rats Fed SAN582H for 104 Weeks
[Combined Chronic/Carcinogenicity Study, MRID 417068-08]

Dose (ppm)	Males				Females				Historical Controls[a]
	0	100	700	1500	0	100	700	1500	
Benign Liver Cell Tumor	0	0	2	6	2	2	0	0	0-1.8
Malignant Liver Cell Tumor	0	0	0	4	-	-	-	-	0-3.6
Benign & Malignant Combined	0	0	2	8		-	-	-	-
Ovarian Tubular Adenoma	-	-	-	-	4	2	4	12	0-5.5

[a] = Historical controls supplied by the registrant on October 9, 1991 are from 9 studies performed during 1985 and 1986. These control animals ate the same stock diet as the rats on this study.