INDEX OF STUDIES

SUBMITTED TO THE FDA

IN SUPPORT OF ASPARTAME

MASTER FILE ENTRY	TITLE/AUTHORS	ABSTRACT/REASON FOR STUDY	DATE SUBMI TO U.S. FD
1-A	Procedures for Chemical Manufacture of Aspartame	Information primarily received from Ajinomoto under confidentiality contract	11/30/72
2-A	Stability of Aspartame, Paris 1-VII	Stability of aspartame in various forms and under various conditions (ongoing)	11/30/72
1-B	Consumption of Sweeteners	Consumption of sweeteners in the U.S. and projected consumption of aspartame	11/30/72
2-B	Use of Aspartame in Foods	Document in General Foods Master File # 135	1/29/73
3-B	Analytical, Microbiochemical, and Organoleptic Evaluation of Aspartame in Food Subjected to Abuse Conditions	Joint study by Searle Analytic, Biochemics and Microbiology to determine function and acceptability of a spoon-for-spoon sweetener under abuse conditions in various foods	2/9/73
1-C	Organoleptic Evaluation of Aspartame	The taste character and intensity of aspartame (as bulk chemical, spoonful equivalent or tablet) were evaluated in a wide variety of applications ranging from threshold sweetness in water to storage testing in vanilla-flavored frozen dessert. Most focused on a coffee system.	11/30/72
2-C	Intended Effect of Aspartame in Food	Document in General Foods Master File #135	1/29/73

MASTER FILE ENTRY	TITLE/AUTHORS	ABSTRACT/REASON FOR STUDY	DATE SUBMI TO U.S. FD
1-D	Analytical Data and Specifications of Food Grade Aspartame Authors: Dr. E. Lau, Dr. G. Anthony J. Damascus, B. Smith	Analytical data of aspartame, specifications for food grade aspartame and its directions for testing	11/30/7
2-D	Analytical Methods for Aspartame and DKP in Processed Food	Document in General Foods Master File # 135	1/29/73
E-1	A Sweetening Agent Pharmacological Studies Author: Donald L. Cook, Ph.D	SC-18862 was subjected to a wide variety of pharmacological tests in order to delineate any possible adverse effects of the compound on the gastrointestinal system, cardiovascular system or central nervous system	8/172
E-2	SC-18862: Four Week Oral Tolerance Study in the Mouse P-T No. 815S69 Authors: K.S. Rao, T.B. Martinez and R.G. McConnell	SC-18862 was administered orally in the diet to 8 week old mice of both sexes for four consecutive weeks to establish a desirable dose range and maximum tolerated dose for subsequent toxicity studies of longer duration	8/1/72
E-3	SC-18862: Four Week Oral Tolerance Study in the Rat P-T 814S69 Authors: K.S. Rao, T.B. Martinez and R.G. McConnell	SC-18862 was administered orally in the diet to 8 week old albino rats of both sexes for four consecutive weeks to establish a desirable dose range and maximum tolerated dose for subsequent toxicity studies of longer duration.	8/1/72
E-4	SC-18862: Nine Week Oral Toxicity Study in the Rat. Authors: R.D. Hemm, K.S. Rao, T.B. Martinez, D.W. Calhoun and J.E. Mayer P-T847S70	To establish a desirable dose range for subsequent behavioral and toxicity studies of longer duration, and to provide preliminary information on the effects of 5% L-phenylalanine or 9% SC-18862 diet on body weight gain, food intake and physical examination, clinical laboratory and postmortem findings after nine weeks of compound administration.	8/1/72

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E-5	Evaluation of Embryotoxic and Teratogenic Potential in the Rat P-T 851S70 Authors: R.E. Schroeder and R.G. McConnell	Evaluate embryotoxic and/or teratogenic potential of SC-18862 when administered orally in the diet to the albino rat. This study design is commonly referred to as Segment II of the Teratology-Reproduction profile.	8/1/72
E-6	SC-19192: Two Week Oral Toxicity Study in the Mouse P-T 885S70 Authors: K.S. Rao, T.B. Martinez, R.D. Hemm and R.G. McConnell	The finished product of SC-18862 may contain 0-1% of a degradation product, SC-19192. Preclinical testing of SC-19192 for its potential toxicity was performed.	8/1/72
E-7	SC-19192: Two Week Oral Toxicity Study in the Rat. P-T884S70 Authors: K.S. Rao, J. Mauro and R.G. McConnell	Same as above.	8/1/72
E-8	SC-19192: Five Week Oral Toxicity Study in the Rat P-T972S71 Authors: K.S. Rao, C. Staunton, R.G. McConnell	SC-19192 administered to young albino rats of both sexes for five consecutive weeks to evaluate safety of multiples of the model estimated daily human dosage and to induce and define adverse effects as might occur only at prodigous multiples of such dosages.	8/1/72
E-9	Toxicological Evaluation in the Neonatal Rat P-T 893I171 Hazelton Laboratories Report	To evaluate and characterize the effects of SC-18862 on hematological and biochemical parameters and on tissues of rats one through 21 days.	10/13/72
E-10	Toxicological Evaluation of SC-18862: Evaluation of Reproductive Performance P-T 857S70 Authors: R.E. Schroeder, K.S. Rao, and R.G. McConnell	To evaluate effects of SC-18862 to the male and female albino rat prior to mating and to the pregnant female during the entire period of gestation and lactation. (Segment I teratology)	10/13/72

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E-11	Two Generation Reproduction Study Rats P-T 867II71 Author: Hazelton Laboratories	To evaluate and characterize effects of SC-18862 on the reproductive performance of albino rats. Dietary administration carried on through 2 parental generations and two one-litter filial generations.	10/13/72
E-12	SC-18862: Mutagenic Study in Rats P-T 869II 70 Final Report Author: Hazelton Laboratories	The purpose of this study was to determine the potential mutagenic effect of test material SC-18862 on the bone marrow and spermatogonial cells of the rat.	10/13/72
E-13	SC-19192: Segment III Perinatal Weaning Study in the Rat P-T 1011II72 Final Report Author: Hazleton Laboratories	This study was conducted to evaluate the potential effects of SC-19192 on the perinatal and postnatal phases of the reproductive process in albino rats, with emphasis on evaluation of parturition, neonatal viability, and growth of the newborn.	10/13/72
E-14	SC-18862: Behavioral Effects of chronic Feeding of L-phenylalanine and SC-18862 to Weaning Rats Biology Document No. 793 Author: W.J. Potts	In an effort to compare APM with phenylalanine, and employing 5% L-phenylalanine diet in rats as the model, a 13 week experiment was conducted in weaning rats. In this behavioral toxicity study, dose levels of APM were chosen so as to provide an amount of phenylalanine equivalent to 2.5% and 5.0% in the diet.	10/13/72
E-15	SC-18862: Metabolism of Aspartame-Volume I Parts I-XIV Author: Dr. R.E. Ranney, et al.	Studies of the pharmacokinetics and metabolism of SC-18862 have been carried out in rats, mice, dogs, rabbits, rhesus monkeys and man.	10/13/72
E-16	Sweetening Agent Bibliography		10/13/72
E-17	SC-18862: The Metabolism of Aspartame Volume II Parts XV - XIX Author: Dr. R.E. Ranney, et al	See E-15	11/30/72

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E-18	SC-18862: The Metabolism of Aspartame Volume III Parts XX-XXIII Authors: Dr. R.E. Ranney, Dr. J.A. Oppermann	See E-15	11/30/7
E-19	SC-18862: A Sweetening Agent: Endocrine Studies Author: Ehard F. Nutting, Ph.D.	The studies reported here were undertaken to assess potential side effects of SC-18862 on the endocrine system and hormonally dependent target tissues. SC-19182, a diketopiperazine which is formed as a degradation product of SC-18862 under certain conditions, was also included in these studies.	11/30/7
E-20	SC-18862: Two Month Oral Administration-Rats P-T 719H68 Final Report Author: Hazleton Laboratories	This study was conducted to evaluate and characterize the effects of subacute administration of SC-18862 in male and female albino rats.	11/30/72
E-21	SC-18862: Two-Month Oral Toxicity-Dogs P-T 720H68 Final Report Author: Hazleton Laboratories	The purpose of this study was to characterize and evaluate the subacute oral toxicity of SC-18862 in dogs. The study was started on August 28, 1968, and terminated on October 25, 1968.	11/30/72
E-22	SC-18862: Chicken Embryo Study-Calcium Cyclamate Sucrose P-T 870H70 Final Report Author: Hazleton Laboratories	SC-18862, was injected into the yolk sac of 50 fertile, White Leghorn eggs prior to incubation at dosage levels of 0.25 and 0.5 mg. per egg. Calcium cyclamate was likewise injected as a comparative control into two groups of 50 eggs each at levels of 0.5 and 2.5 mg. per egg. Sucrose was injected into a single group at 1.0 mg. per egg. All dead embryos (eight days and older) and hatched chicks were examined grossly for signs of abnormalities.	11/30/72

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E-23	SC-18862: Short Term Tolerance of Aspartame by Normal Adults Investigator: Dr. Kenneth Langlois Hill-Top Research, Inc. Cincinnati, Ohio	The primary objective of this study was to determine the effects of aspartame on normal volunteers during a 6-week period in which the daily amount administered was gradually increased to a maximum of 8.1 gm. during week 6. This is more than 13 times the anticipated intake of the sweetener in an ordinary daily diet.	11/31/
E-24	SC-18862: Short Term Tolerance of Aspartame by Obese Adults Investigator: Dr. Richard Hoffman Staten Island Hospital Staten Island, New York	The objective of this study was to compare the effects of aspartame and placebo on the population that might be expected to include the most enthusiastic users of a sugar substitute.	11/30/
E-25	SC-18862: Short Term Tolerance of Aspartame by Adult PKU Heterozygotes Investigators: Dr. Richard Koch, Children's Hospital, Los Angeles, Dr. Raymond M. Peterson, Child Development Center, San Diego, and Dr. Charles R. Scriver Montreal Children's Hospital	No abnormalities of phenylalanine metabolism were seen in any of the adult PKU heterozygotes studied	11/30/7
E-26	SC-18862: Tolerance of Loading Doses of Aspartame by Phenylketonuric (PKU) Homozygous Children Investigator: Richard Koch, M.D.,Children's Hospital of Los Angeles, Los Angeles, California	Single loading doses of aspartame or its L-phenylalanine equivalent did not provoke a clinically significant metabolic upset in the two PKU homozygote patients tested, who were on a restricted and liberalized Lofenalac diet, respectively.	11/30/7
E-27	SC-18892: 46-week Oral Toxicity-Hamster P-T 852S72 Authors: K.S. Rao, J. Mauro and R.G. McConnell	In this toxicity study SC-18862, a nutritive artificial sweetening agent, was administered orally in the diet to weanling Syrian hamsters of both sexes for 46 consecutive weeks. It was the intent of the study to evaluate the safety of multiples of the modal daily anticipated human intake and to induce and define such adverse effects as might occur at prodi-	1/25/7

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E-28	SC-18862: 106 Week Oral Toxicity Study in the Dog Authors: K.S. Rao, J. Mauro and R.G. McConnell	In this toxicity study SC-18862 was administered orally in the diet to Beagle dogs of both sexes for 106 consecutive weeks. It was the intent of the study to evaluate the safety of multiples of the anticipated daily human intake, and to induce and define such adverse effects as might occur only at prodigius multiples of such intake.	1/25/73
E-29	SC-18862 & SC-19192: (3:1) Ratio: Segment II - Teratology Study - Rabbit - P-T 1002H72 Final Report Author: Hazleton Laboratories	The purpose of this study was to evaluate the potential of SC-18862 and 19192 (3:1 ratio) for embryotoxic and/or teratogenic effects in albino rabbits.	1/25/73
E-30	SC-19192: Evaluation of Mutagenic Potential Employing the In Vivo Cytogenics Method in the Rat. P-T 1027H72 Final Report Author: Hazleton Laboratories	SC-19192 was administered orally (intragastric) to four groups of 10 male albino rats each for five consecutive days, at dose levels of 0.25, 0.5, 1.0 and 2.0 g/kg/day given in three equally divided daily doses. Evaluation of chromosome spreads indicated that SC-19192 did not alter (increase) the normal aberration frequencies observed in the control rats, and is thus not mutagenic. All data obtained were within normal limits.	1/25/73
E-31	SC-19192: Evaluation of Mutagenic Potential Employing the Host-Mediated Assay-Rat P-T 1029H72 Final Report Author: Hazleton Laboratories	Evaluation of the mutation frequencies from rats treated with SC-19192 showed no significant alterations from that observed for the negative control animals. Dimethylnitrosamine, employed as a positive control, was shown to be a potent mutagen in this test system evoking a mutation frequency eight times that of the control group.	1/25/73

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E-32	SC-18862: 52-Week Oral Toxicity Study in the Infant Monkey P-T 856ot70 Authors: K.S. Rao, R.G. McConnell and H.A. Waisman	In this toxicity study SC-18862 was administered orally in the milk formula to infant Rhesus monkeys for 52 consecutive weeks. This study was designed to determine the adverse effects if any, of SC-18862 ingestion on the neonatal Rhesus monkey, and also whether all such effects were identical in nature and magnitude to those produced by an equimolar quantity of L-phenylalanine.	1/25/73
E-33	SC-18862: APPENDIX: Two-Year Toxicity Study in the Rat: P-T 838H71	See E-34	1/25/73
E-34	SC-18862: Two-Year Toxicity Study in the Rat: P-T 838H71 Final Report Author: Hazleton Laboratories	Treatment of rats with SC-18862 at levels of 1,2,4, and 8 g/kg/day for up to two years produced no convincing evidence of treatment-related histopathologic changes in any organ or tissue examined, except possible the renal changes in the higher levels of male survivors as listed above. Similarly, the incidence of spontaneous alterations commonly observed in laboratory rats was not appreciably altered when comparing treated and control animals.	1/25/73
E-35	SC-18862: 46-Week Oral Toxicity Study in The Hamster, Supplement No. 1, Part I P-T 852S72 Authors: K.S. Rao, J. Mauro, R.G. McConnell	On August 25, 2971, prepared slides were received from 124 hamsters and on Oct. 28, 1971, paraffin blocks were received from 172 hamsters for histopathological evaluation.	1/31/73

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E-36	SC-18862: 46-week Oral Toxicity Study in the Hamster: Supplement No. 1 - Part II P-T 852S72 Authors: K.S. Rao, J. Mauro, R.G. McConnell	See E-35	1/31/73
E-37	SC-19192: Evaluation of Repreductive Performance in the Rat: Segment I of the Teratology Reproduction Profile P-T 996S72 Authors: R.E. Schroeder, A. Mitchell K.S. Rao and R.G. McConnell	In this study SC-19192 was administered orally to mature male and female albino rats prior to mating and to the pregnant female during the entire period of gestation and lactation. Subsequent neonatal development was observed. Thus, cpd. effects on the gamete, the zygote, on implantation, fetal development and on delivery were evaluated as well as subsequent lactation and postnatal growth.	1/31/73
E-38	SC-19192: An Evaluation of the Embryotoxic and Teratogenic Potential in the Rat: Segment II of the Teratology-Reproduction Profile PT 997S72 Authors: R.E. Schroeder, A. Mitchell K.S. Rao and R.G. McConnell	SC-19192 was administered orally in the diet to pregnant albino rats from gestation day 6 through 15. A hysterotomy was performed on gestation day 20 and the fetuses were examined for anomalies.	1/31/73
E-39	SC-18862: Study of the Pregnant and Lactating Rat and Her Offspring Segment III of the Teratology-Reproduction Profile P-T 897S70 Authors: R.E. Schroder, K.S. Rao, G.J. Youkilis and R.G. McConnell	A similar study with SC-18862 and two of its major constituents, L-Phenylalanine and L-aspartic acid, was also performed (see P-T No. 898S70, E-49).	1/31/73

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E-40	SC-18862: An Evaluation of the Mutagenic Potential in the Rat Employing the Dominant Lethal Assay PT 868S70 Authors: R.E. Schroeder, K.S. Rao, R.G. McConnell and K. Sammeta	In this test one portion of the total mutagenicity test profile compound was administered orally to male rats of proven fertility; two equally divided doses were administered on a single day only. Each male rat was then sequentially mated to 3 separate groups of untreated females, with each successive group being exposed to mating activity for a one week period. Dominant lethal mutations induced in the spermatazoa, when present, were detected by observing the number fetal death after sacrifice at 14 days of gestation.	1/31/73
E-41	SC-18862: An Evaluation of the Mutagenic Potential in the Rat Employing the Dominant Lethal Assay: PT 1007S72 Authors: R.E. Schroeder, A. Mitchell K.S. Rao and K. Sammeta	See E-40. Note differences in lots of materials used.	1/31/73
E-42	SC-19192: An Evaluation of the Mutagenic Potential in the Rat Employing the Dominant Lethal Assay PT 1008S72 Authors: R.E. Schroeder, A. Mitchell, K.S. Rao and R.G. McConnell	A human population consuming SC-18862 would thus be exposed to varying concentrations of SC-19192. The mutagenic potential of this latter agent has been evaluated as part of the comprehensive pre-clinical safety studies program on SC-18862.	1/31/73
E-43	SC-18862: An Evaluation of Mutagenic Potential Employing the In Vivo Cytogenetics Method in the Rat: PT 1026H72 Final Report Author: Hazleton Laboratories	Evaluation of chromosome spreads indicated that SC-18862 did not alter (increase) the normal aberration frequencies observed in the control rats, and is thus not a mutagen. All data obtained were within normal limits.	1/31/73

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E-44	SC-18862: Evaluation of Mutagenic Potential Employing the Host Mediated Assay in the Rat: PT 1028H72 Final Report Author: Hazleton Laboratories	Evaluation of the mutation frequencies from rats treated with SC-18862 showed no significant alterations from that observed for the negative control animals.	1/31/7
E-45	SC-19192: Acute Toxicity Studies in the Rat, Mouse and Rabbit: Authors: James Andress, Tony Martinez, Gene Youkilis	The acute toxicity of SC-19192 (diketopiperazine) has been studied in rats, mice and rabbits. A conversion product of a nutritive sweetening agent (SC-18862) was conducted for the purpose of determining LD-50 values.	1/31/7
E-46	SC-18862: Acute Toxicity Studies in the Rat, Mouse and Rabbit: Authors: James Andress, Tony Martinez, Gene Youkilis	The acute toxicity of SC-18862 was studied in the rat, mouse, and rabbit, with the intent of determining the LD-50 for each species.	1/31/73
E-47	SC-18862: A Study of the Pregnant and Lactating Rat and of her Offspring: PT 858S70 Authors: R.E. Schroeder, K.S. Rao R.G. McConnell	This study was designed and conducted to evaluate the effects of SC-18862, on the pregnant rat and her offspring when administered orally in the diet.	1/31/73
E-48	SC-18862: A Study of the Pregnant and Lactating Rat and Her Offspring, Segment III PT 896S70 Authors: R.E. Schroeder, K.S. Rao G.J. Youkilis and R.G. McConnell	This study, performed in duplicate (see PT 897S70, E-39) was designed and conducted to re-evaluate the effects of daily administration of SC-18862, on the rat during the third trimester of pregnancy and throughout lactation, and on her offspring.	1/31/73
E-49	SC-18862: A Study of the Pregnant and Lactating Rat and of Her Offspring Segment III Comparison by Feeding of Equimolar Quantities of L-Phenylalanine and/or L-Aspartic Acid PT 898S70 Authors: R.E. Schroeder, K.S. Rao G.J. Youkilis, R.G. McConnell	The present experiment was performed to evaluate the maternal and fetal effects of feeding high doses of SC-18862 and equimolar quantities of L-phenylalanine and/or L-aspartic acid to the pregnant rat.	1/31/73

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E-50	A Study of the Possible Reaction of 5-Benzyl-3, 6-dioxo-2-piperazineacetic Acid (DKP) With Aqueous Nitrous Acid Author: Searle Laboratories	Since nitrosamines may be associated with an increased incidence of tumors in animals, it was decided to determine whether or not DKP could react with nitrous acid under acidity conditions approximating those found in the stomach.	1/31/7
E-51	SC-18862: An Evaluation of the Embryotoxic and Teratogenic Potential in the Rabbit Segment II Study PT 1044S72 Authors: R.E. Schroeder, A. Mitchell K.S. Rao, R.G. McConnell	This study was one of several initiated to better elucidate the results from the original rabbit Segment II study. (PT 859S70, E-54)	2/9/73
E-52	SC-18862: Segment II - An Evaluation of the Teratogenic Potential in the Rabbit PT 1045H72 Final Report Author: Hazleton Laboratories	The purpose of this study was to evaluate the potential of SC-18862 for embryotoxic and/or teratogenic effects in albino rabbits.	2/9/73
E-53	SC-18862: An Evaluation of the Embryotoxic and Teratogenic Potential in the Rabbit Segment II Study PT 968S71 Authors: R.E. Schroeder, K.S. Rao R.G. McConnell	This study, performed in duplicate (see PT 941H71, E-55) was designed and conducted to re-evaluate the embryotoxic and teratogenic potential of SC-18862 (APM), when administered via the diet to pregnant albino rabbits from day 6 through 18 of gestation. This study was initiated to better elucidate the results from the original rabbit Segment II study with SC-18862 (PT 859S70, E-54)	

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E-54	SC-18862: An Evaluation of the Embryotoxic and Teratogenic Potential in the Rabbit. Segment II Study PT 859S70 Authors: R.E. Schroeder, R.G. McConnell	The purpose of this study was to evaluate the embryotoxic and/or teratogenic potential of SC-18862, when administered orally in the diet to pregnant albino rabbits from day 6 through 18 of gestation.	2/9/73
E-55	SC-18862: Segment II Teratology Study in the Rabbit PT 941II71 Final Report Author: Hazleton Laboratories	The purpose of this study was to evaluate the potential of SC-18862 for embryotoxic and/or teratogenic effects in albino rabbits.	2/9/73
E-56	SC-18862 & SC-19192: 3:1 Ratio - Segment II Teratology Study in the Rat PT 1001II72 Final Report Author: Hazleton Laboratories	The purpose of this study was to evaluate the potential of SC-18862 and 19192 as a 3:1 ratio (w/w) for embryotoxic and/or teratogenic effects in albino rats.	2/9/73
E-57	SC-19192: Segment II Teratology Study in the Rabbit PT 1003II72 Final Report Author: Hazleton Laboratories	The purpose of this study was to evaluate the potential of SC-19192 for embryotoxic and/or teratogenic effects in albino rabbits.	2/9/73
E-58	SC-18862: A 26 Week Urinary Bladder Tumorigenicity Study in the Mouse by the Intravesical Pellet Implant Technique Final Report PT 1031ot72 Author: George T. Bryan, M.D., Ph.D.	The study was designed to specifically examine and compare the incidence of urinary bladder neoplasia present in the treated groups with that present in the negative control group. Criteria evaluated for compound effect were morbidity, mortality, motor and behavioral activity, growth, general external features, and digital palpation of protruding tissue masses.	2/9/73

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E-59	SC-19192: A 26 Week Urinary Bladder Tumorigenicity Study in the Mouse by the Intravesical Pellet Implant Technique Final Report PT 1032ot72 Author: George T. Bryan, M.D., Ph.D.	The study was designed to specifically examine and compare the incidence of urinary bladder neoplasia present in the treated groups with that present in the negative control groups. Criteria evaluated for compound effect were morbidity, mortality, motor and behavioral activity, growth, general external features, and digital palpation of protruding tissue masses.	2/9/73
E-60	Long Term Tolerance of Aspartame by Normal Adults Investigator: Gunther H. Frey, M.D. Hill Top Research, Inc. Miamiville, Ohio	The primary objective of this study was to study the effects of aspartame on normal volunteers when administered on a long-term basis. The quantity of aspartame ingested each twenty-four hour period was maintained at a constant level (1.8 gm) equivalent to approximately three times the normally expected adult daily consumption of aspartame when used as a sweetener.	2/9/73
E-61	Long Term Tolerance of Aspartame by Normal Children Investigator: Gunther H. Frey, M.D. Hill Top Research, Inc. Miamiville, Ohio	The primary objective of this study was to determine the effects of aspartame when administered for a period of 13 weeks to apparently healthy children and adolescents. The study was double blind in design with individuals randomly assigned to take aspartame or sucrose in each of five age groups. The quantity of aspartame given during a 24-hour period varied according to age, and hence weight, group.	2/9/73

MASTER FILE ENTRY	TITLE/AUTHORS	ABSTRACT/REASON FOR STUDY	DATE SUB TO U.S.
Food Additive Petition filed February 9, 1973. All previous documents referenced in the petitio			
E-62	SC-18862: An Evaluation of the Embryotoxic and Teratogenic Potential in the Rabbit PT 1048S73 A Segment II Study Authors: R.E. Schroeder, A. Mitchell, K.S. Rao, R.G. McConnell	This study, performed in duplicate (see PT 1049H73, E-63) was designed and conducted to re-evaluate the embryotoxic and teratogenic potential of SC-18862 (APM), when adminstered via the diet to pregnant albino rabbits from day 6 through 18 of gestation.	4/13/7
E-63	SC-18862: Segment II An Evaluation of the Teratogenic Potential in the Rabbit PT 1049H73 Author: Hazleton Laboratories	The purpose of this study was to evaluate the potential of SC-18862 for inducing embryotoxic and/or teratogenic effects in albino rabbits.	4/13/7
E-64	SC-18862: Long Term Tolerance of Aspartame by Obese Adults Investigator: Dr. Richard Hoffman Staten Island Hospital Staten Island, New York	The objective of this study was to determine the effects of aspartame (aspartyl-phenylalanine-methylester) on apparently healthy obese adults when administered on a long-term basis.	6/14/7
E-65	SC-18862: Tolerance of Aspartame by Diabetic Subjects: Investigator: Dr. Sheldon J. Bleicher Roslyn Heights, New York Dr. Sol B. Stern New Orleans, LA	The present studies were designed to determine whether diabetic subjects--both insulin-dependent and non-insulin-dependent--can consume 1.8 gm aspartame daily for 90 days without signs or symptoms of intolerance and without elevation of the plasma phenylalanine level. This intake is about three times the expected adult daily consumption of aspartame when used as a sweetener.	6/14/73

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E-66	SC-18862: Tolerance of Loading Doses of Aspartame by Normal Adolescents Investigator: Richard Koch, M.D. Children's Hospital of Los Angeles	The purpose of the present study was to determine the effects of single loading doses of aspartame and phenylalanine on normal adolescents.	6/14/73
E-67	SC-18862: Long-Term Tolerance of Aspartame by Adult PKU Heterozygotes Investigators: Richard Koch, M.D. Children's Hospital of Los Angeles Howard L. Wolfinger, M.D. Child Development Center San Diego, California	The purpose of this study was to determine the effects, if any, of the long-term administration of aspartame on heterozygous carriers for phenylketonuria. Phenylketonuric heterozygotes are defined as the natural parents of a phenylketonuric (PKU) child.	7/12/73
E-68	The metabolism of Aspartame IXXX Further Studies of Nitrosation Formation	Studies reported earlier (Part XII) demonstrated that, under conditions in which the nitrosation of piperidine occured, there was not reaction of SC-19192 with nitrite. However, it seemed likely that the conditions used were less than optimum since the yield of N-nitrosopiperidine was only about 0.5%. In the present study this reaction has been evaluated in detail, and conditions were discovered in which the nitrosation of piperidine was carried to completion with and approximate quantitative yield of the nitroso product.	7/27/73

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E-69	The Effect of Acid Hydrolysis on SC-18862 and SC-19192 Author: Department of Radiochemistry & Metabolism	At the meeting of the FDA and Searle on September 25, 1973 it was asked if SC-18862 and SC-19192 could resist the hydrolytic prodedures employed and, therefore, account for radioactivity associated with their respective Rf values (Part IV-Table IV-9). The present study was undertaken to investigate the products formed after acid hydrolysis of SC-18862 and SC-19192.	11/6/7
E-70	SC-18862: Lifetime Toxicity Study in the Rat. PT 892H72 Final Report Author: Hazleton Laboratories	The test material, SC-18862, was administered in the diet to groups of 40 male and 40 female Charles River albino rats at levels of 2 and 4 g/kg/day for 104 weeks postweaning.	1/14/74
E-71	Study of Possible Nitrosamide Formation from APM and DKP Under Simulated Physiological Conditions Author: Searle Laboratories	In view of the known carcinogenicity of certain nitrosamines, nitrosourethanes, and nitrosoureas, it was necessary to determine whether or not APM or DKP formed ditrosamides under simulated conditions of use, namely: water, hydrochloric acid, sodium nitrite, ph 4, 37°C.	
E-72	SC-18862: A 56 Week Urinary Bladder Tumoringenicity Study in the Mouse by the Intravesical Pellet Implant Technique PT 1035ot72, 1037ot72 PT 1033ot73 Final Report Author: George T. Bryan, M.D., Ph.D. And Addendum to: A 26-Week Urinary Bladder Tumorigenicity Study in the Mouse by the Intravesical Pellet Implant Technique	These data provide no evidence for a statistically significantly augmented incidence of urinary bladder neoplasia associated with SC-18862 as assayed by the intravesical pellet implantation technique with a 56-week period of observation.	1/28/74 11/6/74 (addenda submitte

MASTER FILE ENTRY	TITLE/AUTHORS	ABSTRACT/REASON FOR STUDY	DATE SUBMI TO U.S. FI
E-73	SC-19192: A 56 Week Urinary Bladder Tumorigenicity Study in the Mouse by the Intravesical Pellet Implant Technique. PT 1034ot73, 1036ot72, 1038ot72-Final Report Author: George T. Bryan, M.D., Ph.D. And Addendum to: SC-19192: A 26 Week Urinary Bladder Tumorigenicity Study in the Mouse by the Intravesical Pellet Implant Technique PT1032ot72, E-59	These data provide no evidence for a statistically significantly augmented incidence of urinary bladder neoplasia associated with SC-19192 as assayed by the intravesical pellet implantation technique with 56-week period of observation.	1/28/7 11/6/7 addend submit
E-74	Effects of SC-18862 on Lactation in Rats Authors: H.D, Lennon, L. Metcalf, S.E. Mares, and J.H. Smith	The present study was undertaken to establish effect - no effect ingestion levels of SC-18862 on lactation employing accepted methods for measuring effects on lactation and to measure specific hormone levels in the blood and pituitary gland which may provide insight into the possible mechanism of action of the sweetener on lactation.	10/22/7
E-75	SC-18862: 104-Week Toxicity Study in the Mouse PT 984H73 Final Report Author: Hazleton Laboratories	The test material, SC-18862, was administered in the diet to groups of 36 male and 36 female ICR Swiss mice at levels of 1,2, and 4 g/kg/day for 104 weeks.	10/22/7
E-76	SC-19192: 110-Week Toxicity Study in the Mouse. PT 985H73 Final Report Author: Hazleton Laboratories	The test material, SC-19192, was administered in the diet to groups of 36 male and 36 female ICR Swiss albino mice at levels of 0.25, 0.50, and 1.00 g/kg/day for 110 weeks.	10/22/7

MASTER FILE ENTRY	TITLE/AUTHORS	ABSTRACT/REASON FOR STUDY	DATE SUBMITTED TO U.S. FDA
E-77	SC-19192: 115 Week Oral Tumorigenicity Study in the Rat: Volume I PT 988S73 Authors: K.G. Rao, R. Stejskal and R.G. McConnell	In this toxicity study SC-19197 was administered to young albino rats of both sexes orally in the diet for 115 consecutive weeks. It was the intent of the study to evaluate the safety and tumorigenic potential of SC-19192, and to induce and define such adverse effects as might occur only at prodigious multiples of the estimated daily human intake.	10/22/74
E-78	SC-19192: 115-Week Oral Tumorigenicity Study in the Rat: Volume II Postmortem Evaluation PT 988S73 Authors: R. Stejska, K.S. Rao, R.G. McConnell	Postmortem evaluations of animals in E-77.	10/22/74
E-79	SC-18862: Segment II on Evaluation of the Teratogenic Potential in the Rabbit PT 1062H73 Final Report Author: Hazleton Laboratories	The purpose of this study was to evaluate the potential of SC-18862 for inducing embryotoxic and/or teratogenic effects in albino rabbits.	10/30/74
E-80	SC-18862: The Metabolism of Aspartame Volume 4 Parts XXIV - XXXI Author: Dr. R.E. Ranney, et al	The studies reported in this volume are those completed after the submission of the Food Additive Petition. They cover, in part, specific research projects requested by the FDA, as well as investigations which were designed to confirm and extend some of the initial studies of the metabolism of aspartame that were included in the submitted petition.	11/6/74

MASTER FILE ENTRY	TITLE/AUTHORS	ABSTRACT/REASON FOR STUDY	DATE SUBMI TO U.S. FDA
E-81	SC-18862: An Evaluation of Mutagenic Potential Employing the Host-Mediated Assay in the Mouse PT 1087S73 Author: R.G. Bost	This study was designed to measure the mutagenic potential of SC-18862. To test for mutagenic potential the host-mediated assay was employed.	11/6/74
E-82	SC-19192: An Evaluation of Mutagenic Potential Employing the Host-Mediated Assay in the Mouse PT 1095S73 Authors: R.G. Bost and R.A. Stolt	This study employed the host-mediated assay and was designed to measure the mutagenic potential of SC-19192. The assay employs a bacterial indicator system, Salmonella typhimurium G-46, a histidine auxotroph, and attempts to test indirectly for mutagenic activity in mammalian systems.	11/6/74
E-83	SC-18862 - Placebo: An Evaluation of Embryotoxic and Teratogenic Potential of Specially Prepared Pelleted Diet in the Rabbit PT 1063S73 Authors: R.E. Schroeder, A. Mitchell J.F. Vondruska and K.S. Rao	This study expands the data base for untreated pregnant rabbits consuming the specially prepared control diet during the period of fetal organogenesis.	11/6/74
E-84	SC-18862: Acute Intravenous Toxicity Study in the Rat: PT 1179S74 Authors: K.S. Rao, D.E. Semler, R. Stejskal	In this toxicity study SC-18862, a sweetening agent, was administered once intravenously to young adult male rats who were monitored for 72 hours post-treatment. The purpose of the study was to evaluate the potential toxicity of SC-18862 when administered intravenously.	1/15/75

MASTER FILE ENTRY	TITLE/AUTHORS	ABSTRACT/REASON FOR STUDY	DATE SUBM TO U.S. F
E-85	SC-18862: Acute Intravenous Toxicity Study in the Dog: PT 1178S74 Authors: K.S. Rao, D.M. Ferguson J.H. Smith	In this toxicity study SC-18862, a sweetening agent, was administered once intravenously to adult male Beagle dogs who were monitored for 72 hours post-treatment. The purpose of the study was to evaluate the toxic potential of SC-18862 when administered intravenously.	1/15/7
E-86	SC-18862: A Supplemental Study of Dog Brains from a 106 Week Oral Toxicity Study (PT 855S70) PT 1226 See entry E-28 Author: R.G. McConnell	This 106 week chronic oral toxicity study of SC-18862 employed continuous dietary administration of the test compound to five month old Beagle dogs. All dogs survived the treatment interval and were sacrificed for postmortem examination at 106 weeks.	2/26/7
E-87	SC-18862: A Supplemental Evaluation of Rat Brains from Two Tumorigenicity Studies (PT 838H71 & 892H72, E-34 and E-70) PT 1227	Supplemental histopathologic evaluation of intracranial tissues from two SC-18862 (aspartame) tumorigenicity studies in the rat was performed to determine the presence or absence of neoplasms.	2/26/75
E-88	SC-18862: Experiments in Mated and Pregnant Rhesus Monkeys - A Compilation of Available Fragmentary Data (Supplement to E-32)		6/19/75
E-89	SC-18862: An Evaluation of Embryotoxic and Teratogenic Potential in the Mouse Segment II PT 1218 Authors: J.F. Vonduska, R.E. Schroeder and A. Mitchell	The purpose of this study was to evaluate the embryotoxic and teratogenic potential of SC-18862 (aspartame) when administered by means of dietary incorporation to the pregnant albino mouse during the period of fetal organogenesis.	10/28/7

MASTER FILE ENTRY	TITLE/AUTHORS	ABSTRACT/REASON FOR STUDY	DATE SUBMITTED U.S. FDA
E-90	SC-18862: An Evaluation of Embryotoxic and Teratogenic Potential In The Rabbit Segment II PT 1201 Authors: J.F. Vondruska, R.E. Schroeder and A.L. Mitchell	The purpose of this study was to determine the embryotoxic and teratogenic potential of SC-18862, (aspartame) when administered by gavage to the pregnant rabbit during the period of fetal organogenesis.	10/28/7!
E-91	Data Reassurance Program - Interim Report University of Iowa - University of Illinois	In view of the public questioning of certain Searle animal data, an internal data reassurance program to assure by objective assessment the adequacy and accuracy of animal safety study reports was established. In the first phase (Step A), a senior pharmacologist is assigned to check the internal consistency and accuracy of all data presented in the report. In some cases, a second step (Step B) is recommended, requiring all of the original data to be reviewed. In the cases where the recommendation for a Step B review is made, it will be carried out when the Food and Drug Administration unseals the files containing the original data.	4/8/76
E-92	The Metabolism of the Methyl Moiety of Aspartame Document No. MRC-751-0022 Author: Dr. R.E. Ranney	Aspartame (3-amino-N(α carboxyphenethyl) succinamic acid, methyl ester; the methyl ester of aspartylphenylalanine, SC-18862) is hydrolyzed in the gut to yield aspartic acid, phenylalanine and methanol. This review of the literature describes the metabolic paths followed by methanol in its conversion to CO_2 or its incorporation into body constituents.	12/1/76

MASTER FILE ENTRY	TITLE/AUTHORS	ABSTRACT/REASON FOR STUDY	DATE SUBMITTED TO U.S. FDA
E-93	Effect of aspartame Loading Upon Plasma and Erythrocyte Free Amino Acid Levels in Normal Adult Subjects January 19, 1977 Author: Lewis D. Stegink, Professor, Pediatrics and Biochemistry University of Iowa College of Medicine Iowa City, Iowa	In considering the potential toxic effects of Aspartame in man, it is obvious that such effects would require extreme elevations of aspartate and phenylalanine blood levels above thosefound after normal ingestion of a protein-containing meal. To examine the potential hazard, aspartame was administered either at 34 mg/kg/day body weight, or equimolar quantities of aspartate (13 mg/kg) to normal volunteers, and the effect of such ingestion upon plasma and erythrocyte amino acid levels was determined over time.	2/21/77
E-94	Damage in the Neonatal Mouse Brain Following Ingestion of Aspartame Authors: Naomi Lemkey-Johnston, Ph.D. W. Ann Reynolds, Ph.D. Henri Kulilowski, M.S.	The present report is concerned with the effects of the oral consumption of APM upon the hypothalamus of the neonatal mouse. Of special interest is whether dose levels of APM yield damage similar to that found with equivalent dosages of other acidic amino acids in that very sensitive model, the neonatal mouse.	2/21/77
E-95	Metabolic Studies of Aspartame and MSG Ingested as a Meal Component Author: Lewis D. Stegink, Professor Pediatrics and Biochemistry University of Iowa College of Medicine Iowa City, Iowa	This study was designed to determine the effect of a high protein meal with and without additional monosodium glutamate (34 mg/kg) upon plasma amino acid levels.	2/21/77

MASTER FILE ENTRY	TITLE/AUTHORS	ABSTRACT/REASON FOR STUDY	DATE SUBMITT TO U.S. FDA
E-96	Plasma Animograms of Infants and Adults Fed An Identical High Protein Meal Authors: L.J. Filer, M.D., Ph.D. George L. Baker, M. D. Lewis D. Stegink, Ph.D. Department of Pediatrics University of Iowa	The ability of the infant to metabolize amino acids relative to that of the adult was investigated by feeding an identical high protein meal to fasted subjects, measuring changes in plasma free amino acid concentration with time. Of particular interest was the capacity of the infant to regulate metabolism of the dicarboxylic acids, glutamic and aspartic acids, and phenylalanine.	12/6/77
E-97	SC-18862: An Evaluation of Mutagenic Potential Employing the Ames Salmonella/ Microsome Assay S.A. 1377 Author: Samuel V. Molinary	SC-18862 was examined for mutagenic activity using the Ames Salmonella/ microsome assay with five tester strains of Salmonella typhimurim 9TA1535, TA1537, TA2538, TA98 and TA100). The assay was performed in the presence and in the absence fo a rat-liver homogenate metabolic activation system.	3/6/78
E-98	SC-19192: An Evaluation of Mutagenic Potential Employing the Ames Salmonella/ Microsome Assay S.A. 1378 Author: Samuel V. Molinary	SC-19192 was examined for mutagenic activity using the Ames Salmonella/ microsome assay with five tester strains of Salmonella typhimuim (TA1535, TA1537, TA1538, TA98 and TA100). The assay was performed in the presence and in the absence of a rat-liver homogenate metabolic activation system.	

MASTER FILE ENTRY	TITLE/AUTHORS	ABSTRACT/REASON FOR STUDY	DATE SUBMIT' TO U.S. FDA
E-99	The Metabolism of the Aspartyl Moiety of Aspartame MRC-751-0032 Author: R.E. Ranney, Ph.D.	The available evidence from studies in experimental animals leads to the conclusion that the aspartate moiety of aspartame is metabolized in a manner similar to that of dietary aspartic acid. The major fraction of this moiety is utilized for energy through oxidation in the tricarboxylic acid cycle. Incorporation into protein, other amino acids, and nucleotides are lesser pathways followed by this amino acid.	6/13/78
E-100	The Metabolism of Aspartate in Infant and Adult Mice MRC-751-0021 Author: R.E. Ranney, Ph.D.	After equivalent massive oral doses of either glutamate or aspartate, higher plasma concentrations occurred in newborn mice than in adults. Therefore, this difference may explain the increased susceptability of infant mice to hypothalmic damage produced by massive oral doses of aspartate or glutamate.	6/13/78
E-101	An Evaluation of the Mutagenic Potential of SC-18862 Employing the Ames Salmonella/ Microsome Assay Final Report S.A. 1385 Authors, Vincent F. Simmon, Ph.D. Hsin-Tsan G. Shan, Microbiologist SRI International	SC-18862 was examined for mutagenicity using the Ames Salmonella/mircosome assay with five tester strains TA1535, TA1538, TA98, and TA100. The assay was performed both in the presence and in the absence of a rat liver homogenate metabolic activation system.	6/13/78

MASTER FILE ENTRY	TITLE/AUTHORS	ABSTRACT/REASON FOR STUDY	DATE SUBMI TO U.S. FD
E-102	Authentication Review of Selected Materials Submitted to the Food and Drug Administration Relative to Application of Searle Laboratories to Market Aspartame (3 volumes) Report prepared by Universities Associated for Research and Education in Pathology	Authentication of Studies E-9, E-11, E-19, E-28, E-33, 34, E-70, E-75, E-76, E-86, E-87, E-88, and E-90 conducted by UAREP. These studies were determined by FDA to be pivotol studies in the evaluation of the safety of APM.	12/13/7

MASTER FILE ENTRY	TITLE/AUTHORS	ABSTRACT/REASON FOR STUDY	DATE SUBMI TO U.S. FI
E-103	Effects of Aspartame (SC-18862) on Gonadotropin Secretion in Rats. Authors: S.E. Mares and J.R. Berg (BRD 78D1169)	The purpose of this study was to evaluate the effects of SC-18862 on the pituitary secretion of LH and FSH, as well as prolactin, in rats at a dose of 100 mg/kg/day or 300 mg/kg/day for 10 days.	
E-104	Developmental Assessment of Infant Macaques Receiving Dietary Aspartame or Phenylalanine. Authors: W.A. Reynolds, A.F. Bauman, L.D. Stegink, E. Renn and L.J. Filer, Jr.	The study provides for the intake of aspartame and phenylalanine by a relatively large number of infant monkeys to assess the safety of aspartame as a dietary component during infancy. The doses of APM chosen were 1.0, 2.0 and 3.0 gm/kg per day (all are massive intakes).	
E-105	Aspartame Administration to the Infant Monkey: Hypothalamic Morphology and Blood Amino Acid Levels. Authors: W.A. Reynolds, L.D. Stegink, L.J. Filer, Jr., and E. Renn.	Since there is concern of aspartame and the developing brain, this study searched for any possible hypothalamic effects of administering acute, massive loads of APM in the neonatal period and to determine amino acid metabolism following abuse loads. Dosage: 2 gm/kg of aspartame or 2 gm/kg APM plus 1 gm/kg monosodium glutamate.	
E-106	An Evaluation of the Mutagenic Potential of SC-19192 Employing the Ames Salmonella/Microsome Assay; S.A. 1384 Authors: V.F. Simmon and K. Kauhanen (SRI Project LSC-5992)	SC-19192 was examined for mutagenic activity by in vitro microbiological assays with Salmonella typhimurium strains from 50 to 10,000 µg. An metabolic activation system was included in the assay procedure.	

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E-107	Effect of Aspartame Loading Upon Plasma and Erythrocyte Free Amino Acid Levels and Blood Methanol Levels in Normal One-Year-Old Children Authors: L.D. Stegink, L.D. Filer, Jr. and G.L. Baker	This study was designed to provide information about the effect of aspartame ingestion upon plasma and erythrocyte levels of amino acids, as well as blood methanol levels in young adults. Aspartame was dissolved in Kool-Aid and administered to fasting 8-12 month old infants at 34, 50 and 100 mg aspartame per kg body weight. These levels cover both normal and abuse conditions.	
E-108	Effect of Aspartame on Plasma and Red Cell Amino Acids of Apparently Healthy Female Adults and Presumed Phenylketonuric Heterozygotes. Authors: R. Koch and M. Blaskovics (MED-77-06-055)	Since phenyketonuric persons may be on a diet restricted in phenylalanine, this study established what effect ingestion of Aspartame might have upon the dietary control of phenylalanine intake in phenylketonuric persons. Four normal subjects and four PKU heterozygote mothers were administered 34 mg/kg dose.	
E-109	Effect of aspartame Loading at 100 mg per kg Body Weight Upon Plasma and Erythrocyte Levels of Free Amino Acids in Normal Subjects and Subjects Presumed to be Heterozygous for Phenylketonuria. Authors: L.D. Stegink, L.J. Filer, Jr., G.L. Baker, and J.E. McDonnell	In a previous study, plasma phenylalanine levels differed significantly between normal subjects and heterozygous levels were only slightly above values noted postprandially in the human infant. This study expands to evaluate a potential abuse dose of Aspartame (100 mg/kg body weight) upon plasma and erythrocyte levels of amino acids.	

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E-110	Effect of Aspartame Loading in Subjects Who Report Symptoms of Chinese Restaurant Syndrome After Glutamate Ingestion. Authors: L.D. Stegink, L.J. Filer, Jr., and G.L. Baker	The Reif-Lehrer hypothesis suggests that aspartame might elicit symptoms of CRS in sensitive subjects because of the structual similarity between glutamate and aspartate. This study reports a direct test of Reif-Lehrer's hypothesis in 6 subjects who reported CRS symptoms after glutamate ingestion administered aspartame (34 mg/kg body weight) or sucrose (1 gm/kg body weight) dissolved in orange juice in a randomized double blind, cross-over design. Plasma amino acid levels were measured to determine if these subjects cleared aspartame differently than 12 normal subjects previously studied after aspartame administered at this level.	
E-111	Metabolic Studies of Aspartame and Monosodium Glutamate When Ingested Together As Part of a Soup-Beverage Meal. Authors: L.D. Stegink, L.J. Filer, Jr. and G.L. Baker	The purpose of this study was to determine if soup (which can contain up to .72% MSG) and an aspartame sweetened beverage would result in a higher plasma glutamate and aspartate levels than if the soup was ingested alone. Three systems were used: 1) soup (no added MSG) with unsweetened beverage, 2) soup (with 50 mg/kg MSG) with unsweetened beverage, and 3) soup (with 50 mg/kg MSG) with sweetened beverage (34 mg aspartame/kg body weight).	
E-112	Metabolic Studies of Aspartame and Monosodium Glutamate Ingested as Components of a Hamburger--Milk Shake Meal System in Normal Adult Subjects. Authors: L.D. Stegink, L.J. Filer, Jr., and G.L. Baker	This study determined whether APM addition to the food supply significantly effects plasma glutamate and aspartate levels beyond that caused by the presence of MSG alone. Plasma amino acid levels were measured in normal adult volunteers ingesting hamburger--milk shake meal providing 1 gm. of protein/kg body weight, with and without added MSG and APM. Three meal systems used: 1) meal alone, 2) meal with MSG added at 150 mg/kg body weight, and 3) meal with MSG added at 150 mg/kg body weight and APM	