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

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MAR - 4 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Molinate: Registrant's Response to Agency's Reviews of Mouse Carcinogenicity Study, One-Year Dog Study, and Two-Year Rat Chronic Toxicity/ Carcinogenicity Study

TO: Paul Parsons
PM Team Reviewer (62)
Reregistration Branch/SRRD (H7508C)

FROM: Linda L. Taylor, Ph.D. Linda Lee Taylor 2/28/94
Toxicology Branch II, Section II,
Health Effects Division (H7509C)

THRU: K. Clark Swentzel K. Clark Swentzel 3/1/94
Section II Head, Toxicology Branch II
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and

Marcia van Gemert, Ph.D. Marcia van Gemert 3/1/94
Chief, Toxicology Branch II/HFAS/HED (H7509C)

Registrant: ICI Americas Inc.
Chemical: Molinate; S-ethyl hexahydro-1H-azepine-1-carbothioate
Synonym: Ordram
Caswell No.: 444
Submission No.: S455751
Identifying No.: 041402
DP Barcode: D197902
MRID No.: 430378-01
Action Requested: Please review the additional requested information for studies MRID #'s 41809201, 41781102, 41815101.

Comment: The Registrant has submitted additional information requested in the reviews of the three studies listed above. Each study had been classified Core Supplementary, pending receipt of the additional data.

MRID # 41809201: **18-Month Dietary Mouse Oncogenicity Study with R04572.** The Registrant has clarified the lot number of the test material used in the study and has provided an explanation of the discrepancies noted among tables in the final report with respect

[redacted]

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to survival. With respect to the Lot #, it appears that the Registrant did not observe that the question regarding the #'s was with respect to EHC-0886-30 vs EHC-0866-30. Both of these numbers were associated with the WRC # 4921-8-22 in the mouse study. It is to be noted that the former EHC # was listed in the rat chronic toxicity/carcinogenicity report and the latter EHC # was listed in the chronic dog study report, and both numbers were associated with the WRC # 4921-8-22 also. The WRC # appears to be the appropriate identifier of the test material. The explanation provided with respect to survival is adequate, and the study can be upgraded to Core Minimum. Under the conditions of the study, exposure of Crl:CD®-1 (ICR)BR mice [50/sex/group] to Molinate at dose levels of 10 [1.0 ♂♂/1.3 ♀♀ mg/kg/day], 100 [10.4 ♂♂/13.9 ♀♀ mg/kg/day], 1000 [105 ♂♂/133 ♀♀ mg/kg/day], and 2000 [200 ♂♂/249 ♀♀ mg/kg/day] ppm in the diet for 18 months resulted in decreased survival [62% ♂♂/58% ♀♀ vs 76% in control ♂&♀], lower body weight [85% ♂♂/73% ♀♀ of control]/body-weight gain [64% ♂♂/63% ♀♀ of control], decreased food consumption [89% ♂♂/83% ♀♀ of control], and an increase in the incidence of several clinical observations indicative of neurological involvement [hindlimb muscle weakness, adducted hindlimbs, ataxia, splayed hindlimbs] in both sexes at the highest dose level. Relative brain and liver weight were increased in both sexes, adrenal weight (relative and absolute) was increased in females, and testes weight was decreased in males of the highest dose level. The incidence of several nonneoplastic lesions (1) demyelination and Schwann cell hyperplasia of the sciatic nerve, eosinophilic bodies in the spinal cord and brain and (2) thecal/interstitial cell hyperplasia of the ovaries were increased at the two highest dose levels, and (3) degeneration of the testes was increased at the three highest dose levels. There was no treatment-related increase in neoplastic lesions. **The NOEL for all effects except that on the testes can be set at 100 ppm (15 mg/kg), the LEL at 1000 ppm (150 mg/kg), based on decreased survival [62% ♂♂/58% ♀♀ vs 76% in control ♂&♀], decreased body weight 85% ♂♂/73% ♀♀ of control]/gain [64% ♂♂/63% ♀♀ of control], food consumption 89% ♂♂/83% of control], and increased incidence of nonneoplastic lesion of the brain, spinal cord, sciatic nerve and ovaries. A NOEL of 10 ppm (1.5 mg/kg) can be set for testes, the LEL at 100 ppm (15 mg/kg), based on testicular degeneration.** This study is classified Core Minimum, and it satisfies the guideline requirement [83-2] for a mouse carcinogenicity study.

MRID # 417811-01: **One-Year Toxicity Study with R-4572 in Beagle Dogs.** Information on the purity and stability of the test material has been provided. The purity of WRC4921-8-22, used in both the chronic dog and rat studies and in the mouse carcinogenicity study, is listed as 97.6%, with the average weight percent Molinate of samples analyzed between 1985 and 1991 listed as 97.7% ± 0.5 [standard deviation and coefficient of variation]. These data adequately address the deficiencies identified in the original review of the study, and the study can be upgraded to Core Minimum. The Registrant disagrees with the possible male reproductive tract

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effect noted by the original reviewer, stating that the apparent reduction in ejaculate volume and motility seen in the group mean values are the result of values from one dog in each case and concludes that overall there is no effect on sperm motility or sperm volume. Similarly, with respect to testicular tubular atrophy, with no difference noted in severity in this lesion common to dogs of this age, the Registrant contends that no treatment involvement can be assigned. TB II notes that with respect to sperm volume, at 6 months, none of the control and 1 mg/kg dose group dogs displayed volumes less than 1.0 while 1 of 4 dogs at 10 mg/kg and 2 of four dogs at 50 mg/kg displayed volumes less than 1.0 [the 100 mg/kg dose group did not receive test material after 14 weeks and is not included here]. At 12 months, 1 of 4 control, 0 of 4 low- dose, 3 of 4 mid-dose, and 4 of 4 high-dose dogs display volumes of less than 1.0. With respect to motility, at 6 months the number displaying % ≤ 50 was 1,0,2,2 and at 12 months the number ≤ 60 was 0,1,2,5 for the control, low-, mid-, and high-dose groups, respectively. Viewed along with the known reproductive effects of the test material in other species, an association cannot be ruled out. With respect to tubular atrophy, this was not listed as a treatment-related effect in the LOEL statement. Under the conditions of the study, the oral administration of Molinate via the diet for one year to Beagle dogs [4/sex/group] at dose levels of 0, 1, 10, 50, and 100 mg/kg/day [the 100 mg/kg dose group was dosed with test material for only 14 weeks] resulted in decreased body-weight gain [47% ♂♂/55% ♀♀ of control], adverse effects on the nervous system [ataxia, reduced locomotor activity, splayed hindlimbs, tremors, eosinophilic bodies/vacuolation of the medulla/pons, and spinal cord demyelination], anemia, and decreased ejaculate and percent mobile sperm at the 50 mg/kg/day dose level. **The NOEL for effects other than neurotoxic effects is 10 mg/kg/day, the LEL 50 mg/kg/day, based on decreased body-weight gain [47% ♂♂/55% ♀♀ of control], anemia, and decreased ejaculate and percent mobile sperm.** This study satisfies the guideline requirement [83-1(b)] for a chronic toxicity study in dogs. With respect to neurotoxicity, it has been determined that neurotoxicity testing guideline studies are the appropriate means by which to determine a no-effect dose level for this endpoint.

MRID # 418151-01 **Two-Year Chronic Toxicity/Carcinogenicity Study With R-4572 in Rats.** A certificate of analysis was submitted, which confirms the purity of the test material as 97.6%. The Lot # used in this study is the same one used in the mouse carcinogenicity and chronic dog studies cited above. The method of randomization was not included in the methods' section of the report but was described in the protocol for the study, which was an Appendix [A] to the report. The relevant page of the protocol was submitted, which indicated that the animals would be ranked by body weight and assigned to the study groups "such that all study groups of the same sex will have similar mean body weights." TB II notes that at week 0, there were statistically significant differences in body weight between the 7 ppm and 40 ppm male groups compared to the

male control group and between the 40 ppm and 300 ppm female dose groups compared to the control female group. The information provided is adequate, and the study can be upgraded to Core Minimum. Under the conditions of the study, the oral administration of Molinate via the diet for two years to Crl:CD®(SD)BR rats [50/sex/group plus 20/sex control, 10/sex treated for 12-month sacrifice] at dose levels of 0, 7 [0.3 ♂♂/0.4 ♀♀ mg/kg/day], 40 [1.8 ♂♂/2.0 ♀♀ mg/kg/day], 300 [13 ♂♂/15 ♀♀ mg/kg/day], and 600 [29 ♂♂/35 ♀♀ mg/kg/day] ppm [the 600 ppm dose group was a satellite group sacrificed at 1 year] resulted in decreased body weight [88% ♂♂/87% ♀♀ of control at 54 weeks; 92% ♂♂/95% ♀♀ of control at 12 weeks]/body-weight gain [79% ♂♂/70% ♀♀ of control], food consumption, possible lenticular opacities in males, decreased RBC cholinesterase levels [61-86% ♂♂/67-85% ♀♀ of control], muscle "thinness", organ weight effects, and increased lesions of muscle and reproductive organs at the 300 ppm dose level. Degeneration/demyelination of the sciatic nerve was observed at all dose levels in both sexes at a greater incidence than in the controls and, although statistical significance was not attained, the incidence was dose-related. Additionally, the incidence of atrophy/reserve cell hyperplasia of the skeletal [thigh] muscle was increased at all dose levels [dose-related]. **The NOEL, for effects other than neurotoxicity, is 40 ppm [1.8 ♂♂/2.0 ♀♀ mg/kg/day], the LEL 300 [13 ♂♂/15 ♀♀ mg/kg/day] ppm, based on decreased body weight [88% ♂♂/87% ♀♀ of control at 54 weeks; 92% ♂♂/95% ♀♀ of control at 12 weeks]/body-weight gain [79% ♂♂/70% ♀♀ of control], food consumption, possible lenticular opacities in males, decreased RBC cholinesterase levels [61-86% ♂♂/67-85% ♀♀ of control], muscle "thinness", organ weight effects, and increased lesions of muscle and reproductive organs at the 300 ppm dose level.** This study is classified Core Minimum, and it satisfies the guideline requirement [83-5] for a combined chronic toxicity/carcinogenicity study in rats. With respect to neurotoxicity, it has been determined that neurotoxicity testing guideline studies are the appropriate means by which to determine a no-effect dose level for this endpoint.

cc: KWhitby, CCB

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