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

SEP 23 1993

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Suttocide A (Sodium hydroxymethylamino acetate): Review of a series of toxicological studies

Caswell No. Unknown **MRID No.** see summaries
CASE No. 023638 & 030556 **PC Code.** 128972
DP Barcode: D189874 & 189875 **Submission No.** S436048 & S436051

TO: Valdis Goncarovs / John Lee, PM Team 31
Registration Division (H7505C)

FROM: Whang Phang, Ph.D. 9/20/93
Pharmacologist
Tox. Branch II/ HED (H7509C)

THROUGH: James Rowe, Ph.D. James N. Rowe 9/20/93
Section Head, Section III
and
Marcia van Gemert, Ph.D. 9/21/93
Branch Chief
Tox. Branch II/ HED (H7509C)

Sutton Laboratories, Inc. submitted a series of toxicological studies which consisted of 23 acute toxicity studies, 2 subchronic toxicity studies, 3 mutagenicity studies, and a developmental toxicity study in rats. Majority of the acute toxicity studies were found to be unacceptable for review, and these same studies were also identified by Deborah McCall previously as such (Memorandum of D. McCall to V. Goncarovs, Nov. 5, 1991; Attachment 1). A Data Evaluation Report (DER) for each of these unacceptable acute toxicity studies was not prepared. The reasons for not accepting these studies were similar to those identified by Deborah McCall, and they will not be repeated here (please see Attachment 1). The unacceptable for review studies are listed according to the MRID number following the studies which have been reviewed. The acceptable for review studies were analyzed, and the citation and conclusion of each of these studies are presented below. The DER for each of these studies is attached.

1. Cerven, D. R. (1992) Single dose oral toxicity in rats / LD_{50} in rats: Suttocide A 50% solution. Unpublished study conducted by MB Research Laboratories, Inc; Study No. MB92-1554 A. Sept 10, 1992. Submitted to EPA by Sutton Laboratories. EPA MRID No. 424845-01.

Groups of fasted Wistar rats received (gavage) a single dose of Suttocide A 50% solution at the levels of 1000, 2500, 3200, and 5000 mg/kg. No deaths occurred at 1000 mg/kg. Seven out of 10, 9/10, and 10/10 rats died at 2500, 3200, and 5000 mg/kg, respectively. Lethargy, ataxia, and diarrhea were seen in rats that received 2500 mg/kg or above. Toxic signs such as dyspnea, ptosis, flaccid muscle tone, prostration, and coma were seen in animals which died on study. Based upon these results the LD_{50} was calculated to be 2100 mg/kg bw. The acute oral toxicity Category is III.

The study meets the data requirements for an acute oral toxicity study in rats (Guideline No. 81-1), and is classified as **core guideline.**

2. Cerven, D. R. (1992) Acute dermal toxicity in rabbits / LD_{50} in rabbits: Suttocide A 50% solution. Unpublished study conducted by MB Research Laboratories, Inc; Study No. MB92-1554 B. Aug 27, 1992. Submitted to EPA by Sutton Laboratories. EPA MRID No. 424845-02.

New Zealand White rabbits (5/sex) were dermally applied the test material at a single dose of 2,000 mg/kg bw (3.1-3.8 ml). No deaths nor toxic signs were observed. Skin irritation was reported for the first 7 days, but by day 14, all the affected areas returned to normal. Under the conditions of this study, the LD_{50} for acute dermal toxicity was greater than 2,000 mg/kg bw. The acute dermal toxicity category is III.

The study meets the data requirements for an acute dermal toxicity study in rabbits (Guideline No. 81-2) and is classified as **core guideline.**

3. Shapiro, R. (1992) EPA acute inhalation toxicity - defined LC_{50}: Suttocide A 50% solution. Unpublished study by Product Safety Labs; Study No. T-1557. July 14, 1992. Submitted to EPA by Sutton Laboratories. EPA MRID No. 424845-03.

Groups of Sprague Dawley rats (5/sex/dose) were exposed to Suttocide A 50% solution in aerosol form at the mean concentrations of 4.90, 5.92, and 6.91 mg/L for 4.5 hrs. After exposure, all treated rats showed signs of irregular or labored breathing, hunched posture, and lethargy. For treated male rats, 0/5, 4/5, and 5/5 died in 4.90, 5.92, and 6.91 mg/L groups, respectively. For females rats, 1/5, 3/5, and 2/5 died in 4.90, 5.92, and 6.91 mg/L groups, respectively. Based upon these results, the calculated combined LC_{50} for acute inhalation toxicity study for both sexes was 6.0 mg/L. The Toxicity Category for acute inhalation toxicity is IV.

The study satisfies the data requirements for an acute inhalation toxicity study (Guideline No. 81-3) and is classified as **core guideline.**

4. Mallory, V. T. (1990) Rabbit eye irritation study (with and without wash). Unpublished study conducted by Pharmakon Research International, Inc.; Study No. PH 421-SU-002-90. June 15, 1990. Submitted to EPA by Sutton Laboratories, Inc.; EPA MRID No. 419804-13.

Under the conditions of the study, Suttocide A-50% solution caused eye irritation (conjunctivitis) which was clear by day 10 after instillation into the eye of New Zealand White rabbits. The Toxicity Category for eye irritation was II.

The study meets the data requirements for a primary eye irritation study (Guideline No. 81-4) and is classified as **core minimum.**

5. Cerven, D. R. (1992) Primary dermal irritation in albino rabbits: Suttocide A 50% solution. Unpublished study by MB Research Laboratories Inc.; Study No. MB 92-1554 C. Aug 27, 1992. Submitted to EPA By Sutton Laboratories. EPA MRID No. 424845-04.

New Zealand White rabbits (4 males and 2 females) were dermally applied 0.5 ml of Suttocide A 50% solution. The rabbits were exposed to the test article for 4 hrs. No signs of dermal irritation nor systemic toxicity were seen, and the score for dermal irritation was 0.0. The Toxicity Category for dermal irritation is IV.

The study meets the data requirements for a primary dermal irritation study in rabbits (Guideline No. 81-5) and is classified as **core guideline,**

6. Reagan, E. L. (1984) Suttocide A - Dermal sensitization study: maximization test (GPMT) in guinea pigs. Unpublished study by Food and Drug Research Laboratories, Inc.; Study No. 8158. Dec 5, 1984. Submitted to EPA By Sutton Laboratories. EPA MRID No. 419804-27. powder

Groups of female Hartley-derived albino guinea pigs (10 for test article, 10 for vehicle control, and 6 for positive controls (DNCB)) received the appropriate test material dermally following the maximization test protocol. The results showed that Suttocide A induced delayed hypersensitivity in 7/10 female guinea pig.

The information on the purity and stability of the Suttocide A was not included in the report. At the present, this study is classified as **supplementary**; it does not satisfy the data requirements for a dermal sensitization study (Guideline No. 81-6). However, upon receipt and satisfactory evaluation of the missing information as indicated in the DER, the study can be upgraded.

7. Reagan, E. L. (1985) Suttocide A - Dermal sensitization study: modified Buehler test in guinea pigs. Unpublished study by Food and Drug Research Laboratories, Inc.; Study No. 8453A. June 20, 1985. Submitted to EPA By Sutton Laboratories. EPA MRID No. 419804-26. 50% Sol.

Groups of female Hartley-derived albino guinea pigs [10 for Suttocide A group, 3 naive controls, 6 positive controls, and 6 solvent (acetone) controls] were employed in a modified Buehler test. Based upon the results obtained in this study, a definitive conclusion could not be reached concerning the ability of Suttocide A to induce delayed contact hypersensitivity in female guinea pigs. The 0.5% (w/v) solution (in H_2O) of Suttocide A used in this study did not elicit any dermal responses, and a rationale was not given for selecting a non-irritating concentration for both the induction and challenging phases. Therefore, the study is classified as **supplementary** and does not meet the data requirements for a dermal sensitization study (Guideline No. 81-6).

8. Johnson, W. D. (1984) Suttocide A - 90-day oral (gavage) toxicity study in rats. Unpublished study by Food and Drug Research Laboratories, Inc.; Study No. 7824. May 15, 1984. Submitted to EPA By Sutton Laboratories. EPA MRID No. 420058-01.

Groups of Sprague-Dawley rats (10/sex/dose) received Suttocide A by gavage at doses of 0, 10, 40, and 160 mg/kg bw for 90 days. No compound-related responses were seen in this study. The NOEL for subchronic toxicity was 160 mg/kg bw (HDT). <u>This study by itself would be classified as supplementary because the highest dose tested did not induce any toxicity in the treated animals.</u> However, the registrant also submitted a 28-day subchronic toxicity study which tested higher dose levels (0, 40, 160, and 640 mg/kg bw) in similar strain of rats (Sprague-Dawley) and with gavage administration as in the 90-day study (MRID No. 419804-29; Study No. PH436-SU-001-90).

In the 28-day toxicity study, increased incidence of histopathological changes such as ulceration, gastritis, and congestion were seen in the stomach of females and ulceration in males of 640 mg/kg groups. In addition, statistically

significant decreases in body weights and in serum protein levels were found in 640 mg/kg males, and statistically significant increases in phosphorus and total bilirubin were found in 640 mg/kg bw females. When the results of these two studies were evaluated together, the combination is considered as **core minimum** and satisfies the data requirements for a subchronic toxicity study (Guideline No. 82-1).

9. Margitich, D. J. (1990) Suttocide A - repeated dose oral toxicity study in rats - 28 day. Unpublished study by Pharmakon Research International, Inc. Study No. PH 436-SU-001-90. Dec 11, 1990. Submitted to EPA By Sutton Laboratories. EPA MRID No. 419804-29.

This 28-day oral toxicity study was conducted as a supplemental study to the 90-day oral toxicity study (MRID No. 420056-01) because the highest dose tested (160 mg/kg bw) in the 90-day study was not high enough to provide adequate information concerning the subchronic toxicity of Suttocide A.

In the 28-day oral toxicity study, groups of Sprague-Dawley rats (10/sex/dose) received Suttocide A by gavage at doses of 0, 40, 160, and 640 mg/kg bw for 28 days. In the 640 mg/kg treated rats, an increase in the incidence of gastritis and ulceration in the stomach of females and an increase in the incidence of ulceration in males were seen. In addition, statistically significant decreases in body weights and in serum protein levels were found in 640 mg/kg males, and statistically significant increases in phosphorus and total bilirubin were found in 640 mg/kg bw females. No significant toxicity was seen in the 160 mg/kg rats, and this finding was consistent with that seen in the 90-day toxicity study. Based on the above findings, the NOEL for subchronic toxicity was 160 mg/kg bw; LOEL, 640 mg/kg.

When the results of this study and those of the 90-day study were evaluated together, the combination is considered as **core minimum** and satisfies the data requirements for a subchronic toxicity study (Guideline No. 82-1).

10. Margitich, D. J. (1990) Suttocide A - oral developmental toxicity study in rats. Unpublished study by Pharmakon Research International, Inc.; Study No. PH 328-SU-002-90. Dec 17, 1990. Submitted to EPA By Sutton Laboratories. EPA MRID No. 419804-30.

Group of pregnant female rats (27/dose) received Suttocide A at doses of 0, 150, 300, and 450 mg/kg bw on gestational days 6 to 15, inclusively. No developmental toxicity was seen in any dose groups. An increase in the incidence of post-dosing

salivation was seen in dams of 150 mg/kg or above. An increased incidence of reduced activity was seen in 450 mg/kg dams. A decrease in body weight gain and a reduction in food consumption was also seen in 450 mg/kg dams as well. Based on these results, the developmental NOEL was 450 mg/kg bw (HDT). The NOEL for maternal toxicity could not be established, and the LOEL for maternal toxicity was 150 mg/kg (LDT).

The study satisfies the data requirements for a developmental toxicity in rats (Guideline No. 83-3a), and it is classified as **core minimum**.

11. Haworth, S. R. (1983) Suttocide A - Salmonella/mammalian - microsome plate incorporation mutagenicity assay (Ames test). Unpublished study by Microbiological Associates; Study No. T2114.501. Sept 15, 1983. Submitted to EPA By Sutton Laboratories. EPA MRID No. 419804-31.

Suttocide A was test on Salmonella typhimurium strains TA1535, TA1537, TA1538, and TA98 at concentrations ranging from 15 to 1,000 µg/ml with or without metabolic activation. The results indicated that Suttocide A did not induce reverse gene mutations, under the conditions of the study. This study is classified as **acceptable**, and satisfies the data requirements for a gene mutation assay (Guideline 84-2a).

12. SanSebastian, J. R. (1990) Rat hepatocyte primary culture/DNA repair test on Suttocide A. Unpublished study by Pharmakon Research International, Inc.; Study No. PH311-SU-002-90. Sept 13, 1990. Submitted to EPA By Sutton Laboratories. EPA MRID No. 419804-32.

Under the conditions of the study, Suttocide A at concentrations of 2.5, 7.5, 10, and 20 µg/ml did not induce unscheduled DNA synthesis in primary rat hepatocytes. This study tested concentrations ranging from 0.75 to 100 ug/ml; however, only 2.5, 7.5, 10, and 20 µg/ml treated cells were scored. The study was classified as **unacceptable** because one of the three cover slips for 40 µg/ml treated cell was reported to be scorable for net nuclear grain counts, but the report contained no data for that cover slip. This study could be upgraded upon receipt and satisfactory evaluation of the missing data. The study currently does not meet the data requirements for other genotoxic effects (Guideline No. 84-4).

13. SanSebastian, J. R. (1990) Micronucleus test (MNT) on Suttocide A. Unpublished study by Pharmakon Research International, Inc.; Study No. PH 309-SU-001-87. May 18, 1987. Submitted to EPA By Sutton Laboratories. EPA MRID No.

419804-33.

Groups of CD-1 mice (5/sex/dose) received a single oral administration of Suttocide A 50% solution by gavage at dose levels of 750, 1250 or 1275 mg/kg bw. The bone marrow cells were harvested from the treated mice at 30, 48, or 72 hrs. Although signs of toxicity such as decreased activity, decreased muscle tone, and piloerection were reported in the Suttocide A 50% solution treated animals, induction of micronuclei in bone marrow cells were not found. This study satisfies the data requirements for a structural chromosomal aberration assay (Guideline No. 84-2b) and is classified as **acceptable.**

The studies which are judged to be **unacceptable** for review are listed below, and the reasons for the rejecting these studies are presented in the memorandum from Deborah McCall to Valdis Goncarovs (please see Attachment 1)

	MRID No.	Study Type	Study No.
1.	419804-10	Acute oral toxicity-rats	H-9304
2.	419804-11	Acute oral toxicity-rats	6185a
3.	419804-12	Acute dermal toxicity-rabbits	6185a
4.	419804-14	Primary eye irritation-rabbit	6261a-1
5.	419804-15	Primary eye irritation-rabbit	6261a-2
6.	419804-16	Primary eye irritation-rabbit	H-8712
7.	419804-17	Primary dermal irritation-rabbit	8158
8.	419804-18	Primary dermal irritation-rabbit	6550A
9.	419804-19	Primary dermal irritation-rabbit	04515
10.	419804-20	Primary dermal irritation-rabbit	04516
11.	419804-21	Primary dermal irritation-rabbit	H-8713
12.	419804-22	Primary dermal irritation-rabbit	H-8713A
13.	419804-23	Primary dermal irritation-rabbit	6261a-1
14.	419804-24	Primary dermal irritation-rabbit	6261a-2
15.	419804-25	Primary dermal irritation-rabbit (Dermal range finding study in guinea pigs)	8453A
16.	419804-28	Primary dermal irritation-rabbit	10864

As a summary, the toxicology studies which are required to satisfy the labeling and Tier 1 data needs for an antimicrobial agent, and the studies which have been reviewed and which have either satisfied or have not fulfilled the data requirements are listed below:

Study Type	Tier 1 or labeling Requirements	Satisfied
Acute oral toxicity	Yes	Yes
Acute dermal toxicity	Yes	Yes
Acute inhalation toxicity	Yes	Yes
Primary eye irritation	Yes	Yes
Primary dermal irritation	Yes	Yes
Dermal sensitization	Yes	No
Subchronic oral toxicity	Yes	Yes
Developmental toxicity	Yes	Yes
Mutagenicity Studies		
a. Gene mutation	Yes	Yes
b. Structural chromosomal aberration	Yes	Yes
C. Other genotoxic effects	Yes	No

The 1987 Data Call-In notice states that if a 90-day feeding study is conducted, the relative efficiency of the uptake of the chemical by the animal via dermal and oral exposure must be determined in order that the oral doses can be converted to dermal exposure. Thus far there is no information concerning dermal absorption of Suttocide A. The registrant should provide relevant information concerning dermal penetration of this chemical so that the Agency could appropriately convert from oral exposure (used in developmental and subchronic toxicity studies) to possible dermal exposure when the need arises.

ATTACHMENT 1

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

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: New Chemical Screen on Suttocide A (sodium hydroxymethylglycinate)

HED Project No. 2-0218

TO: Valdis Goncarovs
Product Team 31
Registration Division (H7505C)

FROM: Deborah L. McCall DLMcCall 11-5-91
Toxicology Branch II / Section III / (H7509C)

THROUGH: James Rowe, Ph.D., Section Head James Rowe 11/5/91
Toxicology Branch II / Section III / (H7509C)
- and
Marcia Van Gemert, Ph.D., Branch Chief Marcia Van Gemert 11/5
Toxicology Branch II / HED (H7509C)

In response to the registration application for Suttocide A, a new chemical screen was performed. The registrant submitted 25 studies. Suttocide A does not pass the new chemical screen. At the present time only 6/25 of the studies are acceptable for review. The majority of the studies submitted were incomplete and had insufficent information for evaluation. Also, in order to complete the Tier I AMDCI requirements these studies are required: an Acute Inhalation Study, and 90-Day Dermal Study. The rejection reasons and conclusions are listed below:

1) Acute Oral in Rats (§81-1) (MRID No. 419804-10) - The study is unacceptable as submitted until further information is provided on: identification of test substance, daily observations for mortality and moribundity, individual daily observations for toxic signs, daily body weights, and length of observation period.

2) Acute Oral in Rats (§81-1) (MRID No. 419804-11) -- The study is unacceptable as submitted until further information is provided on: identification of test substance, daily observations for mortality and moribundity, individual observations for entire day of dosing, and justification for the necropsy of dead animals only.

3) Acute Dermal in Rabbits (§81-2) (MRID No. 419804-12) - The study is unacceptable as submitted until further information is provided on: identification of test substance, daily observations for mortality and moribundity, individual observations for the entire day of dosing, justification for use of only 6 rabbits, and justification for why gross necropsy was not performed.

4) Primary Eye Irritation in Rabbits (§81-4) (MRID No. 419804-13) -The study is unacceptable as submitted until further information is provided on: individual observations for the entire day of dosing, and individual observations for mortality and moribundity.

5) Primary Eye Irritation in Rabbits (§81-4) (MRID No. 419804-14) -The study is unacceptable as submitted until further information is provided on: identification of test substance, justification as to why the study stopped on Day 7 and conjunctival effects were still present, the 1 hr observations (postdose), individual observations for the entire day of dosing, and individual observations for mortality and moribundity.

6) Primary Eye Irritation in Rabbits (§81-4) (MRID No. 419804-15) -The study is unacceptable as submitted until further information is provided on: identification of test substance, the 1 hr observations (postdose), individual observations for the entire day of dosing, and individual observations for mortality and moribundity.

7) Primary Eye Irritation in Rabbits (§81-4) (MRID No. 419804-16) -The study is unacceptable as submitted until further information is provided on: identification of test substance, justification for the use of only 2 rabbits, dosing volume, identification of the grading system, the 1 hr observations (postdose), individual observations for the entire day of dosing, and individual observations for mortality and moribundity.

8) Primary Dermal Irritation in Rabbits (§81-5) (MRID No. 419804-17) - The study is unacceptable as submitted until further information is provided on: size of application site, justification for 24 hour exposure, provide grading scores for the 1 and 48 hr observations (postdose), justification for using only 3 rabbits, individual observations for the entire day of dosing, and individual observations for mortality and moribundity.

9) Primary Dermal Irritation in Rabbits (§81-5) (MRID No. 419804-18) - The study is unacceptable as submitted until further information is provided on: identification of test substance, size of application site, justification for 24 hour exposure, provide grading scores for the 1 and 48 hr

observations (postdose), individual observations for the entire day of dosing, and individual observations for mortality and moribundity.

10) Primary Dermal Irritation in Rabbits (§81-5) (MRID No. 419804-19) - The study is unacceptable as submitted until further information is provided on: identification of test substance, justification for 24 hour exposure, provide grading scores for the 1 and 48 hr observations (postdose), justification for using only 3 rabbits, individual observations for the entire day of dosing, and individual observations for mortality and moribundity.

11) Primary Dermal Irritation in Rabbits (§81-5) (MRID No. 419804-20) - The study is unacceptable as submitted until further information is provided on: identification of test substance, justification for 24 hour exposure, provide grading scores for the 1 and 48 hr observations (postdose), justification for using only 3 rabbits, individual observations for the entire day of dosing, and individual observations for mortality and moribundity.

12) Primary Dermal Irritation in Rabbits (§81-5) (MRID No. 419804-21) - The study is unacceptable as submitted until further information is provided on: identification of test substance, size of application site, duration of test, methodology of application, identify scoring system, provide grading scores for the 1 and 48 hr observations (postdose), justification for using only 2 rabbits, individual observations for the entire day of dosing, and individual observations for mortality and moribundity.

13) Primary Dermal Irritation in Rabbits (§81-5) (MRID No. 419804-22) - The study is unacceptable as submitted until further information is provided on: identification of test substance, size of application site, duration of test, methodology of application, identify scoring system, provide grading scores for the 1 and 48 hr observations (postdose), justification for using only 2 rabbits, individual observations for the entire day of dosing, and individual observations for mortality and moribundity.

14) Primary Dermal Irritation in Rabbits (§81-5) (MRID No. 419804-23) - The study is unacceptable as submitted until further information is provided on: identification of test substance, justification for 24 hour exposure, size of application site, provide grading scores for the 1 and 48 hr observations (postdose), individual observations for the entire day of dosing, and individual observations for mortality and moribundity.

15) Primary Dermal Irritation in Rabbits (§81-5) (MRID No. 419804-24) - The study is unacceptable as submitted until further information is provided on: identification of test substance, justification for 24 hour exposure, size of application site, provide grading scores for the 1 and 48 hr observations (postdose), individual observations for the entire day of dosing, and individual observations for mortality and moribundity.

16) Dermal Sensitization in Guinea Pigs (§81-6) (MRID No. 419804-25) - The study is unacceptable as submitted until further information is provided on: positive controls, justification for using only 4 animals, and why wasn't the enclosed protocol followed.

17) Dermal Sensitization in Guinea Pigs (§81-6) (MRID No. 419804-26) - The study is acceptable for review.

18) Dermal Sensitization in Guinea Pigs (§81-6) (MRID No. 419804-27) - The study is acceptable for review.

19) Dermal Sensitization in Guinea Pigs (§81-6) (MRID No. 419804-28) - The study is unacceptable as submitted: incomplete, and submit rationale for intracutaneous dose.

20) Subacute (28-days) Oral in Rats (§82-1) (MRID No. 419804-29) - The study is unacceptable as submitted until further information is provided on the analysis and stability of the test substance.

21) Subchronic Oral in Rats (§82-1) (MRID No. 420058-01) - The study is unacceptable. Highest dose tested - 160 mg/kg did not exhibit any signs of toxicity.

22) Developmental Study (oral) in Rats (§83-3) (MRID No. 419804-30) - The study is acceptable for review.

23) Mutagenicity - Salmonella/Ames (§84-2) (MRID No. 419804-31) - The study is acceptable for review.

24) Mutagenicity - Rat Hepatocyte/DNA Repair (§84-2) (MRID No. 419804-32) - The study is acceptable for review.

25) Mutagenicity - Micronucleus Test (§84-2) (MRID No. 419804-33) - The study is acceptable for review.

cc: Charles Frick