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TXR#: 0050658

DATA EVALUATION RECORD - SUPPLEMENT to HED Document No. 004586, review of MRID 00131089. *This supplement provides an Executive Summary to update the original DER.*

STUDY TYPE: Carcinogenicity - [mice, feeding] OPPTS 870.4200b [§83-2b]; OECD 451.

PC CODE: 121601 **DP BARCODE:** 306534
SUBMISSION NO.: 336536

TEST MATERIAL (PURITY): MON-097 (Acetochlor tech., 94.5% a.i.)

SYNONYMS: 2-chloro-N-(ethoxymethyl)-N-(2-ethyl-6-methylphenyl)acetamide

CITATION: Ahmed, F.E., Tegeris, A.S. and Seely, J.C. (1983) MON 097: 24-Month Oncogenicity Study in the Mouse. Pharmacopathics Research Laboratories, Inc., Laurel, MD. Report No. PR-80-007. May 4, 1983. MRID 00131089. Unpublished study.

Hardisty, J.F. (1997) Pathology Working Group Peer Review of Histiocytic Sarcoma in Female Mice from Two Long-Term Studies with Acetochlor. Experimental Pathology Laboratories, Inc., Research Triangle Park, NC. Laboratory Project ID CTL/C/3196, February 11, 1997. MRID 44496204. Unpublished report.

Hardisty, J.F. (1997) Pathology Working Group Peer Review of Hepatocellular Neoplasms in the Liver of Rats and Mice from Five Long-Term Studies with Acetochlor. Experimental Pathology Laboratories, Inc., Research Triangle Park, NC. Laboratory Project ID CTL/C/3197, February 11, 1997. MRID 44496205. Unpublished report.

Hardisty, J.F. (1997) Pathology Working Group Peer Review of Neoplastic Lesions in the Lung of Male and Female Mice from Two Long-Term Studies with Acetochlor. Experimental Pathology Laboratories, Inc., Research Triangle Park, NC. Laboratory Project ID CTL/C/3198, February 11, 1997. MRID 44496206. Unpublished report.

Hardisty, J.F. (2001) Pathology Working Group Peer Review of Proliferative

Lesions in the Kidney of Female Mice from a 24-Month Oncogenicity Study in the Mouse with Acetochlor, Final PWG Report. Experimental Pathology Laboratories, Inc., Research Triangle Park, NC. EPL Project ID No. EP-2000-227, January 3, 2001. MRID 45367403. Unpublished report.

SPONSOR: Monsanto Agricultural Products Company, St. Louis, MO

EXECUTIVE SUMMARY: In an oral carcinogenicity study (MRID 00131089), MON-097 (acetochlor tech., 94.5% a.i., lot #NBP 1737874) was administered to 50 Swiss-bred CD-1 albino mice/sex/dose in the diet for 23 months at dose levels of 0, 500, 1500 or 5000 ppm (equivalent to an estimated average daily intake of 0, 75, 225 or 750 mg/kg bw/day; calculated using a dietary ppm-to-mg/kg/day conversion factor of 0.15 for mice). Additional groups of 10 mice/sex/dose were administered the same diets for 12 months and sacrificed for a one-year interim evaluation. Pathology Working Group OPWG) Peer Review histopathologic reevaluations were later conducted on several tissues (histiocytic sarcoma, females, MRID 44496204; liver, MRID 44496205, lung, MRID 44496206; kidney, MRID 45367403).

Survival in males at termination (control to high dose, respectively) was 60%, 50%, 50% and 26%, with decreases at 5000 ppm observed beginning at one year. In females, survival was reduced during the last months of the study at 5000 ppm and to a lesser extent at 1500 ppm (62%, 50%, 34% and 26% at termination). At 500 ppm and above, statistically significantly increased absolute/relative kidney weights were observed in males at the interim and terminal sacrifices (at 23 months, abs/rel wt. was increased +39.5%/+39.1%, +42.1%/+45.3% and +14.5%/+38.9% above controls, low to high dose). Statistically significantly increased mean abs/rel liver weights were observed at all dose levels in males at interim and terminal sacrifice (at 23 months, -29.5%/+28.5, +23.5%/+23.7 and +55.6%/+91.4% above controls, low to high dose, respectively), with females showing significant increases only at the interim sacrifice time (abs/rel wt +11.5%/+13.9%, +24.6%/+23.5% and +17.8%/+45.3%). (In the absence of correlated microscopic/clinical chemistry findings, liver and kidney organ weight changes at low and mid dose were not used to establish a LOAEL; increased liver weights at terminal sacrifice in the high dose group may have reflected, in part, the presence of tumors). At 1500 ppm in males, slight effects on mean body weights (-4.7% and -6.5% below controls at 53 and 79 weeks, $p<0.05$ but not significant at termination) and slightly increased incidence of interstitial nephritis (from control to high dose, 50%, 58.3%, 70% and 83.3%) were observed. In females, abs/rel thyroid plus parathyroid weights were increased (+29%/+39% and at 5000 ppm +43%/68%). At 5000 ppm (HDT), mean body weights were significantly reduced in both males and females throughout the study (up to about 20% by study termination), and females showed significant decreases in RBC count (-21% below controls), Hgb (-22.5%) and Hct (-23%); relative thyroid weight in males was increased by +31%; and at 23 months, the incidence of interstitial nephritis was also statistically significantly increased in females (control to high dose 51.6%, 55%, 51.6% and 76.3%, females). A significantly increased incidence of retinal degeneration was seen in females (control to high dose 2/60, 3/60, 1/60 and 8/59). There were no treatment-related effects observed on clinical signs of toxicity, food consumption/feed efficiency, nor in clinical chemistry or urinalysis parameters. **The systemic toxicity LOAEL is 1500 ppm (225 mg/kg/day), based**

on slightly reduced mean decreased body weight and increased incidence of interstitial nephritis in males and increased mortality and abs/rel thyroid plus parathyroid weights in females. The systemic toxicity NOAEL is 500 ppm (75 mg/kg/day).

Dosing was considered adequate, based on reduced survival in females and slightly reduced body weights and increased interstitial nephritis in males at 1500 ppm. Toxicity at 5000 ppm was considered excessive in both sexes based on pronounced effects (sharply reduced survival, anemia, reduced body weight in both sexes and renal toxicity) and tumors observed at that dose were not considered as part of the weight-of-the-evidence. In the original review (using the original study pathology data), the following tumor types were considered to show dose-related increases in incidence: (1) liver - carcinoma of the liver in males, with incidence from control to high dose, of 10%, 11.9%, 16.7% and 37.3% (6/60, 7/59, 10/60 and 22/59) and in females of 1.7%, 0%, 0% and 6.9% (1/60, 0/60, 0/60 and 4/58); combined adenoma and carcinoma of the liver in males 23.3%, 18.6%, 31.7% and 49.1% (14/60, 11/59, 19/60 and 29/59) and females 5%, 0%, 0% and 13.8% (3/60, 0/60, 0/60 and 8/58); (2) lung - in females, alveolar/bronchiolar adenoma 3.3%, 10%, 13.3% and 6.8% (2/60, 0/60, 0/60 and 4/58), carcinoma 0%, 8.3%, 5% and 11.9% (0/60, 5/60, 3/60 and 7/59) and combined adenoma and carcinoma 3.3%, 18.3%, 18.3% and 18.6% (2/60, 11/60, 11/60 and 11/59), with males not showing an increase with dose; (3) histiocytic sarcoma (in the uterus) - 0%, 10.5%, 10% and 8.5% (0/59, 6/57, 6/60 and 5/59); (4) kidney - renal adenoma 0%, 0%, 0% and 5.1% (0/60 all except 3/59 high dose); and (5) ovaries - benign tumors (combined adenoma, granulosa cell tumor and luteoma) 0%, 0%, 8.3% and 5.2% (0/59, 0/60, 5/60 and 3/58). The relationship of tumors to treatment was reevaluated in the fourth cancer peer review of acetochlor (HED TXR# 0052727, 8/4/05) using HED statistical analyses of PWG findings (ovarian tumors were evaluated using original study data). Of the tumors evaluated, only the lung tumors and histiocytic sarcoma in females were considered to show a dose-related increase; liver, kidney and ovarian tumors were not considered to be related to treatment. Incidence (control to high dose, respectively) as analyzed by HED was as follows: (1) lung alveolar/bronchiolar tumors, females: adenomas 2%, 17%, 22% and 23% (1/43, 7/42, 9/40 and 7/31), carcinomas 0%, 9%, 2% and 18% (0/43, 4/43, 1/40 and 6/33); and combined incidence 2%, 23%, 25%, 33% (1/43, 10/43, 10/40 and 11/33; significant positive trend seen at all doses, pairwise significance seen for all groups except carcinomas at 1500 ppm); (2) histiocytic sarcoma (females): 0%, 7%, 15% and 15% (0/47, 3/44, 7/47 and 6/41; pairwise comparisons significant at all doses). It is noted that the PWG reviews themselves concluded that none of the tumors were treatment-related.

This carcinogenicity study in the mice is classified as **Acceptable (guideline)** and satisfies the guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in mice.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.