HED DOC. NO. 014062

DATE: **March 21, 2000**

MEMORANDUM

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

FROM: P. V. Shah, Toxicologist.
Registration Action Branch 1
Health Effects Division (7509C)

THROUGH: Pauline Wagner, Co-Chairman
and
Jess Rowland, Co-Chairman
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Melba Morrow, Branch Senior Scientist
Registration Action Branch 1
Health Effects Division (7509C)

TO: Olga Odiott, Risk Assessor
Registration Action Branch 1
Health Effects Division (7509C)

PC Code: 039003

On November 23, 1999 and December 2, 1999, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of **Metam sodium,** established a Reference Dose (RfD) and selected the toxicological endpoints for acute dietary as well as occupational exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to **Metam sodium** as required by the Food Quality Protection Act (FQPA) of 1996. The Committee's conclusions are presented in this report.
Committee members in attendance were: D. Anderson, W. Burnam, V. Dobozy, P. Hurley, M. Ioannou, T. Levine, S. Markis, N. McCarroll, N. Paquette, K. Raffaele, J. Rowland, P.V. Shah,

B. Tarplee and P. Wagner.

Member in absentia was K. Hamernik.

Data was presented by P. V. Shah of the Registration Action Branch 1.

Also in attendance were: K. Whitby, M. Morrow, O. Odiott, T. Bloem, S. Weiss, M. Christian, and D. Nixon of the HED and R. Pisigan of the EFED.

Data Presentation:
and
Report Presentation

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P. V. Shah
Toxicologist

I. INTRODUCTION

On November 23, 1999 and December 2, 1999, the Health Effects Division (HED) Hazard Identification Assessment Review Committee evaluated the toxicology database of **Metam sodium,** established a Reference Dose (RfD) and selected the toxicological endpoints for acute dietary as well as occupational exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to Metam sodium as required by the Food Quality Protection Act (FQPA) of 1996. The following assessment is based on HIARC's findings.

Metam Sodium (sodium-N-methyldithiocarbamate), also known as Vapam, Metham Sodium, and SMDC is a fumigant-type pesticide used as a non-selective preplant fumigant for control of weeds, nematodes, fungi, bacteria, and insects. There are approximately 35 different products containing metam sodium in concentrations ranging from 18-42% active ingredient. Use patterns for these various formulations include agricultural preplant soil fumigation, wood preservative, slimicide, tree root killer, and aquatic weed control. Approximately 10 million pounds of active ingredient were used in 1990, with 40-45% for agricultural purposes. For control of weeds, soilborne diseases, and nematodes infesting field and vegetable crops, the pesticide is applied at least 14 to 21 days prior to planting. As a slimicide, metam sodium is sprayed inside sewer mains and drain pipes; wood preservative uses involve injection of standing utility poles to control wood-destroying insects and to arrest wood rot.

II. HAZARD IDENTIFICATION

A. Acute Reference Dose (RfD): General Population

Study Selected: None § None

MRID No.: None

Executive Summary: None

Dose and Endpoint for Establishing RfD: Not required

Uncertainty Factor (UF): None

Comments about Study/Endpoint/Uncertainty Factor:

Dietary exposure to metam sodium is considered to be unlikely because (1) metam sodium is highly unstable, degrading quickly to MITC and other products; and (2) it is used agriculturally only as a pre-plant biocide. In addition, there are no established food-use tolerances for metam.

This Risk Assessment **is not required.**

B. Chronic Reference Dose (RfD)

Study Selected: None § None

MRID No.: None

Executive Summary: None

Dose and Endpoint for Establishing RfD: None

Uncertainty Factor(s): None

Comments about Study/Endpoint/Uncertainty Factor:

Dietary exposure to metam sodium is considered to be unlikely because (1) metam sodium is highly unstable, degrading quickly to MITC and other products; and (2) it is used agriculturally only as a pre-plant biocide. In addition, there are no established food-use tolerances for metam.

This risk assessment is not required.

C. Occupational/Residential Exposure

1. Dermal Absorption

Type of Study Proposed: Dermal Absorption Study-Rats **Guideline #:** 85-3

MRID No.: 42670301

Executive Summary:

In a dermal absorption study in Crl:CD (SD) BR rats (MRID 42670301), ^{14}C-Metam sodium was applied to male rats in aqueous formulations at the nominal dose levels of 0.1, 1 and 10 mg/rat to an area of 11.6 cm^2 on the back. The application site was protected by a glass saddle which contained an activated charcoal filter to adsorb any volatile radioactivity which evaporated from the skin surface. Within each group, four animals were killed following a 1, 2, 10 and 24 hours exposure and excreta was collected over the study period. For 4 additional animals in each treatment group, the treatment area was washed 10 hours after administration and excretion monitored over a total of 72 hours. Mean percent dose distribution is summarize as follows:

Dose	Specimen	1 Hr	2 Hr	10 Hr	24 Hr	72 Hr

0.1 mg/rat	Total Unabsorbed Dose$_a$ Treated Skin Total Absorbed Dose$_b$ Total Recovery	92.80 02.66 01.79 92.33	87.61 03.58 02.18 93.37	91.73 07.74 02.36 101.80	71.29 08.42 08.08 78.78	92.95 02.79 02.43 98.17
1.0 mg/rat	Total Unabsorbed Dose$_a$ Treated Skin Total Absorbed Dose$_b$ Total Recovery	82.71 03.62 01.88 88.22	78.22 06.73 03.09 88.08	90.16 04.31 03.68 98.15	76.37 04.11 04.72 85.33	87.65 01.63 03.17 92.45
10.0 mg/rat	Total Unabsorbed Dose$_a$ Treated Skin Total Absorbed Dose$_b$ Total Recovery	64.11 14.88 00.39 79.38	79.34 01.68 05.26 86.35	80.82 01.29 01.51 83.64	80.10 02.39 02.24 84.80	79.07 00.70 03.51 83.39

a. Sum of final application site wash, charcoal, charcoal washings, and sinter washings
b. Sum of urine, feces, cage washings, air traps 1, 2 & 3 and cage debris.

This study is classified as **acceptable/guideline (§85-3)**, and **does satisfy** the guideline requirement for dermal absorption study in the rat.

Percentage (%) Dermal Absorption Proposed for Consideration: Dermal absorption factor of 2.5% was selected based on the dermal absorption study in rats.

2. Short-Term Dermal (1-7 days)

Study Selected: Developmental Toxicity Study in Rats § 83-3

MRID No.: 41577101, 42170101, 92097012

Executive Summary:

In a developmental toxicity study (MRID # 41577101,42170101, 92097012), an aqueous solution of Metam sodium was administered at 0, 10, 40, and 120 mg/kg by gavage to pregnant Wistar rats on days 6-15 of gestation. Maternal toxicity was observed at the 40 and 120 mg/kg levels as significantly decreased body weight gain during the dosing period. The corrected maternal body weight gain was significantly reduced at 120 mg/kg. Although not statistically analyzed, mean maternal feed consumption was reduced during the treatment period. The greatest decrease occurred initially, days 7-8 for the 40 and 120 mg/kg group (-16 and -19% of the control, respectively). The cesarean section data indicate a significant increase in postimplantation loss, and a significant decrease in the percent of live fetuses/dam at the 10 and 120 mg/kg levels. Fetal weights were significantly reduced for male and female fetuses in the 120 mg/kg group. Examination of the viscera of fetuses that underwent skeletal examination revealed a significant increase in variations at the 40 mg/kg level. There were significant increases in the percent fetuses/litter with anomalies, variations, and retardations at the 40 mg/kg level, which were dose-related (except for anomalies). There were significant increases in the percent fetuses/litter with variations and retardations at the 120/mg/kg level which were dose-related. The administration of Metam sodium at high doses [120 mg/kg (HDT in the

main study) and 240 mg/kg (HDT in the range finding study)] resulted in meningocele which was not reported in the historical or concurrent control.

This study cannot be upgraded. The EPA Subdivision F Pesticide Assessment Guidelines (1984) state that one third to one half of each litter should be prepared and examined for skeletal anomalies, and the remaining part of each litter should be prepared and examined for soft tissue anomalies using appropriate methods. The current study evaluated two third's of each litter for skeletal changes and the remaining fetuses were evaluated for soft tissue changes via the Barrow and Taylor technique. Therefore, this study can not be upgraded. Given that the administration of this test substance appears to result in meningocele (in two species - rat and rabbit) it is the opinion of HIARC that examination of two third's of each litter for soft tissue changes as directed in the guidelines would have provided a better assessment of the potential for neural defects. Because of the severity and significance of this effect (meningocele), HIARC used this study for risk assessment. Furthermore, due to the effects observed at the lowest dose tested (10 mg/kg) a NOAEL has not been established. Therefore this study has been classified as supplementary. **The maternal NOAEL is 10 mg/kg/day based on significantly decreased body weight gain during the dosing period observed at 40 mg/kg/day (LOAEL). Developmental Toxicity NOAEL can not be determined.**

This study is classified as **Unacceptable/Guideline** and does not **satisfies** the guideline requirement for a developmental toxicity study (83-3a) in rats. This study can be upgraded if the deficiencies cited in the original DER are met.

Dose and Endpoint for Risk Assessment: Developmental toxicity LOAEL= 4.22 mg/kg/day (actual corrected concentration) is based on decreased in live fetuses.

Comments about Study/Endpoint: This end point is suitable for this short-term risk assessment because the developmental effect (decreased live fetuses) is presumed to occur following single or short exposure. Dermal absorption factor of 2.5 % should be used to convert oral dose to dermal equivalent dose. The MOE of 300 is required (10x for intra- species variability and 10x for inter-species extrapolation and additional 3x for use of a LOAEL)

This risk assessment **is required.**

3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: 90- Day Oral Toxicity Study in Dogs § 82-1

MRID No.: 42600001
Executive Summary:

In a 90-Day subchronic toxicity study in beagle dogs (MRID 42600001), metam sodium was administered by gelatin capsule to male and female dogs at nominal dose levels of 0, 1, 5, and 10 mg/kg/day once daily for 13 weeks. Toxic effects were observed at all dose

levels tested, but were primarily evident at the 5 and 10 mg/kg/day dose levels. These effects included decreased body weight and body weight gain in male and female dogs at 10 mg/kg/day, hematologic alterations (increased cell volume, cell hemoglobin, neutrophils, and monocytes; decreased MCHC) at 5 and 10 mg/kg/day, significant increases in plasma ALT, AST, ALK PHOS, and GGT at 5 and 10 mg/kg/day (including significantly increased ALT in female dogs at 1 mg/kg/day), increased amounts of blood, urobilinogen, bilirubin, and protein in urine at 5 and 10 mg/kg/day, and microscopic evidence of hepatitis at 5 and 10 mg/kg/day. A majority of the toxic effects observed in this study appeared dose- and time- related in treated dogs. No evidence of tumors was found in this study.

Based upon the results of this study, the systemic NOAEL and LOAEL are < 1 mg/kg/day. The systemic LOAEL of # 1 mg/kg/day for female dogs is based upon the increase in plasma ALT observed in female dogs at 1 mg/kg/day and the biliary duct proliferation with inflammatory cell infiltration observed in female dogs at the 1 mg/kg/day dose level. For male dogs, the systemic NOAEL is = 1 mg/kg/day and the systemic LOAEL = 5 mg/kg/day, based upon statistically significant increases in plasma ALT, AST, and alkaline phosphatase, as well as the increased incidence of hepatitis and bile duct proliferation.

The Health Effects Division- RfD/Peer Review Committee met on December 1, 1994 to discuss and evaluate the toxicological database and to assess a Reference Dose (RfD) for the metam sodium. According to the data evaluation record, the NOAEL/LOAEL in the chronic toxicity study in dogs were set at 0.1 and 1.0 mg/kg/day, respectively, for females. The Committee questioned the biological significance of marginal increase in serum alanine aminotransferase (ALT or SGPT) observed in females of the 1 mg/kg/day group especially in the absence of statistical significance and/or histopathological alteration. Therefore, the Committee recommended revising the NOAEL for females from 0.1 mg/kg/day to 1.0 mg/kg/day. It should be noted that, in the subchronic toxicity study in dogs (82-1b, MRID No. 42600001), toxic effects were observed at all dose levels of 1, 5, and 10 mg/kg/day, but were primarily evident at the 5 and 10 mg/kg/day dose levels. These toxic effects included decreased body weight and body weight gain in males and females at 10 mg/kg/day, hematologic alterations (increased cell volume, cell hemoglobin, neutrophils, and monocytes and decreased mean corpuscular hemoglobin concentration) at 5 and 10 mg/kg/day, significant decrease in plasma ALT, AST, ALP and GGT at 5 and 10 mg/kg/day (including significantly increased ALT in females at 1 mg/kg/day) , increased amounts of blood, urobilinogen, bilirubin, and protein in urine at 5 and 10 mg/kg/day, and microscopic evidence of hepatitis at 5 and 10 mg/kg/day. On November 23, 1999 and December 2, 1999, the HIARC recommended that the NOAEL for 90-Day subchronic toxicity study should be **set at 1.0 mg/kg/day** and DER should be revised.

This study is classified as **Acceptable/Guideline** and does **satisfies** the guideline requirement for a subchronic toxicity study (82-1) in dogs.

Dose/Endpoint for Risk Assessment: NOAEL of **1.0 mg/kg/day** was based on effects on

clinical parameters and liver effects.

Comments about Study/Endpoint: This end point is suitable for intermediate dermal risk assessment because the study duration is similar to exposure duration of concern. Use dermal absorption factor of 2.5% to convert oral dose to dermal equivalent dose.

This risk assessment **is required.**

4. Long-Term Dermal (Several Months to Life-Time)

Study Selected: None § None

MRID No.: None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not applicable

Comments about Study/Endpoint:. The current use pattern does not indicate long term dermal exposure (single preplant application) .

This risk assessment **is not required.**

5. Inhalation Exposure (Any Time period)

Study Selected: 90-Day inhalation Study-Rat (with MITC) Guideline #: 82-4

MRID No.: 41221407

Executive Summary:

In a subchronic inhalation study in Wistar rats (MRID 41221407), 3 groups of 10 rats/sex/dose received a nose-only inhalation exposure to MITC at 3.16, 30.67 and 137.13 Fg/L 4 hours/day, 5 days/week over a 12 to 13 week period. The Extrapolated doses from four hours exposure duration to six hours were 2.1, 20.6 and 91.9 Fg/L, respectively. There were two control groups of 10 rats/sex/dose, one maintained in the laboratory without inhalation exposure and the other in the chamber without exposure to MITC.

By extrapolation from a four to six hour exposure (82-4 Guideline Data Recommendation for 6 hour exposure) the **NOAEL and LOAEL levels are 2.1 (low dose) and 20.6 Fg/L (mid dose)**, respectively. Effects reported at the mid dose were decreased body weight, food efficiency and blood protein values accompanied by increased water intake. At the high dose (91.9 Fg/L) the animals exhibited apathy, salivation, nasal discharge and stimulated vocalization. These animals exhibited a decrease in body weight, food intake and food efficiency, accompanied by an increase in water intake. Alterations in clinical

chemistry values at this dose include decreased total protein with increased alkaline phosphatase and alanine aminotransferase values.

This study is classified as **Acceptable/Guideline** and does **satisfies** the guideline requirement for a subchronic inhalation toxicity study (82-4) in rats.

Dose and Endpoint Proposed for Consideration: In this study, the LOAEL of 20.6 Fg/L (mid dose) is based on decreased body weight, food efficiency and blood protein values accompanied by increased water intake. The NOAEL was 2.1 Fg/L.

Comments about Study/Endpoint: This route specific study is suitable for this risk assessment. Metam sodium is expected to be converted to methyl isothiocyanate (MITC) upon contact with soil moisture. The occupational/residential exposure to MITC is likely to occur via inhalation route. Therefore, this study and the end-points are appropriate for this (inhalation) risk assessment. A 100 fold safety factor for extrapolation to humans (10 x for inter-species extrapolation and 10x for intra-species variability) is recommended. The current use pattern (pre-plant biocide, single application) does not indicate long term exposure to MITC.

Risk Assessment for Short and Intermediate -Term Inhalation Exposure is Required

D. Recommendation for Aggregate Exposure Risk Assessments

Acute and chronic aggregate risk assessments are not required since neither dietary nor non- dietary exposures are anticipated. Short and intermediate term dermal and inhalation pathways can not be combined for aggregate risk assessment due to different toxicity endpoints via the dermal (hepatotoxicity) and inhalation (hematopoietic toxicity) routes. Additionally, the Aggregate Risk Index (ARI) should be used since different MOE's are required for short-term dermal (300), intermediate-term dermal (100) and inhalation (100) exposures.

E. Margins of Exposures for Occupational/Residential Exposure Risk Assessments

A MOE of 300 is required for short term dermal Occupational Exposure. A MOE of 100 is adequate for intermediate dermal Occupational Exposure. For short and intermediate term inhalation Occupational Exposure, an MOE of 100 is adequate.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

A. Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No. 43275802

Executive Summary: In a two year combined chronic toxicity/carcinogenicity study (MRID # 43275802), Metam Sodium technical (43.14% a.i.) was administered in drinking water to groups of 64 male and female Hsd/Ola: Wistar Tox strain of rats/dose for either 52 weeks or 104 weeks at dose levels of 0, 0.019, 0.056,. and 0.19 mg/ml (**1.3 mg/kg, 3.9 mg/kg,** and **12.0 mg/kg** for male rats; **2.3 mg/kg, 6.2 mg/kg,** and **16.2 mg/kg** for female rats).

At 0.19 mg/ml, male and female rats showed decreased group mean body weight gain for weeks 1-13 (12% decrease in males, 16% decrease in females) and weeks 1-105 (18% for males, 20% for females). Decreased food consumption, food efficiency, and water consumption were significantly affected at the 0.19 mg/ml dose in both sexes. Effects on hematology (decreased red blood cells, hemoglobin, hematocrit) and clinical chemistry (decreased cholesterol and triglycerides) were also observed in both sexes at the 0.19 mg/ml dose level. Increased number of liver masses and increased incidence of fat vacuolation of the liver were observed in male rats at the 0.19 mg/ml dose, as was increased incidence of wasting of voluntary muscle. Microscopic abnormalities of the nasal cavity (increased incidence of rhinitis, hypertrophy of Bowman's ducts/glands, atrophy and adenitis of Steno's gland, and olfactory epithelium hyperplasia and degeneration), heart and aorta (decreased mineralization), voluntary muscle (increased severity of degenerative myopathy), and sciatic nerve (increased severity of degeneration) were observed in male and/or female rats at the 0.19 mg/ml dose level. **The LOAEL of 0.19 mg/ml is based on the changes in body weight gain, food efficiency, hematologic and clinical chemistry alterations, and macro- and microscopic abnormalities observed at this dose in both sexes. The NOAEL in 0.056 mg/ml.**

According to Cancer Peer Review document (dated March 1, 1995), male rat blood tumor rates were analyzed by the Science Analysis Branch (SAB) of the Health effects Division (HED). There were no statistically significant trends in tumor rates of male rats. However, there was a significant pair-wise comparison in the incidence of hemangiosarcoma in male rats at the low and mid dose levels in comparison to controls, but not at the high dose level tested. Tumor latency was similar between the low dose and mid dose groups. The HIARC agreed to the Cancer Peer Review Committee's decision.

Dosing was considered adequate in male and female rats based upon the decrease in body weight gain, food efficiency, changes in hematology and clinical. chemistry, and microscopic pathology observed at the 0.19 mg/ml dose level.

This study is classified as **acceptable/guideline** and **satisfies** the guideline requirements for §83-5, Combined Chronic Toxicity and Carcinogenicity Study in Rats.

Discussion of Tumor Data According to Cancer Peer Review document (dated March 1, 1995), male rat blood tumor rates were analyzed by the Science Analysis Branch (SAB) of the Health effects Division (HED). There were no statistically significant trends in tumor rates of male rats. However, there was a significant pair-wise comparison in the incidence of hemangiosarcoma in male rats at the low and mid dose levels in comparison to controls, but not at the high dose level tested. Tumor latency was similar between the low dose and mid dose groups.

Adequacy of the Dose Levels Tested Dosing was considered adequate in male and female rats based upon the decrease in body weight gain, food efficiency, changes in hematology and clinical. chemistry, and microscopic pathology observed at the 0.19 mg/ml dose level.

B. Carcinogenicity Study in Mice

MRID No. 43233501

Executive Summary

In a two year carcinogenicity study in mice (MRID # 432335-01), Metam sodium technical (43.15% a.i.) was administered in the drinking water to groups of 55 male and 55 female C57BL/l0JfCD-1/Alpk mice per dose for 104 weeks at nominal dose levels of 0, 0.019, 0.074, and 0.23 mg/ml **(0.047 mg/kg, 0.47 mg/kg, and 1.44 mg/kg** for male mice and **0.06 mg/kg, 0.59 mg/kg, and 1.87 mg/kg** for female mice).

At 0.074 and 0.23 mg/ml, dose-related and statistically significant increases in absolute liver weight were observed in male and female mice (111% and 119% of control at 0.074 mg/ml; 135% and 122% of control at 0.23 mg/ml). At 0.23 mg/ml, decreased body weight gain in male mice (14% for weeks 1-13, 20% for weeks 1-104) was observed. Increases in the incidence of macroscopic pathology were observed in the liver (accentuated lobular pattern, pale appearance) and urinary bladder (wall thickening) were also observed. Non-neoplastic microscopic pathology in male and female mice was increased at 0.23 mg/ml, and included increases in extramedullary hemopoiesis of the spleen and several alterations in the urinary bladder, including epithelial hyperplasia, eosinophilic/hyaline cytoplasmic inclusions, increased submucosal connective tissue, and submucosal hyalinization. Fat vacuolation in the liver was also observed in both sexes at this dose. **The LOAEL of 0.074 mg/ml is based upon the significant increase in liver weight in male and female mice. The NOAEL is 0.019 mg/ml.**

Carcinogenic potential was evidenced in this study by an increase in the incidence of angiosarcoma of the liver, spleen, and subcutaneous tissue, as well as the presence of a transitional cell papilloma in a single high dose male, and a transitional cell carcinoma in a single high dose female.
Dosing was considered adequate in male mice based upon the decrease in body weight gain, increase in liver weight with accompanying pathology, increased incidence of

non-neoplastic urinary bladder pathology, and increase in angiosarcoma incidence observed at the 0.23 mg/ml dose level. Dosing was considered adequate in female mice based on the increased incidence of non-neoplastic urinary bladder pathology and angiosarcoma at the 0.23 mg/ml dose level.

This study is classified as **acceptable/guideline** and **satisfies** the guideline requirements for §83-2, Carcinogenicity Study in Mice.

Discussion of Tumor Data Carcinogenic potential was evidenced in this study by an increase in the incidence of angiosarcoma of the liver, spleen, and subcutaneous tissue, as well as the presence of a transitional cell papilloma in a single high dose male, and a transitional cell carcinoma in a single high dose female.

Adequacy of the Dose Levels Tested Dosing was considered adequate in male mice based upon the decrease in body weight gain, increase in liver weight with accompanying pathology, increased incidence of non-neoplastic urinary bladder pathology, and increase in angiosarcoma incidence observed at the 0.23 mg/ml dose level. Dosing was considered adequate in female mice based on the increased incidence of non-neoplastic urinary bladder pathology and angiosarcoma at the 0.23 mg/ml dose level.

C. Classification of Carcinogenic Potential

The Health Effects Division Carcinogenicity Peer Review committee (CPRC) met on March 01, 1995 to discuss and evaluate the weight -of-the-evidence on metam sodium with particular reference to its carcinogenic potential. The CPRC concluded that metam sodium should be classified as a Group B2 - probable human carcinogen, based on statistically significant increases in malignant angiosarcomas in both sexes of the CD-1 mouse, supported by a similar tumor type (malignant hemangiosarcomas) in male Wistar rats. The CPRC recommended that for the purpose of risk characterization, a low dose extrapolation model be applied to the animal data for the quantification of human risk (Q,*) , based on the total incidence of angiosarcomas in male mice, at all sites combined.

IV. MUTATGENICITY

Metam sodium was tested in the unscheduled DNA synthesis using primary rat hepatocytes at concentrations of 0.5, 1.0, 2.5, 5.0, 10.0, 50.0, 100.0, and 250.0 nl/ml. Results of this study showed that metam sodium caused no significant changes in nuclear labeling of primary rat hepatocytes at the concentrations tested (MRID No. 40305601).

Metam sodium was tested in the Rec-Assay with Bacillus subtilis strains H17 and M45 in the absence and presence of metabolic activation (rat liver S-9) at doses upto 150.0 Fl/plate. Metam sodium failed to induce differential toxicity in Bacillus subtilis strains H17 and M45 at the concentrations tested (MRID No. 40305602).

Metam sodium was non-mutagenic in the Ames Assay using Salmonella typhimurium

strains TA92, TA98, TA100, TA1535, TA1537, and TA1538 in the absence or presence of metabolic activation (rat liver S-9) at doses up to 2500 Fg/plate (MRID No. 40305603).

Metam sodium did not induce chromosomal aberration in the In Vitro cytogenic assay using human lymphocytes in the presence or absence of metabolic activation at doses up to 20 Fg/ml (MRID No. 40305604).

Metam Sodium was tested for clastogenicity in Chinese hamsters after single oral doses of 150, 300, and 600 mg/kg. Five animals per sex were sacrificed at 6, 24, and 48 hours post- dose for examination of bone marrow cells. At the dose levels tested, metam sodium was not positive for clastogenicity in Chinese hamster bone marrow (MRID No. 40305605).

V. FQPA CONSIDERATIONS

A. Neurotoxicity :

Acute Neurotoxicity: (MRID No. 42977801, 42977802)

In an acute neurotoxicity study in rats (MRID 42977801, 42977802), first a range-finding study was conducted with metam sodium to determine dose levels for the definitive acute neurotoxicity study and to estimate time of peak effect of dose administration within 8 hours of dosing in rats. Groups of 2 male and 2 female Sprague-Dawley rats received single oral doses of 150, 300, 600, 800, 1250, and 1500 mg/kg metam sodium (43.15% a.i.), while single male and female rats received single oral doses of 2000 mg/kg. Based on the results of this study, a definitive acute neurotoxicity study was conducted using dose levels of 50 mg/kg, 750 mg/kg (12 rats/sex/dose), and 1500 mg/kg (16 rats/sex/dose). Based on percent active ingredient (43.15%), **actual doses** were **0, 22, 324, and 647 mg/kg.** Viability, clinical signs, body weights, functional observational battery, and motor activity evaluations were performed.

Mortality was observed at the 1500 mg/kg (647 mg/kg actual dose) dose level, where a total of 5 males and 3 females were found dead during the course of the study. Signs of systemic toxicity were observed at the 750 and 1500 mg/kg dose levels, and included alterations in posture and palpebral closure, increased lacrimation and salivation, alterations in respiratory rate, decreased arousal, decreased rearing activity, increased time to first step, lack of approach, olfactory, and pupil responses, absent or reduced tail pinch response, reduced hindlimb strength, and decreased body temperature and body weight. Reductions in mean ambulatory and total motor activity were observed at the 50 mg/kg dose level and above. Inhibition of plasma and red cell cholinesterase was observed at the 1500 mg/kg dose level in male and female rats 24 hours post-dose. **The LOAEL of 22 mg/kg is based on reduced ambulatory and total motor activity observed in male and female rats. The NOAEL is < 22 mg/kg and was not achieved in this study.**

This study is classified **Acceptable/Guideline** and **satisfies** the guideline requirement (§ 81-8) for an acute neurotoxicity study in rats.

Subchronic Neurotoxicity:

In a subchronic neurotoxicity study in male and female Alpk:APfSD (Wistar derived) SPF rats (MRID 42117302), groups 12 males and females received Metam Sodium doses of 0, 0.02, 0.06, and 0.2 mg/ml administered in drinking water for 13 weeks (doses in mg/kg: **1.4, 5.0,** and **12.8 mg/kg** for males; **2.3, 7.0,** and **15.5 mg/kg** for females). Body weight, food consumption, clinical signs, and water consumption were monitored throughout the study. A functional observational battery (including landing foot splay, sensory perception, fore- and hindlimb grip strength) as well as motor activity and histopathology of the nervous system was also performed.

Effects in this study were limited to decreases in body weight for male and female rats at the 0.2 mg/ml dose level (decreases of 7-9% from control), body weight gain (decrease of 14% for males at the 0.2 mg/ml dose level and females at the 0.06 mg/ml dose level; decrease of 18-21% for females at the 0.2 mg/ml dose level), food consumption (decreases similar to body weight), food efficiency (5-7% decrease in males and females at 0.2 mg/ml), and water consumption (decreased at all doses in a dose-related fashion; up to 60% decreased at the 0.2 mg/ml dose). There appeared to be a mild effect at the 0.2 mg/ml dose level on time to tail flick in male rats, but this was not labeled as statistically significant. There were no other significant findings to report from the conduct of the Functional Observational Battery.

Based on the data in this study, the **systemic LOAEL = 0.2 mg/ml** for male rats and **0.06 mg/ml** for female rats (decreased body weight gain), and the **systemic NOAEL = 0.06 mg/ml** for male rats, and **0.02 mg/ml** for female rats. There was no evidence of a neurotoxic effect for metam sodium in this study.

This study is classified as **Unacceptable/guideline** and does **not** satisfy the guideline requirement (§82-1) for a subchronic neurotoxicity study in rats. This study can be upgraded if the deficiencies cited in the DER are met.

B. Developmental Toxicity

Developmental Toxicity Study in Rats: (MRID No. 41577101, 42170101, 92097012)

In a developmental toxicity study (MRID # 41577101,42170101, 92097012), an aqueous solution of Metam sodium was administered at 0, 10, 40, and 120 mg/kg by gavage to pregnant Wistar rats (25 rats/dose) on days 6-15 of gestation. Maternal toxicity was observed at the 40 and 120 mg/kg levels as significantly decreased body weight gain during the dosing period. The corrected maternal body weight gain was significantly reduced at 120 mg/kg. Although not statistically analyzed, mean maternal feed consumption was reduced during the treatment period. The greatest decrease occurred

initially, days 7-8 for the 40 and 120 mg/kg group (-16 and -19% of the control, respectively). The Cesarean section data indicate a significant increase in postimplantation loss, and a significant decrease in the percent of live fetuses/dam at the 10 and 120 mg/kg levels. Fetal weights were significantly reduced for male and female fetuses in the 120 mg/kg group. Examination of the viscera of fetuses that underwent skeletal examination revealed a significant increase in variations at the 40 mg/kg level. There were significant increases in the percent fetuses/litter with anomalies, variations, and retardations at the 40 mg/kg level, which were dose-related (except for anomalies). There were significant increases in the percent fetuses/litter with variations and retardations at the 120/mg/kg level which were dose-related. The administration of Metam sodium at high doses [120 mg/kg (HDT in the main study) and 240 mg/kg (HDT in the range finding study)] resulted in meningocele which was not reported in the historical or concurrent control.

This study cannot be upgraded. The EPA Subdivision F Pesticide Assessment Guidelines (1984) state that one third to one half of each litter should be prepared and examined for skeletal anomalies, and the remaining part of each litter should be prepared and examined for soft tissue anomalies using appropriate methods. The current study evaluated two thirds of each litter for skeletal changes and the remaining fetuses were evaluated for soft tissue changes via the Barrow and Taylor technique. Therefore, this study can not be upgraded. Given that the administration of this test substance appears to result in meningocele (in two species - rat and rabbit) it is the opinion of HIARC that examination of two thirds of each litter for soft tissue changes as directed in the guidelines would have provided a better assessment of the potential for neural defects. Because of the severity and significance of this effect (meningocele), HIARC used this study for risk assessment. Furthermore, due to the effects observed at the lowest dose tested (10 mg/kg) a NOAEL has not been established. Therefore this study has been classified as supplementary. **The maternal NOAEL is 10 mg/kg/day based on significantly decreased body weight gain during the dosing period observed at 40 mg/kg/day (LOAEL). Developmental Toxicity NOAEL can not be determined.**

This study is classified as **Unacceptable/Guideline** and does not **satisfy** the guideline requirement for a developmental toxicity study (83-3a) in rats. This study can be upgraded if the deficiencies cited in the original DER are met.

Developmental Toxicity Study in Rats: (MRID No. 42983701)

In a developmental toxicity (teratology) study in Wistar rats (42983701), from the Barriered Animal Breeding Unit, Biological Services Section, Zeneca Central Toxicology Laboratory, Cheshire, UK received either 0. 5, 20, or 60 mg metam sodium/kg/day (24 rats/dose) by oral gavage on gestation days 6 through 17 inclusive. Insemination was by natural means. Test compound (43% w/w active ingredient in aqueous solution, 525.54 g/l, batch no. BAS/005/OON) was adjusted for the above doses.

Maternal toxicity was noted at the 20 and 60 mg/kg/day dose levels in the form of

decreased body weight gain during the period of treatment, and a decrease in food efficiency during test article administration. The decrease in food efficiency supports a test article related effect during the period of dosing. **Therefore, the Maternal Toxicity NOAEL = 5 mg/kg/day, and the Maternal Toxicity LOAEL = 20 mg/kg/day based on reduced body weight gain and decreased food efficiency.**

Developmental toxicity was suggested at the 20 and 60 mg/kg/day dose levels in the form of an increase in total resorptions and resorptions/dam at the 60 mg/kg/day dose level, and a significant decrease in mean fetal weight at the 20 and 60 mg/kg/day dose levels. Developmental toxicity was also suggested at the 20 and 60 mg/kg/day dose levels in the form of a significant increase in the fetal and litter incidence of unossified centrum of the 4th. 5th, and 6th cervical vertebrae, an increase in the litter incidence of unossified 5th sternebrae at the 60 mg/kg/day dose level. a significant increase in the fetal incidence of unossified odontoid, centrum of the 2nd cervical vertebrum, ventral tubercle, and calcaneum at the 20 and 60 mg/kg/day dose levels. In addition, litter incidence of unossified odontoid, unossified centrum of the 2nd cervical vertebrum, and unossified ventral tubercle were also significantly increased over control at the 60 mg/kg/day dose level. **Therefore, the Developmental Toxicity NOAEL = 5 mg/kg/day and the Developmental Toxicity LOAEL = 20 mg/kg/day based on the increased incidence of skeletal observations and the increase in total resorptions and resorptions/dam.**

This study is classified as **Acceptable/ Guideline** and **satisfies** the Guideline Requirement (§ 83-3a) for a developmental toxicity (teratology) study in rats.

Developmental Toxicity Study in Rabbits: (MRID No. 40330901, 92097013)

In a developmental toxicity study in rabbits (MRID 40330901, 92097013), Metam Sodium Dose Levels were tested at the dose levels of 10, 30, and 100 mg/kg (15 rabbits/dose) by gavage from gestation days 6 through 18 with a 42.2% aqueous solution of metam sodium in Himalayan rabbits. **The Maternal NOAEL is 10 mg/kg/day and Maternal LOAEL is 30 mg/kg/day.**

Maternal Toxicity consisted of reduced body weight gains, reduced food consumption, increased number of dead implantations and reduced numbers of fetuses, and increased post- implantation loss in either mid or high dose group or both.

Developmental Toxicity was apparent in the mid and high dose in the form of increased number of dead implantations and reduced numbers of fetuses, and increased post-implantation loss; however the **Developmental Toxicity NOAEL and LOAEL cannot be determined** with available data; additional information in required.

This study is classified **Unacceptable/Guideline** does **not satisfy** the guideline requirements (83-3) for a teratology study in rabbits. Additional data are required; if those data are supplied and found acceptable to the Agency the study may be upgraded.

Developmental Toxicity Study in Rabbits: (MRID No. 42963101)

In a developmental toxicity (teratology) study (MRID 42963101), rabbits of the New Zealand White strain from Interfauna UK Limited Huntingdon, Cambridgeshire, UK, received either 0, 5. 20, or 60 mg metam sodium/kg/day (20 rabbits/dose) by oral gavage from gestation day 8 through 20, inclusive. The animals were received time-pregnant from the vendor. The test compound 43.14% w/w active ingredient concentration in liquid form (525.54 g/L, Batch 90/2, Y06930/007/001 and YA6930/008) was adjusted for the above doses.

Maternal toxicity was noted in the mid and high dose group in the form of increase incidence of few feces and red/orange staining on the cage tray in the 60 mg metam sodium/kg/day group compared with the control group, a treatment related decrease in body weight gain in the mid and high dose groups during the dosing period with a rebound in the high dose group following dosing. The corrected body weight gains were also decreased during the dosing plus post dosing period and entire gestation period (not including gestation days 0-4) which support this observation (decrease in body weight gain seen at mid and high dose levels). Food consumption was reduced in the mid and high dose groups during the dosing period with a rebound in food consumption to control levels in the high dose group following dosing. Food efficiency was reduced during the dosing period, post dosing period and entire gestation period (minus gd 0-4). and for the corrected body weight periods for the mid and high dose groups. This is evidence of toxicity and supports the body weight gain findings. Therefore the **Maternal Toxicity NOAEL = 5 mg/kg/day, and the Maternal Toxicity LOAEL =20 mg/kg/day based on the reduced body weight gain, reduced food consumption and food efficiency.**

Developmental toxicity was noted in the high dose groups in the form of increased resorptions including total litter resorptions, a decrease. in the number of live fetuses and mean litter size, and an increase in post-implantation loss. There was also a decrease in mean fetal body weight noted in the high dose group. Developmental toxicity was noted in the mid dose group in the form of increased incidence of sutural bones between the parietals, misshapen hyoid, partially ossified transverse process of the cervical vertebrae, and 27 presacral vertebrae. There was an increased incidence in the high dose group in the 27 presacral vertebrae and 7 sternebrae (usually only 6 present). Therefore. the **Developmental Toxicity NOAEL = 5 mg/kg/day and the Developmental Toxicity LOAEL = 20 mg/kg/day** based on the increased incidence of skeletal observations.

The study is classified as **Acceptable/Guideline** and **satisfies** the Guideline Requirement (§ 83-3 b) for a developmental toxicity (teratology) study in rabbits.

The above findings were in general, similar to what was seen in the previous study conducted with metam-sodium. (MRID# 403309-01, *Report* on *the Study of the Prenatal Toxicity of Metam-Sodium (aqueous solution* in *rabbits after Oral Administration (gavage),* BASF Aktiengesellschaft for BASF CORPORATION CHEMICALS DIVISION, Project No. 38RO232/8579, July 15, 1987).

C. Reproductive Toxicity

In a multigeneration reproduction study, male and female Alpk:APfSD rats (30 / sex/dose), obtained from the Specific Pathogen Free (SPF) colony at the Barriered Animal Breeding Unit at Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, UK received the following doses of metam sodium in drinking water: at the 0.01 mg/ml dose level, **1.2 mg/kg/day** (males) and **1.8 mg/kg/day** (females); at the 0.03 mg/ml dose level, **3.2 mg/kg/day** (males) and **3.9 mg/kg/day** (females); at the 0.1 mg/ml dose level, **11.5 mg/kg/day** (males), and **13.5 mg/kg/day** (females). Test drinking water was administered continuously throughout the study. After the first 10 weeks, animals were mated on a one-to-one ratio. At 21 days of age, pups from the F_0 generation were selected as parents for the F_1 generation (30/sex/group).

Systemic toxicity was observed at the 0.1 mg/ml dose level in adult female rats of the F_0 and F_1 generations. This toxicity consisted of Bowman's gland duct hypertrophy with loss of alveolar cells, degeneration/disorganization and/or atrophy of the olfactory epithelium, and dilatation of the Bowman's gland ducts. The change in Bowman's glands was accompanied in all affected animals by degeneration, disorganization, and/or atrophy of the olfactory epithelium. In pups, findings were limited and observed mainly at the high dose. These consisted of a decrease in mean pup weight of 14% vs control on day 22 for the F_1 parents, a 16% decrease in body weight gain for male and female pups in the F_2 litter at the high dose, and decreases of 8-9% in testes and epididymis weights for male pups in the F_{1a} and F_{2a} litters at the high dose. **The NOAEL for systemic toxicity is 0.03 mg/ml (3.2 mg/kg/day** (males) and **3.9 mg/kg/day** (females) **) and the systemic LOAEL is 0.1 mg/ml (11.5 mg/kg/day** (males), and **13.5 mg/kg/day** (females) **).**

There were no apparent effects of metam sodium on reproductive performance in the F_0 or F_1 generations in this study. **The NOAEL for reproductive toxicity is 0.1 mg/ml and the LOAEL for reproductive toxicity is $\geq$ 0.1 mg/ml.**

The study is classified as **core minimum data** and **satisfies** the guideline requirement (§ 83-4) for a multigeneration reproduction study in rats.

D. Additional information from the literature (IF AVAILABLE)

According to Hazardous Substances Databank (HSDB), metam sodium is converted to carbon disulfide in an acidic environment. The rat metabolism study with metam sodium also documents formation of the carbon disulfide (approximately 20% of the administered oral dose). Carbon disulfide is a known potent neurotoxic agent.

E. Determination of Susceptibility

Increased fetal susceptibility was seen in the developmental toxicity study in rats. There was no evidence increased susceptibility in rabbit developmental study or in reproduction studies in rats.

F. Recommendation for a Developmental Neurotoxicity Study:

The RfD Committee concluded that developmental toxicity studies might be required based on the presence (even though at low level) of suspected neural tube defects/brain malformations in rats and rabbits (RfD Report dated January 18, 1995). The HIARC confirms the requirement of developmental neurotoxicity based on neurotoxic effects seen in subchronic and chronic studies, neurotoxic effects seen in fetuses in developmental studies, neuropathology in chronic studies and potential increased fetal sensitivity seen in developmental toxicity study in rats.

G. Hazard-Based Recommendation of the FQPA Safety Factor

Based on the hazard assessment alone, the HIARC recommends to the FQPA Safety Factor Committee that the additional 10x factor should be retained for dietary risk assessments. The final recommendation on the FQPA safety factor is made during risk characterization by the FQPA Safety Committee.

VI. HAZARD CHARACTERIZATION

Metam Sodium (sodium-N-methyldithiocarbamate), also known as Vapam, Metham Sodium, and SMDC is a fumigant-type pesticide used as a non-selective preplant fumigant for control of weeds, nematodes, fungi, bacteria, and insects. There are approximately 35 different products containing metam sodium in concentrations ranging from 18-42% active ingredient.

Metam sodium is acutely of low toxicity. The oral, dermal and inhalation LD_{50} values places it in Category III. Metam sodium is not a skin and eye irritant (Category III and IV, respectively). It is negative for skin sensitization in guinea pigs. In an acute neurotoxicity study, it reduces the ambulatory and total motor activity in both male and female rats.

No dermal toxicity studies are available on metam sodium. In a 90 day drinking water study in rats, it caused decrease in body weight gain, food and water consumption, hematological effects and histological changes in the nasal cavity. In a 90 day drinking water study in mice, it caused a decrease in body weight gain, hematological effects and urinary bladder lesions. In a 90 day

feeding study in dogs, it caused decrease in body weight gain, hematological alterations and altered clinical parameters. Similar effects were also seen in a one year toxicity study in dogs. In a subchronic neurotoxicity study in rats, it caused a decrease in body weights, body weight gains, food consumption and food efficiency. There were no significant findings in the Functional Observatory Battery (FOB) parameters.

Two developmental toxicity studies in rats and rabbits are available in the database. In one study, the Maternal NOAEL is 10 mg/kg based on significantly decreased body weight gain during the dosing period observed at 40 mg/kg (LOAEL). Developmental Toxicity NOAEL can not be determined. The developmental effects such as a significant increase in postimplantation loss, and a significant decrease in the percent of live fetuses/dam at the 10 and 120 mg/kg levels were observed. Fetal weights were significantly reduced for male and female fetuses in the 120 mg/kg group. Examination of the viscera of fetuses that underwent skeletal examination revealed a significant increase in the percent fetuses/litter with anomalies, variations, and retardations. The administration of Metam sodium at high doses resulted in meningocele which was not reported in the historical or concurrent control.

In a second developmental study in Wistar rats, the Maternal Toxicity NOAEL = 5 mg/kg/day, and the Maternal Toxicity LOAEL = 20 mg/kg/day based on reduced body weight gain and decreased food efficiency. Developmental toxicity was suggested in the form of an increase in total resorptions and resorptions/dam, skeletal variations and a significant decrease in mean fetal weight. Developmental Toxicity NOAEL = 5 mg/kg/day and the Developmental Toxicity LOAEL = 20 mg/kg/day based on the increased incidence of skeletal observations and the increase in total resorptions and resorptions/dam.

In a developmental toxicity study in Himalayan rabbits, the Maternal NOAEL is 10 mg/kg/day and LOAEL is 30 mg/kg/day based on reduced body weight gains, reduced food consumption, increased number of dead implantations and reduced numbers of fetuses, and increased post-implantation loss. Developmental Toxicity was apparent in the form of increased number of dead implantations and reduced numbers of fetuses, and increased post-implantation loss; however the Developmental Toxicity NOAEL and LOAEL cannot be determined with available data.

In a second developmental toxicity study in New Zealand White rabbits, maternal toxicity was noted in the mid and high dose group in the form of increase incidence of few feces and red/orange staining on the cage tray, a treatment related decrease in body weight gain, decrease in food consumption and food efficiency . The Maternal Toxicity NOAEL = 5 mg/kg/day. Developmental toxicity was noted in the high dose groups in the form of increased resorptions including total litter resorptions, a decrease. in the number of live fetuses and mean litter size, and an increase in post- implantation loss. The Developmental Toxicity NOAEL = 5 mg/kg/day.

In a multigeneration reproduction study, male and female Alpk:APfSD rats, systemic toxicity was observed at the 0.1 mg/ml dose level in adult female rats of the F_0 and F_1 generations. This toxicity consisted of Bowman's gland duct hypertrophy with loss of alveolar cells,

degeneration/disorganization and/or atrophy of the olfactory epithelium, and dilatation of the Bowman's gland ducts. The change in Bowman's glands was accompanied in all affected animals by degeneration, disorganization, and/or atrophy of the olfactory epithelium. In pups, findings were limited and observed mainly at the high dose. The NOAEL for systemic toxicity is 0.03 mg/ml (3.2 mg/kg/day (males) and 3.9 mg/kg/day (females). There were no apparent effects of metam sodium on reproductive performance in the F_0 or F_1 generations in this study. The NOAEL for reproductive toxicity is 0.1 mg/ml and the LOAEL for reproductive toxicity is $\geq$ 0.1 mg/ml.

Metam sodium was negative in several mutagenicity assays (including the Salmonella assay, an unscheduled DNA synthesis assay, and an aberrations assay with Chinese hamster cells). However, metam sodium demonstrated a dose-dependent and statistically significant increase in the number of chromosomally damaged cells in the presence of metabolic activation in an *in vitro* cytogenetics assay with cultured human lymphocytes.

Carcinogenic potential was evidenced in mice, demonstrated as an increase in the incidence of angiosarcoma of the liver, spleen, and subcutaneous tissue, as well as the presence of a transitional cell papilloma in a single high dose male, and a transitional cell carcinoma in a single high dose female. There were no statistically significant trends in tumor rates of male rats. However, there was a significant pair-wise comparison in the incidence of hemangiosarcoma in male rats at the low and mid dose levels in comparison to controls, but not at the high dose level tested. Tumor latency was similar between the low dose and mid dose groups.

VII. DATA GAPS

The HIARC has identified requirement of developmental neurotoxicity study in rats as a data gap.

VIII. ACUTE TOXICITY

Acute Toxicity of Metam Sodium (P. C. Code 039003)

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral-rat	41277002	LD_{50} =7 80 mg/kg (male rats) 845 mg/kg (female rats)	III
81-2	Acute Dermal-Rats	41277003	LD_{50} = >2020 mg/kg	III
81-3	Acute Inhalation-rat	41277004	LC_{50} = 2.27 mg/L	III
81-4	Primary Eye Irritation	41277005	No corneal/iris involvement; all irritation was absent by 7 days	III
81-5	Primary Skin Irritation-Rabbits	41277006	non-irritating to the skin of male rabbits	IV
81-6	Dermal Sensitization	4127707	Negative in guinea pigs	
81-8	Acute Neurotoxicity-Rats	42977801 and 42977802	The LOAEL of 22 mg/kg is based on reduced ambulatory and total motor activity observed in male & female rats. The NOAEL < 22 mg/kg and was not achieved in this study.	

IX. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY

Acute Dietary	NOAEL= UF =	This risk assessment is not required.	
		Acute RfD =	
Chronic Dietary	NOAEL = UF =	This risk assessment is not required.	
		Chronic RfD =	
Short-Term (Dermal)	NOAEL= 4.22 mg/kg/day MOE=300	Decreases in live fetuses	Developmental Toxicity Study in Rats
Intermediate-Term (Dermal)	NOAEL= 1.0 mg/kg/day MOE=100	Effects on clinical parameters and liver effects	90-Day Subchronic Oral Toxicity Study in Rats
Long-Term (Dermal)	NOAEL=	This risk assessment is not required.	
Short Term (Inhalation)	NOAEL= 0.0021 mg/L MOE=100	Decrease in body weights and food consumption, changes in blood protein values	90-Day Inhalation Toxicity Study in Rats
Intermediate Term (Inhalation)	NOAEL= 0.0021 mg/L MOE=100	Decrease in body weights and food consumption, changes in blood protein values	90-Day Inhalation Toxicity Study in Rats
Long Term (Inhalation)	NOAEL=	This risk assessment is not required.	

2.5% dermal absorption (oral equivalent dose) factor was utilized.