

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
METIRAM

Chemical Code # 493, DPN # 217
SB 950 # 63

September 12, 1991
Revised: 11/13/06

I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, inadequate study, possible adverse effect indicated.
Chronic toxicity, monkey:	Data gap, inadequate study, possible adverse effect indicated.
Chronic, dog	Data gap, inadequate study, possible adverse effect indicated.
Oncogenicity, rat:	Data gap, inadequate study, no adverse effect indicated.
Oncogenicity, mouse:	Data gap, inadequate study, possible adverse effect indicated.
Reproduction, rat:	Data gap, inadequate studies, no adverse effect indicated.
Teratology, rat:	No data gap, possible adverse effect.
Teratology, rabbit:	No data gap, no adverse effect.
Gene mutation:	No data gap, no adverse effect.
Chromosome effects:	No data gap, possible adverse effect.
DNA damage:	No data gap, possible adverse effect.
Neurotoxicity:	Data gap, inadequate study, possible adverse effect indicated.

All record numbers through 900001 and 217853 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T061113

Prepared by H. Green and S. Morris, 11/13/06.

NOTE: EPA's "Guidance for the Re-registration of Pesticide Products Containing Metiram as the Active Ingredient" was published October 1988.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

217-015 036234, "Metiram Toxicity and Tumorigenicity in Prolonged Dietary Administration to the Rat" (Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, Report # BSF 199/7915 and BSF 199/80391, 5/7/81). Metiram 96.82% purity with 2% ETU added was fed in the diet of 80 rats / sex / group for 111 (females) or 119 (males) weeks at 0, 5, 20, 80, or 320 ppm. A **possible adverse effect** was indicated by skeletal muscle atrophy in both sexes at 320 ppm (NOEL = 80 ppm). The study was unacceptable and not upgradeable because of inadequate histopathology and dose justification (C. Aldous, 11/19/85; S. Morris, 12/9/04).

217-002 006412, Summary of 036234.

217-004 006414, Interim report of 036234.

217-012 036229, Duplicate of 006414.

217-015 036235,
036236, Appendices of 036324.

217-016 036237,
036238, Appendices of 036324.

217-038 114361

114365: These documents contain adequate characterizations of the test material purity and dosing solution stability (S. Morris, 12/9/04).

217-039 114370: This document contains additional histopathology data that are not adequate (S. Morris, 12/9/04).

Note: The possible adverse effect indicated is listed in the rat chronic toxicity data gap status and not the rat oncogenicity data gap status.

CHRONIC TOXICITY, RAT

See Combined, Rat above, the supplemental 13-week study in rats below (doc. # 217-003, rec. # 006413) "Subchronic and Chronic Toxicology Investigations on Metiram: The Lack of a Chronic Response in Rodents," Charles, J.M., Tobia, A., van Ravenzwaay, B. (2000). Toxicological Sciences. 54, 481-492.

CHRONIC TOXICITY, DOG

217-040 114373, "52-Week Oral Toxicity (Feeding) Study with Metiram Premix 95% in the Dog," RCC Project No. 206627, BASF 91/10786; S. J. Corney *et al.*; Research and Consulting Company, Ltd., Itingen, Switzerland; 8/22/91. Groups of 5 beagle dogs/sex were fed dietary mixtures of Metiram (Premix 95%, batch # WF 5103, 88.2 – 93.6% stated purity) at 0, 30, 80,

1000 or 3000 ppm for 52 weeks. Average daily compound intake was 0, 0.98, 2.59, 29.9 or 84.8 mg/kg/day. Treatment-related effects included: diarrhea in males at 80 ppm (1/5, not significant) and both sexes at 1,000 and 3,000 ppm; decreased food intake in females at 1,000 ppm and both sexes at 3,000 ppm; transient decrease in body weight gain in females at 1,000 ppm and both sexes at 3,000 ppm; decreased erythrocyte count and hemoglobin in both sexes at 1,000 and 3,000 ppm; increased reticulocytes in females at 1,000 ppm and both sexes at 3,000 ppm; decreased serum glucose in both sexes at 3,000 ppm; increased serum lipids, cholesterol, phospholipids and triglycerides in males at 1,000 ppm and both sexes at 3,000 ppm; decreased thyroxine in males at 1,000 ppm and both sexes at 3,000 ppm; increased alkaline phosphatase in both sexes at 3,000 ppm; increased total serum protein and altered protein-electrophoretic pattern in males at 3,000 ppm and increased focal hepatic pigment deposition in both sexes at 3,000 ppm. A possible adverse effect was indicated by thyroid effects: decreased thyroxine in males at 1,000 ppm and both sexes at 3,000 ppm; increased thyroid weight in both sexes at 3,000 ppm, enlarged/thickened thyroids in females at 1,000 ppm and both sexes at 3,000 ppm and increased thyroid follicular hyperplasia in both sexes at 1,000 and 3,000 ppm. NOEL = 80 ppm, (2.59 mg/kg/day) based on all treatment-related effects. The study is unacceptable but possibly upgradeable with adequate submission of individual pathology data for animals # 18, 19 and 20 (missing pages 693, 694) (J. Kishiyama and S Morris, 11/24/04).

217-039 114372, "19-Week Oral Toxicity (Feeding) Study with Metiram Premix 95% in the Dog," RCC Project 206594; TR Allen et al.; Research and Consulting Company LTD, Itingen, Switzerland; 9/1/89. Groups of 2 beagles/sex were fed dietary mixtures of Metiram (Premix 95%, purity 84.7%) at concentrations of 0, 100, or 1,600 ppm for 19 weeks. One beagle/sex received 400 (days 1-56), 3,200 (days 57-102) and 6,000 ppm (days 103-130) or 400 (days 1-56), 3,200 (days 57-94) and 6,000 ppm (days 95-130). The collective data for the later 2 beagles/sex were called the 400/3,200/6,000 ppm group. There were treatment-related decreases in food consumption in females at 1,600 and 400/3,200/6,000 ppm and males at 400/3,200/6,000 ppm. There was a treatment-related decrease in body weight gain in females at 400/3,200/6,000 ppm. A possible adverse effect was indicated by enlarged thyroids that showed diffuse follicular hypertrophy and hyperplasia in both sexes at 1,600 and 400/3,200/6,000 ppm and basophil hypertrophy of the pituitary in both sexes at 100, 1,600 and 400/3,200/6,000 ppm (NOEL < 100 ppm). The study was unacceptable and not upgradeable because of inadequate analytical data for the test article and dosing material, not enough animals per treatment group, inadequate rationale for the doses, fluctuating exposure levels and missing parts of pages 94 and 102 (J. Kishiyama and S. Morris, 11/3/04).

CHRONIC TOXICITY, MONKEY

217-006 006416, Rodney J. Sortwell et al., "Metiram (Containing 2.2% Ethylenethiourea) Oral Toxicity Study in Rhesus Monkeys", BSF 267/78263, Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, 1/15/79. Suspensions of metiram of unspecified purity with 2.2% ethylenethiourea were given by oral gavage once a day, seven days a week for 26 weeks to 4 rhesus monkeys / sex / group at 0, 5, 15, or 75 mg/kg/day. One animal / sex / group were allowed to recover for 15 weeks. A possible adverse effect was indicated by treatment-related decreases in serum T3 and T4 levels and thyroid hyperplasia seen in the main treatment and recovery groups in both sexes at 15 and 75 mg/kg/day. The study was unacceptable and not upgradeable because of insufficient numbers of animals and duration of dosing (J. Wong, 4/1/85; S. Morris, 3/6/91).

217-006 006416, Rodney J. Sortwell et al., "Investigation of Thyroid Function by Assessing the Uptake of Radiolabeled Iodine (¹³¹I) Following Repeated Oral Administration of Metiram (Containing 2.2% Ethylenethiourea)", Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, 1/15/79. Suspensions of metiram of unspecified purity with 2.2% ethylenethiourea were given by oral gavage once a day, seven days a week for 27 weeks to 2 rhesus monkeys / sex / group at 0, 5, or 75 mg/kg/day. Radiometric assays were used to measure thyroid functions after iv injections of ¹³¹I on weeks -11, -2, 1, 4, 8, 16, and 27. A possible **adverse effect** was indicated by protein-bound serum iodine being increased at 27 weeks in the high dose group and dose-related, transient decreases in thyroid iodine accumulation followed by increases to above-normal values at the end of the study. The study was unacceptable and not upgradeable because of insufficient numbers of animals and duration of dosing (J. Wong, 4/1/85; S. Morris, 3/6/91).

217-002 006410, Summary of 006416.

217-012 036230, Duplicate of 006416.

Note: The supplemental monkey studies are included here because there is no adequate non-rodent study on file and a possible adverse effect is indicated.

ONCOGENICITY, RAT

See Combined, Rat above.

ONCOGENICITY, MOUSE

217-014 036232, "Metiram Tumorigenicity to Mice in Long Term Dietary Administration (Final Report) Part I", (Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, Report # BSF 198/78265, 6/5/79). Metiram, 96.82% purity, with 2% ETU added was fed in the diet for 88 to 96 weeks to 52 mice / sex / group at 0, 100, 300, and 1000 ppm. A **possible adverse effect** was indicated by a treatment-related increase in benign liver cell tumors in males at 1000 ppm. The study was unacceptable and not upgradeable because of insufficient histopathology, lack of blood data, and no dose level justification (C. Aldous, 11/18/85; S. Morris, 12/9/04).

217-014 036233, Appendices for 036232.

217-007 006417, Duplicate of 036232.

217-008 006418, Duplicate of 036233.

217-038 114361: This document contains adequate characterizations of the test material purity (S. Morris, 12/9/04).

217-041 114376

REPRODUCTION, RAT

217-013 036231, "Effect of Metiram Technical on Reproductive Function of Multiple Generations in the Rat" (Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, Report # 200/80692, 3/18/81). Metiram technical of unstated purity with 2% ETU added was fed in the diet for three generations (2 litters / generation) at nominal concentrations of 0, 5, 40, and 320 ppm. There were 12 male and 24 female rats / parental group. There were no treatment-related effects reported. No adverse effects were indicated. The study is unacceptable and not upgradeable because of inadequate toxicity at the highest dose (C. Aldous, 11/14/85).

217-002 006411, Summary of 036231.

217-005 006415

217-011 036228, Interim F2 generation data for 036231.

217-001 900000

900001, Invalid IBT study.

217-041 114377, Comments about DPR's evaluation of the study.

TERATOLOGY, RAT

****217-011 036227**, Anthony K. Palmer and Rona Simons, "Effect of Metiram Technical on Pregnancy of the Rat" (Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, Report # BSF 302/79616, 8/3/79). Metiram technical, 96.82% purity, with 2% ETU added was administered by gavage to 20 pregnant female rats / dose on gestation days 6 thru 15 at 0, 40, 80, or 160 mg/kg/day. There were no significant treatment-related maternal effects. A **possible adverse effect** was indicted by decreased live litter size at 160 mg/kg/day (NOAEL = 80 mg/kg/day). Initially unacceptable but upgraded with submission of clinical observation data, adequate rationale of dose and characterization of the test material (C. Aldous, 11/13/85; S. Morris, 2/28/91; S. Morris, 11/02/06).

217-038; 114361,

217-038; 114362,

217-038; 114363,

217-038; 114365: These documents contain adequate characterizations of the test material purity and dosing solution stability (S. Morris, 12/8/05).

217-041; 114377: This document contained comments about DPR's evaluation of the study that adequately addressed the lack of clinical observations (none were seen) and dose selection.

TERATOLOGY, RABBIT

**** 217-038 114364**, "Report on the Study of Prenatal Toxicity of Metiram Premix 95% in Rabbits after Oral (Gavage) Administration," Reg. Doc. #BASf 88/0154; J. Hellwig; BASf Aktiengesellschaft, Project No. 38R0034/87017; May 26, 1988. Groups of 15 artificially inseminated female Himalayan (Chbb:HM) outbred rabbits were given Metiram (Premix 95%, 97.9% stated purity, 10 ml/kg 0.5% carboxymethyl cellulose vehicle) by oral gavage at 0, 10, 40 or 120 mg/kg/day during gestation days 7 through 19. Dams were sacrificed on gestation day 29 and the fetuses removed by cesarean section. Dams were given gross pathology exams. Uteri

were weighed and examined for number, type and position of implantation sites. Ovaries were examined for the number of corpora lutea. Fetuses were weighed, sexed, and external, internal organ and skeletal examinations performed. Treatment-related maternal effects included reduced food consumption at 40 and 120 mg/kg/day, decreased body weight gain at 120 mg/kg/day and increased abortion at 40 (2/14) and 120 (8/15) mg/kg/day (maternal NOEL = 10 mg/kg/day). Treatment-related fetal effects included: reduced weight at 120 mg/kg/day (fetal NOEL \geq 40 mg/kg/day). No treatment-related effects were observed on fetal development or the incidence fetal malformations. No adverse effect was indicated. The study is acceptable (J. Kishiyama and S. Morris, 3/9/04).

GENE MUTATION

217-011 036225, "Ames Test for Metiram" (Institute of Pharmacology, University of Mainz, Germany, 8/22/77). Metiram of uncertain purity (DMSO solvent) was used in the Ames reverse mutation assay. *Salmonella typhimurium* strains TA98, TA100, and TA1537 were treated in duplicate with and without activation (S9 fraction from Aroclor-induced male Sprague-Dawley rat liver homogenates) at 0 (no DMSO), 0, 3.1, 10.0, 31.0, 100.0, 310.0, 1000.0, and 2000.0 μ g/plate. There were no compound-related increases in reversion rates. The study is unacceptable and not upgradeable because there were only 3 tester strains (J. Gee, 11/22/85).

** 217-011 036226, "Report on the Study of Metiram (techn.), (ZNT Test Substance No.: 84/28), in the Ames Test" (BASF Aktiengesellschaft, Department Toxicology, Report # 85/020, 2/7/85). Metiram technical with 2.2% ETU added (DMSO solvent) was used in the Ames reverse mutation assay. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were treated at 0, 20, 100, 500, 2500, and 5000 μ g/plate with and without activation (S9 fraction from Aroclor-induced male Fischer 344 rat and B6C3F1 mouse liver homogenates), at 0, 1, 10, 50, 100, 500, and 2500 μ g/plate with activation, and at 0, 1, 10, 50, and 100 μ g/plate without activation. There were no compound-related increases in reversion rates. The study is acceptable (J. Gee, 11/22/85).

217-010 038041, Jagannath et al., "Mouse Host-Mediated Assay of Metiram Tech K38/33A, Final Report", Litton Bionetics, Inc., Kensington, MD., Project # 20988, 06/85. Single oral gavages of metiram (technical K38/33A, unstated purity, 2.2% ETU added, 42.7% cleavable CS₂, suspended in 0.5% CMC) were given to 10 male CD-1 mice / dose at 0, 0.5, 1.67, or 5.0 g/kg. Thirty minutes later ip injections were given of histidine-dependent *Salmonella typhimurium* (TA-1530, Z 2X109 cells / animal). Three hours later the mice were sacrificed and samples of peritoneal fluid were plated to determine either total bacteria recovery (complete medium) or reversion rate to histidine-independent growth (minimal medium). No adverse effect was indicated by the lack of a treatment-related increase in revertant rate. The study is unacceptable and not upgradeable because there was no analysis of dosing material, no demonstration of test-material exposure, insensitivity of the assay, and only one tester strain was used (H. Green and S. Morris 04/03/91).

217-010 038043, H. P. Gelbke and R. Jäckh, "Report on a point mutation test carried out on CHO cells (HGPRT locus) with the test substance metiram (techn. purity)", BASF, Department of Toxicology, Ludwigshafen, Germany, report # 85/238, 07/31/85. The forward mutation rate of the HGPRT locus was analyzed by measuring the cloning efficiency of Chinese Hamster Ovary cells in the presence of thioguanine after exposure to metiram (unstated purity, lot # CH K 38/33 A, 2.2% ETU added, 42.7% cleavable CS₂) with or without metabolic activation (S9 fraction of Aroclor 1254 induced, male, Sprague-Dawley rat liver homogenate) at 0, 0.068, 0.100, 0.464,

0.681, 1.00, 4.64, or 6.81 µg/ml and with activation at 10.0, 46.4, 68.1, or 100 µg/ml. A **possible adverse effect** was indicated by treatment-related increases in 6-thioguanine resistant colonies after exposure with and without metabolic activation. The study was unacceptable because there was no GLP statement and no purity analysis. The study is not upgradeable because there was only 1 functional replicate per treatment level and the treated cells were improperly subcultured before selection (H. Green and S. Morris 04/15/91).

** 217-038 114366, "Report on a point mutation test carried out on CHO cells (HGPRT locus) with the test substance of Metiram Premix 95% with B6C3F1 mice microsomal fraction," Project No. 50M0270/894242; R. Jäckh; BASF Aktiengesellschaft; 8/2/90. The potential of Metiram (Premix 95%, 93% stated purity) to produce mutations at the HGPRT locus of CHO ovary cells was evaluated by measuring the frequency of conversion of wild type cells that are killed by 6-thioguanine (TG) to cells that form colonies in the presence of TG. Cells were seed at 2×10^5 / 25 cm² flask, allowed to attach for 24 hours and then exposed to the test material at 0 (media, 2% DMSO), 0.5, 1.0, 5.0, 10, 50, 100 or 500 µg/ml with (+S9) or without (-S9) microsomal metabolic activation system from Aroclor 1254-induced male B6C3F1 mouse liver homogenates. The cells were subcultured 4 times in 8 days. TG 10 (ug/ml) was added to the medium of the last passage in which 3×10^5 cells were seeded per 80 cm² flask and incubated 7 days. The resulting TG-resistant colonies were fixed stained and counted. The test was done twice. Treatment-related increases in TG-resistant colonies were not seen. No adverse effect was indicated. Controls were adequate. The study was acceptable (J. Kishiyama and S. Morris, 11/4/04).

CHROMOSOME EFFECTS

** **217-010 038042**, JL Ivett and CS Spicer, "Mutagenicity Evaluation of Metiram Technical K38/33A in an *In Vitro* Sister Chromatid Exchange Assay in Chinese Hamster Ovary (CHO) Cells, Final Report", Litton Bionetics, Inc., Kensington, MD., Project # 20990, March 1985. Metiram (technical K38/33A, unstated purity, 2.2% ETU added, 42.7% cleavable CS₂) was tested for sister chromatid exchange (SCE) in Chinese Hamster Ovary cells at 0, 40, 60, 80, or 100 µg/ml without metabolic activation and at 0, 125, 150, 175, or 200 µg/ml with S9 metabolic activation system from Aroclor 1254 induced Fischer 344 rat or B6C3F1 mouse liver homogenates. Adequacy of exposure was demonstrated by treatment-related cytotoxicity. The positive controls were adequate. No increase in SCE was reported with the rat activation system. A **possible adverse effect** was indicated by increased SCE without and with the mouse activation system (H. Green and S. Morris, 04/04/91). The study was upgraded with an adequate statement of purity (S. Morris, 12/9/04).

217-039 114369. This record contains adequate analytical data for the test material (batch K38/33A) used in the study at DPR doc. # 217-010, rec. # 038042 (S. Morris, 12/9/04).

217-026 048606, JL Ivett and H Lebowitz, "Mutagenicity Evaluation of Metiram Technical K38/33A, in the Rat Bone Marrow Cytogenetic Assay, Amended Final Report", Litton Bionetics, Inc., Kensington, MD., Project # 22202, August, 1986. Metiram (technical K38/33A, unstated purity, suspended in 0.5% carboxymethylcellulose) was given by oral gavage to male Fischer 344 rats. Thirty rats / dose were given 0, 0.24, 0.80, or 2.40 g/kg and 10 rats / dose were sacrificed at 6, 24, or 48 hours. Ten rats / dose were given 5 consecutive daily doses of 0, 0.02, 0.10, or 0.20 g/kg and sacrificed 6 hours after the last dose. All rats were given 4 mg/kg colchicine, ip, 3 hours prior to sacrifice and their bone marrow cells were harvested, stained and Z 50 metaphase cells /

rat were microscopically examined for chromosome aberrations. There were no treatment related increases in chromosome aberrations. No adverse was indicated. The study is unacceptable but possibly upgradeable with submission of an adequate analysis of dosing material, clarification of sacrificed time point of positive controls, rationale for dose levels, and justification for using only males (H. Green and S. Morris, 04/19/91; S. Morris, 12/9/04).

217-039 114369. This record contains adequate analytical data for the test material (batch K38/33A) used in the study at DPR doc. # 217-026, rec. # 048606 (S. Morris, 12/9/04).

217-039 114368, "Sister Chromatid Exchange Assay in Bone Marrow Cells of the Chinese Hamster with Metiram Premix 95%," ZST Project No. 11M0270/899012, CCR Project 197100; W. Völkner; Cytotest Cell Research GmbH & Co. KG; September 18, 1990. Groups of 5 Chinese hamsters/sex were fasted for 18 hours then dosed with Metiram (93% stated purity) by single oral gavage (0.5% carboxymethylcellulose suspension, 20 ml/kg) at 0, 1,000, 3,330, or 10,000 mg/kg. Each animal was given 40 mg BrdU sq 2 hours before dosing. Each animal was given 2.0 mg/kg colcemid ip 2.5 hours prior to sacrifice. Animals were sacrificed 24 hours after dosing, femur bone marrow was harvested and marrow cell suspensions were prepared for microscopic examination of chromatin. At least 25 metaphase cells/animal were scored for sister chromatid exchanges (SCEs). No treatment-related effect on SCEs were observed. No adverse effect was indicated. The study was unacceptable but possibly upgradeable with adequate submissions of analysis of test article purity and stability and dosing material content, homogeneity and stability (J. Kishiyama and S. Morris, 9/2/04).

DNA DAMAGE

** 217-011 036224, "Evaluation of Metiram Tech. in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay, Final Report" (Litton Bionetics, Inc., Kensington, MD., Project # 20991, 7/5/84). Metiram Technical of unstated purity with 2.2% ETU added was used in an unscheduled DNA synthesis assay with triplicate, 18-19 hour exposures of adult male Fischer 344 rat hepatocytes at 0, 0.492, 1.23, 2.46, 4.92, 12.3, 24.6, 49.2, and 160 µg/ml. Cytotoxicity was seen at 160 µg/ml. No increase in unscheduled DNA synthesis was reported. The study was acceptable (J. Gee, 11/22/85).

217-010 038040, Alice S. Tu et al., "Evaluation of Metiram in the C3H-10T 1/2 Cell System for Transformation and Promotion Activities", Arthur D. Little, Inc., Cambridge, MA., Report # 54045 (1-5527), 6/18/85. Aqueous suspensions of metiram (unstated purity, 2.2% ETU added, 42.7% cleavable CS₂) were tested on cultured C3H-10T 1/2 mouse embryo fibroblasts. Treatment with 1.0 mg/ml of test material produced 80 to 100% decrease in plating efficiency. Exposure to 0, 0.10, 0.25, 0.50, 0.75, or 1.0 µg/ml (18 to 24 plates / concentration) produced no treatment-related increases in transformed foci. A **possible adverse** effect was indicated by increased numbers of transformed foci when a 24-hour treatment with 0.5 mg/ml MNNG was followed by a continuous exposure to 0.30 µg/ml of test material for approximately 5 weeks. The study is unacceptable and not upgradeable because of lack of trials using metabolic activation (H. Green and S. Morris, 04/01/91; S. Morris, 12/9/04).

217-039 114369. This record contains adequate analytical data for the test material (batch K38/33A) used in the study at DPR doc. # 217-010, rec. # 038040 (S. Morris,

12/9/04).

NEUROTOXICITY

217-054; 217852; “Study of the Oral Toxicity of Metiram Premix 95% in Wistar Rats, Administered in the Diet for 3 Months Including the Examination of Neurotoxicology (‘Neurofunctional Observation Battery’),” Project No. 99CD331/90037; W. Mellert; BASF Aktiengesellschaft, Ludwigshafen/Rhein; 10/16/92. Metiram Premix 95% (batch no. WF 5103, 88.2 - 94.8% purity) was fed in the diets of 13 Wistar rats (Chbb:THOM SPF) per sex per dose for 3 months at 0, 5, 80, 320 or 960 ppm (respective mean daily intake for males, 0, 0.4, 5.8, 23.5 or 73.9 mg/kg/day; for females, 0, 0.4, 6.7, 27.3 or 88.8 mg/kg/day). Clinical signs were observed twice daily. Determinations of food consumption and body weight and gross examinations were done weekly. Eyes of the 0 and 960 ppm animals were examined pre study and at termination. Neurofunctional observations were made on all animals on study days -1, 1, 7, 14 (males), 15 (females), 26 (males), 27 (females), 56 and 90. Hematology and clinical chemistry were determined on blood samples on days 29 and 84 for males and day 85 for females. Urinalysis was performed on days 33 and 89 for males and 87 for females. At termination, 10 animals per sex per dose were sacrificed by decapitation and subjected to gross- and histo- pathological assessment. Three animals per sex per dose were sacrificed by perfusion fixation and the visible organs assessed by gross pathology. Treatment-related decreases in body weight gain in both sexes were seen at 960 ppm. Also noted were by ataxia (**possible adverse effect**) in females (3/13), reduced general state in females (3/13), reduced fore limb grip strength in females, reduced hind limb grip strength in both sexes, decreased red blood cells, creatine, inorganic phosphate, calcium, potassium and magnesium in both sexes, decreased hemoglobin, hematocrit, alanine aminotransferase, alkaline phosphatase and sodium in females, decreased urea in males, decreased serum thyroxine in both sexes, increased absolute thyroid weight in males and increased relative weights of thyroid and liver in both sexes at 960 ppm. Treatment-related effects seen at 320 ppm were: decreased red blood cells in both sexes, decreased hemoglobin and hematocrit in females and decreased inorganic phosphate in males (NOEL = 80 ppm). The study is acceptable (S. Morris and P. Leung, 10/30/06).

SUPPLEMENTAL

217-003 006413, Brian Hunter et al., "Metiram Toxicity to Rats in Dietary Administration for 13 Weeks Followed by a 6 Week Withdrawal Period", BSF/197/77612, Huntington Research Centre, Cambridgeshire, England, 11/16/77. Metiram of unstated purity containing 2.2% ETU was fed in the diets of 35 rats / sex / group at 0, 50, 100, 300, or 900 ppm for 13 weeks followed by a 6 week withdrawal. At the end of week 13, 5 rats / sex / group were injected iv with 131I and 4 and 24 hour total plasma levels and plasma protein binding and total and protein-bound thyroid uptake of 131I were measured. Marginally lower body weights and food intake were seen at 900 ppm. A **possible adverse effect** was indicated by decreased thyroid 131I uptake at 50, 100, 300, 900 ppm; skeletal muscle lesions at 300, 900 ppm; lower serum T4 levels at 300, 900 ppm; and thyroid hyperplasia in males and hind limb paralysis in females at 900 ppm (NOEL < 50 ppm). The study is unacceptable and not upgradeable because of insufficient duration and a NOEL was not demonstrated. No worksheet was done (Morris 3/8/91).

Note: The finding of skeletal muscle lesions (doc. # 217-003, rec. # 006413) is consistent with those seen in the unacceptable combined chronic toxicity/oncogenicity study in rat (doc. # 217-015, rec. # 036234) and the thyroid effects are consistent with those seen in the chronic

toxicity study in monkey (doc. # 217-006, rec. # 006416).

217-039 114371. This record contains a protocol for a 3-month oral feeding study in using rats ("Protocol Study of the Oral Toxicity of Metiram Premix 95% in Wistar Rats," BASF Project No. 99C0331/90037). No worksheet was done (S. Morris, 11/30/04).

217-041 114374. This record contains a protocol for a 3-month oral feeding study using mice ("Protocol Study of the Oral Toxicity of Metiram Premix 95% in B6C3F1 Mice Administered in the Diet for 3 Months," BASF Project No. 99C0331/90036). No worksheet was done (S. Morris, 11/30/04)

217-055 217853. This record contains a preliminary report for a 3-month oral feeding study using mice ("Protocol Study of the Oral Toxicity of Metiram Premix 95% in B6C3F1 Mice Administered in the Diet for 3 Months," BASF Project No. 99C0331/90036). Groups of 10 B6C3F1 mice / sex were fed diets containing Metiram Premix 95% at 0, 300, 1,000, 3,000 or 7,500 ppm for 3 months. Transient decreases in body weight gain were reported for males at 7500 and females at 1,000, 3,000 and 7,500 ppm. No adverse effects were reported. No worksheet was done pending submission of the final report for the study (S. Morris, 11/6/06)

217-001 900000
217-001 900001
217-002 006410
217-002 006411
217-002 006412
217-003 006413
217-004 006414
217-005 006415
217-006 006416
217-007 006417
217-008 006418
217-011 036224
217-011 036225
217-011 036226
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