CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
METAM-SODIUM

Chemical Code #: 000616; Tolerance # 50150
SB 950 # 742

December 24, 1986
Revised 9/14/88, 10/23/89, 2/1/91 and 4/27/91, 8/6/91, 8/30/91, 11/12/91, 6/15/92, 4/20/94, 6/20/94, 7/20/94, 11/3/94, 1/20/95, 7/25/95, 9/30/97, 5/15/98, 4/29/99, 6/21/99, 7/7/99, 11/19/01

I. DATA GAP STATUS

Combined (chronic/onco.), rat :	No data gap, possible adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse effect[1]
Teratology, rat:	No data gap, possible adverse effect
Teratology, rabbit:	No data gap, possible adverse effect
Gene mutation:	No data gap, possible adverse effect
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time.

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1 - No adverse effects to the reproductive system were observed, however, pathology was induced in the nasal cavity (see worksheet).
Toxicology one-liners are attached.
No EPA one-liners

** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T011119

Revised: [redacted], 10/89; [redacted], 2/1/91; [redacted] & [redacted], 4/27/91; [redacted], 8/6/91, 8/30/91, 11/12/91, 6/15/92, 4/20/94, 6/20/94, 7/20/94, 11/3/94, 1/20/95, 7/25/95, 9/30/97, 5/15/98, 4/29/99, 6/21/99, 7/7/99, 11/19/01.
Rectified through, Volume #: 50150-149 and Record #: 154554

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

50150-026 087976 Proposed testing program including worker exposure and dermal absorption in the rat (see record no. 088047 under supplemental studies).

50150-027, 028 (duplicate of 027) 085941, 085942, 086080, 086081, 086082 Comments on issues discussed at the January 31, 1990 meeting with members of the Metam-Sodium Task Force. See meeting summary dated February 7, 1990. No additional worksheet. [redacted], 12/27/90). [redacted] produced a rebuttal response which was requested by the registrant (8/13/91).

COMBINED, RAT

Subchronic Studies:

057 096322, "Metam-Sodium: 11 Day Oral Dosing Study in Rats", (D. A. Cave, ICI Central Toxicology Laboratory, Report No: CTL/T/2727, 1/16/91). Metam-Sodium (purity = 32.8 g/l) was administered daily by gavage at concentrations of 20, 50, or 200 mg/kg (no treatment controls) to 4 Wistar rats/sex/group for 11 consecutive days. **No adverse effect indicated. NOEL** = 20 mg/kg (Body weight and food consumption values were lower for the high dose group compared to low and mid dose groups. Ulceration to non glandular areas was present in the stomachs of all high dose and 2 female mid dose animals and was absent in the low dose group. Post dosing salivation was also observed at $\geq$ 50 mg/kg/day.) Untreated control animals were not included for this study. **These data are supplemental.** ([redacted] & [redacted], 4/10/91).

057 096323, "Metam-Sodium: 21 Day Drinking Water Study in Rats", (D. A. Cave, ICI Central Toxicology Laboratory, Report No: CTL/T/2716, 1/18/91). Metam-Sodium (purity = 32.8 g/l) was administered to AlpK:APfSD (Wistar derived) rats (5/sex/group) in the drinking water (pH 9.0) with initial concentrations at 0 (water only), 1, 3, or 6 mg/ml for 2 days. Doses were changed after a 5 day rest period to 0, 0.1, 0.3, or 0.7 mg/ml, since the animals would not drink the water containing metam-sodium at the original doses. After the change in dosage, the 2 lower doses were accepted in a dose dependent manner during the next 21 days. NOEL < 0.1 mg/ml/day (Decreased water consumption and body weight gain was observed at all doses.) Reduced body weight gain for low and mid dose groups and food consumption for mid dose group was associated with reduced water consumption.) These data are supplemental. ([redacted] & [redacted], 4/12/91)

057 096324, "Metam-Sodium: 90 Day Drinking Water Study in Rats", (D. A. Cave, ICI Central Toxicology Laboratory, Study No: PR0797, 8/30/90. The report is a summary of 90 day interim data for study 062 098866.) [redacted] & [redacted] 4/12/91.

**** 062 098866** "Metam Sodium: 90 Day Drinking Water Study in Rats," (Allen, S.L., ICI Central Toxicology Laboratory, UK, 9/26/91). Metam sodium (purity = 525.54 g/l, CTL reference #: Y06930/007 & Y06930/008) was administered Alpk:APfSD rats (12/sex/dose) in drinking water at 0, 0.018, 0.089 or 0.443 mg/ml for 90 days. NOEL = 0.018 (Clinical signs, primarily in females--subdued, stains around nose and thin--were observed at $\geq$ 0.089 mg/ml. Males at 0.443

mg/ml and females at ≥ 0.089 mg/ml showed a significant decrease in body weight. Both sexes showed a significant decrease in food consumption at 0.443 mg/ml. Males at 0.443 mg/ml and females at ≥ 0.089 mg/ml showed a significant decrease in water consumption. Several hematology effects at ≥ 0.089 mg/ml and clinical biochemistry effects were reported at 0.443 mg/ml in both sexes. Urinalysis effects in both sexes were reported at ≥ 0.089 mg/ml. Absolute adrenal, brain, liver, kidney (male only) and lung weights were significantly decreased at 0.443 mg/ml. Kidney tubular basophilia increase was reported in both sexes at 0.443 mg/ml.) **Possible adverse effect indicated**: Effects in the nasal cavity (primarily in females) was reported at 0.443 mg/ml (disorganization, prominent/vacuolated Bowman's glands/ducts and vacuolated olfactory epithelium). [redacted], 11/1/91. This study has been re-evaluated and is considered to be acceptable, according to FIFRA Guidelines. [redacted], 7/7/99.

** 50150-019, 092 068675, 119892 "Subchronic Inhalation With VAPAM® Technical in Rats," (Knapp, H.F., Stauffer Chemical Company, Farmington, CN, 8/31/83). Metam sodium technical (Vapam, 32.7% pure) was administered to Sprague-Dawley CD® rats (18/sex/dose) in an aerosol chamber for 6 hours/day, 5 days/week (65 days) at 0, 6.5, 45 (actual dose, where the nominal dose was 32 mg/m^3) or 160 mg/m^3. NOEL = 6 mg/m^3 (Body weights and food consumption were decreased in both sexes at ≥ 32 mg/m^3. Clinical observations included increased salivation, dullness, chromodacryorrhea, dehydration, rough coat and wet coat at ≥ 32 mg/m^3. Males had increased seminal plugs at 160 mg/m^3. Clinical blood chemistry was affected in both sexes at ≥ 32 mg/m^3. Relative kidney and lung weights (males) and relative liver, brain, heart, kidney, adrenal, lung and gonad weights (females) were significantly increased at 160 mg/m^3. Gross necropsy showed an increase in focal discolorations of stomach lining. Histopathology showed an increase in liver lymphogranulomatous hepatitis (males only--toxicologically significant at ≥ 32 mg/m^3), erosive gastritis and pulmonary histiocytosis, primarily at 160 mg/m^3. Lymphocytic rhinitis and mucogenic epithelial hyperplasia were increased and were toxicologically significant at ≥ 32 mg/m^3) No adverse effect indicated. The study was previously evaluated to have a LOEL of 6 mg/m^3 ([redacted] 5/15/98). Upon re-evaluation of histopathology, the effects were considered to be of toxicological significance at ≥ 32 mg/m^3. Therefore, the study has now has a NOEL of ≥ 6 mg/m^3, based on the effects listed above. [redacted], 4/29/99. This study has been re-evaluated and is considered to be acceptable, according to FIFRA Guidelines. [redacted], 7/7/99.

092 119892 "Metam Sodium: A CTL Re-Examination of Liver Sections From a Sub-Chronic Inhalation Study With Vapam Technical in Rats - Study Number: T-11006," (Duffell, S.J., ICI Central Toxicology Laboratory, Alderley Park, UK; Report #: CTL/T/2815, Study #: T-11006, 10/29/92). In this report, liver sections from the 90-day study (DPR volume/record #: 019-068675) were re-examined to determine the nature and incidence of the "lymphogranulomatous hepatitis" as reported by Stauffer. ICI pathologists term this lesion "mononuclear cell infiltration of the liver." The pathologist considers it to be a background lesion in rats which occurrs minimally and does not warrent the term lymphogranulomatous hepatitis (a more significant lesion). The report considers there is no increase in incidence in mononuclear infiltration of the liver between the high dose and the control animals. [redacted]. [redacted], 2/1/94.

071 113030 This volume contains an exact duplicate of **062 098866** "Metam Sodium: 90 Day Drinking Water Study in Rats," (Allen, S.L., ICI Central Toxicology Laboratory, UK, 9/26/91). [redacted], 6/10/92.

Combined Study (preliminary reports):

059 089861 "Metam Sodium: Two Year Drinking Study in the Rat. CTL Study #: PR0838. Progress Report to 9 May 1991," (ICI Central Toxicology Laboratory, 5/91). Metam sodium was administered in drinking water at 0, 0.02, 0.06 and 0.2 mg/ml (2-6 weeks of a 2 year study) to rats. Achieved concentrations of metam sodium were within expected range. There have been no mortalities or adverse clinical signs related to treatment. At 0.2 mg/ml, a significant decrease in body weight gain (14%) was reported along with a decrease in food consumption (food utilization was unaffected). This was a summary report. No worksheet. [redacted], 8/29/91.

074 113447 "Metam Sodium: Two Year Drinking Study in Rats," Progress report for weeks 27-39, (Allen, S.L., ICI Central Toxicology Laboratory, Alderley Park, UK, 2/10/92). This volume contains an update on the status of the rat combined study. **Report of Weeks 27-39:** Doses received were 0, 1.6, 4.8 and 12.7 mg/kg (males-- 0.02, 0.06 and 0.2 mg/ml, respectively) or 3.1, 8.1 and 18.5 mg/kg (females). A significant decrease in body weight gain, food consumption and water intake were observed in females at $\geq$ 0.06 mg/ml and in males at 0.2 mg/ml. These data are supplemental. [redacted], 6/10/92.

081 115335 "Metam Sodium: Two Year Drinking Study in Rats," Progress report for weeks 40-53, (Rattray, N.J., ICI Central Toxicology Laboratory, Alderley Park, UK, 6/15/92). This volume contains an update on the status of the rat combined study. **Report of Weeks 40-53:** Doses received were 0, 1.5, 4.46 and 12.07 mg/kg (males-- 0.02, 0.06 and 0.2 mg/ml, respectively) or 2.94, 7.78 and 18.17 mg/kg (females). There was a decrease in body weight gain and food consumption in both sexes, primarily at the high dose. Decreased water consumption was observed in females at 0.2 mg/ml. Hematology effects (decreased Hb, HCT & RBC's) was observed in both sexes at 0.2 mg/ml. These data are supplemental. [redacted], 2/1/94.

089 118188 "Metam Sodium: Two Year Drinking Study in Rats," Progress report for weeks 54-70, (Rattray, N.J., ICI Central Toxicology Laboratory, Alderley Park, UK, 9/21/92). This volume contains an update on the status of the rat combined study. **Report of Weeks 54-70:** Doses received were 0, 1.46, 4.31 and 11.81 mg/kg (males-- 0.02, 0.06 and 0.2 mg/ml, respectively) or 2.86, 7.72 and 17.93 mg/kg (females). There was a decrease in body weight gain and food consumption in both sexes, primarily at the high dose. Decreased water consumption was observed in females at $\geq$ 0.2 mg/ml. These data are supplemental. [redacted], 2/1/94.

090 119582 "Metam Sodium: Two Year Drinking Study in Rats," Progress report for weeks 71-84, (Rattray, N.J., ICI Central Toxicology Laboratory, Alderley Park, UK, 12/2/92). This volume contains an update on the status of the rat combined study. **Report of Weeks 71-84:** Doses received were 0, 1.4, 4.2 and 11.7 mg/kg (males-- 0.02, 0.06 and 0.2 mg/ml, respectively) or 2.8, 7.4 and 17.7 mg/kg (females). Analytical results show that the amount of compound administered was within 20% of nominal. This is an unacceptably high variation. These data are supplemental. [redacted], 2/1/94.

057 Appendix 1 contains a series of letters from Imperial Chemical Industries (ICI) to the U.S. Environmental Protection Agency, regarding the doses of metam sodium to be used in the 2 year drinking water studies to be performed in mice and rats. It was stated that metam sodium would be administered in drinking water, instead of by gavage to eliminate the direct irritant effect of metam sodium on the stomach. In addition, information about the stability of metam sodium in drinking water and the appropriate pH to promote stability was given:

Percentage Loss

Metam sodium (mg/ml)	12 hours	24 hours
0.3	38	55
0.02	38	50

The pH of the drinking water will be adjusted to 9.0 and the solution will be degassed to remove oxygen. Control animals will receive pH 9.0 water and apparently ICI has sufficient historical data for animals given normal, neutral pH drinking water to account for results attributed solely to the use of pH 9.0 drinking water. [redacted], 4/17/91).

057 Appendix 8 contains a letter from Imperial Chemical Industries (ICI) which confirmed that ICI Central Toxicology Laboratory has been contracted by the Metam Sodium Task Force to conduct a combined chronic toxicity and oncogenicity in rats and an oncogenicity study in mice with metam sodium. It was stated that the 2 year mouse study would start on February 18, 1991 and a draft of the report would be submitted by February of 1994. The rat study was delayed due to a viral infection at the on-site breeding unit. An alternate supplier is providing the rats and the study should start as of March 18, 1991. A draft of the final report is to be issued in March of 1994. ([redacted], 4/17/91).

Combined Study:

**** 114 130830** "Metam Sodium: Two Year Drinking Study in Rats," (N.J. Rattray, Zeneca CTL, Cheshire, UK; Report #: CTL/P/4139, Study #: PRO838; 5/23/94). Metam Sodium (43.148% pure, w/w) was given in drinking water to Hsd/Ola: Wistar Tox rats (50/sex/dose) at 0 (drinking water), 0.019, 0.056 and 0.19 mg/ml (1.5, 4.3 & 12.5 mg/kg--males; 2.7, 6.8 & 16.8 mg/kg--female) for 104 weeks. Chronic NOEL = 0.019 mg/ml (Reduced hindlimb function & decreased body weight at 0.19 mg/ml. Decreased food and water consumption were observed at $\geq$ 0.056 mg/ml. A decrease in hemoglobin, hematocrit and RBC count (both sexes at 0.056 mg/ml). Males at 0.19 mg/ml showed decreased monocyte count & females at 0.19 mg/ml showed increased MCV, MCH and glucose (0.056 mg/ml) levels. Females at 0.19 mg/ml also showed decreases in some of the clinical chemistry parameters. Both sexes at $\geq$ 0.056 mg/ml showed urinalysis effects. **Adverse effect (both chronic and oncogenic): Chronic:** Nasal cavity at 0.19 mg/ml (rhinitis, hypertrophy of Bowman's Gland, hyperplasia/degeneration of olfactory epithelium, atrophy & adenitis of Steno's gland and respiratory epithelial hyperplasia.) Oncogenic NOEL = 0.019 mg/ml (**Oncogenic:** An increased incidence in hemangiosarcomas and meningiomas was observed at $\geq$ 0.056 mg/ml.) Previously reviewed as unacceptable [redacted], 7/18/94), upon receipt and review of requested information, the study is now considered acceptable. [redacted], 7/20/95.

CHRONIC TOXICITY, DOG

Subchronic Studies:

**** 50150 - 093 1120016** "Metam Sodium: 90-Day Oral Dosing Study in Dogs," (Brammer, A., ICI Central Toxicology Laboratory, Alderley Park, UK, Laboratory Project ID #: CTL/P/3679, 11/11/92). Metam sodium (purity = 43.15% w/w) was administered to Beagle dogs (4/sex/dose) by gelatin capsule at 0 (gelatin capsule), 1, 5 or 10 mg/kg/day for 90 days. Initially reviewed as having a NOEL = 1 mg/kg ([redacted], 2/3/94), upon re-evaluation of bile duct proliferation and ALT and ALP levels, the NOEL is considered to be less than 1 mg/kg, resulting in the study having a NOAEL = 1 mg/kg (ALT and ALP in the subchronic (and at longer time points in the 1 year study) study were increased at 1 mg/kg, along with the bile duct proliferation seen at all doses. Mortality was increased at 10 mg/kg in

both sexes. Regurgitation of food after dosing, decreased food consumption and a resulting decrease in body weight and body weight gain were observed at ≥ 5 mg/kg. Effects were observed in hematology tests at ≥ 5 mg/kg (coagulation parameters, MCV, neutrophilia, monocytosis, MCH were increased; HG, HCT, RBC's, MCHC were decreased). Abnormal urine color (orange or orange/brown) was noted at ≥ 5 mg/kg. Kidneys increased in absolute and relative weight at 10 mg/kg. At necropsy, livers showed yellow discoloration, pallor with accentuated lobular pattern and red depressed areas at 10 mg/kg (5 mg/kg showed red depressed areas) and the thymus was reduced in size at 10 mg/kg. Histopathology confirmed liver damage with hepatocyte necrosis & degeneration, inflammatory cell infiltration, increased pigmentation in hepatocytes & Kupffer cells, collapse of hepatic cords with an influx of blood and bile duct proliferation (> 1 mg/kg) with inflammatory cell infiltration at ≥ 5 mg/kg. Thymus showed a reduction in cortical lymphocytes and the urinary bladder epithelium showed a minimal to slight increase in mitotic figures at 10 mg/kg. At 10 mg/kg 1 male showed testes and prostate gland that were immature in appearance.) **Possible adverse effect in liver and immune system.** Acceptable. [redacted] 11/19/01.

077 114176 "Metam Sodium: Range Finding Oral Toxicity Study in Dogs," (Brammer, A., ICI Central Toxicology Laboratory, Alderley Park, UK, 4/7/92.) Metam sodium (52.55% pure w/v; Batch K2654 1-3; CTL Ref. #: Y06930/008) was administered as a daily oral dose (neat, gelatin capsule or as an aqueous dilution by gavage) to Beagle dogs (1/sex/dose) at 0 (Group 1), 2.5 (Group 2), 10 (Group 3), 25 (Group 4, dose later lowered to 15 mg/kg), and 15 (Group 5) or 15 (Group 6) mg/kg. Groups 2-4 received 20, 35 and 50 mg/kg, respectively, during week 7 (after withdrawl from treatment week 6). Subsequently, the same animals from groups 2-4 were brought back to 2.5, 10 and 15 mg/kg, respectively (after withdrawl from treatment week 8). **The same animals were used in both dosing regimens**. Group 5 received 20 mg/kg during week 8. All treatment during week 8 (Groups 1 & 6 only) were treated by gavage. Dogs were fed 100 g of diet 30 mins prior to dosing. The remainder was fed 2-3 hours after dosing. This regimen reduced to incidence of vomiting at 15 mg/kg (but not at 25 mg/kg). Milk was tested for its ability to relieve the local irritant effect of metam sodium but it was not an effective emollient. Gavage was also attempted, but not found to relieve the local gastric irritantcy of metam sodium. Results & Conclusion: Effects seen at 10 or 15 mg/kg (primarily within groups 3-4) may have been induced by the high levels of exposure during week 7 or by the 25 mg/kg used for the first 5 weeks of the study for Group 4. The 2 male dogs terminated intercurrently showed marked liver pathology. One of those dogs (#207) was treated at 25, then 50, then 15 mg/kg (killed week 20 on study). Clinical data (no individual data) are of limited use, since animals were treated with different doses on and off during the study. For instance the 2 dogs at 2.5 mg/kg (no vomiting incidences) were treated with 20 mg/kg during week 7. Subsequently, vomiting increased and dosing was discontinued. No further vomiting occurred when the dogs were returned to 2.5 mg/kg. Animals at 10 and 25 mg/kg also received much higher doses for a short period and then were returned to the lower doses (the original 25 mg/kg group was further lowered to 15 mg/kg). The vomiting pattern was similar for these groups (e.g. vomiting increased with the higher dose, then decreased when the doses were lowered). However, data were reported as vomiting incidences/group for the duration of the study, with no mention of the treatment differences at the appropriate intervals. No significant clinical effects occurred at ≤ 10 mg/kg. Only males showed effects on body weight, organ weights, clinical chemistry, pathology and histopathology at 15 mg/kg. Due to the dosing regimen, a NOEL for this study cannot be determined, since the effect of these manipulations on the outcome of the data is unknown. [redacted], 6/8/92.

089 118193 This volume contains a draft of the 90-day oral dosing study in dogs (9/23/93). The completed study was subsequently reviewed at DPR (093 120016) and was considered to be

acceptable. [redacted], 2/1/94

066 111352 This volume contains an adverse effects disclosure regarding the findings in the 9 week preliminary study (077 114176). The letter from ICI Agricultural Products (dated November 20, 1991) stated that male dogs at 15 mg/kg showed marked hepatitis with hepatic necrosis and liver degeneration with slight to moderate hepatocyte pigmentation. [redacted], 6/9/92.

A letter from ICI Agricultural Products (dated May 27, 1992--pages only, no volume or record #'s) summarized the current status of a 90-day oral dosing study in dogs. The dogs were treated at 0, 1, 5 and 10 mg/kg with 4/sex/dose. Histopathology showed liver lesions at ≥ 5 mg/kg (along with increases in plasma enzyme activities indicative of liver injury). A female at 1 mg/kg showed an increased plasma alanine transaminase activity and liver histopathology indicative of early stages of a liver lesion similar to that observed at ≥ 5 mg/kg. Accompanying this letter was a letter (dated May 13, 1992) from ICI General Toxicology Laboratory with information identical to that in the adverse effects disclosure letter (May 27, 1992). [redacted], 6/9/92.

Chronic study:

** 115 130929 "Metam Sodium: 1 Year Oral Toxicity Study in Dogs," (Brammer, A., Zeneca CTL, Cheshire, UK; Report #: CTL/P/4196, Study #: PD0905, 5/23/94). Metam Sodium (43.148% pure) was given orally in gelatin capsules to Beagle dogs (4/sex/group) at 0 (purified water in gelatin capsules), 0.05, 0.1 or 1.0 mg/kg/day for 1 year. NOEL = 0.1 mg/kg (The Kaolin-cephalin time, plasma chloride & alkaline phosphatase levels were increased in both sexes throughout the study at 1.0 mg/kg/day. Plasma triglycerides were reduced in females at 1.0 mg/kg/day.) NOAEL > 1.0 mg/kg (HDT). Acceptable. No adverse effects. [redacted], 7/19/94.

ONCOGENICITY, MOUSE

Subchronic Studies:

** 061 098777 "Metam Sodium: 90 Day Drinking Water Study in Mice With a 28 Day Interim Kill," (Whiles, A.J., ICI Central Toxicology Laboratory, 9/26/91). Metam Sodium (purity = 525.54 g/l; batch #: BAS 005 00N; CTL reference #: Y06930/007 & Y06930/008) were administered in drinking water to C57BL/10JfAP/Alpk mice at 0, 0.018, 0.088, 0.35 or 0.62 mg/ml for 29 (interim kill--5/sex/dose) or 90 days (10/sex/dose). NOEL = 0.018 mg/ml (At ≥ 0.35 mg/ml both sexes showed a significant reduction in body weight. Water consumption was significantly decreased, primarily in females, at ≥ 0.088 mg/ml. Hemoglobin was decreased and mean cell volume was increased in males at ≥ 0.35 mg/ml and in females at ≥ 0.088--hemoglobin and 0.62 mg/ml--mean cell vol. Hematocrit was decreased in males at 0.62 mg/ml and in females at ≥ 0.088 mg/ml. RBC's were decreased in both sexes at ≥ 0.35 mg/ml. Mean cell Hb concentration was increased at ≥ 0.088 mg/ml--males and ≥ 0.35 mg/ml--females. Interim and terminal liver weights for both sexes were increased at ≥ 0.35 mg/ml. Terminal adjusted kidney weights were increased at ≥ 0.35 mg/ml, as were terminal adjusted liver weights at ≥ 0.088 mg/ml for both sexes. Terminal histopathology showed an increase in bladder eosinophilic granules in the cells in both sexes at ≥ 0.088 mg/ml, cystitis at ≥ 0.35 mg/ml and bladder mucosal hyperplasia at ≥ 0.088 mg/ml in females and ≥ 0.35 mg/ml in males.) **No adverse effect indicated.** [redacted], 10/30/91. This study has been re-evaluated and is considered to be acceptable, according to FIFRA Guidelines. Although bone marrow (interim & main study), bladder, liver and kidneys (interim kill) were not examined histologically, this did not ultimately detract

from evaluating the effects of metam sodium from drinking water (90 day treatment) in mice. [redacted], 7/7/99.

057 096325, "Metam-Sodium: 90 Day Drinking Water Study in Mice with a 28 Day Interim Kill," (A. J. Whiles, ICI Central Toxicology Laboratory, Study No: PM0808, 9/13/90). Metam Sodium administered in the drinking water at concentrations of 0 (vehicle = drinking water), 0.018, 0.088, 0.35 or 0.62 mg/ml to 15 C57/10JfAP/Alpk mice/sex/group for 90 days (5/sex/group were scheduled for a 28 day interim kill). The report indicates that instability of Metam Sodium in the vehicle could reduce the mean dose up to 50% and states that mean dosages for this study were 2.7, 11.7, 52.5, and 78.7 mg/kg for males and 3.6, 15.2, 55.4, 83.8 mg/kg for females. NOEL = 0.018 mg/ml. This report is a preliminary version of 061 098777 and is considered supplementary. ([redacted] & [redacted], 4/15/91).

Oncogenicity Study (preliminary reports):

057 096326 (appendix 9). An agreement between Imperial Chemical Industries (ICI) and the Metam Sodium Task Force to perform a 2 year drinking study in mice is presented. In addition, a proposed protocol is given. ([redacted] & [redacted], 4/17/91).

059 089860 "Metam Sodium: Two Year Drinking Study in Mice. CTL Study #: PM0841. Progress Report Weeks 1-11," (ICI Central Toxicology Laboratory, 8/19/91). Metam sodium was given in purified drinking water to mice (55/sex/dose) at 0, 0.02, 0.08 and 0.25 mg/ml or 2.6, 9.9 and 34.9 mg/kg/day (males) and 3.6, 13.7 and 41.9 mg/kg/day (females) for 11 weeks (of a 2-year study). Metam sodium was within 10% of nominal concentrations and was reported to decrease from 0-30% over 24 hours. There were no treatment-related mortalities. Body weight gains were significantly reduced in both sexes, however body weights were reduced by only 4 and 2% in males and females, respectively (inconsistent). Food consumption was slightly depressed in males at $\geq$ 0.08 mg/ml. Both sexes at 0.08 mg/ml showed a significant decrease in water consumption, but only males showed a significant decrease at 0.25 mg/ml. This was a summary report. No worksheet. [redacted] 8/29/91.

073 113443 "Metam Sodium: Two Year Drinking Study in Mice," Progress report for weeks 37-50, (Allen, S.L., ICI Central Toxicology Laboratory, Alderley Park, UK, 2/10/92). This volumes contains an update on the status of the mouse oncogenicity study. **Report of Weeks 37-50:** The concentration of metam sodium in water decreased by 35% after 24 hours. Doses received were 0, 2.2, 8.3 and 32.4 mg/kg (in males at 0, 0.02, 0.08 and 0.25 mg/ml, respectively) and 0, 2.9, 11.2, 36.7 mg/kg for females. Body weight gain was decreased by 18% in males at 0.25 mg/kg (corresponds with a 7% lower mean body weight). Water consumption was slightly (but statistically significantly) decreased at 0.08 mg/kg but was significantly increased at 0.25 mg/kg in males. These data are supplemental. [redacted], 6/10/92.

089 118189 "Metam Sodium: Two Year Drinking Study in Mice," Progress report for weeks 51-63, (No author specified. ICI Central Toxicology Laboratory, Alderley Park, UK, 9/21/92). This volumes contains an update on the status of the mouse oncogenicity study. **Report of Weeks 51-63:** The concentration of metam sodium in water decreased by 10% after 24 hours. Doses received were 0, 2.1, 8.0 and 31.6 mg/kg (in males at 0, 0.02, 0.08 and 0.25 mg/ml, respectively) and 0, 2.8, 10.8, 35.6 mg/kg for females. Body weight gain was decreased by 17% in males at 0.25 mg/ml (corresponds with a 7% lower mean body weight). These data are supplemental. [redacted], 2/1/94.

089 118190 "Metam Sodium: Two Year Drinking Study in Mice," Progress report for weeks 63-75, (No author specified. ICI Central Toxicology Laboratory, Alderley Park, UK, 9/21/92). This volumes contains an update on the status of the mouse oncogenicity study. **Report of Weeks 63-75:** The concentration of metam sodium in water decreased by 10% after 24 hours. Doses received were 0, 2.0, 7.8 and 30.9 mg/kg (in males at 0, 0.02, 0.08 and 0.25 mg/ml, respectively) and 0, 2.7, 10.6, 34.7 mg/ml for females. Body weight gain was decreased by 18.5% in males at 0.25 mg/kg (corresponds with a 7% lower mean body weight). These data are supplemental. [redacted], 2/1/94.

091 119383 "Metam Sodium: Two Year Drinking Study in Mice," Progress report for weeks 75-88, (No author specified. ICI Central Toxicology Laboratory, Alderley Park, UK, 12/2/92). This volume contains an update on the status of the mouse oncogenicity study. **Report of Weeks 75-88:** Doses received were 0, 2.0, 7.7 and 30.8 mg/kg (males-- 0.02, 0.08 and 0.25 mg/ml, respectively) or 2.6, 10.2 and 34.2 mg/kg (females). Few treatment-related effects were observed. These data are supplemental. [redacted], 2/1/94.

Oncogenicity Study:

**** 111 130416** "Metam Sodium: Two-Year Drinking Study in Mice," (Horner, S.A., Report #: CTL/P/4095; Study #: PM0841, Zeneca CTL, Cheshire, UK, 4/20/94). Metam Sodium (purity = 43.148%, 525.54 g/l a.i. concentration) was added to drinking water and given to C57BL/10JfCD-1/Alpk mice (55/sex/dose) at 0 (drinking water), 0.019, 0.074 and 0.23 mg/ml for 104 weeks. **Chronic NOEL = 0.019 mg/ml** (Decreased body weights in both sexes at 0.23 mg/ml and decreased water consumption at ≥ 0.074 mg/ml was observed. Some hematology effects were observed at 0.23 mg/ml. Brain (males at 0.23 mg/ml), kidneys (both sexes at ≥ 0.074 mg/ml) and liver (both sexes at ≥ 0.074 mg/ml) weights were increased. Both sexes showed increased subcutaneous masses and pale livers at 0.23 mg/ml. Epididymal weights (≥ 0.074 mg/ml) were decreased. There was an increase in hepatocytic fat vacuolization (both sexes), splenic hemosiderosis, bladder pathology (epithelial hyperplasia--females at ≥ 0.074 mg/ml, mononuclear cell infiltration, eosinophilic/hyaline cytoplasmic inclusions in epithelium, increased submucosal connective tissue and submucosal hyalinization) observed at 0.23 mg/ml). **Oncogenicity NOEL = 0.074 mg/ml Possible adverse effect** (There was an increase in angiosarcomas in both sexes at 0.23 mg/ml. A transitional cell papilloma of the urinary bladder (1 male) and a transitional cell carcinoma of the urinary bladder (1 female) were observed at 0.23 mg/ml (extremely rare tumor types). Acceptable. [redacted], 6/16/94.

148 154552, 154553 This volume contains a report of carcinogenicity classification of metam sodium. The discussion includes background, critical in vivo oncogenicity studies, analysis of genetic toxicology studies, structure-activity considerations and conclusions. No worksheet. [redacted], 9/29/97.

REPRODUCTION, RAT

Preliminary reports:

079 114745 "Metam Sodium: Multigeneration Study in the Rat," (Progress Report - Completion of F1A Litter, 5/27/92). This volume contains data for F0 males and females (mating period), and the

F1A litter to day 29 post partum. The final litter was submitted for post partum examination on 3/30/92. Animals were treated at 0, 0.01, 0.03 and 0.1 mg metam sodium/ml drinking water. Metam sodium has been stable under the conditions of the study. On day 22 of gestation, female body weights were 13% lower than controls at 0.1 mg/ml. During lactation, body weights were somewhat depressed (6%) compared to control at 0.1 mg/ml. Water consumption at 0.1 mg/ml was depressed 35 and 17% during pregnancy and lactation, respectively. There appears to be no significant effects on F1A litters based on the data shown. These data are preliminary and supplemental. [redacted], 6/12/92.

089 118192 "Metam Sodium: Multigeneration Study in the Rat," (Progress Report - Completion of F2A Litter, 9/21/92). This volume summarizes the study through the completion of the F2a litter to day 29 post partum. Animals were treated at 0, 0.01, 0.03 and 0.1 mg metam sodium/ml drinking water. Metam sodium has been stable under the conditions of the study. Results showed a lower body weight for F1 females during pregnancy and lactation (for the F2a pups). At 0.03 mg/ml, effects were similar to those observed in the previous generation. There was also a lower number of pups/litter (possibly incidental) observed at 0.01 mg/ml. There were no reproductive effects observed. These data are preliminary and supplemental. [redacted], 2/1/94.

A letter from ICI Agricultural Products (dated March 5, 1992) accompanies a submission of the first progress report for the rat reproduction study. Data for the 10 week mating period for F0 males and females are included. The rats were dosed at 0, 0.01, 0.03 and 0.1 mg metam sodium/ml drinking water. The compound is stable under conditions of this study. Water consumption is reduced 7-17% at 0.03 mg/ml (males and females, respectively) and 18-35% at 0.1 mg/ml (males and females, respectively). No data presented. This information is supplementary. [redacted], 6/9/92.

059 This volume contains a letter from P.H. Rose, Project Director from ICI Central Toxicology Laboratory, stating that a multigeneration study has been scheduled to start Dec. 91/Jan. 92. A final report will be issued as of January, 1994. [redacted], 8/29/91. (NOTE: The final report has been submitted and reviewed (See 110 128620).

Definitive Study:

** 110 128620 "Metam Sodium: Multigeneration Study in the Rat," (Milburn, G.M., Zeneca Central Toxicology Laboratory, Cheshire, UK, 2/18/94; Report #: CTL/P/3788, Study #: RRO564/F0 & RRO564/F1). Metam sodium (43.148% w/w; batch #: BAS/005/00N & CTL reference #: Y06930/008) was given in drinking water at 0, 0.01, 0.03 or 0.10 mg metam sodium/ml to Alpk:APfSD rats (30/sex/dose) for two generations. Parental Systemic NOEL = 0.01 mg/ml (There is a decrease in food consumption, water consumption and body weight in both sexes of both parental generations at 0.1 mg/ml. Females in the F1 parental generation also showed a decrease in water consumption at 0.03 mg/ml.) **Possible adverse chronic effect:** Histopathology in the nasal cavity was reported (Bowman's duct hypertrophy with loss of alveolar cells, disorganization/degeneration/atrophy of olfactory epithelium, hyperplasia of olfactory epithelium and dilatation of ducts of Bowman's glands) at 0.1 mg/ml. Parental Reproductive NOEL > 0.1 mg/ml (There were no significant reproductive effects at any dose.) Pup NOEL = 0.03 mg/ml (Pups showed a tendency at 0.1 mg/ml to have decreased body weight from day 22 (males) in the F1a generation and from day 5 (males) in the F2a generation). [redacted], 4/15/94.

TERATOLOGY, RAT

**** 107 126844** "Metam Sodium Developmental Toxicity Study in the Rat," (Tinston, D.J., Zeneca Central Toxicology Laboratory, Cheshire, UK, Report #: CTL/P/4052, Study #: RR0624, 10/5/93). Metam sodium (purity = 43.15%) was administered by gavage to mated Alpk:APfSD female rats (24/dose) at 0 (deionized water), 5, 20 or 60 mg/kg during days 7-16 of gestation. On gestation day 22, the rats were killed and the uteri were inspected for live fetuses and intra-uterine deaths. **Maternal NOEL =** 5 mg/kg (There was an increase in clinical signs, a decrease in food consumption and body weight at ≥ 20 mg/kg.) **Developmental NOEL** = 5 mg/kg (There was a decrease in fetal weights at ≥ 20 mg/kg. **Possible adverse effect:** An increase in severe malformations (meningocele, anophthalmia, hydrocephaly) was observed at 60 mg/kg. In addition, numerous skeletal developmental delays were observed at ≥ 20 mg/kg. Manus and pes scores indicated there was delayed ossification in hand and foot bones at 60 mg/kg.) ACCEPTABLE. [redacted], 1/20/94.

**** 013, 024 063704, 074424** "Report on the Study of the Prenatal Toxicity of Metam-Sodium in Rats After Oral Administration (gavage)," (BASF Aktiengesellschaft, Germany, project #: 34RO232/8569, 3/25/87). Metam-Sodium, purity = 42.2%, administered by gavage at 0 (distilled water), 10, 40 or 120 mg/kg/day (day 6 to 15 of gestation) to mated Wistar rats (25/group; two sections). Maternal NOEL = 10 mg/kg/day (reduced feed intake was concurrent with decreases in body weight and body weight gain reported at ≥ 40 mg/kg/day). **Possible adverse effect.** Developmental NOEL < 10 mg/kg/day (the increase in dead implantations at 10 mg/kg and 120 mg/kg, compared to the control was reported as not substance-related. However, this study, the pilot study [higher doses] and another related study [063703] strongly suggests a relationship between Metam-Sodium and post-implantation loss). Previously reviewed as unacceptable (Parker, 8/2/88), upon receipt of the requested information regarding formulated material and historical data for post implantation loss, the study has been re-evaluated as ACCEPTABLE**.** ([redacted], 9/25/89).

TERATOLOGY, RABBIT

** **104 126664**, "Metam Sodium: Developmental Toxicity Study in the Rabbit", (M.C.E. Hodge, Zeneca Central Toxicology Laboratory, Report No CTL/P/4035, Study No. RB0623, 9/6/93). Metam Sodium (purity = 43.14% w/w) was administered by gavage at concentrations of 0 (deionized water), 5, 20, or 60 mg/kg/day to 20 time-mated female New Zealand White rabbits/group on gestation Days 8-20. **Maternal NOEL =** 5 mg/kg/day (Food consumption and body weights were significantly decreased at ≥ 20 mg/kg. Some clinical signs were evident at 60 mg/kg. Post-implantation loss, early intra-uterine deaths, and total litter resorptions were increased at 60 mg/kg.) **Developmental NOEL =** 5 mg/kg/day (Mean live litter size, mean litter and fetal weights and proportion of males/females was significantly decreased at 60 mg/kg. There was an increase in severe defects at 60 mg/kg and in skeletal variations at ≥ 20 mg/kg.) **Possible adverse effect: incidence of cleft palate and meningocele was increased in fetuses at 60 mg/kg.** ACCEPTABLE. ([redacted] & [redacted], 1/21/94).

**** 012, 024 063703, 074421-074223** "Report on the Study of the Prenatal Toxicity of Metam-Sodium (aqueous solution) in Rabbits after Oral Administration (gavage)," (BASF Aktiengesellschaft, FRG, project #: 38RO232/8579, 7/15/87). Metam-Sodium, purity 42.2%, administered by gavage at 0 (distilled water only), 10, 30, or 100 mg/kg/day (day 6 to 18 p.i.) to 15 artificially inseminated Himalayan rabbits/group (study in 3 sections at 7 day intervals). Maternal NOEL = 30 mg/kg/day. Food consumption decreased (during treatment) for the 100 mg/kg group. **Possible adverse**

effect. Developmental NOEL = 10 mg/kg/day. Incidence of dead implantations increased at 30 and a marked increase was noted at 100 mg/kg/day. Originally reviewed as unacceptable (Parker, 7/29/88), upon submission of the requested information regarding the formulated product and use of X-rays for skeletal assessment, the study has been re-evaluated and found to be ACCEPTABLE**.** ([redacted], 9/25/89).

GENE MUTATION

** 011, 024 060982 "Report on the Study of Metam-Sodium in the Ames Test," (BASF Aktiengesellschaft, FRG; Project #: 40/1MO232/85; 6/5/87). Salmonella typhimurium strains TA1535, TA1537, TA1538, TA92, TA98 and TA100 were exposed to Metam-Sodium for 48 hours, with and without metabolic activation, in duplicate standard plate tests and duplicate preincubation tests using triplicate plates. 1. Standard plate test with 0, 20, 100, 500, 2500 or 5000 ug/plate. 2. Standard plate test with 0, 500, 1000, 1500, 2000 or 2500 ug/plate. 3. Preincubation test with 0, 4, 20, 100, 500 or 2500 ug/plate. 4. Preincubation test with 0, 4, 20, 100, 200 or 300 ug/plate without metabolic activation for TA1535, TA1537 and TA100; 0, 4, 20, 100, 500 or 1000 ug/plate without metabolic activation for TA1538, TA92 and TA98. No adverse effect. There was no evidence for mutagenicity. Previously reviewed as unacceptable (Davis, 9/1/88), upon submission of information regarding formulated product, the study has been upgraded to ACCEPTABLE. ([redacted], 9/27/89).

**** 015, 024 064485, 074427** "Report on the Study for Gene Mutations in vitro of Metam-Sodium in Chinese Hamster Ovary Cells (HGPRT locus) With and Without Metabolic Activation," (BASF Aktiengesellschaft, FRG; Project #: 40/1MO232/85; 8/3/87). Chinese hamster CHO-K1 cells were exposed to 0, 0.0000464, 0.0001, 0.000215, 0.000464, 0.001, 0.00215, 0.00464 and 0.01 mg/ml of the formulated product, Metam-Sodium (batch ZH 130585; purity 42.2%) for 4 hours with and without metabolic activation in an HGPRT forward mutation assay. **Possible adverse effect** (equivocal mutagenicity with metabolic activation). Previously reviewed as unacceptable (Davis, 9/6/88), upon receipt and evaluation of the requested information about the formulated product and historical control data, the study has been upgraded to ACCEPTABLE. ([redacted], 10/2/89).

SUMMARY: Although the evidence for mutagenicity in the mammalian cell assay is equivocal and although the bacterial assay was negative, there is sufficient basis for identifying a possible adverse effect. ([redacted], 10/89).

CHROMOSOME EFFECTS

147 154551 "Metam sodium: *In Vitro* Cytogenetic Assay in Human Lymphocytes," (Mackay, J.M., CTL, Alderley Park, Cheshire, UK; Report #: CTL/E/0103; Study #: SV0759; 6/17/96). Metam sodium technical (32.3% pure) was used on cultures of human lymphocytes at 0, 5, 20 or 40 ug/ml (+S9 mix) and 0, 2.5, 20 or 30 ug/ml (-S9 mix) for 72 hours (duplicate cultures from a single donor). Mitotic index was determined by examining 1000 lymphocytes/culture. There **was an increase in clastogenesis in cultures with S9 at ≥ 20 ug/ml.** Unacceptable, not upgradeable (There was only one sampling time point and there was no repeat trial.) [redacted], 9/26/97.

** 146 154550 "Metam Sodium: An Evaluation in the Mouse Micronucleus Test," (Barber, G. & Mackay, J.M.; CTL, Alderley Park, Cheshire, UK; 4/18/96, Report #: CTL/E/0104). Metam Sodium (purity = 32.3%) was used in a micronucleus test, which was performed in 2 phases. **Phase I:** The MTD was determined based on lethalities or toxicity observed over a 4 day period after a single oral

dose to CD-1 mice (2/sex/dose) at 0, 800, 1250 and 2000 mg/kg. Subsequently, 5/sex/dose were gavaged with a single dose at 500, 800 and 1250 mg/kg. Based on results, the MTD for each sex was 500 mg/kg/day. **Phase II:** The micronucleus study was performed with a single gavage dose to CD-1 mice (5/sex/dose) at 0 and 500 mg/kg. Bone marrow samples were taken at 24 and 48 hours after dosing. **Results:** Mice displayed the following clinical signs: subdued nature, partial closure of the eyes and hunched posture. There was no increase in mucronuclei in this study. Acceptable. No adverse effect. [redacted], 9/29/97.

**** 011, 024 060983** "Report on the in vitro Cytogenetic Investigations in Human Lymphocytes With Metam Sodium," (BASF Aktiengesellschaft, FRG; Project #: 30MO232/8574; 3/9/87). The formulated product, Metam-Sodium (Batch ZH 130585; purity = 42.2%) was applied to duplicate cultures of human lymphocytes at 0, 1, 5, 10 and 20 ug/ml without activation (24 hours) and 0, 10, 20 and 40 ug/ml with activation (2 hours). 200 metaphase cells (100/culture) were scored for each dose level. **Possible adverse effect** (increased frequencies of aberrations with and without activation were observed). Previously reviewed as unacceptable (Davis, 9/6/88), upon submission of information regarding the formulated product, the study is now ACCEPTABLE. ([redacted], 9/28/89).

**** 011, 024 060984, 074426** "Cytogenetic Study in vivo of Metam-Sodium in Chinese Hamsters, Bone Marrow Chromosome Analysis. Single Oral Administration," (BASF Aktiengesellschaft, FRG; Project #: 10M0232/85116; 6/30/87). Groups of SH (chin) Ki, SPF Chinese Hamsters (5/sex/group) were dosed orally with the formulated product, Metam-Sodium, (batch ZH 130585; purity = 42.2%) at 0, 150, and 300 mg/kg groups (sacrificed at 24 hours) and at 600 mg/kg (sacrificed at 6, 24 and 48 hours). 1000 metaphase cells (100/hamster) were scored for each dose level. **Possible adverse effect** (increased frequency of chromosome aberrations in the high dose group with a sacrifice at 24 hours and increased frequencies of polyploidy in all groups.) Previously reviewed as unacceptable (Davis, 9/7/87), upon submission of the requested historical control data and information on the formulated material, the study is now ACCEPTABLE**.** ([redacted], 9/27/89).

DNA DAMAGE

011, 024 060981, 074425 "Report on the Mutagenicity Test on Metam-Sodium in the Rec-Assay with Bacillus Subtilis," (Hazleton Biotechnologies, The Netherlands; HBC Study #: E-9642-0-404; 3/27/87). The matched pair of Bacillus subtilis strains [H17 (rec+) & M45 (rec-)] was treated with the formulated product Metam-Sodium (batch ZH 130585; purity 42.2%) in three assays each with and without activation; 0, 0.1, 1.0, 5.0, 10.0, 25.0, 50.0, 100.0 and 150.0 ul/plate in two assays and 0, 0.1, 0.5, 1.0, 2.5, 5.0, 7.5, 10.0, and 15.0 ul in the third assay (triplicate plates; 24-48 hours exposure). Previously reviewed as unacceptable, the status remains unchanged after submission of information regarding positive controls and formulated material. UNACCEPTABLE. Positive control agents were marginally effective and it was difficult to determine from test results whether or not there was an increase in the zone of inhibition due to metam-sodium. Results appeared equivocal, even though a repeat test was performed. The positive control agent used with activation (sterigmatocystin), is not normally used in a rec-assay with B. subtilis. Not upgradeable. [redacted], 9/26/89).

** 011, 024 060980 "Report on the Mutagenicity Test on Metam-Sodium in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay," (Hazleton Laboratories America, Inc.: HLA Study No. 9736-0-447; 7/1/87). A primary liver cell line from an adult male Fischer 344 rat was treated in triplicate cultures with the formulated product, Metam-Sodium (batch ZH 130585; purity = 42.2%) at

0, 0.5, 1.0, 2.5, 5.0, 10, 50, 100 and 250 nl/ml for 18 hours. Fifty cells/culture were scored for unscheduled DNA synthesis. No adverse effect. There was no evidence for DNA damage. Previously reviewed as unacceptable (Davis, 9/7/88), upon submission of information regarding the formulated product, the study has been upgraded to ACCEPTABLE. ([redacted], 9/27/89).

149 154554 This volume contains a summary of all the primary genotoxicity studies with metam sodium. The overall conclusion is that metam sodium shows no in vitro or in vivo genotoxicity up to concentrations/dose levels inducing significant toxicity in the target cells/animals. This report was performed by Mackay, J.M., from CTL, Cheshire, UK. No worksheet. [redacted], 9/29/97.

NEUROTOXICITY

106, 124 126745, 132352 "An Acute Neurotoxicity Study of Metam Sodium in Rats", (I.C. Lamb, WIL Research Laboratories, Inc., WIL-188009, 9/27/93). Metam Sodium (purity = 43.15% w/w) was administered in one dose by gavage to SD Crl:CDBR rats (12-16/sex/dose) at concentrations of 0 (deionized water), 50, 750 or 1500 mg/kg. Acute Systemic NOEL = 50 mg/kg (There was a significant decrease in body weight and body weight gain at ≥ 750 mg/kg in both sexes.) There was an increase in clinical signs (found dead, gait alterations, high carriage hypoactive, hypothermia, ptosis, decreased defecation & urination and small size feces at ≥ 750 mg/kg in both sexes.) Mortality was 31% and 19% for high dose males and females, respectively.) Acute Neurotoxicity NOEL < 50 mg/kg (There was an increase in effects in the functional observational battery at ≥ 750 mg/kg. Locomotor activity tests showed significant effects in both sexes at all doses (day 0).) **No adverse effect indicated.** Originally reviewed 1/31/94 ([redacted]), additional supplemental information (individual clinical observations for all animals) was subsequently submitted by the registrant. The additional data were included with the original report. [redacted], 11/3/94.

105 126740, "A Range-Finding Acute Study of Metam Sodium in Rats", (I.C. Lamb, WIL Research Laboratories, Inc., WIL-188008, 9/22/93). Metam Sodium (purity = 43.15% w/w) was administered by gavage (single dose) to Sprague-Dawley Crl:CDBR rats (2 - 3/sex/dose) at concentrations of 150, 300, 600, 1250, 1500, 1750 & 2000 mg/kg (Part A); 50 & 2000 mg/kg (Part B); 1750 mg/kg (Part C); or 100 & 1750 mg/kg (Part D). Observation times for Part A = 15, 30, 45, 60 & 90 min., 2, 3, 4, 5, 6, 7 & 8 hr and for Parts B-D = 30, 45, 60 & 90 min., 2, 3 & 4 hr., then all groups were given detailed physical examinations for up to 8 days post treatment. NOEL = 50 mg/kg (Neurotoxic effects, decreased body weight gain and mortality were considered to be treatment-related at ≥ 100 mg/kg.) **Possible adverse effect.** These data are considered to be supplemental. ([redacted] & [redacted], 1/26/94).

113 130705 "Metam Sodium: Subchronic Neurotoxicity Study in Rats," (Allen, S.L., Zeneca CTL, Cheshire, UK; Report #: CTL/P/4334, Study #: PRO959; 5/5/94). Metam sodium (purity = 43.148%) drinking water was given to Alpk:APfSD rats (12/sex/dose) at 0 (drinking water), 0.02, 0.06 and 0.2 mg/ml (2.0, 6.0 & 14.7 mg/kg--males; 3.3, 8.4 & 17.8 mg/kg--females) for 13 weeks. Subchronic NOAEL = 0.02 mg/ml (Decreased water and food consumption in males at ≥ 0.06 mg/ml and in females at ≥ 0.02 mg/ml. Bodyweights were decreased ≥ 9% at 0.2 mg/kg in both sexes). Neurotoxic NOEL cannot be determined due to the high control level of neurone necrosis and nerve fiber degeneration. Not acceptable, but possibly upgradeable (request historical control data on neurone necrosis & nerve fiber degeneration; neurohistopathology performed on animals treated at 0.02 & 0.06 mg/ml; positive control data for FOB.) Supplemental study, at this time for SB950. [redacted], 7/6/94.

SUPPLEMENTAL STUDIES

070 113029 "3-Weeks-Toxicity of Metam Fluid (methyl-dithio carbamic sodium) lot BAS 00500N - Called for Short "Metam Fluid: - During Local Administration in Rabbits," (Leuschner, F., Laboratorium fur Pharmakologie and Toxikologie, Hamburg, FRG., 2/12/79). NOTE: This study is an exact duplicate of 029 088047 reviewed 12/26/90 [redacted]). Metam sodium (42.4% pure) was applied daily (21 days, 8 hours/day) to White Russian purebred rabbits (10/sex/dose) at 0 (1 ml 0.8% aqueous hydroxy-propylmethylcellulose gel--Type E 4 M), 31.25, 62.50 and 125 mg/kg. Each dose level had 5/sex with abraded and 5/sex with unabraded skin. For 2/sex/dose, the treatment was followed by a 21 day observation. NOEL = 31.25 mg/kg (Macroscopically erythema was observed in abraded and unabraded skin of both sexes at ≥ 62.50 mg/kg. Rhagades and edema were also recorded in abraded and unabraded skin of both sexes at 125 mg/kg. Histopathologically, erythema and epidermo-dermatitis occurred in both sexes with abraded and unabraded skin at ≥ 62.50 mg/kg. Edema was observed in females with abraded and both sexes with unabraded skin at 125 mg/kg. In males with abraded skin, edema occurred at ≥ 62.50 mg/kg.) Systemic NOEL > 125 mg/kg (No significant systemic effects were observed at any dose. These data are supplemental. [redacted] 6/10/92.

029 088047 This volume is an exact duplicate of 070 113029. [redacted], 6/10/92.

063 098867 "Pilot Dermal Absorption Study With (14C)-Metam Sodium in Female Rats," (Stewart, F.P., Hazleton UK, 10/7/91). The purpose of this study was to design a method for trapping non-absorbed volatiles and expired metabolites following dermal application of the (14C)-metam sodium to rat. Metam sodium technical (purity not stated, conc. = 512.8 g/l; batch #: CP 2891) and (14C)-metam sodium (Batch #: BAS 00500N (390/2); radiochemical purity > 99%; specific activity = 64.52 uCi/mg), buffered at pH 8 (potassium phosphate), were dermally administered to female Crl:CD(SD)BR rats (5 for pretests/2 for the definitive study) at 10 mg/rat (20 uCi/rat). A "saddle" apparatus (consisting of glass) was attached to the backs of an area clipped free of hair and glued on with cyanoacrylate adhesive. Males were excluded, as their coarse body hair might have prevented adhesion of the saddle to the skin. 24 Hours later, metam sodium was applied with a glass syringe and spread evenly over the test area. Activated charcoal was suspended between 2 sinters in the saddle and covered with gauze. Rats were then put in metabolism cages with excreta collection vessels. At 10 hours post application, the gauzes and the top sinters were removed, the charcoal was collected and the lower sinters removed. The treated area of skin and the inside of the saddle were swabbed with mild detergent and warm water before being rinsed and dried. Rats were placed back in the metabolism cages for the remainder of the study. Urine (0 - 4, 4 - 10, 10 - 24, 24 - 48 and 48 - 72 hours), feces (same as urine) and expired air were collected over 72 hours. Volatiles were collected in four expired air traps in series: 1) trap for methyl isothiocyanate, 2) carbon dioxide, 3) carbon disulphide, 4) any volatiles which may pass through the first 3 traps (air trap collection times for traps 1, 2 & 3 = same as urine; trap 4 = 0 - 72 hours). At termination, urine, feces, cage washings, cage debris, expired air traps, charcoal adsorbant, back and gauze washings (including elastic bands and sinters) were assessed for radioactivity. Rat blood was also sampled, as was residual carcass.

RESULTS: Stability of metam sodium was virtually 100% of radioactivity at 24 hours. The saddle provided a non-occluded, enclosed application site with an adsorbant suspended above it. Saddles remained firmly attached for 12-72 hours. No pharmacological or toxicological signs were observed in test animals that were metam sodium induced. After a single dermal application of (14C)-metam sodium to 2 animals, a mean of 85% of radioactivity was recovered within 72 hours, primarily in

charcoal adsorbant wash (38%), application site washings (38%) and urine (4.1%). There was a marked difference between animals in the levels of radioactivity recovered from the absorbant and application site washings. No explanation was offered in the report. MITC (0.7%) and carbon dioxide (1.9%) were the only radioactive components detected in the expired air traps. MITC was detected at a maximum between 10 - 24 hours (after removal of saddle packing). Radioactivity in feces, carcasses, cage washings, air trap 4 washings and the trap for carbon disulphide were low or below the limit of detection throughout the study. The report concluded that metam sodium was not readily absorbed during 10 hours of exposure, since < 8.2% of the applied radioactivity was recovered in urine, feces, expired air traps, cage wash and carcass. In question is the fate of the unaccounted for 15% radioactivity. These data are supplementary. [redacted], 11/4/91.

147030 088048 "The Biokinetics and Metabolism of ^{14}C-Metam Sodium in the Rat." (Hawkins, D. R. et al., Huntingdon Research Centre, Eng.; BASF # 88/0030, 11/12/87) ^{14}C-Metam-sodium was given by oral gavage to CrL:COBS (SD)CD rats at 10 or 100 mg/kg in a single dose. Five per sex per group were followed for excretion in the urine, feces and expired air as well as tissue retention. Additional animals were used for plasma levels over time and for kidney and liver contents. Metabolites were separated by thin layer chromatography. Components in the urine were similar after both doses. More radioactivity was expired as MITC at the high dose and more as radioactive CO_2 at the low dose. Study was reviewed as unacceptable (no multiple dosing regimen included) and not upgradeable as an individual study. ([redacted], 12/27/90).

50150-026 087977 Summary pages for 088048. No worksheet. ([redacted] 12/27/90).

50150-026 087978 Protocol for <u>in vitro</u> dermal absorption study and a proposed <u>in vivo</u> study for 24 hour exposure. No worksheet. ([redacted], 12/27/90).

SUPPLEMENTAL STUDIES FOR MITC

50150 112 130622 "Phase 3 Summary of MRID 41221407: Methyl Isothiocyanate: A 12-13 Week Inhalation Study in the Rat (T22)," (Davis, C.J., Schering AG, Berlin, FRG; Laboratory I.D.#: 374/77, 4/13/90). This summary showed that an inhalation study was performed on rats (10/sex/group) using MITC technical (95.69% pure) at 0 (untreated control), 0 (sham dose in the inhalation chamber), 1, 10 and 45 ppm for 12-13 weeks (5 days/week, 4 hours/day, nose only). NOEL = 10 ppm (Decreased food consumption and body weight gain in both sexes and decreased water consumption in females was observed at 45 ppm. Relative adrenal and brain weights in both sexes and relative testes and heart weights in males were increased at 45 ppm. Relative ovary, liver and thyroid weights were increased in females and absolute liver, spleen, kidney, pituitary and lymph node weights were decreased in males at 45 ppm. Clinical signs showed increased apathy, stimulated vocalization and increased salivation and discharge from the nose during exposure at 45 ppm. Ophthalmological effects were not observed at any dose.) The report was a summary only (no worksheet). No adverse effects indicated. [redacted], 1/19/95.