

October 30, 2009: Over 8 years ago I spoke to Jerome Bressler and thanked him for speaking out in this report. He told me the report was worse than what I had read because when the FDA had retyped it they left out the worst 20%, two mouse studies, and a cover letter. Doctors H. J. Roberts and Russell Blaylock both spoke to Bressler and got the same information.

Dr. Roberts wrote his Senator, Bill Nelson on November 27, 2001 stating that important information had been withheld. He said, "Specifically, I need original copies of the two (2) mouse studies done at Searle Laboratories, which were reviewed by the inspection team of the Chicago District of the Center for Food Safety & Applied Nutrition between April – September 1977.

Jane Kirby for Melinda Plaisier, Associate Commissioner for Legislation wrote Senator Bill Nelson on April 18, 2002 and said: "Additionally, some documents are considered confidential under FDA's FOI regulations and in some instances the Agency cannot acknowledge the existence of such documents."

The rest of the Bressler Report was kept under FDA seal for 3 decades. The investigation of these studies was the epitome of other Searle studies, sloppy, inefficient and never showed safety. The Bressler Report itself is revealing the things that Searle did so the FDA would not find out how unsafe aspartame is. They not only filtered out neoplasms but even excised brain tumors from rats, putting them back in the study and then resurrecting them on paper when they died. The report found that 98 of the 196 animals died during one of Searle's studies and weren't autopsied until later dates, in some cases over one year after they died. Records for approximately 30 animals showed substantial differences between original observations on pathology sheets and the observations on pathology sheets submitted to the FDA. There were numerous other inconsistencies. A uterine polyp and ovarian neoplasms were found in animals but not reported or diagnosed in Searle's reports. The FDA investigators found dose-related uterine polyps in 15% of 34 animals.

It was obvious even with fraud aspartame couldn't be proven safe and on January 10, 1977 in a 33 page letter, FDA Chief Counsel Richard Merrill recommended to U.S. Attorney Sam Skinner that a grand jury investigate Searle for "apparent violations of the Federal Food, Drug and Cosmetic Act, 21 USC 331 (e), and the False Reports to the Government Act, 18 U.S.C. 1001, for "their willful and knowing failure to make reports to the Food and Drug Administration required by the Act, 21 USC 355 (i) and for concealing material facts and making false statements in reports of animal studies conducted to establish the safety of (aspartame)."

U.S. Prosecutor Sam Skinner as well as William Conlon hired on with the defense team and the statute of limitations expired.

Finally in 1980 the FDA Board of Inquiry revoked the petition for approval which would have been signed into law if Searle had not sued. Donald Rumsfeld, CEO of Searle, hired to get aspartame approved, was on Reagan's transition team. FDA Commissioner Jere Goyan at 3:00 AM was called by a member of the transition team and fired. Reagan wrote an Executive Order making the FDA powerless to do anything about aspartame including signing the revoked petition into law until he could get Arthur Hull Hayes there as the new FDA Commissioner to over-rule the Board of Inquiry. Then the Executive Order was expunged from the record, which is illegal. This is mentioned in the movie, Sweet Misery: A Poisoned World, www.soundandfury.tv

So science never proved aspartame safe. It proved only fraud. But you hear the manufacturer constantly claiming there were 200 studies that proved safety. Informants say when Rumsfeld came to work for Searle people working there and knowing what was going on were fired and the studies were removed.

Jan Marie Kinnard, wrote in Feb, 2008 that she was the one who was hired to shred the Searle studies, and send a copy to France. She said: "They were the lab results from the tested rats and other animals. The results were outrageous. This stuff killed everything it touched."

The investigation of the two mouse studies the FDA did not want the public to read was kept from the record all these years. I even wrote FDA Freedom of Information and was told too it was confidential. When I stated it was not confidential but a matter of public record I was told that the information had been destroyed.

http://www.mpwhi.com/fda_gate.htm

Fortunately Dr. John Olney back in the 1970's had been able to get a copy of the deleted information and still had these records, which are now scanned in below to complete the Bressler Report. In one conversation with Jerome Bressler he said even Dr. Collins, chief FDA scientist's signature had been deleted from the report. He said the Bressler Report was not complete without it. An attempt to get Dr. Collins to speak on the subject was unsuccessful.

So below you will see the rest of the report and understand these mouse studies are just representative of the way Searle did studies, and there is no way for aspartame to ever be proven safe.

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www.mpwhi.com, www.dorway.com and www.wnho.net
Aspartame Toxicity Center, www.holisticmed.com/aspartame

The missing 20% has been added to the end of
the Report.

DW #50

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ESTABLISHMENT INSPECTION ENDORSEMENT		Page	of	Page
1. ESTABLISHMENT	a. ESTABLISHMENT NAME Searle Laboratories Div. of G.D. Searle & Co.	b. DISTRICT Chicago	c. CENTRAL FILE NO.	
	d. ESTABLISHMENT ADDRESS (Include Zip Code, Area Code and Telephone No.) 4901 Searle Parkway Skokie, IL 60576		e. DATE INSPECTED 4/25/77-8/A/	
2. ROUTING	a. HEADQUARTERS UNIT TO WHICH REFERRED (Use organizational symbol) Bureau of Foods, HFF-330 Attn: Mr. Richard Ronk	HEADQUARTERS USE ONLY c. DATE REFERRED PROFILE NOT NEEDED BY <i>HR</i> DATE 8-1		
	b. REASON FOR REFERRAL To Be Reviewed by the Bureau of Foods	d. AF NUMBER		
3. DISTRICT REMARKS	a. DISTRICT ENDORSEMENT This top priority investigation was made to compare all available raw and summary data, along with all related material including methodologies, against the FDA submission. This inspection covers one study. E-77/78 (P.T. 988573), SC-19192: 115 Week Oral Tumorigenicity Study in the Rat - Diketopiperazine Study E-77/78 was initiated on November 8, 1971. The FDA submission is dated September 1974. Three hundred and sixty weanling albino rats, Charles River CD strain, 130 of each sex, were used. The rats were divided into twelve housing groups, (six groups per sex), thirty rats in each housing group. Each housing group was composed of a random distribution of Control, Low, Mid, and High Dose animals. The rats were fed Diketopiperazine (SC-19192) at 0, 0.75, 1.5, and 3.0 grams per kilogram of body weight per day respectively Our investigation of this study shows that no homogeneity tests were performed on any batches of the diet. We found evidence that the diets were not homogeneous. Two unidentified infectious disease outbreaks were reported in the FDA submission. In both instances the control and treated animals were reportedly affected with equal frequency and severity. All morbid rats were injected with potassium penicillin G. Our review of the records show a third occurrence of infectious disease and penicillin administration took place, which was not reported in the submission to FDA. We found an additional polyp of the uterus in the mid dose group which was not diagnosed or reported in the submission			
	b. REVIEWING OFFICER (Name and title) Jerome Bressler	c. SIGNATURE <i>Jerome Bressler</i>	d. DATE 8/7/77	
c. DISTRIBUTION C: CHI-DO CC: HFF-330, HFF-1, HFO-1, HFA-224, HFR-5140				

ENDORSEMENT
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by Searle. The finding of one additional uterine polyp increases the incidence in the mid dose to 5 polyps of 34 animals (15%). The incidence of polyps of the uterus appears to be dose related.

Serum cholesterol determinations were done at days 796 and 798 (terminal bleeding), but not included in the submission to FDA. The submission reported a significant decrease in serum cholesterol that was more perceptible toward the end of the study and may have been dose related. Therefore, the exclusion of data from days 796 and 798 could be significant.

In some instances raw data was not available for review especially in the areas of clinical chemistry and microscopic pathology. In other instances there were inconsistencies in the raw data making it difficult to authenticate the study. As the investigation proceeded we learned that not all of the data was under seal. We discovered a number of documents. It is quite probable that there are still some laboratory notebooks missing. The majority of the responsible individuals that worked on this study are no longer with Searle.

FOLLOW-UP: To be reviewed by the Bureau of Foods

4/25/77 to 8/4/77

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SUMMARY OF FINDINGS

Authentication of this study was performed primarily by comparing available raw data with the submission to FDA. This was a problem, at times, due to the lack of some data and difficulty in locating other material. The majority of material relating to Aspartame was already under FDA seal at Searle. However, during this investigation we discovered various documents and notebooks that were not.

In some cases original data could be recorded in several areas, making it difficult, and sometimes impossible to determine which was actually the original. This was a particular problem in dealing with dates of deaths, as some conflicted on the "source" documents. Many of the responsible individuals involved with the study, including stability testing of DKP, are no longer employed by Searle. Dr. K.S. Rao, Study Monitor, the only individual who could have possibly answered some questions, had left Searle. He was contacted, but permission for an interview was refused by his attorney. Due to the absence of various individuals it was not always possible to accurately determine methods used in some analyses and operations carried out in conducting this study. In a number of areas, including chemistry, statistics, diet preparation and feeding, it was necessary to use assumptions, or information supplied by current employees who were not involved with the study.

At the beginning of this investigation, Mr. James R. Phelps, Vice-President and General Counsel for G.D. Searle & Co., advised us that an attorney and scientific coordinator would have to be present at all times to protect their interest in the data. This did not present any insurmountable problems, but on several occasions an attorney would question our request for data, stating that it was not relevant for authentication. At no time did we make any statement to the effect that our goal was to authenticate the study. Two memos were discovered dealing with reaction of animals to the diet. This was a significant factor in the study. Permission to copy them was initially refused, but finally granted after Searle was contacted by FDA General Counsel. We were not allowed to make xerox copies of any documents for about two and one-half weeks, due to Searle's concern over confidentiality. This was eventually reconciled between Searle and FDA General Counsel.

The major discrepancies concerning Study PT 988S73, SC-19192:
115 Week Oral Tumorigenicity Study in the Rat, are as follows:

A. Design & Conduct of Study

- 1) Control and treated animals were randomly distributed on the same rack. (See diagram of housing group attached as exhibit 7.)
- 2) No ear clips or other methods of uniquely identifying each animal were used. Identification consisted of two types of cards attached to the front of each cage.
- 3) Compound inventory cards were deficient in that only one of 18 such cards stated the purpose (study 988S73) for withdrawing the compound from inventory. Three of the cards did not include the date withdrawn, amount withdrawn, or signature of requestor. Therefore it was impossible to reconcile the amount withdrawn and the amount used. (See exhibit #28.)
- 4) Food jars were not individually identified, yet all the filled jars for a given housing group (control, low, mid, and high dose) were placed on a mobile cart, which was wheeled to the housing rack. The position of the jar (in rows) on the cart was the only means of identifying the proper dose level. The arrangement of the food cups on the cart is shown in exhibit #8.
- 5) A total of 79 "observations for drug effects" records were not signed or initialed.
- 6) 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.
- 7) Records indicated that at the scheduled 104 week bleeding, animal E2CM was substituted for AllCM. Records also indicated that animal AllCM was alive on this date and therefore should have been bled as scheduled.
- 8) Records indicated that penicillin was administered to four rats beginning on May 16, 1973, and continuing daily through May 28, 1973. This third occurrence of infectious disease and penicillin administration was not reported in the submission to FDA.

- 9) In many cases the actual number of tissues embedded was less than the 24 (control and high dose) or 19 (low and mid dose) specified in the final histology lab protocol dated 1/21/74.
 - 10) Ophthalmoscopic examination records were present for animals H26MF and J29CM, yet the findings were not reported in the submission to FDA. Two other discrepancies of this type were noted.
 - 11) Records indicate that a tissue mass measuring 1.5 X 1.0 cm was excised from animal B3HF on 2/12/72, and that a "skin incision over mass" was performed on animals C22LM and G25LM on Feb. 10, 1972.
- B. Stability and Homogeneity of DKP in Diet Mixture
- 1) There were no batch records to show the quantities of DKP and basal diet weighed, type of mixer used, mixing time, dates, or names of individuals performing the weighing and blending operations.
 - 2) There was no evidence that any tests had been done to determine the blending characteristics of the mixer, or to validate the mixing time.
 - 3) No homogeneity tests were performed on any batches of diet used in the study, and two stability study assay reports (A7738) and A7739) indicated that samples were not homogeneous. (See exhibit #29.)
 - 4) A stability study was conducted with DKP in 1972. However, the 115 week rat study employed Basal Diet from week 62 to its conclusion, and no stability studies had been conducted with Basal Diet.
 - 5) Methods of assay for DKP in the diet were deficient in that: The titration method was discontinued after 1 week of the stability study. Some of the TLC photographs showed no DKP reference standards and photographs also showed that there was something in the basal diet itself producing a spot on the TLC plate which had an Rf value corresponding to DKP. Only one solvent system was used for development of the TLC Plates. Some of the chromatograms showed poor separation.

- 6) No reserve samples of any of the lots of DKP used in this study were retained by Searle.
- 7) Three different sets of specifications for DKP were found, and Searle could not determine with any degree of certainty which of the three were applicable to the 7 lots of DKP used in the study.
- 8) The analytical records for DKP lots IR through 5R refer to reference standard IR #3701. None of the three sets of DKP specifications lists reference #3701. No data was made available as to dates, methods of preparation and authentication of DKP reference standards.
- 9) Analytical record A-9129 for DKP lot 5R showed an assay of 100.0%. Examination of laboratory notebooks showed that eleven (11) samples had been analyzed from this lot, and the analytical record only reflected an average of the last three of these. The other assays (not reported) ranged from 87.93% to 114.83%.

C. Dosage, Body Weight and Food Consumption

- 1) Examination of the raw data sheets revealed the following discrepancies:
 - a. Empty feed cup weights were missing for the D housing group at the 12th week, in the raw data sheets. (See exhibit #75.)
 - b. In several instances, the dietary concentration shown on the weight sheets did not agree with the concentration listed for the same level in the other housing groups. (For example; C group Males, mid & high levels for week 13,; A group Males, high levels for week 99)
- 2) Comparison of the Searle submission and the independent FDA analysis of the raw body weight and food consumption data revealed the following discrepancies:
 - a. We found a total of 15 differences of 1 gram or more in the average body weight and of 0.1 percentage points or more in weight gain. (See table 1.)

- b. We found approximately 82 discrepancies of one gram or more in the food intake when expressed in grams/day. (See table 2).
- c. We found approximately 40 errors of 5 or more grams in food intake when expressed in grams/kg./day. (See table 2).
- d. Most of our dosage calculations differed from Searle's dosage calculations by 10 or more mg., when the dosage is expressed as mg/kg/day. (See table 2).

D. Gross and Microscopic Pathology

- 1) 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.
- 2) 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.
- 3) Records indicated that animal F6HF, a high dose female, was found dead at 787 days of treatment and the gross 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) Records for approximately 30 animals showed substantial differences between gross observations on pathology sheets, when compared with the gross observations on pathology sheets submitted to FDA. A detailed description of 10 of these is included in the report. Copies of all the gross pathology sheets, and the pathology summaries submitted to FDA are attached as exhibits.
- 5) Dr. Charles H. Frith, D.V.M., Ph.D., Director, Pathology Services, NCTR, examined slides for a total of 150 animals, or about 42 percent of the animals on study. He noted the following discrepancies:
 - a. The reporting of a mass (by Searle) as missing which was actually present (animal MILF).

- b. The finding of a polyp of the uterus which was not diagnosed by Searle (animal K9MF). The finding of this additional uterine polyp by Dr. Frith increases the incidence in the mid dose to 5 of 34. (15 percent).
 - c. The finding of ovarian neoplasms in animals H10CF, H19CF, and H7HF, and the finding of diffuse hyperplasia in animal D29CF, which were not diagnosed by Searle.
 - d. The finding of additional inconsistencies in 21 animals.
- 6) No microscopic worksheets or other "raw data" relating to microscopic pathology could be found for this study.

7) A mammary tumor found in animal F27CF was described as a papillary cystadenoma on the pathology summary sheet, (page 105, Vol. II of the submission) and as an adenocarcinoma on summary table 12 (P. 96, Vol. I of the submission).

8) In several instances the histopathology technician made notes at the bottom of the gross pathology sheet to indicate that certain organs were not present in the bottle of fixative (and were therefore not available for sectioning). Yet, in three of these instances (animals A4CM, K23CF, and J3CM) a diagnosis appears in the submission to FDA.

E. Organ Weights

1) Organ weights were entered on the gross pathology sheets at the time of autopsy. We compared all of the individual organ weights on appendix table 5 in the submission to FDA (Vol. 1, pgs. 222-226) with the original data on the gross pathology sheets. A total of eleven (11) errors were noted in transcribing the raw data from the pathology sheets to the tables in the submission to FDA.

F. Survival

1. We were unable to determine the exact method used by Searle in constructing the survival table in the submission to FDA. We constructed a survival table using the body/feeder weight teletype sheets. A Life Table Analysis was constructed from our survival table by Dennis Wilson, FDA Department of Mathematics. The female control population differed from the high level population ($p < 0.05$) and the male control population differed from the mid and high level population ($p < 0.05$). In all cases the differences are due to the higher mortality in the controls.

G. Clinical Laboratory Procedures

1. Laboratory records of one sort or another for all assays reported in the submission were obtained. In some cases data sheets were noted with results of assays carried out at treatment days not indicated in the submission Methods or Results section but indicated in the protocol or protocol amendment. For example, serum cholesterol determinations were done at days 796 and 798 (terminal bleeding) but not included in the submission to FDA. Because the submission to FDA (vol. 1 p. 286) 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, the omitted data is of some importance.
2. No data was seen for two assays (serum insulin and serum ornithine carbamyl transferase) which were called for in an amendment to the protocol.
3. Original data was not always available for authentication of results or examination of procedures for conversion of raw data into the calculated values submitted to FDA.
4. Data pages for clinical chemistry and urinalysis were initialled by a technician who transcribed data but apparently was not directly involved in the assays indicated. He stated in an interview that Dr. Rao told him to initial the data sheets.
5. The methodology as referenced in the submission to FDA is incomplete and not always an accurate reflection of the methodology actually used in the study. The fact that more than one method was sometimes used for a particular assay during different times of the study was not indicated in the submission to FDA.
6. A total of 21 disparities between individual clinical laboratory analysis values appearing in the submission Volume I and those values appearing in data sheets and/or laboratory notebooks were found.
7. A total of 49 disparities were noted between statistical computations reported by Searle in the submission and those calculated by FDA. The disparities are constituted by the values for 6 means, 23 standard errors, and 20 significant differences (as measured by T tests).
8. Some of the data sheets for urinalysis had erroneously labeled the phenylketones test values as "phenylalanine".

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PURPOSE OF INVESTIGATION

Assignment memo dated May 16, 1977 from Donald Heaton, Acting Director of Regional Operations, confirmed an earlier oral assignment to Chicago District for a directed inspection of certain non-clinical studies submitted to FDA in support of a food additive petition for the sweetener aspartame.

The investigation began on 4/25/77, and encompassed the authentication of all data, both raw and summary, relating to the studies jointly chosen for review by Bureau of Foods and EDRO. Two studies actually done at G.D. Searle were selected for initial coverage, and a decision to expand the investigation to a third study was made at a later date.

Following are the titles of the three studies selected for review:

- 1.) E-5 (P.T. #851S70), Evaluation of Embryotoxic and Teratogenic Potential in the Rat, conducted with SC-18862 (aspartame).
- 2.) E-89 (PT #1218S75), An Evaluation of the Embryotoxic and Teratogenic Potential in the Mouse, conducted with SC-18862 (aspartame).
- 3.) E-77/78 (PT #988S73), 115 Week Oral Tumorigenicity Study in the Rat, conducted with SC-19192 (diketopiperazine).

This report is concerned only with study E-77/78. The report of E-5 and E-89 was submitted separately.

HISTORY OF BUSINESS

G. D. Searle & Co. provides a wide range of health care products and services on a worldwide basis. Its business is divided among three principal areas: pharmaceuticals, medical instruments and optical products, and hospital and laboratory products. The firm's corporate offices are located in Skokie, Illinois, with various branches and facilities throughout the world.

Effective June 1, 1977, Donald H. Rumsfeld assumed duties as President and Chief Executive Officer. Mr. Daniel C. Searle, formerly Chief Executive Officer is now Chairman of the Board, while William L. Searle and Wesley M. Dixon, former Chairman and President respectively, are now Vice-Chairmen.

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Effective March 1, 1977, the firm underwent a major realignment, shifting to a managerial system based on product lines. This resulted in the establishment of four main product-line groups, which are: Pharmaceutical/Consumer Products, Diagnostics, Hospital Supplies and Optical Products. Each group is headed by a President who will report to Searle's Executive Vice-President for Operations, Dr. James A. Buzard. A copy of the G. D. Searle & Co. annual report for 1976 which is attached as Exhibit #1 further expands on the firm's operations and lists Corporate Officers.

Mr. O. B. Parrish is President of the Pharmaceutical/Consumer Products Group and also a Corporate Vice-President. An organizational chart for this group is attached as Exhibit #2. Mr. Guy Labrosse is now Group Executive Vice-President for U. S. Commercial Pharmaceutical Operations. In the U. S., this is known as Searle Laboratories. The facility at 4901 Searle Parkway, Skokie, Illinois is a part of U. S. Operations, e.g. Searle Laboratories, yet houses the majority of the Research and Development Group.

Worldwide Pharmaceutical Research and Development is also a part of the Pharmaceutical/Consumer Products Group, but not of Searle Laboratories. The Research and Development of Aspartame is a function of this group. Copies of organizational charts for this group are attached as Exhibit #3. Dr. Robert A. Moe recently resigned and his position is temporarily being filled by George V. O'Bleness, Corporate Vice-President for Compliance and Administration.

Commercial aspects of Aspartame are being handled by an "Aspartame Division", under the direction of Elwood H. Ensor, Corporate Vice-President. There is no longer a division entitled "New Ventures".

PERSONS INTERVIEWED

Credentials were shown and a written Notice of Inspection was issued to Dr. William M. Merino, Director, Domestic Pharmaceutical Products, Regulatory Affairs Department on April 25, 1977. The following Searle personnel were present at the initial meeting on 4-25-77.

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Robert A. Moe, PhD. - Executive Vice-President
George Clay, PhD. - Group Leader, CNS Pharmacology
Robert Bost, PhD. - Director of Food Products,
Regulatory Affairs
Holly Ru Probst - Director, Corporation Information
Management Group
Dave Britton - Director Corporation Information
Department
William Merino, PhD. - Director, Domestic Pharmaceutical
Products
Richard Viktora - Attorney
James Phelps - Vice-President, General Counsel
Elwood H. Ensor, PhD. - Vice-President
Paul Klimstra, PhD. - Vice-President Pre-Clinical
Research and Development
Roger Thies - Attorney

During the course of our investigation one or more of the following Searle personnel were present in the Conference Room which we used for our data review.

Richard Viktora - Attorney
Roger Thies - Attorney
George Clay, PhD. - Group Leader, CNS Pharmacology
Robert Bost, PhD. - Director of Food Products,
Regulatory Affairs
Don Cook, PhD. - Associate Director, Department of
Bio Research
Dick Aspinol, PhD. - I. I. D. Group Leader
Bill Jenkins, PhD. - Director, Product Affairs
Fred McIlreath, PhD. - Director, Regulatory Affairs
Paul Landefeld, Attorney

Most of the time one attorney (R. Viktora or R. Thies) and one scientist were present. During our initial meeting with Searle personnel, James Phelps stated that a Searle monitor must be with us at all times during our data review in order to "protect the data".

During the course of our investigation, various individuals were interviewed in an attempt to obtain all available raw data and reconstruct the manner in which the study was conducted, as accurately as possible. Since many employees involved in the study or support areas are no longer employed at Searle, others were interviewed who had general knowledge of such parameters as statistics and chemistry.

Significant interviews are attached as Exhibits, as referenced. Individuals interviewed were as follows:

1. Donna Helms - Administrative Assistant to Dr. McConnell on 5-18-77, 6-30-77 and 7/1/77 (Exh. #46).
2. Judith Beauchamp - Hematology Lab Supervisor on 6-2-77 (Exh. #47).
3. Barbara Bickford (Nee Ross) - Technician, Department of Analytical Research on 6-1-77 and 6-2-77 (Exh. #48).
4. Clifford J. Seul - Supervisor, Department of Analytical Research and Development on 6-2-77 (Exh. #49).
5. Bartolome R. Tangonan - Research Technician, Pathology Toxicology Department on 6-1-77 (Exh. #50).
6. Tony Martinez - Research Assistant and Toxicology Lab Supervisor on 5-19-77, 6-3-77, 7-7-77, 7-20-77 and 8-2-77 (Exh. #51).
7. Ted Reichert - Supervisory Systems Analyst on 5-24-77 (Exh. #52).
8. Phil Polli - Systems Analyst on 5-24-77 (Exh. #53).
9. Judith Schmal - Clinical Chemistry Section Supervisor on 6-2-77 and 6-7-77 (Exh. #54).
10. Jane Drury - Analytical Chemist, Bioanalytical Dept. 6-7-77.
11. Alan Mitchell - Teratologist on 7-20-77 (Exh. #56).
12. Raymond G. Schroeder - Former Searle Teratologist on 7-18-77 (Exh. #57).
13. Dr. Rudolph Stejskal - Pathologist on 6-23-77.
14. Patricia Erdenberger - Research Assistant and Histopathology Lab Supervisor on various dates (Exh. #58).

Dr. Robert McConnell, Pathology-Toxicology Advisor at the time of this study, was not directly involved with daily procedures. He is no longer employed at Searle.

An attempt was made to interview Dr. K. S. Rao, Monitor of Study P. T. #988S73 on 7-25-77. We were referred to Dr. Rao's attorney, who refused permission for an interview (see Jerome Bressler's memo dated 7-27-77, Exh. #33).

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PURPOSE OF STUDY PT 988S73 (E-77/78)

SC-19192: 115 Week Oral Tumorigenicity Study in the Rat

According to the submission to FDA, this study was intended to evaluate the safety and tumorigenic potential of SC-19192, diketopiperazine (5-benzyl-3, 6-dioxo-2-piperazine-acetic acid), which is a conversion product of aspartame, and to induce and define such adverse effects as might occur only at prodigious multiples of the estimated daily human intake. The commercial grade of aspartame (SC-18852) may contain up to 2 percent of the conversion product (D&P), according to Searle's specifications.

DATES

Study E-77/78 (PT #988S73) was initiated on November 8, 1971. The study was to be terminated at 104 weeks, but was extended to 115 weeks. The reason for extending the study was stated as follows in protocol amendment #3 dated September 6, 1973: "it was decided to extend or continue the study until the mortality of either sex reduced the control group to 20 animals per sex, provided the survival in the treated groups is not less than 10 animals/sex/treated group prior to that period. This approach is consistent with current FDA desires." A copy of the study protocol is attached as exhibit #11.

Initiation of treatment was staggered over a two week period as follows:

<u>HOUSING GROUP</u>	<u>DATE PLACED ON STUDY</u>	<u>SCHEDULED SACRIFICE</u>	<u>DAYS ON STUDY</u>
A - Male	11/8/71	1/21/74	805
B - Female	11/9/71	1/22/74	805
C - Male	11/9/71	1/22/74	805
D - Female	11/10/71	1/23/74	805
E - Male	11/11/71	1/24/74	805
F - Female	11/12/71	1/25/74	805
G - Male	11/15/71	1/28/74	805
H - Female	11/16/71	1/29/74	805
J - Male	11/17/71	1/30/74	805
K - Female	11/17/71	1/30/74	805
L - Male	11/18/71	1/31/74	805
M - Female	11/19/71	2/1/74	805

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PROTOCOL AND AMENDMENTS

A copy of the protocol for this study was obtained and is attached to this report (See Exhibit #11). The protocol includes 4 amendments which are dated Aug. 20, 1973, (amendments #1 and 2), Sept. 6, 1973 and Jan. 9, 1974.

Amendment #1 dated Aug. 20, 1973 specified 4 additional clinical chemistry laboratory measurements: 1.) serum insulin, 2.) serum ornithine carbamyl transferase, 3.) serum protein electrophoresis, 4.) serum total protein.

Two of the above assays (serum insulin, and serum ornithine carbamyl transferase) were apparently not done, because no data for these two parameters was submitted to FDA, and we could find no raw data or other evidence that they were done.

Amendment #2 dated Aug. 20, 1973, specified 8 coronal sections of brain to be examined microscopically, and also described the procedure for sectioning the urinary bladder. Four transverse sections from each urinary bladder were to be examined microscopically.

Amendment #3 dated Sept. 6, 1973 extended the study until it reached a point where mortality reduced the control group to 20 animals per sex, provided survival of treated groups was not less than 10 per sex per group. (This represented a survival of approximately 30%).

Amendment #4 dated Jan. 9, 1974 added serum cholesterol to the clinical chemistry measurements to be made at terminal sacrifice, and terminated the study after 114 weeks of treatment. Terminal sacrifice was to begin on 1-24-74 and continue through 2-1-74.

Our examination of the original data showed that serum cholesterol determinations were done at day 796 and 798 (terminal bleeding) as specified in the above amendment, but the data was not included in the submission to FDA. The submission to FDA (Vol. 1 p. 286) 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. Therefore, the omitted data may have been important.

Serum cholesterol determinations were also done at day 546 (78 weeks) and not reported in the submission to FDA.

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The protocol for Clinical Chemistry procedures specified that BUN determinations were to be done at 78 weeks (546 days). The submission to FDA contained no BUN data for day 546, but our review of the raw data indicated that BUN's had been done at day 546. Some BUN's were also done at day 735 (105 weeks) and not reported in the submission to FDA, but this data was not complete for all animals.

Attached to the protocol is a memo dated Oct. 31, 1972 which describes an acute infection spreading in the rat colony, and the administration of penicillin to combat the infection, and a memo dated May 8, 1973 listing scheduled dates to be added to Body and Feeder Weights of housing groups A & B.

The final Histology Lab Protocol, dated 1-21-74, specifies 24 organs to be embedded for control and high dose animals, and 19 organs to be embedded for low and mid dose groups. The organs which were to be embedded for the control and high dose groups but to be omitted in the low and mid dose groups include: lymph node, nerve, bone, eye, and salivary glands.

Pathology sheets (blank forms) to be used at terminal sacrifice were reproduced (xeroxed) with check marks, time (death to tissue fix), fixative, study, and project number already entered. Twenty-seven (27) organs were checked off, to be embedded. However, as stated above, the control and high dose animals were to have 24 organs embedded, according to the protocol, and the mid and low dose 19. Therefore, all pathology sheets for animals killed by design have incorrectly identified the specific organs and tissues to be embedded.

In addition to the above error, in many cases the actual number of tissues embedded was less than the 24 (control and high dose) or 19 (low and mid dose) specified in the final Histology Lab Protocol dated 1-21-74. Specific figures for numbers of tissues embedded at terminal sacrifice are as follows:

	<u>ACTUAL RANGE</u>	<u>ACTUAL AVERAGE</u>	<u>NUMBER SPECIFIED IN PROTOCOL</u>	<u>NO. OF ANIMALS NOT IN ACCORD WITH PROTOCOL</u>
CONTROLS	10-24	20	24	129 of 144
LOW DOSE	12-23	19	19	19 of 72
MID DOSE	4-24	18	19	28 of 72
HIGH DOSE	9-25	22	24	51 of 72

PERSONNEL AND RESPONSIBILITY

The names of Dr. K.S. Rao, Dr. R. Stejskal, and Dr. R.G. McConnell appear on the final study report, indicating that they are the authors of the report, and were responsible for the study.

Following are the principal persons involved with study E-77/78 and their specific areas of responsibility:

- 1.) Dr. Robert G. McConnell - Director, Pathology-Toxicology Section 1970 through 1974. Dr. McConnell functioned as the Path-Tox advisor on study E-77/78. He is no longer employed by Searle.
- 2.) Dr. Suryanarayana K. Rao - Manager, General Toxicology Laboratory, June 1971 until he left Searle in May of 1977. Dr. Rao was the Path-Tox monitor for Study E-77/78. In 1971 Dr. Rao monitored 30 studies, in 1972 forty-seven (47) studies, in 1973 twenty-nine (29) studies and in 1974 twenty-five (25) studies.
- 3.) Dr. Rudolph Stejskal - Senior Research Investigator, Pathologist. Dr. Stejskal was responsible for the microscopic findings and accuracy of these findings in the study report of E-77/78. Because Dr. Stejskal joined Searle in July, 1973, he had no input into the pathology protocol. Also, he did not examine all of the slides for this study, but was assisted in that task by Dr. Joseph H. Smith M.D.
- 4.) Dr. Joseph H. Smith, M.D. - Group Leader and Senior Pathologist at Michael Reese Hospital, Chicago, IL., before joining Searle in June of 1973. Dr. Smith examined some of the slides for Study E-77/78, and supervised the necropsy laboratory.
- 5.) Tony Martinez - Toxicology Laboratory Supervisor, 1970 through 1973. Mr. Martinez participated in twelve (12) studies in 1971, seventeen (17) studies in 1972, and thirteen (13) studies in 1973. Mr. Martinez supervised the technicians who worked on study E-77/78 and was responsible for the day-to-day conduct of the study. He also performed some necropsies.

- 6.) David K.T. Kie, B.S., Research Assistant in Pathology Laboratory. He performed some of the necropsies on E-77/78.
- 7.) Robert Spaet - Research Assistant. He also performed necropsies.
- 8.) Bartolome R. Tangonan - Research Technician II - He was involved with preparation of diet mixtures, daily observations, weighing and feeding animals, etc.
- 9.) Donna K. Helms - Manager, Safety Evaluation, Project Scheduling, Reporting, and Data Storage, Path-Tox Dept. and Administrative Assistant to Dr. McConnell.
- 10.) Patricia Erdenberger - Research Assistant, and Histology Lab Supervisor.
- 11.) Dr. Eugene Joseph Youkilis - Senior Research Investigator. He performed the ophthalmoscopic examinations in study E-77/78.
- 12.) Judy A. Henderson - August 1972 to present, Research Technician III, Histopathology Dept. She was involved with tissue processing on study E-77/78.
- 13.) Judith R. Schmal - Nov. 1971 to present, Supervisor, Clinical Chemistry Section of Bioanalytical Laboratory.
- 14.) Judith A. Beauchamp - Employed Aug, 1970 to present; Supervisor Hematology Laboratory since April 1973.
- 15.) Barbara (Ross) Bickford - Research Technician, Quality Control Department. She performed analyses of DKP diet mixtures for study E-77/78.
- 16.) Clifford J. Seul - Supervisor, Method Development, Stability Evaluation Laboratory. He was Barbara Bickford's supervisor at the time the DKP stability study was performed.
- 17.) Jack Droggt - 1967 to present, Senior Research Assistant, Chemical Development. Mr. Droggt manufactured the 7 lots of DKP used in study E-77/78.
- 18.) Dr. John E. Dutt - Math-Stat. Dept.
- 19.) John Mellman, Math-Stat Dept.

20.) Fred Hunter, Technician.

Since the Task Force investigation in 1975, there has been a major internal reorganization. The current organization of Worldwide Pharmaceutical Research & Development is attached as Exhibit #3). The only change has been the resignation of Dr. Robert A. Moe, Executive Vice-President. Mr. George V. O'Bleness, Corporate Vice-President, is temporarily filling this position.

Organizational charts for Preclinical Research and Development of Product Safety Assessment are also attached as Exhibits 4 & 5. There have been no changes in these areas to date.

Worldwide Pharmaceutical Research and Development is responsible for research and development of Aspartame and is a part of the Pharmaceutical/Consumer Product group. The group President is O.B. Parrish, who reports to James A. Buzard, Executive Vice - President for Operations, G.D. Searle & Co. The current corporate structure of G.D. Searle & Co. has been discussed under History of Business.

P.T. No. 988S73, 115 Week Oral Tumorigenicity Study in the Rat was conducted between November 1971 and February 1974. The final FDA submission was dated September 1974. Following is a yearly breakdown of key personnel during this study:

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 Section.

Tony Martinez - Toxicology Laboratory Supervisor.

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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
Department.

Robert McConnell - Director, Pathology-Toxicology Department.

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

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 listing of personnel in the Department of
Science, from 1971-1975 is attached as Exhibit No. 64.
This includes the Pathology - Toxicology Department and other
ancillary areas.

Curriculum vitae for individuals performing significant func-
tions in the study are attached as Exhibit 12.

MANUFACTURE AND TESTING OF SC-19192

Seven batches of SC-19192 (diketopiperazine) were used in this
study. All batches were manufactured in-house by Searle Chemist
Jack Drogt. The lot numbers, analytical numbers, and quantities
are as follows:

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<u>Lot Number</u>	<u>Analytical Number</u>	<u>Quantity (After Milling)</u>
1R	6906	
2R	7274	
3R	7273	
4R	7291	
5R (JDR-5-18A)	9129	
6R (JDR-5-30A)	9805	
7R (JDR-5-30B)	9829	
	Total	

Batch records covering the manufacture of lots 1R through 5R were reviewed. Batch records for lot 6R and 7R could not be located by Searle personnel. Analytical reports for all seven batches were reviewed. Copies of the batch records and analytical records were obtained and are attached to this report, along with copies of pages from Jack Drogdt's laboratory notebook, and other laboratory notebooks relating to the analysis of lots 1R through 7R of DKP. (See Exhibits 13-23.)

We obtained copies of three different specification sheets for DKP. (See exhibits 16-18.) We could not determine with certainty which of the three specification sheets was in effect at the time that the 7 lots of DKP used in this study were assayed, because only one of the three specification sheets was dated. This resulted in ambiguities for two of the parameters measured: melting point and identity (IR Spectrum). Specification memorandum dated Dec. 4, 1969 listed a melting range of 252-256 degrees C. Another specification sheet (not dated) entitled "Tentative Specification For SC-19192" listed a melting range of 241-246 degrees C. A third specification sheet entitled "Specifications for SC-19192, Specification No. C 40506C" (not dated) listed a melting range "at about 243 degrees C."

For identity (IR Spectrum) the first sheet (dated 12/4/69) specified that "The reference standard shall be considered to be TJT-12-32 until something better comes along". The second and third sheets specify that the DKP "Conforms to IR #2358".

No data was made available as to dates, method of preparation and authentication of DKP reference standards used.

Searle attorney Roger Thies was contacted about this point Aug. 1, 1977 and said he would attempt to obtain information regarding this point but later registered doubt as to whether anything would be found.

We asked Searle personnel to tell us which of the specification sheets was valid for the DKP used in study E-77/78. We were

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told that the third sheet, identified with "No. C4060C", could not have been used since the number corresponded to a date in June, 1974.

It is not clear as to the exact date that the first sheet (dated 12/4/69) was superceded by the second one, identified "tentative specifications for SC-19192" because the second sheet was not dated or numbered. However, Searle Attorney Roger Thies told us that their "best guess" was that the sheet marked "tentative specifications for SC-19192" was the one used.

Accordingly, we have used the specifications from the sheet marked "tentative specifications" for the following chart, which compares the specifications with the actual results of analysis.

DKP LOTS

SPECIFICATIONS 1R 2R 3R 4R 5R 6R 7R

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DKP LOTS (Continued)
SPECIFICATIONS IR 2R 3R 4R 5R 6R 7R

The only discrepancy apparent in the above chart is in the criteria for identity. The specification lists reference standard IR #2358, while the analytical record for lots IR through 5R refer to Reference #3701.

Examination of the laboratory notebooks referenced on the analytical records revealed other possible discrepancies. For example, the analytical record A-9129 for DKP Lot 5R showed an assay (titration) of 100.0 percent. The analytical record referenced two different lab notebooks assigned to two different analysts. Examination

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of lab notebook AR-68 assigned to Sandra Ann Carey revealed that she had analyzed 3 samples of lot 5R on 11/9/72. Results of the analysis showed that sample one had an assay (by titration) of 89.70 percent, sample two, 87.93 percent and sample three was discarded.

Apparently not satisfied with her results she repeated the assay on the same day (11/9/72) and obtained 93.23 percent (the average of 3 samples), still well below the specification of 99.0 percent. The other lab notebook referenced was AR-57, assigned to E. Aranda. This notebook showed that analyst Aranda performed an assay (titration) of lot 5R on 12/1/72 the results of which were 114.83 percent for 3 samples. Apparently not satisfied with the results, he repeated the assay on 12/6/72 and obtained 100.4, 99.9, and 99.8 percent for an average of 100.0 percent. This result (100.0 percent) was the only one reported on the analytical record A-9129.

The analytical record (A-7291) for DKP lot 4R shows a result of "less than 20 PPM" for the heavy metals test. Two laboratory notebooks are referenced: VSH-1, pages 260-263, and AR-23, page 269. Examination of both of these books revealed no mention of a heavy metals test.

The analytical record (A-9805) for DKP lot 6R (JDR-5-30A) also showed a result of "less than 20 PPM" for the heavy metals test. Examination of the referenced laboratory notebook (AR-77, page 83-86) revealed no evidence of a test for heavy metals.

The analytical record (A-9829) for DKP lot 7R (JDR-5-30B) again showed "less than 20 PPM" heavy metals. Examination of the referenced lab notebook (AR-93) again showed no evidence of a heavy metals test.

The above discrepancies were the only ones noted with respect to lots 1R through 7R of DKP. All other criteria for identity and purity of DKP as shown in the reports of analysis, conforms to Searle specification sheet marked "tentative specifications for SC-19192". It should be noted however that none of the seven lots of DKP met the specifications on sheet dated 12/4/69, with respect to melting range.

STABILITY AND HOMOGENEITY OF DIET MIXTURES

A stability study was initiated in January 1972, 2 months after the rat study (E-77/78) had begun. The objective of the study

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was to evaluate the stability of SC-19192(DKP) when mixed with Rockland mouse/rat diet and held at room temperature (73 degrees F.). Two concentrations of diet mixture were tested: 3.0 % and 6.0% DKP. A preliminary analysis was performed on 1-31-72 to test the analytical method (T.L.C.), and recovery of DKP. Assays were performed at one-week intervals on 2-16-72, 2-23-72, 3-1-72, 3-8-72, 3-15-72, 3-23-72, and 3-29-72. Copies of all analytical reports were obtained and are attached to this report, along with a copy of the protocol. (See exhibits #24-27).

The titration method of DKP analysis was used initially, along with the TLC method. The titration method was discontinued after the 1-week analysis on 2-23-72. Thin layer chromatography was used thereafter. It should be noted that the titration method was the only reliable quantification method for DKP analysis.

Page #54 of laboratory notebook #51 (See Exhibit #26) indicated (from the photograph) that there was something in the basal diet itself producing a spot on the TLC plate which had an Rf. value corresponding to DKP. This would make quantification of DKP by this method difficult.

Some of the photographs of the TLC plates attached to laboratory notebook #51 showed no DKP reference standards. The analysis described on pages #69-72 did use a DKP standard but those on pages #88-89, #106-107, #144-145, and #284-285 showed no reference standard. (See Exhibit #26)

Only one solvent system was used for development of TLC plates throughout the study, even though it was apparent that some material in the basal diet was producing a spot on the TLC plate with an Rf. value corresponding to DKP. With the above method of analysis, only materials reacting with the potassium iodine starch reagent would be detected. Another solvent system was available for TLC analysis of DKP (See Exhibit #19) but apparently was not used in the stability study.

It should also be noted that some of the chromatograms showed poor separation (day 28 on pages #144-145, and day 35 on pages #156-157 of notebook #51). (See Exhibit #26)

In general, the data described in the reports of analysis corresponded well with the laboratory notebooks, although the poor chromatograms were not mentioned in the reports of analysis.

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The level of impurities as indicated by TLC was low; the major impurity, an unknown substance, represented about 2% of the DKP. The remaining impurities were also low, as apparent from the density of the TLC spots compared with the DKP spots, but were not quantified.

A glossary of terms for aspartame and its diketopiperazine is attached as exhibit #9 and copies of specifications for DKP are attached as exhibits #16-18.

No homogeneity tests were performed on any batches of diet mix used in E-77/78, and evidence exists that homogeneity was a problem with the DKP diet mixtures. Two of the stability study assay reports, analytical numbers A7738 and A7739 both dated 2-16-72, contained the statement: "These samples were not homogeneous. They had to be regrind before they could be sampled". The assay reports were signed by Barbara Bickford, a Searle analyst.

We examined the laboratory notebook #51 assigned to Barbara Bickford and noted that a B & W polaroid photograph of the non-homogeneous sample in question was attached to page #58 of the notebook. The photograph clearly shows discrete lighter colored particles of diverse size and shape distributed non-uniformly throughout the mixture. These lighter colored particles appear to be distinct from the fairly fine granular nature of the chow itself.

A copy of this photograph was made and is attached to the report as exhibit #29. When questioned about the size of the white square sheet of paper in the photograph (on which the diet mixture was placed) Ms. Bickford and C. Seul both stated that it was 6"x6", when we interviewed them on 6-2-77. When the photograph was enlarged until the sample paper was 6"x6" (actual size) we measured the large particles (which were identified as DKP by Ms. Bickford) and found them to be 4 to 6mm in size.

When we interviewed Ms. Bickford on 6-1 and 6-2-77, she stated that she had nothing to do with the preparation of the diet mixtures. She said that the samples had probably been received from the toxicology lab and stored at room temperature. Her procedure was to weigh out a predetermined amount of the sample, and if not a uniform powder she would re-grind it with a mortar and pestle, and would make a note of this in her lab notebook. We asked Ms. Bickford if she ever reported this lack of homogeneity to Dr. Rao, and she replied that she did not.

We could not determine whether the samples assayed in the stability study were from diet mixtures actually fed to the animals, in spite of the fact that we were told so by some employees.

On 6-2-77, we interviewed Analyst Barbara Bickford and Clifford Seul, who was Mrs. Bickford's supervisor at the time that the stability samples were analyzed (Feb. 15, 1972). Clifford Seul told us that the samples analyzed on 2-16-72 and described on page #58 of laboratory notebook #51, were obtained from the admixture being fed the rats on study, and not a special mixture prepared for the stability study.

On 6-1-77 we interviewed Bart Tangonan, whose duties included observing, weighing, and feeding the animals, and mixing the diet for study E-77/78. Mr. Tangonan did not remember if there were any written instructions for mixing the diets but thought that it was mixed for a specified length of time. He said that if the diet appeared to need more mixing, it was mixed longer. He could not remember anything about the samples obtained for the stability study.

On 6-3-77 we interviewed Tony Martinez who was a supervisor in the Toxicology Laboratory in 1972. He told us that although the analytical report indicated that the sample was submitted by Dr. Rao, actually anyone in the toxicology laboratory could have submitted the sample. According to Mr. Martinez, the normal procedure in such cases was to collect a sample just after mixing compound and diet and then repeat this in four weeks. He could not specifically recall what was done with regard to the stability study in question, and could not remember whether the samples had been taken from the diets being fed the animals on study P.T. 988S73 (E-77/78). He did not remember any problems with mixing, but did say that a longer mixing time was required at higher compound concentrations.

A point to be considered, however, is that although the analytical report states that the material analyzed was prepared to contain 3.0 and 6.0% DKP, none of the diets reported to be fed contained these exact amounts of DKP according to the records of food concentration calculations, which were used to prepare the diets for study #E-77/78. (See chart attached as Exhibit #30.) In addition, the stability study protocol (Exhibit #24) specified that the test batches would be 1 kg. in size. If the protocol was followed, the small (1 kg.) test batches would not have been sufficient in size to feed a single dose group of the animals on study. (See Protocol, Exhibit #24)

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Additional evidence of homogeneity problems was revealed when a former Searle employee, Raymond Schroeder, was interviewed by the other FDA team on 6-22-77 concerning teratology studies E-5 and E-89. At that time Mr. Schroeder volunteered the information that homogeneity may have been a problem in the DKP diet mixtures, but not in the aspartame diet mixtures. A follow-up phone call to Mr. Schroeder was made on 7-13-77, and at that time he stated that he observed the DKP diet mixtures being fed to the animals, and that in his opinion, the particles of DKP were large enough to allow the rats to discriminate between the DKP and the basal diet. (See Thomas F. X. Collins memos (2) dated 7-14-77 (attached as Exhibit #31). An interview was arranged for July 18, 1977 between Mr. Schroeder and members of the FDA team investigating study E-77/78. The interview was conducted at

..., Mr. Schroeder's current place of employment. Also participating in the interview by means of a conference phone were Thomas F. X. Collins, and Leonard Friedman. Mr. Schroeder stated that he was not certain of the date, or even the year, when he observed the rats being fed DKP diets. He further stated that he could not be absolutely certain that the rats he observed were on study E-77/78. He was not certain about the dose levels of the diets he observed, and could not remember how many times he observed the DKP diets. He estimated that he observed the DKP diets "one or two times". When he was shown an actual-size enlargement of the DKP diet mixture (See Exhibit #29) he stated that to best of his knowledge, the white particles that he observed were not as large as the largest particles in the photo, but may have been similar to the smaller white particles. He said that he may have mentioned the appearance of the DKP diets to Dr. Rao.

Mr. Schroeder seemed reluctant to make any positive statements during this interview. Dr. Collins reminded Mr. Schroeder that he had previously volunteered the information that the DKP diets appeared to be non-homogeneous and that the rats could probably discriminate between the DKP particles and the basal diet. Mr. Schroeder replied that he had had some time to think over his previous statements and now wasn't sure about them. He told us that there must be people at Searle who knew more about the DPK diets than he did. (See memo dated 7-19-77, attached as exhibit #32, which describes our interview with Mr. Schroeder).

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When we arrived at [redacted] on 7-18-77 at approximately 2:40 P.M., we were asked by the receptionist to sign a log book. While signing the log, we noted that a G. D. Searle employee (W. R. Pool) had signed in on 7-15-77. W. R. Pool works in the Toxicology Section (Safety Assessment Division) at Searle Laboratories.

During our interview, we asked Mr. Schroeder if he had been contacted by anyone from Searle during the period from June 22, 1977-July 18, 1977. He replied that he had not.

We again interviewed Tony Martinez on 7-19-77, and specifically asked him if he was aware of any homogeneity problems with the DKP diet mixtures fed the rats in study #988S73 (E-77/78). He replied that he was not aware of any problems. We asked whether any samples of DKP had been retained by Searle Laboratories. We were told that a small quantity of DKP remained in the compound file, but that it was a lot other than those used in study E-77/78. Upon request, we were then shown a jar containing 4.9 grams of DKP, lot #TJT-12-32. Its appearance was that of a fine white crystalline material with a tendency to adhere to the sides of the jar. Mr. Martinez said that this was the only lot of DKP remaining at Searle.

We also interviewed Teratologist Alan Mitchell, on 7-19-77. We had previously noticed his name on one of the DKP compound inventory cards, and his name had also been mentioned by Raymond Schroeder, in connection with DKP. Mr. Mitchell stated that he had done two teratology studies with DKP, both with rats, and both in 1972. In one study the DKP was administered I.G. (as a suspension), and the other was a dietary feeding study. Mr. Mitchell told us that he didn't recall any problems with homogeneity in the dietary feeding study. He said he never remixed or reground any DKP diets. He admitted, however, that when he prepared the diet mixtures, he first sifted the DKP through a hand flour sifter.

We attempted to interview a former Searle employee, Dr. Rao, after learning that he still lived in the Chicago area. Dr. Rao had been in charge of the DKP stability study and was the monitor for study E-77/78. After reaching Dr. Rao by telephone on July 25, 1977 he stated that he would like to talk to his attorney before consenting to the interview. We then received a call from his attorney, Mr. John H. Bickley, Jr., who told us that the interview would be of no advantage to his client, and he therefore refused to allow it. A memo

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of telephone conversation between J. Bressler and Mr. Bickley is attached as Exhibit #33.

CALCULATING DIET CONCENTRATION & BLENDING OF TREATMENT MIXTURES

There were no batch records to show the quantities of DKP and basal diet weighed, type of mixer used, mixing time, dates, or names of individuals performing the weighing and blending operations. We were told that mixing was performed in a Hobart mixer, and that mixing times were about 10 minutes. There was no evidence that any tests had been done to determine the blending characteristics of the mixer, or to validate the 10 minute mix time. Fresh batches were mixed on a weekly, bi-weekly, or monthly basis, and batch size ranged from 6 kilograms to 28 kilograms during the study.

The concentration of DKP in the basal diet was calculated by the Math-Stat Department on a weekly, bi-weekly, or monthly basis (based on the food consumption for the previous time period), and submitted to the Path-Tox Department as a Food Concentration Prediction record. The concentration was expressed as grams of DKP per kilogram of basal diet. The Path-Tox Department Personnel then multiplied the grams of compound indicated on the prediction record by the number of kilograms of diet mix needed to arrive at the proper quantities of DKP and basal diet to be blended. The concentrations were calculated to yield the proper dosage levels of 0.75, 1.5, and 3.0 grams of DKP per kilograms of body weight per day, for the low, medium, and high dose groups. (Copies of Diet Calculation Records are attached as Exhibit #34). At the end of each treatment period, the remaining treatment mixtures were discarded and fresh batches were made.

No reserve sample of either the DKP or the DKP/diet mixtures used in this study were retained according to Searle.

DKP was withdrawn from stock by means of a compound inventory card, which was filled out by the person requesting the material. Tony Martinez was the person that usually requested DKP for use in study E-77/78. We examined eighteen (18) compound inventory cards which accounted for 177.0 kg of DKP withdrawn from stock. According to our calculations a total of 152.81 kg of DKP would have been necessary to

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achieve the diet concentrations and batch sizes that were reportedly used in the study. A total of 230.0 kg of DKP was manufactured by Searle Chemist Jack Drogt. Following are tables showing the quantities of DKP manufactured, calculated quantity required for the study, and quantities withdrawn from stock.

QUANTITIES MANUFACTURED

<u>Lot #.</u>	<u>Quantity (After Milling)</u>
1R	
2R	
3R	
4R	
5R	
6R	
7R	

TOTAL

CALCULATED QUANTITIES REQUIRED FOR THE STUDY

<u>Dose Group</u>	<u>Calculated Quantity Required</u>
Low Dose Males	kg
Mid Dose Males	kg
High Dose Males	kg
Low Dose Females	kg
Mid Dose Females	g
High Dose Females	g
TOTAL	g

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QUANTITIES WITHDRAWN FROM STOCK (FROM COMPOUND INVENTORY CARDS)

<u>Date Withdrawn From Stock</u>	<u>Quantity</u>	<u>Lot #</u>
10/29/71	kg	1R
1/4/72	kg	1R
2/28/72	kg	4R
3/11/72	kg	3R
3/29/72	kg	2R
9/11/72	kg	3R
10/10/72	kg	2R
*	kg	2R
12/1/72	kg	3R
*	kg	4R
12/27/72	kg	5R
*	kg	2R
1/25/73	kg	5R
3/22/73	kg	6R
4/18/73	kg	5R
7/10/73	05 kg	6R
8/10/73	05 kg	6R
9/7/73	kg	6R
11/2/73	kg	7R
TOTAL	kg	

* These three cards were not signed or dated.

It should be noted that only two of the 18 compound inventory cards specified that the DKP withdrawn from stock was to be used in study E-77/78 (PT 988S73). Thirteen of the cards list "Toxicity" or "Toxicology" as the reason for withdrawal. Three of the cards have no entries at all, except for the word "empty". (Copies of the compound inventory cards are attached as Exhibit #28).

The total quantity withdrawn from stock is kg in excess of the amount necessary to achieve the diet concentrations used in the study. (Based on the diet calculation records attached as Exhibit #34, which we used to construct the diet calculation summary table attached as Exhibit #30).

It is not known whether any of the kg of DKP accounted for on the 18 compound inventory cards was withdrawn for use in studies other than E-77/78. We could find no other records to verify the amount of DKP withdrawn for, or used in this study.

