Image

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

014056

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: March 16, 2000

MEMORANDUM

SUBJECT: **FERBAM** - Report of the Hazard Identification Assessment Review Committee.

FROM: David Nixon, D.V.M., Toxicologist. David Nixon 3/22/2000
Reregistration Review Branch 4
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair 3/20/00
and
Elizabeth Doyle, Co-Chair E A Doyle 3/20/00
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Susan Hummel, Branch Senior Scientist
Reregistration Review Branch 4
Health Effects Division (7509C)

PC Code: ~~034804~~ 034801

On Februrary 10, 2000, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendation of the toxicology reviewer to determine whether data for **ziram** could be used to satisfy the data requirements for **ferbam**. The conclusions drawn at this meeting are presented in this report.

Committee Members in Attendance

Members present were: William Burnam, Vicki Dellarco, Elizabeth Doyle, Pamela Hurley, Tina Levine, Elizabeth Mendez, David Nixon, Nicole Paquette, Jess Rowland, and Brenda Tarplee.

Member(s) in absentia: None

Data evaluation prepared by: David Nixon, D.V.M.,TOXICOLOGIST, RRB4

Also in attendance were: Gary Otakie (HED), Sanjivani Diwan (HED), Ray Kent (HED), Laura Parsons (SRRD).

Data Evaluation / Report Presentation

David Nixon, D.V.M.
Toxicologist

1. INTRODUCTION

On Februrary 10, 2000, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendation of the toxicology reviewer to determine whether data for **ziram** could be used to satisfy the data requirements for **ferbam.**

Ziram and ferbam are dimethyldithiocarbamate compounds. After a Phase 4 screening of the ziram toxicological database, the registrant was granted a data waiver by HED/Toxicology Branch I on February 8, 1991, for subchronic, chronic, carcinogenicity, developmental/reproduction, mutagenicity, and metabolism studies (D159794; S388171) until a more thorough evaluation of the database could determine what data would be required. Ziram and ferbam, although somewhat similar in structure, may vary in toxicity quantitatively due to the differing number of dimethyldithiocarbamate ligands surrounding the metal ion. The registrant maintains that via the oral route, in chronic situations, this may be the only difference between ferbam and ziram if both of these compounds dissociate to dimethyldithiocarbamic acid, or carbon disulfide and dimethyl amine in the stomach. Both compounds are complex molecules that involve coordinate bonding of metal ions to dimethyldithiocarbamate ligands. It is probable that these two compounds not only have differing crystalline structures, but also differing thermodynamic and kinetic stabilities which may be factors in determining toxicity. The registrant claims that ferbam "may be expected to be broken more easily" than ziram and liberate the dimethyldithiocarbamates for further chemical action resulting in more rapid degradation. However, liberation of these molecules may also allow for more toxic damage by the dimethyldithiocarbamate or the degradates such as CS_2. Also, even though ferbam appears to be less toxic than ziram in the acute studies, this difference is probably due to the acute toxicological properties of the metal ions and the results cannot necessarily be extrapolated to longer term studies. The registrant has conducted a literature search for toxicological studies using ferbam and has submitted these studies to the Agency. These studies have been evaluated, and the relevant data on ziram and ferbam are summarized below.

2. LITERATURE REVIEW

2.1 Hodge, H.C., E.A. Maynard, W.L. Downs, R.D. Coye, Jr., and L.T. Steadman. (1956) Chronic oral toxicity of ferric dimethyldithiocarbamate (ferbam) and zinc dimethyldithiocarbamate (ziram). Journal of Pharmacology and Experimental Therapeutics 118(2):174-181.

MRID 00083231

In a two-year chronic feeding study, ziram and ferbam were fed to 25 rats/sex/group at dosage levels of 0, 0.0025, 0.025, or 0.25 %. The purity of the compounds and whether or not the dose was based on a.i. were not noted. All of the rats in the 0.25% ferbam group died (both sexes) and the life-span was shortened (430 days as compared to 607 days in controls). Also, reduced growth rate and neurological changes (abnormal hindleg

3

grasping action) at 2 or more months post-dosing were seen at 0.25% in both ferbam and ziram groups in both sexes. No treatment-related effects on hematology, urinalysis, organ weights, or incidences of tumors were noted. Cystic lesions in the cerebral cortex and cerebellum were observed in most of the females and several male rats in the 0.25% ferbam group, but since no correlation with neurological signs occurred, the significance could not be ascertained. However, such lesions have been seen in other studies in rats chronically fed tetramethyl- or tetraethylthiuram disulfide.

In a one-year chronic feeding study, ziram and ferbam were fed to 1 adult beagle dog/sex/group at dosage levels of 0, 0.5, 5 and 25 mg/kg/day. In both the ziram and ferbam groups at 25 mg/kg/day, all but one dog had periodic convulsive seizures and all dogs at this dose for both compounds died after five to nine months. No treatment-related effects on hematology, urinalysis, organ weights, or histopathology were noted.

2.2 **Lee, C., J. Russell, and J. Minor. (1978) Oral toxicity of ferric di-methyl dithiocarbamate (ferbam) and tetramethylthiuram disulfide (thiram) in rodents. Journal of Toxicology and Environmental Health 4:93-106.**

MRID 00143817

In a 13-week subchronic feeding study, ferbam (76% a.i.) was fed in the diet to 20 male rats/group at dosage levels of 0, 0.05, 0.12, 0.25, or 1.2% (0, 23, 55, 109, or 331 mg/kg/day, respectively). All mg/kg/day doses were based on the a.i., not formulation. A treatment-related effect was noted on mortality at 109 (6 deaths between day 3 and week 5) and 331 mg/kg/day (20 deaths within the first week) and on body weight gain (reduced) at 23 (90% of controls), 66 (79% of controls), and 109 mg/kg/day (58% of controls). Food consumption was also reduced at the same doses that body weight gain decreased. Increased incidences of golden pigmentation in RE cells of the spleen and mesenteric lymph nodes were noted at 109 and 331 mg/kg/day.

In a 80-week chronic feeding study, ferbam (76% a.i.) was fed in the diet to 24 rats/sex/group at dosage levels of 0, 0.01, 0.04, or 0.1%, then 0, 0.015, 0.06, or 0.15% at the beginning of the 10th week, and then 0, 0.02, 0.08, or 0.2% at the beginning of the 22nd week. This resulted in a relatively constant intake of 0, 8, 32, or 80 mg/kg/day of ferbam for males and 0, 9, 37, or 96 mg/kg/day for females. Two high-dose females appeared to be partially paralyzed caudal to the lumbar region of the spine during the 52nd and 53rd week. They had alopecia and weight loss, but no remarkable lesions were observed on necropsy. During the 54th week, another female in the high-dose group developed similar problems with ataxia, which included an unusual gait, spreading of the hind limbs, and dragging the hind feet.

Males showed decreased body weight gain at all doses with food consumption generally reduced parallel with body weight gain decreases. Females showed reduced body weight

4

gain and food consumption only at 96 mg/kg/day (high dose) until the 8th month, then the mid-dose group began to have the same parameters affected.

No treatment-related effects on hematology or clinical chemistries were noted. Relative spleen weights were increased compared to the controls in both sexes at the mid and high doses and relative thyroid weights were increased in both sexes at the high dose. In males, relative testes weights were increased at the mid and high doses.

Male rats had an increased incidence of squamous metaplasia in the thyroid and increased incidence and severity of fatty infiltration in the pancreas that appeared to be dose-related, but the effect seemed to plateau at the middle dose. No concurrent neurological lesions were noted in ataxic rats. No treatment-related findings were noted in females. No treatment-related increased incidences of tumors were seen in males or females.

2.3 **Short, Jr., R., J. Russel, J. Minor, and C. Lee. (1976) Developmental toxicity of ferric dimethyldithiocarbamate and bis(dimethylthiocarbamoyl)disulfide in rats and mice. Toxicology and Appl. Pharmacol. 35:83-94.**

MRID 00143816

Reproduction in male rats: In a reproduction study, ferbam (76% a.i.) was fed in the diet to 20 male rats/group at dosage levels of 0, 0.05, 0.12, or 0.25% (0, 23, 66, or 109 mg/kg/day, respectively) for 13 weeks. All mg/kg/day doses were based on a.i., not formulation. Body weight and food consumption were significantly decreased at 66 and 109 mg/kg/day. Six of the high-dose animals died between the 2nd and 6th weeks of treatment. No treatment-related effects were noted on reproduction indices (fertility, gestation, viability, and lactation) in females mated to the treated males.

Reproduction in female rats: In a reproduction study, ferbam (76% a.i.) was fed in the diet to 20 virgin female rats/group at dosage levels of 0, 0.04, or 0.2% (0, 15, or 51 mg/kg/day, respectively) for at least 14 days prior to mating. Mean body weight was significantly reduced at 51 mg/kg/day after 2 weeks while food consumption was significantly reduced at 15 and 51 mg/kg/day. Reproduction indices were not affected by treatment with ferbam. Females were mated with untreated males.

Teratology in rats: Female rats were treated with ferbam (76% a.i.) at 0, 11, or 114 mg/kg/day on gestation days 6-15. There was 25% mortality at the high dose. Total body weight change during gestation was significantly reduced in both treatment groups as compared to the controls. Numbers of implants/dam and fetuses/dam were reduced at the high dose plus the number of resorptions significantly increased. Fetal body weight was decreased by 10.5% as compared to controls at 11 mg/kg/day and decreased by 23.7% at 114 mg/kg/day. Increased incidences of developmental anomalies were

5

mentioned only for the high-dose group and included unossified sternebrae, slightly collapsed cranium, malformed cranium, hydrocephalus, hematoma, and cleft palate.

Teratology in mice: Female mice were treated with ferbam (76% a.i.) at 0, 23, or 228 mg/kg/day on gestation days 6-14. No treatment-related effects on survival or body weight change of dams during gestation was observed. No treatment-related effects on litter size, resorptions or fetal body weight were noted. Increased incidences of developmental anomalies were mentioned only for the high-dose group and included thick atrial wall, thin ventricular wall, hydroureter, hydronephrosis, collapsed cranium, extraossification of supraoccipitals, and malaligned sternebrae.

Peri- and postnatal effects in rats: Groups of 10-20 dams were fed ferbam (76% a.i.) in the diet at dosage levels of 0, 0.015, or 0.15 (0; 7.6mg/kg/day before birth, 23 mg/kg/day after birth; 41 mg/kg/day before birth, 152 mg/kg/day after birth, respectively) from gestation day 16 through postpartum day 21. Another group was fed a restricted diet to evaluate the effects of malnutrition on the growth and viability of pups. Dams in the high-dose and restricted diet groups had reduced body weight gain and food consumption as compared to the controls. The average length of gestation was between 21 and 22 days. Parturition was normal. Pups born from dams on the high-dose diet had reduced viability and lactation indices and reduced body weight as compared to controls. These indices were not affected in the food-restricted group, but body weight was reduced. Normal pups from control dams nursed by dams on the high-dose diet had poor viability and growth. Pups from dams on the high-dose diet but nursed by dams on the control diet had good viability and normal body weight by day 21.

2.4 **Sherman, H. (1966) Three-generation Reproduction Study: Haskell Laboratory Report No. 13-66. Unpublished study received Feb 28, 1966 under 6F0475; submitted by E.I. du Pont de Nemours & Co., Inc., Wilmington, Del.**

MRID 00085454

In a reproduction study, ferbam (77.1% a.i.) was fed in the diet to 16 rats/sex/group at dosage levels of 0 or 0.025% for 3 months. Matings from these groups produced F_{1a} and F_{1b} litters. Sixteen male and 16 female rats were selected from each of the dosage groups from the F_{1b} litters and fed the above diets for 3 months. Matings from the second generation produced F_{2a} and F_{2b} litters and the same procedure was performed to produce F_{3a} and F_{3b} litters. No treatment-related effects were noted on pregnancy rate, number of pups born, number of pups born alive, or fertility, gestation, viability, or lactation indices in any generation. No treatment-related effects on incidences of developmental anomalies were observed in the F_{3b} litters.

3 DISCUSSION OF LITERATURE REVIEW

3.1 Hodge *et al.* (1956) Study - Comparison of ziram and ferbam chronic toxicity in the rat and dog.

The results of the chronic rat study suggest that ziram and ferbam show similar clinical effects in rats at the same doses, but ferbam appears to cause increased mortality at doses where no mortality is seen with ziram. No apparent differences in chronic toxicity occur in dogs.

3.2 Comparison of ziram guideline studies with ferbam literature studies.

In the ziram subchronic rat study (MRID 42450301) submitted to the Agency, the LOAEL was 21.4 mg/kg/day based on decreases in body weight, body weight gain, and food consumption. The NOAEL was 7.4 mg/kg/day. The ziram subchronic neurotoxicity rat study (MRID 43413701) had a LOAEL of 34 mg/kg/day based on reduced body weight and body weight gain with a NOAEL of 14 mg/kg/day. In the Lee *et al* (1978) ferbam subchronic study, decreased body weight gain occurred at 23, 66 and 109 mg/kg/day. Treatment-related mortality was noted at 109 and 331 mg/kg/day. The LOAEL for this study was 23 mg/kg/day and no NOAEL was determined.

In the ziram chronic rat study (MRID 43404201) submitted to the Agency, the LOAEL was 2.5 mg/kg/day based on increased hemosiderosis in the spleen, increased epithelial hyperplasia and subepithelial edema in the non-glandular region of the stomach, increased incidence of narrowed peripheral muscle fiber bundles in skeletal muscle, and increased cortical hypertrophy with vacuolation in the adrenals in males and an increased incidence of prominent ultimobranchial cysts in the thyroid in females. No NOAEL was determined. Body weight gain was decreased at 23.7 mg/kg/day. In the Lee *et al* (1978) ferbam chronic rat study, the LOAEL was 8 mg/kg/day based on decreased body weight gain and food consumption and possibly increased incidence of squamous metaplasia in the thyroid and fatty infiltration in the pancreas. No NOAEL was determined. The paralysis seen in three females in the high-dose group was not observed in the guideline study, but the high dose tested in the literature was much higher than the high dose in the study submitted to the Agency.

In the ziram reproduction rat study (MRID 43935801) submitted to the Agency, the LOAEL for systemic toxicity was 37.5 mg/kg/day based on reduced body weight, body weight gain and decreased food consumption by F_0 and F_1 males and females. The NOAEL was 14.8 mg/kg/day. No effects performance were observed in males or females. The LOAEL for offspring toxicity was 42.8 mg/kg/day ased on reduced pup body weights at birth in F_2 pups and during lactation in both F_1 and F_2 pups. The NOAEL was 16.8 mg/kg/day. In the Short *et al* (1976) ferbam reproduction rat study, mean body weight was reduced at 66 mg/kg/day in males and 51 mg/kg/day in females. The NOAELs for males and females were 23 and 15 mg/kg/day, respectively. No effects on reproductive parameters were noted in either sex. In a separate substudy, pups from

the high-dose dams (41 mg/kg/day) had reduced viability and lactation indices and reduced body weights. Pup growth and viability appeared to be affected *in utero* and during lactation. The NOAEL for this phase of the study was 7.6 mg/kg/day. There was no effect on gestation length or parturition.

In the ziram developmental rat study (MRID 41908701) submitted to the Agency, the LOAEL for maternal toxicity was 16 mg/kg/day bosed on decreased body weight, and food consumption and an increase in salivation. The NOAEL was 4 mg/kg/day. The developmental toxicity LOAEL was 16 mg/kg/day based on diaphragmatic thinning. The NOAEL was 4 mg/kg/day. No other treatment-related external or internal malformations/variations were seen in any fetuses from any group. In the Short *et al* (1976) ferbam reproduction rat study, a separate substudy was performed to look at developmental effects. There was 25% mortality among the dams at 114 mg/kg/day. No mortality was mentioned at 11 mg/kg/day. Maternal body weight change and fetal body weight were reduced at both the high and low dosages. Numbers of implants/dam and fetuses/dam were reduced at the high dose plus the number of resorptions significantly increased. Also, increased incidences of developmental anomalies were mentioned only for the high-dose group and included unossified sternebrae, slightly collapsed cranium, malformed cranium, hydrocephalus, hematoma, and cleft palate.

Comparisons of acute and longer term studies of ziram and ferbam are summarized in Tables 1 and 2, respectively.

Table 1. Acute Toxicity of Ziram and Ferbam

Guideline No.	Study Type	Chemical	MRIDs #	Results	Toxicity Category
81-1	Acute Oral	Ziram Ferbam	41340401 40561501	LD_{50} = 320 mg/kg LD_{50} > 5000 mg/kg	II IV
81-2	Acute Dermal	Ziram Ferbam	41340402 40561502	LD_{50} > 2000 mg/kg LD_{50} > 4000 mg/kg	III III
81-3	Acute Inhalation	Ziram Ferbam	41442001 41508101	LC_{50} = 0.07 mg/L LC_{50} = 0.40 mg/L	II II
81-4	Primary Eye Irritation	Ziram Ferbam	41643001 40561503	Severe eye irritant Slight eye irritant	I III
81-5	Primary Skin Irritation	Ziram Ferbam	41643002 40561505	Not a dermal irritant Not a dermal irritant	IV IV
81-6	Dermal Sensitization	Ziram Ferbam	41643003 40561504	Moderate dermal sensitizer Weak dermal sensitizer	-
81-8	Acute Neurotoxicity	Ziram	44075849	LOAEL = 15 mg/kg (LDT) NOAEL = ND	-

Table 2. Comparison of ziram and ferbam NOAELs/ LOAELs and corresponding endpoints.

STUDY	NOAELs and LOAELs for ziram and ferbam studies (mg/kg/day)					
	ZIRAM (Guideline studies)			FERBAM (Literature studies)		
	NOAEL/LOAEL		ENDPOINT	NOAEL/LOAEL		ENDPOINT
90-Day Rat	7 / 21		Decreased Body Wt.	- / 23		Decreased Body Wt.
SC Neurotox. Rat	14 / 34		Decreased Body Wt.	-		-
1-Year Dog	1.6 / 6.6		Decreased Body Wt.	5 / 25		Convulsions/Death
Chronic Rat	- / 2.5		Abnormal Histopath	- / 8		Decreased Body Wt. Abnormal Histopath
Develop. Rat	Maternal 4 / 16	Develop. 4 / 16	Developmental Diaphragm. Thinning	Maternal - / 11	Develop. - / 11	Developmental Decreased Fetal Body Wt.
Reproduction Rat	Parental 15 / 38	Offspring 17 / 43	Offspring Decreased Body Wt.	Parental 15 / 51	Offspring 8 / 41	Offspring Dec. BW, Viability and Lactation Indices
Develop. Rabbit	Maternal 3 / 8	Develop. 3 / 8	Developmental Reduced Atrium	-	-	-
Develop. Mouse	-	-	-	Maternal 23 / 228	Develop. 23 / 228	Developmental Atrium Effects

Comparison of toxicological effects of ziram and ferbam in the guideline and literature studies submitted to the Agency are summarized in Table 3.

9

Table 3. Comparison of ziram and ferbam toxicological effects.

STUDY	Toxicological Effects	
	ZIRAM	FERBAM
Hodge *et al.* (1956) Chronic Rat	Reduced growth rate, Abnormal hindleg grasping action at highest dose tested	Death, Decreased life-span, Reduced growth rate, Abnormal hindleg grasping action, Cystic lesions in cerebral cortex and cerebellum at highest dose tested (same as ziram)
Hodge *et al.* (1956) Chronic Dog	Convulsions/Death at highest dose tested	Convulsions/Death at highest dose tested (same as ziram)
	ZIRAM (Guideline studies)	FERBAM (Literature studies)
90-Day Rat	Decreased body weight	Decreased body weight at similar doses as ziram
SC Neurotox. Rat	Decreased body weight, Inhibition of plasma cholinesterase occurred at a lower dose	No studies available
1-Year Dog	Decreased body weight	Convulsions/Death occurred at higher doses than ziram LOAEL (See Hodge *et al.* above)
Chronic Rat	Abnormal Histopathology	Lee *et al.* study Decreased body weight (seen at lower doses than in ziram guideline study) Abnormal histopath. - Thyroid effects occurred, but not seen in ziram study See Hodge *et al.* above
Developmental Rat	Develop. - Diaphragm. thinning	Develop. - Decreased fetal body weight. No NOAEL, but LOAEL similar to ziram study. No teratology seen at LOAEL
Reproduction Rat	Offspring - Decreased body weight	Offspring - Decreased body weight and viability/lactation indices at similar doses as in ziram study
Develop. Rabbit	Develop. - Reduced Atrium	No studies available

10

Develop. Mouse	No studies available	Develop. - Atrium/ventricular effects and other teratology only at high dose

3.3 Conclusions

1. Chronic toxicity

   Mortality was noted in the rats fed ferbam, but not seen in rats fed ziram at the same dosage, in the Hodge *et al.* (1956) chronic rat study.
   Body weight effects were observed in the Lee *et al.* (1978) ferbam chronic rat study at lower dosages than seen in the ziram guideline study (MRID 43404201).
   Thyroid effects were observed in the Lee *et al.* (1978) ferbam chronic rat study which were not noted in the ziram guideline study (MRID 43404201) at similar dosages.

2. *Reproductive and Developmental toxicity*

   There is no evidence in the rat of increased fetal or offspring susceptibility to ferbam, that ferbam has a higher developmental toxicity than ziram, or that ferbam produces more severe developmental anomalies than ziram. No studies in the rabbit were available.

3. Neurotoxicity

   The abnormal hindleg grasping action that was observed in the Hodge *et al.* (1956) study and which occurred in both ferbam- and ziram-treated animals had no corresponding central nervous system pathology that was common to both treated groups. There is the possibility this may be due to a peripheral neuropathy.
   Cerebral and cerebellar cystic lesions were seen in the ferbam-treated animals, but not in the ziram-treated animals at the same dosage in the same study.

4 DATA REQUIREMENTS

The Hazard Identification Assessment Review Committee recommends that the following studies be submitted in order to qualify ferbam for reregistration:

Subchronic Neurotoxicity Study - Rat

Due to evidence of possible peripheral neuropathy in the literature and a strong structural activity relationship to ziram which is a known neurotoxicant, plus the presence of cerebral and cerebellar cystic lesions noted in the literature, this study is required

Oral Developmental Toxicity Study - Rat

Due to concerns of fetal malformations seen in mice with ferbam and lack of data on rabbit developmental effects of ferbam, this study is required. Ziram showed developmental effects in the rabbit at slightly lower doses than in the rat.

Chronic Toxicity/ Carcinogenicity Study - Rat

This study is required because:
1. No long-term guideline studies are available for ferbam.
2. Long-term literature studies suggest ferbam may be more toxic chronically than ziram, thus, the database for ferbam is inadequate to assess long-term exposure.
3. The Lee *et al.* (1978) did not adequately evaluate the carcinogenicity of ferbam (e.g. not enough animals per dose group over too short an exposure period).
4. Ziram is classified "likely to be a human carcinogen."

21-Day Dermal Toxicity Study - Rat

This study is required due to the lack of data on dermal toxicity and absorption, which have a potential use in the ORE risk assessment.

Mutagenicity Studies

Due to conflicting data on the mutagenicity of ziram (See HIARC and CARC reports for ziram) and since these studies are a basic requirement with the six acute studies for most chemicals, these studies are required.

Chronic Toxicity Study - Dog

Not required at this time because of comparable toxicity seen with both compounds.

Carcinogenicity Study - Mouse

Not required at this time since the registrant, in requesting the bridging of ziram carcinogenicity studies to ferbam, in fact, agreed to the application of the ziram Q_1* to ferbam.