DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

September 26, 1979

CHICAGO DISTRICT
1222—POST OFFICE BUILDING
433 WEST VAN BUREN STREET
CHICAGO, ILLINOIS 60607
TELEPHONE: 312-353-5863

John W. Olney, M. D.
Department of Psychiatry
Barnes and Renard Hospitals
4940 Audubon Avenue
St. Louis, Missouri 63110

Re: FOI # 79-21004
CHI- 1766

Dear Dr. Olney:

This is in response to your request of August 20, 1979 for records from the Food and Drug Administration pursuant to the Freedom of Information Act: Paragraph III of your letter re: G. D. Searle's product: Aspartame.

X We are enclosing the requested record(s) consisting of EIR dated 4/25 - 8/4/77 regarding study of E 77/78 and EIR dated 5/2 - 7/8/77 regarding study E-5 and E89.

X As you will note, minor deletions of material have been made in the records furnished to you. In the judgment of the Food and Drug Administration, the information deleted does not fall within the scope of your request and, in any case, is not required to be disclosed under the Freedom of Information Act. If, however, you do desire to review the deleted material, please make an additional request. If the agency should then deny you this information, you would have the right to appeal such denial to the Department of Health, Education, and Welfare. Any letter of denial will tell you how to make this appeal.

____ No deletions were made from this material.

____ The requested record(s) will be sent at a later date.

X I apologize for the quality of the 5/2 - 7/77 EIR. The problems were with our original copy. Please contact me at 312-353-5863 if you have problems.

X We are assessing the following charges:

125 pages	@ $ .10 =	$12.50
2 hours search time -1/2 hour	@ 3.00 =	4.50
Total		$17.00

An invoice is attached.

____ The charges will be aggregated to your bill.

____ There will be no charge for furnishing record(s).

Sincerely,

George F. Bailey

George F. Bailey
Freedom of Information Officer

Enclosure: a/s
GFB/ed

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-89 (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-89 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).

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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. Noverske the Searle Teratologist. (see exhibit 39, photo 2) 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 Coll 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%

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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. Neveroske - Group Leader of Toxicology
Dr. Fred M. Radzialowski - Section Leader of Cardio-vascular Pharmacology
Dr. K. 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-99:

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 D. 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 "NF 851570" (Searle Doc #1144652)

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)