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MEMORANDUM

MAY 11 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Toxicology Chapter for the Methiocarb (Mesurol)
Registration Eligibility Document (RED)

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Appended to this cover sheet is the Toxicology Branch
Chapter for the Methiocarb (Mesurol) RED.

Methiocarb (Mesurol, Mercaptodimethur), chemical name 3,5-dimethyl-4-(methylthio)phenyl-N-methylcarbamate, is a carbamate insecticide/molluscicide/acaricide/avian repellent whose primary mechanism of toxicity is cholinesterase inhibition.

The registrant (Miles, Inc.) currently wishes to maintain only selected non-food uses of Methiocarb. These include ornamental, greenhouse, turf/lawn, and other outdoor residential uses. Formulation types include a granular, pellets/tablets, a wettable powder, and a spray.

①



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HUMAN HEALTH ASSESSMENT

The registrant has chosen to eliminate the food uses for this chemical and wishes to support only selected non-food uses. However, this health assessment includes comments on data which the registrant submitted in the past to support food uses of Methiocarb (Mesurol).

1. Toxicology Assessment

a. Acute Toxicity

Acute toxicity data for Mesurol technical are listed in the table below.

SUMMARY OF MESUROL TECHNICAL GRADE ACUTE TOXICITY DATA

Test	Result	Category
Oral LD ₅₀ (rat) ^{1,2}	30 mg/kg (both sexes) ^a 14 mg/kg (males) ^b 16 mg/kg (females) ^b	I
Dermal LD ₅₀ (rabbit) ³	> 2000 mg/kg	III
Inhalation LC ₅₀ (rat) ⁴	0.585 mg/l (males) 0.433 mg/l (females)	II
Eye Irritation ⁵	Not an irritant	IV
Dermal Irritation ⁶	Not an irritant	IV
Dermal Sensitization	Data Gap	N/A
Delayed Neurotoxicity ^{7,c}	Negative	N/A

1-7 Reference MRID numbers are listed for each study at the end of this Toxicology Assessment.

a Test material in ethanol and propylene glycol vehicle.

b Test material in polyethylene glycol 400 (Lutrol) vehicle.

N/A Not applicable

c Study available but not required for carbamates.

b. Subchronic Toxicity

Existing 90-day rat and 90-day dog feeding studies are judged to be inadequate, however, acceptable chronic feeding studies for the rodent and non-rodent are available.

Twenty-one day dermal toxicity data submitted for evaluation included four studies^{8,9,10,11}. A six day initial range-finding study in rabbits⁸ and a 21-day repeated dermal toxicity study in rabbits [interrupted at day 14] were performed by the same laboratory. In the dose-ranging study, doses of 0 (saline vehicle), 15.7, 31.3, 62.5, 125, 250, 500, 1000, or 2000

mg/kg/day of Mesurol technical were administered. Death occurred in one out of two females per group at doses of 250, 500, and 1000 mg/kg/day and in both of the high dose females. One out of two males per group died at doses of 1000 mg/kg/day and above. All deaths were ascribed to treatment since no other explanation was provided in the study report. Other clear-cut clinical signs of toxicity were noted at the top two doses. The interrupted 21-day study, in which doses of 0 (saline vehicle), 60, 150, or 375 mg/kg/day of Mesurol technical were being administered, was stopped due to three accidental deaths at the high dose. No treatment-related effects were observed by day 14 at the lower doses.

Two rabbit 21-day dermal toxicity studies^{10,11}, which were performed at later dates by a different laboratory, were also submitted. In the first of these studies, Mesurol technical was administered at doses of 0 (saline vehicle), 60, 150, or 375 mg/kg/day and, in the second study, Mesurol technical was administered at doses of 0 (saline vehicle) or 500 mg/kg/day. There are no clear adverse findings in these studies, particularly when they are looked at together, thus, a convincing LOEL cannot be established.

Although inconsistencies are noted in the data from the two laboratories and the quality of the data from the two completed 21-day dermal studies^{10,11} exceeds that of the earlier studies^{8,9}, the deaths in the dose ranging study⁸ cannot be ignored. Therefore, when all the data are taken together, the LOEL for subchronic dermal toxicity is 250 mg/kg/day based on mortality in females at doses of 250 mg/kg/day and above⁸ and the NOEL is 150 mg/kg/day (the next lower dose tested from amongst the studies in which no treatment-related effects were noted).

c. Chronic Toxicity

In a rodent chronic feeding study, four dose groups of 60 rats/sex/group were fed 0, 67, 200, or 600 ppm of Mesurol technical in the daily diet for two years. The systemic NOEL was determined to be 600 ppm (30 mg/kg/day). At this dose, in both sexes, body weight decreases, relative to controls, were observed which were considered to be a secondary effect of cholinesterase inhibition. Both erythrocyte and plasma cholinesterase inhibition occurred at the high dose. The LOEL for cholinesterase inhibition was judged to be 200 ppm (10 mg/kg/day), at which dose transitory erythrocyte cholinesterase inhibition was observed. The NOEL for cholinesterase inhibition was set at 67 ppm (3.35 mg/kg/day)¹².

In a non-rodent chronic feeding study, sixteen male and sixteen female six-month old pure bred beagle dogs were divided into four groups of four animals/sex and were fed 0, 5 (reduced from 15 ppm at study week three), 60, or 240 ppm of Mesurol

technical in the diet for two years. Effects which appeared to be treatment-related were sporadic incidences of hind limb weakness and tremor in the high dose group animals fed 240 ppm (6 mg/kg/day) of test material (systemic LOEL) and plasma cholinesterase inhibition of 30% or greater, with respect to controls, at dose levels of 15 ppm (0.375 mg/kg/day) and above. The NOEL for systemic effects and the LOEL for cholinesterase inhibition were judged to be 60 ppm (1.5 mg/kg/day) and 15 ppm respectively and the NOEL for cholinesterase inhibition was determined to be 5 ppm (0.125 mg/kg/day)^{13,14}.

d. Carcinogenicity

Mesurool technical was not found to be carcinogenic in a two year rat feeding/oncogenicity study in which the highest dose tested was 600 ppm (30 mg/kg/day)¹⁵.

The data presented in a two-year mouse oncogenicity study are not sufficient to fully evaluate the carcinogenic potential of the test material in the mouse¹⁶. The requirement for an acceptable mouse oncogenicity study was waived when the registrant dropped food-uses for the chemical¹⁷.

e. Developmental Toxicity

Daily oral doses of vehicle, 1, 3, or 10 mg/kg/day of Mesurool technical were administered to groups of 19 to 20 fertilized female FB-30 rats from the sixth to the fifteenth day of pregnancy inclusive. Although a decrement in weight gain was noted in the high dose group compared to controls, there was apparently no evidence of developmental toxicity in the study. The LOEL and NOEL for maternal toxicity were respectively 10 mg/kg/day and 3 mg/kg/day. The NOEL for developmental effects was greater than 10 mg/kg/day¹⁸.

From day 6 to 18 inclusive of gestation, groups of 17 New Zealand White rabbits were dosed orally with vehicle, 1, 3 or 10 mg/kg/day of Mesurool technical. Cholinergic signs and body weight loss were observed in the high dose group (maternal toxicity LOEL and NOEL were 10 mg/kg/day and 3 mg/kg/day respectively). However, there was no apparent evidence of developmental toxicity in the study (NOEL for developmental toxicity was greater than 10 mg/kg/day)¹⁹.

Mesurool technical was administered by the dermal route to 16 Chinchilla rabbits (CHbb:CH, hybrids, SPF quality) per group during gestational days 6 through 18 at doses of 0 (1% Cremophor vehicle), 10, 50, or 250 mg/kg/day. The NOEL for maternal toxicity was > 250 mg/kg/day while the NOEL for developmental toxicity was 10 mg/kg/day. The LOEL for developmental toxicity was judged to be 50 mg/kg/day based on statistically significant increases relative to controls, in the number of litters (but not

fetuses) with non-ossification of sternebra 5 and in the number of fetuses (but not litters) with incomplete ossification of sternebra 5, at doses of 50 mg/kg/day and above. Also considered to be treatment-related at the highest dose tested were statistically significant increases in litters with non-ossification of the medial phalanx 3 of the left and right forelimb and in incomplete ossification of multiple sites in the hind limb phalanges²⁰.

f. Reproduction

An acceptable reproduction study is not available. The requirement for an acceptable reproduction study was waived when the registrant dropped food-uses for the chemical²¹.

g. Mutagenicity

The 1987 Methiocarb Registration Standard listed data gaps for three categories of mutagenicity studies based on the 1982 Pesticide Assessment Guidelines: I. Gene Mutation; II. Structural Chromosomal Aberration; and III. Other Genotoxic Effects. Three studies, the results of which are summarized below, were submitted by the registrant to fill the data gaps:

1. Gene Mutation - Mesurol was not mutagenic in the presence or absence of rat liver S9 homogenate in the Salmonella typhimurium/mammalian microsome mutagenicity assay²².
2. Structural Chromosomal Aberration - In a sister chromatid exchange assay in chinese hamster ovary (CHO) cells, Mesurol was not genotoxic²³. The guidance given under the 1982 guidelines for mutagenicity was that a sister chromatid exchange assay could be used to satisfy the requirement for a study in either Mutagenicity Study Category II or III (even though it is really a test for DNA damage, Category III).
3. Other Genotoxic Effects - In an in vitro unscheduled DNA synthesis assay in primary rat hepatocytes, Mesurol was not genotoxic at up to and including cytotoxic concentrations²⁴.

The current mutagenicity guideline requirements (starting from 1991) for mutagenicity testing include an Ames assay, a mammalian cell gene mutation assay, and an in vivo cytogenetics assay. According to this guidance, there would be two data gaps for Mesurol mutagenicity testing. However, since the available mutagenicity studies for Mesurol fulfill data requirements in existence at the time of issuance of the data call-in notice for Mesurol (Methiocarb) based on the 1987 Methiocarb Registration Standard, since the submitted studies are acceptable and negative, and since food uses for Mesurol have been withdrawn, no

additional mutagenicity testing will be required at this time (although circumstances could occur in which the Agency might ask for these data in the future).

h. Metabolism

A metabolism study was performed in rats. More than 80% of the ^{14}C -carbonyl label was eliminated in 48 hours. Radioactivity was distributed in expired CO_2 , urine, feces, and body tissues. The study was considered to be inadequate due to a number of deficiencies (only one dose level was tested, an insufficient number of animals was used, and a number of metabolites were not clearly identified)²⁵. The requirement for an acceptable metabolism study was waived when the registrant dropped food-uses for the chemical¹⁷.

i. Neurotoxicity Testing

Both an acute and a subchronic (90-day) neurotoxicity study must be performed with Mesurol technical since these studies are now required for carbamate pesticides (even for non-food uses). However, the lack of these studies at this time will not be a reason for delaying the reregistration of Mesurol.

j. Ocular Toxicity Testing

Ocular toxicity testing is not currently required for the carbamate class of pesticides.

k. Dermal Absorption

A dermal absorption study is not required at this time.

l. Domestic Animal Safety

A domestic animal safety study is not required at this time.

m. Other Toxicological Considerations

1. When food uses existed for Mesurol, an amendment to the 1987 Methiocarb Registration Standard Toxicology Chapter required that a 30-day dog feeding study (including measurement of cholinesterase activities) be performed using Mesurol sulfoxide, a cholinesterase-inhibiting metabolite of Mesurol. Mesurol sulfoxide had been shown in some studies to be more acutely toxic than Mesurol and to comprise a much larger portion of certain post-application non-removable residues than the parent compound. The 30-day dog study was waived¹⁷ when food uses were dropped for Mesurol, however, it will be required again if food uses are requested at a later date.

2. If in the future, the registrant wishes to petition for reinstatement of food uses for this chemical, toxicity studies which have been waived will again be required. In addition the entire database for Mesurol (Methiocarb) will be reexamined for adequacy according to whatever standards and guidelines for pesticide toxicity testing exist at the time of the rereview.

3. Current non-food use patterns suggest that potential acute dermal exposure to mixers, loaders, and applicators of Mesurol-containing products and from domestic turf/lawn applications of Mesurol should be evaluated by the Occupational and Residential Exposure Branch. The suggested toxicological endpoint for assessing potential toxicity from acute dermal exposure to Mesurol is the rabbit dermal developmental toxicity study with a NOEL of 10 mg/kg/day and an LOEL of 50 mg/kg/day²⁰. Rabbit skin has been shown in some studies to be more permeable to chemicals in various forms than is human skin. This difference in permeability might be factored into acute dermal exposure assessment calculations.

n. Reference Dose

On February 25, 1993, the Health Effects Division RfD/Peer Review Committee recommended that the RfD for Mesurol (Methiocarb) be established at 0.005 mg/kg/day. This value was based on a NOEL of 1.5 mg/kg/day for tremors and muscle weakness observed at 6 mg/kg/day in a long-term feeding study in dogs using an uncertainty factor (UF) of 100 to account for inter-species extrapolation and intra-species variability. Even though a waiver was granted for a reproduction study, the RfD Committee recommended that an additional UF of 3 be added to compensate for the lack of adequate reproduction data, as per Agency policy.

LIST OF REFERENCES USED IN METHIOCARB (MESUROL) RED TOXICOLOGY CHAPTER

Reference Number	Study Type	Reference
1	Acute Oral	MRID 36477
2	Acute Oral	MRID 83437
3	Acute Dermal	MRID 36478
4	Acute Inhalation	MRID 404042-01
5	Eye Irritation	MRID 55163
6	Dermal Irritation	MRID 55163
7	Acute Delayed Neurotoxicity	MRID 83438
8	Subchronic Dermal Range-Finding Study	No MRID EPA Correspondence ID# 16-738, dated 2/28/92
9	21-Day Dermal [Interrupted]	Same as 8 above
10	21-Day Dermal	MRID 409223-01
11	21-Day Dermal	MRID 417717-01
12	Rodent Chronic Feeding/Onco	MRID 115226
13	Non-rodent Chronic Feeding	MRID 128939
14	Supplement to 13 above	MRID 149362
15	Rodent Chronic Feeding/Onco	MRID 115226
16	Mouse Oncogenicity (HED Doc # 005219)	No MRID Acc. Nos. 072227 072228 Record #158957 D175225
17	Memo from P. Hurley to N. Tompkins, dated 4/16/92	
18	Rat Oral Developmental	MRID 124617
19	Rabbit Oral Developmental	MRID 143213
20	Rabbit Dermal Developmental	MRID 424964-01
21	Memo from K. Hamernik to W. Miller, dated 10/24/88	Record #228785
22	Mutagenicity	MRID 405081-01
23	Mutagenicity	MRID 405081-02
24	Mutagenicity	MRID 407008-01
25	Metabolism (1987 Methiocarb Reg.Std. HED Doc No. 005739)	No MRID or other Reference. See 1987 Reg Std.