ESTABLISHMENT INSPECTION ENDORSEMENT

Page 1 of 1 Pages

1. ESTABLISHMENT

a. ESTABLISHMENT NAME: HAZLETON LABORATORIES AMERICA, INC.

b. DISTRICT: BALT.

c. CENTRAL FILE NO.: 11534

d. ESTABLISHMENT ADDRESS: 9200 Leesburg Pike
Vienna, Virginia 22180

e. DATE INSPECTED: 12/3 & 4/75

2. ROUTING

a. HEADQUARTERS UNIT TO WHICH REFERRED (Use organizational symbol)

Carlton Sharp
G. D. Searle Investigation Task Force

b. REASON FOR REFERRAL

Aspartame Investigation

HEADQUARTERS USE ONLY

c. DATE REFERRED

d. AF NUMBER

3. DISTRICT REMARKS

a. DISTRICT ENDORSEMENT

As requested by Carlton Sharp of the Searle Investigation Task Force, we visited this firm to place all original records, slides, and tissue blocks from studies on Aspartame conducted for Searle Laboratories under FDA seal. Hazleton Laboratories did not object to this procedure, and all material from the following studies were officially sealed and left in the possession of the firm:

SEARLE PT #	HAZLETON #	TITLE
E11 367H71	700-239	Two generation reproduction study in rats
E3 4838H71	700-233	Two Year Toxicity Study in rats and supplemental study on brains
E10 892H72	700-240	Lifetime Toxicity Study in rats and supplemental study on brains.
E25-934H73	700-259	104 Week Toxicity Study in mice
E24 985H73	700-260	110 Week Toxicity Study in mice
E9 893H71	700-241	Toxicological evaluation in Neonatal rats
E5 1011H72	700-255	Segment III Perinatal weaning study in rats
E20-719H68	700-200	Two month oral administration in rats
E21 720H68	700-201	Two month oral toxicity study in dogs

F/U: These studies will be reviewed at a later date.

b. REVIEWING OFFICER (Name and title)

c. SIGNATURE

d. DATE

e. DISTRIBUTION

FD FORM 481a (7/69) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

37

February 18, 1976

ASPARTAME

INTRODUCTION

This investigation covered preclinical animal studies conducted with Aspartame (L-Aspartyl-L phenylalanine Methyl Ester), a sweetening agent, and its breakdown product (metabolite), diketopiperazine (DKP).

Searle has completed approximately 90 preclinical studies relating to the sweetener Aspartame and its breakdown product DKP. In addition a number of studies are still in progress. Of the preclinical studies, approximately 25 were conducted at Hazleton Laboratories, five at the University of Wisconsin, and the remainder at Searle Laboratories. Attached as Exhibit G-1 is the index of Master File No. 134 for Aspartame.

During this investigation, we examined four chronic toxicity studies and one acute toxicity study, which are as follows:

1. P.T. #988S73-115 Week Oral Tumorigenicity study in the rat, conducted with SC-19192 (DKP). The study was conducted at Searle Laboratories, from November 1971 to February 1974.

2. P.T. #852S72 - 46 Week Oral Toxicity Study in the hamster, conducted with SC-18862 (Aspartame), at Searle Laboratories from April 1970 to March 1971.

3. P.T. #855S70 - 106 Week Oral Toxicity in the dog, conducted with SC-18862, at Searle Laboratories, from March 1970 to April 1972.

4. P.T. #8560T70 - 52 Week Oral Toxicity Study in the infant monkey, with SC-18862, performed at the University of Wisconsin Primate Center, January 1970 to April 1971.

5. Acute Toxicity Studies in the rat, mouse, and rabbit, with SC-19192 conducted at Searle Laboratories from January 1970 to September 1972.

The aspartame utilized by the firm for both clinical and preclinical studies was manufactured in Japan by Ajinomoto Company, Inc. A few pilot batches of Aspartame were manufactured in-house by Searle chemists in the Chemical Research and Development Sections in 1969 and 1970. Some of these early batches may have been used in some early LD_{50} studies, but none were used in the preclinical studies that we examined. Currently, all aspartame is received from Ajinomoto in 250 kg. batches.

The breakdown product (DKP) utilized for preclinical studies was manufactured in-house by Searle chemist Jack Drogt.

SCOPE OF INVESTIGATION

The following raw data was checked against the Food Additive Petition to FDA, for each study examined: Randomization tables; body weight/food intake records; hematology/clinical chemistry records; gross and microscopic pathology records; organ weight records; and records concerning statistical analysis, which were performed by the Math-Stat Department. We also reviewed correspondence files and examined the animal housing facilities, animal receiving and quarantine areas, compound weighing and treatment blending equipment, and quality control records for both compounds.

SUMMARY OF FINDINGS

Following is a summary of our findings for each of the four chronic toxicity studies, and the acute toxicity study, which were the subject of this investigation.

SC-19192: 115 Week Oral Tumorigenicity Study in the Rat (i) E77/8

The following deficiencies, and/or objectionable conditions were noted with respect to the 115 week rat study: P.T. 988S73

1. With respect to the housing and control of animals, and the blending, control and administration of treatment mixtures used in the study, we observed the following:

a. Control and treated animals were randomly distributed on the same rack. This procedure is still in effect.

b. Animals were not individually identified, except by means of a card on the front of each cage. This procedure is still in effect.

c. Containers for treatment mixtures are inadequately identified in that old identification labels for different dosage levels, are not removed before affixing new labels. This procedure is still in effect.

d. There were no running inventory records of either treatment mixtures or test compound used in treatment mixtures.

e. There were no records covering the weighing of the test compound and blending of treatment mixtures.

f. No assays were conducted for homogeneity of treatment mixtures used in this study. A stability study was conducted with Rockland basal diet in 1971, to generate background stability data on SC-19192 in the rat/mouse diet at room temperature. However, the 115 week rat study employed Purina basal diet from week 62 to its conclusion, and no stability studies had been conducted with Purina basal diet.

g. Food cups were not individually identified, yet all cups for a given housing group were removed from cages and placed on a moveable cart for filling. After weighing and filling, the cups were returned to the cages. The arrangement of food cups on the cart is shown in Exhibit R-17. This procedure is still in effect.

h. The submission to FDA states that 12 different batches of SC-19192 were used in this study. Each batch used adds an unnecessary variable to the study. All batches could have been blended into one homogeneous batch.

2. Approximately 98 of the 196 animals that died during the study were fixed in toto and autopsied at some later date, in some cases more than one year later. The procedure for fixing in toto was also deficient in that the fixative was approximately 1500 ml (less than the accepted volume of 20 times the mass of the animal), and there was no evidence that the fixative was changed.

3. Records indicated that animal F6HF, a high dose female, was found dead at 787 days of treatment, and the pathology sheet reported a tissue mass measuring 5.0 x 4.5 x 2.5 CM. The submission to FDA reported no tissue mass and the animal was excluded from the study due to marked autolysis.

4. A total of 20 animals were excluded from the study due to excessive autolysis. Of these 17 had been fixed in toto and autopsied at a later date.

5. Records for approximately 30 animals showed significant discrepancies between gross observations on pathology sheets, when compared with the individual pathology summaries submitted to FDA: (a detailed description of 10 of these discrepancies is included in the report).

6. Animals were examined for tumors at 1 month intervals after the first 12 weeks of the study, and since this was a tumorigenic study, animals should have been examined more often at the tumor bearing age.

7. Records indicated that one tissue mass, measuring 1.5 x 1.0 CM was excised from animal B3HF.

8. Records indicated that a "skin incision over mass" was performed on two treated animals, C22LM and G25LM, on February 10, 1972. The reason for this unusual procedure was to "take a look and see what was inside."

9. Ante-mortem observations of tissue masses do not include an accurate measurement of the mass, but only a visual estimate of the size.

10. The protocol states that one half of each kidney was to be serially blocked and frozen and that 4 blocks of liver were to be fixed and frozen. There were no records to indicate that this was done and we were told that no frozen sections were taken of liver or kidney.

11. Protocol specified that female breast tissue was to be embedded. We were told that breast tissue was examined from both male and female rats. The gross pathology report for animal J1CM indicated that the hisopathology technician noted the absence of mammary tissue submitted for sectioning. The submission to FDA does not exclude breast tissue from the tissues examined. Our examination of slides revealed no section of mammary gland.

12. Records indicated that at the scheduled 104 week bleeding, animal E02CM was substituted for animal A11CM. Records also indicated that animal A11CM was alive on this date and therefore should have been bled as scheduled.

13. Clinical chemistry determinations were not made at the termination (114 weeks) of the study. The protocol indicated that clinical chemistry determinations, including serum cholesterol, were to have been performed at termination. Page 28b, Volume I of the submission reported a significant decrease in serum cholesterol that was more perceptible towards the end of the study, and may have been related to compound administration. Nevertheless, the terminal blood samples were not analyzed for serum cholesterol or other clinical chemistry parameters and we were told that the blood samples were discarded.

14. Animals were infected with a disease at approximately the 78th week of the study, which was not reported in the submission to FDA. Penicillin was administered I.M. during the course of this disease.

15. Daily observation records were sometimes signed or initialed prior to the completion of these records, and the data entered later by another person, whose signature or initials did not appear on the record.

16. Observation records indicated that animal A23LM was alive at week 88, dead from week 92 through week 104, alive at week 108, and dead at week 112.

17. The above mentioned record pertaining to the monthly observation of animal A23LM also has a discrepancy in dates: Week 88 is dated July 16, 1973, and week 92 is dated June 13, 1973.

18. The table on page 25 of the submission to FDA has an erroneous value for food intake and dosage, low dose males, at 7 to 14 days; the value of 15.9 is erroneous, and should be more than 20, according to our calculations. This error is fully explained under the caption Body Weights and Food Intake.

19. A 100 gram error in body weight was noted in the computer printout attached as Exhibits R-51 and R-52.

20. Records indicate that errors of 17% to 33% occurred in calculating dosage concentrations for treatment mixtures during one feeding period.

21. Table 1, page 12 of the submission to FDA indicates that there were 28 survivors of 36 animals in the mid dose female group at 96 weeks of treatment. The original weekly mortality records indicate 25 survivors. Biology research reports for 44 weeks of treatment also have erroneous data when compared with the original mortality data sheets.

22. Page 164 of the submission to FDA shows hematology data, including RBC values for treatment day 735. The original hematology records show the treatment day to be 734, and the values listed in the submission do not agree with the orignal data.

23. Page 4 of the submission to FDA states that food spillage by individual animals was recorded; whereas food spillage was not quantitatively determined or recorded.

SC-18862: 52 Week Oral Toxicity Study in the Infant Monkey (xii) E32

This study was conducted at the Wisconsin Regional Primate Center, University of Wisconsin, Madison, Wisconsin.

The study was conducted by Dr. Harry A. Waisman, M.D., Ph.D., with Mr. Gunther Scheffler, Technician, doing most of the actual work with the monkeys. Dr. Waisman was acting as a consultant and recieved a documented total of [redacted] for his services.

The study was originally scheduled for 52 weeks "+". The study was initiated 1-14-70. There were a total of seven monkeys used during the study. Two were at the low dose level, three at the medium dose level, and two at the high dose level. Historical controls were employed. The study was terminated after Dr. Waisman's death on March 19, 1971.

Dr. Robert G. McConnell, Director, Department of Pathology/Toxicology, said the protocol was written "retrospectively after discussion with Dr. Waisman". The protocol was written by Dr. McConnell after the study had started but prior to termination of treatment. The protocol has written notations along the left border which states "VAD JAB Waisman 3-1-70 RAM 10-21-70": VAD is Victor A. Drill, JAB is James A. Buzard and RAM is Robert A. Moe.

The final report was co-authored by Dr. Suryanarayana K. Rao, D.V.M., M.S., Ph.D., and Dr. McConnell. The report is dated October 10, 1972. It was submitted to FDA on or about January 25, 1973.

A review of available data at Searle Laboratories, Primate Research Center, University of Wisconsin, and from the submission to FDA revealed the following discrepancies.

I. Protocol

A. No behavioral testing was done.

B. The protocol calls for six animals and seven were used.

C. No documentation that prothrombin times were monitored at 26 and 52 weeks.

D. GPT (glutamic pyruvic transaminase) was not analyzed at 26 and 52 weeks. There is no documentation that this was done. Plasma GOT (glutamic oxalacetic transaminase) was done.

E. No documentation that chlorine values were determined.

F. No eye examinations were performed.

II. Use of historical controls without giving all comparative values in the submission for parameters measured in animals on the study.

III. Submission to FDA

A. Monkeys were reported as being randomly divided into three groups. Actually the high dose group was placed on the study first, and mid dose second and the low dose last.

B. No mention is made in the submission of obvious birth defects in monkey P53. This is specifically referred to in a memo dated as received June 23, 1971, and a handwritten memo which is dated and unsigned.

C. No mention is made in the submission that a technician at the University of Wisconsin had stated that the newborn infant monkeys were not entirely suitable because of questionable nutritional status and reproductive history of the mothers. Maternal animals had been employed in earlier studies.

D. Submission states that availability of acceptable historical and contemporary data on untreated monkeys from Waisman's group reduced the necessity of a concurrent control group. Dr. McConnell stated in a memo of January 19, 1972, that the historical control data relied on by Waisman was no longer available to Searle. Dr. McConnell further states that he suggested the monkeys not be purchased. This memo was written approximately 9 months prior to the submission to FDA.

S 305 None

E. Submission states that animals were not available for sacrifice and necropsy at the termination of compound administration due to a shortage of personnel and supervision following Dr. Waisman's death. The submission also states that medium and high dose monkeys were kept under observation for 3 months on powdered Similac following termination of treatment. However, a memo "received (Davenport) 6-23-71 RgMCK" states that all six of the surviving monkeys are available. This memo is dated 3 months after Dr. Waisman's death. A second memo dated January 19, 1972, from Dr. McConnell some 10 months after Waisman's death states "these six monkeys have been

housed (and maintained on basal diet and are currently available for purchase and subsequent postmortem work-ups). These memos and the statement in the submission covering availability of monkeys are contradictory. The actual situation was that the monkeys were available but Searle decided not to purchase them.

F. Submission states that administration of aspartame to infant monkeys from birth and continuing for 30 consecutive weeks caused no biologically meaningful alterations in physical or behavioral findings. No documented behavioral testing was done. During an interview with Dr. Davenport and technician Gunther Scheffler, employees at the Primate Center, they confirmed no behavioral testing was done.

G. The records of frequency of seizures in the mid and high dose animals are not available in the submission and the data.

H. Submission does not mention the confirmed proteus infection of the animals. The infection was listed as Shigella which was not documented as a confirmed diagnosis.

I. Submission reports monkey M-38 died after 300 days on the treatment. The daily observation records indicates the monkey died after 281 days of treatment.

J. The intake of aspartame and diketopiperazine (DKP), the conversion product, cannot be calculated from data submitted. The compound concentration was varied when the taste was found to be disagreeable. In order to calculate compound intake the raw data for each animal would have had to have been submitted.

K. Dr. Rao is listed as primary author. He was not employed at Searle until approximately three months after termination of treatment.

IV. Three lots of compound were used during this study. One lot was not analyzed for diketopiperazine.

V. Absence of interim reports referred to in documents.

A. Report covering Dr. Waisman's seminar given at Searle in October 1970.

B. Data of reports covering behavioral testing as referred to in the submission to FDA.

Interviews held with Dr. Rao and McConnell, co-authors of the submission to FDA, led to little or no clarification of questions raised during the investigation.

III. SC-18862: 46 Week Oral Toxicity Study in the Hamster (x) E27/35

This study was initiated on April 20, 1970, and was scheduled for termination at 104 weeks. The study was terminated after 46 weeks due to a high mortality rate in all animals due to a disease referred to as "wet tail". The intent of the study, was "to evaluate the safety of multiples of the modal daily anticipated human intake and to induce and define such adverse effects as might occur only at prodigious multiples of such intake".

The authors of the report are Dr. K. S. Rao and Robert S. McConnell of Searle Laboratories and Dr. J. Mauro, Microscopy for Biological Research Ltd., Department of Pathology, Albany, New York. Tissue slides were submitted to and read by Dr. Mauro.

Deviations noted during the review of data at Searle include the following:

1. Statements made in submission which were not confirmed during examination of original data:

a. Litters were culled or arbitrarily reduced to a maximum of 10 pups to be nursed. Some litters had more than 10 pups alive at the start of the test.

b. Sixty pregnant hamsters were used. However 66 pregnant hamsters were purchased but pups from only 59 were used.

c. Glucose values were reported at 26 weeks of treatment, however, these values were actually determined at 38 weeks.

d. Submission states that "animals which died during the experiment and all survivors were necropsied promptly whereas some animals which were fixed in toto were autopsied more than 1 year after fixation.

2. Animals were not individually identified.

3. Record Keeping:

a. Hamsters which had excessive food spillage (documented by records) were given additional food. Other animals with no documented food spillage were given the same amount of additional food indicating that the record keeping is inept or food intake records are meaningless.

b. Observation for drug effect records which show when an animal dies or is sacrificed have inconsistent dates. Hamster N14LM was shown to have been sacrificed on February 12, 1971, and another record shows the animal to have been found dead on February 14, 1971.

c. Observation for drug effects records are inconsistent. Records for hamster No. N9LM indicate this animal was not alive on October 23, 1970, alive on November 20, 1970, not alive on December 18, 1970 and January 15, 1971 and alive February 12, 1971, and was found dead on February 25, 1971.

d. Records for observations of abnormality, specifically diarrhea or "wet tail", are not consistently recorded. Some gross pathology records state diarrhea was observed prior to death. Observation for drug effect records and/or body and feeder weight records do not substantiate the statement on the gross pathology records.

4. Some control animals were administered Neomycin Sulfate. This finding was not reported in the submission to FDA. Furthermore, the records indicate that this treatment exacerbated the flora inbalance of these animals and appeared to enhance the mortality rate of these control animals that were treated with antibiotics. If this stated assumption is correct, the mortality data as submitted in the FAP is misleading for the control group.

5. Survival:

a. An animal at the very high dose level was reported lost. However, this animal was included as a fatality in the mortality table.

b. Another very high dose animal died from an overdose of ether during blood sampling. This animal was reported as a fatality in the mortality table with no explanation.

6. Discrepancies between individual animal values and mean values which were submitted in summary tables in the FAP.

a. Mean values for BUN at 26 weeks of treatment could not be determined for control and low dose males when compared to the data in appendix table 4.

b. Mean values for final body weight as submitted in table 9 could not be confirmed when compared with individual body weight submitted in appendix table 5.

7. At necropsy the prosector took seminal vesicles and prostate from animal H5CF designated as a female. Review of slides for this animal indicate it was; indeed a female. Nine tissues were found to correspond with the legend for stomach, lung, heart, kidney, liver, spleen, adrenal, ovary, and urinary bladder. Unless more than one organ tissue was placed on the same slide, bile duct, pancreas and lymph nodes were not examined as stated in the submission to FDA.

8. Dr. K. S. Rao, principal author of the report, was not employed at Searle Laboratories until approximately 3 months after the study was terminated.

SC-18862: 106 Week Oral Toxicity Study in the Dog E28 (ii)

Following is a summary of the deficiencies and/or objectionable conditions noted during our investigation of the above study:

1. No assays were conducted for potency or homogeneity of treatment mixtures used in this study.

2. The submission states that dogs ranged from 150 to 160 days of age, whereas 3 male dogs were actually 220 to 235 days of age. All three of the older dogs were in the treatment groups, none having been assigned to the control group.

3. The submission states that powdered KASCO dog basal diet was fed throughout the study, whereas records show that Purina meal, KASCO mini-chunks, and Wayne dog pellets were also used during the study.

4. The submission states that an evaluation of motor and behavioral activity, locomotion, external appearance, and digital palpation for tissue masses were conducted prior to initiation of treatment and concurrent with each body weight measurement, and that unusual signs were routinely recorded. We found no records in which the above findings were recorded.

5. The submission states that no significant variations in body weight were observed between the control and treated dogs. However, raw data indicates that at 16, 26, 40 and 44 weeks, the percent body weight gain is definitely less in the high dose group. For example at 26 weeks the percent body weight increase for control male dogs was 93.3% and 51.5% for the high dose male dogs. In addition, Dr. McConnell stated, in an internal memorandum that there was definitely a compound related effect in both sexes at 26 weeks of treatmert.

6. Records indicate that approximately 70.3 kg. of SC-18862 was used for the first 20 weeks of the study. Our calculations indicate that approximately 79.0 kg would be necessary to achieve these dosage levels for the same time period.

7. Daily food consumption records, when compared with summary tables, show conflicting figures for the amount of compound ingested for one dog at 76 to 80 weeks of feeding. The figures were 12.8 and 13.3 g, respectively.

8. The submission indicates that there was no DKP in the four Aspartame lots used for the first 20 weeks of the study. The records showed that one of these four lots was not analyzed for DKP and another contained 0.5% DKP.

9. Results of cholesterol and triglyceride values which were determined at 95 weeks were not included in the submission to FDA.

10. Obvious errors in mean values were observed in summary tables when compared with individual values in the submission. Two of these errors involved geometric means.

11. The submission states that all dogs remained in good health throughout the study. Records indicated that one dog (D19HM) was sick for three weeks and was administered somthing orally.

12. Records indicate that animal D19HM had a mass (skin growth) during the period from July 7, 1970 (71) to August 1, 1970 (71), which had fallen off. This mass was not reported to FDA.

13. Animal B17HM was administered an antibiotic and had two surgical amputations of its tail. Neither the administration of antibiotics, or the surgery, was reported in the submission to FDA.

14. The gross pathology record for animal D4CM, as submitted to FDA, omitted any reference to the brain. The original pathology sheet reported a "notable symmetrical dilatation of the lateral ventricles".

HISTORY OF BUSINESS

Searle Laboratories, a Division of G. D. Searle & Company, currently manufactures and/or distributes approximately 22 drug products. An additional 12 or 13 products, including most of the firm's oral contraceptives, are manufactured in the Puerto Rico plant. World wide, G. D. Searle has subsidiaries in 41 countries. Attached to the report is a copy of the firm's annual report for 1974, and the third quarter report for 1975 (Exhibit G-2). Also attached (Exhibit G-3) is a current list of products manufactured by Searle Labs, with the total units produced in 1975, through the third quarter.

At the present time, Aspartame is being manufactured by Ajinomoto Co., Ltd., in Japan, and is being shipped to Searle by boat, in lots of 250 kg. The product is currently being stored in a commercial storage facility, General Warehouse, 21 W. Lake St., Northlake, Illinois. According to the third quarter report, the firm currently has an [redacted] inventory of Aspartame. The annual report also states that [redacted] dollars have been commited for a new Aspartame manufacturing plant.

G. D. Searle & Company has established a new division, called New Ventures, which was created for the commercial development and marketing of Aspartame. The Director of this new company is James H. Ensor, Vice President (Exhibit G-8). Mr. Ensor is Chairman of G. D. Searle International Company.

Following is the current chain of command at Searle Laboratories:

Dr. James A. Buzard
Executive Vice President, G. D. Searle & Company.

Robert Moe
Senior Vice President, Scientific Affairs.

Dr. Robert G. McConnell
Director, Pathology-Toxicology.

Some recent changes in management have occurred. Dr. Paul Klimstra formerly was second in command, but has been replaced by Robert Moe as of July 15, 1975. A new position, Director of Drug Safety, has been created but has not yet been filled.

PERSONS INTERVIEWED AND INDIVIDUAL RESPONSIBILITY

Credentials were shown, and a written Notice of Inspection was issued to Dr. William M. Merino, Director, Domestic Pharmaceutical Products, Regulatory Affairs Department.

The pre-clinical studies examined during this investigation encompassed the period from January 1970, to January 1974.

In 1970, Victor A. Drill was Director of the Biological Research Department, and was responsible for all pre-clinical and clinical research performed at that time. Robert McConnell was Director of Pathology-Toxicology Section. In 1971, Robert Moe assumed the position of Director, Biological Research Department, replacing Victor Drill, who retired.

Following is a year by year breakdown of the key personnel involved in the pre-clinical research:

1970

Victor A. Drill - Director, Biological Research Department.

David Calhoun - Manager, Biostatistics Section.

Robert McConnell - Director, Pathology-Toxicology Section.

Tony Martinez - Toxicology Laboratory Supervisor.

1971

Robert Moe - Director, Biological Research Department.

Robert McConnell - Director, Pathology-Toxicology Section.

K. S. Rao (June, 1971) - Manager, Toxicology Laboratory.

Tony Martinez - Toxicology Laboratory Supervisor.

1972

Robert Moe - Director, Biological Research Department (January through April).

F. Saunders - Director, Biological Research Department (May through December).

Robert McConnell - Director, Pathology-Toxicology Section.

K. S. Rao - Manager, Toxicology Laboratory.

Tony Martinez - Toxicology Laboratory Supervisor.

1973 (January to June)

Francis Saunders - Director, Biological Research Department.

Robert McConnell - Director, Pathology-Toxicology Section.

K. S. Rao - Manager, General Toxicology Laboratory.

Tony Martinez - Toxicology Laboratory Supervisor.

1973 (July to December)

Paul Klimstra - Director, Pre-clinical Research & Development.

Robert McConnell - Director, Pathology-Toxicology Department.

K. S. Rao - Manager, General Toxicology Laboratory.

Tony Martinez - Manager, General Toxicology Laboratory.

1974

Paul Klimstra - Vice President, Pre-clinical Research & Development.

Robert McConnell - Director, Pathology-Toxicology Department.

K. S. Rao - Manager, General Toxicology Laboratory.

D. Semler - Toxicology Laboratory Supervisor.

A more complete tabulation of personnel in the Pathology-Toxicology Department, from 1966 through 1975, is attached as Exhibit G-4.

Also attached to this report, as Exhibit G-6, is a complete list of studies monitored by K. S. Rao, 1971, through 1974, and a list of studies in which Tony Martinez participated in, 1970 through 1973. Following is a summary of the numbers of studies involved:

1971

Thirty studies monitored by K. S. Rao.

52

Twelve studies participated in by Tony Martinez.

1972

Forty-seven studies monitored by K. S. Rao.

Seventeen studies participated in by Tony Martinez.

1973

Twenty-nine studies monitored by K. S. Rao.

Thirteen studies participated in by Tony Martinez.

1974

Twenty-five studies monitored by K. S. Rao.

No studies participated in by Tony Martinez.

Following are the key personnel, who were directly involved in the four chronic studies examined during this investigation.

Dr. Robert G. McConnell, Director, Pathology-Toxicology Dept: Dr. McConnell was the Path-Tox Advisor for the 115 Week Rat Study, the 106 Week Dog Study, and the 46 Week Hamster Study. In addition, he was the co-author (with Dr. Rao) of the report on the 52 Week Monkey Study.

Dr. Rao, Senior Research Investigator. Dr. Rao was Path-Tox monitor for the 115 Week Rat Study and the 106 Week Dog Study. He co-authored the Hamster and Monkey Study with Dr. McConnell even though the studies were terminated prior to his employment.

Following is a list of persons interviewed during the investigation concerning their specific areas of responsibility:

1. Robert G. McConnell, Director, Department of Pathology-Toxicology.

2. Suryanarayana K. Rao, Director, D.V.M., M.S., Ph.D. Senior Research Investigator, Toxicology.

3. Rudolph Stejskal, D.D.S., M.S., Ph.D., Senior Research Investigator, Pathologist.

4. Tony Bernard Martinez, Supervisor, Science Services.

5. David K. T. Kie, B.S., Research Assistant in Pathology Labs.

6. Bartolome R. Tangonan, Research Technician II.

7. Donna K. Helms, Manager, Safety Evaluation Project Scheduling/Reporting and Data Storage Operations, Pathology-Toxicology Department.

8. Thomas C. Hutsell, Group Leader.

9. David W. Calhoun, Manager, Computer and Statistical Services.

10. Patricia Erdenberger, HT, ASCP, Research Assistant and Histology Laboratory Supervisor.

11. Philip E. Muellner, Research Technician II, Department of Pathology-Toxicology.

12. Robert A. Moe, Senior Vice President, Scientific Affairs.

13. James A. Buzard, Ph.D., Executive Vice President, Operations.

14. Dr. Richard Charles, Director of Quality Control.

15. Dr. James Young, Director of Development.

16. Margaret Baier, Manager, Stability Section.

17. Gaylord Anthony, Manager, Analytical Development Lab.

18. Sue Gallagher.

19. Dr. Theodore Harris, D.V.M., Manager, Veterinary Services.

20. James Andress, Research Technician.

21. Dr. John Witt, Manager of Synthesis Development.

Throughout the investigation, we were accompanied by two Searle employees, Dr. George Clay, Group Leader, CNS Pharmacology, and Ms. Kathy McLarney, Manager, Clinical/Regulatory Affairs Liaison. These two Searle employees acted as our escorts for the Aspartame team. They responded to our

requests for records, xerox copies and various types of technical information; they also arranged for our interviews with Searle employees, and accompanied us during physical inspection of various Searle facilities.

During all of our interviews with Searle employees, one or more of the following Searle attorneys were present: Thomsen Russell, Richard E. Viktora, Roger Thies, Thomas G. Walter, Michael G. Berkman, W. P. Richmond and Jeffery W. Rogers. At times, two or three attorneys were present during our interviews. They sometimes objected to our questions and would occasionally tell us that the person did not know the answer to the question, without letting him answer for himself. We also noted that some of the employees we interviewed were extremely evasive in their answers to our questions. The most evasive were Dr. McConnell, Dr. Rao, Dr. Charles, and Dr. Young.

We were quite startled at Dr. Charles' apparent lack of knowledge concerning the test compound, Aspartame, especially in view of his title "Director of Quality Control". For example, when we interviewed him on October 13, 1975, he stated that he did not know the meaning (code translation) of Aspartame lot numbers; that he did not know what type of development work that Fermco (a Searle subsidiary located 15 miles from Searle Laboratories) performed on Aspartame; that he did not know what type of containers had been tested for marketing of Aspartame, and that he did not know anything about the solubility of Aspartame.

After a number of interviews similar to the one described above, it became obvious that the records would have to speak for themselves. Consequently, we did not attempt to interview Searle personnel concerning each discrepancy that we encountered.

Exhibit G-7 shows specifications for food grade Aspartame. Other miscellaneous Exhibits are shown in G-8.

GENERAL EXHIBITS

G-1 Index of Master File No. 134 for Aspartame.

G-2 Searle's annual report January 1974 and the third quarter report for 1975.

G-3 Products and total units produced by Searle through the third quarter of 1975.

G-4 Personnel

G-5 Memo of September 25, 1970, from Dr. McConnell to Dr. Drill showing concern of use of insecticides and pesticides in animal quarters. Pertains to "Animal Facilities".

G-6 Studies monitored by Dr. Rao and studies in which Mr. Martinez participated.

G-7 Specifications for food grade aspartame.

G-8 Miscellaneous exhibits