A6

ESTABLISHMENT INSPECTION ENDORSEMENT

Page 1 of 3 Pages

a. ESTABLISHMENT NAME	b. DISTRICT	c. CENTRAL FILE NO.
Searle Laboratories Div. of G.D. Searle & Co.	Chicago	

d. ESTABLISHMENT ADDRESS (Include Zip Code, Area Code and Telephone No.)	e. DATE INSPECTED
1001 Searle Parkway Skokie, Illinois 60076	5/2/77-7/8/77

f. HEADQUARTERS UNIT TO WHICH REFERRED (Use organizational symbol)	HEADQUARTERS USE ONLY g. DATE REFERRED
Bureau of Foods BFF-330 Attn: Dr. Richard Merk	
h. REASON FOR REFERRAL To be Reviewed by the Bureau	d. AF NUMBER

i. DISTRICT ENDORSEMENT

This was priority investigation was made to authenticate all available raw and summary data against specific FDA submissions made by the firm. This inspection covers two studies.

B-3 (FY1211870), SC-18862: Evaluation of Embryotoxic and Teratogenic Potential in the Rat - aspartame.

B-29 (FY1218273), SC18862: Evaluation of Embryotoxic and Teratogenic Potential in the Mouse - aspartame.

Study B-3 was initiated on January 28, 1970. Laparotomies were performed during February 9, through February 19, 1970. The study was received by the Bureau of Foods on August 7, 1973. Ninety females and thirty male albino rats, Charles River Caesarian derived virgin females and males were used. The ninety females were distributed into three groups: Control, Low and High Dose. The rats were fed SC-18862 aspartame at 2.5% and 5.0% concentration respectively. The females were sacrificed on the 20th day of gestation.

Investigation of Study B-3 shows the following: Dates seen on visceral examination sheets, for 329 visceral examinations indicate these examinations may have been done on two days; February 27 and March 5, 1970. Mr. Schroeder, former employee involved with this study, stated that he could examine approximately thirty fetuses a day, although this number may vary slightly because of other duties. He found no evidence of other dates on the material examined. We were unable to resolve the question of the length of time it took to complete the visceral examinations of over 300 fetuses. It would be extremely difficult to make this kind of examination in only two days. The records are dated but not signed or initialed to identify the individuals that examined the visceral sections, skeletons and performed laparotomies.

b. REVIEWING OFFICER (Name and title)	c. SIGNATURE	d. DATE
Jerome Bressler, Team Leader		July 19, 1977

j. DISTRIBUTION: cc: BFF-330, BFO-1, BFF-1, BFA-224, C-DC

FORM FD 481a (11/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

INSPECTION SUMMARY

DATA BY PROJECT/HIA–DCC

(Enter appropriate code, from list at right, in each column.)

PROJECT	COMMODITY	CORRECTION NOTED AFTER	INSPECTION CLASSIFICATION	DO CONCLUSIONS	RE-SCHEDULE DATE	PRIORITY
(1)	I					
	II					
	III					
	IV					
(2)	I					
	II					
	III					
	IV					
(3)	I					
	II					
	III					
	IV					
(4)	I					
	II					
	III					
	IV					
(5)	I					
	II					
	III					
	IV					

CODES

CORRECTION NOTED AFTER

No Correction Noted	0	Injunction/ Prosecution	6
Seminar or Workshop	1	State/Local Action	7
Inspection	2	Recall	8
Warning Letter	3	Termination of Prior Approval	9
Citation	4	Voluntary Action	&
Seizure	5		

INSPECTION CLASSIFICATION

No Action Indicated	1	Not Official Establishment Inventory	7
Official Action Indicated	3	Inactive	8
Voluntary Action Indicated/Provisional	6	Out of Business	9

DISTRICT OFFICE CONCLUSIONS

*Disapproval	D	*Remove Fror Shipper List	
*Use Prohibited	P		

*These District Office Conclusions are for use in identifying inspection Classifications for Consultative Programs

Routine Follow-Up	0	Referred to State, Local, or Other Federal Authorities	7
Collect Official Samples	1	Recall	8
Reinspect	2	Inactive, O/B, or not OEI, not referred to state, local or other Federal authority for action	9
Regulatory Letter	3	Other	&
Citation	4		
Injunction/ Prosecution	6		

REINSPECTION PRIORITIES

Compliance	1	Surveillance	2

U.S. GOVERNMENT PRINTING OFFICE: 1976—626-394/1018 3-1

There are no individual fetus records for the skeletal examinations. The data is listed by litter only under the dam numbers, which are not dated.

The visceral examination records do not list the respective fetus identification numbers for about 18% of the 329 fetus and visceral specimens.

There were no records to document the source and age of the male rats, nor were there any specifications or assay reports for the basal diet. There were no batch records for the mixing of the powdered aspartame with the meal form of Purina basal diet. This treatment mixtures (two dose levels) was not assayed for potency, homogeneity or stability.

A comparison of the laparotomy sheets and visceral examination sheets uncovered at least 35 discrepancies. Twenty-one of these discrepancies consisted of the listing of a different sex for the respective fetus number on the laparotomy sheet, as compared to the visceral examination sheets.

Study E-39 was initiated on January 15, 1975 when the protocol was finalized. Laparotomy sheets indicate that laparotomies were performed from May 19, 1975 through June 18, 1975. The study was submitted to FDA in July 1975. One hundred pregnant Charles River albino mice, were used. The hundred females were distributed into four groups: Control, Low, Medium and High dose. The mice were supposed to be fed SC18962, aspartame, at .75%, 1.5% and 3.0% concentrations respectively, however, the mice actually received approximately 40% more than the intended dose.

Our investigation of Study E-39 shows the following: Abnormal findings of the firm's examination of visceral sections were not submitted to the FDA. A review of the raw data revealed a major malformation of a segmented uterus in a low dose fetus and a cleft palate in a medium dose fetus both of which were missing from the FDA submission. An on-site-examination of the visceral sections by Dr. T. Collins confirmed these findings. He also found a slight hydrocephalus of a low dose fetus, which was not in the raw data or the FDA submission.

We could find no signatures or initials to identify the individuals that worked on the skeleton examinations. There were no assay reports or specifications on the basal diet, nor were there any batch records for the mixing of the aspartame with the basal diet. The three treatment mixtures were not assayed for potency, homogeneity or stability.

The only identification of the skeleton specimens is on the caps of the vials with the respective fetus number and the PT number, 1218. There is a possibility of a mix-up occurring with the identification on the cap instead of on the body of the vial.

Follow-up: To be reviewed by the Bureau of Foods.

Jerome Bressler

ESTABLISHMENT INSPECTION REPORT

(See reverse for codes for commodity groups, establishment type, value, activity, and refusals)

1. ESTABLISHMENT STATUS ☐ NEW FIRM ☐ CHANGE OF ADDRESS ☐ CHANGE OF NAME ☐ CHANGE OF OWNERSHIP ☐ OUT OF BUSINESS ☐ FIRM REGISTERED ☐ CANCEL DRUG REGISTRATION ☐ NEW DRUG REGISTRATION ☐ NOT OEI

2. ESTABLISHMENT NAME: Searle Laboratories Div. of G.D. Searle Co.

3. DISTRICT: Chicago

4. CENTRAL FILE NO.:

5. ESTABLISHMENT ADDRESS *(Include Zip Code, Area Code and Phone No.)*: 4901 Searle Parkway Skokie, IL 60676

7. JUDICIAL DISTRICT/TRAVEL AREA:

8. COUNTY:

6. RELATED FIRMS:

9. DATES INSPECTED: 5/2-7/8/77

10. INSPECTION OPERATION
☐ CONSTRUCTION (09)
☐ IN-DEPTH (10)
☐ LIMITED (11)
☐ REGULAR (12)

11. COMMODITY AND ESTABLISHMENT TYPE	I	II	III	IV
a. COMM CODE / ESTAB TYPE	9 2 7 9			
b. COMM CODE / ESTAB TYPE				
c. COMM CODE / ESTAB TYPE				
d. COMM CODE / ESTAB TYPE				

12. APPROXIMATE ANNUAL VALUE	I	II	III	IV
	a. $10,000,000	b. $	c. $	d. $

13. EMPLOYEE'S HOME DISTRICT: ~~ATL-DO~~ MIK-DO

14. HIA & DATA CONTROL CODE	15. PROJECT	16. HOURS EXPENDED BY POSITION CLASSIFICATION AND EMPLOYEE NUMBER												
		a. 1ST PC EMPL NO.	2ND PC EMPL NO.	3RD PC EMPL NO.	b. 1ST PC EMPL NO.	2ND PC EMPL NO.	3RD PC EMPL NO.	c. 1ST PC EMPL NO.	2ND PC EMPL NO.	3RD PC EMPL NO.	d. 1ST PC EMPL NO.	2ND PC EMPL NO.	3RD PC EMPL NO.
		033	119	999	034								
(1) AC 4-001	09	268	295	180	140								
(2)													
(3)													
(4)													

17. OTHER PRODUCTS NOT INSPECTED: Drugs

18. PRODUCTS INSPECTED
a. Aspartame
b. Aspartame
c.
d.

19. TOTAL ESTABLISHMENT SIZE, FDA REGULATED PROD: 9

20. U.S. BUSINESS — RECEIVED: ☒ YES ☐ NO; SOLD: 95 %

21. PRINCIPAL ESTABLISHMENT TYPE: M

22. RECALL NUMBER:

23. REFUSAL CODE:

24. FDA 483/2275 ISSUED ☐ YES ☐ NO

25. HEADQUARTERS INITIATED ASSIGNMENT *(Enter Documentary Reference)*
HDQ/CHI-20 assignment memo 5/16/77
Special Investigation of Aspartame

26. OTHER FEDERAL GOVERNMENT INSPECTION OR GRADING
OSHA, EPA

27. FOR INSPECTION OF CONVEYANCES
NO. CONV. INSP. | NO. VAI | NO. OAI

28. SAMPLE(S) COLLECTED
NONE

29. EMPLOYEE(S) *(Name and Number)*
Carl E. Lafferman
Johnny F. Boles - Thomas F.X. Collins

30. EMPLOYEE(S) SIGNATURE(S)

PAGE OF PAGES

FORM FD 481 (8/75) PREVIOUS EDITION MAY BE USED.

COMMODITY CODES

CODE	DESCRIPTION
95	Aircraft
04	Alcoholic Beverages
56	Antibiotics
02	Beverage Bases
05	Bread, Rolls, Buns and Sweet Goods *(Except Custard or Cream Filled)*
08	Breakfast Cereals, Ready to Eat
96	Buses
15	Butter and Butter Products
34	By-products for Animal Feeds
13	Candy, Chewing Gum, Chocolate and Cocoa Products
16	Cheese and Cheese Products
03	Coffee and Tea
93	Colors for Foods, Drugs and Cosmetics
94	Cosmetics
80	Devices
58	Diagnostic Reagents and Drugs, Drug Excipients, Vehicles, Flavors; and Containers and Closures for Drugs
50	Dietary Specialities, Artificial Sweeteners, Conventional Foods with Nutritional Claims, and Miscellaneous Dietary Food Items
26	Dressings and Condiments
92	Drug Control and Research Establishments
57	Drugs, Crude and Bulk
60	Drugs, Non-Prescription
70	Drugs, Prescription
59	Drug Storage and Warehousing
90	Drugs, Veterinary *(Except Vitamins, Code 55 and Antibiotics, Code 56)*
20	Eggs and Egg Products
25	Extracts and Flavors
33	Feeds, Animal
21	Fish and Fish Products *(Except Smoked)*
23	Fish, Shellfish and Crustaceans, Smoked
48	Food Chemicals
47	Food Storage
32	Fruit Products
29	Fruits and Juices, Canned
27	Fruits and Juices, Fresh

CODE	DESCRIPTION
28	Fruits and Juices, Frozen
30	Fruits, Dried
09	Grains and Beans *(Whole)*, Bulk
11	Grains, Processed; and Starch Products, Human
19	Ice Cream and Related Products
49	Infant, Junior, and Geriatric Foods
31	Jams, Jellies, Preserves, and Butters
07	Macaroni and Noodle Products
35	Meat and Meat Products
91	Medicated Animal Feeds
18	Milk and Milk Products, Dried
17	Milk and Milk Products, Fluid
51	Miscellaneous Food-Related Establishments
46	Miscellaneous Food Use Items
12	Mixes, Prepared, Dry *(Flour or Meal Base)*
44	Mixes, Dessert and Pudding, Dry
36	Nuts and Nut Products
99	Other Acts and Miscellaneous Preparations
45	Prepared Multiple Foods
10	Pretzels, Chips and Specialty Items
97	Railroad Cars
22	Shellfish, Crustaceans and other Aquatic Animals *(Except Smoked)*
01	Soft Drinks and Waters
24	Spices and Salt
06	Sweet Goods, Custard or Cream Filled
14	Syrups, Sugars and Honey
37	Vegetable Oil Seed, Oil Stock and Crude Vegetable Oil
38	Vegetable Oils, Refined; and Vegetable Shortening and Oleomargarine
43	Vegetable Products, Cured
42	Vegetables, Dried or Dehydrated
39	Vegetables, Fresh
41	Vegetables *(with or without sauces)* and Vegetable Juices, Canned
40	Vegetables *(with or without sauces)* and Vegetable Juices, Frozen
98	Vessels
55	Vitamins

CODE	ESTABLISHMENT TYPE
B	Blood Banks
J	Caterers
K	Catering Point
H	Construction *(Conveyance, Support Facilities, Components)*
C	Control Research Labs
F	Conveyance Company
D	Dealer *(Retailer)*
E	Elevator
G	Grower
I	Investigator, Clinical
M	Manufacturer

CODE	ESTABLISHMENT TYPE
T	Methadone & Other Drug Abuse Treatment Programs
O	Other
L	Own Label Distributor
P	Public Food Service *(Restaurants, Cafeterias, Wet Stands, etc.)*
R	Repacker
X	Salvage Operation *(Retailers, Wholesalers, Repackers, Underwriters, etc.)*
V	Service Area
W	Warehouse
U	Watering Point

CODE	INSPECTION REFUSAL REASON[1]
∅	No Refusal
1	Refusal to permit entry
2	Refusal to allow inspection except by appointment or other condition
3	Refusal to furnish qualitative or quantitative formulae
4	Refusal to disclose or permit observations of manufacturing procedures
5	Refusal to permit review of control records

CODE	INSPECTION REFUSAL REASON[1]
6	Refusal to permit review of complaint files
7	Refusal to permit review of sales or shipping records
8	Refusal to permit collection of samples
9	Refusal to permit photography
&	Refusal to permit review of underlying data regarding material submitted to FDA *(Regarding food additives, color additives, pesticide petitions, etc.)*

CODE	VALUE OR SIZE
∅	$ 0 - $ 24,999
1	25,000 - 49,999
2	50,000 - 99,999
3	100,000 - 499,999
4	500,000 - 999,999

CODE	VALUE OR SIZE
5	$ 1,000,000 - $ 4,999,999
6	5,000,000 - 9,999,999
7	10,000,000 - 24,999,999
8	25,000,000 - 49,999,999
9	50,000,000 and over

[1] *Enter one Refusal Code in Item 23. Select the most significant when there is more than one.*

*U.S. GOVERNMENT PRINTING OFFICE: 1975—O 631-536/1498 R3

This from Dr Olney JV2

EIR 5/2-7/8/77
CEL, JFS, TC

Searle Laboratories
Div. G.D. Searle & Co.
4901 Searle Parkway
Skokie, Illinois 60076

SUMMARY OF FINDINGS

We made a detailed inspection of the raw data versus the final report on two teratology studies on SC 18862 (aspartame). These studies, numbered E-5 (PT851S70) and E-59 (PT1218S75) were selected for our inspectional coverage by headquarters personnel of the Bureau of Foods. Study number E-5, "SC-18862: Evaluation of Embryotoxic and Teratogenic Potential in the Rat" had not been previously inspected by FDA personnel at Searle Laboratories. Study number E-59 was included as one of five teratology/reproduction studies that were covered by an FDA inspection team during the period of December 1 through 19, 1975.

Our inspection of Study E-5 included the following findings:

1. The individual doing the examinations of the visceral and skeleton specimens was aware of the dose levels. The examinations were not done blind.

2. There are no individual fetus records for the skeletal examinations. The skeletal examination data is listed only by litter under the dam number. The skeletal examination records are not dated.

3. There are no examination sheets that specify the abnormalities that are included in their examination of visceral sections. Their visceral examination records indicate only "O.K." if no abnormalities were found. The visceral examination sheets do not list the respective fetus identification numbers for about 10% of the 329 fetus visceral specimens. These incompletely identified fetus specimens are identified on the examination sheet with only the dam number and fetus sex.

4. According to the visceral examination records, a total of 329 visceral examinations might have been done on two days. We were unable to examine any visceral sections from study E-5 because they had been discarded.

5. There were no signatures or initials to identify the individuals who did the work on the skeletal, visceral, and laporotomy examination sheets.

6. There was no identification on the body of the vials holding the skeleton specimens; the respective fetus number was on the vial cap (See exhibit 39, photo 1).

7. There was no record to verify the source and age of the male rats.

8. There were no specifications or assay records on the basal diet.

9. There were no batch records for the mixing of the powdered SC 18862 (aspartame) with the meal form of Rockland diet (Teklad Inc.) Mrs. D. Helms, Research Assistant, could not remember the details of mixing - such as the total mixing time or the order of adding the SC 18862 and the Rockland Diet to the mixer.

10. The treatment mixtures (two dose levels) were not assayed for potency, homogeneity or stability.

11. The examination of the fetal skeletons of 5 litters of each dose level by Dr. T. Collins revealed only a few differences from their original skeletal examination data as compared to the FDA submission. A few differences in the results are not unusual between 2 individuals when they are doing examinations. These findings are detailed in the body of the report.

Our inspection of study number E-89 included the following findings:

1. The individual who did the visceral and skeleton examination was aware of the dose level of the specimens that were being examined.

2. There are no examination sheets that specify the abnormalities that are included in Searle's examination of visceral sections.

3. The only identification of the skeleton specimens is on the caps of the vials with the respective fetus number and the PT number, 1218.

4. The records covered receipt of only 10 of the 36 male ~~rats~~.

5. There were no signatures or initials to identify the individuals who did the work on the skeleton examination records.

6. There were no assay reports or specifications on the basal diet.

7. There were no batch records for the mixing of the aspartame with the chow. The three treatment mixtures were not assayed for potency, homogeneity or stability.

8. Searle did not include any abnormal findings of visceral examination in the report that was submitted to FDA. The raw

data included major malformations of a segmented uterus in a low dose fetus 20407 and a cleft palate in a medium dose fetus 32012 neither of which was included in the FDA submission. Dr. Vondruska was shown this data and said this omission was an oversight (see Vondruska's interview). Dr. Collins examined visceral sections that included verification of the aforementioned findings. Dr. Collins also noted a slight hydrocephalus of fetus 20407, low dose, that was not in the raw data or the FDA submission. This was confirmed by Dr. J. Neveroske the Searle Teratologist. (see exhibit 39, photo 3) Dr. Collins disagreed with Searle's classification of "renal pelvic cavitation of the kidney not enlarged" of the fetus 41101 as an artifact and not a malformation. (see exhibit 39, photo 4) Dr. Collins does not agree that this is an artifact and he is of the opinion that it is due to the blockage of the urinary tract.

Dr. Vondruska stated that in retrospect "artifact" was probably a poor word to use. He said that Cell might have sectioned the kidneys at an incorrect angle, thereby, giving the appearance of an enlarged renal pelvis. (see Vondruska interview)

9. It would appear that the visceral sections were cut too thick. There would be a possibility that some visceral abnormalities would be missed.

10. It was noted in the FDA submission that there was a significantly greater number of fetuses in the medium dose level with poorly ossified supraoccipital bones, when compared to the control group. Because of this finding, the supraoccipital bones of the fetuses in the high dose level were examined. Dr. Collins scanned the supraoccipital bone for poor ossification in each of the skeletal fetuses of the control and high dosage groups. His examination of the supraoccipital bone revealed the following percentage differences from the FDA submission.

Supraoccipital Bone Poorly Ossified	Control Fetuses	High Dose Fetuses
FDA Submission	3%	6%
Examination by Dr. T. Collins	4.46%	8.47%

Searle Laboratories
Div. G.D. Searle & Co.
Skokie, Illinois 60076

11. C. Kirby, Reasearch Technician whose duties included the visceral and skeletal fetal examinations and laparotomies for study E-89 completed about three years of college. She started employment with Searle Laboratories in August of 1974 and performed visceral and skeletal exams on E-89 in May and June of 1975. This was the only study where she performed the visceral exams. She stated that her on-the-job training consisted of a total of about 3 months.

12. There are no dates of examination on the skeleton tables (exhibit 30). On the back of the laparotomy sheets, the major skeletal variations are listed. Most of the skeletal examinations are dated 5/19/75 and 6/4/75. It would be impossible for one individual to do a complete skeletal examination of over 500 fetuses in 2 days. It is unclear over what period of time these fetuses were read.

PURPOSE OF INVESTIGATION

Assignment memo dated May 16, 1977 from Donald Healton, Acting Executive 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 investigating began on 4/25/77 (see EIR E 77/78) and encompassed the authentication of all data, both raw and summary, relating to the studies jointly chosen for review by the 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.

We began our investigation of E-5 (PT-851S70) Evaluations of Embryotoxic and Teratogenic Potential in the rat, using SC18862 (Aspartame), on May 2, 1977.

On May 11, 1977, after clearance from the Bureau of Foods, we initiated the investigation of E-89 (PT-1218S75) an Evaluation of Embryotoxic and Teratogenic Potential in the mouse, using SC-18862 (Aspartame), see assignment attached.

This report is concerned with the above two studies. The report involving E-77/78 will be reported separately.

REFUSALS

Attached as exhibit 40 is a memorandum dated June 29, 1977 from Mr. Roger Thies, Attorney refusing our request for an additional interview of Ms. Gail Kirby, a technician who worked on E-89 (PT-1218S75), Evaluation of Embryotoxic and Teratogenic Potential in the mouse (aspartame).

We were concerned with the dates shown on the back of the laparotomy sheets, "6/14/75" and "5/19/75." Dr. Collins is of the opinion that it would be extremely difficult to completely examine 300 skeletons in two days, if these dates, so indicate. In our interview with Mr. Schroeder, a former employee, he told us that he was able to examine thirty skeletons in a day. (see Schoeder interview attached) In our interview with Dr. Vondruska, he could not not explain the dates shown on the back of the laparotomy sheets. He told Dr. Collins that he would have to ask Ms. Gail Kirby.

Our failure to interview Ms. Gail Kirby leaves the question of the dates unresolved. G.D. Searle's refusal to allow us to conduct a telephone interview is given in the menorandum from Mr. Thies (see exhibit 40). We do not consider his reasons for refusal as valid.

PERSONS INTERVIEWED

Investigators Carl E. Lorentzson and Johnny F. Salas presented their credentials and issued a Notice of Inspection on May 2, 1977 to Richard E. Viktora, Attorney. Dr. Thomas F.X. Collins issued a Notice of Inspection on May 4, 1977 to Dr. William M. Merino, Director of Regulatory Affairs. Dr. Collins was at Searle Laboratories on May 4-6, 23-27, June 6-7, and July 7 and 8, 1977. Investigators Carl E. Lorentzson and/or Johnny F. Salas were both present on each date of inspection with the exception of July 7 and 8, 1977 Investigator J. Salas was present at Searle Laboratories for the inspection of studies E-89 and E-5 on May 17, 1977, when Investigator C. Lorentzson was not at Searle Laboratories. An attorney and/or a Ph.D. from one of the research units of Searle Laboratories was present whenever we reviewed records, inspected the facilities, examined

fetal skeletons or interviewed personnel. These individuals were:

Dr. Robert Post - Director of Food Products, Regulatory Affairs
Dr. George Clay - CNS Group Leader
Richard Viktora - Attorney
Roger Thies - Attorney
Dr. J. Noveroske - Group Leader of Toxicology
Dr. Fred A. Radzialowski - Section Leader of Cardio-vascular Pharmacology
Dr. W. Jenkins - Director of Product Affairs
Dr. Richard L. Aspinall - Group Leader of Immunology & Inflammatory Diseases

We interviewed Research Assistant Mrs. D. Helms at Searle Laboratories regarding her duties on study E-5.

We made arrangements to interview Raymond Schroeder, a former employee whose title at the time was Senior Research Assistant, and whose principal duties were on study E-5 and relatively limited duties on study E-99. This interivew was conducted in New Jersey because Raymond Schroeder is now residing in Somerville, N.J.

We interviewed the following individuals regarding their duties on study E-89:

1. Gail Kirby - Research Technician
2. Jeanne Thompson - Research Technician
3. Dr. J.F. Vondruska - Senior Investigator
4. Alan Mitchell - Teratologist

Richard Viktora provided us with the date that Raymond E. Schroeder left this firm, namely May 2, 1975. However, Mr. Viktora said that he would not furnish a copy of a record to substantiate this termination date because it would be a violation of the Equal Employment Opportunity Regulations. We were allowed to review and make notes from the following records. However, Roger Thies, Attorney, did not allow photocopies because he did not consider these records to be primary data on study E-5, namely:

1. A preliminary draft of the summary and conclusions for the final report on "77 851570" (Searle Doc #1146652)

2. A list of the studies which either have been completed or were in progress with aspartame to determine the relative toxicity of aspartame and Diketopiperazine in several species of animals (Searle Doc #1272358)

3. A "galley copy" of the report that was submitted to FDA

4. An inventory list of the teratology specimens that were stored in a basement storage area. The record included a listing of the fetal skeleton preparation from the rat, in study E-5 (PT-851S70) in box numbers T-043A, T015.

SCOPE OF OUR INSPECTION

We requested all of the records pertaining to study E-5 on the first day of our inspection, May 2, 1977. It was brought to our attention by Jerome Bressler, FDA inspection team leader, that the data pertaining to this teratology study had been previously placed under FDA seal. We then visited their R&D central file room to locate these records. We determined that the data including primary records pertaining to their teratology studies on SC 18862 (aspartame) was stored under FDA seal in two file drawers. We initially attempted to remove the data from these file drawers that pertained only to study E-5. In order to facilitate our detailed examination of these records on teratology studies, we then removed the records on all of the teratology studies in their two file drawers to a room on the first floor of "J" building. Whenever we did not personally guard these records, we maintained the data on these teratology studies in a locked metal cabinet under FDA seal. We obtained almost all of the records for our E-5 study from their central file room. We subsequently requested additional records pertaining to the study E-5 such as the lab testing of the component, SC 18862, invoice for purchase of female rats; curriculum vitae and chain of responsibility. We made photocopies of essentially all primary data and other records pertaining to study E-5. Exhibit numbers 1 through 13, 38 and 3 photos in Exhibit 39 pertain to study E-5.

We made a detailed review of all raw data against the report that was submitted to FDA. This review included fetal and maternal body weights, maternal food consumption, crown rump measurements, number of corpora lutea, number of live and dead fetuses and examination records on visceral and skeletal fetal specimens. Dr. T. Collins examined skeletal specimens from study E-5, and skeletal and visceral specimens from study E-89.

After we completed the majority of our inspectional work at Searle Laboratories on study E-5, we received authorization from personnel

of the Bureau of Foods on May 11, 1977 to institute an inspection of an additional teratology study, S-89 (PT-1218675) entitled - "SC-18862 - An Evlauation of the Embryotoxic and Teratogenic Potential in the Mouse". We made copies of all primary data and other records pertaining to study S-89. Exhibit numbers 16 through 38 and photo numbers 2, 3, and 4 of Exhibit 39 pertain to study S-89. We made a comprehensive review of all raw data with one minor exception. We estimate that we checked more than one third of the food consumption primary data for accuracy. The previous inspection of December 1-19, 1975 included study S-89 and stated in part that maternal food consumption was transferred without error from the raw data. The FDA submission on study S-89 states in part that the pregnant animals actually consumed dose levels for the low, medium, and high dose groups respectively which are approximately 40% more than the originally intended doses of 1.0, 2.0 and 4.0 g/Kg.

PERSONNEL ON THE S-5 STUDY

Individual	Title & Background	Duties
Mrs. Donna Helms	Research Assistant Her educational background includes B.S. Univ. of Wisconsin with a major in Zoology in 1966. She started work for Searle Laboratories in 1969 and is currently employed by the firm.	Donna Helms stated that her duties included: weighing of the animals; setting up the study; food consumption data; transfer of data from cage cards to laboratory sheets; and performing hysterotomies.
Raymond F. Schroeder	Senior Research Assistant in Teratology. His education includes a M.S. in Zoology from the Univ. of Illinois in 1967. He was employed by Searle Laboratories from Dec., 1967 to May 2, 1975.	According to Donna Helms, the duties of Ray Schroeder included external observation of the fetuses; supervision of the laparotomy; and performance of the visceral sections and skeletal examinations.

Searle Laboratories
Div. G.D. Searle & Co.
Skokie, Illinois 60076

Margaret S. Faber (Hoppenrath)	Bio Research Technician	Donna Salas stated that Margaret Faber might have done some of the crown rump measurements. Donna Salas was unable to recall any other work that was done by Margaret Faber on study SC-5. Raymond Schroeder informed us during his interview that the duties of Margaret Faber (Hoppenrath) included: killing of animals, mixing of the diet, crown-rump measurements, weighing of fetuses, staining of skeletons, and cutting the visceral sections.

Copies of Curriculum vitae for key personnel and a listing of the responsible individuals of Searle Laboratories during the years 1969 and 1970 are attached as exhibits numbered 1 and 2. Study number I-5 was conducted during the first half of 1970. The Director of Biology of Searle Laboratories during this time period was V.A. Drill. The authors of the report are R.E. Schroeder and R.G. McConnell, Dept. of Pathology-Toxicology, Division of Biological Research.

Study I-5 (PT 851570)

SC-18662: Evaluation of the Embryotoxic and Teratogenic Potential in the Rat

Date study initiated: Jan. 20, 1970

Dates of performing laparotomies: Feb. 9 through Feb. 19, 1970

Date study was received by Bureau of Foods: August 7, 1972

Animals:

Species and Strain - Albino rat, Charles River caesarian derived virgin females and proven males

Number and Sex - 90 females, 30 males - there were no records to indicate source and age of male rats. We verified that the females were approximately 10[illegible] days old at time of mating - Invoice (Exhibit 4) indicates date of receipt: 12/30/69.

Experimental Design:

Ninety females were distributed into the following three groups. Mrs. D. Helms said that she used a randomization method that involved drawing animal numbers from pieces of paper in a hat. She didn't remember if the first number drawn was assigned to a control group.

Dosage Group	No of animals	Dose Level - mg/kg
Control	30	0
Low	30	2000
High	30	4000

The respective identification number of each of the rats was punch marked on their ears.

Donna Helms could not state definitely whether the animals from each dose group had a unique color marking on their tail. Three females, one from each of three dosage groups were housed together in a breeding cage. At 4:30 p.m. one male was placed into each cage; he was removed at 8:30 a.m. the following morning. At that time females were examined for a copulatory vaginal plug and/or spermatozoa in the vaginal smear. Observation of either of these signs indicated mating and was designated day 0 of pregnancy. Such females were removed from the breeding cage and housed individually. They put this rat in the next empty cage going from left to right. This procedure was continued until a minimum of 24 females from each group were mated. Copies of the cage identification cards are attached as Exhibit number 6. We were informed that any daily observations would be recorded on these cage cards. There are no records of abnormal observations on these cards.