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(E-91)

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(University of Iowa)

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A. INTRODUCTION

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.

The data reassurance program consists of three major phases. 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. The pharmacologist and qualified assistants compare the tables in the report with the data presented in the appendices regarding accuracy and completeness. This requires recalculation of mean values. The narrative is also reviewed with special attention to cross-check the Methods section against the Results section. The protocol is also cross-checked against the Methods section. All exceptions are identified and reviewed by a senior person in the Pathology/Toxicology department. A document which identifies all of the exceptions is prepared. In some cases, the original data files are checked as part of the first phase, but this step is only performed in cases where the data appended to the study report has raised a question.

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.

6

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Vol

3

In the third phase (Step C), the Data Reassurance Program Director (Dr. John Rust)* reviews the study report and the documentation of the exceptions reported in the Step A document. The Program Director is responsible for determining whether the conclusions reached in the study report are valid, whether the protocols were followed, and whether the study design was appropriate.

* Professor (Emeritus) Radiobiology
and Pharmacology and in the
Franklin McLean Memorial Research
Institute
University of Chicago
Pritzker School of Medicine

ERRORS continued - page 2

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3	XXI	XXI-7	5 para. 2			desiccator	desiccator

B. "PIVOTAL" ANIMAL SAFETY STUDIES

In his testimony at a hearing of the U. S. Senate subcommittee on Health chaired by Senator Kennedy, Food and Drug Administration Commissioner Schmidt identified several animal safety studies as "pivotal" and others as containing "significant findings". The long term animal safety studies which he mentioned in his testimony, as well as several other studies, have been reviewed via the data reassurance program outlined in the Introduction section. These studies are listed on the following pages.

115-We
Diketo

Two-We
P-T 83

Two Ge
Aspart

52-Wee
Aspart

Lifeti
P-T 85

A Supp
Stu

110-We
pipera

104-We
P-T 98

A Supp
Toxic

An Eva
the Mo

An Eva
the Ra

Acute
SC-191

Acute
SC-188

Two-We
Diketo

Two-We
pipera

Toxic
Aspart

Segmen
Diketo

115-Week Oral Tumorigenicity Study in the Rat (of SC-19192, Diketopiperazine) P-T 988573.

Two-Year Toxicity Study in the Rat (of SC-18862, Aspartame) P-T 838H71.

Two Generation Reproduction Study in Rats (of SC-18862, Aspartame) P-T 867H71.

52-Week Oral Toxicity Study in the Infant Monkey (of SC-18862, Aspartame) P-T 856ot70.

Lifetime Toxicity Study in the Rat (of SC-18862, Aspartame) P-T 892H72.

A Supplemental Study of Rat Brain from Two Tumorigenicity Studies (of SC-18862, Aspartame) P-T 838H71 & 892H72.

110-Week Toxicity Study in the Mouse (of SC-19192, Diketopiperazine) P-T 985H73.

104-Week Toxicity Study in the Mouse (of SC-18862, Aspartame) P-T 984H73.

A Supplemental Study of Dog Brains from a 106-Week Oral Toxicity Study (of SC-18862, Aspartame) P-T 855S70 & 1226.

An Evaluation of Embryotoxic and Teratogenic Potential in the Mouse (of SC-18862, Aspartame) P-T 1218.

An Evaluation of Embryotoxic and Teratogenic Potential in the Rabbit (of SC-18862, Aspartame) P-T 1201.

Acute Toxicity Studies in the Rat, Mouse, and Rabbit (of SC-19192, Diketopiperazine) (E45).

Acute Toxicity Studies in the Rat, Mouse, and Rabbit (of SC-18862, Aspartame) (E46).

Two-Week Oral Toxicity Study in the Mouse (of SC-19192, Diketopiperazine) P-T 885S70.

Two-Week Oral Toxicity Study in the Rat (of SC-19192, Diketopiperazine) P-T 884S70.

Toxicological Evaluation in the Neonatal Rat (of SC-18862, Aspartame) P-T 893H71.

Segment III Perinatal Weaning Study in the Rat (of SC-19192, Diketopiperazine) P-T 1011H72.

Two-Month Oral Toxicity in Dogs (of SC-18862, Aspartame)
P-T 720H68.

46-Week Oral Hamsters Study (of SC-18862, Aspartame)
P-T 852S72.

106-Week Oral Toxicity Dog Study (of SC-18862, Aspartame)
P-T 855S70.

Chick Embryo Study with SC-18862 (Aspartame) and Other
Substances P-T 870H70.

Evaluation of Embryotoxic and Teratogenic Potential in the
Rat (of SC-18862, Aspartame) P-T 851S70.

Evaluation of Embryotoxic and Teratogenic Potential in the
Rat (of SC-19192, Diketopiperazine) P-T 997S72.

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C. OVERVIEW OF DATA REASSURANCE ACTIVITIES

The attached memorandum outlines the overview of the reviews of the aspartame reports.

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EXHIBITS

April 5, 1976

MEMO TO: Dr. R. McConnell

COPY TO: Dr. P. Klimstra

FROM: Dr. John H. Rust
Director
Data Reassurance Program

Dr. J. Potts
Dr. I. C. Winter
Dr. F. McIlreath
Dr. W. Merino

SUBJECT: Report on the Step C Portion of the Data Reassurance Program
for Pathology-Toxicology Studies on Aspartame (APM or SC-16862)
and Diketopiperazine (DKP or SC-19192) conducted for the
Searle Laboratories (1976)

I have acted, during the past few months in my capacity as an outside consultant, as a final reviewer in a program organized by the Searle Laboratories to assure themselves, and the concerned regulatory agencies, of the accuracy of their data and the correctness of their assessments. My portion of the task is called Step C. Prior to my receiving a report for review, an in-house team under the leadership of one or more of Searle's senior scientists, reviews the available data, raw and treated, for its accuracy. They also review the original protocol and ascertain whether or not it was adequately followed. Claims and conclusions are checked to see whether or not they are justified by the findings reported.

My task follows theirs and I determine whether or not the study was appropriate, carried out effectively, and if the conclusions are supported by the data developed. In conducting my part of the program, I have usually reexamined the data in another manner than was done by the original report writers. I have drawn upon my training and experience in veterinary pathology, laboratory animal medicine, and experimental pharmacology and toxicology in making my assessment. Of the reports, 23 in number, two were rejected. In both cases it was because of an intercurrent disease. In one hamster study there was an epizootic called "Wet-tail," a subacute debilitating disease of young and juveniles. In one monkey study, infant and juvenile monkeys had recurrent bouts with a subacute epizootic of shigellosis.

I could find no evidence for toxicity for either aspartame or diketopiperazine in any study. Several animal species were used; mice, rats, hamsters, rabbits, dogs, and monkeys. One possible exception to the statement about toxicity was seen in the female rabbit. This will be discussed later. Many dose schedules (low to very high) and time schedules (acute, subacute and chronic patterns) were used. In all studies that I reviewed the APM or DKP were administered in the food or in some few cases by gastric gavage. Often, in the latter cases, the amount nearly reached the maximum concentration of the test substance or the physical capacity of the test animal in order that the animals be fully challenged by the route by which APM and DKP would be ordinarily received.

Dr. R. McConnell
April 5, 1976
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There was no evidence for carcinogenicity of aspartame or diketopiperazine in any animal species tested in any of the studies reviewed by me.

Two findings that bear reporting were observed. The first because it was common and the second because it was uncommon. It was very common that animals on a diet in which the aspartame or diketopiperazine was considered to be high or very high, i.e., four or six grams per kilogram of body weight daily of aspartame and approximately a similar amount for diketopiperazine, tended to have a depressed weight gain when compared with those animals on a lesser dietary amount or the controls. If those fed lesser amounts were similarly affected it was lost in the variance and could not be detected. Several ideas have been tried to determine the cause. None have been fully successful. These ideas are three; physical reduction of available and useable feed; distaste for the heavy sweetness in the high level diets; and, depression of appetite by the amino acids phenylalanine or aspartic acid. For the last two of these ideas there is no supporting evidence. I have developed some data that suggest to me that in some instances the actual reduction in useable feed was probably the cause. I made crude approximations of Feed Efficiency Indices subtracting the mass of aspartame or diketopiperazine and found that no treated animals suffer any reduction in feed efficiency, a sensitive means of measuring chronic toxicity. The similarly corrected feed consumption per unit of body weight, also a sensitive chronic toxicity detector, was not altered by either substance in the diet up to the maximum employed, i.e., six grams per kilogram body weight daily for up to two years in some cases. Also, I could find no clinical laboratory test that suggested any adverse changes that could be attributed to or be related to the depression in weight gain. Likewise, the negative necropsy and histopathology reports made no positive contribution to the understanding. I believe that these findings demonstrate that the depression of body weight gain was because of the reduced consumption of useable dietary substances and it was not a matter of toxicity.

The uncommon second finding occurred in a teratology study with rabbits at high doses of phenylalanine and of aspartame (four grams per kilogram body weight daily during early pregnancy) given by gastric gavage. It was observed that about half of the female rabbits in a teratology-embryotoxicity study had a severe adverse somatic response - some dying - some that had failed to conceive; some aborted stillborn pups; some had resorption sites in excess numbers; and, there were more than the expected malformations in the fetuses. The remainder of the same group, while they showed some minor adverse responses, carried their pups to term. The pups were within the usual ranges, of this laboratory, for the teratogenic and embryotoxic parameters that were measured. The biphasic nature of the response called to mind a pharmacogenetic pattern which is considered to be evidence of a gene polymorphism within a population. Data of a bio-

INTRODUCTION

ASPARTAME is a dipeptide whose structure is shown below. The molecule

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Page 3

chemical nature in an exploratory study demonstrated a high phenylalanine to tyrosine ratio in four pregnant female rabbits, with macerated fetuses or stillborn pups, out of five in the study. The studies were too small to set a population genetic ratio but an estimate made from the 50 females in the teratology study suggested that about one-half were affected. All were from a single rabbit breeder with a relatively high consanguinity index.

The immediate concern was whether or not this occurred in other animals and most particularly in man. An inspection of the data for other animal species gave no direct or indirect evidence that the pharmacogenetic trait existed in those populations. Other rabbit populations are known by direct evidence to be free of the trait. No evidence for a polymorphic biphasic patterns of such a nature for phenylalanine could be developed from any data, for any other animal species, including other families of rabbits.

There was available some data derived from human volunteers who were fed a placebo and aspartame in doses ascending from 0.6 grams to 8.1 grams daily. The phenylalanine to tyrosine ratios were determined for these 69 male and female subjects. As noted above, this is a key parameter which became high in the pregnant rabbits that were demonstrating the adverse response. It was found that the phenylalanine to tyrosine ratios in human males and females, without respect to the challenge by aspartame, were clustered around 1.00 on a histogram. After a suitable statistical test indicated that none of the groups differed, the data were pooled.

These data to be used for a histogram were developed:

Phenylalanine to Tyrosine Ratios (Sexes and Treatment Combined)

<u>Decade of Ratio</u>	<u>Number of Subjects in Decade</u>
0.80	1
0.90	6
1.00	15
1.10	12
1.20	10
1.30	7
1.40	6
1.50	3
1.60	2
1.70	3
1.80	3
1.90	1

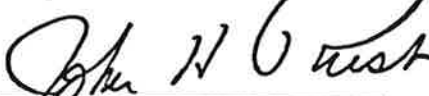
N = 69

amino acids are required to produce the lesion (2). The effects of glutamate and aspartate are additive in producing neuronal necrosis (3). Although Olney and his colleagues have reported neuronal necrosis after glutamate...

Dr. R. McConnell
April 5, 1976
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It can be seen that the curve describing these data is skewed to the right. The most frequently occupied decade of ratio is at 1.00. The curve is platykurtotic, as are most normal curves of this nature, and skewed to the infinite side. It is a classic monophasic curve with no hint of the biphasic polymorphic curve that was clearly associated with the unique rabbits which came from the rabbit breeder.

Based upon this evidence, I have judged that the special rabbit population in question was not following the Hardy-Weinberg Law for a stable mutation in a large population; a possibly hazardous situation. On the contrary, it was following the Sewall Wright Postulation; genetic drift within a small population. These most frequently become extinct in time and affect small isolated populations. It is believed that if such a mutation has ever occurred in man it has not stabilized and has a very low probability of occurrence. Most likely it is on its way to extinction from any small human population in which it may have occurred. This is the most common consequence of the Sewall Wright Postulation.



John H. Rust, D.V.M., Ph.D.
Director
Data Reassurance Program

das

REVIEW OF METABOLISM STUDIES

Even though the metabolism studies have not been challenged by the FDA, the reports have been reviewed and submitted to an outside expert (Dr. Edwin Mertz) for evaluation. Dr. Mertz's conclusions as well as the documentation of the errors found upon internal review are summarized in the attached letter.

daily ingestion, IN A SINGLE DOSE.

The plasma and erythrocyte free amino acid levels found in these

PURDUE UNIVERSITY

DEPARTMENT OF BIOCHEMISTRY
WEST LAFAYETTE, INDIANA 47907

March 29, 1976

Dr. R. E. Ranney, Director
Department of Drug Metabolism and Radiochemistry
Searle Laboratories
Box 5110
Chicago, IL 60680

Dear Dr. Ranney:

I have read every page of the original documents which you submitted to the Food and Drug Administration on your new sweetening agent, Aspartame, and have also read each of the corrected pages of your Food Additive Petition.

I have compared the corrections with the original submission and it is my opinion that the corrections do not change any of the interpretations in the original documents.

In my opinion, the data in the original documents provide convincing evidence for the interpretations presented in the Food Additive Petition. The data show that Aspartame is digested in all species in the same way as are natural constituents of the diet, and the end-products of Aspartame digestion follow the normal metabolic pathways known to exist in animals and man.

As I read through the original document and the corrected pages I noted several typographical errors, and I am enclosing a correction sheet containing these errors.

Sincerely yours,

Edwin T. Mertz, Ph.D.

Edwin T. Mertz
Professor of Biochemistry

enclosure

ETM:riw

LIST OF ERRORS: METABOLISM: ASPARTAME; VOLUMES 1-4

Vol.	Report	Page	Line	Table	Figure	Is	Action/should be
1	I	1-4	17			L-phe was added	L-phe were added
		Ref. 4				Nautre	Nature
		Ref. 9				Telphy	Tephly
		Ref. 16				Inglr	Check spelling
	II	II-2	13			organleptic	organoleptic
	IV	IV-2	1, para. 3			plamsa	plasma
	V	V-2	2			cellusolve	cellosolve
				V-1		66.78	66.78
	V	V-5	3			(Table VI-8)	no such table
	VI	VI-1	5			were then	was then
			6, para. 2			et cetra	et cetera
				VII-8			need footnote on units
	VII	VII-4					why was page retyped?
				VIII-6		glucose-analine	glucose-aniline
	VIII	VIII-11	11, para. 2			analagous	analogous
1			12, para. 2			analagous	analogous
	IX	IX-5	1, para. 3			procede	proceed
	XIV	XIV-2	3, para. 1			methyl cellusolve	methyl cellosolve
			2, para. 2			methyl cellusolve	methyl cellosolve
2		XIV-7	8, para. 2			anaylzed	analyzed
	XVI	XVI-2	8			methyl cellusolve	methyl cellosolve
		XVI-4	2			dired	dried
		XVI-7	4, para. 3			asaprtic	aspartic
		Ref. 36				"in rat liver"	"on rat liver"
		XVII-4	5, para. 2			concomttant	concomitant
		XVIII-2	20			cellusolve	cellosolve

Vol.	Report	Page	Line	Table	Figure	Is	Action/should be
3	XXI	XXI-7	5 para. 2			desicator	desiccator
		XXI-8	2 para. 2			hydrolyzed	hydrolyzed
		XXI-10	6 para. 1			(Table XXI-7	(Table XXI-7)
		XXI-10	1 para. 3			unhydrolyzed	unhydrolyzed
			3 para. 3			hydrolyzed	hydrolyzed
			1 para. 4			discernable	discernible
		XXII-9	5 para. 3			desicator	desiccator
		XXII-10	2 para. 2			hydrolyzed	hydrolyzed
						hydrolyzed(title)	hydrolyzed (title)
3	XXII	XXII-30		24 tables			
		to XXII-53					
	XXIII	XXIII-12	5 para. 2			desicator	desiccator
		XXIII-13	1 para. 2			unhydrolyzed	unhydrolyzed
	XXIII		2 para. 2	23 tables		hydrolyzed	hydrolyzed
		XXIII-35 to XXIII-57				hydrolyzed	hydrolyzed
4	Index		7	XXVIII		aminotic	amniotic
	Expanded summary		2	XXVIII		aminotic	amniotic
	XXVIII	XXVIII-5	3 para. 2			Longnecker	Longenecker

alanine levels increased, but with the increases being lower than those found in plasma

PROGRESS' REPORT ON ASPARTAME STUDIES

March 24, 1976

TO

G. D. Searle & Company
Chicago, Illinois

FROM

L. D. Stegink, Ph.D.
L. J. Filer, Jr., M.D., Ph.D.
George L. Baker, M.D.
Roy M. Pitkin, M.D.
University of Iowa College of Medicine
Iowa City, Iowa 52242

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PROGRESS REPORT ON ASPARTAME STUDIES

PART A: HUMAN STUDIES

EFFECT OF ASPARTAME LOADING UPON PLASMA AND ERYTHROCYTE
FREE AMINO ACID LEVELS IN NORMAL ADULT SUBJECTS

March 24, 1976

TO

G. D. Searle & Company
Chicago, Illinois

FROM

Lewis D. Stegink, Ph.D.
L. J. Filer, Jr., M.D., Ph.D.
George L. Baker, M.D.

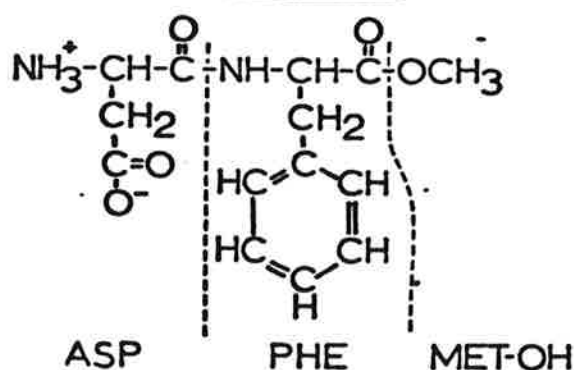
University of Iowa College of Medicine
Iowa City, Iowa 52242

Lewis D. Stegink 3/25/76
Lewis D. Stegink, Ph.D.
Associate Professor
Pediatrics & Biochemistry

INTRODUCTION

ASPARTAME is a dipeptide whose structure is shown below. The molecule is an aspartyl-phenylalanyl-methyl ester, and it is between 180-200 times sweeter than sucrose. It is metabolized in the intestinal mucosa to its component amino acids and methanol which are handled in a manner similar to those arising from dietary protein and methylated polysaccharides.

ASPARTAME



Questions about ASPARTAME safety have risen because of concern about the potential toxic effects of its component amino acids, phenylalanine and aspartate. Each of these components, like all chemical substances, may exert toxic effects at high levels, although species and age susceptibility vary.

Aspartate:

The dicarboxylic amino acids glutamate and aspartate produce neuronal necrosis in the hypothalamus of the infant mouse when administered in large doses either orally or by injection (1). Older mice are also susceptible to dicarboxylic amino acid-induced neuronal necrosis, but much higher levels of

amino acids are required to produce the lesion (2). The effects of glutamate and aspartate are additive in producing neuronal necrosis (3). Although Olney and his colleagues have reported neuronal necrosis after glutamate administration to the neonatal primate (4,5), other investigators have been unable to produce the lesion in the neonatal primate (6-10). This failure occurs despite demonstration that enormous elevations in the blood glutamate levels occurred in the neonatal animals studied (10). No lesions were seen when glutamate was injected into the primate fetus in utero (11).

In the most susceptible animal species, the neonatal mouse, we have shown that plasma glutamate plus aspartate levels must reach 60-70 μ moles/dl before the first signs of neuronal necrosis are noted (12). In the infant monkey, plasma glutamate plus aspartate levels up to 500 μ moles/dl did not result in neuronal necrosis (10).

In summary: Plasma glutamate plus aspartate levels of up to 50 μ moles/dl did not produce neuronal lesions in the most susceptible species, the neonatal mouse. Plasma levels of 60-70 μ moles/dl did produce minimal neuronal necrosis. In contrast, neuronal necrosis was not noted in infant primates even in the presence the plasma glutamate plus aspartate levels of 500 μ moles/dl.

Phenylalanine:

A genetic disorder called phenylketonuria results from either the absence, or the presence of an inactive enzyme(s) required for the conversion of phenylalanine to tyrosine. In the children with so-called "classical phenylketonuria", plasma levels of phenylalanine exceed 180 μ moles/dl (30 $\text{mg}\%$) and range from 180 to 660 μ moles/dl (30-100 $\text{mg}\%$) (14-16). These levels of phenylalanine are associated with mental retardation. To prevent retardation, the infants must be placed on diets low in phenylalanine content to decrease blood phenylalanine levels. The exact cause(s) of the mental retardation in

children with classical phenylketonuria is not clear, but is thought to result from both high levels of phenylalanine, and metabolites of phenylalanine such as phenylpyruvate, on brain metabolism (14-18).

Although some investigators feel that there is no benign persistent phenylalanemia, and recommend diet therapy for any patient with phenylalanine levels ranging from 10-20 mg% (60-120 umoles/dl), most investigators now feel that dietary therapy is not needed when blood phenylalanine levels are below 10 mg% and excess phenylalanine metabolites are not present. This assumption is based largely on the clinical records of children with phenylalanemia (PKU-Variants) who have persistent blood phenylalanine levels of 6-10 mg% without ill effect (14-16).

In summary: Plasma phenylalanine levels of up to 60 umoles/dl (10 mg%) appear to be relatively benign. Conditions which cause continued elevations of phenylalanine markedly above this level tend to be associated with mental retardation.

EFFECT OF ASPARTAME LOADING AT 34 MG PER KG BODY WEIGHT UPON BLOOD LEVELS OF AMINO ACIDS IN NORMAL VOLUNTEERS

In considering potential toxic effects of ASPARTAME in man, it is obvious that such effects would require extreme elevations of aspartate and phenylalanine blood levels. To examine potential hazard, we administered either ASPARTAME or aspartate to normal volunteers and determined the effect of such ingestion upon plasma and erythrocyte amino acid levels.

A total of 12 subjects were studied, 6 male and 6 female. ASPARTAME (34 mg/kg body weight) or equimolar quantities of aspartate (13 mg/kg body weight) were dissolved in orange juice and administered to fasting subjects at 8 AM. The order of administration was randomized in a latin square design. Subjects remained fasting throughout the 8 hour period, with only water permitted. Blood samples for amino acid analyses were obtained at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 8 and 24 hours after loading.

As illustrated in Table I, the load of ASPARTAME administered to these subjects is considerable. A 70 kg man may be considered to have a requirement for about 2500 Calories per day to maintain body weight. Approximately 17% of these calories are ingested as sucrose. Thus, sucrose ingestion for the day is about 1.5 gm/kg body weight. Considering the range of ASPARTAME sweetening power to be 180-200 times that of sucrose, if such an individual ingested all the sucrose sweetening power as ASPARTAME, ASPARTAME intake would be between 7.5-8.5 mg/kg per day. Similarly, if we assume total carbohydrate intake to be 50% of total calories, about 313 gms of carbohydrate are ingested. If all of this carbohydrate were ingested as sucrose, the subject would ingest about 4.5 gm/kg per day. If the sweetening equivalent of this amount of sucrose were ingested as ASPARTAME, an intake of 23-25 mg/kg ASPARTAME per kg body weight would be ingested over the course of the entire day. In this study, we administered ASPARTAME at 34 mg/kg, well over the 99th percentile of

daily ingestion, IN A SINGLE DOSE.

The plasma and erythrocyte free amino acid levels found in these subjects with time are contained in the computer print-out sheets labeled Exhibit 1 and Exhibit 2.

A brief summary of these data is found in the following paragraphs.

Figure 1 shows the response of plasma aspartate, asparagine, glutamate and glutamine to both ASPARTAME and aspartate load. No significant changes were noted in plasma aspartate, asparagine and glutamine levels with either compound. A small, nonsignificant rise in plasma glutamate levels was noted with either ASPARTAME or aspartate. This rise may reflect the conversion of some aspartate to glutamate. This effect may also be due to the stress of catheter insertion for blood sampling. Heath et al. (19) have reported stress may result in glutamate release. In any case, all levels remained within ± 1 normal fasting range for plasma glutamate values.

Figure 2 demonstrates that plasma taurine, methionine and cystine levels are not affected. Figure 3 shows similar results for threonine, histidine and lysine. Figure 4 shows the absence of effect upon plasma serine, glycine, citrulline, ornithine and arginine levels.

Plasma levels of the branched chain amino acids, valine, isoleucine and leucine, decrease slightly with time after loading (Figure 5) but return to initial values within 4 hours. No difference between ASPARTAME and aspartate loading was noted.

Plasma levels of alanine and proline increased after both ASPARTAME and aspartate loads as shown in Figure 6. However, a similar response was noted in subjects receiving lactose (50 mg/kg) in orange juice and is not considered to be due to the ASPARTAME or aspartate.

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As shown in Figure 7, plasma phenylalanine and tyrosine levels were not altered after aspartate ingestion. However, ASPARTAME ingestion resulted in an increase of phenylalanine levels from fasting levels (6 ± 3 umoles/dl) to the normal postprandial range (12 ± 3 umoles/dl). Plasma phenylalanine levels were close to fasting levels by 4 hours after the load and were at fasting levels 8 hours after load. Plasma tyrosine levels increased slightly after Aspartame load, as expected, from the conversion of phenylalanine to tyrosine.

Erythrocyte amino acid levels were also measured with time after loading. In view of recent data indicating that amino acids may be transported in the red cell, under some circumstances, to a greater extent than in plasma (20-22), we felt that it was important to determine if ASPARTAME had any effect upon erythrocyte amino acid levels not reflected in the plasma.

In contrast to most amino acids, glutamate and aspartate levels are normally much higher in the erythrocyte than in the plasma, as shown in Table 2.

Erythrocyte levels of asparagine, aspartate and glutamate were not affected by either aspartate or ASPARTAME ingestion (Figure 8). The data in Figure 9 demonstrate no effect upon plasma erythrocyte glutamine levels. A small increase in erythrocyte alanine and proline levels was noted, as expected from the increases in plasma levels (see Figure 6). Erythrocyte phenylalanine and tyrosine levels were not affected after aspartate loading (Figure 10). This was expected in view of a lack of effect on plasma levels (Figure 7). Phenylalanine levels and tyrosine levels were increased in subjects administered ASPARTAME (Figure 10). The increases were similar to those noted in plasma.

No changes were noted in the levels of other erythrocyte amino acids.

Summary:

The administration of ASPARTAME at 34 mg/kg body weight in a single dose to normal male and female subjects resulted in: (A) no change in plasma or erythrocyte glutamate or aspartate levels; and (B) increased phenylalanine levels from normal fasting levels to the postprandial range. Phenylalanine levels returned rapidly to normal.

We conclude that no risk arises from ASPARTAME ingestion at 34 mg/kg body weight. Plasma aspartate levels are unchanged (0.2-0.8 umoles/dl). Even the most susceptible species, the neonatal mouse, does not sustain neuronal necrosis until plasma levels reach 50-70 umoles/dl (12). The infant primate does not sustain damage at plasma levels of 500 umoles/dl (10). Phenylalanine levels were maintained within normal postprandial ranges set for this laboratory (23,24). Phenylalanine levels are considered toxic only at levels far above this level. Children with variants of phenylketonuria have blood phenylalanine levels 3 to 5 times the normal postprandial levels with no apparent ill effects (14,15).

EFFECT OF ASPARTAME OR LACTOSE INGESTION AT 50 MG PER KG BODY WEIGHT UPON PLASMA, ERYTHROCYTE AND BREAST MILK AMINO ACID LEVELS IN LACTATING WOMEN

At the present time about 38% of women who have babies in the United States breast feed their infants. Present data indicate that this trend will increase. About 1 of 5 mothers in this country continues to breast feed her infant beyond two months of age. This study was designed to determine if ASPARTAME ingestion will have any significant effect upon the breast milk of lactating women.

We examined the response of the plasma, erythrocyte and breast milk amino acid levels in established lactating women after ASPARTAME loads of 50 mg/kg body weight. The subjects were also studied after administration of an equivalent quantity of lactose in a cross-over design. ASPARTAME or lactose were administered in 300 ml cold orange juice to fasting subjects in a randomized manner. The subjects were fasted for the 4 hours following administration of the test substance. Plasma and erythrocyte free amino acid levels were measured at 1, 0.25, 0.5, 0.75, 1, 1.5, 2, 3 and 4 hours after administration. Breast milk samples were obtained at 0, 1, 2, 3, 4, 8, 12 and 24 hours after loading.

In view of the results of ASPARTAME ingestion at 34 mg/kg body weight showing no effect upon aspartate levels in plasma or erythrocyte, it was decided to determine the effect of ASPARTAME ingestion at 50 mg/kg body weight. As noted in Table 1, ASPARTAME ingestion would be about 25 mg/kg daily if: (a) all carbohydrate calories were ingested as sucrose; and (b) the equivalent sweetening power were ingested as ASPARTAME. The level used in this study is twice that amount and was given as a single dose rather than being ingested across the entire day.

The detailed plasma, erythrocyte and breast milk free amino acid levels are found in the attached computer print-out sheets labeled Exhibits 3 and 4.

A brief summary of the most important data is given in the following paragraphs.

Effects On Plasma Amino Acid Levels: No significant effect of either ASPARTAME administration or lactose administration were noted upon plasma aspartate levels as shown in Figure 11. As expected, plasma phenylalanine levels were increased to a peak value of 17 ± 2 umoles/dl after ASPARTAME ingestion but were not affected by lactose. The level of phenylalanine noted was only slightly higher than those noted postprandially (12 ± 3 umoles/dl) in adults and infants (23,24). Small increases in plasma tyrosine levels were also noted after ASPARTAME ingestion as the result of phenylalanine conversion to tyrosine. Tyrosine levels did not exceed the normal postprandial range for this laboratory of 12 ± 3 umoles/dl (23,24).

A small increase in plasma glutamate levels was noted after ASPARTAME ingestion, but not after lactose ingestion. This increase likely represents some conversion of the aspartate in ASPARTAME to glutamate. Glutamate levels were still well within the normal postprandial range for this laboratory (23,24). The increase in plasma glutamate levels was similar to that noted after ASPARTAME ingestion at 34 mg/kg and aspartate ingestion at 13 mg/kg.

As noted in the previous study, plasma proline and alanine levels were increased after both ASPARTAME and lactose ingestion at 34 mg/kg and aspartate at 13 mg/kg body weight. The effect on other amino acids was not significant and was similar to that noted in the previous study (see Figures 1-10).

Effect On Erythrocyte Levels: No significant differences were noted between lactose or ASPARTAME ingestion for most amino acids, including glutamate, aspartate, asparagine or glutamine. As expected, erythrocyte phenylalanine and tyrosine levels increased after ASPARTAME load, but to a lesser degree than that noted in plasma. Similarly, erythrocyte proline and

alanine levels increased, but with the increases being lower than those found in plasma.

Breast Milk Levels: Comparison of the breast milk aspartate and phenylalanine levels in the subjects studied indicate a small increase in both phenylalanine and aspartate levels in the subjects administered ASPARTAME (Figure 12). Breast milk levels of phenylalanine increased from 0.5 μ moles/dl to about 2 μ moles/dl, while aspartate levels increased from 2 μ moles/dl to about 4.7 μ moles/dl. However, the levels of aspartate and phenylalanine observed were not significantly higher than levels of these amino acids observed in another group of patients given lactose previously (13). In any case, the quantity of increased amino acids in the milk is not a significant portion of the total daily intake. Infants fed ad libitum with a milk-based formula providing the same caloric content as human breast milk (67 kcal/100 ml) may ingest about a mean of 171 ml/kg/day. Infants ingesting the milk at this level might ingest an increase of about 3.2 μ moles/kg phenylalanine per day (0.53 mg/kg) compared to the total normal requirement of about 120 mg/kg/day phenylalanine. Similarly, about 4 μ moles (0.64 mg) more aspartate would be ingested per kg per day. This is only a trace portion when compared to the total quantity of aspartate ingested from the protein of breast milk, which would be 109 mg/kg/day (26).

In summary: No significant increases in breast milk phenylalanine and aspartate were noted.

EFFECT OF ASPARTAME LOADING AT 100 MG PER KG BODY WEIGHT UPON PLASMA AND
ERYTHROCYTE FREE AMINO ACID LEVELS: COMPARISON OF SOLUTION VS SLURRY

In previous studies, we had failed to demonstrate an increase in plasma or erythrocyte aspartate levels after ASPARTAME ingestion at 34 or 50 mg/kg body weight. In those studies, ASPARTAME had been dissolved in 300 ml of cold orange juice. In future studies, we wished to determine the effect of high doses of ASPARTAME. Animal studies suggested that slurry administrations of ASPARTAME were less well absorbed. This study was designed to determine the effect of ASPARTAME ingestion at 100 mg/kg upon blood amino acid levels and to determine the effects, if any, of ingestion of abuse doses of ASPARTAME in solution or in slurry.

Six normal adult subjects were studied, 3 male and 3 female. The subjects were administered ASPARTAME (100 mg/kg body weight) either dissolved in 500 ml of cold orange juice or as a slurry in 1.2 ml of orange juice per kg body weight, in a cross-over design. The order of administration of ASPARTAME in solution or slurry was randomized. Blood samples were obtained at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8 and 24 hours after administration for plasma and erythrocyte amino acid analysis.

The detailed amino acid analyses are found in the computer print-out sheets labeled Exhibits 5 and 6. A brief summary of the most important points is found in the following paragraphs.

Effect On Plasma Levels: ASPARTAME ingestion at 100 mg/kg in solution had little statistical effect upon plasma aspartate levels as shown in the orange line of Figure 138. When ASPARTAME was ingested in slurry form (green line, Figure 138), an increase in plasma aspartate levels was noted, with a peak value of about 1.5 μ moles/dl noted. However, variation in the individual responses of the 6 subjects to the slurry form was noted. Four of the 6 subjects studied had no change in plasma aspartate levels, and the values

obtained for these subjects were identical to the curves obtained when ASPARTAME was given in solution (orange line in Figure 13B). However, two subjects showed a very rapid increase in plasma aspartate levels (Figure 13A) reaching peak values of 3.6 to 5.8 μ moles/dl. These subjects apparently had a very rapid gastric emptying with slurry ingestion. ASPARTAME administration in solution resulted in an increase of plasma phenylalanine levels to approximately 25 μ moles/dl as shown in Figure 14 (dashed line). ASPARTAME administration in slurry form resulted in the separation of the 6 subjects into 3 distinct groups of two subjects each. The first group had a rapid gastric emptying (solid line), with rapid peaking of plasma phenylalanine levels. These two subjects also showed a rapid increase in plasma aspartate levels (Figure 13A). The second group (dashed line, Figure 14) had a response identical to that of the subjects ingesting ASPARTAME in solution. The third group had a delayed gastric emptying time (dotted line, Figure 14). Phenylalanine levels rose more slowly, and the peak was lower and broader.

As expected, plasma tyrosine levels increased to a mean of about 10 μ moles/dl, still well within normal postprandial limits. Increases in plasma glutamate, alanine and proline were similar to those noted at lower ASPARTAME doses.

Effect On Erythrocyte Levels: No effect upon erythrocyte aspartate, asparagine, glutamine or glutamate levels was noted. Erythrocyte phenylalanine, tyrosine, proline, and alanine levels increased as expected from the observed increases in plasma levels. Increases in the erythrocyte were lower than those noted in the plasma.

Summary: Administration of ASPARTAME at 100 mg/kg resulted in a small increase in plasma aspartate levels in 2 of the 6 subjects receiving it in slurry form. Aspartate levels were not affected in the other four subjects

EXHIBITS 1-9
See listing on next page

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ingesting ASPARTAME in a slurry form or in the 6 subjects ingesting ASPARTAME in solution. The peak aspartate levels noted are far below the toxic levels in even the most sensitive species, the neonatal mouse. Aspartate levels must reach 60-70 umoles to produce an effect in this animal (12). Mean plasma phenylalanine levels did not differ greatly between the slurry and solution. A peak level of about 20-25 umoles/dl (4 mg%) was noted. This value is far below any toxic level of phenylalanine. However, the variability in blood levels was very large when given as a slurry. Future high dose studies will be carried out by suspending the dose in 500 ml of orange juice to avoid this effect.

EFFECT OF ASPARTAME LOADING AT 150 MG PER KG BODY WEIGHT UPON PLASMA AND ERYTHROCYTE FREE AMINO ACID LEVELS IN NORMAL ADULT VOLUNTEERS

The purpose of this study was to investigate the effect of high dose levels of ASPARTAME upon plasma and erythrocyte amino acid levels to determine hazard, if any, from abuse level ingestion of the product.

ASPARTAME (150 mg/kg body weight) was suspended in 500 ml of cold orange juice and administered to fasting subjects at 8 AM. Six subjects were studied, 3 male and 3 female. The subjects were fasted (water permitted) for the 8 hours following ingestion. Blood samples for amino acid analysis were obtained at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8 and 24 hours after loading.

The detailed amino acid analyses are found in the computer print-out sheets labeled Exhibit 7. A brief summary of the most important points follows.

Effect Upon Plasma Amino Acid Levels: Very small changes in plasma aspartate levels were noted after ASPARTAME ingestion as shown in Figure 15 (blue line). Because of the sensitivity of the Beckman 121M amino acid analyzer, small differences in plasma aspartate levels are detected. Note, however, that these levels are still below those noted postprandially in young infants fed formula diets (23,24). Plasma phenylalanine levels increased to a peak of about 35 μ moles/dl after loading (blue line, Figure 16), and plasma tyrosine levels increased to a peak of about 11 μ moles/dl (blue line, Figure 17). As in previous ASPARTAME studies, a small increase in plasma glutamate to about 6 μ moles/dl was noted.

Effect Upon Erythrocyte Levels: Erythrocyte levels of glutamate and aspartate are unchanged (Figure 18). Erythrocyte levels of phenylalanine and tyrosine increase to levels nearly identical to those found in the plasma (Figure 19).

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In Summary: ASPARTAME ingestion at 150 mg/kg body weight had only a minimal effect upon plasma aspartate levels and no effect upon erythrocyte levels. The levels obtained are still very much below those required to produce any damage in the most susceptible species, the neonatal mouse. Phenylalanine levels reached a peak level of 35 μ moles/dl (5.8 mg%). This concentration is also well below that which would cause any toxic effect.

doses either orally or by injection (1). Older mice are also susceptible to dicarboxylic amino acid-induced neuronal necrosis, but much higher levels of

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EFFECT OF ASPARTAME LOADING AT 200 MG PER KG BODY WEIGHT UPON PLASMA AND ERYTHROCYTE AMINO ACID LEVELS IN NORMAL ADULT SUBJECTS

The purpose of this study was to investigate the effect of ASPARTAME ingestion at 200 mg/kg body weight upon blood amino acid levels. The ingestion level of 200 mg/kg is considered to be the maximum abuse level of the product. This would be the potential dose received by a 3-year-old child accidentally ingesting the entire contents of the family jar of ASPARTAME coffee sweetener. A similar level of ingestion was calculated for a soldier in the tropics ingesting his entire water intake for the day (20 liters maximum) as ASPARTAME sweetened beverage.

ASPARTAME (200 mg/kg body weight) was suspended in 500 ml of cold orange juice and administered to fasting subjects at 8 AM. Six subjects were studied, 3 male and 3 female. The subjects were fasted (water permitted) for 8 hours following ingestion. Blood samples for amino acid analysis were obtained at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4; 5, 6, 7, 8 and 24 hours after loading.

The detailed amino acid analyses are found in the computer print-out sheets labeled Exhibit 8. A brief summary of the most important points follows.

Effect upon plasma amino acid levels: Very small changes in plasma aspartate levels were noted after ASPARTAME ingestion as shown in Figure 15 (green line). The small differences in aspartate levels noted are still well below those noted postprandially in young infants fed formula diets (23,24). Plasma phenylalanine levels increased to a mean of about 49 μ moles/dl (8 mg%) after loading, and decreased rapidly (Figure 16--green line). Plasma tyrosine levels increased to a mean of about 14 μ moles/dl (Figure 17--green line) after loading. As in all previous ASPARTAME studies, a small increase in plasma glutamate levels (6 μ moles/dl) was observed.

the infants must be placed on diets low in phenylalanine content to decrease blood phenylalanine levels. The exact cause(s) of the mental retardation in

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Effect upon plasma amino acid levels: Erythrocyte levels of glutamate and aspartate were not altered. Erythrocyte levels of phenylalanine and tyrosine increased to values close to those noted in plasma.

Summary: ASPARTAME ingestion at an acute abuse level of 200 mg/kg body weight had only a minimal effect upon plasma aspartate levels, and no effect upon erythrocyte levels. The concentrations achieved are far below those required to produce neuronal damage in even the acutely sensitive neonatal mouse. Phenylalanine levels reached a mean peak of 48 umoles/dl, with one subject reaching about 72 umoles/dl. These levels are also below those which would cause any toxic effect upon such short term elevation of blood levels.

sucrose were ingested as ASPARTAME, an intake of 23-25 mg/kg ASPARTAME per kg body weight would be ingested over the course of the entire day. In this study, we administered ASPARTAME at 34 mg/kg, well over the 99th percentile of

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ASPARTAME LOADING AT 34 MG PER KG BODY WEIGHT IN FEMALE SUBJECTS PRESUMED TO BE HETEROZYGOTES FOR PHENYLKETONURIA

Individuals affected with the disease phenylketonuria fail to metabolize phenylalanine effectively, resulting in abnormally elevated plasma and erythrocyte phenylalanine levels. It is known that pregnant females with phenylketonuria whose phenylalanine levels are not controlled give birth to retarded children whether or not those children have phenylketonuria. The incidence rate for the heterozygote of phenylketonuria is estimated at about 1:50. It is likely that such heterozygote subjects would ingest ASPARTAME. This raises two questions: First, do such heterozygote subjects metabolize ASPARTAME in a normal manner? Second, if unusual metabolism of ASPARTAME is noted, would the levels of phenylalanine produced be detrimental to the fetus in utero if the individual becomes pregnant?

To answer these questions, a total of four female subjects known to be heterozygotes for phenylketonuria were studied. Subjects were administered ASPARTAME dissolved in orange juice at 34 mg/kg, and plasma and red cell amino acid levels were followed with time. Blood samples were obtained at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4 and 8 hours after ASPARTAME ingestion.

The detailed amino acid analyses are found in the computer print-out sheets labeled Exhibit 9. A brief summary of the most important points follows.

Effect Upon Plasma Amino Acid Levels: Plasma amino acid effects were very similar to those noted in normal subjects ingesting ASPARTAME at 34 mg/kg (see page 4 of this report). Plasma aspartate levels were not affected. Plasma phenylalanine levels were slightly higher in the phenylketonuric heterozygotes than in the 12 normal subjects studied previously (Figure 20). The heterozygotes showed a broader absorption curve than the normal subjects. However, the differences between groups are very small and the differences

are not sufficient to pose a risk either to the heterozygote or, in the event of pregnancy, to the fetus.

Effect Upon Erythrocyte Levels: Erythrocyte levels are similar to those noted in normal subjects.

Summary: Aspartate levels are not affected by ASPARTAME ingestion at 34 mg/kg. Plasma phenylalanine levels are slightly higher in the PKU heterozygote than in the normal subject, but the level is still well below that which would present any hazard. Normal postprandial phenylalanine levels are 12 ± 3 μ moles/dl (23,24), and the levels obtained are close to this value.

GENERAL SUMMARY OF HUMAN DATA ON EFFECTS OF ASPARTAME LOADING AT 34, 50, 100, 150 and 200 MG PER KG IN NORMAL VOLUNTEERS

The toxicity of ASPARTAME centers upon its effect on the blood levels of its constituent components: aspartate, phenylalanine and methanol. Each of these components may exert toxic effects, although species and age susceptibility vary.

I. Aspartate:

There is no doubt that the dicarboxylic amino acids will produce neuronal necrosis in the infant mouse when given in large doses. The ability of the dicarboxylic amino acids to produce neuronal necrosis in the neonatal primate is highly controversial. Although Olney and his colleagues have reported neuronal necrosis after glutamate administration to the neonatal primate (4,5), other investigators have been unable to produce the lesion in the primate with glutamate (6-9). This failure occurs despite demonstration that enormous elevations in blood glutamate levels occurred in the neonatal animals studied (10).

In the most susceptible species, the neonatal mouse, we have shown that plasma glutamate plus aspartate levels must reach 60-70 umoles/dl before the first signs of neuronal necrosis are noted (12). In the infant monkey, plasma glutamate plus aspartate levels up to 500 umoles/dl did not result in neuronal necrosis (10).

Experimental Data: We have undertaken studies in which ASPARTAME, dissolved in orange juice, was administered to normal volunteers at 34, 50, 100, 150 and 200 mg/kg. Plasma and red cell levels of all amino acids were measured with time to determine if potentially toxic levels were attained. At 34 and 50 mg/kg load levels, essentially no change was noted in plasma or red cell aspartate levels. Mean plasma aspartate levels increased slightly

from 0.20 $\mu\text{m}/\text{dl}$ to about 0.35 $\mu\text{moles}/\text{dl}$, but the changes were not statistically significant. At higher dose levels of ASPARTAME, slightly larger changes in plasma aspartate levels were noted (Figure 15). At 100 mg/kg (solution) aspartate levels increased to about 0.4 $\mu\text{moles}/\text{dl}$, and at dose levels of 150 to 200 mg/kg body weight, mean plasma aspartate levels reached 0.6 to 2.0 $\mu\text{moles}/\text{dl}$. All of these levels are below normal postprandial plasma aspartate levels in young infants fed conventional infant formulas. Plasma aspartate levels may reach 2 to 4 $\mu\text{moles}/\text{dl}$ in such infants. Even the levels attained at 150 to 200 mg/kg ASPARTAME are far below those required (60 to 70 $\mu\text{moles}/\text{dl}$) for the production of a lesion in the acutely sensitive neonatal mouse (12).

At ASPARTAME loading of 100 mg/kg , the effects of administration as a solution or slurry were compared. Greater elevations in plasma aspartate levels were noted when ASPARTAME was administered as a slurry (Figure 13B). When ASPARTAME is administered as a slurry, considerable variation in gastric emptying occurs. This results in large variations in the absorption curves. Of the 6 subjects studied with ASPARTAME slurry at 100 mg/kg , 2 exhibited rapid gastric emptying with peak levels reached at about 45 minutes, 2 exhibited curves exactly like subjects given 100 mg/kg in solution, and 2 had delayed gastric emptying with peak levels being reached much later. In those subjects with rapid absorption, plasma aspartate levels reached 4 to 6 $\mu\text{moles}/\text{dl}$ (Figure 13A). This is reflected in the slightly increased aspartate levels noted after administration of ASPARTAME as a slurry (Figure 13B). It would be expected that higher loads (200 mg/kg) administered as a slurry would produce similar variations in such individuals, and that levels of 8-12 $\mu\text{moles}/\text{dl}$ might be attained.

Glutamate and aspartate have effects upon each other's metabolism. Our

studies of glutamate metabolism in man have shown that glutamate loads produce a rise both in plasma glutamate and aspartate (13). Similar effects were noted in our studies of ASPARTAME. ASPARTAME administration at all levels studied produced a very small increase in plasma glutamate levels. Plasma concentrations increased from approximately 3.8 umoles/dl at baseline to peak values of about 5.5 to 6 umoles/dl (Figure 21A). This small increase was not proportional to increasing APM loads.

Studies from other laboratories have demonstrated that the dicarboxylic amino acids may be carried by the red cell to a greater extent than plasma (20,21,22). In such situations increased glutamate levels are noted in the red cell but not in the plasma. No changes in red cell glutamate or aspartate levels are noted at any level, as shown in Figure 18 for individuals given ASPARTAME at 150 mg/kg.

In summary: Aspartate levels are not significantly increased in the blood after ASPARTAME loading.

II. Phenylalanine:

A genetic disorder called phenylketonuria results from either the absence or the presence of an inactive enzyme required for the conversion of phenylalanine to tyrosine. Other children have a decreased ability to metabolize phenylalanine because of decreased quantities of a transaminase enzyme. In the children with "classical phenylketonuria", plasma levels of phenylalanine exceed 180 um/dl (30 mg%) and range from 30-100 mg% (14). These levels are associated with mental retardation. Lower phenylalanine levels (30-60 um/dl or 5 to 10 mg%) noted in the variant forms of phenylalanemia are not associated with mental retardation.

Data Obtained: Plasma and red cell phenylalanine levels were followed with time in normal adult volunteers administered ASPARTAME dissolved in orange

juice at 34, 50, 100, 150 and 200 mg/kg body weight in an attempt to determine whether potentially toxic phenylalanine levels would be obtained at acute or chronic abuse levels.

A dose-related response of plasma phenylalanine levels to increasing levels of ASPARTAME was noted (Figure 16). In the absence of ASPARTAME, phenylalanine levels did not increase in the time period studied. As expected, plasma tyrosine levels also increase (Figure 17). The peak levels of phenylalanine and tyrosine observed are listed below:

<u>APM Dose</u> (mg/kg)	<u>Phenylalanine</u> (umoles/dl)	<u>Tyrosine</u> (Umoles/dl)
0	6	5.5
34	11	6.5
50	15	8.0
100	20-26	9.5-10.8
150	35	11.0
200	49	13.6

At 34 mg/kg body weight, phenylalanine levels approached the levels noted after a meal (12 ± 3 umoles/dl). At higher dose levels, APM loads produced higher and broader curves (Figure 14).

At the highest dose studied (200 mg/kg), mean plasma phenylalanine levels were 49 umoles/dl (8 mg%). Although this is a considerable phenylalanine concentration, this level is well within the range permitted in phenylketonuric subjects during diet therapy (16). Considerable variation in peak phenylalanine levels were noted at the 200 mg/kg level, with peak values ranging from 30 to 70 umoles/dl.

As mentioned in the discussion of aspartate results, the physical form in which ASPARTAME is administered affects absorption and peak levels. This is readily demonstrated from plasma phenylalanine levels obtained after ASPARTAME loading at 100 mg/kg in which the effects of slurry vs. solution

were tested (Figure 14). Note three distinct groups of absorption patterns. However, mean peak phenylalanine levels for the slurry group as a whole were similar to those noted when the subjects received ASPARTAME in solution (Figure 16).

Red cell levels of phenylalanine and tyrosine were similar to those found in plasma, as expected (Figure 19).

Maternal Phenylketonuria: In children with classical phenylketonuria, elevated phenylalanine levels are associated with mental retardation. In such children phenylalanine levels vary between 30-100 mg% or 180-600 umoles/dl. However, a number of children have been indentified whose phenylalanine levels range from 10-20 mg% or 60-120 umoles/dl who are not normally mentally retarded.

The exact cause(s) of the mental retardation in children with PKU is not clear, but may result from the effects of metabolites of phenylalanine such as phenylpyruvate on metabolism.

Although some investigators feel that there is no benign persistent phenylalanemia and recommend dietary therapy for any patient with a phenylalanine level ranging from 10-20 mg% (60-120 umoles/dl), most investigators do not treat patients with phenylalanine levels below 10 mg% (60 umoles/dl) if excess phenylalanine metabolites are not present (14-16).

In the pregnant female with PKU, the large elevations in maternal phenylalanine levels are amplified by the placenta, concentrating the levels on the fetal side. The placenta maintains a gradient of most amino acids of about 2:1 toward the fetal circulation. Thus, maternal phenylalanine levels of 30 mg% (180 umoles/dl) will result in fetal levels of 50-65 mg%. In view of these findings, it is not surprising that normal or heterozygote children born to such mothers are mentally retarded.

As a result of these findings a few attempts have been made to control the mother's phenylalanine levels during pregnancy in an attempt to spare the fetus.

At the present time, apparently normal children have been born to phenylketonuric mothers whose blood phenylalanine levels were maintained between 3-6 mg% during pregnancy. This has led to the suggestion that mental retardation may be prevented by maintaining maternal phenylalanine levels between 3-8 mg%. These data are in line with recent studies indicating that PKU children treated with diets maintaining phenylalanine levels between 5-9.9 mg% were not significantly different from children in whom phenylalanine levels were maintained between 1-4 mg%. The data suggest that phenylalanine levels below 10 mg% are not detrimental under most circumstances (14-16).

These data can be applied to our present knowledge of ASPARTAME. Under acute abuse loads of 200 mg/kg, mean peak plasma phenylalanine levels are 8 mg% (49 umoles/dl) and ranged from 6-12 mg% or 35-75 umoles/dl over the course of a few hours. Since the developing infant appears to tolerate continued exposure to phenylalanine levels in this range, it would appear that little danger, if any, is involved even upon acute abuse ingestion with its relatively short exposure time.

In summary: ASPARTAME administered at 34 mg/kg increased plasma phenylalanine levels only slightly, from fasting to postprandial levels. Doses of ASPARTAME which might be ingested under acute toxicity conditions (200 mg/kg) produced a mean phenylalanine level of about 49 umoles/dl (8 mg%), with a range of 30-75 umoles/dl. No toxic effects would be expected at this level.

III. Methanol:

ASPARTAME is a methyl ester. As such, methanol is released upon digestion and is absorbed. Plasma methanol levels have been measured in all normal

subjects administered ASPARTAME to date through the 200 mg/kg level (Figure 22). Mean peak methanol levels are as follows:

<u>ASPARTAME Load</u>	<u>Peak Methanol Level</u>
mg/kg	mg%
0	0.25
34	0.53
50	0.78
100	1.55
150	2.33
200	3.40

According to the studies of Tephly and others (27-30), the toxic effects of methanol ingestion appear to be due to formate accumulation. In studies of the primate, no acidosis is noted until formate levels reach 30 to 40 mg%. A blood methanol level of 200 to 300 mg% is present when the above levels of formate are reached. Thus, an approximate methanol-to-formate ratio of 8:1 is noted. From these data we may predict the following:

<u>Blood Methanol (mg%)</u>	<u>Blood Formate Predicted (mg%)</u>
1	0.125
2	0.25
4	0.5
8	1.0

Based on our experiments to date, we expect acute abuse loads of 200 mg/kg ASPARTAME to produce blood methanol levels of about 3-4 mg%. Formate levels of 0.5 mg% might then be predicted. We have looked for formate in the blood and urine of subjects receiving ASPARTAME at 150 and 200 mg/kg without success. This was expected, however, since the limit of the assay is 1 mg%.

In summary: There appears to be no danger from the methanol produced from ASPARTATE hydrolysis in the gut. No detectable quantities of formate are noted.

PROGRESS REPORT ON ASPARTAME STUDIES

PART B: ANIMAL STUDIES

TO

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PLACENTAL TRANSPORT OF ASPARTATE IN THE PREGNANT PRIMATE

During pregnancy, most amino acids are found at higher concentrations in the fetal plasma than in maternal plasma. This gradient is maintained by the placenta so that most amino acids are present at about 2 times the maternal level in fetal plasma. In certain conditions this is detrimental. Pregnant women who are homozygous for phenylketonuria have markedly elevated phenylalanine levels. These levels are amplified by the placenta so that the fetus is exposed to enormous elevations of this amino acid. It is not surprising therefore that normal or heterozygote children born to such mothers are mentally retarded.

We had previously shown that the amino acid glutamate is an exception to such concentration by the placenta, since it does not cross the placenta unless enormous elevations of maternal glutamate levels occur (31).

It has been suggested that ingestion of large quantities of ASPARTAME by the pregnant woman might result in elevated maternal aspartate levels and that these increases would be multiplied by the placenta to increase fetal aspartate levels. To test this possibility, we have infused pregnant rhesus monkeys with sodium aspartate at three levels and followed maternal and fetal amino acid levels with time. The aspartate was infused at either 0.1 gm/kg, 0.2 gm/kg or 0.4 gm/kg over the course of one hour.

In animals infused at 0.1 gm/kg, maternal aspartate levels increased from 0.5 umole/dl to between 45-75 umoles/dl at the end of the hours infusion (Figure 23). As the infusion was terminated, maternal aspartate levels rapidly returned

to normal. During this time period a very slight elevation in fetal aspartate level was detected, rising from 0.15 $\mu\text{mole/dl}$ to 0.5-0.9 $\mu\text{mole/dl}$. As the maternal levels decreased, fetal levels fell rapidly to normal. This level has no effect upon the fetus. For example, the newborn infant commonly has postprandial aspartate levels of 1 to 2.5 $\mu\text{moles/dl}$. In the animal infused at 0.2 gm/kg, maternal levels increased to about 100 $\mu\text{moles/dl}$, and fetal levels briefly reached 3 $\mu\text{moles/dl}$ (Figure 23). Thus, we seem to be approaching a point at which a small amount of transfer is permitted when maternal levels reach 100 $\mu\text{moles/dl}$.

In animals infused with aspartate at 0.4 gm/kg, maternal aspartate levels increased from 0.5 $\mu\text{moles/dl}$ to between 400 to 800 $\mu\text{moles/dl}$ at the end of the infusion (Figure 24). As the infusion was terminated, maternal aspartate levels fell rapidly toward normal. At the same time, fetal aspartate levels increased from 0.2 $\mu\text{moles/dl}$ to between 70 to 90 $\mu\text{moles/dl}$. Again, these levels fell rapidly toward baseline levels upon termination of the infusion. This indicates ready metabolism of aspartate by the fetus.

These data demonstrate that aspartate, unlike most amino acids, is not concentrated toward the fetal circulation, and that in fact a barrier toward its transfer to the fetal circulation exists, requiring enormous increases in maternal aspartate levels before aspartate in even small amounts reaches the fetal circulation.

In view of the minimal changes produced in plasma aspartate levels upon ASPARTAME loading of normal volunteers at 200 mg/kg (see page 16 of this report), these data conclusively demonstrate no risk to the fetus from the aspartate content of ASPARTAME. Note that maternal aspartate levels of 40-75 $\mu\text{moles/dl}$ cause only a barely perceptible rise in fetal aspartate levels. The maximum levels we have observed in man after 150 or 200 mg/kg ASPARTAME loads has been only 5 $\mu\text{moles/dl}$.

In view of our mouse toxicity data (12) suggesting that dicarboxylic amino acid levels of at least 60 umoles/dl are necessary to produce minimal neuronal necrosis in the highly susceptible infant mouse, it would appear that loads of ASPARTAME which produce maternal aspartate levels in excess of 400 umoles/dl must be attained before any effects would be noted on even the acutely sensitive neonatal rodent. It is virtually impossible for an individual to be force fed the quantity of ASPARTAME which would produce this level (see studies with neonatal primate force fed 2 gm/kg in next section).

ASPARTAME NEUROTOXICITY STUDIES: AMINO ACID LEVELS IN NEONATAL PRIMATES STUDIED BY DR. W. ALAN REYNOLDS IN NEUROPATHOLOGY STUDIES.

Dr. Reynolds has been studying the effects of ASPARTAME administration upon the brain of the infant primate. These studies are being carried out at dose levels of 2 gm/kg ASPARTAME, and dose levels of 2 gm ASPARTAME plus 1 gm monosodium glutamate per kg. Olney and colleagues (4,5) have reported that the neonatal primate develops neuronal necrosis after glutamate administration to the neonatal primate. Although other investigators have failed to reproduce this neuronal necrosis in the infant primate (4-10), Olney contends that the addition of ASPARTAME to the food supply poses an additional "risk" because of its additive effect with glutamate (32).

We have collaborated with Dr. Reynolds of the University of Illinois Medical Center to determine the blood levels which are attained in neonatal primates administered high doses of ASPARTAME and ASPARTAME plus glutamate.

Current estimates of ASPARTAME intake suggest that a dose of 20 mg/kg body weight represents the 90th percentile of daily usage. We have already demonstrated that no increase of biological significance in plasma or erythrocyte aspartate levels at 10 times this dose (200 mg/kg) as noted on page 16 of this report. In the absence of alterations in blood aspartate levels, no hazard from aspartate occurs. In this study, we have examined the effect of ASPARTAME ingestion at 100 times this 90th percentile figure in the neonatal primate. These studies were also carried out in the presence of added glutamate (1 gm/kg).

As described in Dr. Reynolds previous report to Searle, neonatal primates were administered either ASPARTAME (2 gm/kg) or ASPARTAME (2gm/kg) plus monosodium glutamate (1 gm/kg). The test compound was administered as a 20% slurry

to unanesthetized infants by stomach tube. A small amount of water follows the dose to clear the feeding tube. Following dosing, each infant is returned to an incubator and observed closely over the ensuing 60 minutes for any sign of vomiting, cyanosis, tremors etc. In those instances in which sequential blood samples are obtained, the infant is lightly tranquilized with phencyclidine and secured on a warming pad for the duration of the experimental period. A listing of the primates studied and their identification numbers is found in Table 3 for ASPARTAME treated animals, and in Table 4 for animals administered ASPARTAME plus glutamate.

Dr. Reynolds informs me that no lesions have been observed in any primate studied either with ASPARTAME or ASPARTAME plus glutamate.

Plasma amino acid levels: Plasma glutamate and aspartate levels in 4 animals administered ASPARTAME at 2 gm/kg are shown in Figure 25. As expected, a substantial portion of the aspartate present in ASPARTAME is converted to glutamate. Smaller increases in plasma aspartate levels were noted. In most animals aspartate levels did not exceed 25 umoles/dl, although in animal A-5 a more rapid response occurred with plasma levels reaching about 80 umoles/dl. Figure 26 shows plasma glutamate and aspartate levels in animals studied after administration of ASPARTAME (2 gm/kg) and glutamate (1 gm/kg). As expected, plasma glutamate levels increased to about 200 umoles/dl and aspartate levels increased to 80-100 umoles/dl. A considerable variation in absorption curves was noted. Thus undoubtedly reflects the fact that ASPARTAME must be administered as a slurry to achieve this dose level. As our studies in man have shown (see page 11 of this report), slurry administration produces differences in gastric emptying--absorption rates leading to a variety of blood response curves.

Plasma phenylalanine levels for both groups of animals are found in Figure 27. Again, variability in the absorption curves is noted, with phenylalanine levels

ranging from 100-200 μ moles/dl in most animals. One animal (A-10) exhibited a higher and broader absorption curve. Examination of the plasma aspartate curve of this animal (Figure 26) indicates a normal curve, thus the dose appears to be correct. It seems likely that this animal has a decreased ability to metabolize phenylalanine. Erythrocyte phenylalanine levels paralleled those in plasma.

Summary: The studies of Dr. Reynolds indicate no neuronal necrosis in any animal. As expected, moderate increases in plasma aspartate levels occurred. Even the acutely sensitive neonatal mouse requires dicarboxylic amino acid levels of about 60-70 μ moles/dl to produce the first signs of toxicity (12). Thus, in most of the neonatal primates studied with ASPARTAME at 2 gm/kg, plasma glutamate plus aspartate levels barely reached this threshold value. We have shown that the neonatal primate tolerates much higher blood levels of the dicarboxylic amino acids (at least 500 μ moles/dl) without neuronal necrosis (10), in contrast to the rodent. The data presented here agree with those findings. First, no neuronal necrosis was noted in any animal, even in animals given ASPARTAME plus glutamate. Secondly, the blood levels of glutamate plus aspartate are well within the range which we have previously demonstrated give no effect in the neonatal primate (10).

REFERENCES

1. Olney, J.W. *Science* 164, 719 (1969).
2. Lemkey-Johnston, N. and Reynolds, W.A. *J. Neuropath. Exptl. Neurol.* 33, 74 (1974).
3. Olney, J.W. and Ho, O.L. *Nature* 227, 609 (1970).
4. Olney, J.W. and Sharpe, L.G. *Science* 166, 386 (1969).
5. Olney, J.W., Sharpe, L.G. and Felgen, R.D. *J. Neuropath. Exptl. Neurol.* 31, 464 (1972).
6. Reynolds, W.A., Lemkey-Johnston, N., Filer, L.J., Jr. and Pitkin, R.M. *Science* 172, 1342 (1971).
7. Abraham, R.W., Dougherty, W., Golberg, L. and Coulston, F. *Exp. Mo. Path.* 15, 43 (1971).
8. Newman, A.J., Heywood, R., Plamer, A.K., Barry, D.H., Edwards, F.P. and Worden, A.N. *Toxicology* 1, 197 (1973).
9. Wen, C., Hayes, K.C. and Gershoff, S.M. *Am. J. Clin. Nutr.* 26, 803 (1973).
10. Stegink, L.D., Reynolds, W.A., Filer, L.J., Jr., Pitkin, R.M., Boaz, D.P. and Brummel, M.C. *Am. J. Physiol.* 229, 746 (1975).
11. Reynolds, W.A., Lemkey-Johnston, N., Pitkin, R.M., Stegink, L.D., Filer, L.J., Jr. and Bingle, A. *IX Int. Congress Nutr., Abstracts*, p. 203 (1972).
12. Stegink, L.D., Shepherd, J.A., Brummel, M.C. and Murray, L.M. *Toxicology* 2, 285 (1974).
13. Stegink, L.D., Filer, L.J., Jr. and Baker, G.L. *Proc. Soc. Exptl. Biol. Med.* 140, 836 (1972).
14. Blaskovics, M.E. Phenylketonuria and Other Phenylalaninaemias. In: *Clinics in Endocrinology and Metabolism* 3, 87 (1974).
15. Koch, R., Blaskovics, M., Wenz, E., Fishler, K. and Schaeffler, G. Phenylalaninemia and Phenylketonuria. In: *Heritable Disorders of Amino Acid Metabolism* (W.L. Nyham, ed.), J. Wiley, New York, 1974, p. 169.

16. Williamson, M., Koch, R. and Dobson, J. C. PKU-Collaborative Study--Current Status. A report presented at 3rd IASSMD Congress, the Hague, the Netherlands (1973).
17. Halestrap, A. P., Brand, M. D., and Denton, R. M. *Biochim. Biophys. Acta* 367, 102 (1974).
18. Mowbray, J., *FEBS Letters* 44, 344 (1974).
19. Heath, D. F., George, D. R., and Rose, J. G. *Biochem. J.* 125, 765 (1971).
20. Elwyn, D. H. *Federation Proceedings* 35, 854 (1966).
21. Felig, P., Wahren, J. and Raf., L. *Proc. Natl. Acad. Sci., U.S.*, 70, 1775 (1973).
22. Aoki, T. T., Brennen, M. F., Muller, W. A., Moore, F. D. and Cahill, G. F., Jr., *J. Clin. Invest.* 51, 2889 (1972).
23. Stegink, L. D. and Baker, G. L., *J. Pediatrics* 78, 595 (1971).
24. Stegink, L. D., Schmitt, J. L., Meyer, P. D. and Kain, P. H., *J. Pediatrics* 79, 648 (1971).
25. Fomon, S. J. Voluntary Food Intake and Its Regulation: In: *Infant Nutrition*, (S. J. Fomon, ed.) 2nd Edition, W. B. Saunders Co., Philadelphia, 1974
26. Stegink, L. D. Calculations of glutamate, aspartate, phenylalanine and tyrosine intake in human breast-fed infants. Confidential preliminary communication--attached to report.
27. Tephly, T. Personal Communication, 1976
28. Clay, K. L, Murphy, R. C. and Watkins, W. D. *Toxicology & Applied Pharmacology* 34, 49 (1975).
29. Tephly, T. R., Parks, R. E., Jr. and Mannering, G. J. *J. Pharmacol. Exp. Ther.* 143, 292 (1964)
30. Tephly, T. R., Watkins, W. D. and Goodman, J. I. *The Biochemical Toxicology of Methanol. Essays in Toxicology*, Vol. 5, Chap. 6, Academic Press, New York, 1974.
31. Stegink, L. D., Pitman, R. M., Reynolds, W. A., L. J. Filer, Jr., Boaz, D. P., and Brummel, M. C. *Am. J. Obst. Gyn.* 122, 70 (1975).
32. Olney, J. W. *Fd. Cosmet. Toxicol.* 13, 595 (1975).

Data Obtained: Plasma and red cell phenylalanine levels were followed with time in normal adult volunteers administered ASPARTAME dissolved in orange

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TABLE 1

ESTIMATE OF ASPARTAME INTAKE IN THE 70 KG MAN

CALORIC REQUIREMENT 2500 CAL/DAY

SUCROSE INTAKE (17% OF CALORIES)

<u>CALORIES</u>	<u>SUCROSE</u>	<u>SUCROSE INTAKE</u>	<u>ASPARTAME EQUIVALENT</u>
425	104 GMS	1500 MG/KG	7.5-8.5 MG/KG

TOTAL CARBOHYDRATE INTAKE (50% OF CALORIES)

<u>CALORIES</u>	<u>CARBOHYDRATE</u>	<u>SUCROSE EQUIVALENT</u>	<u>ASPARTAME EQUIVALENT</u>
1250	313 GMS	4470 MG/KG	23-25 MG/KG

of these findings, it is not surprising that normal or heterozygote children born to such mothers are mentally retarded.

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TABLE 2

COMPARISON OF FASTING PLASMA AND ERYTHROCYTE GLUTAMATE AND ASPARTATE LEVELS

<u>AMINO ACID</u>	<u>PLASMA</u>	<u>ERYTHROCYTE</u>
GLUTAMATE	$4.5 \pm 2.7 \mu\text{MOLES/DL}$	$20.2 \pm 7.8 \mu\text{MOLES/DG}$
ASPARTATE	0.3 ± 0.18	22.9 ± 6.0

are noted.

37

TABLE -3

ASPARTAME MONKEY EXPERIMENTS PROGRESS SHEET

Monkey #	Age (Days)	Sex	Species	Weight (g)	Treatment (Via Stomach Tube)	Processing	Hypothalamus Sections Comments	Perfusion Comments	Perfusion Date
PARTAME ONLY:									
740 A-1)	22	♂	<u>M. mulatta</u>	530	2 g APH/kg	samples from 2 blocks; 57 slides	good fix; no lesion, dark staining and large, medium dark staining cells, blebs (photos)	perfusion went very well, brain yellow, no blood	10/15/7
746 A-2)	3	♀	<u>M. arctoides</u>	470	2 g APH/kg	samples from 3 blocks; 113 slides	large dark cells, blebs (photos)	fluorescein eye studies; large blood vessels prominent and red in cerebral cortex; tissue firm but not hard	10/18/7
742 A-3)	8	♀	<u>M. fascicularis</u>	280	2 g APH/kg	in perfusate	none	good perfusion; cerebral cortex surface firm but not yellow	10/22/7
747 A-4)	1	♀	<u>M. arctoides</u>	430	2 g APH/kg	in perfusate	none	good perfusion; cerebral cortex surface firm but not yellow	11/ 4/7
758 A-5)	1 1/2	♀	<u>M. mulatta</u>	370	2 g APH/kg	1 block, 10 slides	fix - decent, very large ventricle, sections rostral to arcuate nucleus so far	went well, intubation via tracheostomy, fix patchy (in spots brain is pink), ventricle quite large, opens far rostral to optic chiasm	11/ 5/7

Sequential blood samples obtained throughout for amino acid analysis

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TABLE 3 (Cont.)

ASPARTAME MONKEY EXPERIMENTS PROGRESS SHEET

Monkey #	Age (Days)	Sex	Species	Weight (g)	Treatment (Via Stomach Tube)	Processing	Hypothalamus Sections Comments	Perfusion Comments	Perfusion Date
ASPARTAME ONLY (Continued):									
2836 (A-12)	5	♀	<u>M. arctoides</u>	500	2 g APM/kg	1 block, 120 micro-slides; color projection slides	bilateral cell disruption in arcuate area, some large dark cells, blebs, cell clusters	went very well, brain yellow and hard	1/1
2830 (A-13)	2	♂	<u>M. arctoides</u>	430	2 g APM/kg	in perfusate	none	brain hard but not all yellow, some areas had blood in superficial vessels	1/2
2859 (A-14)	30	♀	<u>M. mulatta</u>	410	2 g APM/kg	in perfusate	none	brain firm and bloodless	1/3

Sequential blood samples obtained throughout for amino acid analysis

ASPARTAME MONKEY EXPERIMENTS PROGRESS SHEET

Monkey #	Age (Days)	Sex	Species	Weight (g)	Treatment (Via Stomach Tube)	Processing	Hypothalamus Sections Comments	Perfusion Comments	Perfusion Date
ASPARTAME & MSG:									
2823 •(A-6)	1	♂	<u>M. mulatta</u>	460	2 g APM & 1 g MSG/kg	samples from 2 blocks; 100 slides	no lesion, bleb	cyanotic episode, vomiting, 12/ 4 redosing; probably died before fix administered, fix not very good	
2796 •(A-7)	1	♂	<u>M. arctoides</u>	460	2 g APM & 1 g MSG/kg	samples from 2 blocks; 114 slides	no lesion, nuclei clustered in homogeneous matrices, cell clusters, multiple cell types in large bleb underlaid with blood vessels	dehydrated (blood fluid not replaced); good perfusion	12/11
2822 •(A-8)	2	♀	<u>M. arctoides</u>	380	2 g APM & 1 g MSG/kg	in perfusate	none	very good perfusion, no blood fluid replacement; plasma orange before dosing, later noticed white precipitate in it; brain nice and yellow with no blood on surface	1/1/ 2
2832 •(A-9)	2	♀	<u>M. mulatta</u>	370	2 g APM & 1 g MSG/kg	in perfusate	none	resuscitated severely depressed infant, perfused with old fixative 1 1/2 hours after dosing	1/1/
2831 •(A-10)	3	♂	<u>M. mulatta</u>	380	2 g APM & 1 g MSG/kg	in plastic blocks	none	good perfusion but brain not 1/ 3, as yellow as would like but uniformly firm and bloodless	

Sequential blood samples obtained throughout for amino acid analysis

gastric emptying--absorption rates leading to a variety of blood response curves.

Plasma phenylalanine levels for both groups of animals are found in Figure 27. Again, variability in the absorption curves is noted, with phenylalanine levels

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TABLE 4 (Cont.)
ASPARTAME MONKEY EXPERIMENTS PROGRESS SHEET

Monkey #	Age (Days)	Sex	Species	Weight (g)	Treatment (Via Stomach Tube)	Processing	Hypothalamus Sections Comments	Perfusion Comments	Perfusion Date
ASPARTAME & MSG (Continued):									
2835 *(A-11)	1	♀	M. mulatta	422	2 g APH & 1 g MSG/kg	in plastic blocks	none	poor perfusion; saline didn't flow well; unilateral perfusion, right hemisphere hard and yellow, left soft, blood in meninges, pink ex- tends toward hypothalamus; ventricle located extra- ordinarily "high"	1/ 8,

* Sequential blood samples obtained throughout for amino acid analysis

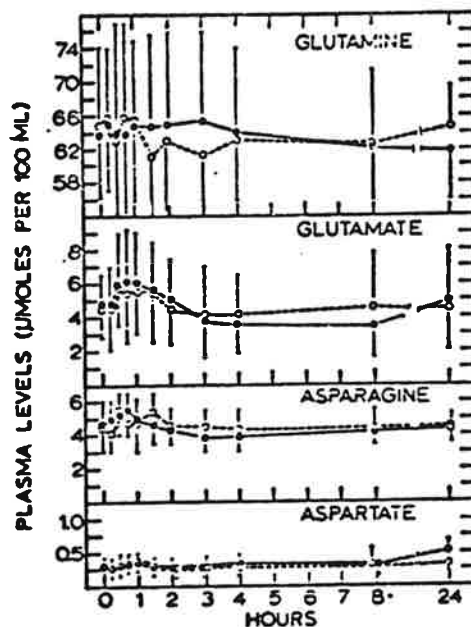


Figure 1: Plasma glutamine, glutamate, asparagine and aspartate levels in normal adult volunteers administered 34 mg ASPARTAME (0—0) or 13 mg aspartate (0==0) per kg body weight.

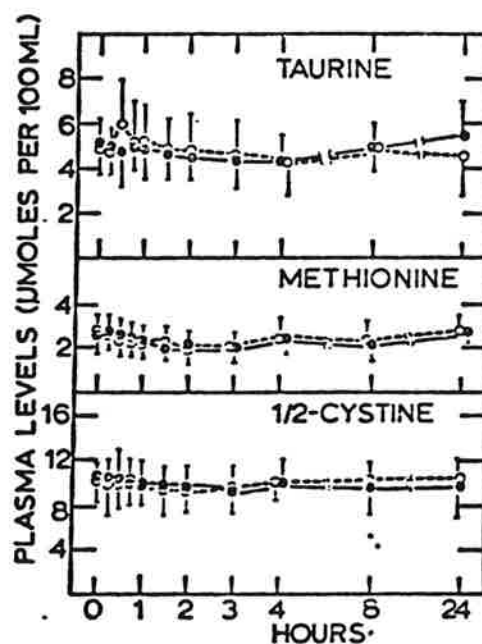


Figure 2: Plasma taurine, methionine and cystine levels in normal adult volunteers administered 34 mg ASPARTAME (—○—) or 13 mg aspartate (---○---) per kg body weight.

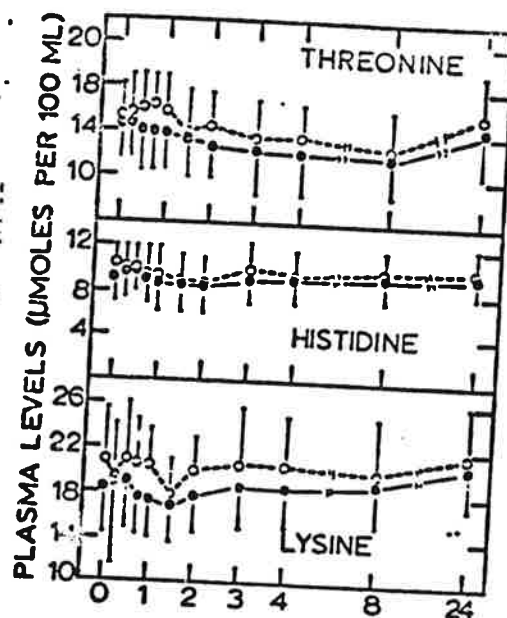


Figure 3: Plasma threonine, histidine and lysine levels in normal adult volunteers administered 34 mg ASPARTAME (○—○) or 13 mg aspartate (●—●) per kg body weight.

FIGURE 16 Plasma phenylalanine response noted to Aspartame loading at:

—●— 200 mg/kg solution

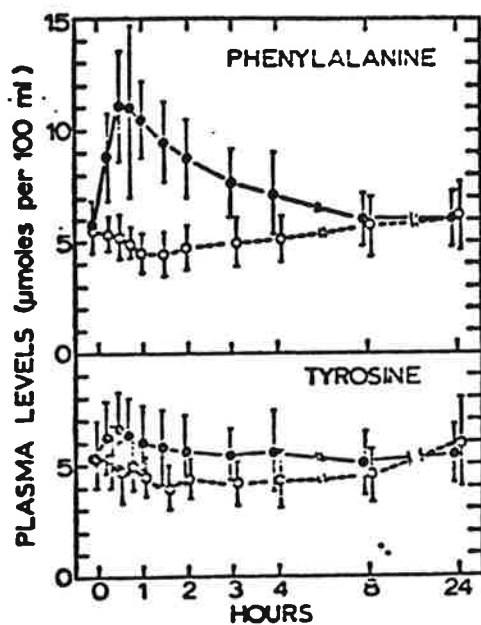


Figure 7: Plasma tyrosine and phenylalanine levels in normal volunteers administered 34 mg ASPARTAME (O—O) or 13 mg aspartate (O---O) per kg body weight.

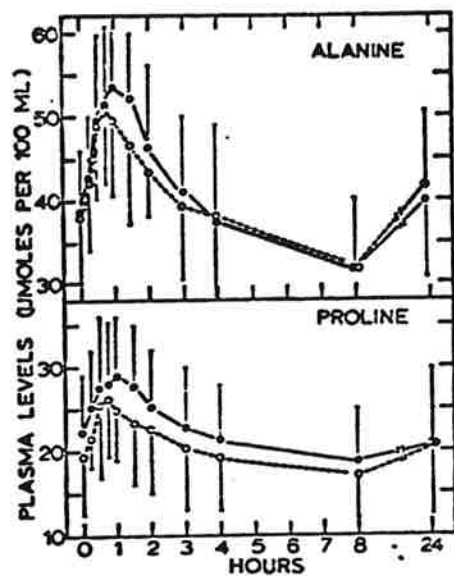


Figure 6: Plasma alanine and proline levels in normal adult volunteers administered 34 mg ASPARTATE (○—○) or 13 mg aspartate (●—●) per kg body weight.

LEVELS OF TYROSINE AND PHENYLALANINE IN PLASMA AND RBC (μMOLES/DL)

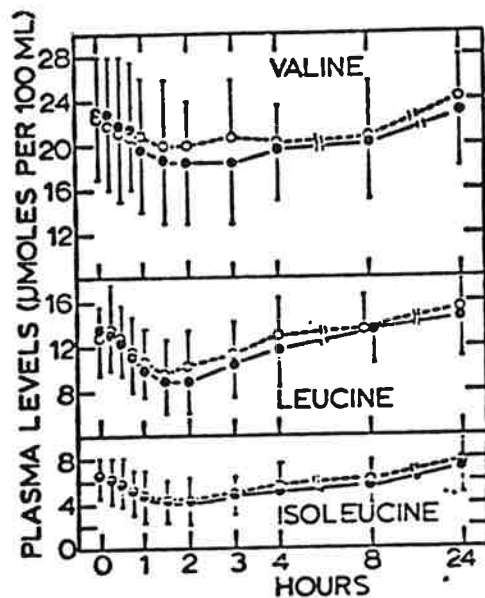


Figure 5: Plasma valine, leucine and isoleucine levels in normal adult volunteers administered 34 mg ASPARTAME (○—○) or 13 mg aspartate (□—□) per kg body weight.

Effect of Aspartame loading at 150 mg/kg body weight on red cell glutamate and aspartate levels. This similar no effect response was noted at all lower doses in which the studies are complete. It

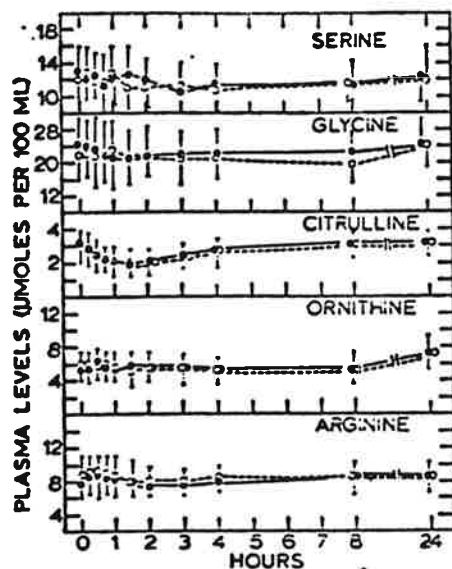


Figure 4: Plasma serine, glycine, citrulline, ornithine and arginine levels in normal adult volunteers administered 34 mg ASPARTAME (●—●) or 13 mg aspartate (○—○) per kg body weight.

FIGURE 17 Plasma tyrosine levels noted in response to Aspartame loading:

- 200 mg/kg
- ▲— 150 mg/kg

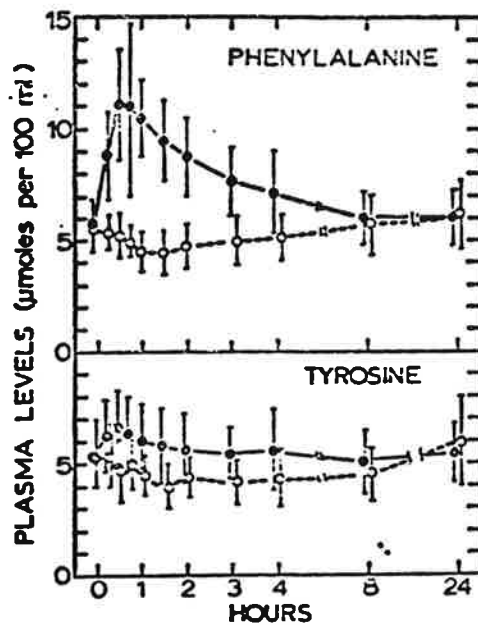


Figure 7: Plasma tyrosine and phenylalanine levels in normal volunteers administered 34 mg ASPARTAME (●—●) or 13 mg aspartate (○---○) per kg body weight.

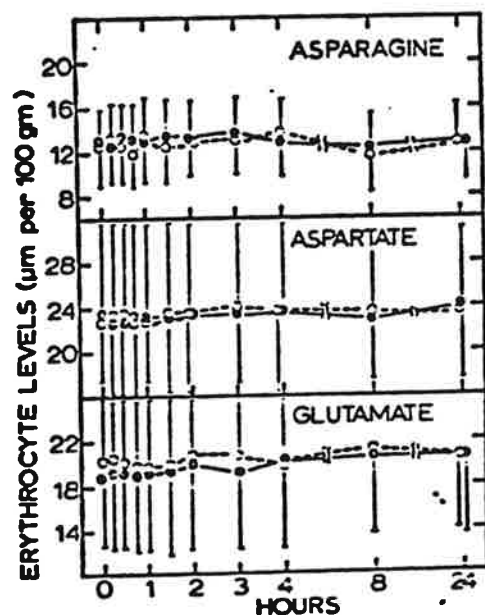


Figure 8: Erythrocyte asparagine, aspartate and glutamate levels in normal adult volunteers administered 34 mg ASPARTAME (0—0) or 13 mg aspartate (0-----0) per kg body weight.

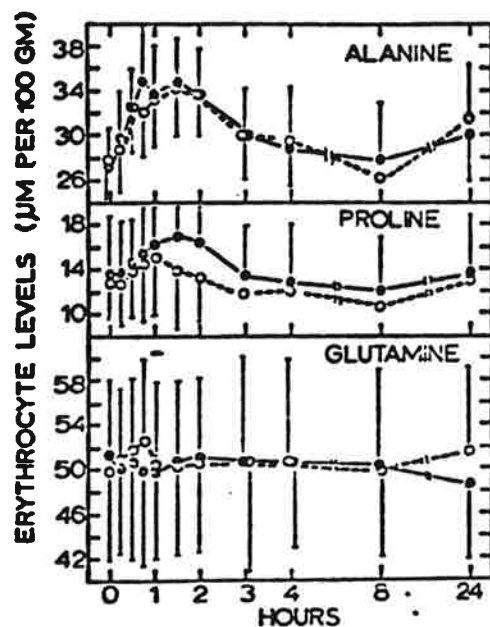


Figure 9: Erythrocyte alanine, proline and glutamine levels in normal adult volunteers administered 34 mg ASPARTAME (●—●) or .13 mg aspartate (○---○) per kg body weight.

FIGURE 21

Effect of Aspartame ingestion on plasma glutamate levels. Aspartame administration at all levels (34, 50, 100, 150 and 300 mg/kg) had no significant effect on plasma glutamate levels.

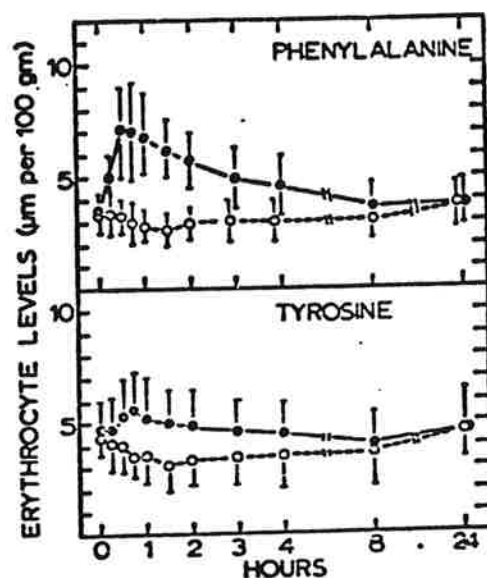
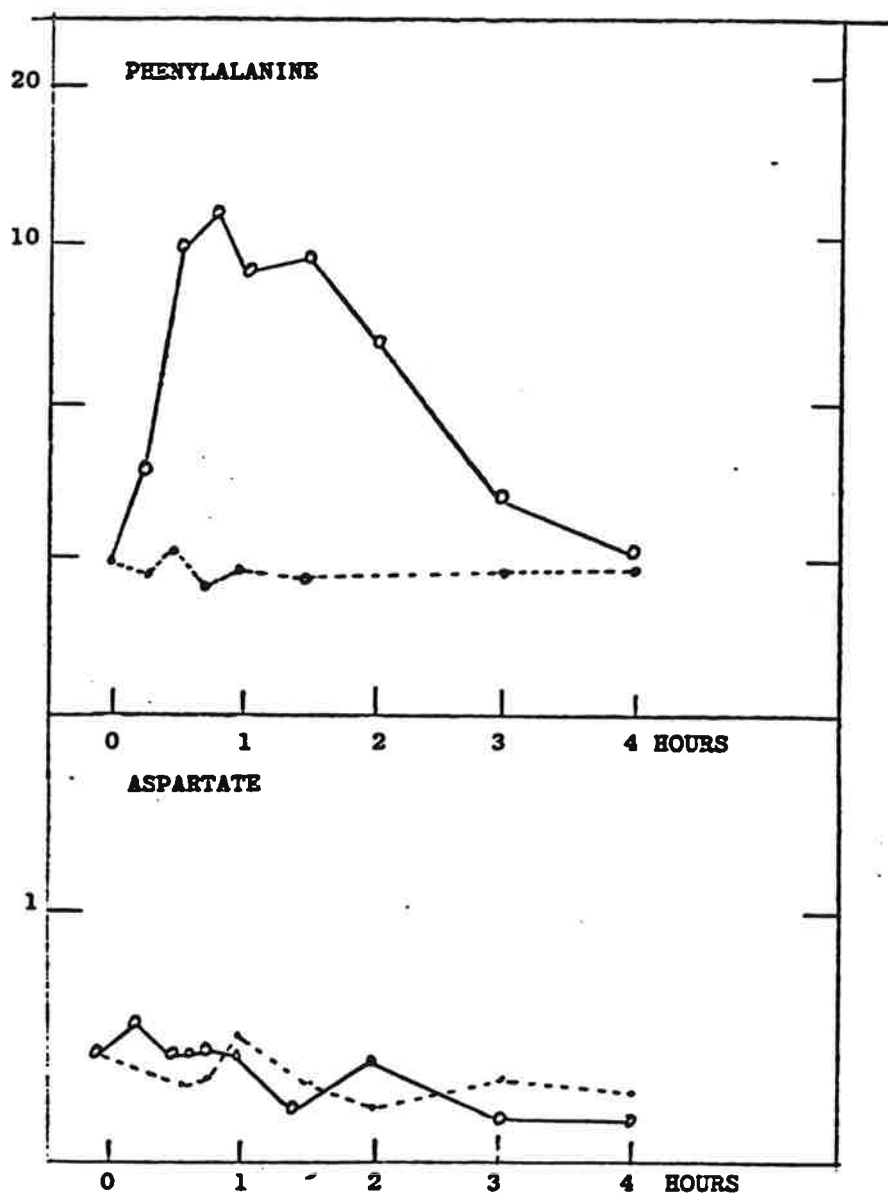


Figure 10: Erythrocyte phenylalanine and tyrosine levels in normal adult volunteers administered 34 mg ASPARTAME (●—●) or 13 mg aspartate (○----○) per kg body weight.

FIGURE 22 EFFECT OF ASPARTAME LOADING UPON BLOOD METHANOL LEVELS IN NORMAL ADULT VOLUNTEERS.

FIGURE 11 Effect of Aspartame (o—o) or lactose (— — —) administration at 50 mg/kg upon plasma phenylalanine and aspartate levels in lactating women



PLASMA AMINO ACID LEVELS IN LACTATING WOMEN GIVEN LACTOSE OR ASPARTAME (μMOLES/DL)

Figure 23: Plasma amino acid levels in maternal and fetal circulation of pregnant primate infused with aspartate for 1 hour at 0.1 or 0.2 gm/kg body weight. Note the difference in scale for fetal and maternal plasma levels

FIGURE 12 Effect of Aspartame (o-----o) or lactose loading (---) upon breast milk phenylalanine and aspartate levels when given at 50 mg/kg body weight. (x---x) shows values in previous study for lactating women receiving lactose. (13).

NOTE: The values at 8 and 12 hours represent the influence of normal meals upon breast milk levels. Subjects fasted only for first 4 hours and then were allowed to eat their regular diet. Thus the values at 8 and 12 hours represent normal postprandial breast milk levels. The 24 hour value is after overnight fast.

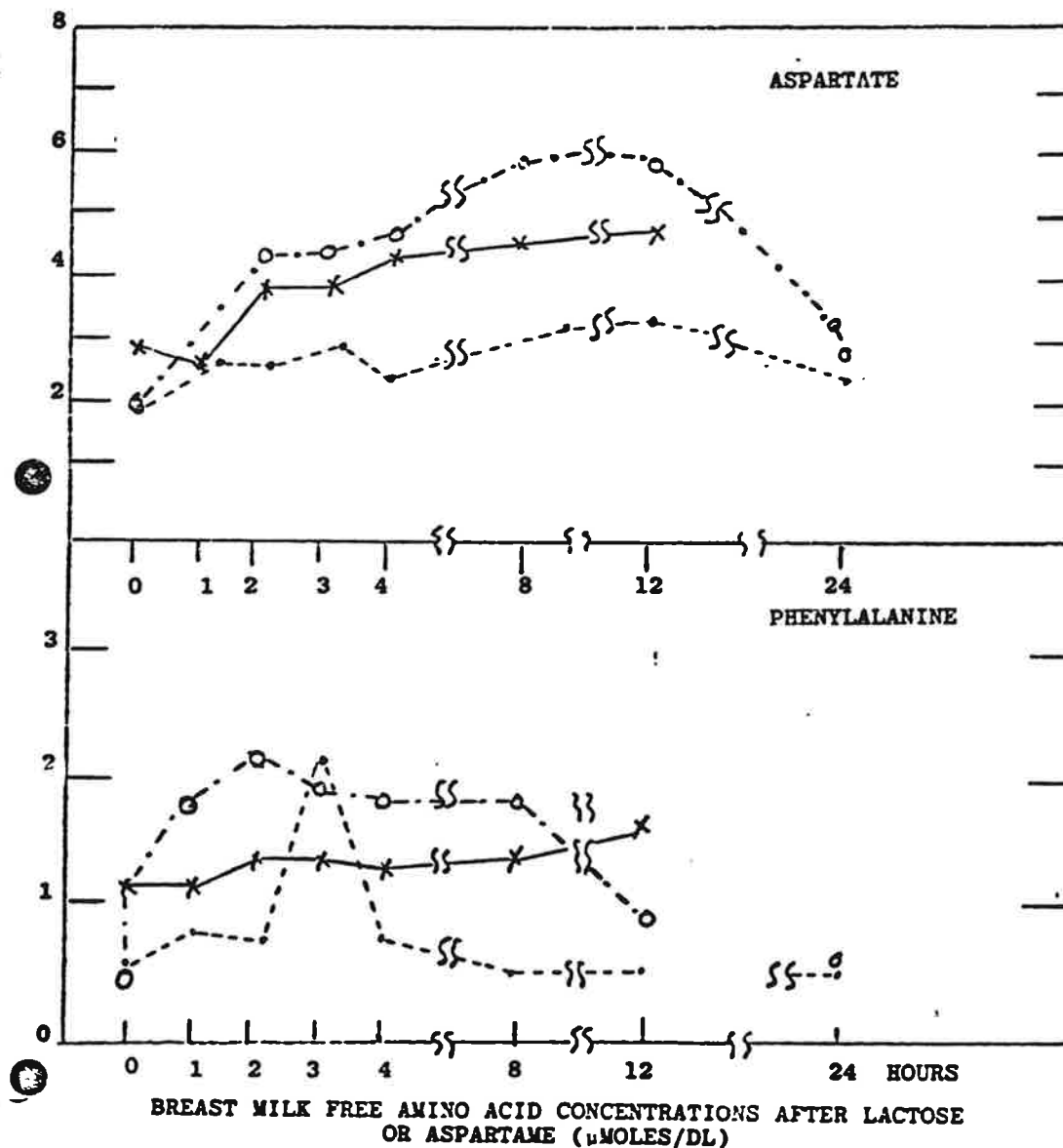


Figure 24: Plasma amino acid levels in maternal and fetal circulation of pregnant primates infused with aspartate at 0.4 g/kg over the course of 1 hour.

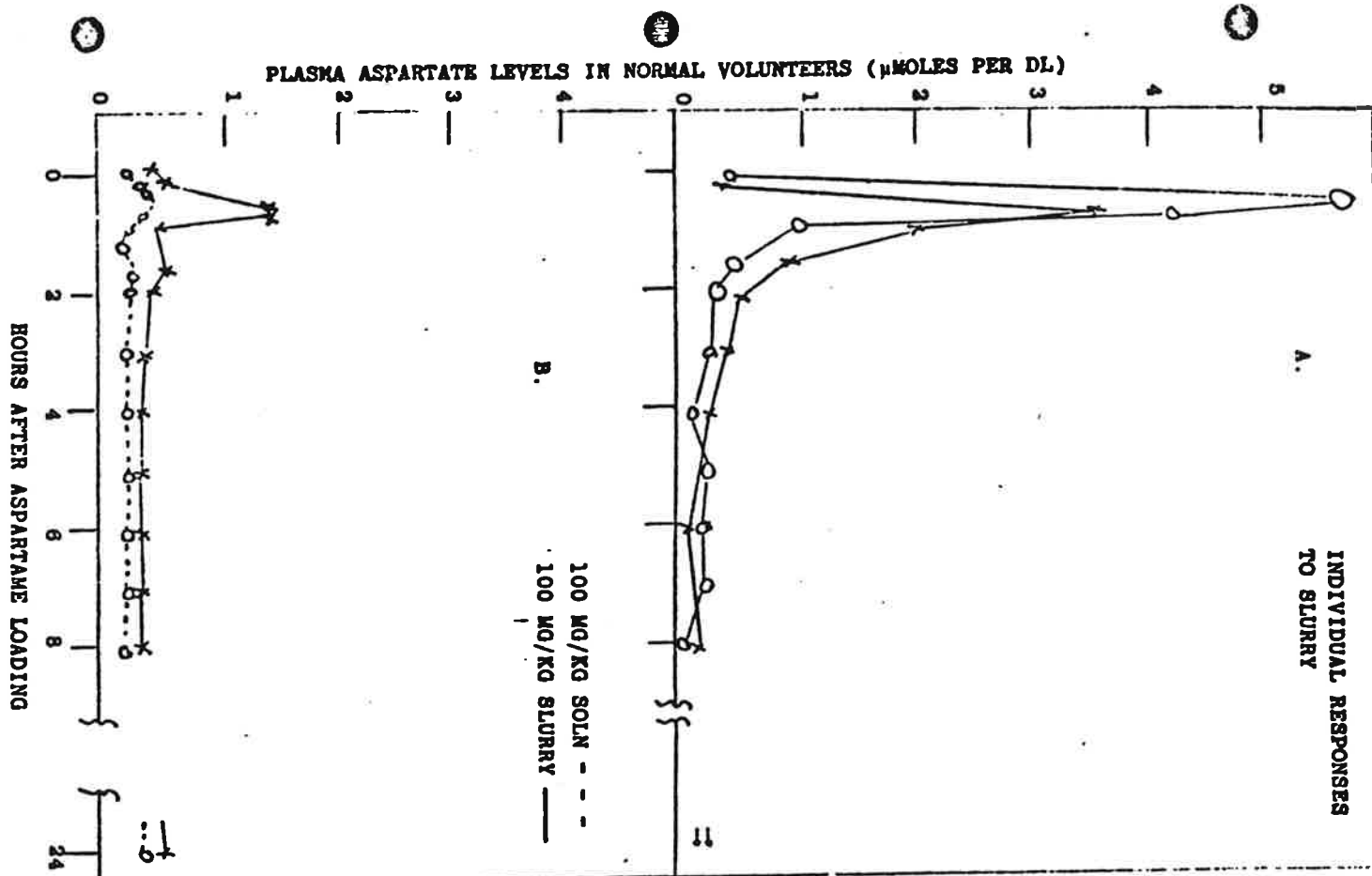


FIGURE 13 A) Variation in individual subjects plasma aspartate levels after Aspartame ingestion at 100 mg/kg in slurry form. Note that the 4 individuals studied had curves similar to those shown for Aspartame ingestion at 100 mg/kg in solution as shown in part B below (o - - o) curve.)
 B) Comparison of plasma aspartate levels of 6 individuals given Aspartame at 100 mg/kg either in solution (o - - -o curve) or in slurry (x—x curve). The difference in response is due to two individuals shown in part A (above) who had rapid gastric emptying in the slurry part of the test.

Figure 25: Plasma glutamate and aspartate levels in neonatal primates administered ASPARTAME at 2 gm/kg.
 See Table 3 for a listing of the primates studied

FIGURE 14 Plasma phenylalanine levels in normal volunteers administered Aspartame as a slurry at 100 mg/kg body weight. The response of the 6 subjects studied... divided nicely into 3 groups of two subjects each. The first group had rapid gastric emptying (solid line), with a rapid peak in phenylalanine levels. The second group (dashed line) had our usual response, and were identical to subjects receiving Aspartame in 500 ml solution. The third group had a delayed gastric emptying time (dotted line), and phenylalanine levels rose more slowly and the peak was lower and broader.

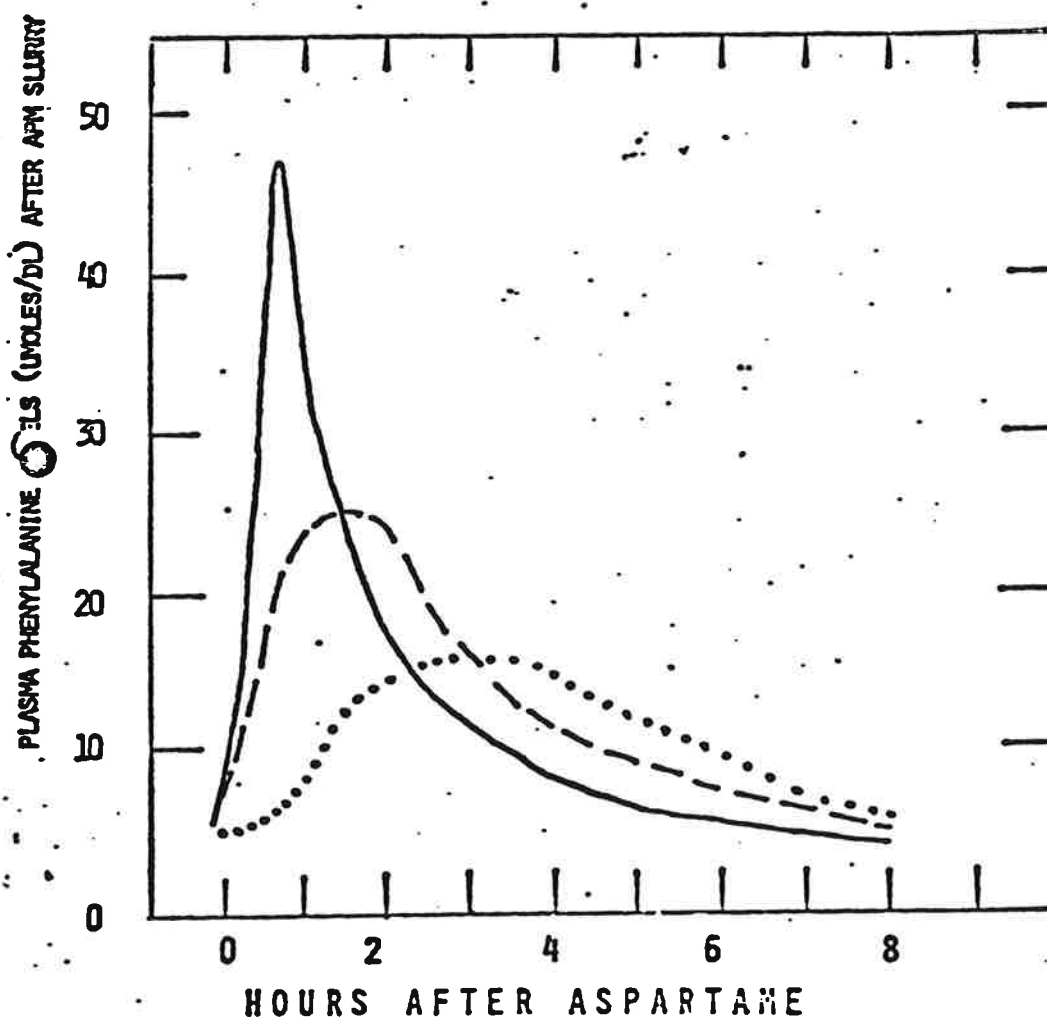
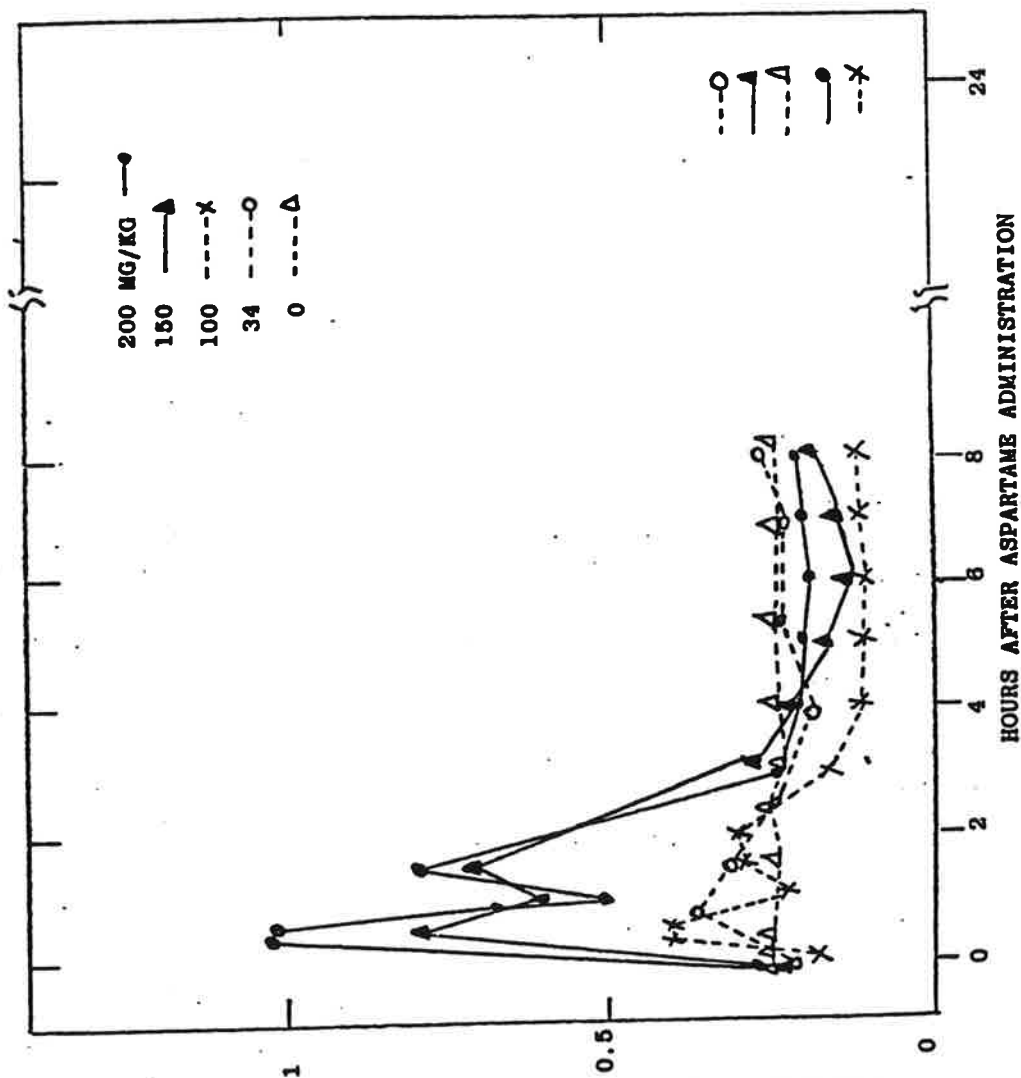


Figure 26: Plasma glutamate and aspartate levels in neonatal primates administered ASPARTAME (2 gm/kg) plus glutamate (1 gm/kg). See Table 4 for a listing of the animals studied.



PLASMA ASPARTATE LEVELS IN NORMAL VOLUNTEERS (µMOLES/DL)

FIGURE 15 Plasma aspartate levels in normal volunteers administered Aspartame at the dose levels shown in orange juice solution. Please note: Because of the accuracy of the Beckman 121M analyzer, small differences in plasma aspartate levels are found, and are shown on the scale shown. All levels observed are below those noted postprandially in young infants fed formula diets (2.5 ± 1.5 µmoles/dl).

FIGURE 16 Plasma phenylalanine response noted to Aspartame loading at:

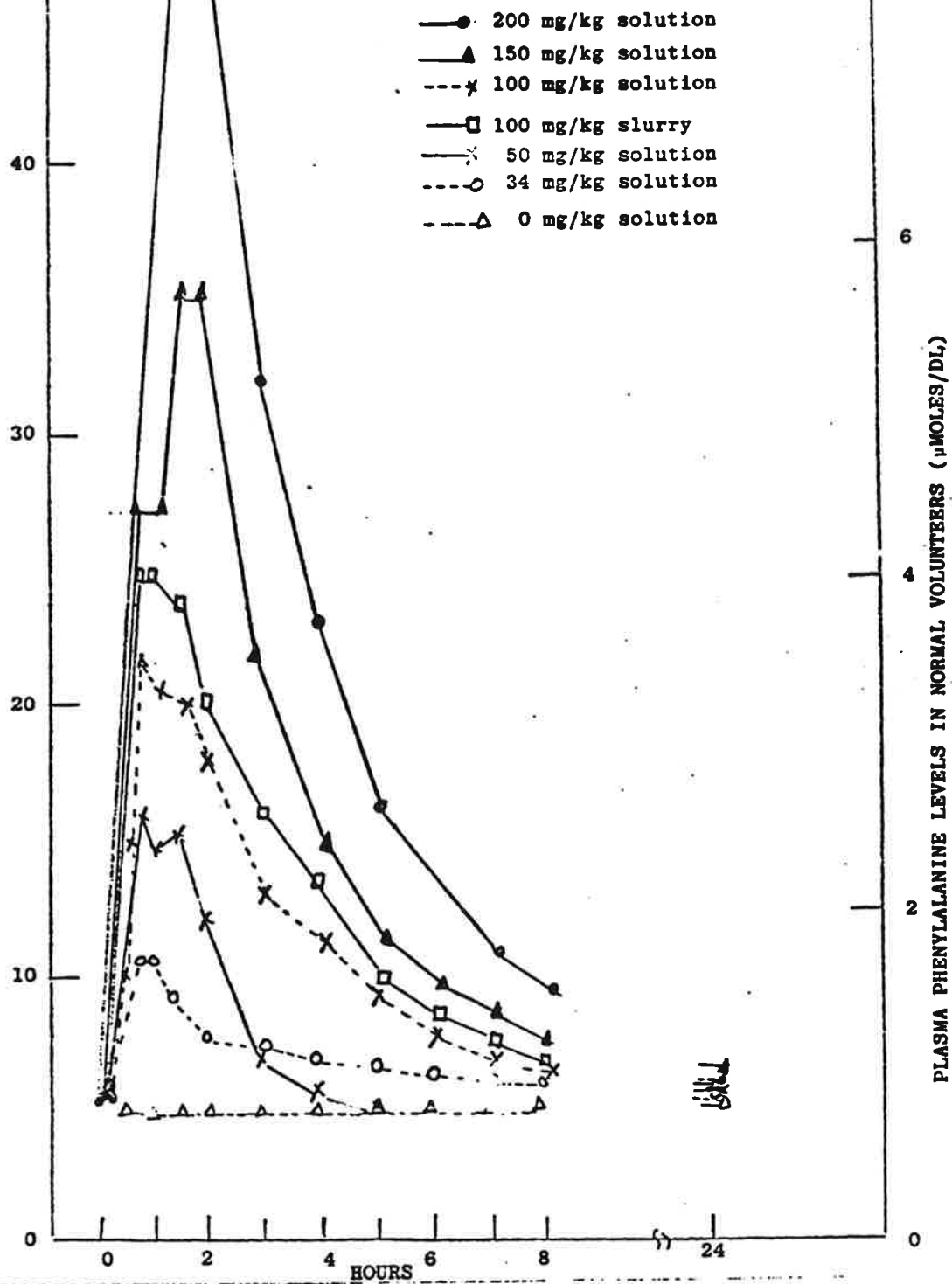
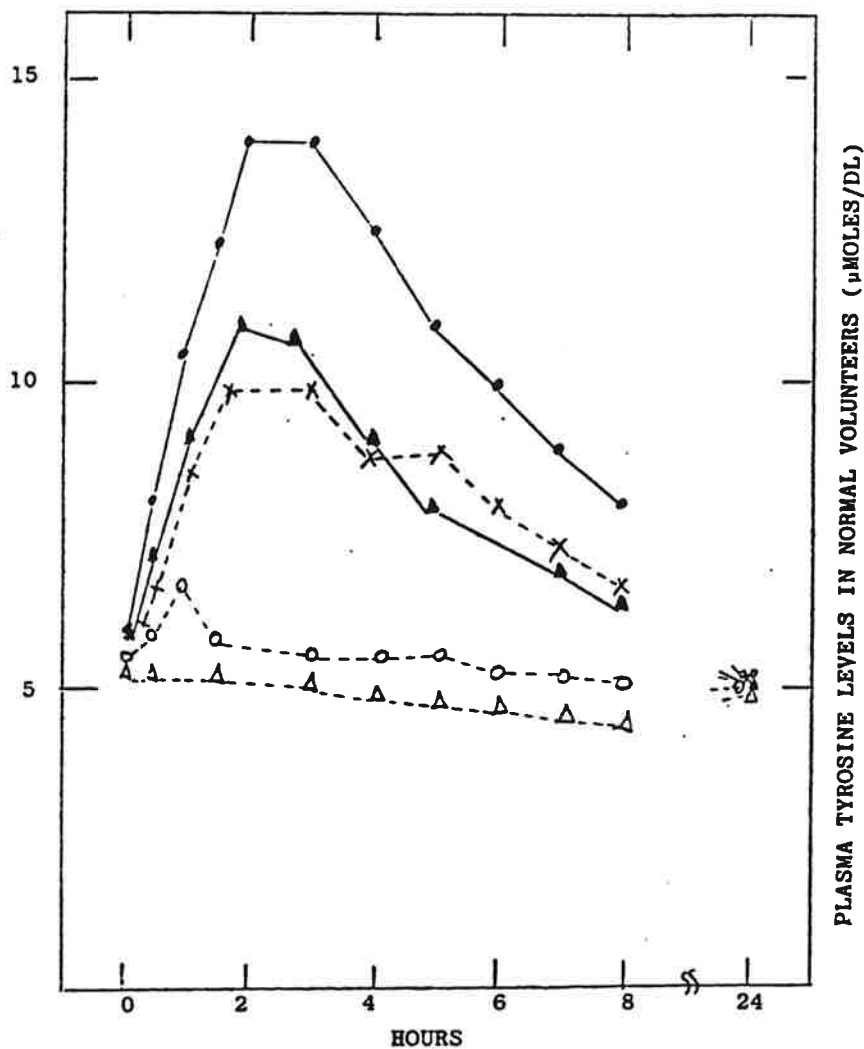


FIGURE 17 Plasma tyrosine levels noted in response to Aspartame loading:

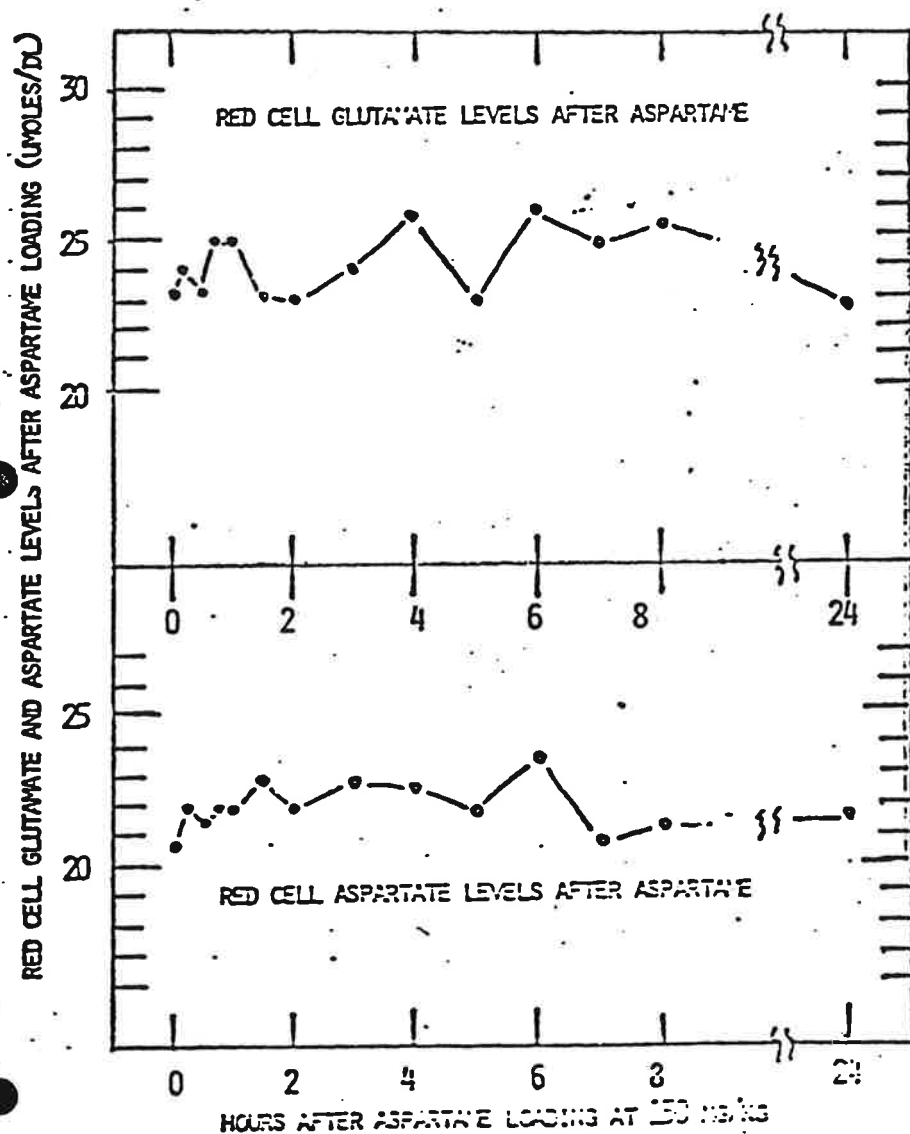
- 200 mg/kg
- ▲— 150 mg/kg
- x--- 100 mg/kg
- 34 mg/kg
- △--- 0 mg/kg



RED CELL GLUTAMATE AND ASPARTATE LEVELS AFTER ASPARTAME LOADING (μMOLES/DL)

Effect of Aspartame loading at 150 mg/kg body weight on red cell glutamate and aspartate levels. This similar no effect response was noted at all lower doses in which the studies are complete. It also appears that similar results are obtained at 200 mg/kg Aspartame loading, although the analytical data are not complete at the moment.

FIGURE 18



LEVELS OF TYROSINE AND PHENYLALANINE IN PLASMA AND RBC (μ MOLES/DL)

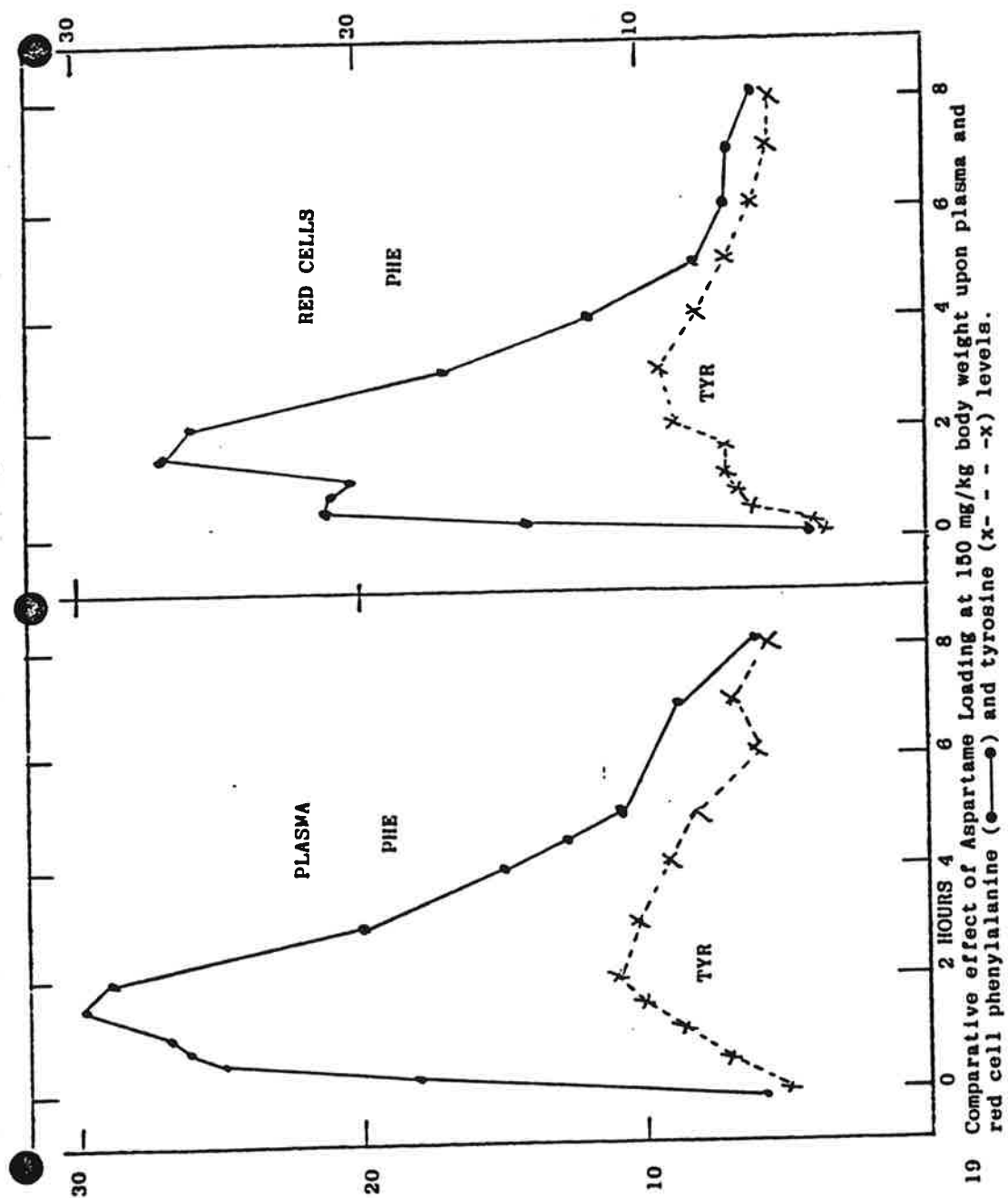


FIGURE 19 Comparative effect of Aspartame Loading at 150 mg/kg body weight upon plasma and red cell phenylalanine (e—e) and tyrosine (x—x) levels.

FIGURE 20: EFFECT OF ASPARTAME LOADING AT 34 MG PER KG UPON PLASMA PHENYLALANINE LEVELS IN IOWA NORMAL SUBJECTS AND PKU HETEROZYGOTES

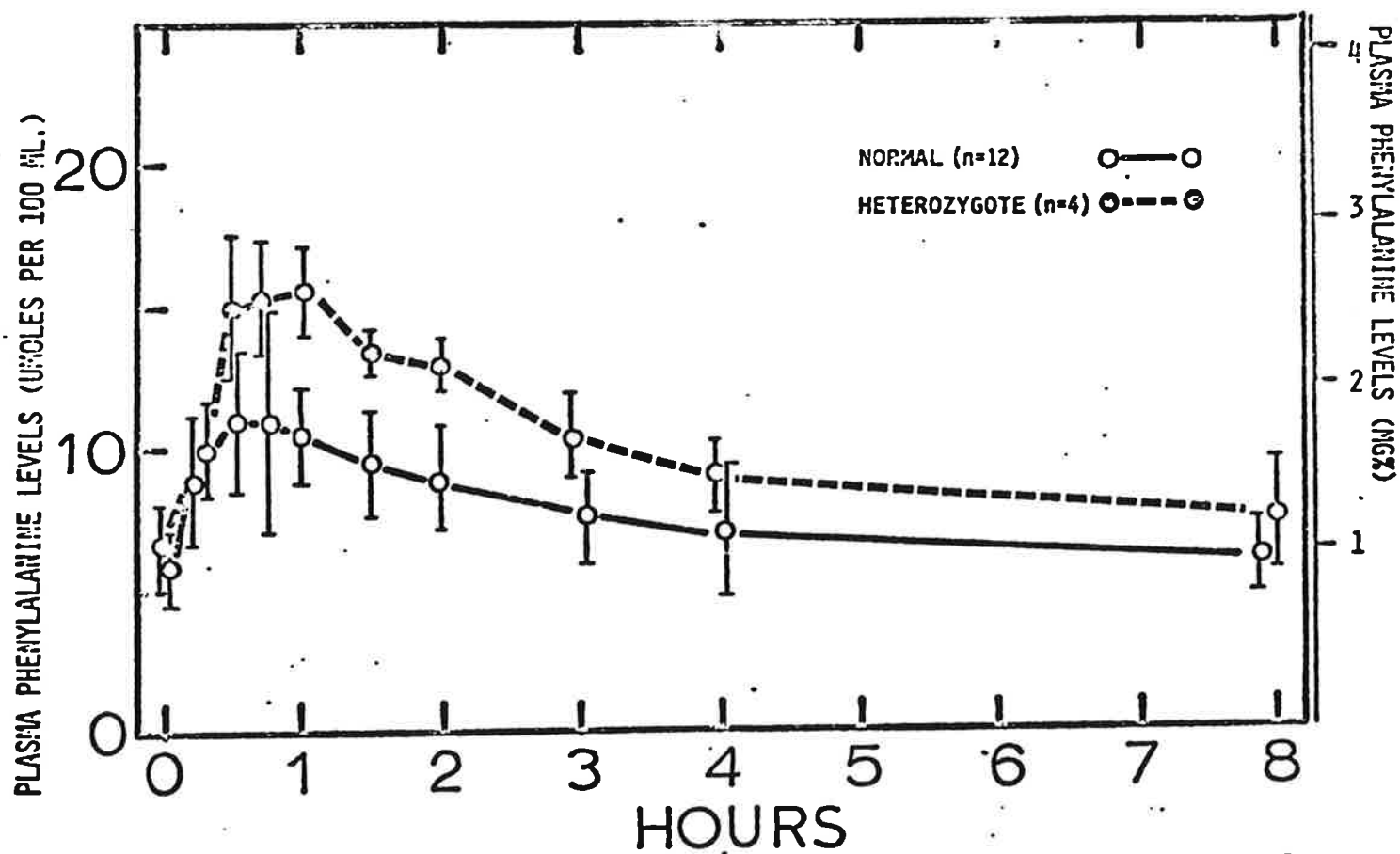


FIGURE 21

Effect of Aspartame ingestion on plasma glutamate levels. Aspartame administration at all levels (25, 50, 100, 150 and 200 mg/kg) had an identical effect on plasma glutamate levels as shown by the \circ — \circ curve. A small nearly identical rise in glutamate was noted in each case. However, no dose related effect was noted. Similar results after lactose ingestion are shown in the control curve (x—x).

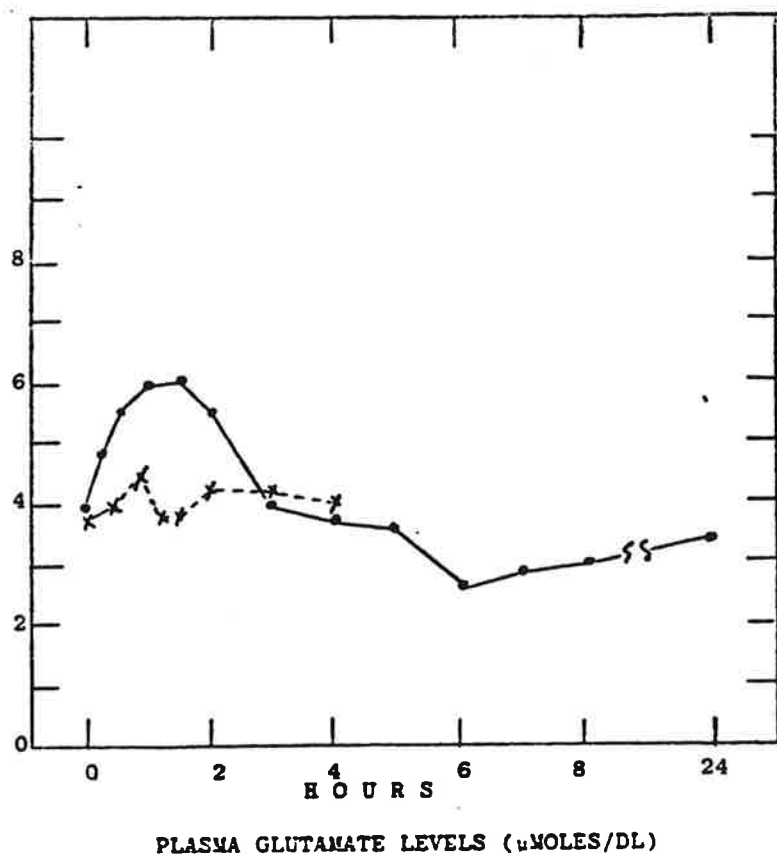


FIGURE 22 EFFECT OF ASPARTAME LOADING UPON BLOOD METHANOL LEVELS IN NORMAL ADULT VOLUNTEERS.

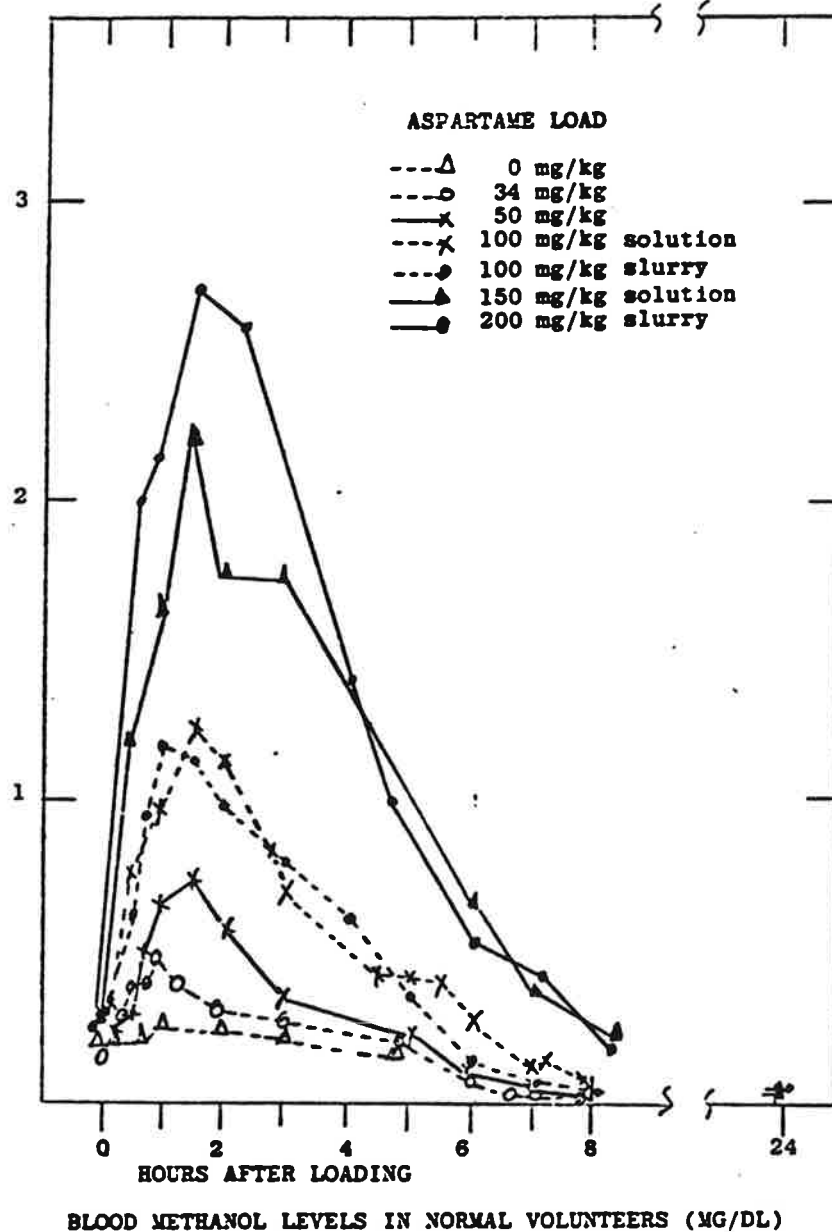
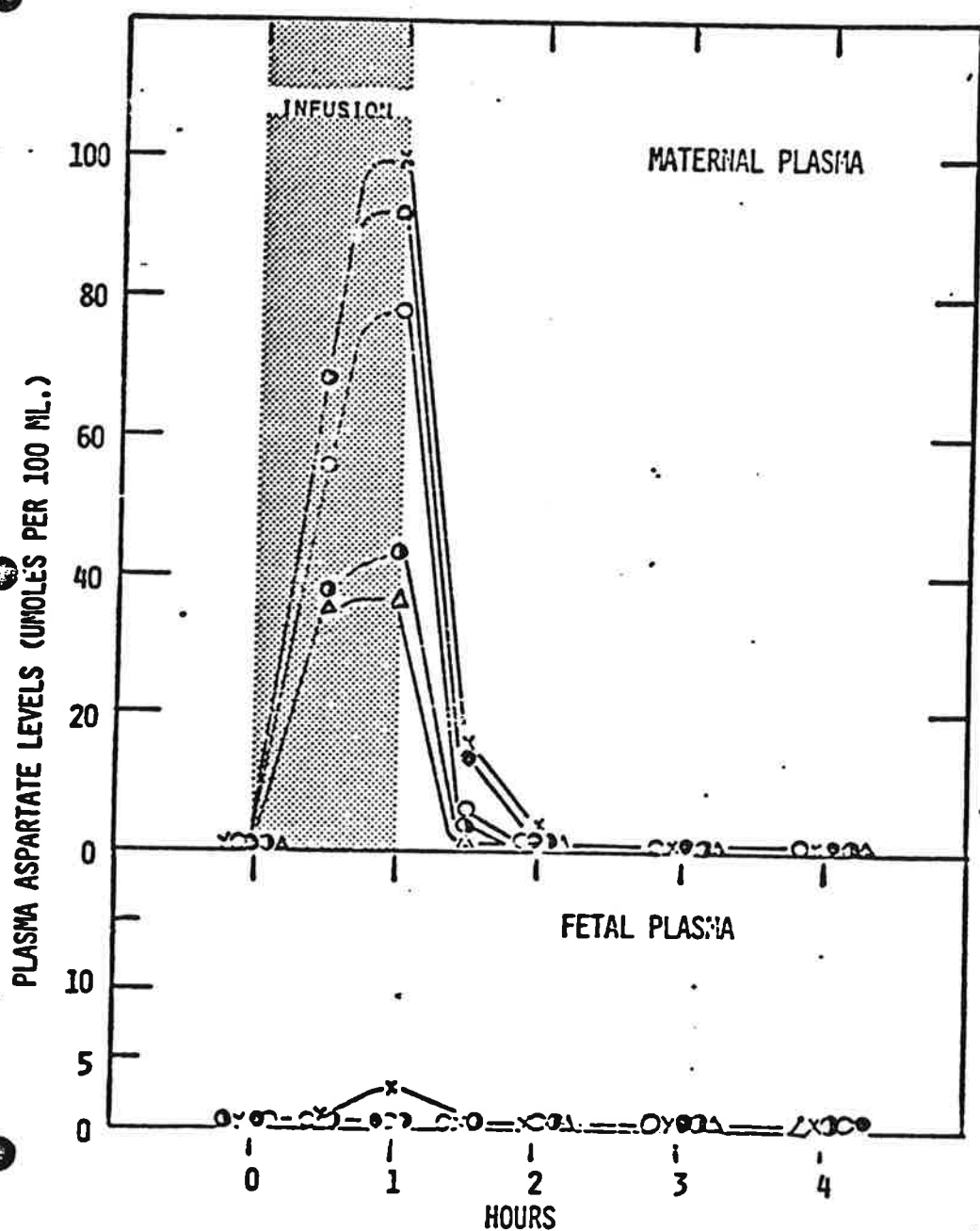


Figure 23: Plasma amino acid levels in maternal and fetal circulation of pregnant primate infused with aspartate for 1 hour at 0.1 or 0.2 gm/kg body weight. Note the difference in scale for fetal and maternal plasma levels



PLASMA ASPARTATE LEVELS (µMOLES PER 100 ML.)

Figure 24: Plasma amino acid levels in maternal and fetal circulation of pregnant primates infused with aspartate at 0.4 gm/kg over the course of 1 hour.

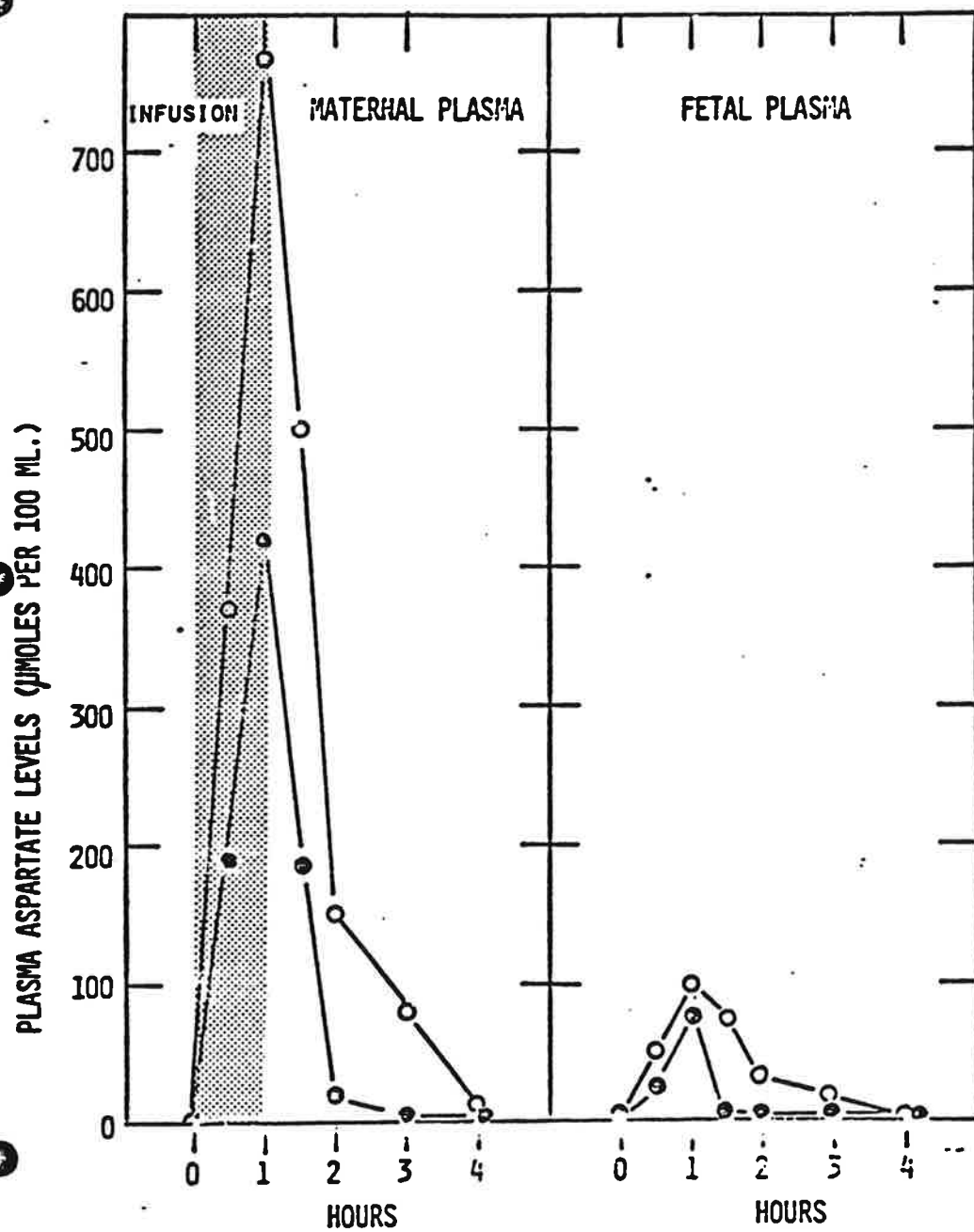


Figure 25: Plasma glutamate and aspartate levels in neonatal primates administered ASPARTAME at 2 gm/kg.
See Table 3 for a listing of the primates studied

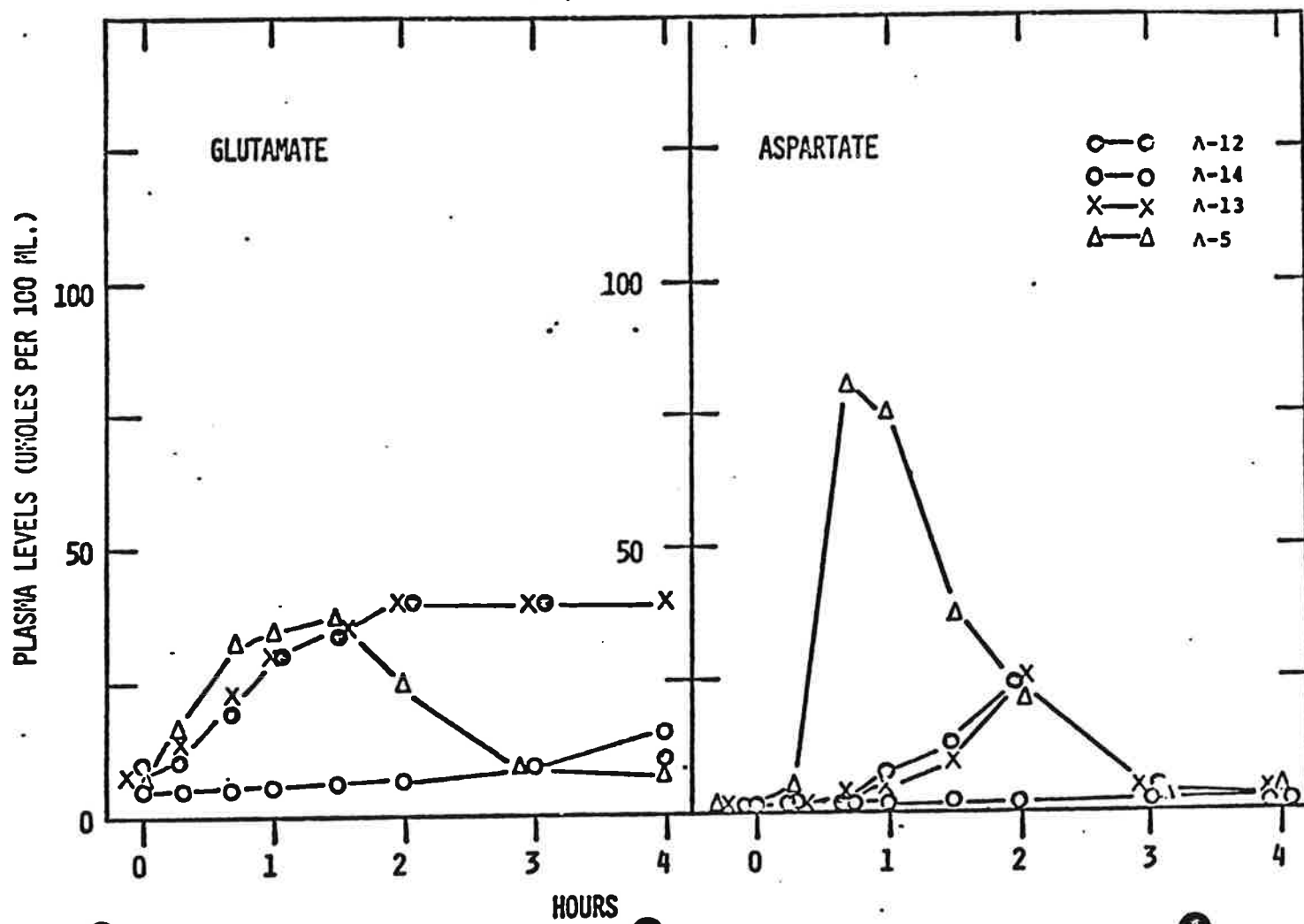
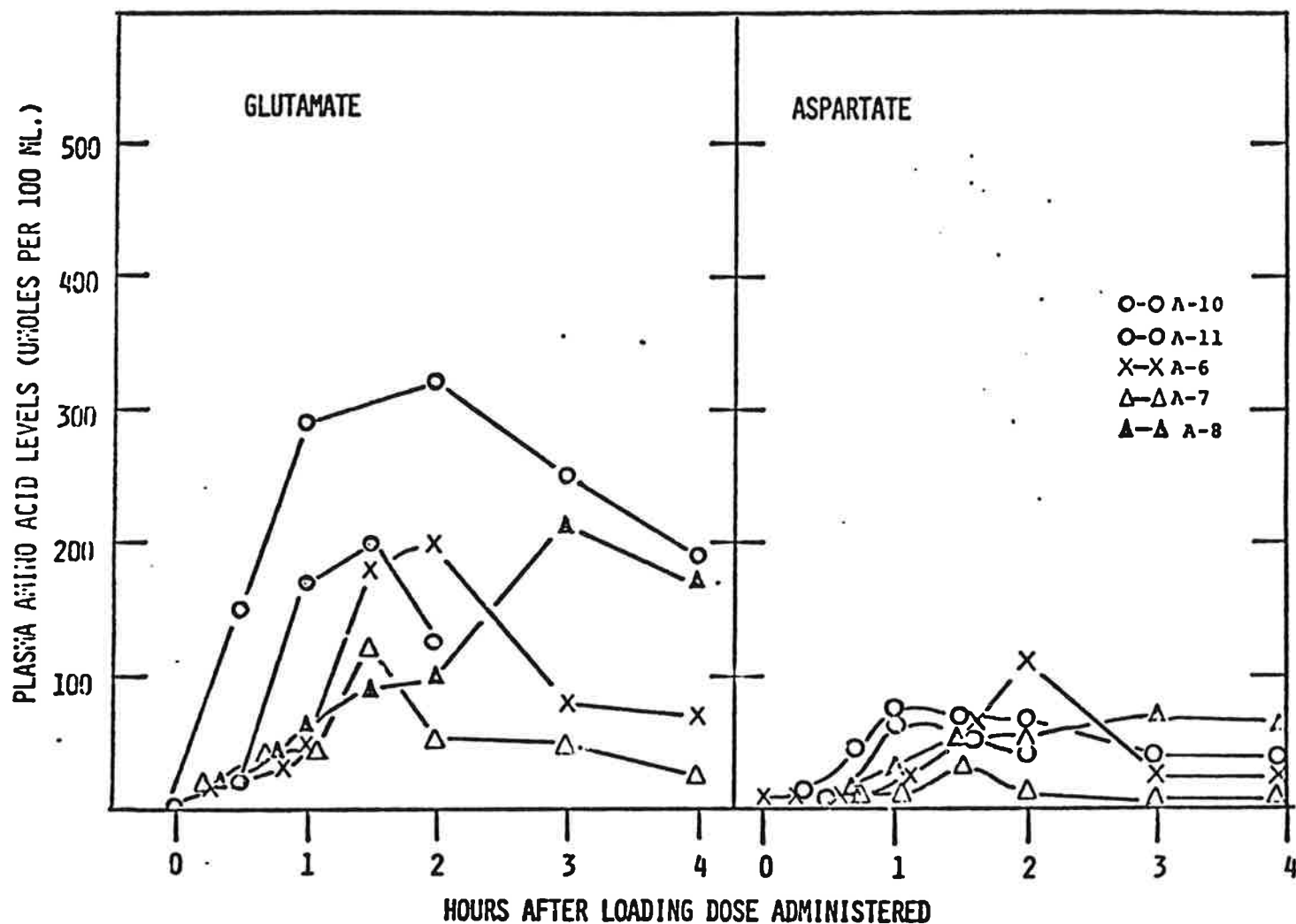
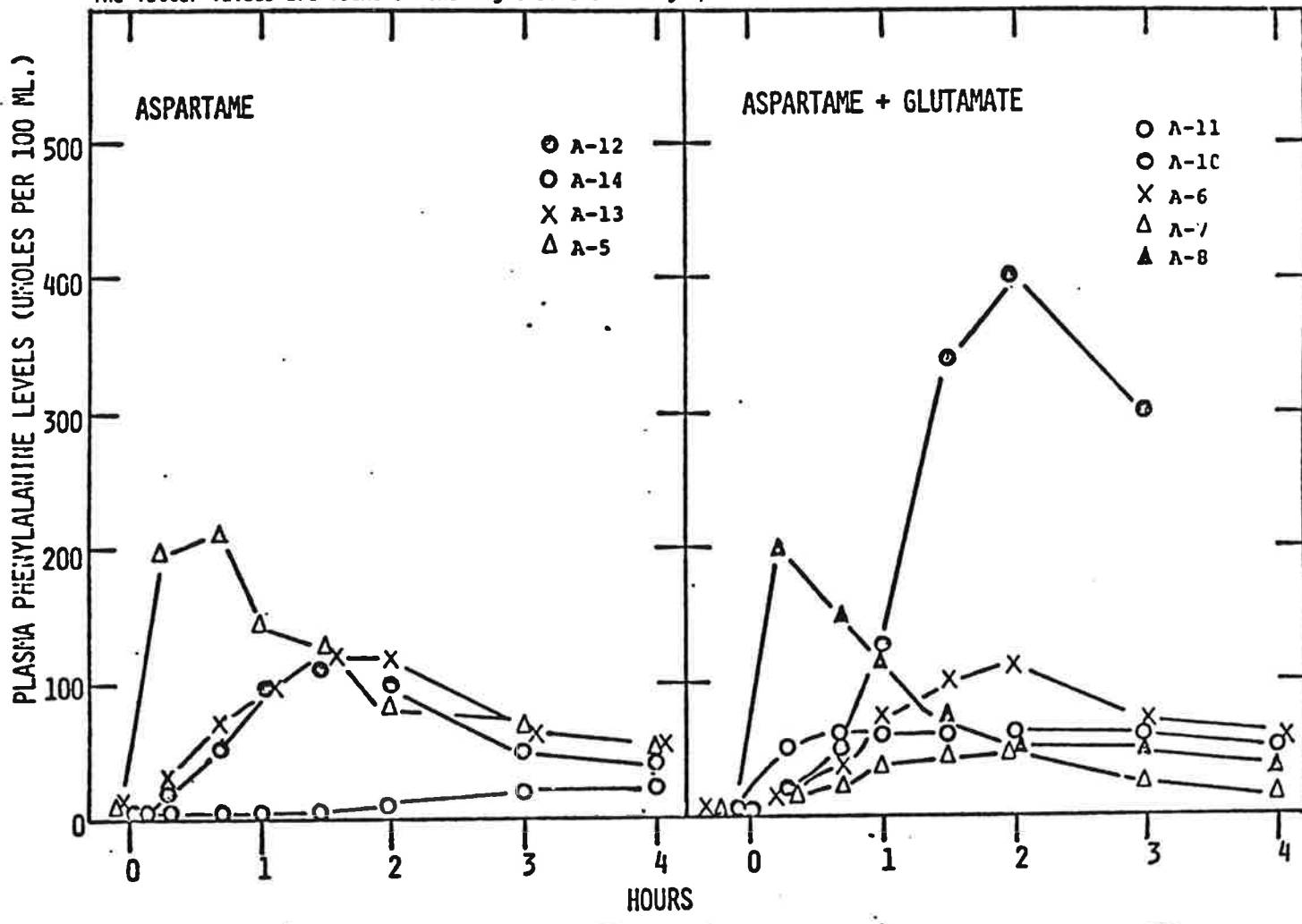


Figure 26: Plasma glutamate and aspartate levels in neonatal primates administered ASPARTAME (2 gm/kg) plus glutamate (1 gm/kg). See Table 4 for a listing of the animals studied.



E91

Figure 27: Plasma phenylalanine levels in neonatal primates administered ASPARTAME (2 gm/kg) found on the left side of the graph and those primates administered ASPARTAME (2 gm/kg) plus glutamate (1 gm/kg). The latter values are found on the right side of the graph. See Tables 3 & 4 for other details.



APPENDIX 1

CALCULATIONS OF GLUTAMATE, ASPARTATE, PHENYLALANINE AND TYROSINE
INTAKE IN HUMAN BREAST-FED INFANTS

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Exhibit 2 Plasma amino acid levels in normal subjects administered aspartate at 13 mg/kg.

2A

ASPA AMINO ACIDS, DOSE = 13 4 SUBJECTS = 12

45 (1981) 0.0 0.25 0.50 0.75 1.00 1.25 2.50 3.00 4.00 5.00 6.00 7.00

BASIC DATA USED IN MAKING THE CALCULATIONS AND REFERENCESBREAST MILK INTAKE IN HUMAN INFANTS (1)

3.5 Kg infant ingests a mean volume of 600 ml/day, with the 90% confidence limits being 400-800 ml/day.

5.5 Kg infant ingests a mean volume of 850 ml/day, with the 90% confidence limits being 700-1000 ml/day.

FREE AMINO ACID CONTENT OF HUMAN BREAST MILK (2)

Glutamate	150 umoles/dl	22 mg%
Aspartate	5 umoles/dl	0.67 mg%
Phenylalanine	1.44 umoles/dl	0.24 mg%
Tyrosine	1.25 umoles/dl	0.23 mg%

AMINO ACID CONTENT IN PROTEIN OF HUMAN BREAST MILK (3)

Total Glutamate*	230 mg%
Total Aspartate**	116 mg%
Corrected Glutamate†	133 mg%
Corrected Aspartate‡	64 mg%
Phenylalanine	48 mg%
Tyrosine	61 mg%

FOOTNOTES

- * Total after hydrolysis, includes glutamine.
- ** Total after hydrolysis, includes asparagine.
- † Corrected using the data of Jukes et al. (4) which indicate that 58% of the total glutamate released from an average protein upon hydrolysis comes from glutamate, while 42% comes from glutamine.
- ‡ Corrected using the data of Jukes et al. (4) which indicate that 55% of the total aspartate released from an average protein upon hydrolysis comes from aspartate while 45% comes from asparagine.

REFERENCES

1. Fomon, S.J. Infant Nutrition, Second Edition. W.B. Saunders, Philadelphia, 1974.
2. Stegink, L.D., Filer, L.J., Jr., and Baker, G.L. Proc. Soc. Exptl. Biol. Med., 140:836-841 (1972).
3. Macy, I.G., and Kelly, H.J. Human Milk and Cow's Milk in Infant Nutrition. In: Milk: The Mammary Gland and Its Secretion. (S. Kon and A.T. Cowie, editors), Vol. II, Chapter 13. New York, Academic Press, 1961, p. 265.
4. Jukes, T.H., Holmquist, R., and Moise, H. Science, July:50-51 (1975).

GLUTAMATE AND ASPARTATE INTAKE IN BREAST-FED INFANTS

BREAST MILK INTAKE

<u>INFANT SIZE</u>	<u>MEAN</u>	<u>RANGE</u>
	<u>ml/kg/dy</u>	
3.5 Kg	171	114-228
5.5 Kg	154	127-200

FREE GLUTAMATE INTAKE

<u>INFANT SIZE</u>	<u>TOTAL DAILY INTAKE</u>		<u>INTAKE PER MEAL (6/DAY)</u>	
	<u>MEAN</u>	<u>RANGE</u>	<u>MEAN</u>	<u>RANGE</u>
	<u>mg/kg</u>		<u>mg/kg</u>	
3.5 Kg	38	25-50	6.5	5-10
5.5 Kg	34	28-44	5.7	4.7-7.4

FREE ASPARTATE INTAKE

<u>INFANT SIZE</u>	<u>TOTAL DAILY INTAKE</u>		<u>INTAKE PER MEAL (6/DAY)</u>	
	<u>MEAN</u>	<u>RANGE</u>	<u>MEAN</u>	<u>RANGE</u>
	<u>mg/kg</u>		<u>mg/kg</u>	
3.5 Kg	1.15	0.76-1.52	0.19	0.13-0.25
5.5 Kg	1.03	0.85-1.34	0.17	0.14-0.22

TOTAL PROTEIN BOUND GLUTAMATE INTAKE

<u>INFANT SIZE</u>	<u>TOTAL DAILY INTAKE</u>		<u>INTAKE PER MEAL (6/DAY)</u>	
	<u>MEAN</u>	<u>RANGE</u>	<u>MEAN</u>	<u>RANGE</u>
	<u>mg/kg</u>		<u>mg/kg</u>	
3.5 Kg	393	262-524	65.5	44-87
5.5 Kg	354	292-460	59	49-77

TOTAL PROTEIN BOUND ASPARTATE INTAKE

<u>INFANT SIZE</u>	<u>TOTAL DAILY INTAKE</u>		<u>INTAKE PER MEAL (6/DAY)</u>	
	<u>MEAN</u>	<u>RANGE</u>	<u>MEAN</u>	<u>RANGE</u>
	<u>mg/kg</u>		<u>mg/kg</u>	
3.5 Kg	198	132-264	33	22-44
5.5 Kg	178	147-232	30	24.5-38.7

CORRECTED GLUTAMATE INTAKE--PROTEIN BOUND

<u>INFANT SIZE</u>	<u>TOTAL DAILY INTAKE</u>		<u>INTAKE PER MEAL (6/DAY)</u>	
	<u>MEAN</u>	<u>RANGE</u>	<u>MEAN</u>	<u>RANGE</u>
	<u>mg/kg</u>		<u>mg/kg</u>	
3.5 Kg	227	151-303	38	25-50.5
5.5 Kg	204	169-266	34	28-44

Exhibit 2 (cont.) Plasma amino acid levels in normal subjects administered aspartate at 13 mg/kg.

ASMA AMINO ACIDS, DOSE = 13 4 SUBJECTS = 12

ASMA 2.0 0.25 0.50 0.75 1.00 1.50 2.00 3.00 4.00 5.00 6.00 7.00

CORRECTED ASPARTATE INTAKE--PROTEIN BOUND

<u>INFANT SIZE</u>	<u>TOTAL DAILY INTAKE</u>		<u>INTAKE PER MEAL (6/DAY)</u>	
	<u>MEAN</u>	<u>RANGE</u>	<u>MEAN</u>	<u>RANGE</u>
		mg/kg		mg/kg
3.5 Kg	109	73-146	18	12-24.3
5.5 Kg	98.6	81-128	16.4	13.5-21.3

FREE PHENYLALANINE INTAKE

<u>INFANT SIZE</u>	<u>TOTAL DAILY INTAKE</u>		<u>INTAKE PER MEAL (6/DAY)</u>	
	<u>MEAN</u>	<u>RANGE</u>	<u>MEAN</u>	<u>RANGE</u>
		mg/kg		mg/kg
3.5 Kg	0.41	0.27-0.55	0.068	0.044-0.091
5.5 Kg	0.37	0.30-0.48	0.061	0.049-0.080

FREE TYROSINE INTAKE

<u>INFANT SIZE</u>	<u>TOTAL DAILY INTAKE</u>		<u>INTAKE PER MEAL (6/DAY)</u>	
	<u>MEAN</u>	<u>RANGE</u>	<u>MEAN</u>	<u>RANGE</u>
		mg/kg		mg/kg
3.5 Kg	0.39	0.26-0.52	0.064	0.043-0.087
5.5 Kg	0.35	0.29-0.46	0.058	0.048-0.077

PROTEIN BOUND PHENYLALANINE INTAKE

<u>INFANT SIZE</u>	<u>TOTAL DAILY INTAKE</u>		<u>INTAKE PER MEAL (6/DAY)</u>	
	<u>MEAN</u>	<u>RANGE</u>	<u>MEAN</u>	<u>RANGE</u>
		mg/kg		mg/kg
3.5 Kg	82	55-109	13.7	9.2-18.2
5.5 Kg	74	61-96	12.3	10.1-16.0

PROTEIN BOUND TYROSINE INTAKE

<u>INFANT SIZE</u>	<u>TOTAL DAILY INTAKE</u>		<u>INTAKE PER MEAL (6/DAY)</u>	
	<u>MEAN</u>	<u>RANGE</u>	<u>MEAN</u>	<u>RANGE</u>
		mg/kg		mg/kg
3.5 Kg	104	69-139	17.3	11.5-23.1
5.5 Kg	93	77-122	15.5	12.8-20.3

EXHIBITS 1 AND 2

PLASMA AND ERYTHROCYTE FREE AMINO ACID LEVELS IN NORMAL VOLUNTEERS
ADMINISTERED ASPARTAME AT 34 MG/KG (EXHIBIT 1) OR ASPARTATE (EXHIBIT 2)
AT 13 MG/KG BODY WEIGHT

VALUES LISTED ARE THE MEAN AND STANDARD DEVIATION GIVEN IN UMOL/L PER 100 ML.

Exhibit

PLASMA AMINO
ACIDS (HR)

ASPARAGINE

SPARAGINE

HISTIDINE

LEUCINE

SPARAGINE

LUTAMINE

LUTAMINE

COLINE

TRULLIN

LYCINE

ANINE

AMINO

72

Exhibit 2 (cont.) Erythrocyte amino acid levels in normal subjects administered aspartate at 13 mg/kg

20

AMINO ACIDS, DOSE = 13 # SUBJECTS = 12
IF (HR) 0.0 0.25 0.50 0.75 1.00 1.50 2.00 3.00 4.00 5.00 6.00 7.00 8.00

Exhibit 1 Plasma levels in normal volunteers administered ASPARIN/MI. at 34 mg/kg

IA

ASPARIN/MI (HR)	AMINO ACIDS, DOSE = 34 # SUBJECTS = 12						2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.00
	0.0	0.25	0.50	0.75	1.00	1.50								
AURINE	5.23 1.37	5.07 0.80	4.76 1.26	4.90 1.01	4.93 1.02	4.61 1.33	4.52 1.30	4.48 1.50	4.39 0.67	0.0 0.0	0.0 0.0	0.0 0.0	4.87 1.14	5.4 2.0
SPAR	0.30 0.08	0.25 0.11	0.31 0.08	0.31 0.15	0.33 0.18	0.30 0.14	0.31 0.06	0.29 0.15	0.26 0.13	0.0 0.0	0.0 0.0	0.0 0.0	0.31 0.19	0.4 0.2
UREON	14.58 3.57	13.86 4.14	14.22 4.89	13.96 3.61	13.98 4.32	13.30 4.44	12.83 4.00	12.43 3.40	12.46 3.31	0.0 0.0	0.0 0.0	0.0 0.0	11.88 2.80	14.5 3.8
ERINE	12.91 3.17	12.08 2.43	12.54 3.40	11.07 2.43	11.98 2.71	12.38 4.24	11.69 2.35	10.55 3.10	11.38 2.90	0.0 0.0	0.0 0.0	0.0 0.0	11.12 2.29	12.6 2.6
SPARAGN	4.48 1.48	4.89 1.61	5.24 1.40	5.49 1.75	4.45 2.04	4.55 1.67	4.41 1.90	3.71 1.24	3.89 1.30	0.0 0.0	0.0 0.0	0.0 0.0	4.53 1.74	4.2 1.9
UTAMIN	63.53 11.78	65.05 8.85	63.75 8.54	63.67 12.82	64.94 10.35	64.81 10.40	65.02 11.74	65.54 10.76	64.02 11.79	0.0 0.0	0.0 0.0	0.0 0.0	62.53 12.50	61.4 8.0
UTAMAT	4.84 1.55	4.64 2.25	5.64 2.08	6.19 3.04	6.06 3.48	5.06 2.64	4.99 2.54	3.72 1.91	3.58 1.46	0.0 0.0	0.0 0.0	0.0 0.0	3.40 1.80	4.8 2.8
COLINE	22.30 7.62	25.27 6.91	27.61 9.20	27.98 8.74	29.16 7.95	27.93 8.13	25.28 7.15	22.02 8.79	21.37 6.24	0.0 0.0	0.0 0.0	0.0 0.0	18.72 5.87	20.3 8.5
TRIILLN	3.25 0.93	2.85 0.74	2.29 0.68	2.15 0.68	2.00 0.62	1.83 0.63	2.12 0.60	2.54 0.67	2.73 0.73	0.0 0.0	0.0 0.0	0.0 0.0	3.03 0.84	3.2 0.9
YCINE	24.43 6.52	24.01 7.23	22.72 7.51	21.57 7.01	20.87 6.90	20.75 6.35	21.70 7.15	22.18 6.38	22.01 6.86	0.0 0.0	0.0 0.0	0.0 0.0	22.09 7.49	24.0 7.0
ANINE	38.66 8.18	42.67 8.60	49.49 9.63	51.84 9.04	53.51 10.08	52.04 11.52	46.31 11.15	41.05 11.64	37.80 11.65	0.0 0.0	0.0 0.0	0.0 0.0	31.70 9.24	39.0 14.0
AMINGB	1.84 0.39	1.94 0.56	1.83 0.70	1.87 0.44	1.75 0.53	1.78 0.46	1.73 0.60	1.73 0.72	1.87 0.57	0.0 0.0	0.0 0.0	0.0 0.0	1.90 0.45	2.0 0.5

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Exhibit 1 (cont). Plasma levels in normal volunteers administered ASPARTAME at 34 mg/kg

10

ASPARAME (HR)	AMINO ACIDS, DOSE =	34	4	SUBJECTS =	12									
	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.0
GLUTAMINE	23.14 5.73	22.95 5.10	21.72 6.08	21.62 5.45	19.36 5.10	18.84 4.98	18.23 5.63	18.65 5.22	19.78 5.21	0.0 0.0	0.0 0.0	0.0 0.0	20.61 4.87	22.6 5.81
GLUTAMINE	10.37 1.45	9.76 0.93	10.27 2.08	10.27 1.32	9.78 1.42	9.35 1.30	9.38 2.14	9.41 1.74	10.25 2.62	0.0 0.0	0.0 0.0	0.0 0.0	10.24 1.77	10.5 3.61
ETHION	2.79 0.74	2.80 0.50	2.63 0.67	2.35 0.35	2.24 0.61	2.06 0.32	1.99 0.32	2.22 0.35	2.48 0.70	0.0 0.0	0.0 0.0	0.0 0.0	2.48 0.74	2.9 0.73
ISOLEUCINE	6.49 2.05	6.36 1.91	5.96 1.78	5.69 1.87	5.02 1.69	4.21 1.48	4.15 1.57	4.71 1.47	5.08 1.65	0.0 0.0	0.0 0.0	0.0 0.0	6.06 1.74	7.3 2.51
GLUTAMINE	13.55 4.10	13.62 2.88	12.99 3.83	11.15 3.33	10.14 2.98	8.94 2.70	9.00 2.58	10.59 2.32	11.73 3.53	0.0 0.0	0.0 0.0	0.0 0.0	13.77 4.34	14.5 4.31
ARGININE	5.41 1.52	6.08 1.66	6.62 1.77	6.39 1.72	5.99 1.67	5.85 1.67	5.59 1.57	5.48 1.16	5.54 1.12	0.0 0.0	0.0 0.0	0.0 0.0	5.14 1.30	5.3 1.61
ETHYLAL	5.66 1.21	8.83 2.21	11.11 2.49	11.05 4.01	10.53 1.74	9.54 1.84	8.80 1.85	7.74 1.58	7.14 2.36	0.0 0.0	0.0 0.0	0.0 0.0	6.04 1.32	6.01 1.32
GLUTAMINE	5.57 1.37	5.97 1.24	6.22 1.60	5.75 1.45	5.71 1.51	5.47 1.55	5.47 1.48	5.26 1.30	5.05 1.48	0.0 0.0	0.0 0.0	0.0 0.0	5.23 1.36	6.02 1.11
GLUTAMINE	18.37 3.52	19.79 4.09	19.13 4.71	17.62 3.03	17.38 2.86	16.75 2.68	17.76 3.57	18.63 3.61	18.45 3.55	0.0 0.0	0.0 0.0	0.0 0.0	19.00 3.72	20.4 3.54
STIODIN	9.00 1.77	9.71 1.32	9.73 2.83	8.97 1.45	8.81 1.56	8.77 1.68	8.60 1.57	9.07 1.40	9.10 1.77	0.0 0.0	0.0 0.0	0.0 0.0	9.19 1.75	10.05 1.85
GLUTAMINE	7.71 1.76	8.56 2.06	8.88 2.52	8.34 1.68	8.07 1.77	8.10 1.68	7.36 1.66	7.48 1.83	7.93 1.27	0.0 0.0	0.0 0.0	0.0 0.0	8.30 2.06	8.75 2.14

Exhibit 1 (cont.) ERYTHROCYTE AMINO ACID LEVELS IN NORMAL SUBJECTS ADMINISTERED ASPARTAME AT 34 MG/KG														
TIME (HR)	AMINO ACIDS, DOSE = 34 & SUBJECTS = 12													
	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	2
ERINE	21.16 6.73	22.84 4.76	20.17 4.81	20.70 6.40	19.09 6.49	20.86 6.48	19.33 6.21	20.19 6.07	21.32 4.66	0.0 0.0	0.0 0.0	0.0 0.0	20.80 5.33	22
URINE	6.67 6.67	4.75 2.38	5.76 2.61	6.53 7.18	5.54 6.08	4.71 4.14	5.52 6.09	4.20 3.47	9.46 12.47	0.0 0.0	0.0 0.0	0.0 0.0	6.98 9.81	6
PARTAT	23.60 7.28	22.84 7.08	22.93 6.92	23.17 7.15	23.02 6.72	23.21 7.42	23.61 7.45	23.25 7.50	23.56 7.28	0.0 0.0	0.0 0.0	0.0 0.0	22.79 7.00	24
RECININ	10.24 2.64	9.94 2.34	10.50 2.42	10.00 2.38	9.71 2.84	9.57 2.95	9.44 3.01	8.97 3.05	9.25 2.77	0.0 0.0	0.0 0.0	0.0 0.0	8.40 1.98	10
RINE	12.32 3.00	11.45 2.03	11.52 1.69	11.29 2.12	11.18 2.31	11.09 1.72	11.40 3.50	10.83 1.86	11.60 2.11	0.0 0.0	0.0 0.0	0.0 0.0	10.64 2.02	11
PARAGN	13.07 2.90	12.54 3.28	13.51 3.15	13.27 2.47	13.21 1.85	13.35 3.76	13.00 3.59	13.48 2.88	12.83 2.64	0.0 0.0	0.0 0.0	0.0 0.0	12.29 2.66	12
UTAMIN	51.61 9.09	50.24 9.81	50.63 8.47	49.97 9.19	49.70 9.76	51.32 8.22	51.23 8.81	50.82 9.57	51.08 9.13	0.0 0.0	0.0 0.0	0.0 0.0	50.16 9.13	48
JTAMAT	18.83 7.08	19.22 6.92	19.33 7.25	19.07 6.82	19.59 7.26	19.80 7.38	20.02 7.08	19.19 6.01	20.19 6.46	0.0 0.0	0.0 0.0	0.0 0.0	20.69 6.95	20
OLINE	13.78 5.43	13.69 5.45	14.40 6.35	15.48 6.81	16.20 6.35	16.97 5.52	16.36 5.62	13.59 5.11	12.71 4.60	0.0 0.0	0.0 0.0	0.0 0.0	11.99 4.10	13
ICINE	31.66 4.82	31.45 3.87	32.65 4.00	31.33 3.92	31.77 4.68	31.73 4.60	32.16 3.89	31.29 4.61	31.42 4.25	0.0 0.0	0.0 0.0	0.0 0.0	31.00 4.81	31
WINE	27.39 4.41	29.86 4.29	32.62 6.49	34.79 5.52	33.68 4.09	34.91 3.48	33.40 3.93	29.95 3.81	28.88 4.70	0.0 0.0	0.0 0.0	0.0 0.0	27.84 5.76	29
WINDOB	0.88 0.63	0.99 0.70	0.99 0.81	0.88 0.58	1.14 1.08	0.95 0.79	1.08 0.78	0.97 0.73	1.12 1.37	0.0 0.0	0.0 0.0	0.0 0.0	1.00 0.81	1

Exhibit 1 (cont.) Erythrocyte amino acid levels in normal subjects administered ASPARTAME at 34 mg/kg

TIME (HR)	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24
ALINE	17.13 4.45	16.43 4.65	16.27 5.25	15.90 5.16	14.59 4.79	14.06 4.64	14.35 4.58	13.88 4.02	13.88 3.68	0.0 0.0	0.0 0.0	0.0 0.0	15.85 4.56	17.13 4.45
ISTINE	1.01 1.02	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
THION	0.12 0.41	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
OLEUCN	3.76 1.17	3.47 1.05	3.31 1.06	3.09 1.59	2.86 1.51	2.28 1.06	2.48 0.96	2.63 0.82	2.88 0.93	0.0 0.0	0.0 0.0	0.0 0.0	3.44 0.95	4.45 1.17
UCINE	8.62 1.75	8.21 1.72	8.00 1.93	7.18 1.96	6.64 1.64	5.80 1.83	6.25 1.88	6.52 1.52	7.54 1.65	0.0 0.0	0.0 0.0	0.0 0.0	8.22 1.90	9.00 2.00
ROSINE	4.84 1.64	4.76 1.96	5.34 1.87	5.54 2.21	5.18 1.91	5.05 2.05	4.81 1.63	4.67 1.92	4.45 1.50	0.0 0.0	0.0 0.0	0.0 0.0	4.13 1.45	4.45 1.17
ENYLAL	3.53 0.87	5.04 1.01	7.21 1.95	7.13 2.25	6.78 1.80	6.25 1.59	5.83 1.34	4.95 1.63	4.58 1.47	0.0 0.0	0.0 0.0	0.0 0.0	3.85 1.20	3.85 1.17
VITHIN	11.99 3.64	12.41 3.68	12.94 3.39	13.39 3.40	13.05 3.41	13.03 3.43	12.49 3.60	11.49 2.93	11.49 3.21	0.0 0.0	0.0 0.0	0.0 0.0	10.43 2.51	12.41 3.68
SINE	13.39 3.02	12.46 2.94	12.14 3.20	12.38 2.54	11.83 2.54	12.23 2.74	12.33 3.31	12.37 2.43	12.21 3.09	0.0 0.0	0.0 0.0	0.0 0.0	12.36 2.33	12.41 3.68
STIDIN	8.60 1.91	7.96 1.65	8.03 1.80	8.22 1.39	7.86 1.23	7.91 1.71	7.79 1.67	7.81 1.93	7.65 1.58	0.0 0.0	0.0 0.0	0.0 0.0	7.61 1.53	7.96 1.65
GININE	1.84 1.10	1.54 0.75	1.70 0.90	1.71 1.23	1.58 1.06	1.81 1.51	1.35 0.63	1.62 0.83	1.50 0.91	0.0 0.0	0.0 0.0	0.0 0.0	2.69 0.90	1.84 1.10

Exhibit 2 Plasma amino acid levels in normal subjects administered aspartate at 13 mg/kg.

2A

ASMA ME (HR)	AMINO ACIDS, DOSE = 13 4 SUBJECTS = 12												24	
	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00		8.00
URINE	5.03 1.36	4.75 1.28	6.01 2.36	4.97 1.55	5.42 1.67	4.84 1.08	4.78 0.93	4.68 1.10	4.33 0.88	0.0 0.0	0.0 0.0	0.0 0.0	5.05 1.44	4.0 1.0
PART	0.30 0.18	0.26 0.18	0.30 0.19	0.36 0.18	0.39 0.22	0.29 0.20	0.25 0.16	0.27 0.15	0.36 0.34	0.0 0.0	0.0 0.0	0.0 0.0	0.32 0.15	0.0 0.0
REDN	15.31 3.25	15.87 3.59	16.39 4.17	16.40 3.80	15.82 3.83	14.06 3.79	14.49 3.38	13.77 2.97	13.97 3.25	0.0 0.0	0.0 0.0	0.0 0.0	12.97 2.63	15.0 3.0
RINE	11.75 2.06	13.01 3.21	11.60 1.74	11.47 3.45	12.92 2.89	11.05 2.20	10.99 2.44	11.31 3.35	10.87 2.34	0.0 0.0	0.0 0.0	0.0 0.0	11.46 2.38	13.0 1.0
PARAGN	4.40 1.60	4.00 1.38	5.64 1.51	4.75 2.21	4.61 1.10	5.16 1.66	4.61 1.38	4.49 1.68	4.42 1.75	0.0 0.0	0.0 0.0	0.0 0.0	4.40 0.96	4.0 1.0
UTAMIN	64.98 8.72	66.09 11.00	63.01 6.79	65.93 8.43	65.59 9.69	61.51 5.04	63.06 5.79	61.35 6.84	62.92 8.35	0.0 0.0	0.0 0.0	0.0 0.0	62.57 8.59	64.0 11.0
UTAMAT	4.50 2.71	4.42 2.98	5.95 3.63	5.35 3.17	5.53 3.31	5.50 3.37	4.51 2.92	4.21 2.98	4.26 2.38	0.0 0.0	0.0 0.0	0.0 0.0	4.59 3.24	4.0 2.0
GLINE	19.61 6.69	21.51 4.25	25.64 8.47	26.16 7.54	24.82 7.66	23.35 6.48	22.68 7.58	20.21 7.21	19.20 5.87	0.0 0.0	0.0 0.0	0.0 0.0	17.05 5.98	20.0 8.0
TRULLN	3.25 0.76	2.90 0.78	2.41 0.92	2.28 0.67	2.17 0.85	1.94 0.75	2.14 0.84	2.46 0.90	2.76 0.90	0.0 0.0	0.0 0.0	0.0 0.0	2.97 1.23	2.0 0.0
YCINE	22.30 5.96	22.56 5.32	21.82 6.39	22.25 5.67	23.42 7.75	20.39 5.37	21.81 4.04	20.86 5.48	21.13 4.88	0.0 0.0	0.0 0.0	0.0 0.0	19.74 5.55	22.0 6.0
ININE	38.07 9.22	41.84 9.62	48.71 10.95	50.98 8.72	49.50 9.97	46.47 10.64	43.31 7.18	39.39 10.62	38.16 9.28	0.0 0.0	0.0 0.0	0.0 0.0	31.76 7.75	41.0 13.0
AMINOB	1.95 0.95	2.10 0.77	3.32 3.73	2.15 0.75	1.92 0.82	1.86 0.83	2.36 1.53	1.98 0.71	2.00 0.71	0.0 0.0	0.0 0.0	0.0 0.0	2.29 0.51	2.0 0.0

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Exhibit 2 (cont.) Plasma amino acid levels in normal subjects administered aspartate at 13 mg/kg.

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ASMA	AMINO ACIDS, DOSE = 13 4 SUBJECTS = 12														
TIME (HR)	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.0	
GLUTAMINE	22.60 5.21	21.71 4.92	21.52 5.91	20.79 4.71	21.10 6.04	20.06 5.73	20.04 4.41	20.77 4.92	20.33 4.47	0.0 0.0	0.0 0.0	0.0 0.0	20.97 5.29	24.15 5.53	
GLUTAMINE	10.65 1.80	10.58 1.80	10.33 1.53	10.52 1.33	10.12 1.17	10.01 1.56	9.88 1.19	9.83 1.09	10.05 1.31	0.0 0.0	0.0 0.0	0.0 0.0	9.93 1.44	9.89 1.34	
THION	2.52 0.40	2.62 0.36	2.67 0.52	2.51 0.47	2.40 0.42	2.03 0.30	2.28 0.17	2.22 0.37	2.47 0.42	0.0 0.0	0.0 0.0	0.0 0.0	2.26 0.29	2.55 0.54	
LEUCINE	6.30 1.76	6.09 1.37	5.87 2.18	5.12 1.45	4.02 1.72	4.20 1.21	4.45 1.03	5.05 1.03	5.63 1.34	0.0 0.0	0.0 0.0	0.0 0.0	5.84 1.62	7.83 2.91	
GLUTAMINE	13.64 3.55	13.61 2.95	12.77 3.38	11.95 2.83	11.14 2.82	7.67 2.57	10.68 2.22	11.55 2.54	13.11 2.85	0.0 0.0	0.0 0.0	0.0 0.0	13.62 3.67	15.61 4.47	
GLUTAMINE	5.39 1.49	5.25 1.39	4.82 1.39	5.02 1.10	4.51 0.89	3.97 1.02	4.35 0.85	4.24 1.03	4.30 1.33	0.0 0.0	0.0 0.0	0.0 0.0	4.46 1.24	6.17 2.30	
GLUTAMINE	5.63 1.24	5.45 0.88	5.30 1.05	4.97 0.74	4.58 0.86	4.49 0.96	4.82 0.95	4.98 1.15	5.19 1.10	0.0 0.0	0.0 0.0	0.0 0.0	5.74 1.41	6.35 1.50	
GLUTAMINE	6.04 1.89	5.68 1.88	6.04 1.85	6.18 1.32	5.67 1.49	5.11 1.52	5.36 1.14	5.19 1.44	5.13 1.21	0.0 0.0	0.0 0.0	0.0 0.0	5.27 1.61	6.36 1.74	
GLUTAMINE	20.97 5.69	18.90 6.57	20.97 3.97	20.65 3.55	20.53 2.92	17.87 2.79	20.00 2.90	20.47 4.95	20.37 4.39	0.0 0.0	0.0 0.0	0.0 0.0	19.75 4.80	21.74 4.89	
GLUTAMINE	10.31 2.28	10.13 2.31	10.07 2.09	9.01 3.23	9.64 1.54	9.10 1.46	9.02 1.83	10.10 2.29	9.58 2.06	0.0 0.0	0.0 0.0	0.0 0.0	9.89 2.08	9.71 1.87	
GLUTAMINE	8.82 1.23	9.34 1.31	9.39 2.03	9.06 1.98	8.66 2.14	7.95 2.57	7.92 1.62	7.91 1.22	8.46 0.97	0.0 0.0	0.0 0.0	0.0 0.0	8.41 1.20	8.70 1.06	

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Exhibit 2 (Cont.) Erythrocyte amino acid levels in normal subjects administered aspartate at 13 mg/kg														20
AMINO ACIDS, DOSE = 13 & SUBJECTS = 12														
IE (HR)	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24
RINE	22.86 6.41	22.53 7.34	20.38 5.68	20.75 5.76	19.43 5.04	18.86 7.83	21.08 8.51	23.06 7.19	21.75 5.90	0.0 0.0	0.0 0.0	0.0 0.0	21.64 6.06	21.64 5.90
IRINE	6.50 4.47	6.82 5.45	4.93 2.28	5.51 3.39	4.24 2.36	5.00 2.64	5.73 4.00	7.12 6.55	8.47 5.99	0.0 0.0	0.0 0.0	0.0 0.0	7.05 5.69	8.47 7.05
ARTAT	22.87 6.00	23.50 7.39	23.63 6.83	23.27 6.99	23.07 7.06	23.50 6.55	23.57 6.35	24.09 6.97	23.53 6.72	0.0 0.0	0.0 0.0	0.0 0.0	23.25 6.71	23.25 6.71
EDNIN	11.12 2.68	10.95 2.31	11.12 2.24	11.30 2.32	10.95 2.67	10.28 2.72	11.08 2.93	10.29 1.95	9.92 2.20	0.0 0.0	0.0 0.0	0.0 0.0	9.37 2.21	12.17 3.07
INE	12.17 2.73	11.66 2.07	11.61 2.23	11.51 1.84	11.34 1.95	11.02 2.40	11.51 2.45	11.34 2.04	11.22 2.00	0.0 0.0	0.0 0.0	0.0 0.0	10.82 2.38	12.17 2.73
ARAGN	12.62 3.08	13.34 3.59	12.77 3.60	11.87 2.42	13.52 3.87	12.47 3.68	12.89 3.54	12.99 4.37	13.74 3.60	0.0 0.0	0.0 0.0	0.0 0.0	11.69 2.76	12.62 3.08
TAMIN	50.20 8.22	51.10 8.76	51.91 8.13	52.83 8.41	50.63 8.29	50.83 8.05	50.67 8.58	50.74 9.24	50.84 7.65	0.0 0.0	0.0 0.0	0.0 0.0	49.58 7.64	51.10 10.00
TAMAT	20.21 7.76	20.74 7.36	20.03 6.92	19.91 7.13	20.11 6.74	20.20 7.30	20.93 7.81	20.79 7.69	20.32 6.84	0.0 0.0	0.0 0.0	0.0 0.0	21.55 6.66	20.21 7.76
LINE	12.85 4.41	12.77 3.96	13.99 3.84	14.51 3.87	15.06 4.25	13.81 3.59	13.38 3.97	11.71 3.52	12.22 2.83	0.0 0.0	0.0 0.0	0.0 0.0	10.45 3.43	13.99 5.00
CINE	32.54 4.64	32.36 3.44	33.13 2.85	32.87 2.90	32.86 4.30	31.13 5.11	34.78 9.25	32.03 2.99	31.71 3.19	0.0 0.0	0.0 0.0	0.0 0.0	31.16 5.07	31.16 4.64
NINE	27.79 4.24	28.88 4.83	32.67 4.40	32.13 5.52	33.42 3.10	34.29 3.31	33.90 3.22	30.03 2.93	29.48 3.04	0.0 0.0	0.0 0.0	0.0 0.0	25.93 4.90	31.16 8.00
MINOB	1.26 0.80	1.31 0.65	1.36 1.00	1.25 0.69	1.33 0.91	1.29 0.92	1.26 1.03	1.33 0.87	1.46 1.53	0.0 0.0	0.0 0.0	0.0 0.0	1.13 0.60	1.26 0.80

*Note: 4 hour threonine level contained an error. The corrected value is 10.54 ± 2.74

* on Quinine, necessary to be used.

Exhibit 2 (cont.) Erythrocyte free amino acid levels in normal subjects administered aspartate at 13 mg/kg

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TIME (HR)	AMINO ACIDS, DOSE = 13 & SUBJECTS = 12													
	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.
GLUTAMINE	15.95 5.45	16.53 3.44	16.36 3.37	15.39 3.62	14.75 3.56	13.67 3.06	14.45 2.49	14.64 3.29	15.05 3.47	0.0 0.0	0.0 0.0	0.0 0.0	14.95 3.58	17.8 5.8
GLUTAMINE	0.0 0.0	0.0 0.0	0.35 0.12	0.32 0.10	0.41 0.17	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
THIONINE	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.03 0.09	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
LEUCINE	3.79 1.14	3.38 0.93	3.25 0.86	2.81 0.80	2.75 0.67	2.42 0.64	3.12 1.71	2.83 0.58	3.06 0.61	0.0 0.0	0.0 0.0	0.0 0.0	3.52 0.72	4.5 1.5
ISOLEUCINE	8.72 1.66	8.49 1.65	7.84 1.88	7.39 1.90	6.89 1.50	6.31 1.23	7.19 1.48	7.57 1.31	7.90 1.48	0.0 0.0	0.0 0.0	0.0 0.0	8.73 1.62	10.2 2.8
PROLINE	4.45 1.36	4.17 1.29	3.99 1.43	3.55 1.12	3.66 1.42	3.16 1.07	3.56 1.21	3.45 1.30	3.56 1.34	0.0 0.0	0.0 0.0	0.0 0.0	3.58 1.24	5.0 2.2
GLYCYLAL	3.58 0.98	3.37 1.05	3.21 1.11	2.98 0.77	2.84 0.92	2.64 0.94	3.01 1.06	3.02 1.04	3.19 0.99	0.0 0.0	0.0 0.0	0.0 0.0	3.23 0.78	3.9 1.3
VALINE	12.27 2.45	12.15 2.24	12.91 2.59	12.06 1.92	13.25 2.48	12.02 2.62	12.38 2.98	11.94 2.96	12.31 2.77	0.0 0.0	0.0 0.0	0.0 0.0	10.32 3.08	12.4 2.8
SERINE	12.69 2.58	12.35 2.59	12.94 3.21	11.34 2.11	12.35 2.87	12.10 3.10	12.67 2.25	12.83 3.42	13.23 3.56	0.0 0.0	0.0 0.0	0.0 0.0	12.46 2.56	14.2 3.3
ISTIDINE	7.58 1.14	7.72 0.90	7.86 1.10	7.43 1.06	7.60 1.27	7.64 1.59	7.77 1.27	7.76 1.57	7.88 1.67	0.0 0.0	0.0 0.0	0.0 0.0	7.52 1.44	8.0 1.8
SININE	1.59 0.85	1.54 0.75	2.05 1.70	2.08 2.33	1.87 1.77	1.79 1.49	1.78 1.40	1.66 1.11	1.68 1.17	0.0 0.0	0.0 0.0	0.0 0.0	2.84 1.38	2.4 1.2

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EXHIBITS 3 AND 4

PLASMA, ERYTHROCYTE AND BREAST MILK FREE AMINO ACID LEVELS IN
LACTATING WOMEN ADMINISTERED ASPARTAME (EXHIBIT 3) OR LACTOSE
(EXHIBIT 4) AT 50 MG PER KG BODY WEIGHT

VALUES LISTED ARE THE MEAN AND STANDARD DEVIATION GIVEN IN UMOL/L PER 100 ML

EXHIBIT

50MG/KG

LASHA
THE (HR)

AURINE

ASPART

THREON

SERINE

ASPARAG

GLUTAM

GLUTAMA

PROLINE

CITRUL

GLYCINE

ALANINE

L-AMINO

EXHIBIT 3 PLASMA amino acid levels in LACTATING WOMEN administered ASPARTAME AT 50 mg/kg

3A

50MG/KG ASPARTAME

PLASMA AMINO ACIDS, DOSE = 50, # SUBJECTS = 6	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.0
TIME (HRS)	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.0
URINE	4.38	3.96	4.57	4.08	4.13	3.93	4.24	4.04	4.09	0.0	0.0	0.0	0.0	0.0
	0.97	0.81	1.05	0.81	0.75	1.53	0.98	0.67	0.79	0.0	0.0	0.0	0.0	0.0
SPART	0.42	0.42	0.54	0.31	0.34	0.30	0.30	0.17	0.23	0.0	0.0	0.0	0.0	0.0
	0.33	0.24	0.55	0.15	0.19	0.17	0.15	0.05	0.12	0.0	0.0	0.0	0.0	0.0
UREON	10.42	11.08	11.20	10.40	10.33	10.18	9.68	9.15	8.74	0.0	0.0	0.0	0.0	0.0
	1.92	2.22	2.26	2.54	3.13	2.37	2.80	2.16	1.99	0.0	0.0	0.0	0.0	0.0
ERINE	13.99	14.85	15.59	14.19	14.11	13.13	13.68	13.23	12.66	0.0	0.0	0.0	0.0	0.0
	2.69	2.87	3.68	3.96	3.33	3.31	3.17	2.10	2.55	0.0	0.0	0.0	0.0	0.0
ASPARAGN	3.83	5.51	5.47	5.82	5.31	5.77	4.39	4.56	5.71	0.0	0.0	0.0	0.0	0.0
	1.35	2.44	2.36	3.08	2.39	1.76	1.40	2.60	2.19	0.0	0.0	0.0	0.0	0.0
GLUTAMIN	58.11	53.64	58.42	54.17	55.67	56.59	55.65	56.27	55.66	0.0	0.0	0.0	0.0	0.0
	7.31	8.52	8.61	11.00	10.33	7.70	10.39	6.77	7.93	0.0	0.0	0.0	0.0	0.0
GLUTAMAT	3.20	2.57	4.66	4.62	4.52	5.24	4.22	3.16	3.06	0.0	0.0	0.0	0.0	0.0
	2.17	1.83	2.60	2.36	2.21	3.00	2.12	1.43	1.72	0.0	0.0	0.0	0.0	0.0
PROLINE	18.65	22.34	23.64	24.93	24.24	26.48	23.05	19.51	17.59	0.0	0.0	0.0	0.0	0.0
	5.99	7.32	7.07	6.69	6.76	6.04	7.20	5.30	5.30	0.0	0.0	0.0	0.0	0.0
CITRULLN	2.25	2.17	1.67	1.23	1.22	1.29	1.39	1.88	1.88	0.0	0.0	0.0	0.0	0.0
	1.12	1.50	0.95	0.67	0.84	0.65	0.64	0.90	0.93	0.0	0.0	0.0	0.0	0.0
GLYCINE	37.51	36.68	37.76	36.26	37.42	37.72	36.57	36.15	32.77	0.0	0.0	0.0	0.0	0.0
	14.15	10.97	15.52	16.02	17.37	19.49	14.51	12.92	13.04	0.0	0.0	0.0	0.0	0.0
ALANINE	32.63	33.00	44.19	45.48	47.59	47.15	43.76	34.57	31.87	0.0	0.0	0.0	0.0	0.0
	5.96	7.29	7.66	5.24	7.29	7.68	9.23	8.10	4.66	0.0	0.0	0.0	0.0	0.0
AMINO B	2.47	3.10	2.99	2.58	2.60	2.04	2.35	2.31	2.33	0.0	0.0	0.0	0.0	0.0
	0.99	0.81	1.27	1.04	1.05	0.72	0.87	0.73	0.76	0.0	0.0	0.0	0.0	0.0

EXHIBIT 3 (Cont.) PLASMA amino acid levels in LACTATING WOMEN administered ASPARAGINE at 50 mg/kg

3B

ASPARAGINE (HR)	AMINO ACIDS	DOSE = 50	# SUBJECTS = 6	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.00
LINE	22.07	23.35	23.06	20.07	19.59	17.26	17.94	18.12	18.89	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	4.63	3.13	4.00	2.73	3.00	2.83	1.93	1.39	2.54	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
ISTHINE	9.22	9.02	9.47	9.29	9.12	9.76	9.51	8.79	8.55	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	1.55	1.41	1.12	1.58	1.66	1.57	1.71	1.49	1.37	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
ETHION	1.94	2.07	2.26	1.70	1.74	1.62	1.49	1.63	1.47	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	0.36	0.57	0.82	0.34	0.51	0.33	0.40	0.27	0.16	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
ISOLEUCINE	5.12	5.39	5.19	4.16	3.63	3.48	3.28	3.89	4.22	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	1.47	1.40	1.77	0.99	1.11	1.24	0.92	0.74	0.65	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
EUCINE	11.39	11.98	11.44	9.50	8.54	7.81	7.81	8.73	9.68	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	2.46	1.37	2.20	1.69	1.63	1.82	1.16	0.92	1.28	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
PROSINE	5.16	6.39	7.98	8.12	7.37	7.94	7.83	7.13	5.78	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	1.61	1.62	2.64	1.49	1.64	3.02	2.00	1.99	1.66	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

HENYLAL	4.61	8.34	14.49	16.21	14.17	15.66	12.77	8.07	6.42	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	1.72	2.72	4.47	4.86	4.08	6.19	3.78	2.28	2.02	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
ARNITHIN	7.07	7.31	7.54	7.00	7.55	7.13	6.35	6.54	5.86	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	1.43	1.31	0.99	0.56	2.20	0.78	1.15	0.84	1.15	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
YSINE	16.02	17.86	16.02	14.45	14.24	14.19	14.25	13.91	14.15	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	4.24	3.41	4.06	3.15	3.13	3.63	3.88	2.86	3.34	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
ISTIDIN	6.96	7.51	7.29	6.76	6.63	7.09	6.58	6.54	6.32	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	1.04	1.13	1.35	1.34	1.65	1.56	1.71	1.10	1.22	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
ARGININ	8.22	10.16	10.44	9.65	9.57	9.59	8.62	7.74	7.52	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	1.50	1.33	1.96	1.88	2.64	2.56	2.60	1.78	1.78	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

EXHIBIT 4 (Cont.) ERYTHROCYTE amino acid levels in lactating women administered LACTOSE at 50 mg/kg

4C

50MG/KG LACTOSE

EXHIBIT 3 (cont.) ERYTHROCYTE amino acid levels in lactating women administered ASPARTAME at 50 mg/kg

3C

MG/KG ASPARTAME

AMINO ACIDS, DOSE = 50 # SUBJECTS = 6															
TIME (HR)	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.0	
LINE	5.19	10.98	12.79	8.74	9.74	13.71	10.67	10.90	8.05	0.0	0.0	0.0	0.0	0.0	
	2.84	5.14	7.70	3.96	5.46	5.97	8.76	8.08	4.08	0.0	0.0	0.0	0.0	0.0	
ARTAT	23.97	31.11	22.09	22.84	21.65	25.32	22.33	22.62	23.71	0.0	0.0	0.0	0.0	0.0	
	17.71	15.33	16.82	17.37	16.52	22.41	17.46	17.27	18.48	0.0	0.0	0.0	0.0	0.0	
EDONIN	8.06	9.71	8.49	9.64	8.37	9.34	7.83	7.47	7.39	0.0	0.0	0.0	0.0	0.0	
	3.78	2.68	3.02	2.89	2.83	3.79	2.97	2.92	2.57	0.0	0.0	0.0	0.0	0.0	
LINE	14.71	16.57	14.70	15.03	14.19	14.12	13.94	13.68	14.05	0.0	0.0	0.0	0.0	0.0	
	4.73	3.11	3.77	4.27	4.07	4.58	3.57	3.48	3.65	0.0	0.0	0.0	0.0	0.0	
PARAGN	11.26	14.14	14.44	11.38	11.74	10.33	13.44	12.61	10.84	0.0	0.0	0.0	0.0	0.0	
	4.45	5.40	5.81	5.40	3.92	1.41	3.74	4.42	4.21	0.0	0.0	0.0	0.0	0.0	
ITAMIN	47.36	43.96	47.09	45.59	43.30	51.04	44.98	43.75	43.35	0.0	0.0	0.0	0.0	0.0	
	9.58	7.73	8.66	10.00	10.43	7.07	10.93	11.26	10.05	0.0	0.0	0.0	0.0	0.0	
ITAMAT	26.42	27.00	27.79	27.41	27.13	29.05	27.91	28.41	28.37	0.0	0.0	0.0	0.0	0.0	
	5.49	5.86	6.48	6.57	4.85	5.22	5.77	3.54	4.87	0.0	0.0	0.0	0.0	0.0	
LINE	12.61	14.57	15.29	14.69	15.08	18.60	15.06	13.97	12.52	0.0	0.0	0.0	0.0	0.0	
	4.99	5.18	6.44	5.73	6.61	8.68	7.25	6.73	7.22	0.0	0.0	0.0	0.0	0.0	
CINE	45.18	45.95	46.26	44.26	45.03	47.58	46.71	45.20	45.72	0.0	0.0	0.0	0.0	0.0	
	12.63	12.54	14.24	14.29	15.87	17.47	15.00	14.78	15.41	0.0	0.0	0.0	0.0	0.0	
ANINE	25.35	28.60	28.23	30.53	29.69	35.51	33.13	29.95	28.90	0.0	0.0	0.0	0.0	0.0	
	9.14	7.45	6.54	6.98	6.42	12.59	9.84	9.26	9.58	0.0	0.0	0.0	0.0	0.0	
AMINO B	1.47	3.26	1.37	1.40	1.31	2.07	1.38	1.56	1.11	0.0	0.0	0.0	0.0	0.0	
	1.72	1.91	1.56	1.72	1.43	1.76	1.47	1.93	1.38	0.0	0.0	0.0	0.0	0.0	

EXHIBIT 4 (Cont.) ERYTHROCYTE amino acid levels in lactating women administered ENLITIDE at 50 mg/kg

AMINO ACIDS, DOSE = .50 # SUBJECTS = 6														
DC														
TIME (HR)	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.

EXHIBIT 3 (Cont.) ERYTHROCYTE amino acid levels in lactating women administered ASPARTAME at 50 mg/kg.

3D

AMINO ACIDS, DOSE = 50 # SUBJECTS = 6	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.
ALINE	15.07 3.24	16.39 0.72	14.12 3.02	14.88 2.11	13.26 2.20	12.68 2.74	12.11 2.46	13.03 1.98	12.45 2.99	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
YSTINE	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
ETHION	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
SOLEUCN	3.96 1.85	4.12 1.32	3.04 1.12	2.83 1.12	2.45 1.28	2.26 0.75	2.29 1.57	2.40 0.72	2.56 0.92	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
EUCINE	8.16 2.02	8.45 0.49	7.81 1.62	6.56 1.46	5.85 1.16	5.31 1.36	5.79 1.78	6.24 1.15	6.62 1.43	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
YROSINE	4.71 1.89	5.64 1.43	6.41 1.81	6.65 1.90	6.24 2.22	6.80 3.15	7.11 1.63	6.14 2.06	5.43 1.77	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
HENYLAL	2.98 1.23	6.20 1.05	11.04 4.34	11.16 4.32	9.33 2.64	10.14 3.34	8.44 1.74	5.93 2.60	4.72 2.23	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
ARNITHIN	12.40 3.44	13.93 3.40	13.63 3.05	14.49 3.04	13.82 2.67	14.87 5.22	13.36 3.08	13.17 3.42	12.70 3.78	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
YSINE	13.28 3.97	14.72 3.22	12.67 2.85	12.77 2.32	12.48 3.14	12.47 2.11	12.71 2.52	12.67 2.37	12.47 2.84	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
ISTIDIN	7.28 1.26	7.61 0.44	6.37 0.55	6.66 0.62	6.62 1.06	7.13 0.62	6.38 1.33	6.09 1.42	6.80 1.10	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
RGININE	2.27 0.67	2.98 0.52	2.95 1.08	2.17 0.76	2.20 0.92	2.02 1.11	2.08 0.82	1.79 0.93	2.46 0.96	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0

EXHIBIT 4 (Cont.) BREAST MILK amino acid levels in lactating women administered LACTOSE at 50 mg/kg.

4E

10MG/KG LACTOSE

AMINO ACIDS, DOSE = 50 # SUBJECTS = 6

3E

[illegible]

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AMINO ACIDS, DOSE = 50.0 SUBJECTS = 6

EXHIBIT 3 (Cont.) BREAST MILK amino acid levels in lactating women administered ASPARTAME at 50 mg/kg.

3F

AMINO ACIDS, DOSE = 50 # SUBJECTS = 6	0.0	1.0	2.0	3.0	4.0	8.0	12.0	24.0						
TIME (HR)														
ALANINE	3.71 0.90	3.83 0.68	4.01 0.31	4.24 0.58	4.34 0.57	5.23 2.22	5.45 1.47	4.73 1.06	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
CYSTINE	4.07 1.46	4.04 1.29	4.41 2.15	5.51 2.74	4.33 1.15	4.93 2.07	5.19 1.42	4.68 1.54	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
METHIONINE	0.28 0.10	0.34 0.17	0.41 0.20	0.45 0.23	0.41 0.18	0.73 0.51	0.65 0.38	0.45 0.22	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
ISOLEUCINE	0.73 0.25	0.81 0.51	0.92 0.58	0.79 0.52	0.75 0.55	1.17 0.89	1.55 0.66	1.00 0.35	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
LEUCINE	2.28 0.50	2.32 0.55	2.35 0.56	2.65 0.93	2.62 0.95	3.83 2.23	3.82 1.02	2.87 0.25	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
TYROSINE	0.76 0.30	1.17 0.46	1.55 0.66	1.66 0.76	1.76 0.52	2.17 1.31	1.76 1.18	1.23 0.74	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
PHENYLALANINE	0.48 0.27	2.06 1.11	2.29 1.07	2.08 0.94	1.99 0.88	2.22 1.69	1.69 1.59	0.74 0.43	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
GLUTAMINE	0.46 0.11	0.64 0.23	0.61 0.27	0.72 0.23	0.57 0.17	0.69 0.25	0.57 0.27	0.63 0.21	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
GLYCINE	1.10 0.73	1.22 1.19	1.36 0.97	1.52 1.21	1.64 1.31	2.52 1.89	3.22 3.59	1.69 1.65	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
HISTIDINE	1.31 0.70	1.51 0.57	1.62 0.72	1.63 0.78	1.62 0.48	1.93 0.89	2.05 1.00	1.68 0.80	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
ARGININE	0.93 0.39	1.10 0.60	1.12 0.54	1.23 0.70	1.28 0.62	2.12 1.50	1.58 0.68	1.02 0.47	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0

EXHIBIT 4 PLASMA amino acid levels in lactating women administered LACTOSE at 50 mg/kg.

4A

MG/KG LACTOSE

PLASMA AMINO ACIDS, DOSE = 50, # SUBJECTS = 6	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24
GLUCOSE	4.58	4.35	3.85	3.90	4.57	4.05	3.68	3.96	3.42	0.0	0.0	0.0	0.0	0.0
	1.98	1.12	1.71	1.67	1.66	1.07	1.40	1.48	1.46	0.0	0.0	0.0	0.0	0.0
ASPARTATE	0.32	0.28	0.24	0.23	0.40	0.24	0.17	0.22	0.21	0.0	0.0	0.0	0.0	0.0
	0.20	0.07	0.09	0.05	0.40	0.14	0.05	0.03	0.03	0.0	0.0	0.0	0.0	0.0
ALANINE	12.79	11.45	12.74	11.41	12.07	11.58	11.29	11.13	10.79	0.0	0.0	0.0	0.0	0.0
	4.02	3.08	3.04	3.16	3.60	3.67	2.98	2.50	2.69	0.0	0.0	0.0	0.0	0.0
GLUTAMINE	13.38	12.48	13.50	12.06	12.88	12.58	12.11	12.33	12.05	0.0	0.0	0.0	0.0	0.0
	2.62	2.86	2.25	2.46	2.94	3.04	2.47	1.57	2.81	0.0	0.0	0.0	0.0	0.0
PARACETAMOL	5.87	5.82	6.89	6.46	6.31	6.19	5.58	5.13	5.12	0.0	0.0	0.0	0.0	0.0
	1.76	1.38	1.27	2.78	1.86	1.70	2.13	1.22	2.30	0.0	0.0	0.0	0.0	0.0
UTAMIN	52.30	49.91	53.33	50.11	53.22	52.62	50.12	54.52	54.69	0.0	0.0	0.0	0.0	0.0
	12.17	10.53	10.31	9.62	8.49	12.02	6.69	11.39	9.18	0.0	0.0	0.0	0.0	0.0
UTAMAT	4.46	4.16	4.65	4.09	4.67	4.78	4.24	4.25	3.98	0.0	0.0	0.0	0.0	0.0
	1.54	1.58	2.22	1.97	1.77	2.06	1.74	1.64	2.49	0.0	0.0	0.0	0.0	0.0
GLICINE	23.87	22.68	29.40	27.86	29.03	27.38	25.02	22.65	21.58	0.0	0.0	0.0	0.0	0.0
	8.27	6.84	8.02	8.55	8.15	10.20	8.94	7.28	7.57	0.0	0.0	0.0	0.0	0.0
TRULLIN	2.75	2.15	2.03	1.71	1.82	1.76	1.76	2.22	2.19	0.0	0.0	0.0	0.0	0.0
	1.05	0.84	0.57	0.56	0.47	0.61	0.42	1.03	1.00	0.0	0.0	0.0	0.0	0.0
YCINE	36.96	33.00	37.05	34.11	36.98	37.25	37.08	35.99	36.72	0.0	0.0	0.0	0.0	0.0
	10.32	10.03	11.64	10.41	13.67	12.98	12.33	11.34	13.63	0.0	0.0	0.0	0.0	0.0
ANINE	37.65	33.45	41.06	40.85	45.40	41.54	36.32	31.91	32.29	0.0	0.0	0.0	0.0	0.0
	8.15	7.16	8.15	7.79	9.90	12.37	11.67	5.20	5.77	0.0	0.0	0.0	0.0	0.0
AMINO	2.23	2.08	2.28	2.00	2.02	2.08	2.01	2.17	2.19	0.0	0.0	0.0	0.0	0.0
	1.02	0.90	0.77	0.72	0.66	0.63	0.55	0.58	0.66	0.0	0.0	0.0	0.0	0.0

EXHIBIT 4 (Cont.) PLASMA amino acid levels in lactating women administered LACTOSE at 50 mg/kg.

40

PLASMA AMINO ACIDS, DOSE = 50, # SUBJECTS = 6	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.00
TIME (HR)														
ALANINE	23.83 4.96	21.12 4.28	21.93 3.12	19.21 3.34	19.87 2.75	19.27 3.21	18.66 2.30	19.83 2.43	20.12 2.79	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
CYSTINE	9.45 1.52	8.40 1.48	9.99 1.62	9.19 1.75	9.47 1.50	9.33 1.45	9.42 1.51	9.46 1.90	10.07 2.09	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
ETHIONINE	2.32 0.99	1.83 0.47	2.07 0.48	1.83 0.46	2.01 0.70	1.71 0.41	1.73 0.39	1.71 0.35	1.78 0.37	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
ISOLEUCINE	5.68 1.54	4.92 1.68	4.92 1.41	4.01 1.31	4.06 1.51	3.67 1.06	3.69 0.86	4.16 0.94	4.46 0.83	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
LEUCINE	11.60 2.91	9.95 2.64	10.22 2.03	8.49 2.12	8.72 2.69	7.63 1.39	7.89 1.41	8.89 1.46	9.97 1.84	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
TYROSINE	5.97 1.24	5.27 1.15	5.78 1.16	4.89 1.26	5.02 0.71	4.65 0.90	4.68 0.89	4.80 0.75	5.02 1.10	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
PHENYLALANINE	5.04 1.13	4.47 0.81	4.99 0.98	4.23 0.95	4.45 0.85	4.33 0.83	4.38 0.90	4.62 0.86	4.98 1.18	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
ORNITHINE	5.72 2.19	5.48 2.46	5.66 1.57	5.15 1.75	5.38 1.30	5.38 2.12	5.15 1.21	4.88 1.26	5.11 1.51	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
GLYSINE	17.49 4.39	15.66 3.37	16.40 2.55	14.39 2.60	15.42 2.78	15.08 3.04	15.10 2.78	15.74 2.66	16.19 3.94	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
HISTIDINE	7.12 1.55	6.51 1.19	7.47 1.36	6.82 1.55	6.85 1.26	6.55 1.50	6.54 1.12	7.08 1.57	7.45 1.85	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
ARGININE	8.26 1.86	8.38 1.59	10.08 1.32	8.91 1.95	8.85 2.02	8.01 1.92	7.88 1.64	8.99 2.67	8.13 1.98	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0

EXHIBIT 4 (Cont.) ERYTHROCYTE amino acid levels in lactating women administered LACTOSE at 50 mg/kg.

.4C

OMG/KG LACTOSE.

TIME (HR)	AMINO ACIDS, DOSE = 50. # SUBJECTS = 6													
	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24
LEUCINE	20.52	19.48	17.62	18.57	19.71	21.44	24.13	21.25	25.68	0.0	0.0	0.0	0.0	0.
	6.15	7.79	6.74	4.85	7.81	5.52	5.84	5.29	4.21	0.0	0.0	0.0	0.0	0.
ISOLEUCINE	8.22	6.13	6.10	11.73	7.55	6.82	8.61	7.68	7.71	0.0	0.0	0.0	0.0	0.
	3.89	3.48	3.09	10.39	2.78	3.34	3.81	3.71	3.95	0.0	0.0	0.0	0.0	0.
ASPARTATE	18.47	18.04	17.78	17.90	18.04	18.41	18.55	19.09	21.97	0.0	0.0	0.0	0.0	0.
	11.62	12.06	11.98	11.92	11.36	12.36	11.54	11.77	13.20	0.0	0.0	0.0	0.0	0.
GLYCERONIN	10.93	10.25	11.32	10.43	10.19	9.63	9.53	9.36	9.25	0.0	0.0	0.0	0.0	0.
	3.12	3.56	3.42	4.15	3.04	2.72	1.69	2.29	2.66	0.0	0.0	0.0	0.0	0.
LEUCINE	15.06	14.29	15.03	14.16	14.80	13.82	13.94	14.16	14.66	0.0	0.0	0.0	0.0	0.
	1.96	2.47	1.72	2.21	2.09	2.79	2.44	3.22	5.23	0.0	0.0	0.0	0.0	0.
ASPARAGINE	13.39	15.11	14.33	14.69	13.59	14.04	16.17	14.38	14.69	0.0	0.0	0.0	0.0	0.
	5.18	4.01	3.73	6.30	5.49	5.75	4.72	4.77	5.67	0.0	0.0	0.0	0.0	0.
GLUTAMINE	50.18	49.89	49.72	48.23	47.78	44.17	45.78	43.61	42.18	0.0	0.0	0.0	0.0	0.
	13.36	12.07	12.15	11.02	11.53	14.89	12.39	11.60	11.61	0.0	0.0	0.0	0.0	0.
GLUTAMATE	26.72	25.14	24.86	25.19	25.35	26.29	27.71	26.88	26.99	0.0	0.0	0.0	0.0	0.
	4.83	4.68	3.70	5.00	3.59	4.69	4.22	3.87	3.55	0.0	0.0	0.0	0.0	0.
PROLINE	12.09	12.18	13.30	13.73	13.89	13.78	13.84	12.48	13.80	0.0	0.0	0.0	0.0	0.
	4.35	3.70	3.08	3.15	3.44	4.02	3.52	2.95	4.93	0.0	0.0	0.0	0.0	0.
GLYCINE	44.60	46.15	44.72	46.63	45.60	45.00	47.75	44.08	46.11	0.0	0.0	0.0	0.0	0.
	10.66	11.57	10.29	12.38	11.42	11.83	14.34	11.63	15.12	0.0	0.0	0.0	0.0	0.
ALANINE	26.53	26.19	27.72	29.23	31.28	30.97	31.73	28.65	32.59	0.0	0.0	0.0	0.0	0.
	7.36	5.70	6.86	7.55	5.48	7.22	7.48	6.48	9.34	0.0	0.0	0.0	0.0	0.
AMINOACIDS	1.31	0.57	1.33	0.87	0.78	0.96	1.31	1.24	1.05	0.0	0.0	0.0	0.0	0.
	1.81	0.99	1.84	1.20	1.13	1.41	1.98	1.70	1.08	0.0	0.0	0.0	0.0	0.

EXHIBIT 5 (Cont.) ERYTHROCYTE amino acid levels in normal adults administered ASPARTAME at 100 mg/kg in SOLUTION

.5C

AMINO ACIDS, DOSE = 100. # SUBJECTS = 6

EXHIBIT 4 (Cont.) ERYTHROCYTE amino acid levels in lactating women administered LACTULOSE at 50 mg/kg

TIME (HR)	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00
ALANINE	16.63 5.61	15.33 4.50	16.82 4.45	14.80 4.01	13.07 1.51	12.99 3.21	12.74 3.53	13.66 2.65	12.31 1.01	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
CYSTINE	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
METHION	0.22 0.36	0.42 0.60	0.48 0.55	0.23 0.42	0.13 0.26	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
ISOLEUCIN	3.98 1.28	4.22 1.17	3.70 0.90	3.02 1.40	2.84 1.33	2.13 0.93	2.47 1.13	2.99 0.84	3.62 1.01	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
LEUCINE	8.19 1.98	7.62 1.51	7.32 1.25	6.59 1.10	5.97 1.15	5.31 1.22	5.57 0.80	6.26 0.51	6.96 0.48	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
TYROSINE	5.33 1.74	4.68 1.37	4.32 1.29	4.06 1.21	3.94 1.10	3.67 0.86	3.53 0.87	3.61 0.89	3.84 0.73	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
PHENYLAL	3.28 1.13	2.59 1.08	2.44 1.14	2.48 1.07	2.18 1.15	2.34 1.02	2.60 0.89	2.52 1.25	2.93 0.93	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
CARNITIN	11.95 1.71	12.15 2.10	12.71 2.61	12.06 4.14	13.35 2.53	12.14 2.55	12.39 1.92	11.71 2.23	10.84 1.95	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
LYSINE	14.76 2.05	12.21 2.56	11.77 3.72	11.97 3.56	12.65 1.86	12.06 2.14	12.79 2.43	12.60 3.10	12.20 2.14	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
HISTIDIN	7.96 1.05	6.71 1.82	6.51 2.35	7.03 1.80	7.01 1.71	6.00 2.26	6.67 2.10	6.51 2.26	6.42 1.89	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
ARGININE	3.36 2.39	3.09 2.21	3.08 1.99	3.47 1.78	2.66 2.03	2.77 2.29	2.96 2.22	2.55 1.71	3.58 2.70	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0

Exhibit 5 (Cont.) Erythrocyte amino acid levels in normal adults administered ACETAMINOPHEN at 100 mg/kg in SOLUTION

EXHIBIT 4 (Cont.) BREAST MILK amino acid levels in lactating women administered LACTULOSE at 50 mg/kg. 4E
 MG/KG LACTULOSE

K E (HR)	AMINO ACIDS. DOSE = 50 # SUBJECTS = 6															
	0.0	1.0	2.0	3.0	4.0	8.0	12.0	24.0								
LINE	27.85	24.45	26.81	25.48	23.70	28.42	27.98	22.01	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	18.61	17.53	22.07	18.12	15.43	21.64	22.45	18.58	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
ART	13.32	14.21	12.60	12.64	10.36	11.12	12.14	11.83	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	19.69	18.57	15.91	15.60	11.29	12.24	14.30	14.79	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
ECN	5.81	5.52	6.46	6.27	5.80	5.57	5.82	5.58	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	2.98	2.27	2.32	2.08	2.57	1.73	2.84	2.66	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
INE	11.37	10.15	11.52	10.98	9.28	9.60	10.73	11.05	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	4.78	4.21	4.67	4.19	3.93	3.53	4.69	3.76	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
PARAGN	5.49	5.66	5.52	5.39	5.36	5.35	6.98	6.22	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	8.58	7.67	7.63	7.50	6.17	5.88	7.91	6.86	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
UTAHIN	46.08	42.64	46.42	45.31	41.70	32.06	35.30	38.43	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	45.57	43.40	44.65	46.31	45.89	32.66	38.91	38.81	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
UTAHAT	76.78	68.37	77.72	77.34	79.41	59.83	78.04	56.86	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	28.46	30.43	31.25	33.75	33.32	45.83	32.75	35.59	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
OLINE	43.60	41.86	42.80	46.25	42.80	45.67	46.11	40.20	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	65.00	59.93	63.44	68.91	63.16	68.73	68.61	59.53	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
TRULLN	1.26	1.22	1.44	1.32	1.16	1.22	1.06	1.24	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	1.13	1.09	1.26	1.00	1.22	1.33	1.35	1.39	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
YCINE	12.04	10.65	12.66	11.92	10.22	12.23	11.23	10.36	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	5.07	5.06	5.52	4.95	5.16	5.76	4.83	4.03	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
ANINE	17.69	18.20	21.97	19.72	15.41	19.13	18.95	15.72	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	6.03	5.66	5.57	4.89	6.22	6.99	9.20	7.19	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AMINO B	1.57	1.31	1.50	1.39	1.19	1.22	1.24	1.24	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	1.12	0.90	0.88	0.90	0.63	0.73	0.71	0.68	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

EXHIBIT 4 (Cont.) MILK amino acid levels in lactating women administered LACTULOSE at 50 mg/kg

MILK TIME (HR)	AMINO ACIDS, DOSE = 50, # SUBJECTS = 6								HOURS					
	0.0	1.0	2.0	3.0	4.0	8.0	12.0	24.0						
VALINE	3.99 0.80	3.87 0.94	4.23 0.75	4.63 1.75	3.72 1.03	3.50 0.76	3.54 0.88	4.72 0.91	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
CYSTINE	3.81 1.64	3.79 1.50	4.10 1.82	3.80 1.52	3.42 1.31	3.88 1.36	3.02 0.89	3.17 1.21	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
METHION	0.37 0.11	0.41 0.12	0.47 0.21	0.57 0.63	0.46 0.35	0.24 0.24	0.33 0.35	0.48 0.37	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
ISOLEUCN	0.77 0.33	0.89 0.48	0.89 0.82	1.33 2.10	0.99 1.16	0.84 0.40	1.03 0.52	1.18 0.52	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
LEUCINE	2.45 0.63	2.64 0.98	2.96 1.94	4.65 6.28	3.50 3.27	5.72 7.22	2.76 0.99	3.54 1.28	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
TYROSINE	0.84 0.24	0.78 0.32	0.87 0.49	1.02 0.94	0.71 0.37	0.84 0.58	2.82 4.62	1.22 0.72	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
PHENYLAL	0.80 0.35	0.89 0.39	0.87 0.32	1.40 1.85	0.90 0.53	0.81 0.34	0.93 0.59	0.86 0.24	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
CARNITHN	0.66 0.78	0.67 0.94	0.58 0.63	0.51 0.36	0.35 0.28	0.41 0.36	0.54 0.75	0.38 0.38	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
LYSINE	1.08 0.59	0.99 0.75	1.09 0.75	1.48 1.66	1.15 0.86	1.80 1.85	1.74 1.72	1.44 1.37	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
HISTIDIN	1.76 1.43	1.70 1.17	1.85 1.02	1.86 0.97	1.53 1.00	1.68 1.24	1.58 1.61	1.68 1.16	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
ARGININ	0.83 0.42	1.53 1.43	1.43 1.13	0.86 0.40	0.83 0.35	1.31 0.79	1.25 0.76	1.08 0.69	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0

EXHIBITS 5 AND 6

PLASMA AND ERYTHROCYTE FREE AMINO ACID LEVELS IN NORMAL ADULT
VOLUNTEERS ADMINISTERED ASPARTAME EITHER
IN SOLUTION (EXHIBIT 5) OR AS A SLURRY (EXHIBIT 6)
AT 100 MG/KG BODY WEIGHT

VALUES LISTED ARE THE MEAN AND STANDARD DEVIATION GIVEN IN UMOL/L PER 100 ML

Lxh
LASMA
TME (HR)
AIRINE
SPART
HREON
ERINE
SPARAGN
LUTAMIN
LUTAMAT
ROLINE
ITRULLN
LYCINE
ANINE
AMINO

Exhibit 5: Plasma amino acid levels in normal adults administered ASPARAME at 100 mg/kg in SOLUTION

5A

PLASMA AMINO ACIDS, DOSE = 100 / SUBJECTS = 6													
TIME (HR)	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00
ALANINE	5.62 1.56	5.46 1.67	5.14 1.81	6.15 1.62	5.19 1.80	5.17 1.92	5.65 2.13	4.51 1.29	4.63 1.43	4.47 1.29	4.70 1.43	4.45 1.51	4.51 1.82
SPART	0.16 0.05	0.38 0.15	0.43 0.23	0.29 0.15	0.20 0.09	0.29 0.14	0.27 0.19	0.14 0.08	0.11 0.04	0.09 0.02	0.09 0.04	0.08 0.06	0.08 0.05
UREON	15.29 2.13	15.39 2.46	15.51 1.65	16.11 1.69	15.57 2.37	14.64 2.75	13.84 2.39	12.60 2.29	12.16 2.45	12.31 2.51	12.44 2.44	11.64 2.14	11.72 2.18
ERINE	14.06 3.25	14.26 3.59	14.56 3.49	15.12 3.25	14.24 3.01	13.61 3.20	12.58 1.85	12.57 2.87	12.32 2.77	12.60 2.80	12.67 1.74	12.39 1.61	12.43 1.68
SPARAGN	8.67 1.16	9.67 1.88	10.13 2.11	11.05 2.53	11.90 2.55	10.37 1.75	8.99 1.33	7.55 1.10	7.44 1.12	7.43 1.43	8.56 1.03	7.09 1.15	6.56 1.80
LIJAMIN	68.04 11.98	64.94 11.50	65.77 10.78	66.18 9.70	61.33 7.00	60.87 2.18	60.36 5.39	58.70 6.70	56.64 5.96	57.89 6.30	59.20 7.75	58.48 5.86	58.17 4.56
LIJAMAT	3.93 2.65	3.34 1.19	5.10 1.50	5.08 1.54	3.83 1.66	4.51 2.50	4.98 2.13	3.69 1.99	3.37 1.83	2.96 1.44	2.63 0.99	3.14 1.59	2.51 1.25
COLINE	19.74 5.65	23.11 4.80	25.67 5.67	26.11 5.30	25.31 4.36	25.85 5.07	21.81 5.90	20.93 5.50	18.98 4.91	18.16 5.31	17.60 5.21	16.16 4.51	15.93 4.24
ITRILLN	2.93 0.47	2.68 0.97	2.29 1.11	1.70 0.38	1.41 0.59	1.22 0.57	1.24 0.40	1.81 0.56	2.16 0.50	2.30 0.52	2.54 0.58	2.38 0.66	2.12 0.61
LYCINE	26.45 9.07	24.65 8.61	24.02 8.34	24.18 7.21	22.65 7.07	21.61 6.28	20.38 1.95	20.76 5.88	19.92 6.41	20.05 6.71	20.33 5.81	19.99 5.71	20.00 5.61
ANINE	38.75 12.16	43.61 13.92	52.18 16.85	59.00 17.22	56.95 15.44	59.58 20.01	51.21 12.59	42.48 10.08	40.49 18.51	36.08 11.96	32.47 9.58	28.33 7.23	28.58 6.10
AMINO B	1.71 0.53	1.72 0.42	1.75 0.52	1.72 0.50	1.71 0.43	1.54 0.41	1.74 0.48	1.53 0.37	1.44 0.32	1.50 0.37	1.56 0.43	1.63 0.42	1.74 0.41

Exhibit 5 (cont.). Plasma amino acid levels in normal adults administered ASPARTANIL at 100 mg/kg in SOLUTION

56

PLASMA AMINO ACIDS, DOSE = 100 # SUBJECTS = 6														
TIME (HR)	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	
VALINE	22.21 5.20	20.83 3.83	20.29 4.02	19.90 4.11	18.17 4.01	16.84 4.02	16.63 3.18	16.84 2.63	16.44 3.62	17.57 3.47	18.45 3.92	18.18 3.70	18.16 3.46	2
CYSTINE	10.23 1.43	10.19 1.66	10.23 1.69	10.63 1.20	9.71 1.70	23.19 33.71	9.78 1.43	9.65 1.11	9.63 1.45	9.96 1.29	10.16 1.46	10.19 0.95	10.06 1.27	
METHION	3.17 0.61	3.36 0.74	3.12 0.53	3.04 0.47	2.71 0.42	2.47 0.47	2.51 0.53	2.33 0.36	2.26 0.36	2.46 0.39	2.56 0.47	2.40 0.36	2.58 0.34	
ISOLEUCIN	6.06 1.55	5.76 1.86	4.98 1.20	4.57 1.21	3.84 1.17	3.26 1.19	3.37 0.93	3.45 0.56	3.53 0.83	4.18 0.95	4.51 0.83	4.59 0.81	4.89 0.79	
LEUCINE	12.53 2.43	11.57 2.08	10.60 2.02	9.85 2.06	8.44 1.82	7.17 1.88	7.39 1.62	7.56 1.13	7.90 1.92	9.44 1.69	10.35 1.73	10.66 1.94	11.33 1.70	1
TYROSINE	5.64 1.18	6.76 1.60	7.90 2.37	8.77 3.01	8.77 3.18	9.53 3.10	9.43 3.22	9.55 3.06	9.05 2.59	8.75 2.11	7.86 1.75	7.02 1.50	6.63 1.30	
PHENYLAL	5.40 1.05	13.18 3.55	20.14 5.24	20.22 6.77	18.98 5.38	20.25 2.05	18.08 2.66	13.70 1.71	11.62 2.28	9.38 1.52	7.82 1.44	6.75 1.02	6.30 0.90	
ORNITHIN	7.85 5.53	7.59 4.72	7.49 4.29	7.75 3.93	6.68 2.81	7.62 4.97	7.04 5.75	7.20 4.50	6.73 4.26	6.69 4.32	6.90 4.32	6.36 3.43	6.38 3.85	
LYSINE	20.28 1.20	19.54 1.60	19.29 2.27	19.07 2.72	17.62 2.28	17.31 2.10	17.66 0.67	18.00 1.71	17.75 2.55	18.52 2.69	18.56 3.59	18.14 3.40	18.70 2.42	2
HISTIDIN	10.49 1.78	10.25 1.98	10.09 1.59	10.14 1.29	9.36 1.69	9.19 2.13	8.84 1.68	8.97 1.92	9.10 2.05	9.55 2.09	9.34 2.69	9.13 2.40	9.62 2.12	1
ARGININ	9.86 2.05	10.61 1.68	11.19 2.32	11.24 2.34	10.12 1.86	9.50 1.73	8.89 1.62	8.85 1.59	8.50 1.37	8.82 1.61	8.75 1.72	8.77 1.26	8.85 2.06	

24

TABLE 5 (cont) Erythrocyte amino acid levels in normal adults administered ASPARTAMID at 100 mg/kg in SOLUTION

56

AMINO ACIDS, DOSE = 100 # SUBJECTS = 6														
TIME (HR)	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.00
ALANINE	22.49 7.74	20.72 4.88	19.00 7.24	18.98 7.45	23.47 10.68	25.78 7.93	24.32 7.06	26.12 6.84	28.81 5.60	30.07 12.05	27.38 10.00	29.69 10.81	33.70 9.75	29.9 11.4
GLUTAMINE	4.66 3.19	5.25 3.05	4.51 4.07	7.82 4.29	4.84 2.82	3.41 1.41	2.99 2.20	3.45 1.71	3.58 3.07	6.02 5.18	8.42 7.00	5.90 6.20	7.31 9.58	3.4 0.9
ASPARTATE	23.59 3.82	24.44 5.34	24.91 5.00	23.43 3.77	24.75 4.60	25.86 5.91	23.81 4.18	24.68 6.07	24.40 5.04	23.94 4.89	24.19 4.93	24.03 4.11	23.38 4.35	25.4 5.4
GLUTAMINE	10.78 2.46	11.60 2.53	11.51 2.55	10.91 2.54	10.70 3.42	9.58 2.89	9.41 3.23	9.79 1.92	9.39 2.73	9.42 2.05	8.50 2.07	8.16 1.70	7.40 1.88	10.8 3.00
GLUTAMINE	11.05 2.23	11.81 2.23	14.05 1.60	13.68 1.40	13.43 2.41	12.52 1.72	13.00 1.83	13.36 1.95	13.59 2.28	13.99 2.15	13.28 2.30	13.19 2.07	13.22 2.51	13.5 2.5
ASPARAGINE	14.39 2.60	15.09 3.73	14.96 3.00	16.45 4.14	15.07 3.56	13.66 4.07	12.58 6.69	13.57 4.87	14.39 4.94	13.17 4.11	13.49 4.88	14.73 4.42	13.40 3.15	13.65 3.56
GLUTAMINE	50.36 8.28	50.41 8.79	48.86 7.16	49.49 4.56	49.29 6.79	48.21 6.97	48.93 7.23	48.72 8.12	47.74 6.52	47.57 6.86	45.05 7.80	43.79 7.54	44.21 8.57	43.94 7.58
ASPARTATE	23.17 4.83	23.88 4.77	24.92 5.60	25.06 6.03	24.65 5.31	24.12 6.91	23.76 6.02	24.72 6.10	24.80 5.86	24.16 5.42	23.27 4.51	23.70 2.49	25.14 1.53	24.47 4.09
GLUTAMINE	11.46 3.62	12.53 3.94	13.85 4.91	14.48 3.49	15.67 4.21	14.66 4.25	13.81 6.23	14.46 6.64	13.51 6.02	12.23 5.82	11.33 5.09	9.98 3.76	10.81 3.12	13.35 3.06
GLUTAMINE	29.80 3.29	29.41 3.56	30.42 3.08	30.30 3.37	29.26 2.60	30.58 3.11	29.55 3.01	28.49 3.59	29.64 2.59	28.56 2.85	27.85 3.29	23.37 9.98	20.80 2.39	29.25 2.10
GLUTAMINE	27.63 5.36	30.04 4.07	30.88 4.97	34.23 6.00	36.18 5.52	31.80 6.32	36.41 4.35	38.58 11.75	35.01 12.39	31.94 11.74	27.82 9.83	25.27 6.46	23.90 5.67	25.00 3.67

2511 SQRT NEGATIVE ARGUMENT=-0.9536743E-06

CEBACK ROUTINE CALLED FROM ISN REG. 14 REG. 15 REG. 0 REG. 1

SORT	0038	52090832	00092328	00000008	000878DC
STAT	0050	62089786	00089708	00000004	00083950
IN		0000BDC2	0108	00	FF000018
					000A0F60

TABLE 7 PLASMA amino acid levels in normal adults administered ASPARTAMID at 150 mg/kg

7A

AMINO ACIDS, DOSE = 150 # SUBJECTS = 6														
TIME (HR)	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.00
ALANINE	5.38	5.00	4.81	5.28	4.61	5.28	5.26	5.15	4.93	4.93	4.93	4.82	5.77	4.2

Exhibit 5 (cont.) Lymphocyte amino acid levels in normal adults administered ASPARTAME at 100 mg/kg in SOLUTION

50

IC	AMINO ACIDS, DOSE = 100 1 SUBJECTS = 6						2.00	3.00	4.00	5.00	6.00	7.00	8.00	24
	TIME (HRS)	0.0	0.25	0.50	0.75	1.00								
ALINE	14.21 4.62	14.89 5.55	14.41 5.40	15.49 5.41	14.87 4.76	15.13 4.22	14.17 3.44	13.37 4.54	12.62 3.77	13.60 3.69	13.53 3.92	13.23 3.63	13.30 4.51	16.0 3.5
ISTINE	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
ETHICN	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.30 0.51	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
OLEUCN	5.18 2.37	5.05 2.78	5.22 2.42	2.66 0.81	2.85 1.54	2.24 0.64	2.34 0.85	2.22 0.52	2.58 0.98	2.65 0.57	3.07 1.59	3.07 0.97	3.11 0.44	5.3 1.6
UCINE	8.35 2.16	8.18 2.06	7.67 1.76	6.42 1.15	6.06 1.01	5.36 1.36	4.90 1.47	4.68 0.95	5.25 1.49	6.40 1.44	8.16 5.37	6.75 1.41	7.31 0.98	9.1 1.8
ROSINE	4.74 1.60	5.95 2.17	6.74 2.76	7.42 3.23	7.65 3.41	7.58 4.02	8.34 3.92	9.02 3.31	8.49 3.12	7.78 2.99	6.69 2.48	5.31 1.71	5.43 1.56	4.6 0.6
ENYLAL	3.60 1.05	10.36 3.83	15.13 5.00	14.42 5.25	14.40 4.68	14.97 3.43	14.28 2.98	12.05 3.30	8.80 2.68	6.56 2.02	5.63 1.52	4.34 1.13	4.26 1.16	3.7 0.6
NITHIN	12.02 3.70	12.62 3.68	12.83 3.20	12.58 2.13	12.87 3.59	12.92 2.11	12.92 2.67	12.67 4.13	12.49 3.70	12.00 2.49	11.96 2.69	12.07 3.32	11.05 3.80	12.9 3.5
SINE	11.79 2.07	12.19 1.69	11.25 1.79	11.18 1.00	11.90 1.81	11.04 1.77	11.60 1.74	11.46 2.80	11.45 2.99	10.95 2.60	10.06 1.69	10.76 2.14	10.01 2.54	12.7 2.7
STIDIN	7.50 1.37	8.32 1.02	7.67 1.36	7.32 1.45	8.39 1.14	7.04 1.46	8.01 1.51	7.37 1.32	7.76 1.79	7.20 1.90	7.15 1.04	7.33 1.03	6.98 1.42	7.8 1.3
GININE	2.29 0.95	2.34 1.13	2.31 1.17	2.08 1.00	2.14 1.32	1.81 1.18	2.28 1.31	2.50 1.19	2.09 0.79	2.29 1.17	1.82 1.01	1.82 0.93	2.71 1.06	1.8 0.6

96

Exhibit 7 (cont.) PLASMA amino acid levels in normal adults administered ASPARTAME at 150 mg/kg body wt.

711

PLASMA AMINO ACIDS, DOSE = 150 & SUBJECTS = 6														
TIME (HR)	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24
ALINE	20.82	20.82	20.18	18.34	17.58	16.87	16.89	16.09	17.49	17.87	18.27	19.49	18.90	20.0

Exhibit 6 Plasma amino acid levels in normal adults administered ASPARTAME at 100 mg/kg in 24 hours

ASMA ME (HR)	AMINO ACIDS, DOSE = 100					V SUBJECTS = 6									
	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.	
URINE	5.86 1.52	6.24 1.25	6.14 1.15	6.10 1.32	5.79 0.90	5.78 1.68	5.82 2.04	5.46 1.65	5.48 1.52	5.16 1.25	5.69 1.32	5.27 1.05	5.68 0.89	5.8 1.3	
PART	0.46 0.28	0.43 0.18	1.48 2.16	1.51 1.85	0.53 0.43	0.63 0.42	0.40 0.38	0.30 0.22	0.23 0.13	0.21 0.09	0.24 0.07	0.16 0.09	0.13 0.07	0.1 0.0	
REON	14.31 4.21	13.87 4.44	14.58 5.01	14.16 4.85	15.36 5.25	13.38 4.27	13.40 4.60	12.92 4.29	12.39 3.70	11.88 3.19	12.21 3.06	11.91 3.56	11.73 3.34	14.0 4.3	
RINE	13.08 2.63	13.00 1.97	13.69 2.53	13.67 2.38	14.61 2.42	14.24 1.63	13.61 1.41	13.28 1.18	12.88 1.12	12.54 0.71	12.61 0.82	12.64 0.72	12.31 1.24	13.3 0.2	
PARAGN	6.52 1.78	6.35 1.41	6.76 1.04	6.84 0.84	7.15 0.73	6.62 0.57	6.93 1.70	5.19 1.35	5.05 0.90	4.88 1.06	4.41 1.02	4.47 0.41	4.95 1.70	5.7 1.6	
UTAMIN	62.69 5.59	60.91 6.37	62.39 10.73	63.22 13.16	66.92 13.61	65.52 8.31	61.93 5.12	62.13 4.27	60.80 5.66	63.62 5.09	62.88 5.31	61.39 5.39	62.66 6.55	61.3 6.3	
UTAMAT	2.79 1.30	4.32 2.15	5.23 2.99	5.39 3.50	4.53 3.01	4.85 3.03	5.30 5.46	3.30 2.72	2.77 1.68	2.71 1.80	2.99 1.46	3.00 2.00	2.78 1.76	2.5 1.0	
COLINE	19.17 5.55	18.71 6.55	19.84 7.96	20.17 7.05	20.88 6.64	21.63 5.06	18.25 4.86	17.75 5.23	16.74 5.27	15.65 4.90	15.59 4.29	15.44 4.25	15.33 4.07	20.1 6.3	
TRULLN	2.51 0.57	2.25 0.65	1.91 0.69	1.73 0.57	1.65 0.74	1.54 0.75	1.57 0.86	1.89 0.81	1.98 0.70	2.20 0.64	2.21 0.56	2.30 0.71	2.11 0.85	2.3 0.7	
YCINE	24.33 5.30	23.08 5.11	22.63 5.44	22.07 5.58	22.45 5.30	22.24 4.53	21.14 4.39	20.76 4.27	19.85 4.11	19.11 4.61	19.33 3.94	19.60 3.92	19.46 3.90	23.2 3.7	
ANINE	33.64 7.04	32.80 7.64	38.48 9.10	42.45 10.58	45.25 8.32	46.38 4.62	43.63 9.12	37.99 9.67	32.91 6.12	29.25 4.22	27.92 4.21	26.12 4.51	25.93 4.88	32.3 6.8	
AMINO B	1.92 1.00	2.05 1.13	2.21 1.33	2.16 1.31	2.27 1.32	2.28 1.11	2.01 1.11	1.87 0.92	1.90 0.98	1.95 0.88	2.14 0.85	2.08 1.05	2.19 1.06	2.1 0.9	

Exhibit 7 (cont) ERYTHROCYTE amino acid levels in normal adults administered ASPARTAME at 150 mg/kg

70

C	AMINO ACIDS, DOSE = 150					V SUBJECTS = 6										
ME (HR)	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.0		
URINE	15.82	15.68	15.14	17.24	17.14	14.65	15.07	17.64	18.04	18.72	18.78	18.22	18.01	18.0		

EXHIBIT 6 (cont.). Plasma amino acid levels in normal adults administered ASPARTAME at 100 mg/kg in SLURRY

63

ASMA TIME (HR)	AMINO ACIDS, DOSE = 100 # SUBJECTS = 6													
	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.0
LINE	20.34 6.48	19.93 6.84	19.91 7.30	19.35 6.94	19.07 6.64	19.32 6.37	15.98 5.51	16.68 4.69	17.35 5.14	17.67 4.91	18.61 4.65	18.51 5.39	18.93 4.96	22.04 6.91
STINE	9.79 1.05	9.78 1.27	9.94 1.78	9.86 1.51	10.14 1.37	10.03 0.97	9.27 1.08	9.16 1.27	8.85 1.47	9.16 1.25	9.36 1.01	9.40 2.01	9.54 1.70	9.61 1.46
THION	2.72 0.48	2.69 0.49	2.69 0.58	2.57 0.46	2.54 0.41	2.57 0.45	2.68 0.63	2.29 0.32	2.35 0.34	2.31 0.33	2.34 0.35	2.43 0.47	2.40 0.37	3.03 0.54
OLEICN	5.42 1.28	5.03 1.32	4.96 1.57	4.65 1.37	4.40 1.22	4.28 1.28	3.71 1.33	3.68 0.76	4.01 0.74	4.15 0.85	4.43 0.83	4.82 1.29	4.93 1.11	6.15 1.55
ICINE	11.85 2.44	11.36 2.74	11.17 3.19	10.57 2.84	10.11 2.68	9.78 2.39	7.98 2.15	8.71 1.48	9.57 1.70	10.03 1.77	11.01 1.81	11.23 2.19	11.97 2.26	12.91 3.38
ROSINE	5.27 0.95	5.92 1.63	7.36 2.76	8.06 3.08	9.08 3.11	10.77 3.33	10.34 2.15	10.15 1.40	9.75 1.23	8.62 1.52	7.74 1.53	7.28 1.39	6.87 1.50	6.05 1.60
ENYLAL	5.48 0.68	8.73 3.61	21.03 14.28	25.95 18.86	25.13 16.25	24.59 6.91	20.45 7.10	16.05 2.55	13.49 2.85	10.19 2.65	8.37 2.28	7.27 1.36	7.06 2.04	5.78 1.06
NITHN	5.19 1.09	4.92 1.23	5.20 1.32	5.22 1.21	5.05 1.01	5.73 1.30	4.85 0.65	4.92 0.71	4.99 0.65	4.67 0.52	5.23 0.83	4.91 0.74	4.60 0.75	5.80 1.01
SINE	15.96 3.58	16.24 4.26	16.66 5.09	16.32 4.72	16.16 4.81	15.76 4.11	14.57 4.23	15.35 3.21	16.05 3.57	15.78 3.04	16.52 2.97	16.53 4.49	16.37 4.67	18.37 5.72
STIDIN	9.03 1.50	9.08 1.37	9.24 1.88	8.92 1.82	9.13 1.77	8.54 1.14	8.42 1.73	8.78 1.31	9.35 1.88	9.04 1.48	9.57 0.50	10.02 1.40	9.46 1.70	10.96 1.58
MININ	8.11 1.30	7.78 2.03	8.06 2.59	8.13 2.49	8.61 2.31	7.90 1.94	7.38 1.75	7.55 1.75	8.09 2.21	7.73 1.82	7.98 1.90	7.80 2.48	8.30 2.69	8.38 3.20

EXHIBIT 7 (cont.). LYTHROCYTE amino acid levels in normal adults administered ASPARTAME at 150 mg/kg

71

ASMA TIME (HR)	AMINO ACIDS, DOSE = 150 # SUBJECTS = 6													
	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.0

Exhibit 6 (cont). L-TRYPTOPHAN amino acid levels in normal adults administered ASPARAGINE at 100 mg/kg in SLURRY

BC TIME (HR)	AMINO ACIDS, DOSE = 100 # SUBJECTS = 6															
	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24		
SERINE	19.75 6.45	18.21 8.83	21.68 13.28	19.42 10.05	23.08 10.78	24.24 6.69	26.14 9.29	29.90 10.31	23.20 9.72	20.66 5.60	28.78 9.40	33.39 10.71	31.07 11.08	29.5 13.5		
ASPARAGINE	3.25 0.98	6.84 7.96	6.01 5.49	4.55 5.14	9.84 8.43	8.97 8.15	5.01 3.56	5.70 5.81	10.54 6.92	5.66 3.63	6.61 4.06	3.20 1.33	6.88 2.87	5.8 3.0		
SPARTAT	21.37 4.79	22.28 5.34	22.17 3.57	21.73 6.36	23.16 3.69	24.90 2.64	23.31 5.53	22.84 5.20	23.23 5.30	22.22 5.72	23.91 6.18	25.75 5.06	24.03 4.40	24.3 4.6		
UREONIN	8.93 3.28	9.45 3.79	10.14 5.43	9.57 4.88	10.26 4.36	9.22 3.53	10.10 4.37	9.26 3.97	10.05 4.45	7.80 2.85	7.62 2.84	6.74 2.15	7.77 3.50	9.1 4.3		
ERINE	11.30 2.02	12.23 2.26	12.79 3.32	12.05 3.39	12.42 1.85	13.39 2.49	13.03 1.95	11.98 2.23	13.61 2.15	11.85 1.97	12.15 2.60	12.36 2.10	12.31 3.05	12.8 2.6		
SPARAGN	12.85 4.11	11.63 1.62	13.05 3.52	12.07 3.80	13.03 2.40	11.16 2.39	13.58 3.96	13.06 5.96	13.26 4.12	10.89 4.10	12.03 4.76	12.73 2.39	13.34 4.24	13.5 4.5		
UTAMIN	43.25 8.74	45.77 9.27	47.95 11.35	43.72 10.78	45.01 7.99	47.39 10.17	44.77 7.14	44.86 9.26	46.09 7.50	41.35 10.01	42.44 10.09	43.78 8.44	41.20 8.77	43.2 7.9		
UTAMAT	22.79 5.69	25.05 5.38	24.69 6.13	22.83 6.47	23.87 4.57	23.94 3.65	26.16 5.39	26.77 5.51	25.40 5.70	24.23 5.26	25.12 4.69	23.71 9.65	27.82 4.54	26.5 5.5		
COLINE	8.01 2.05	8.90 2.39	9.30 2.26	9.48 3.01	9.93 1.53	10.73 1.98	10.59 2.24	9.13 2.47	9.47 2.34	8.31 2.95	8.35 2.86	9.39 2.56	8.38 2.35	10.8 2.1		
YCINE	28.98 4.60	29.35 5.08	31.29 4.61	29.11 5.86	31.43 3.45	32.71 3.69	31.47 2.64	31.15 4.20	31.01 1.29	28.17 3.63	28.79 3.15	27.01 3.10	28.12 4.46	29.7 4.0		
ANINE	21.66 5.56	23.26 5.77	25.40 6.88	25.54 6.25	27.78 3.73	33.31 8.17	29.58 4.78	26.93 5.07	27.98 3.39	23.19 5.63	23.09 5.37	23.02 4.45	20.59 4.33	24.3 3.4		
AMINO	4.74 3.69	4.34 4.47	4.07 4.67	3.45 1.94	2.43 1.03	4.50 4.81	5.64 3.81	1.37 0.31	1.90 1.00	1.21 1.46	1.91 3.65	1.76 1.07	1.25 1.10	1.1 0.3		

Excreted in (percent). Excretion of amino acid levels in normal adult, administered ASPARTATE at 100 mg/kg in 500cc of water

AMINO ACIDS, DOSE = 100 # SUBJECTS = 6															
TIME (HR)	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.	
GLUTAMINE	15.78 5.13	14.94 5.39	14.94 5.84	12.89 5.97	12.51 5.72	9.81 3.78	12.77 4.15	12.44 3.19	12.30 3.52	11.23 3.28	12.48 3.73	13.35 2.67	11.57 4.35	15.2 4.8	
GLUTAMINE	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	1.98 3.92	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	
GLUTAMINE	0.11 0.25	0.11 0.28	0.0 0.0	0.0 0.0	0.10 0.22	0.0 3.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	
GLUTAMINE	4.32 3.80	4.06 2.59	3.04 0.91	3.60 2.43	3.95 2.61	2.80 1.21	2.61 0.96	3.38 1.64	2.68 0.94	2.60 0.91	2.76 0.91	3.80 1.63	3.70 2.04	4.7 1.8	
GLUTAMINE	7.00 1.93	7.13 1.85	6.92 1.97	6.36 1.59	6.57 1.83	4.89 1.76	5.35 1.32	5.67 1.42	6.62 1.98	6.21 2.35	6.56 1.61	7.89 2.34	7.95 1.82	8.9 2.4	
GLUTAMINE	3.47 0.50	4.32 1.07	6.11 1.89	5.98 2.13	7.03 2.71	10.16 1.77	9.32 1.48	9.23 1.30	9.08 1.57	6.96 1.87	6.42 2.31	6.14 2.20	5.28 1.29	5.3 1.91	
GLUTAMINE	3.19 0.95	5.60 2.52	15.00 9.45	16.87 10.87	17.43 11.56	18.78 2.83	14.88 1.81	12.42 2.88	10.82 2.52	7.33 3.16	5.54 2.62	4.89 2.53	4.26 1.50	4.4 1.01	
GLUTAMINE	11.22 4.52	10.52 3.18	9.43 3.08	11.15 4.69	10.29 2.76	11.11 3.74	11.23 4.93	10.85 3.48	11.15 1.57	10.29 4.46	11.17 4.15	10.84 2.73	9.80 2.78	10.8 2.7	
GLUTAMINE	10.34 3.34	10.43 3.20	8.71 2.95	10.04 3.03	9.69 2.60	9.30 3.14	10.80 3.20	10.59 2.56	10.03 2.83	9.74 2.63	10.57 3.38	11.12 3.20	10.45 2.54	11.5 3.3	
GLUTAMINE	7.19 1.32	7.56 1.27	6.53 1.52	7.17 1.62	6.91 1.22	6.56 0.87	7.60 1.90	7.34 1.15	7.27 1.77	6.64 1.24	7.31 1.67	7.63 1.89	6.97 1.78	8.01 1.71	
GLUTAMINE	2.33 2.41	1.99 1.34	1.92 1.42	1.62 1.31	1.80 1.06	1.96 1.04	1.95 1.25	2.30 1.25	1.64 0.72	1.67 0.92	1.55 0.76	2.13 1.40	2.59 1.37	1.9 1.2	

100 9.00 24.

ASMA AMINO AC
TIME (HR) 0.0

EXHIBIT 7

PLASMA AND ERYTHROCYTE FREE AMINO ACID LEVELS IN
NORMAL ADULT VOLUNTEERS ADMINISTERED ASPARTAME AT 150 MG/KG BODY WEIGHT

VALUES LISTED ARE THE MEAN AND STANDARD DEVIATION GIVEN IN UMOLES PER 100 ML

AMINO ACIDS, DOSE = 150 # SUBJECTS = 6														/A	
TIME (HR)	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.	
LINE	5.38 1.99	5.00 1.94	4.81 1.76	5.28 1.82	4.61 1.53	5.28 1.48	5.26 1.52	5.15 1.52	4.93 1.66	4.93 1.32	4.93 1.06	4.82 1.20	5.77 1.34	4.3 0.7	
ART	0.27 0.10	0.65 0.50	1.00 0.70	0.65 0.42	0.47 0.17	0.79 0.47	0.57 0.36	0.24 0.11	0.19 0.15	0.17 0.13	0.17 0.15	0.20 0.13	0.29 0.19	0.1 0.0	
EN	13.68 2.40	13.83 2.63	13.61 2.00	12.32 2.13	12.66 1.91	12.60 2.13	12.95 2.89	12.23 2.31	11.25 1.79	11.23 2.27	10.37 2.00	11.73 2.22	11.11 2.67	13.1 2.6	
NE	10.50 1.99	11.37 3.16	11.72 3.22	11.72 2.88	11.15 3.20	11.09 2.80	11.61 2.30	10.70 2.24	10.75 2.41	10.79 1.64	10.59 1.53	11.26 1.58	10.91 0.94	11.4 1.4	
ARAGN	7.16 2.77	7.50 3.26	8.46 3.95	7.56 2.47	7.10 2.55	7.67 1.89	6.61 2.05	6.85 1.00	6.63 2.03	5.57 1.33	6.43 1.16	7.94 3.17	7.08 1.77	8.7 1.6	
AMIN	61.55 12.64	59.72 10.16	59.43 11.16	60.91 6.55	57.27 11.50	61.29 12.59	59.88 9.53	58.15 10.67	58.72 7.60	60.11 6.92	62.60 2.37	61.06 7.57	63.16 7.46	63.4 7.9	
AMAT	3.43 1.40	4.92 3.05	6.77 2.94	7.08 2.75	6.45 1.47	7.23 2.93	6.53 3.01	4.44 2.28	5.02 2.40	4.33 2.78	3.76 3.24	3.06 2.52	3.27 2.26	2.8 1.46	
IVE	19.63 6.00	22.16 5.12	24.42 7.49	25.24 7.38	23.00 7.18	24.87 6.97	24.51 5.18	20.39 4.24	18.27 4.40	17.01 4.11	17.81 4.16	17.20 4.29	15.55 3.98	21.18 6.21	
ULLN	2.42 1.07	2.37 0.95	1.98 0.88	1.84 0.48	1.31 0.84	1.35 0.77	1.40 0.79	1.72 0.72	2.21 0.91	2.31 0.76	2.56 0.46	2.47 0.81	2.28 0.71	2.66 0.9	
INE	21.37 9.16	20.84 10.81	19.16 9.37	19.23 7.72	16.92 8.10	16.59 8.08	17.10 8.47	17.27 9.28	17.73 10.52	17.46 9.32	18.41 8.67	18.98 11.13	17.38 7.72	22.51 10.0	
INE	37.36 6.46	42.43 7.96	52.23 11.19	58.75 8.86	57.25 12.81	61.14 12.46	59.92 9.23	46.18 7.91	38.26 5.20	35.42 6.18	35.53 3.02	35.43 6.02	31.67 2.98	41.24 5.75	
INO8	1.63 0.77	1.69 0.75	1.70 0.83	1.81 0.66	1.60 0.70	1.61 0.73	1.59 0.68	1.45 0.58	1.50 0.63	1.58 0.60	1.65 0.61	1.76 0.89	1.61 0.64	1.61 0.75	

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Exhibit 7 (cont.) PLASMA amino acid levels in normal adults administered ASPARAGINE at 150 mg/kg body wt.

711

PLASMA TIME (HR)	AMINO ACIDS, DOSE = 150 & SUBJECTS = 6													
	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.00
ALANINE	20.82 5.39	20.82 4.76	20.18 4.73	18.34 4.55	17.58 4.22	16.87 3.85	16.89 3.46	16.09 2.93	17.49 3.63	17.87 3.71	18.27 3.60	19.49 3.72	18.90 3.43	20.71 5.91
ASPARAGINE	9.31 1.60	9.99 1.52	9.50 1.46	8.84 1.23	9.04 0.92	8.87 1.17	9.32 1.14	8.53 1.29	8.45 1.31	8.58 1.38	8.39 1.05	8.61 1.88	9.13 0.96	9.11 1.00
CYSTEINE	2.49 0.75	2.50 0.49	2.70 0.82	2.23 0.44	2.03 0.54	1.97 0.49	1.84 0.31	1.77 0.27	2.05 0.30	2.00 0.32	2.29 0.36	2.26 0.25	2.33 0.34	3.00 0.60
ISOLEUCINE	6.03 1.41	5.82 1.35	5.64 1.51	4.79 1.11	4.29 1.23	3.58 0.95	3.39 0.55	3.30 0.55	3.94 0.70	4.26 0.66	4.53 0.68	4.95 0.85	5.07 0.67	6.71 1.51
GLUCINE	12.23 3.51	11.98 3.03	11.30 3.26	9.77 2.85	8.79 3.00	7.59 2.39	7.23 1.56	7.33 1.42	9.10 1.85	10.05 2.11	11.12 1.99	12.31 2.06	12.27 1.73	13.61 3.21
PROLINE	5.89 2.44	6.07 1.98	7.44 2.39	8.58 2.87	8.59 2.80	10.11 3.42	11.03 2.80	9.46 1.83	9.36 2.07	8.42 2.24	7.82 1.60	7.24 1.81	6.50 1.55	6.11 2.41
PHENYLALANINE	6.72 1.93	18.10 6.85	28.58 8.77	27.47 6.73	26.64 7.41	34.83 9.43	35.12 11.34	22.73 5.44	16.05 5.30	12.97 4.12	10.85 2.98	9.62 2.43	8.11 2.18	7.21 1.51
GLUTAMINE	5.25 1.87	5.27 1.78	5.70 2.07	5.75 1.94	5.01 1.68	5.52 1.85	5.43 1.46	5.14 1.68	4.92 1.38	5.04 1.66	5.64 1.18	5.68 1.26	5.80 1.39	6.51 2.21
GLUTAMINE	16.71 6.61	17.17 4.75	16.75 5.12	14.63 5.09	14.31 4.13	14.30 4.28	14.75 4.07	14.74 3.88	15.89 3.99	16.51 4.76	16.55 3.78	17.63 2.38	18.04 2.78	21.71 5.91
GLUTAMINE	9.11 2.14	8.93 1.92	8.71 1.83	7.50 1.70	7.63 1.56	7.66 1.90	7.88 2.18	7.36 1.04	8.12 1.64	8.60 2.32	8.33 2.14	8.45 1.11	9.44 2.45	10.91 2.51
ARGININE	9.81 3.64	10.01 2.42	10.67 3.57	9.69 3.44	8.92 2.89	9.11 2.62	9.23 2.45	7.52 2.30	8.24 1.95	7.91 1.93	8.11 1.57	8.13 1.66	8.55 1.58	10.71 1.71

Exhibit 7 (cont) ERYTHROCYTE amino acid levels in normal adults administered ASPARTAME at 150 mg/kg

7C

ACID NAME (HR)	AMINO ACIDS, DOSE = 150 # SUBJECTS = 6						7C								
	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.00	
LEUCINE	15.52 2.01	15.98 1.60	19.14 4.33	17.24 3.57	13.14 3.65	14.95 2.98	15.07 2.66	17.94 2.18	18.94 1.71	13.72 6.92	13.75 5.44	13.23 5.92	20.04 3.92	34.45 31.82	
ISOLEUCINE	6.52 3.91	4.87 2.08	4.99 2.60	5.64 6.45	3.41 0.60	7.18 7.85	4.91 2.23	11.91 21.37	6.74 5.33	5.94 4.59	11.65 10.29	4.75 2.64	6.36 3.21	5.92 2.89	
ASPARTATE	21.13 3.94	22.53 4.50	21.69 4.01	22.50 4.18	21.98 5.28	22.54 4.52	22.82 4.06	22.73 5.50	22.84 4.43	21.56 4.72	23.93 5.74	21.49 4.00	21.32 3.80	22.07 4.14	
ARGININE	9.63 1.88	10.49 2.04	9.57 2.59	10.02 1.44	9.39 2.00	9.57 1.86	9.84 2.17	9.01 2.17	9.25 1.93	8.19 2.25	7.91 1.54	8.56 3.34	8.37 1.86	10.48 2.34	
GLUTAMINE	11.75 3.18	11.59 2.01	11.07 2.15	11.87 1.96	10.94 2.28	11.41 1.82	11.85 2.06	11.08 1.88	11.65 2.03	10.53 1.72	11.42 1.69	10.60 1.53	11.20 1.70	11.99 1.20	
PARACETAMOL	12.76 2.91	11.62 3.81	11.55 3.05	13.86 2.93	12.23 3.70	13.47 2.62	12.91 3.23	13.46 4.09	13.20 3.35	11.55 2.78	12.71 3.29	12.18 3.65	10.95 1.00	12.09 2.42	
UTAMINE	47.00 9.88	47.51 8.34	43.71 6.93	45.51 7.20	44.32 6.07	45.40 8.43	47.65 8.43	48.38 8.53	49.11 6.28	41.97 5.93	45.84 7.79	42.70 7.06	45.02 5.77	45.67 4.14	
UTAMATE	23.46 5.94	23.53 7.36	22.52 7.17	25.53 8.74	24.62 8.32	23.37 7.97	23.25 6.61	24.20 7.92	25.19 7.51	24.25 8.04	27.12 6.81	25.75 7.24	26.19 7.62	23.46 5.70	
GLUTAMINE	11.72 2.57	12.05 2.79	12.42 3.29	12.76 3.37	13.12 2.61	13.14 2.66	14.05 3.59	13.35 3.30	12.36 2.84	11.01 2.93	11.01 3.22	9.85 3.25	9.24 2.48	12.47 3.10	
GLYCINE	30.14 5.67	30.80 5.13	30.55 5.43	29.49 5.84	28.45 5.94	29.97 3.51	28.93 4.52	29.43 6.76	29.73 5.37	29.69 3.89	29.81 4.80	29.97 3.27	30.51 5.61	30.47 3.02	
AMINE	29.36 4.21	32.26 5.37	32.41 3.39	35.94 1.68	36.07 0.96	37.84 3.04	37.33 3.42	38.17 4.27	36.68 3.96	33.99 5.01	35.19 3.94	34.26 5.24	31.55 5.53	36.47 4.77	
AMINOACIDS	0.85 0.55	0.72 0.41	0.66 0.47	0.87 0.53	0.78 0.35	0.68 0.47	0.83 0.76	0.58 0.53	0.77 0.44	0.67 0.52	0.70 0.57	0.61 0.43	0.60 0.44	0.77 0.44	

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EXHIBIT / (cont.) LYMPHOCYTE amino acid levels in normal adults administered ASPARAGINE at 150 mg/kg

77

TIME (HR)	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.
ALANINE	13.54 4.47	14.06 4.09	13.25 4.09	12.17 4.32	11.97 4.00	11.73 2.67	12.29 2.98	11.46 1.94	12.49 3.20	11.53 3.75	11.49 2.36	12.09 2.66	13.05 1.65	16.4 4.6
ASPARAGINE	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
CYSTEINE	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
ETHIONINE	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
ISOLEUCINE	3.80 1.14	3.57 0.82	3.34 0.83	2.98 0.84	2.44 0.83	2.19 0.70	1.95 0.96	1.92 0.56	2.70 0.83	2.38 0.52	2.60 0.64	2.68 0.74	2.99 0.55	3.9 1.2
LEUCINE	7.83 2.39	7.51 2.04	7.01 1.91	6.42 2.10	5.28 1.96	4.85 1.18	4.61 1.62	4.58 0.71	6.17 1.26	5.58 1.24	6.81 1.91	6.96 1.69	7.68 1.28	9.2 2.2
PROLINE	3.65 1.65	4.84 1.92	6.04 1.86	7.29 2.10	7.34 2.23	8.71 2.73	9.47 2.95	8.15 2.72	7.83 2.95	6.32 2.35	6.03 2.54	5.82 2.35	5.60 2.01	5.0 2.3
PHENYLALANINE	3.14 1.09	13.89 6.51	21.59 6.27	21.22 6.49	20.05 6.49	26.38 8.70	26.30 9.19	16.41 6.21	11.99 5.61	8.10 3.20	7.31 3.13	6.58 2.61	5.76 2.10	4.2 1.0
THIAMINE	10.7 2.69	11.49 3.05	11.39 3.09	13.51 3.16	12.09 2.59	12.29 3.20	12.33 4.88	10.97 4.48	9.94 2.39	11.21 3.59	12.24 3.38	10.16 3.73	10.91 4.53	12.3 4.1
VALINE	10.53 1.69	10.62 1.75	10.18 1.69	10.66 1.67	10.57 1.69	10.22 2.01	10.05 2.56	10.36 2.49	10.65 2.68	10.51 2.13	10.90 3.17	10.34 2.16	11.71 2.42	12.9 2.6
STROPHANTHINE	6.83 1.25	6.86 1.06	6.87 1.20	7.27 1.20	7.23 0.95	7.06 0.75	6.94 1.20	6.93 1.35	6.98 1.20	6.81 1.00	6.95 1.39	6.26 0.80	7.45 1.42	7.6 1.3
ARGININE	2.54 0.60	2.70 0.84	3.75 3.21	2.77 1.19	2.56 0.93	2.24 1.05	2.56 0.86	2.94 1.12	2.91 1.33	2.51 1.34	2.69 1.68	2.42 1.51	2.92 0.92	2.3 0.8

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EXHIBIT 8

PLASMA AND ERYTHROCYTE FREE AMINO ACID LEVELS IN NORMAL
ADULT VOLUNTEERS ADMINISTERED ASPARTAME AT 200 MG PER KG BODY WEIGHT

VALUES LISTED ARE THE MEAN AND STANDARD DEVIATION GIVEN IN UMOL/L PER 100 ML

1 mg/kg.

0.1

6.00 7.00 8.00 24

0.0 0.0 17.86 0.1

Exhibit 8: PLASMA amino acid levels in normal volunteers administered ASPARTAME at 200 mg/kg

HA

PLASMA AMINO ACIDS, DOSE = 200 # SUBJECTS = 5														
TIME (HR)	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	9.00	24.00
ASPARAGINE	3.41 0.52	3.22 0.55	3.17 0.81	3.55 0.72	3.53 0.84	3.37 0.63	3.56 0.45	3.13 0.29	3.06 0.37	2.96 0.46	3.02 0.30	2.89 0.29	3.03 0.43	3.11 0.51
ASPARTATE	0.22 0.08	0.50 0.47	0.76 0.57	0.65 0.47	0.57 0.23	0.71 0.38	0.58 0.28	0.27 0.08	0.23 0.08	0.20 0.05	0.13 0.03	0.11 0.02	0.25 0.16	0.21 0.01
THREONINE	12.48 3.08	13.13 3.84	13.67 4.36	13.26 4.15	13.36 5.35	12.51 5.09	11.53 4.16	10.20 2.94	9.99 3.47	9.38 2.87	9.82 2.73	9.71 3.07	9.38 2.34	12.71 2.71
GLUTAMINE	10.00 2.18	12.79 3.08	11.45 3.05	11.24 2.97	11.69 4.50	11.21 3.83	10.70 3.18	9.81 2.22	9.54 1.91	9.34 1.99	9.64 2.02	9.66 2.21	9.60 2.10	11.61 1.71
ASPARAGINE	6.79 1.26	7.86 2.11	8.49 2.47	8.29 2.52	8.72 2.70	7.97 2.62	7.46 1.64	6.85 1.23	6.40 1.64	5.76 1.33	7.00 1.38	5.86 1.12	5.66 0.85	8.71 1.71
L-GLUTAMINE	60.71 5.86	59.67 7.84	60.53 6.83	58.70 7.50	59.01 11.76	56.80 9.77	56.03 8.76	58.09 7.36	55.64 7.49	56.37 7.19	54.19 7.98	55.16 6.82	53.73 9.03	61.61 12.51
L-GLUTAMATE	2.80 1.50	3.40 2.62	4.50 3.38	5.52 2.95	5.49 2.54	5.96 2.42	5.60 2.50	3.25 1.63	3.19 1.94	3.50 2.52	2.43 1.13	2.66 1.75	2.86 1.24	2.91 1.01
GLUTAMINE	19.51 6.60	21.70 7.09	24.16 7.19	25.00 6.81	25.93 7.97	26.47 6.83	24.51 5.05	20.33 5.23	18.57 4.96	16.97 4.69	16.96 4.64	16.10 3.97	15.24 3.66	21.31 8.41
ISOLEUCINE	2.45 0.64	2.09 3.59	1.73 0.49	1.36 0.35	1.25 0.38	0.97 0.36	1.04 0.41	1.60 0.91	1.81 0.87	1.96 0.86	2.00 0.61	2.09 0.61	2.02 0.51	2.61 0.61
LYCINE	21.99 5.12	20.98 5.73	19.73 5.58	18.13 5.59	17.46 6.38	16.43 5.23	16.23 5.56	16.02 4.09	15.22 3.81	15.01 2.94	15.84 3.05	15.57 2.98	15.72 3.09	23.81 3.81
GLUTAMINE	30.22 5.94	34.30 9.32	42.13 10.02	48.78 11.16	56.66 21.47	58.22 20.50	55.51 18.31	40.97 7.09	36.01 7.17	30.85 6.17	30.59 4.95	25.88 5.71	25.43 3.61	37.61 11.61
AMINO ACIDS	1.91 0.89	1.87 0.82	1.79 0.90	2.01 0.82	1.77 0.75	1.75 0.70	1.74 0.80	1.61 0.73	1.70 0.56	1.92 0.72	2.19 0.75	2.11 0.59	2.15 0.86	2.61 0.71

EXHIBIT 9 (Cont) ERYTHROCYTE free amino acid levels in PKU HETEROZYGOTES administered ASPARTAME at 34 mg/kg

50

PKU	AMINO ACIDS, DOSE = 34 # SUBJECTS = 4													
TIME (HR)	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.00

TABLE 11 (Cont.) PLASMA amino acid levels in normal volunteers administered ASPARTAME at 200 mg/kg

SMA E (HR)	AMINO ACIDS, DOSE = 200 # SUBJECTS = 5														
	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.0	
INE	20.12 4.45	19.99 4.08	19.88 4.24	19.05 4.19	19.12 5.55	16.15 3.69	15.13 3.36	15.93 3.76	16.01 3.11	16.47 3.81	17.57 3.82	17.53 3.08	17.71 3.30	21.8 3.0	
INE	10.17 1.32	10.34 1.54	10.43 1.24	10.67 1.33	10.59 1.53	10.44 1.27	9.79 1.57	9.70 1.24	9.50 1.04	9.38 1.74	9.58 1.23	9.98 1.27	9.76 1.38	11.2 1.0	
IGN	3.77 0.60	3.58 0.72	3.53 0.74	3.34 0.72	2.97 0.41	2.79 0.64	2.58 0.31	2.40 0.28	2.55 0.28	2.74 0.67	3.01 0.45	3.14 0.63	3.30 0.55	4.4 0.6	
LEUCN	6.94 1.23	6.20 0.96	5.99 1.28	5.40 1.24	4.44 1.19	3.81 1.13	3.24 1.04	3.14 0.67	3.61 0.90	4.15 1.26	4.85 0.91	5.13 1.30	5.64 0.91	7.8 1.2	
INE	12.65 1.94	12.16 0.99	11.75 1.02	10.44 1.11	8.73 1.26	7.49 0.99	6.78 2.15	6.85 1.13	8.16 1.30	9.33 1.77	10.59 1.91	11.39 1.62	11.63 1.41	14.2 1.5	
OSINE	5.69 0.78	6.78 1.31	7.93 1.39	9.14 1.75	10.68 2.48	12.04 2.58	13.49 3.46	13.65 4.01	12.80 3.62	11.79 2.74	10.34 1.39	8.93 1.64	7.74 1.59	6.9 1.1	
NYLAL	5.26 0.67	17.20 7.16	32.80 7.31	37.68 8.06	42.32 14.61	48.72 15.49	58.12 15.25	31.68 7.98	22.78 5.14	16.30 3.78	13.22 2.80	10.75 2.13	8.67 1.42	6.4 1.3	
ITHN	5.05 1.09	5.12 0.81	5.39 1.14	5.10 0.93	5.00 1.03	4.95 1.01	4.75 1.17	4.51 1.00	4.19 0.88	3.97 1.01	4.00 1.12	4.73 1.85	3.99 0.95	5.8 1.2	
INE	17.41 2.63	17.25 2.48	17.15 2.25	15.65 1.84	14.99 2.54	14.19 2.00	13.74 2.24	14.30 1.36	14.41 1.29	14.67 0.96	15.36 1.23	15.81 1.52	15.76 1.14	20.1 1.9	
IDIIN	9.19 1.80	9.37 1.82	9.51 2.19	9.01 2.00	8.33 1.77	7.84 1.91	7.27 1.34	7.48 1.25	7.88 1.35	8.26 1.05	8.40 1.37	8.76 1.59	8.54 1.45	10.5 2.2	
ININ	10.86 3.27	11.61 3.92	12.02 3.04	11.35 3.00	11.50 5.03	10.51 3.78	9.90 3.91	8.75 2.65	8.46 2.83	8.45 2.18	8.69 2.41	8.96 2.40	8.73 2.20	11.6 2.9	

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EXHIBIT 9 (Cont.) ERYTHROCYTE free amino acid levels in PKU HETEROZYGOTES administered ASPARTAME at 34 mg/kg.

90

SC	AMINO ACIDS, DOSE = 34 # SUBJECTS = 4													
TIME (HR)	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24
ALANINE	15.50	16.34	16.03	15.10	13.56	13.22	13.72	14.92	15.39	0.0	0.0	0.0	15.15	0.0
	0.58	0.41	1.35	1.54	1.14	0.79	0.37	0.34	1.21	0.0	0.0	0.0	0.50	0.0

Exhibit U (cont.) ERYTHROCYTE amino acid levels in normal adults administered ASPARTAME at 200 mg/kg

BC

AMINO ACIDS, DOSE = 200 # SUBJECTS = 6														
(HR)	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.
INE	0.33 0.01	0.50 0.25	0.62 0.52	0.47 0.18	0.32 0.07	0.35 0.28	0.66 0.41	0.26 0.02	0.33 0.06	0.32 0.14	0.20 0.06	0.66 0.37	0.52 0.36	0.6 0.3
INE	5.08 2.46	6.48 3.34	8.67 3.82	9.10 9.71	6.85 3.00	10.62 5.46	7.50 1.26	14.36 20.74	10.94 11.35	10.27 11.45	8.18 5.21	5.12 2.38	10.59 10.49	15.5 9.1
RTAT	13.05 5.57	13.69 5.84	13.52 5.77	13.67 6.05	12.85 5.80	13.04 5.97	13.53 6.17	14.20 6.65	13.99 5.99	14.66 6.61	12.75 4.07	14.16 6.80	14.04 5.63	14.2 6.4
ONIN	10.38 3.62	10.77 3.16	10.85 3.30	10.95 3.76	10.72 3.77	11.06 4.43	10.09 3.66	9.95 3.19	0.83 2.87	8.25 2.87	8.28 2.43	8.10 1.75	8.70 2.09	10.2 2.0
INE	12.00 2.24	11.87 2.08	11.94 2.14	11.95 2.50	11.69 2.63	11.08 2.49	11.55 2.39	11.93 2.15	11.30 2.14	11.09 1.57	11.41 2.26	11.12 2.56	11.59 2.06	11.9 1.4
RAGN	12.08 4.10	11.08 2.84	12.01 4.13	12.68 3.62	11.32 4.36	11.52 4.40	11.65 3.76	9.43 2.36	12.17 2.77	12.24 2.55	12.07 2.21	11.58 4.61	10.92 1.45	11.7 4.1
AMIN	51.71 7.13	49.13 8.27	49.42 8.78	48.29 9.16	47.51 9.21	46.03 8.90	47.24 9.57	47.60 10.45	45.91 7.77	45.63 8.81	45.36 7.59	44.00 11.23	45.82 9.11	48.0 13.6
AMAT	22.05 5.82	21.17 5.11	22.61 6.16	23.11 6.48	23.11 5.82	22.85 6.46	23.00 6.24	22.87 5.51	23.26 7.04	23.14 7.40	22.71 7.45	23.48 7.12	23.95 6.82	22.7 6.7
INE	10.81 3.95	11.54 4.14	11.31 4.30	13.31 4.75	13.20 4.42	13.04 4.75	13.39 4.17	11.83 3.54	10.21 3.21	10.01 2.90	8.76 2.29	8.39 2.81	8.93 2.69	12.2 4.8
INE	36.72 7.76	35.31 6.59	35.44 6.67	34.91 5.32	34.90 6.84	34.15 6.67	34.10 5.98	34.09 6.08	32.83 6.18	33.07 6.73	32.72 7.50	31.06 9.22	32.33 6.69	36.1 5.6
INE	27.57 5.85	27.68 6.30	31.58 8.11	34.65 8.29	37.92 9.59	41.09 10.83	42.55 10.02	41.24 5.31	35.80 6.45	31.53 5.23	28.31 3.91	25.23 3.28	23.70 3.24	29.0 8.8
INOB	1.75 1.08	1.96 0.68	1.72 0.96	2.27 0.86	2.87 1.86	2.22 0.80	2.03 0.94	2.21 0.82	2.48 0.99	2.44 0.96	5.59 8.77	1.94 0.97	1.77 1.09	1.2 0.8

Exhibit 2(Cont.) ERYTHROCYTE amino acid levels in normal adults administered ASPARAME at 200 mg/kg

(u)

AMINO ACIDS	DOSE = 200													
	6 SUBJECTS = 6													
TIME (HR)	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.
ALINE	19.08 4.21	10.53 5.08	19.43 4.38	18.73 4.17	16.83 3.91	16.45 4.01	14.40 3.51	16.16 4.29	16.65 2.95	16.27 4.36	16.54 3.19	17.34 3.16	17.21 4.17	18.1 2.9
YSTINE	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
ETHION	1.87 0.36	1.84 0.40	1.88 0.42	1.71 0.39	1.60 0.58	1.66 0.90	1.35 0.49	1.26 0.31	1.26 0.42	1.32 0.37	1.35 0.23	1.30 0.25	1.36 0.21	1.4 0.5
SOLEUCN	4.44 2.37	1.10 2.23	3.77 1.32	2.85 0.32	2.26 0.35	2.17 1.50	1.98 1.06	2.23 1.73	2.20 1.06	2.81 2.02	3.41 2.18	3.29 1.89	3.72 2.19	5.1 2.6
ECINE	8.44 1.04	7.84 0.93	7.63 0.72	6.78 0.65	5.60 0.89	4.78 0.79	3.90 0.78	4.56 0.94	5.18 1.00	6.03 1.15	7.31 1.74	7.29 1.34	8.00 1.50	9.2 2.0
YRCSINE	4.25 0.60	5.11 1.54	6.94 1.13	7.96 1.21	8.78 1.61	9.83 1.64	11.31 2.26	12.15 3.09	12.15 5.61	9.54 2.17	7.62 1.97	5.92 1.90	5.19 0.98	4.8 1.3
MENYLAL	2.81 0.64	13.56 7.12	25.63 6.02	29.08 6.55	31.44 10.12	35.71 10.04	36.23 10.19	24.34 5.71	16.66 4.12	11.81 2.49	8.77 2.35	6.21 2.57	4.78 1.38	3.0 1.3
ARNITHIN	9.51 1.57	9.15 1.86	9.35 1.25	9.94 1.72	9.59 1.37	9.20 1.13	9.19 1.38	9.42 1.15	8.62 1.61	8.71 1.55	7.68 1.87	8.31 1.49	8.09 2.41	9.1 1.8
YSINE	12.03 1.98	11.11 2.17	10.89 1.76	10.32 1.73	10.42 1.69	9.67 2.01	9.24 1.67	10.80 0.90	10.42 1.25	10.41 1.58	10.16 1.73	10.28 1.38	11.21 1.70	11.2 1.5
ISTIDIN	8.00 1.26	7.51 1.74	7.63 1.53	7.68 1.52	7.42 1.54	7.26 1.64	6.80 1.54	7.22 1.22	7.19 1.13	6.93 1.72	6.90 1.20	6.98 1.32	7.05 1.61	7.1 1.3
RGININE	3.73 1.28	3.59 0.89	4.26 1.18	4.15 1.16	4.11 1.45	4.41 1.43	4.09 1.62	3.83 1.50	3.41 1.02	3.25 0.85	3.32 1.04	3.03 0.92	3.92 1.29	4.0 1.0

EXHIBIT 9

PLASMA AND ERYTHROCYTE FREE AMINO ACID LEVELS IN HEALTHY
FEMALE SUBJECTS PRESUMED TO BE HETEROZYGOTES FOR PHENYLKETOSURIA AFTER
ASPARTAME ADMINISTRATION AT 34 MG PER KG BODY WEIGHT

VALUES LISTED ARE THE MEAN AND STANDARD DEVIATION GIVEN IN MICROLES PER 100 ML

EXHIBIT

IOWA PKU

PLASMA
TIME (HR)

TAURINE

ASPART

THREON.

SERINE

ASPARAGN

GLUTAMIN

GLUTAMAT

PROLINE

CITRULLN

GLYCINE

ALANINE

AMINO

EXHIBIT 9, PLASMA amino acid levels in PKU HETEROZYGOES administered ASPARTAME at 34 mg/kg

9A

IOWA PKU

PLASMA AMINO ACIDS, DOSE = 34 # SUBJECTS = 4	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.
TIME (HR)														
AURINE	4.13	4.12	3.74	3.90	3.73	4.15	4.29	4.34	3.81	0.0	0.0	0.0	4.12	0.0
	1.93	1.42	1.34	1.18	1.22	1.84	1.35	1.61	1.50	0.0	0.0	0.0	0.61	0.0
SPART	0.26	0.16	0.20	0.15	0.14	0.16	0.15	0.13	0.11	0.0	0.0	0.0	0.23	0.0
	0.18	0.12	0.13	0.08	0.09	0.10	0.11	0.08	0.08	0.0	0.0	0.0	0.09	0.0
THREON	19.34	19.72	21.01	20.40	19.71	18.80	16.40	17.65	18.55	0.0	0.0	0.0	19.88	0.0
	8.76	8.98	9.13	9.15	8.23	8.35	9.69	7.72	7.38	0.0	0.0	0.0	6.04	0.0
SERINE	11.76	12.04	13.14	12.86	12.48	11.79	11.44	11.04	11.87	0.0	0.0	0.0	13.68	0.0
	4.33	3.95	4.57	5.15	4.68	3.98	3.95	3.73	4.29	0.0	0.0	0.0	2.73	0.0
ASPARAGN	7.29	9.65	10.97	10.99	10.15	8.76	9.08	7.48	9.04	0.0	0.0	0.0	7.85	0.0
	3.51	1.92	2.26	2.07	1.73	1.84	1.60	1.26	1.81	0.0	0.0	0.0	1.99	0.0
GLUTAMIN	56.26	56.57	59.00	58.31	60.46	61.71	56.28	53.43	58.12	0.0	0.0	0.0	54.01	0.0
	10.45	8.46	10.95	12.19	11.96	9.73	12.13	4.35	12.64	0.0	0.0	0.0	19.66	0.0
GLUTAMAT	2.62	2.03	2.46	2.65	3.51	3.21	3.61	2.02	2.21	0.0	0.0	0.0	1.37	0.0
	0.80	0.87	1.76	1.63	3.37	3.29	2.15	0.82	1.19	0.0	0.0	0.0	0.08	0.0
PROLINE	17.41	18.84	21.52	22.23	21.05	19.70	18.80	16.95	17.08	0.0	0.0	0.0	13.87	0.0
	4.00	3.63	5.16	5.66	5.38	3.99	4.18	3.13	4.98	0.0	0.0	0.0	4.89	0.0
CITRULLN	2.15	1.75	1.54	1.47	1.39	1.33	1.43	1.72	1.88	0.0	0.0	0.0	2.27	0.0
	1.30	0.80	0.85	0.84	0.73	0.68	0.72	0.73	0.79	0.0	0.0	0.0	1.33	0.0
GLYCINE	27.52	29.08	27.18	26.31	25.99	27.72	24.72	24.67	24.61	0.0	0.0	0.0	26.32	0.0
	12.42	15.41	12.32	13.83	13.90	16.05	13.04	11.67	11.39	0.0	0.0	0.0	20.67	0.0
ALANINE	34.90	37.97	45.81	48.04	49.07	44.66	40.53	37.60	35.56	0.0	0.0	0.0	29.21	0.0
	3.53	3.49	6.25	7.21	5.16	3.66	5.40	4.37	5.83	0.0	0.0	0.0	2.19	0.0
AMINOB	1.08	1.06	1.11	1.07	1.05	0.95	0.97	0.92	0.94	0.0	0.0	0.0	1.38	0.0
	0.32	0.35	0.35	0.33	0.32	0.36	0.27	0.43	0.35	0.0	0.0	0.0	0.08	0.0

EXHIBIT 9 (Cont.) PLASMA amino acid levels in PKU HETEROZYGOTES administered ASPARTAME at 34 mg/kg.

99

ASMA AMINO ACIDS, DOSE = 34 4 SUBJECTS = 4	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24
LINE	20.80 3.16	19.95 1.84	20.29 2.65	19.22 3.22	18.98 3.27	18.28 2.32	17.71 1.80	17.55 2.39	16.18 1.40	0.0 0.0	0.0 0.0	0.0 0.0	17.86 0.66	0.0 0.0
STINE	9.26 0.55	9.06 1.59	8.87 1.78	8.58 1.28	8.83 1.72	8.81 2.63	8.50 2.10	8.12 1.44	8.56 2.37	0.0 0.0	0.0 0.0	0.0 0.0	7.86 1.32	0.0 0.0
THICN	2.77 0.85	3.08 0.73	2.87 0.87	2.66 1.03	2.46 1.04	2.84 1.27	2.21 0.59	2.50 0.85	2.67 0.96	0.0 0.0	0.0 0.0	0.0 0.0	2.84 1.18	0.0 0.0
OLEUCN	5.39 0.85	5.74 0.47	5.38 0.57	4.71 0.84	4.45 0.93	4.67 1.68	4.00 0.68	4.33 0.70	5.11 0.68	0.0 0.0	0.0 0.0	0.0 0.0	5.37 0.29	0.0 0.0
UCINE	10.82 1.32	10.84 1.29	10.94 1.96	9.76 2.27	9.12 2.59	8.76 2.36	8.44 1.54	9.19 1.27	10.34 0.73	0.0 0.0	0.0 0.0	0.0 0.0	11.47 1.46	0.0 0.0
ROSINE	4.60 1.50	4.88 1.18	5.45 1.52	5.67 1.70	5.15 2.10	5.74 1.26	5.43 1.31	5.25 1.15	5.46 1.32	0.0 0.0	0.0 0.0	0.0 0.0	4.40 2.04	0.0 0.0
ENYLAL	6.56 1.43	9.98 1.11	14.93 2.54	15.34 1.95	15.67 1.50	13.40 0.90	12.79 0.84	10.39 1.63	9.27 1.32	0.0 0.0	0.0 0.0	0.0 0.0	7.45 2.18	0.0 0.0
NITHN	4.47 1.05	4.21 0.82	4.54 0.88	4.59 1.07	4.28 0.97	4.28 1.20	4.12 1.35	4.13 1.13	4.25 1.01	0.0 0.0	0.0 0.0	0.0 0.0	4.05 0.79	0.0 0.0
SINE	18.83 3.09	18.99 2.40	18.89 2.78	18.58 4.06	17.79 3.63	17.58 3.03	17.20 3.79	17.64 3.08	18.49 2.50	0.0 0.0	0.0 0.0	0.0 0.0	17.87 4.23	0.0 0.0
STIDIN	10.88 1.32	10.83 0.87	11.11 1.47	11.02 2.17	10.71 1.93	10.23 1.31	9.75 1.91	9.73 1.38	10.01 0.71	0.0 0.0	0.0 0.0	0.0 0.0	10.11 2.79	0.0 0.0
GININ	8.96 2.00	10.07 2.56	10.82 2.93	10.31 3.67	9.60 2.94	8.76 2.22	7.99 2.46	8.14 2.51	8.88 2.76	0.0 0.0	0.0 0.0	0.0 0.0	8.35 4.45	0.0 0.0

EXHIBIT 9 (Cont) ERYTHROCYTE free amino acid levels in PKU HETEROZYGOTES administered ASPARTAME at 34 mg/kg

90

ICMA PKU

TIME (HR)	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24.
SERINE	14.09	13.34	13.29	13.47	14.82	14.49	12.68	20.08	20.48	0.0	0.0	0.0	27.91	0.0
	2.01	2.34	3.33	1.05	3.28	2.33	2.38	4.98	3.25	0.0	0.0	0.0	2.95	0.0
AURINE	6.07	11.57	10.51	11.64	16.07	13.21	14.21	9.81	15.86	0.0	0.0	0.0	19.32	0.0
	3.29	5.12	8.74	7.50	13.81	8.28	7.53	3.63	7.04	0.0	0.0	0.0	0.30	0.0
SPARTAT	22.17	21.21	21.66	21.66	21.09	21.16	20.83	22.55	21.60	0.0	0.0	0.0	22.61	0.0
	4.45	4.10	4.56	3.57	3.46	4.20	3.49	3.34	3.76	0.0	0.0	0.0	4.50	0.0
UREONIN	14.51	14.04	14.87	14.01	13.61	13.12	11.65	12.68	12.28	0.0	0.0	0.0	13.29	0.0
	4.96	5.16	6.81	4.99	5.21	5.05	5.13	5.22	5.46	0.0	0.0	0.0	5.66	0.0
ERINE	12.91	12.58	12.88	12.55	11.25	11.38	11.96	12.10	11.53	0.0	0.0	0.0	13.94	0.0
	3.60	2.98	3.37	3.75	2.90	2.49	3.50	3.28	3.02	0.0	0.0	0.0	2.31	0.0
SPARAGN	11.80	10.77	11.29	13.15	11.45	12.33	9.45	10.82	11.22	0.0	0.0	0.0	12.15	0.0
	4.92	2.52	3.78	3.98	2.38	4.08	1.87	1.94	1.58	0.0	0.0	0.0	3.76	0.0
LUTAMIN	50.66	47.72	46.44	45.86	45.44	44.83	47.58	45.21	43.20	0.0	0.0	0.0	39.97	0.0
	10.34	7.97	10.55	8.29	7.56	8.50	7.60	8.00	7.80	0.0	0.0	0.0	10.18	0.0
LUTAMAT	24.37	23.27	24.63	24.58	23.70	23.34	22.99	25.26	25.24	0.0	0.0	0.0	31.51	0.0
	5.57	6.30	6.97	6.52	7.38	7.22	7.23	4.83	5.80	0.0	0.0	0.0	0.85	0.0
COLINE	11.19	10.42	12.41	12.08	11.90	11.53	10.96	10.15	9.18	0.0	0.0	0.0	7.89	0.0
	2.55	1.73	2.60	2.44	1.75	2.29	1.11	1.12	1.38	0.0	0.0	0.0	1.92	0.0
LYCINE	27.08	26.79	27.39	28.67	28.02	29.29	27.66	27.21	26.80	0.0	0.0	0.0	23.52	0.0
	3.99	3.50	4.42	4.81	5.32	3.07	5.21	6.05	5.55	0.0	0.0	0.0	1.97	0.0
LANINE	29.76	31.08	31.92	31.62	34.20	33.82	30.88	27.96	27.67	0.0	0.0	0.0	23.50	0.0
	2.04	3.05	4.84	3.86	4.31	3.97	1.19	4.55	3.12	0.0	0.0	0.0	1.45	0.0
AMINO B	0.99	0.88	0.75	0.64	0.63	0.61	0.91	0.66	0.75	0.0	0.0	0.0	0.67	0.0
	0.77	0.64	0.19	0.21	0.33	0.17	0.74	0.21	0.21	0.0	0.0	0.0	0.20	0.0

EXHIBIT 9 (Cont.) ERYTHROCYTE free amino acid levels in PKU HETEROZYGOTES administered ASPARTAME at 34 mg/kg. 90

AMINO ACIDS DOSE = 34 4 SUBJECTS = 4														
TIME (HR)	0.0	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	24
GLUTAMINE	15.50	16.34	16.03	15.10	13.56	13.22	13.72	14.92	15.39	0.0	0.0	0.0	15.15	0.0
	0.58	0.41	1.35	1.54	1.14	0.79	0.37	0.34	1.21	0.0	0.0	0.0	0.50	0.0
GLUTAMINE	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
THIOMALONIC	0.57	0.53	0.54	0.48	0.38	0.35	0.37	0.45	0.41	0.0	0.0	0.0	0.0	0.0
	0.66	0.61	0.63	0.56	0.45	0.42	0.43	0.52	0.47	0.0	0.0	0.0	0.0	0.0
ISOLEUCINE	3.10	3.43	3.33	2.32	1.97	1.93	2.14	2.32	2.41	0.0	0.0	0.0	3.13	0.0
	0.94	1.60	1.50	0.76	0.85	0.85	0.52	0.65	0.71	0.0	0.0	0.0	0.18	0.0
VALINE	7.21	6.83	6.66	5.63	5.00	4.66	5.13	5.90	6.26	0.0	0.0	0.0	7.39	0.0
	0.82	0.96	1.16	0.98	1.32	0.71	1.06	0.62	0.73	0.0	0.0	0.0	0.56	0.0
PROLINE	3.13	2.95	3.62	3.65	3.66	3.66	3.34	3.60	3.18	0.0	0.0	0.0	2.93	0.0
	0.73	0.49	1.30	1.40	1.36	1.09	0.67	0.87	0.52	0.0	0.0	0.0	0.88	0.0
PHENYLALANINE	4.03	6.03	9.62	9.10	8.92	8.16	7.32	6.56	5.35	0.0	0.0	0.0	4.42	0.0
	1.05	1.21	2.36	2.16	1.28	1.26	0.49	1.47	1.23	0.0	0.0	0.0	0.59	0.0
METHIONINE	9.06	9.58	10.50	10.39	9.44	9.79	8.38	8.73	8.34	0.0	0.0	0.0	9.60	0.0
	3.27	4.07	4.90	4.89	4.34	4.15	3.42	3.15	2.64	0.0	0.0	0.0	0.11	0.0
CYSINE	11.18	10.31	10.51	9.71	9.35	9.78	9.22	9.55	9.19	0.0	0.0	0.0	9.46	0.0
	1.79	1.91	2.33	1.76	1.69	1.82	1.68	1.45	1.50	0.0	0.0	0.0	1.17	0.0
HISTIDINE	7.57	6.76	7.30	6.88	6.79	6.66	6.26	6.49	6.16	0.0	0.0	0.0	6.36	0.0
	1.15	0.65	1.19	1.01	0.86	0.74	0.81	0.80	0.69	0.0	0.0	0.0	1.00	0.0
ARGININE	1.59	1.63	1.87	1.96	1.77	1.32	1.61	1.29	1.01	0.0	0.0	0.0	1.36	0.0
	0.82	0.71	0.97	1.06	0.98	0.76	1.02	0.70	0.43	0.0	0.0	0.0	0.71	0.0

CONCLUSION

Re-examination of the results of the toxicology and teratology studies via the data reassurance program has not altered the original conclusion that aspartame is a safe and non-toxic substance when used as a sweetening agent. This intensive re-evaluation of aspartame has led to the conclusion that several of the studies do not provide valid scientific information.

The metabolic studies and the human studies reported by Stegink clearly demonstrate that aspartame in all species studied, including humans, is handled in a manner identical to any other peptide or protein source of phenylalanine and aspartic acid. Aspartame, under any conceivable conditions of use, causes only a negligible increment in the amount of those amino acids metabolized daily.

Finally, the methyl moiety of aspartame under any condition tested is far below that which can cause any disturbance, while the diketopiperazine produced in the manufacture of aspartame is non-toxic in many multiples of quantities which could possibly be ingested with aspartame.