Clinical Assessment of SALATRIM, a Reduced-Calorie Triacylglycerol

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SALATRIM is a reduced-calorie fat composed of triacylglycerols containing mixtures of short-chain aliphatic acids and long-chain saturated fatty acids. Studies have been conducted in a clinical environment to confirm the predictable metabolism of ingested SALATRIM in humans. An acute tolerance test (study I) was conducted initially with a single ingestion (45 or 60 g) in a double-blind-crossover design with 10 subjects. The levels selected were chosen to significantly exceed expected exposure levels from consumption of foods containing SALATRIM (13.5 or 29.8 g/day at the mean and 90th percentile, respectively). A second more extensive study (study II) was conducted with 36 subjects in a repeated-measures design. Half of the subjects were exposed to either 45 or 60 g of SALATRIM/day for 7 days depending on overall caloric need. The study consisted of a 7-day pretrial period during which subjects received products containing hydrogenated coconut oil, a 7-day period during which half of the subjects received products with SALATRIM and half of the subjects received products with hydrogenated coconut oil, and a final 10-day period during which all subjects received products made with hydrogenated coconut oil. Of 35 physiological indices measured, no clinically significant biochemical responses were observed. Small increases were observed in plasma serum enzymes (AST, ALT, and LDH) with the high SALATRIM exposure, however, mean values for these enzymes remained within the normal range. Some subjects initially experienced mild gastrointestinal effects associated with the high exposure levels of test material, but none asked to leave the trial. A third clinical trial (study III) was undertaken involving 24 subjects in a triple-crossover study with exposure to 0, 30, and 60 g of SALATRIM/day for 4 consecutive days with a 4-day maintenance diet using hydrogenated coconut oil between treatments. Responses similar to those observed in study II were found at 60 g of SALATRIM/day (i.e., no clinically significant biochemical responses of the 35 measured indices but a slight elevation in serum AST and ALT and reported mild gastrointestinal symptoms). None of the indices measured were altered by the ingestion of 30 g of SALATRIM/day. A fourth study (study IV) which consisted of a single bolus exposure to levels up to 15 g of SALATRIM was conducted to determine if increases in serum ketones were involved with observed clinical effects. When subjects received 15 g of SALATRIM, a slight increase in serum acetate was observed, but no increase in acetoacetate or β-hydroxybutyrate was observed. It is concluded that SALATRIM ingestion produces no significant clinical effects when consumed at the anticipated use level of about 30 g/day.

INTRODUCTION

SALATRIM is a family of structured triacylglycerols produced by the interesterification of hydrogenated vegetable oil with triacylglycerol(s) composed of short-chain aliphatic acids (triacetin and/or tripropionin and/or tributyrin). The SALATRIM preparations resulting from these interesterification reactions represent a family of reduced-calorie fats with useful functional properties in a variety of food systems. [The caloric availability of ≈5.0 kcal/g for various SALATRIM preparations has been reported by Finley et al. (1994).] SALATRIM was without effect in preclinical testing, including genetic toxicology, and in subchronic 13-week studies in rodents (Hayes and Riccio, 1994; Hayes et al., 1994a–d). The lack of effect of SALATRIM on gut microflora in rats has been reported by Scheinbach et al. (1994). In all of these studies it appears that SALATRIM fed at 10% of the diet had no significant adverse impact in rodents and the lower caloric availability of the material was also confirmed.

In an analysis based on the 1987–1988 NFCS data (Douglass et al., 1992) exposure from use in cookies, crackers, margarine and spreads, chocolate, salted snacks, nuts, ice cream, ice milk, frozen novelties, sour cream, cream cheese, coffee creamers, whipped toppings, and milk-based weight control beverages was estimated to be 13.5 and 29.8 g/day for the mean and 90th percentile, respectively.

Table 1. Formulation for Chocolate Bars and Chocolate/Raisin Crisp Bar

ingredients	% composition
chocolate bars	
sugar	43.24
Dezaan N-11-N cocoa	7.78
low heat nonfat dry milk	8.65
salt	0.17
added fat[a]	38.70
sorbitan tristearate	1.20
vanilla no. 6	0.25
chocolate bars with Rice Krispies and raisins	
sugar	38.92
Dezaan N-11-N cocoa	7.01
low heat nonfat dry milk	7.78
salt	0.16
added fat[a]	34.83
sorbitan tristearate	1.08
vanilla no. 6	0.23
rice krispies	5.00
raisins	5.00

[a] Hydrogenated coconut fat, hydrogenated soy fat, SALATRIM, or hydrogenated soy/SALATRIM blend.

In this paper we report the results of four studies testing up to 60 g/day of SALATRIM in human subjects in a clinical environment. A large number (i.e., 35) of blood

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Table 2. Randomization and Demographics of Subjects for Study I

subject	sex	body wt (lb)	age	test protocol day 4/day 8	diet (kcal/day)	exposure levels (g/day)
101	M	167.5	23	control/test	2500	60
102	M	186.0	38	test/control	2500	60
103	M	187.5	37	control/test	2500	60
104	F	163.0	33	test/control	2500	60
105	M	167.5	28	control/test	2500	60
106	M	172.0	30	test/control	2500	60
107	M	175.0	64	control/test	2500	60
108	F	169.5	55	test/control	2500	60
109	F	138.0	36	control/test	1800	45
110	F	146.5	47	test/control	1800	45

Table 3. Study I Sampling Schedule

test	day of study											
	1	2	3	4	5	6	7	8	9	10	11	12
HIV/HepB and urine drug screen[a]	X											
serum HCG[b] (females)	X											
routine blood chemistry[c]	X				X				X			X
PT and PTT[d]	X				X				X			X
serum β-hydroxy-butyrate			X	X	X		X	X	X			
reserve serum												X
complete urinalysis	X				X				X			X
urine dipstick		X	X									
hemocult	X				X				X			X

[a] Human immunodeficiency virus, hepatitis B virus. [b] Human chorionic gonadotropin. [c] Complete clinical chemistry series. [d] Prothrombin time and partial thromboplastin time.

and urine parameters were monitored to assess any changes in physiological/biochemical function. The absorption of stearic acid from SALATRIM was estimated by measuring fecal stearic acid excretion.

TEST MATERIALS

SALATRIM was prepared by interesterification of triacetin and tripropionin with either hydrogenated canola (SALATRIM 23CA used in studies I and II) or hydrogenated soy oil (SALATRIM 23SO used in studies III and IV) at a ratio of 11:1:1 according to the method of Klemann et al. (1994). The SALATRIM preparations were then refined by deodorization prior to incorporation into test carrier foods. The fatty acid profiles for the hydrogenated coconut, hydrogenated soy SALATRIM 23CA and SALATRIM 23SO were determined after saponification. The short-chain fatty acids were determined by direct injection of the aqueous phase, and the long-chain fatty acids were determined after methylation (Softly et al., 1994). The triacylglycerol contents of the SALATRIM test materials were determined as described by Huang et al. (1994). Unsaponifiables, tocopherols, phytosterols, free fatty acids, and trace minerals were determined by conventional methods as reported by Softly et al. (1994).

A number of different carrier foods containing SALATRIM wee used in the studies to add variety. In study I delivery vehicles were vanilla sandwich cookies and bonbons. In study II delivery vehicles were vanilla sandwich cookies, bonbons, and chocolate ice cream. In study III the carrier foods were a chocolate raisin/crisp bar and a chocolate beverage (see Table 1). Sandwich cookies were vanilla biscuits (Consolidated Biscuit Co., McComb, OH) with a filling composed of 50% hydrogenated coconut oil (Karlsham, Columbus, OH) or SALATRIM 23CA and 50% confectionery sugar. Each cookie contained 10 g of filling, thereby delivering 5 g of fat. Bonbons were prepared with a center of 50% coconut oil or SALATRIM 23CA and 50% confectionery sugar and were coated with a compound coating prepared with partially hydrogenated coconut oil. Each bonbon delivered 5 g of fat. Chocolate ice cream was prepared according to the method of Arbuckle (1986), incorporating 10% of either coconut oil or SALATRIM 23CA as the only fat source. The ice cream (150 ± 3 g) was packed into individual serving size cups to deliver 15 g of fat per serving. Chocolate raisin/crisp bars and the chocolate for the beverages used in study III were prepared according to the formulas in Table 1, using either SALATRIM 23SO, hydrogenated coconut oil, hydrogenated soy oil (Fuji DE 76, Fuji Vegetable Oil Co., White Plains, NY), or a 50:50 blend of SALATRIM 23SO and hydrogenated soy oil. Chocolate raisin/crisp bars and the bars of chocolate for the beverage were molded to deliver 28.7 and 25.8 g per bar, respectively, so that both delivered 10 g of fat per serving. The chocolate beverage was served warm and prepared by blending the chocolate bar into 1 cup of 60 °C skim milk. For study IV, 15 g of medium-chain triglyceride was delivered in 1 cup of skim milk flavored with chocolate.

Table 4. Demographics of Subjects and Exposure Levels for Study II

A. Individual Statistics

subject	body wt (lb)	height (in.)	sex	age	caloric level fed	diet,[a] days 8–14	exposure (G/day)
201	183	69.0	M	62	2500	C	60
202	160	70.5	M	61	2500	C	60
203	160	72.5	M	62	2500	T	60
204	145	66.0	F	56	1800	C	45
205	136	61.0	F	58	1800	C	45
206	160	63.0	F	52	1800	T	45
207	142	69.0	F	39	1800	T	45
208	153	71.0	M	43	2500	C	60
209	182	69.5	M	35	2500	C	60
210	125	61.0	F	41	1800	C	45
211	133	67.0	F	40	1800	C	45
212	140	67.5	F	25	1800	T	45
213	175	73.0	M	30	2500	T	60
214	159	71.0	M	30	2500	T	60
215	167	70.3	M	32	2500	T	60
216	134	64.0	F	19	1800	C	45
217	150	71.0	M	22	2500	T	60
218	142	71.0	M	21	2500	C	60
219	131	64.0	F	20	1800	T	45
220	137	65.6	F	24	1800	C	45
221	122	65.0	F	19	1800	T	45
222	124	62.0	F	26	1800	C	45
223	144	71.5	M	35	1800	C	45
224	157	74.0	M	32	2500	T	60
225	170	65.0	M	26	2500	T	60
226	172	76.0	M	24	2500	T	60
227	173	71.0	M	53	2500	C	60
228	173	72.0	M	26	2500	T	60
229	110	62.5	F	20	1800	C	45
230	175	69.0	M	32	2500	C	60
231	145	72.5	M	25	2500	C	60
232	135	65.6	F	21	1800	T	45
233	178	68.5	F	25	2500	C	60
234	165	73.5	M	26	2500	T	60
235	141	65.6	M	23	2500	T	60
236	161	66.5	M	30	2500	T	60

B. Group Demographics

demographics	groups: test	groups: control
av age (years)	29.9	37.1
sex		
males	12	9
females	6	9
av wt (lb)	154.4	149.9
av height	69.1	67.4
no. of subjects	18	18

[a] C, control group; T, test group.

ANALYTICAL PROCEDURES

Routine clinical analyses for all four studies were performed at General Medical Laboratories, Madison, WI, using a Hitachi 727 blood analyzer for blood assays and routine clinical procedures for urinalysis. The test performed and normal laboratory values are listed in appropriate tables under Results.

In study II, serum lipoproteins were separated and high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol

Table 5. Blood and Urine Sampling Schedule (Study II)

	exposure schedule[a] (control/test)																							
	coconut/coconut, day							coconut/SALATRIM, day							coconut/coconut, day									
test	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
HIV/Hep B panel, urine drug screen[b]	X																							
serum HCG (females)[c]	X																							
lipid profile	X							X			X			X			X			X			X
chemistry, CBC, hemoccult[d]	X							X			X			X			X			X			X
PT and PTT[e]	X							X		X		X		X		X		X		X			X
serum β-hydroxybutyrate	X						X	X				X		X	X	X		X		X			X
sensitive TSH, T4, and lipase																								X
vitamin A, D, E								X							X									X
reserve serum sample								X							X									X
complete urinary analysis[f]	X							X			X			X			X			X			X
24-h urine collection	X				X	X	X					X	X	X					X	X	X			
urine dipstick					X	X	X			X		X				X		X			X			
hemocult	X							X			X			X			X			X				X
composite stool 2						C[g]	C	C					C	C	C					C	C	C		

[a] Schedule for exposure to coconut fat or SALATRIM in control and test groups. [b] Human immunodeficiency virus, hepatitis B virus. [c] Human chorionic gonadotropin. [d] Complete clinical chemistry series (SMAC). [e] Prothrombin time and partial thromboplastin time. [f] Complete urinanalysis. [g] Composite stool sample for 3-day periods.

Table 6. Demographics of Subjects for Study III

subject	age	sex	height (in.)	wt (lb)
101	19	F	65	134
102	23	M	75	160
103	19	M	70.5	148
104	23	M	73	169
105	21	F	65.5	142
106	30	F	68	149
107	21	F	66	120
108	19	F	66.5	139
109	24	M	70	159
110	33	F	61	134
111	21	F	64	132.5
112	19	M	72.75	168
113	21	M	71	156.5
114	20	F	65.5	149
115	24	M	73	159
116	21	F	67	141
117	22	M	72.5	172
118	22	F	63	135
119	20	F	70	130
120	36	M	73.5	168.5
121	27	M	66	164
122	18	F	65.5	123
123	24	M	68	155
124	22	M	67.5	166.25

(LDL), and very low density lipoprotein cholesterol (VLDL) were determined. The centrifugation and cholesterol analysis were performed in the laboratory of Dr. Earl Shrago, Departments of Medicine and Nutrition, University of Wisconsin, Madison, WI. Serum from a 13-mL SST tube was divided into three portions. After separation, analyses were conducted on the fractions using appropriate kits from Sigma Chemical Co., St. Louis, MO. The first fraction was analyzed for total cholesterol (Sigma Kit Procedure 352) and triglyceride (Sigma Kit Procedure 336). Low-density lipoprotein (LDL) was precipitated from the second aliquot with phosphotungstic acid/magnesium chloride. The high-density lipoprotein cholesterol was determined with Sigma Kit procedure 352. The third aliquot (5 mL) of serum was ultracentrifuged per NIH guidelines (36 000 rpm in a 40.3 rotor for 22 h). The centrifuged serum was analyzed for HDL and LDL cholesterol with Sigma Kit Procedure 352. Very low density lipoprotein (VLDL) cholesterol was calculated as the difference between total cholesterol and precipitated cholesterol from ultracentrifugation. LDL cholesterol was determined as the difference between ultracentrifugal precipitated cholesterol and the HDL cholesterol isolated from the second aliquot.

In study II, fecal samples for each subject were collected and pooled for the last 3 days of each 7-day test period. The fecal samples were homogenized and sampled for analysis. For each sample total fat, stearic acid, calcium, magnesium, and zinc were measured. Total fat was measured according to AOAC Method 922.06 (AOAC, 1990b); stearic acid from fatty acid analysis was determined according to AOCS Method Ce 1-62 (AOCS, 1990); and minerals were determined according to AOAC Method 984.27 (AOAC, 1990a).

CLINICAL STUDIES

All clinical trials were conducted at the G. H. Besselaar Associates/Hazelton Clinic on the Meriter Park Hospital campus in Madison, WI. All study protocols were reviewed and approved by the Hazelton Clinic Institutional Review Board. Subjects were healthy volunteers recruited from the local area. They were confined to the clinical setting throughout the trial. The following measures were used to evaluate volunteer health and eligibility: height and weight; complete medical and nutritional history; a physical examination; biochemical, hematological, and urological profiles; screening for drugs of abuse; and, for females, a pregnancy test.

Dietary plans were developed for each subject, utilizing the Nutritionist III software from N-Squared Computing Analytical Software (Salem, OR). Diets were designed to deliver either 1800 or 2500 kcal/day depending on the subject's body weight (including calories from the control or SALATRIM-containing test vehicles). For this calculation the caloric density of control oil and SALATRIM was assumed to be 9 kcal/g. These diets provided an average of 15%, 38%, and 47% calories from protein, fat, and carbohydrate, respectively.

Routine blood and urine assays were conducted at appropriate times as described later for specific studies. All clinical chemistry was conducted at General Medical Laboratories (Madison, WI). Blood measurements included serum sodium, potassium, chloride, carbonate, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, bilirubin, β-hydroxybutyrate, and protein. Hematologic measures included complete blood count (basophils, neutrophils, eosinophils, monocytes, lymphocytes) and platelets as well as prothrombin time and partial thromboplastin time. In addition, routine urinalysis was conducted including analysis for excretion of uric acid, blood urea nitrogen, and creatinine.

Study I. 1-Day Crossover. This study utilized a randomized, double-blind, crossover design, in which subjects received the test SALATRIM and control (coconut oil) materials for 1 day. The test and reference materials, either 60 (for those consuming the 2500-kcal diet) or 45 g/day (for those consuming the 1800-kcal diet), were introduced into the diet in the form of cookies and bonbons each containing 5 g of either SALATRIM or control fat.

Ten subjects (6 males and 4 females between the ages of 18 and 65, with a mean age of 38.3 years) participated in the study. Test protocol and demographics of subjects for study I are reported in Table 2. On day 4, five subjects received the test material, while five subjects received the control material. The substitution of test material was reversed on day 8. A maintenance diet (either 1800 or 2500 kcal/day) including the control material was administered on all other study days. A standardized 4-day meal plan was repeated for three cycles during the study (days 1–3, 4–7, 8–11).

Table 7. Study III

A. Treatment Schedule

	square 1			square 2		
days	SQ1[a]	SQ2	SQ3	SQ4	SQ5	SQ6
01–04	W60	W60	W60	W60	W60	W60
05–08	C60	T30	T60	C60	T30	T60
09–12	W60	W60	W60	W60	W60	W60
13–16	T30	T60	C60	T60	C60	T30
17–20	W60	W60	W60	W60	W60	W60
21–24	T60	C60	T30	T30	T60	C60

B. Crossover Design

males			females		
subject	days	treatment[b]	subject	days	treatment[b]
104	4–8	C60	114	4–8	C60
104	13–16	T30	114	13–16	T30
104	21–24	T60	114	21–24	T60
102	4–8	T30	118	4–8	T30
102	13–16	T60	118	13–16	T60
102	21–24	C60	118	21–24	C60
112	4–8	T60	108	4–8	T60
112	13–16	C60	108	13–16	C60
112	21–24	T30	108	21–24	T30
117	4–8	C60	111	4–8	C60
117	13–16	T60	111	13–16	T60
117	21–24	T30	111	21–24	T30
113	4–8	T30	119	4–8	T30
113	13–16	C60	119	13–16	C60
113	21–24	T60	119	21–24	T60
121	4–8	T60	101	4–8	T60
121	13–16	T30	101	13–16	T30
121	21–24	C60	101	21–24	C60
115	4–8	C60	110	4–8	C60
115	13–16	T30	110	13–16	T30
115	21–24	T60	110	21–24	T60
123	4–8	T30	106	4–8	T30
123	13–16	T60	106	13–16	T60
123	21–24	C60	106	21–24	C60
124	4–8	T60	105	4–8	T60
124	13–16	C60	105	13–16	C60
124	21–24	T30	105	21–24	T30
103	4–8	C60	116	4–8	C60
103	13–16	T60	116	13–16	T60
103	21–24	T30	116	21–24	T30
109	4–8	T30	122	4–8	T30
109	13–16	C60	122	13–16	C60
109	21–24	T60	122	21–24	T60
120	4–8	T60	107	4–8	T60
120	13–16	T30	107	13–16	T30
120	21–24	C60	107	21–24	C60

[a] Latin square treatment sequence. Squares replicated for males and females (see section B). W60 = 60 g/day hydrogenated coconut fat delivered pretreatment and between treatment periods; C60 = 60 g/day control hydrogenated soybean oil (Fuji Melano 51); T60 = 60 g/day SALATRIM 23SO; T30 = 60 g/day 50:50 SALATRIM 23SO/Fuji Melano 51. [b] C60, 60 g/day control hydrogenated soybean oil (Fuji Melano 51); T60, 60 g/day SALATRIM 23SO; T30, 60 g/day 50:50 SALATRIM 23SO/Fuji Melano 51.

The daily schedule for administration of the control and test materials was as follows:

eating occasion	1800 kcal/day	2500 kcal/day
lunch	2 cookies	3 cookies
afternoon snack	3 cookies	3 cookies
dinner	2 cookies	3 cookies
evening snack	2 bonbons	3 bonbons

Each subject was weighed prior to breakfast each morning. If a subject's body weight decreased by more than 3 lb over 2 consecutive days from baseline, a daily caloric supplement of 12 fat-free crackers (approximately 10 calories each) was provided to the subject for the remainder of the study.

Blood, urine, and stool samples were collected according to the schedule in Table 3. All scheduled blood and urine samples were obtained prior to breakfast. Individual stool samples from each subject were collected when voided.

Each evening subjects completed a questionnaire pertaining to side effects and the presence of any postprandial symptoms.

Subjects were monitored by medical personnel throughout the study and instructed to report any clinical symptoms. These were recorded in terms of the nature of the event, its onset and ending times, and its severity. Mild and moderate symptoms such as headache, nausea, diarrhea, or constipation were described as severity 1 or severity 2 clinical events. The severity was subjectively described by each subject. Acute toxicity and any indication of general clinical safety factors requiring intervention would have been described as severity 3 clinical events.

Study II. 7-Day Noncrossover. This study utilized a randomized, double-blind design, in which subjects received either the test SALATRIM or control (coconut oil) materials over a 7-day period. The test and control materials, either 60 (for those on a 2500-kcal diet) or 45 g/day (for those on a 1800-kcal diet), were introduced into the diet in the form of cookies, bonbons, and ice cream.

Thirty-six subjects (19 males and 17 females between the ages of 18 and 65, with a mean age of 33.4 years) participated in the study. The demographics and assignments of subjects in study II are shown in Table 4A. The group demographics for the study are summarized in Table 4B. All subjects received a maintenance diet (either 1800 or 2500 kcal/day) containing the control material on days 1–7. On days 8–14, 18 subjects received the test material (either 60 or 45 g/day) in the form of cookies, bonbons, and ice cream; 18 additional subjects continued on the maintenance diet with materials containing control fat. One subject (232), on test material, withdrew for personal reasons, unrelated to the test, on day 10. On days 15–24, all subjects returned to the maintenance diet, with control materials as shown in Table 5. A standardized seven day meal plan was followed for three cycles throughout the study.

The daily schedule for administration of the control and test materials was as follows:

eating occasion	1800 kcal/day	2500 kcal/day
lunch	2 cookies	3 cookies
afternoon snack	1 cup ice cream	1 cup ice cream
dinner	2 cookies	3 cookies
evening snack	2 bonbons	3 bonbons

As in study I, subject weight was monitored, blood, urine, and stool samples were collected as indicated in Table 5, subjects completed stool assessment questionnaires and side effect questionnaires, and subjects were monitored for clinical symptoms. Fecal material for each subject was collected, weighed, and pooled for the last 3 days of each feeding period.

Multivariate repeated measures analysis of variance was also employed to measure the change occurring between the two groups over the test period. This technique estimates the change in the level of any physiological or biochemical responses associated with SALATRIM over time. The SAS PROC GLM procedure was used to study the changes occurring over time in the blood, urine, and stool chemistry. The REPEATED statement with CONTRAST option estimated the effect of time and the GROUP × TIME interaction that may exist between the groups on the control and SALATRIM diets (Littell et al., 1991).

Study III. 4-Day Triple Crossover. A crossover design, consisting of two 3 × 3 Latin squares, described by Cochran and Cox (1957), was employed to measure the effect of SALATRIM on the biochemical and physiological responses of 12 males and 12 females. The subjects were assigned to each pair of squares at random (only males or females could be assigned to an individual square). The males and females received 2500 and 1800 kcal/day diets, respectively. The subjects ranged in age from 18 to 36 years, with a mean age of 22.9 years (Table 6).

The subjects received test vehicles prepared with SALATRIM at 30- (plus 30 g of control fat) and 60-g usage levels and a 60-g hydrogenated soybean material (control) for a 4-day period. The 30- and 60-g SALATRIM levels, and the control levels were identified as T30, T60, and C60, respectively. Before and after receiving each test vehicle, the subjects were given a 60-g hydrogenated coconut oil vehicle for 4 days. This vehicle was prepared from the same coconut oil used in the previous studies and served as a washout medium (identified as W60) between the SALATRIM and control treatments. The assignment of the

Table 8. Blood and Urine Sampling Schedule for Study III

	exposure schedule																								
	coconut fat, day				test period 1, day				coconut fat, day				test period 2, day				coconut fat, day				test period 3, day				
test	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
blood	X				X				X				X				X				X				X
urine	X				X				X				X				X				X				X

Table 9. Fatty Acid Composition of Test and Control Fat

fatty acid	% fatty acid as methyl ester			
	hydrogenated coconut oil[a]	hydrogenated soy oil[a]	23CA[b]	23SO[b]
acetic			21.10 ± 0.10	23.39 ± 1.12
propionic			2.58 ± 0.02	2.92 ± 0.11
caprylic	5.27			
capric	4.88			
lauric	46.21	0.50	0.07 ± 0.00	0.02 ± 0.00
myristic	19.2			0.09 ± 0.01
palmitic		12.14	2.37 ± 0.04	7.96 ± 0.03
stearic	10.41	10.01	57.00 ± 1.00	60.67 ± 1.05
oleic	3.09	69.61	0.57 ± 0.01	0.14 ± 0.00
linoleic	0.76	0.25	0.07 ± 0.00	0.02 ± 0.00
arachidic	0.14	0.39	1.50 ± 0.03	0.45 ± 0.02
behenic			0.67 ± 0.01	0.25 ± 0.02
lignoceric			0.34 ± 0.00	0.14 ± 0.01

[a] Single determination. [b] Mean of triplicate determination ± standard deviation.

Table 10. Acylglycerols in SALATRIM 23CA and 23SO

acyl carbon no.[a]	23CA lot 014	23SO lot 026
20	2.26	7.45
21	0.67	1.46
22	57.97	61.99
23	11.49	11.54
24	2.10	0.71
25	0.35	ND[b]
26	0.61	0.25
27	0.13	ND
28	0.33	ND
34	0.04	0.25
36	1.22	1.66
37	0.09	0.42
38	11.87	8.31
39	0.94	ND
40	0.52	1.31
41	0.17	ND
42	0.20	ND
44	0.22	ND
52	0.11	0.45
54	0.71	0.80
56	0.10	ND
triacylglycerols	92.10	96.60
diacycglycerols	3.61	2.33
total acylglycerols	95.71	98.93

[a] ACN represents the sum of the carbons in all acid moieties. [b] ND indicates not detected.

subjects to the Latin squares and the treatment order with the coconut oil washout vehicle are presented in Table 7 (sections A and B, respectively).

The blood, urine, and stool responses were analyzed as a crossover design by using the SAS procedure PROC GLM. The method for analyzing these data is illustrated in the SAS publication *SAS System for Linear Models* (Littell et al., 1991). The mathematical model for each response measured in study III included subjects, sample presentation order within a square, test vehicles, and especially constructed residual variables for estimating any carry-over effects. In addition, the data obtained during the first 20 days of the study were analyzed by repeated-measures analysis of variance (PROC GLM). This procedure was used for obtaining additional information as to how the responses from the control and SALATRIM compared with those responses obtained from the washout (coconut oil) vehicles.

Questionnaires were given to the subjects to obtain information on their general overall well-being, bowel movement characteristics, or any event not covered above. These data were tabulated

Table 11. Minor Constituents of SALATRIM 23CA and SALATRIM 23SO

major fractions	SALATRIM 23CA	SALATRIM 23SO
inorganics		
Al (ppm)	0.4	<0.308
As (ppm)	<2.5	<2.5
Cd (ppm)	<0.088	<0.088
Cu (ppm)	0.7	0.10
Co (ppm)	<0.088	<0.088
Ca (ppm)	1.1	0.698
Cr (ppm)	0.1	0.08
Fe (ppm)	0.8	0.092
Mg (ppm)	<0.555	<0.555
Mn (ppm)	<0.09	<0.090
Ni (ppm)	<0.092	<0.092
K (ppm)	<5.07	<5.07
Na (ppm)	4.7	<0.655
Zn (ppm)	1.0	0.11
Pb (ppb)	<72	<72
P (ppm)	1.71	<0.622
phytosterols (mg/100 g)	0.22	0.04
tocopherols (%)	0.022	0.086
free fatty acids (%)	0.82	0.41

and analyzed by the SAS PROC FREQ and PROC GLM procedures SAS (1985a,b).

The weight of all subjects was monitored daily. When the weight of a subject deviated by more than 3 lb, the caloric intake was changed with the objective of bringing the subject's weight within the ±3-lb range of their average weight.

Table 6 contains the demographics of the subjects, and the sequence assignments are shown in Table 7. A standardized 8-day meal plan was repeated three times throughout the study.

The daily schedule for administration of the control and test materials delivering 10 g of fat/serving (control fat, SALATRIM, a 50:50 blend control fat/SALATRIM) was as follows:

eating occasion	carrier/vehicle
breakfast	hot chocolate beverage
morning snack	chocolate bar with raisins and Rice Krispies
lunch	chocolate bar with raisins and Rice Krispies
afternoon snack	chocolate bar with raisins and Rice Krispies
dinner	chocolate bar with raisins and Rice Krispies
evening snack	hot chocolate beverage

As in studies I and II, subject weight was monitored, blood and urine samples were collected, and clinical effects questionnaires were completed daily. Blood and urine samples were obtained prior to breakfast following a 10-h fast as shown in the study schedule in Table 8. Clinical chemistry and hematology were monitored as described for the earlier studies.

Study IV. Single Exposure. A randomized, blind study was conducted with 42 subjects (6 per group) to determine the effect of a single dose of SALATRIM 23SO on serum levels of acetate, acetoacetate, and β-hydroxybutyrate. A single dose of SALATRIM 23SO, hydrogenated soy control (Fuji DE76, Fuji Vegetable Oil Co), or a medium-chain triglyceride (MCT) Neobee M-5, Stephan Co., Maywood, NJ) was administered to each subject.

All fat samples were delivered in 1 cup of chocolate-flavored beverage in the morning following a 10-h fast. The subjects were randomly assigned to one of seven treatment groups: SALATRIM 23SO, 7.5, 10, 12.5 or 15 g; control hydrogenated soy, 7.5 or 15 g; or MCT, 15 g. Assignments were made to allow balance of groups based on age and gender.

Blood samples were drawn into chilled 10-mL Vacutainer tubes at the following time points: 0 h (before administration), 15 and 30 min, and 1, 2, 3, and 4 h after administration. Blood samples were immediately placed on ice and allowed to clot for 30–60

Table 12. Clinical Measurements before and after Acute Exposure to Control Fat and SALATRIM for Study I

test	units	normal range min	normal range max	group no.[a]	day 1[b]	after control days 5 and 9	after SALATRIM,[b] days 5 and 9	after washout,[b] day 12
bilirubin	mg/dL	0.1	1.1	1	0.72 ± 0.31	0.52 ± 0.22	0.52 ± 0.33	0.56 ± 0.21
				2	0.82 ± 0.31	0.64 ± 0.21	0.56 ± 0.23	0.56 ± 0.22
alanine aminotransferase (ALT)	milliunits/mL	3	35	1	27 ± 21	27 ± 14	25 ± 15	27 ± 13
				2	21 ± 8	21 ± 7	37 ± 32	38 ± 31
asparate aminotransferase (AST)	milliunits/mL	0	50	1	33 ± 8	28 ± 3	33 ± 5	30 ± 3
				2	27 ± 3	28 ± 8	39 ± 22	35 ± 19
lactate dehydrogenase	milliunits/mL	100	225	1	119 ± 13	142 ± 15	167 ± 15	141 ± 20
				2	118 ± 17	132 ± 14	145 ± 16	135 ± 26
alkaline phosphatase	milliunits/mL	15	105	1	58 ± 15	60 ± 16	61 ± 16	62 ± 18
				2	55 ± 12	59 ± 13	65 ± 25	70 ± 33
γ-glutamyltransferase	milliunits/mL	0	60	1	16.0 ± 9.9	18.8 ± 9.9	19.2 ± 10.2	19.4 ± 10.1
				2	14.0 ± 5.1	16.6 ± 7.1	21.0 ± 20.9	25.4 ± 29.0
creatine	mg/dL	0.6	1.5	1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.3 ± 0.2
				2	1.1 ± 0.1	1.2 ± 0.8	1.2 ± 0.8	1.2 ± 0.1
blood urea nitrogen	mg/dL	6	25	1	14.0 ± 5.2	13.4 ± 1.8	13.4 ± 2.7	14.6 ± 2.1
				2	14.4 ± 3.5	14.6 ± 3.9	14.2 ± 3.2	16.4 ± 3.97
β-hydroxybutyrate	mmol/L	0	0.25	1	0.022 ± 0.004	0.036 ± 0.009	0.018 ± 0.014	NA[c]
				2	0.022 ± 0.014	0.040 ± 0.014	0.020 ± 0.012	
uric acid	mg/dL	4	8.5	1	5.7 ± 0.4	6.0 ± 1.0	5.7 ± 0.8	6.2 ± 1.1
				2	5.7 ± 1.0	6.0 ± 0.8	5.8 ± 0.8	6.1 ± 0.9
total protein	g/dL	5.8	8.3	1	6.9 ± 0.3	7.3 ± 0.1	7.1 ± 0.1	7.8 ± 0.1
				2	7.0 ± 0.4	7.3 ± 0.6	7.1 ± 0.5	7.8 ± 0.2
serum albumin	g/dL	3.2	5.2	1	4.5 ± 0.19	4.6 ± 0.13	4.6 ± 0.13	4.7 ± 0.08
				2	4.5 ± 0.15	4.6 ± 0.33	4.5 ± .33	4.7 ± 0.27
glucose	mg/dL	75	125	1	100.2 ± 2.07	97.0 ± 5.74	96.8 ± 7.66	97.6 ± 5.86
				2	94.8 ± 1.64	87.4 ± 2.07	88.6 ± 3.44	90.2 ± 2.86
hematocrit	%	36	52.6	1	43.9 ± 4.2	44.8 ± 4.1	44.5 ± 3.6	45.1 ± 3.8
				2	42.4 ± 2.6	43.7 ± 1.29	42.8 ± 1.8	44.6 ± 1.4
hemoglobin	g/dL	13.7	17.7	1	14.9 ± 1.5	15.2 ± 1.5	15.1 ± 1.5	15.2 ± 1.3
				2	14.5 ± 0.8	15.1 ± 0.6	14.7 ± 0.9	15.4 ± 0.9
red blood cell count	millions/μL	4.42	5.95	1	4.8 ± 0.5	5.0 ± 0.6	4.9 ± 0.5	5.0 ± 0.5
				2	4.7 ± 0.4	4.8 ± 0.4	4.9 ± 0.3	5.1 ± 0.4
mean corpuscular hemoglobin	pg	28.5	33.5	1	30.7 ± 1.4	30.6 ± 1.4	30.6 ± 1.3	30.4 ± 1.4
				2	30.6 ± 0.8	30.8 ± 0.8	30.6 ± 0.5	30.6 ± 0.8
mean corpuscular Hb concentration	%	32	36	1	33.9 ± 1.4	33.8 ± 0.5	33.8 ± 0.8	33.8 ± 0.7
				2	34.3 ± 1.3	34.6 ± 1.1	34.3 ± 1.3	34.6 ± 1.2
mean corpuscular volume	fL	85	98.4	1	90.8 ± 4.7	90.4 ± 4.1	90.7 ± 4.3	90.1 ± 4.5
				2	89.5 ± 4.7	89.2 ± 5.2	89.5 ± 5.0	88.7 ± 5.1
iron	μg/dL	30	180	1	117 ± 51	105 ± 29	35 ± 16	106 ± 28
				2	99 ± 21	86 ± 18	33 ± 12	95 ± 14
partial thromboplastin time	s	29	35	1	27.5 ± 2.0	26.5 ± 2.6	27.6 ± 3.2	27.2 ± 2.0
				2	27.3 ± 1.9	27.3 ± 2.0	26.3 ± 1.7	27.5 ± 1.4
prothrombin time	s	10.2	13	1	11.5 ± 0.5	11.1 ± 0.4	11.3 ± 0.3	11.5 ± 0.7
				2	12.0 ± 0.2	11.7 ± 0.3	11.6 ± 0.3	12.0 ± 0.6
white blood cell count	thousands/μL	3.5	10.7	1	6.1 ± 1.3	5.6 ± 1.1	8.0 ± 1.5	5.9 ± 0.9
				2	8.0 ± 2.0	7.3 ± 1.7	9.5 ± 2.6	7.7 ± 2.3
neutrophils	%	36	70	1	54.5 ± 6.1	55.2 ± 8.4	71.0 ± 7.9	55.8 ± 6.3
				2	47.8 ± 14.2	48.1 ± 12.1	63.2 ± 16.9	44.2 ± 9.6
lymphocytes	%	18	50	1	32.6 ± 6.3	33.0 ± 7.8	19.4 ± 5.3	32.2 ± 5.5
				2	39.5 ± 13.7	40.8 ± 14.3	27.3 ± 16.6	44.0 ± 13.4
basophils	%	0	2	1	0.74 ± 0.40	0.86 ± 0.47	0.48 ± 0.26	0.92 ± 0.61
				2	0.76 ± 0.30	0.68 ± 0.27	0.64 ± 0.46	0.92 ± 0.36
monocytes	%	2	10	1	8.5 ± 2.8	7.1 ± 0.7	6.7 ± 1.6	8.5 ± 3.1
				2	9.1 ± 1.6	8.1 ± 2.6	6.9 ± 1.4	8.5 ± 3.3
eosinophils	%	0	8	1	3.5 ± 1.1	3.9 ± 2.1	2.4 ± 1.4	2.5 ± 1.1
				2	3.0 ± 1.1	2.4 ± 0.9	1.9 ± 0.4	2.4 ± 1.4
platlets	thousands/μL	150	400	1	290 ± 71	304 ± 74	286 ± 71	308 ± 72
				2	254 ± 34	264 ± 35	257 ± 44	289 ± 40
sodium	mmol/L	136	145	1	139.5 ± 0.6	142.2 ± 1.8	140.6 ± 1.8	141.6 ± 1.1
				2	139.0 ± 1.7	141.0 ± 1.2	141.4 ± 1.7	141.4 ± 1.1
potassium	mmol/L	3.5	5.1	1	4.2 ± 0.3	4.9 ± 0.2	4.7 ± 0.2	4.2 ± 0.1
				2	4.0 ± 0.3	4.4 ± 0.5	4.4 ± 0.2	4.3 ± 0.3
chloride	mmol/L	98	108	1	104 ± 1.3	103 ± 1.7	105 ± 1.6	101 ± 0.7
				2	104 ± 1.1	105 ± 0.9	104 ± 1.6	102 ± 1.5
calcium	mg/dL	8.2	10.5	1	9.4 ± 0.14	9.7 ± 0.13	9.7 ± 0.15	9.8 ± 0.16
				2	9.4 ± 0.25	9.7 ± 0.46	9.3 ± 0.34	9.8 ± 0.26
phosphorus	mg/dL	2.1	5	1	3.4 ± 0.8	3.8 ± 0.5	3.7 ± 0.6	3.7 ± 0.5
				2	3.7 ± 0.4	4.1 ± 0.4	3.7 ± 0.3	3.8 ± 0.3
magnesium	mg/dL	1.6	2.8	1	1.8 ± 0.15	1.9 ± 0.18	1.9 ± 0.10	1.9 ± 0.14
				2	1.9 ± 0.15	2.0 ± 0.18	1.9 ± 0.16	2.0 ± 0.26
carbonate	mmol/L	22	32	1	27.7 ± 2.5	28.3 ± 1.6	28.0 ± 1.3	28.5 ± 2.0
				2	26.9 ± 2.0	28.4 ± 1.7	27.0 ± 1.6	28.2 ± 1.5

Table 12 (Continued)

test	units	normal range min	normal range max	group no.[a]	day 1[b]	after control days 5 and 9	after SALATRIM,[b] days 5 and 9	after washout,[b] day 12
cholesterol	mg/dL	130	300	1	210 ± 59	221 ± 56	207 ± 52	222 ± 51
				2	185 ± 33	199 ± 51	183 ± 45	203 ± 57
triglycerides	mg/dL	30	175	1	234 ± 319	123 ± 62	155 ± 94	103 ± 43
				2	89 ± 36	91 ± 36	84 ± 23	84 ± 22

[a] Group no. of crossover design. [b] Mean values ± SD. [c] Not available.

Table 13. Number of Subjects Reporting Gastrointestinal Symptoms[a] during Study I

exposure group	before exposure	exposure day	after exposure
1800 kcal	0	0	1
2500 kcal	6	1	5

[a] Nausea, stomach cramps, discomfort.

min, after which time the samples were centrifuged for 15 min. The serum was separated into two equal aliquots of 1–2 mL in screw-cap polypropylene tubes. The samples were immediately flash frozen and stored at −70 °C prior to shipment to Product Safety Labs, Dayton, NJ, for analysis. Acetic acid was determined according to the method of Smith et al. (1986); acetoacetate was determined according to the method of McMurray et al. (1984) using an enzymatic kit supplied by GDS, Elkhart, IN. β-Hydroxybutyrate was determined according to the protocol of Zivin and Snarr (1972) using GDS Diagnostics Reagent Application HR100, and glucose was determined according to the method of Tietz (1990).

RESULTS

SALATRIM Composition Background. The fatty acid profiles for the test and control oils are reported in Table 9. The oleic acid values include all 18-carbon single double bond fatty acids. The principal triacylglycerol components for the two SALATRIM family members used in these studies are shown in Table 10. From the data in the table it can be seen that approximately 60% of the SALATRIM 23CA and SALATRIM 23SO is diacetylstearoylglycerol. In Table 11 we report the other components measured in SALATRIM.

Study I. 1-Day Crossover. Study I was intended as a pilot study using a blind crossover design, with a single day of exposure, to either 45 or 60 g of SALATRIM 23CA delivered in cookies and bonbons. In Table 12 the clinical observations before exposure, at the end of exposure to SALATRIM, and after the posttreatment period are presented for the 10 subjects in the study. Also, in Table 12 we report normal ranges for humans. It can be seen that all of the means in the study were well within the normal ranges. No clinically important differences were observed as a result of exposure to SALATRIM.

In Table 13 we summarize the gastrointestinal symptoms reported after a single exposure of 45 or 60 g/day with SALATRIM. These data show that a single exposure to SALATRIM did not elicit any significant increase in gastrointestinal symptoms.

Study II. 7-Day Noncrossover. Given no significant clinical changes in study I, a longer term exposure study was undertaken with SALATRIM 23CA. Study II was a noncrossover design with 18 subjects per group.

Diets were analyzed for fatty acids, and the data are presented in Table 14. It can be seen that as planned the diets were low in stearic acid and provided adequate levels of linoleic acid.

Throughout the study, body weights were monitored daily. No subjects exhibited body weight changes of more than ±3 lb for the duration of the study. There were no

Table 14. Fatty Acid Composition of Basal Diets for All Subjects (Study II)

fatty acid	g/100 g of diet[a] 1800 kcal/day diet	g/100 g of diet[a] 2500 kcal/day diet
capric	0.01 ± 0.01	0.01 ± 0.01
lauric	0.01 ± 0.01	0.01 ± 0.01
myristic	0.05 ± 0.03	0.04 ± 0.04
palmitic	0.32 ± 0.13	0.40 ± 0.12
palmitoleic	0.04 ± 0.06	0.03 ± 0.01
stearic	0.16 ± 0.06	0.18 ± 0.06
oleic	0.62 ± 0.14	0.72 ± 0.20
linoleic	0.51 ± 0.11	0.57 ± 0.18
linolenic	0.05 ± 0.01	0.05 ± 0.02
arachidic	0.01 ± 0.00	0.01 ± 0.00
eicosenoic	0.01 ± 0.00	0.01 ± 0.00
arachidonic	0.01 ± 0.00	0.01 ± 0.00

[a] Mean and standard deviation of daily composite diet analysis for 28 days of study.

significant changes in any individual body weights or between groups.

Subjects were fed a hydrogenated coconut oil diet for 7 days to establish a stable baseline for the test. On day 8, prior to the switching of test diets, blood samples were drawn, and the biochemical parameters from the day 8 samples were the basis of comparison for all subsequent biochemical tests.

Clinical chemistry data (reported in Table 15) provided an assessment of the biochemical/physiological status of the subjects throughout study II. Included in Table 15 are the accepted minimum and maximum values for the laboratory tests (i.e., "normal" ranges). SALATRIM was presented to the test group on days 8–14. From the data in Table 15 it can be seen that there are statistically significant changes resulting from exposure to SALATRIM but, importantly, all parameters remained well within the normal range.

Significant differences in the ALT levels were observed between treatment and control groups over the course of the study. From the data in Table 15 it can be seen that ALT increased during the treatment period. The mean increase in ALT was 19% above the value prior to exposure to SALATRIM. Three individuals showed values above the normal maximum of 35 milliunits/mL. The initial values for these individuals ranged from 28 to 37 milliunits/mL and the percentage increase during the test period was 41% or less. This was similar to the percentage change exhibited by other subjects in the study.

AST, like ALT, increased significantly in SALATRIM-exposed subjects (Table 15). All mean values remained within the normal range of 0–50 milliunits/mL. One subject presented a 51% increase (from 32 to 53 milliunits/mL). All other subjects showed changes of less than 33%. From Table 15 it can be seen that the initial increase in AST appeared to be followed by a steady decline in AST to control levels.

Lactate dehydrogenase (LDH) activity also increased during the exposure period to SALATRIM even though all values remained within the normal range throughout the test. From the data in Table 15 it can be seen that

Table 15. Results of Clinical Tests To Assess Changes over Time for Test and Control Groups

test	units	normal min	normal max	group	day 1 mean	day 8 mean	day 11 mean	day 14 mean	day 17 mean	day 20 mean	day 24 mean	*P* value[a]
bilirubin	mg/dL	0.1	1.1	C	0.77 ± 0.28	0.63 ± 0.25	0.58 ± 0.26	0.60 ± 0.23	0.62 ± 0.25	0.62 ± 0.27	0.70 ± 0.27	NS
				T	0.74 ± 0.34	0.61 ± 0.19	0.49 ± 0.16	0.54 ± 0.15	0.61 ± 0.18	0.59 ± 0.16	0.70 ± 0.26	
				diff	0.03	0.02	0.09	0.06	0.01	0.03	0.00	
aspartate aminotransferase	milliunits/mL	3	35	C	30.3 ± 5.67	30.3 ± 4.97	29.4 ± 5.56	28.8 ± 5.92	30.1 ± 5.98	27.9 ± 4.90	28.8 ± 5.60	**
				T	28.9 ± 5.15	28.4 ± 5.04	36.2 ± 6.25	34.3 ± 7.01	30.1 ± 6.09	26.5 ± 5.06	28.1 ± 5.65	
				diff	1.40	1.90	−6.80	−5.50	0.00	1.40	0.70	
alanine aminotransferase	milliunits/mL	0	50	C	21.80 ± 9.84	21.50 ± 8.15	22.10 ± 9.89	21.40 ± 11.20	21.50 ± 11.69	20.50 ± 10.63	21.70 ± 11.81	**
				T	20.20 ± 8.43	21.00 ± 11.02	26.10 ± 12.70	27.40 ± 14.95	24.50 ± 15.96	21.30 ± 13.96	23.20 ± 16.33	
				diff	1.60	0.50	−4.00	−6.00	−3.00	−0.80	−1.50	
lactate dehydrogenase	milliunits/mL	100	225	C	126.80 ± 20.81	122.30 ± 16.83	120.20 ± 15.61	121.20 ± 14.26	125.20 ± 14.76	115.90 ± 15.40	130.20 ± 16.80	**
				T	131.50 ± 26.28	124.50 ± 25.12	142.70 ± 29.11	138.60 ± 28.43	136.30 ± 30.82	120.70 ± 24.91	136.50 ± 28.72	
				diff	−4.70	−2.20	−22.50	−17.40	−11.10	−4.80	−6.30	
alkaline phosphatase	milliunits/mL	15	105	C	53.80 ± 18.05	54.40 ± 16.72	52.80 ± 16.44	49.70 ± 15.92	49.40 ± 16.06	49.20 ± 15.76	51.20 ± 15.83	NS
				T	57.70 ± 14.61	59.70 ± 15.86	60.70 ± 15.64	57.10 ± 14.45	55.60 ± 14.01	54.10 ± 13.35	55.50 ± 11.56	
				diff	−3.90	−5.30	−7.90	−7.40	−6.20	−4.90	−4.30	
γ-glutamyltransferase	milliunits/mL	0	60	C	18.7 ± 15.49	17.4 ± 13.20	16.2 ± 14.44	16.2 ± 14.82	14.3 ± 12.05	14.5 ± 10.72	14.6 ± 10.93	*
				T	14.6 ± 8.25	15.8 ± 8.53	15.3 ± 9.72	16.9 ± 10.83	15.3 ± 10.23	15.6 ± 8.97	16.3 ± 9.64	
				diff	4.10	1.60	0.90	−0.70	−1.00	−1.10	−1.70	
creatinine	mg/dL	0.6	1.5	C	1.10 ± 0.13	1.09 ± 0.14	1.12 ± 0.15	1.12 ± 0.14	1.13 ± 0.14	1.19 ± 0.14	1.13 ± 0.15	NS
				T	1.14 ± 0.17	1.13 ± 0.15	1.12 ± 0.17	1.12 ± 0.16	1.16 ± 0.17	1.24 ± 0.16	1.16 ± 0.16	
				diff	−0.04	−0.04	0.00	0.00	−0.03	−0.05	−0.03	
blood urea nitrogen	mg/dL	6	25	C	13.9 ± 3.19	12.8 ± 2.41	14.8 ± 2.31	14.4 ± 1.82	13.3 ± 2.16	14.7 ± 2.47	13.4 ± 2.40	NS
				T	13.9 ± 3.51	11.9 ± 2.35	14.4 ± 2.53	13.5 ± 1.97	12.4 ± 2.12	13.5 ± 2.24	13.1 ± 2.05	
				diff	0.00	0.90	0.40	0.90	0.90	1.20	0.30	
uric acid	mg/dL	4	8.5	C	5.04 ± 0.91	5.09 ± 0.94	5.59 ± 0.99	5.14 ± 0.96	5.43 ± 1.02	5.27 ± 0.99	5.30 ± 0.97	NS
				T	5.45 ± 1.16	5.08 ± 0.90	5.57 ± 1.06	5.05 ± 0.88	5.50 ± 1.01	5.35 ± 0.92	5.57 ± 0.98	
				diff	−0.41	0.01	0.02	0.09	−0.07	−0.08	−0.27	
total protein	g/dL	5.8	8.3	C	7.33 ± 0.45	7.36 ± 0.54	7.33 ± 0.34	7.30 ± 0.43	7.13 ± 0.39	7.03 ± 0.35	7.31 ± 0.47	NS
				T	7.27 ± 0.42	7.19 ± 0.36	7.33 ± 0.45	7.28 ± 0.29	7.24 ± 0.40	7.04 ± 0.28	7.36 ± 0.54	
				diff	0.06	0.17	0.00	0.02	−0.11	−0.01	−0.05	
serum albumin	g/dL	3.2	5.2	C	4.43 ± 0.19	4.64 ± 0.33	4.51 ± 0.21	4.43 ± 0.23	4.42 ± 0.30	4.41 ± 0.22	4.6 ± 0.29	NS
				T	4.56 ± 0.28	4.68 ± 0.27	4.64 ± 0.26	4.55 ± 0.22	4.55 ± 0.29	4.54 ± 0.24	4.73 ± 0.33	
				diff	−0.13	−0.04	−0.13	−0.12	−0.13	−0.13	−0.13	
glucose	mg/dL	75	125	C	92.80 ± 6.99	80.60 ± 7.24	89.00 ± 6.58	83.90 ± 5.59	82.80 ± 6.34	83.20 ± 5.48	75.70 ± 5.46	NS
				T	93.20 ± 5.94	81.90 ± 8.53	89.40 ± 6.51	85.40 ± 5.57	86.20 ± 5.66	85.50 ± 5.19	76.20 ± 5.96	
				diff	−10.40	1.30	−13.70	−42.79	−42.52	−40.82	−31.85	
hematocrit	% (male)	40.6	52.6	C	41.57 ± 2.98	42.97 ± 3.44	43.59 ± 3.37	42.72 ± 3.12	41.46 ± 4.07	40.83 ± 3.32	42.20 ± 4.18	NS
	% (female)	36.0	45.0	T	42.61 ± 3.80	43.68 ± 3.61	44.68 ± 2.88	44.35 ± 3.04	43.44 ± 4.19	42.44 ± 3.67	44.24 ± 3.96	
				diff	−1.04	−0.71	−1.09	−1.63	−1.98	−1.61	−2.04	
hemoglobin	g/dL	13.7	17.7	C	14.19 ± 1.17	14.57 ± 1.25	14.44 ± 1.10	14.36 ± 1.22	14.11 ± 1.47	13.98 ± 1.22	14.38 ± 1.50	NS
				T	14.68 ± 1.46	14.96 ± 1.38	14.97 ± 1.10	15.12 ± 1.17	14.88 ± 1.47	14.74 ± 1.36	15.15 ± 1.50	
				diff	−0.49	−0.39	−0.53	−0.76	−0.77	−0.76	−0.77	
red blood cell count	millions/μL	4.42	5.95	C	4.61 ± 0.38	4.73 ± 0.47	4.78 ± 0.41	4.67 ± 0.42	4.58 ± 0.48	4.53 ± 0.43	4.67 ± 0.52	NS
				T	4.80 ± 0.46	4.90 ± 0.44	5.02 ± 0.33	5.00 ± 0.39	4.94 ± 0.48	4.81 ± 0.45	4.97 ± 0.49	
				diff	−0.20	−0.17	−0.24	−0.33	−0.37	−0.28	−0.30	
mean corpuscular hemoglobin	pg	28.5	33.5	C	30.84 ± 1.64	30.86 ± 1.56	30.29 ± 1.53	30.80 ± 1.55	30.87 ± 1.59	30.95 ± 1.52	30.85 ± 1.50	NS
				T	30.57 ± 1.51	30.53 ± 1.45	29.84 ± 1.56	30.29 ± 1.70	30.13 ± 1.58	30.70 ± 1.64	30.53 ± 1.69	
				diff	0.27	0.33	0.45	0.51	0.74	0.25	0.32	
mean corpuscular Hb concentration	%	32	36	C	34.13 ± 1.03	33.9 ± 0.88	33.14 ± 1.01	33.59 ± 0.91	34.03 ± 1.10	34.25 ± 1.00	34.07 ± 0.87	NS
				T	34.42 ± 0.82	34.21 ± 0.71	33.48 ± 0.87	34.09 ± 0.90	34.27 ± 1.22	34.72 ± 0.83	34.25 ± 0.89	
				diff	−0.29	−0.31	−0.34	−0.50	−0.24	−0.47	−0.18	
mean corpuscular volume	fL	85	98.4	C	90.36 ± 3.49	90.98 ± 3.40	91.34 ± 3.18	91.61 ± 3.38	90.71 ± 3.27	90.38 ± 3.35	90.56 ± 3.33	**
				T	88.82 ± 3.74	89.22 ± 3.74	89.10 ± 3.51	88.82 ± 3.68	87.98 ± 3.74	88.40 ± 3.86	89.19 ± 4.28	
				diff	1.54	1.76	2.24	2.79	2.73	1.98	1.37	
iron	μg/dL	30	180	C	107.80 ± 46.10	101.20 ± 27.66	69.70 ± 18.10	74.90 ± 20.91	74.60 ± 22.51	75.70 ± 22.42	84.30 ± 26.57	NS
				T	120.60 ± 55.85	108.10 ± 27.03	66.80 ± 26.47	79.60 ± 23.55	94.10 ± 23.23	87.70 ± 30.05	102.80 ± 39.82	
				diff	−12.80	−6.90	2.90	−4.70	−19.50	−12.00	−18.50	

partial thromboplastin time	s	20	35	C	26.64 ± 2.65	28.47 ± 3.32	27.22 ± 2.64	26.82 ± 3.16	27.11 ± 2.68	29.20 ± 8.29	27.26 ± 2.65	NS
				T	27.72 ± 2.78	29.08 ± 3.01	28.44 ± 2.22	28.87 ± 2.36	29.65 ± 3.16	27.87 ± 2.42	27.87 ± 2.51	
				diff	−1.08	−0.61	−22.20	−2.05	0.00	1.33	−0.61	
prothrombin time	s	10.2	13	C	11.79 ± 0.35	11.58 ± 0.37	11.47 ± 0.36	11.72 ± 0.40	11.59 ± 0.37	11.82 ± 0.44	11.53 ± 0.37	NS
				T	11.83 ± 0.44	11.56 ± 0.43	11.49 ± 0.50	11.88 ± 0.58	11.79 ± 0.50	11.75 ± 0.48	11.59 ± 0.56	
				diff	−0.04	0.02	−11.00	0.04	0.00	0.07	−0.06	
white blood cell count	thousands/μL	3.5	10.7	C	5.76 ± 1.25	6.04 ± 1.16	6.42 ± 1.37	6.83 ± 1.69	6.56 ± 1.21	6.21 ± 1.21	6.27 ± 1.96	NS
				T	5.81 ± 1.04	6.27 ± 1.33	6.80 ± 1.35	7.22 ± 1.15	6.88 ± 1.10	6.45 ± 0.99	5.83 ± 0.92	
				diff	−5.81	−6.27	−6.80	−7.22	−6.88	−6.45	−5.83	
neutrophils	%	36	70	C	56.47 ± 5.81	57.18 ± 6.83	52.98 ± 6.09	56.17 ± 5.64	54.54 ± 6.38	55.24 ± 6.09	57.70 ± 7.74	NS
				T	55.70 ± 6.18	57.68 ± 5.69	54.46 ± 5.09	57.17 ± 4.18	43.41 ± 5.02	54.32 ± 4.68	57.35 ± 6.09	
				diff	0.77	−0.50	−1.48	−1.00	11.13	0.92	0.35	
lymphocytes	%	18	50	C	33.12 ± 5.49	32.72 ± 7.04	35.00 ± 5.99	34.24 ± 5.71	33.88 ± 6.39	35.20 ± 6.11	31.67 ± 7.12	**
				T	34.23 ± 4.28	33.09 ± 4.79	32.06 ± 4.18	33.66 ± 4.03	35.21 ± 5.04	36.22 ± 4.79	32.64 ± 5.09	
				diff	−1.11	−0.37	2.94	0.58	−1.33	−1.02	−0.97	
basophils	%	0	2	C	0.88 ± 0.42	0.69 ± 0.52	0.76 ± 0.37	0.74 ± 0.38	0.77 ± 0.45	0.77 ± 0.35	0.75 ± 0.41	NS
				T	0.74 ± 0.31	0.64 ± 0.22	0.59 ± 0.29	0.58 ± 0.16	0.69 ± 0.30	0.73 ± 0.26	0.82 ± 0.42	
				diff	0.15	0.05	0.17	0.16	0.07	0.04	−0.07	
monocytes	%	2	10	C	6.01 ± 1.34	6.97 ± 2.18	8.37 ± 2.27	6.07 ± 1.22	8.18 ± 2.23	5.88 ± 1.43	7.29 ± 2.29	**
				T	5.43 ± 1.37	5.91 ± 1.62	9.37 ± 1.85	5.69 ± 1.23	7.80 ± 1.49	5.41 ± 0.84	6.47 ± 1.42	
				diff	0.57	1.06	−1.01	0.38	1.01	0.47	0.82	
eosinophils	%	0	8	C	3.48 ± 1.63	2.44 ± 1.21	2.89 ± 1.66	2.77 ± 1.64	2.63 ± 1.47	2.91 ± 1.76	2.58 ± 1.44	NS
				T	3.90 ± 1.86	2.66 ± 1.30	3.49 ± 1.69	2.89 ± 1.21	2.89 ± 1.24	3.32 ± 1.49	2.73 ± 0.90	
				diff	−0.42	−0.22	−0.60	−0.12	−0.26	−0.41	−0.15	
platlets	thousands/μL	150	400	C	296.70 ± 68.80	313.70 ± 60.14	331.70 ± 68.51	320.80 ± 63.33	325.90 ± 74.58	317.50 ± 69.08	322.60 ± 74.97	NS
				T	265.60 ± 37.73	285.90 ± 43.42	295.70 ± 49.87	292.60 ± 37.45	305.40 ± 38.08	285.50 ± 40.82	287.00 ± 43.03	
				diff	31.10	27.80	36.00	28.20	20.50	32.00	35.60	
sodium	mmol/L	136	145	C	138.80 ± 2.28	140.60 ± 1.10	137.90 ± 1.37	138.90 ± 1.98	140.40 ± 1.82	141.60 ± 1.89	139.70 ± 2.25	NS
				T	139.20 ± 1.38	140.90 ± 1.51	137.90 ± 1.37	138.80 ± 1.68	140.80 ± 1.51	142.20 ± 1.38	140.50 ± 1.87	
				diff	−0.40	−0.30	0.00	0.10	−0.40	−0.60	−0.80	
potassium	mmol/L	3.5	5.1	C	4.19 ± 0.30	4.01 ± 0.34	4.44 ± 0.50	4.23 ± 0.31	4.29 ± 0.42	4.27 ± 0.27	3.66 ± 0.23	NS
				T	4.31 ± 0.38	3.94 ± 0.21	4.23 ± 0.29	4.05 ± 0.28	4.19 ± 0.32	4.23 ± 0.22	3.74 ± 0.26	
				diff	−0.12	0.07	0.21	0.18	0.10	0.04	−0.08	
chloride	mmol/L	98	108	C	101.90 ± 2.07	103.50 ± 1.89	100.50 ± 1.29	102.10 ± 1.28	101.80 ± 1.26	104.80 ± 1.20	102.90 ± 2.14	NS
				T	102.20 ± 1.34	104.10 ± 1.35	100.80 ± 1.80	101.70 ± 1.31	101.40 ± 1.50	105.10 ± 1.54	103.30 ± 1.96	
				diff	−0.30	−0.60	−0.30	0.40	0.40	−0.30	−0.40	
calcium	mg/dL	8.2	10.5	C	9.57 ± 0.33	9.83 ± 0.36	9.81 ± 0.29	9.68 ± 0.30	9.69 ± 0.39	9.66 ± 0.31	9.60 ± 0.31	*
				T	9.68 ± 0.31	9.91 ± 0.29	9.71 ± 0.27	9.56 ± 0.25	9.77 ± 0.34	9.78 ± 0.27	9.75 ± 0.31	
				diff	−0.11	−0.08	0.10	0.12	−0.08	−0.12	−0.15	
phosphate	mg/dL	2.1	5	C	3.64 ± 0.48	3.88 ± 0.39	4.01 ± 0.41	4.00 ± 0.43	3.96 ± 0.49	4.06 ± 0.45	3.73 ± 0.40	NS
				T	3.74 ± 0.45	3.84 ± 0.42	3.86 ± 0.48	3.92 ± 0.49	3.96 ± 0.44	3.96 ± 0.43	3.65 ± 0.49	
				diff	−0.10	0.04	0.15	0.08	0.00	0.10	0.08	
magnesium	mg/dL	1.6	2.8	C	1.91 ± 0.13	1.91 ± 0.16	1.90 ± 0.21	1.90 ± 0.17	1.96 ± 0.22	1.94 ± 0.21	1.98 ± 0.19	NS
				T	1.88 ± 0.15	1.87 ± 0.18	1.84 ± 0.18	1.86 ± 0.17	1.91 ± 0.15	1.94 ± 0.12	1.99 ± 0.17	
				diff	0.03	0.04	0.06	0.04	0.05	0.00	−0.01	
carbonate	mmol/L	22	32	C	27.21 ± 1.62	27.19 ± 1.31	27.39 ± 1.89	26.84 ± 1.27	25.88 ± 1.85	25.90 ± 2.04	25.32 ± 1.59	**
				T	27.45 ± 1.37	27.16 ± 1.25	25.84 ± 1.89	25.92 ± 1.81	26.30 ± 1.78	26.05 ± 1.75	25.54 ± 1.81	
				diff	−0.24	0.03	1.55	0.92	−0.42	−0.15	−0.22	
cholesterol	mg/dL	130	300	C	184.70 ± 46.09	216.50 ± 43.29	205.90 ± 50.31	206.40 ± 52.64	198.10 ± 50.79	201.70 ± 53.45	213.90 ± 54.85	**
				T	189.00 ± 45.54	214.90 ± 53.58	184.10 ± 48.92	175.90 ± 49.96	182.50 ± 50.79	199.90 ± 47.92	225.60 ± 59.27	
				diff	−4.30	1.60	21.80	30.50	15.60	1.80	−11.70	
triglycerides	mg/dL	30	175	C	99.10 ± 61.08	107.20 ± 71.16	96.40 ± 65.29	95.40 ± 62.46	86.70 ± 54.14	89.10 ± 60.43	91.90 ± 63.85	NS
				T	86.20 ± 35.69	102.10 ± 41.83	107.80 ± 24.24	106.50 ± 39.11	85.30 ± 39.53	86.20 ± 41.64	92.10 ± 40.00	
				diff	12.90	5.10	−11.40	−11.10	1.40	2.90	−0.14	

[a] Probability that the control and test groups are significantly different from day 8 through day 24. *P* values, group × time interaction: NS, not significant; *, significant at $P < 0.05$; **, significant at $P < 0.01$.

Table 16. Serum Triglycerides and Cholesterol Distribution for Control and SALATRIM-Consuming Groups throughout Study II

	mean ± SD				
group	triglyceride (mg/dL)	cholesterol (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	VLDL (mg/dL)
control					
1	105 ± 15	193 ± 11	47 ± 3	123 ± 11	23 ± 3
8	111 ± 17	219 ± 11	56 ± 4	136 ± 10	27 ± 4
11	101 ± 17	212 ± 12	54 ± 4	139 ± 10	19 ± 3
14	99 ± 15	205 ± 12	51 ± 3	132 ± 10	22 ± 4
17	96 ± 14	200 ± 12	48 ± 3	136 ± 10	16 ± 3
20	96 ± 15	202 ± 6	47 ± 3	139 ± 10	15 ± 3
24	98 ± 16	212 ± 13	49 ± 3	137 ± 11	26 ± 4
SALATRIM					
1	91 ± 9	194 ± 10	43 ± 2	131 ± 10	21 ± 3
8	106 ± 10	217 ± 12	51 ± 2	144 ± 11	23 ± 3
11	106 ± 6	189 ± 12	42 ± 2	129 ± 11	18 ± 2
14	104 ± 9	178 ± 12	36 ± 2	118 ± 11	26 ± 3
17	91 ± 10	181 ± 12	37 ± 2	132 ± 11	12 ± 2
20	90 ± 10	202 ± 12	40 ± 2	145 ± 11	16 ± 2
24	97 ± 10	224 ± 14	46 ± 2	153 ± 11	24 ± 4

there was a slight rise in LDH upon initial exposure to SALATRIM followed by a decline to near control levels (statistically equivalent) on day 17.

In Table 15 mean corpuscular volume, monocytes, serum calcium, carbonate, and γ-glutamyltransferase (GGT) were all significantly altered in the SALATRIM-exposed individuals. All values remained within the normal range, and none of the changes were considered to be clinically relevant.

Since SALATRIM is a reduced-calorie fat, particular attention was paid to blood lipids. Cholesterol distribution in lipoprotein fractions was measured to determine the potential impact of SALATRIM on serum cholesterol distribution. From Table 16 it can be seen that there was a significant reduction in total cholesterol during the test period for the group receiving SALATRIM. From day 1 to day 8 there was a significant increase in total cholesterol which was associated with the ingestion of hydrogenated coconut oil. During the test period (days 8–14) there was a significant drop in the total and LDL cholesterol of the group receiving SALATRIM, whereas values for the control group remained elevated.

No significant changes were seen in urine pH, protein, glucose, creatinine, potassium, sodium, and nitrogen throughout the study. The results are summarized in Table 17.

Results of stool analyses are summarized in Table 18. During exposure to SALATRIM, excretion of fecal fat and stearic acid increased dramatically. In Figure 1 the fecal levels of the principal fatty acids are illustrated. From the figure it can be seen that in week 2, when SALATRIM was included, several fatty acids were excreted at slightly higher levels. Palmitic (16:0) and oleic (18:1) acids show increases, although all changes are small compared to that for stearic acid (18:0). The observed increase in stearic acid was expected on the basis of the poor absorption of stearic acid observed in rats. The impact of these changes on caloric availability is discussed by Finley et al. (1994). There were no signficant differences in fecal nitrogen, moisture, calcium, magnesium, or zinc excretion in subjects consuming SALATRIM.

In this study subjects completed questionnaires daily to document subjective clinical symptoms. Symptoms reported for test and control groups for the pretrial period, the test period, and the posttreatment period are shown in Table 19. From the data represented, it can be seen that nausea, abdominal pain, and headaches were the most frequent symptoms reported. The group fed SALATRIM reported more headaches and gastrointestinal symptoms during the test period. The effects reported were mild and did not cause anyone to drop from the study or require clinical intervention.

It should be noted that the 45 and 60 g/day exposure levels are much higher than the 13.5 and 29.8 g/day estimates for mean and 90th percentile exposure to SALATRIM.

The results of study II with SALATRIM were consistent with the predictability of its metabolism and caloric availability. However, two responses, while not clinically significant, were deemed to be of sufficient interest to investigate more thoroughly. These were the slightly higher activities of some serum enzymes and the clinical symptoms associated with SALATRIM consumption.

Study III. 4-Day Triple-Crossover. Study III was a crossover design in which all subjects served as their own controls, each subject being exposed to 60 g/day of control soy oil and 30 and 60 g/day of SALATRIM, with a washout period of exposure to 60 g/day of coconut oil in between. No clinically significant differences were seen between exposure to control and 30 g/day SALATRIM. When subjects ingested 60 g/day SALATRIM, a statistically significant increase was observed in ALT, AST, and LDH and a decrease in cholesterol (Table 20). These shifts were well within the normal ranges for these assays and not considered to be clinically important. All values approached pretest levels after subjects were shifted onto the coconut oil washout diets.

Table 17. Mean Values from Urianalysis of Control and SALATRIM Groups from Study II

	pH		nitrogen (g/24 h)		glucose (g/24 h)		creatinine (g/24 h)		sodium (mg/dL)		potassium (mg/dL)	
day	control	SALATRIM	control	SALATRIM	control	SALATRIM	control	SALATRIM	control	SALATRIM	control	SALATRIM
						Pre-exposure Period						
1	5.4	5.3										
2			11.1	11.6	0.15	0.17	1.27	1.42	118	111	61	63
3												
6			10.6	10.7	0.13	0.15	1.23	1.39	75	82	58	57
7			13.0	12.1	0.21	0.22	1.29	1.44	101	105	65	67
						Test Exposure Period						
8	6.2	6.1	10.4	11.3	0.28	0.25	1.23	1.40	141	155	62	70
11	5.6	5.1										
13												
14			11.8	11.8	0.18	0.18	1.28	1.38	103	99	67	57
						Post-exposure Period						
15			11.1	11.2	0.16	0.18	1.29	1.39	138	129	65	56
17	5.7	5.8										
20	6.2	6.0	11.5	11.0	0.17	0.17	1.35	1.44	100	105	62	57
21			11.3	11.5	0.16	0.17	1.31	1.54	106	120	68	65
22			10.9	11.9	0.14	0.18	1.26	1.47	125	136	65	69
24	5.6	5.7										

Table 18. Stool Chemistry for Control and Test Groups for Study II

	week	control, 1800 kcal/day	SALATRIM, 1800 kcal/day	control, 2500 kcal/day	SALATRIM, 2500 kcal/day
moisture (%)	1	76.02 ± 4.42	77.84 ± 2.97	74.28 ± 3.09	71.69 ± 5.43
	2	73.58 ± 5.84	77.14 ± 4.30	74.14 ± 3.68	71.80 ± 4.85
	3	73.18 ± 5.32	76.24 ± 3.55	74.41 ± 3.37	71.84 ± 5.81
nitrogen (g/day)	1	1.56 ± 0.30	1.68 ± 0.29	2.00 ± 0.55	1.85 ± 0.41
	2	1.31 ± 0.41	1.79 ± 0.57	2.03 ± 0.63	2.25 ± 0.36
	3	1.19 ± 0.42	1.74 ± 0.47	2.36 ± 1.06	1.69 ± 0.48
total fat (g/day)	1	3.74 ± 1.19	3.86 ± 1.01	6.23 ± 1.80	5.59 ± 1.60
	2	3.25 ± 1.02	12.39 ± 4.44	6.34 ± 2.44	21.06 ± 4.32
	3	3.36 ± 0.62	3.35 ± 0.83	6.96 ± 3.66	4.90 ± 1.84
stearic acid (g/day)	1	0.41 ± 0.23	0.27 ± 0.12	0.89 ± 0.53	0.71 ± 0.36
	2	0.26 ± 0.13	7.41 ± 2.69	0.84 ± 0.57	13.25 ± 3.26
	3	0.35 ± 0.14	0.30 ± 0.17	0.95 ± 0.76	1.00 ± 1.41
Ca (g/day)	1	3.22 ± 0.57	3.04 ± 0.45	3.48 ± 0.87	3.36 ± 0.72
	2	2.72 ± 0.77	2.72 ± 0.77	3.56 ± 0.99	3.60 ± 0.60
	3	2.56 ± 1.06	3.25 ± 0.71	4.19 ± 1.47	2.92 ± 0.69
Mg (g/day)	1	0.86 ± 0.15	0.83 ± 0.13	1.10 ± 0.30	0.97 ± 0.12
	2	0.75 ± 0.20	0.76 ± 0.24	1.18 ± 0.42	1.10 ± 0.19
	3	0.71 ± 0.30	0.87 ± 0.19	1.29 ± 0.65	0.86 ± 0.20
Zn (g/day)	1	0.037 ± 0.008	0.039 ± 0.008	0.051 ± 0.011	0.049 ± 0.009
	2	0.032 ± 0.010	0.034 ± 0.012	0.052 ± 0.017	0.049 ± 0.009
	3	0.030 ± 0.013	0.044 ± 0.009	0.062 ± 0.024	0.046 ± 0.012

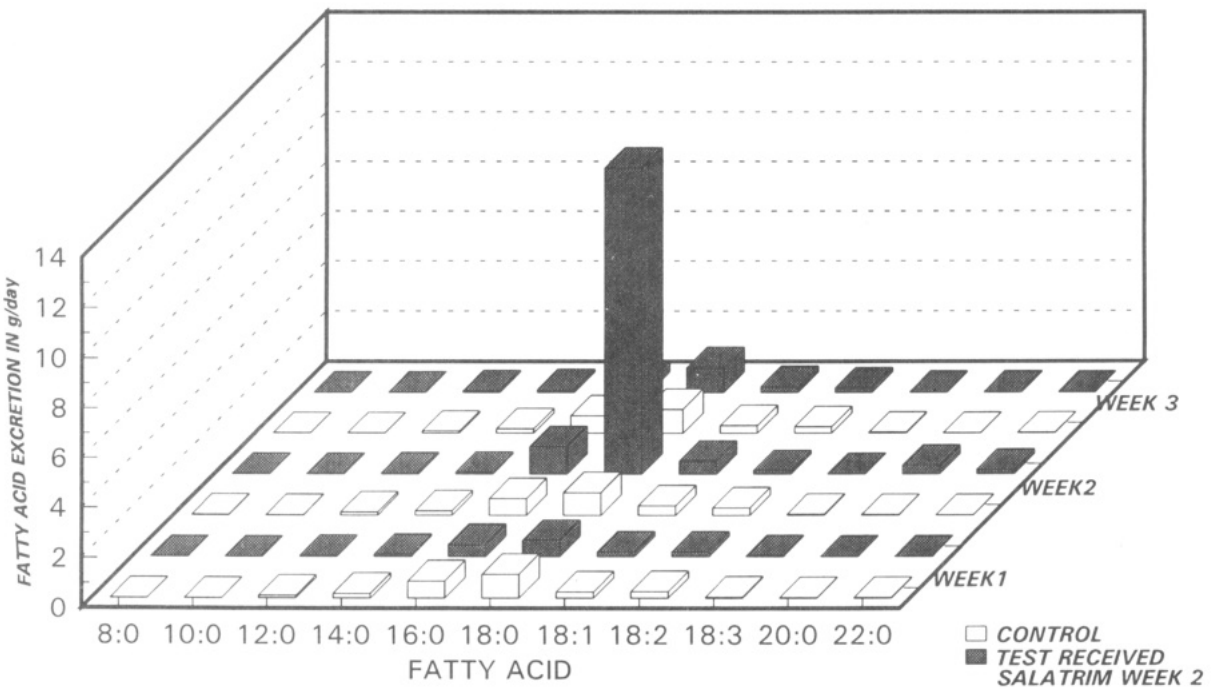

Figure 1. Mean fecal fatty acid distribution (from 3-day composite) of subjects receiving 60 g/day of either SALATRIM or coconut fat for each period of the study.

Table 21 reports subjective clinical symptoms observed by the subjects. Most of the reported symptoms are associated with gastrointestinal upsets and headaches. Table 22 breaks down reported symptoms by gender of the subjects, with a higher incidence of reports coming from the female subjects. Given the lower body weights of the female subjects, there may be a relationship between exposure level and body weight responsible for this higher level of complaints. This supports the conclusion that levels of less than 30 g/day SALATRIM do not cause any significant upset. It should be noted that the 60 g/day level is about twice the anticipated 29.8 g/day exposure from intended uses.

In an attempt to determine if there was a relationship between changes in serum enzyme values and gastrointestinal symptoms, an analysis of variance was conducted. No significant differences were observed in the AST, ALT,and GGT levels of the subjects reporting, and the subjects not reporting, gastrointestinal symptoms (Table 23).

Table 19. Clinical Symptoms Reported by Subjects (Study II)

		number of responses during study period		
symptom	group	pretest	test period	posttest
abdominal pain	test	1	21	0
	control	3	1	2
constipation	test	1	1	0
	control	2	0	0
diarrhea	test	0	3	0
	control	0	0	0
flatulence	test	0	0	0
	control	4	3	2
headache	test	6	16	1
	control	2	1	0
nausea	test	1	32	2
	control	0	2	0

Table 20. Clinical Chemistry Results from Study III

clinical test	units	normal min	normal max	test cycle[a]	mean ± SD	significance[b]
bilirubin	mg/dL	0.1	1.1	C60	0.70 ± 0.22	ab
				T30	0.75 ± 0.25	a
				T60	0.67 ± 0.23	b
alanine aminotransferase (SGPT)	milliunits/mL	3	35	C60	16.08 ± 6.49	a
				T30	16.51 ± 5.74	a
				T60	22.66 ± 8.47	b
aspartate aminotransferase (SGOT)	milliunits/mL	0	50	C60	26.41 ± 4.19	a
				T30	26.89 ± 3.69	a
				T60	34.28 ± 6.26	b
lactate dehydrogenase (LDH)	milliunits/mL	100	225	C60	127.88 ± 13.89	a
				T30	128.29 ± 13.97	a
				T60	139.07 ± 13.80	b
alkaline phosphate	milliunits/mL	15	105	C60	52.39 ± 11.82	a
				T30	52.53 ± 12.52	a
				T60	52.22 ± 12.20	a
γ-glutamyltransferase	milliunits/mL	0	60	C60	12.90 ± 4.60	a
				T30	12.90 ± 5.04	a
				T60	13.28 ± 4.81	a
β-hydroxybutyrate	mmol/L	0	0.25	C60	0.1 ± 0.06	a
				T30	0.1 ± 0.06	a
				T60	0.2 ± 0.10	b
creatinine	mg/dL	0.6	1.5	C60	1.22 ± 0.17	a
				T30	1.23 ± 0.20	a
				T60	1.20 ± 0.18	b
blood urea nitrogen	mg/dL	6	25	C60	12.61 ± 1.74	a
				T30	12.64 ± 2.04	a
				T60	12.75 ± 2.07	a
uric acid	mg/dL	4	8.5	C60	4.87 ± 1.05	a
				T30	4.91 ± 1.13	a
				T60	4.91 ± 1.24	a
total protein	g/dL	5.8	8.3	C60	7.14 ± 0.38	a
				T30	7.24 ± 0.36	a
				T60	7.21 ± 0.33	a
serum albumin	g/dL	3.2	5.2	C60	4.51 ± 0.26	a
				T30	4.57 ± 0.28	a
				T60	4.57 ± 0.26	a
glucose	mg/dL	75	125	C60	86.55 ± 5.01	a
				T30	88.23 ± 6.18	a
				T60	87.00 ± 5.48	a
hematocrit	%			C60	44.35 ± 4.17	a
	male	40.6	52.6	T30	44.56 ± 3.89	a
	female	36	45	T60	44.74 ± 4.06	a
hemoglobin	g/dL	13.7	17.7	C60	14.90 ± 1.43	a
				T30	14.99 ± 1.41	a
				T60	15.05 ± 1.42	a
red blood cell count	millions/μL	4.42	5.95	C60	4.97 ± 0.50	a
				T30	5.01 ± 0.50	a
				T60	5.04 ± 0.47	a
mean corpuscular hemoglobin	pg	28.5	33.5	C60	30.04 ± 1.54	a
				T30	29.95 ± 1.55	a
				T60	29.89 ± 1.49	a
mean corpuscular Hb concentration	%	32	36	C60	33.61 ± 0.94	a
				T30	33.64 ± 1.00	a
				T60	33.64 ± 0.90	a
mean corpuscular volume	fL	85	98.4	C60	89.35 ± 3.35	b
				T30	89.03 ± 3.44	a
				T60	88.81 ± 3.47	a
iron	μg/dL	30	180	C60	95.16 ± 24.77	a
				T30	97.67 ± 21.81	a
				T60	88.63 ± 24.37	a
white blood cell count	thousands/μL	3.5	10.7	C60	6.46 ± 1.10	a
				T30	6.58 ± 1.16	a
				T60	7.16 ± 1.39	b
neutrophils	%	36	70	C60	53.37 ± 6.20	a
				T30	53.74 ± 7.21	a
				T60	54.44 ± 5.73	a
lymphocytes	%	18	50	C60	36.69 ± 6.04	a
				T30	36.72 ± 6.66	a
				T60	36.06 ± 5.67	a
basophils	%	0	2	C60	0.50 ± 0.27	a
				T30	0.68 ± 0.41	b
				T60	0.53 ± 0.34	ab
monocytes	%	2	10	C60	6.56 ± 1.49	a
				T30	6.18 ± 1.73	a
				T60	6.54 ± 1.05	a

Table 20 (Continued)

clinical test	units	normal min	normal max	test cycle[a]	mean ± SD	significance[b]
eosinophils	%	0	8	C60	2.88 ± 1.30	a
				T30	2.68 ± 0.97	ab
				T60	2.46 ± 0.86	b
platelets	thousands/μL	150	400	C60	302.42 ± 56.93	a
				T30	320.8 ± 55.49	b
				T60	336.97 ± 76.12	c
sodium	mmol/L	136	145	C60	141.2 ± 1.38	b
				T30	140.76 ± 1.29	a
				T60	140.48 ± 1.56	a
potassium	mmol/L	3.5	5.1	C60	4.34 ± 0.46	a
				T30	4.28 ± 0.33	a
				T60	4.28 ± 0.32	a
chloride	mmol/L	98	108	C60	104.12 ± 1.63	a
				T30	103.46 ± 1.47	b
				T60	103.87 ± 1.50	ab
calcium	mg/dL	8.2	10.5	C60	9.46 ± 0.28	a
				T30	9.43 ± 0.35	a
				T60	9.23 ± 0.29	b
phosphate	mg/dL	2.1	5	C60	4.20 ± 0.44	a
				T30	4.20 ± 0.42	a
				T60	4.04 ± 1.45	a
magnesium	mg/dL	1.6	2.8	C60	2.11 ± 0.17	a
				T30	2.10 ± 0.14	a
				T60	2.07 ± 0.16	b
cholesterol	mg/dL	130	300	C60	179.15 ± 35.85	a
				T30	180.43 ± 38.17	a
				T60	167.71 ± 35.41	b
triglycerides	mg/dL	30	175	C60	79.34 ± 22.36	a
				T30	87.51 ± 29.16	ab
				T60	92.74 ± 24.02	b

[a] C60, cycle receiving 60 g/day of soy fat; T30, cycle receiving 60 g/day of a 50:50 blend soy fat and SALATRIM; T60, cycle receiving 60 g/day of SALATRIM. [b] Means having different letters are significantly different at $P \leq 0.05$.

Table 21. Number of Reported Symptoms in Study III

	no. of reports				
	test periods				
category	C60 (4 days)	T30 (4 days)	T60 (4 days)	washout (12 days)[a]	total
GI tract related					
nausea	5	3	19	5	32
abdominal pain	0	4	14	11	29
flatulence	3	0	4	4	11
eonesis	1	0	2	0	3
stomach upset	0	0	2	0	2
stomatitis	0	0	1	0	1
non-GI tract related					
headache	4	3	8	7	22
fatigue	2	0	2	2	6
myalgia	2	2	0	2	6
menses discomfort	4	0	0	1	5
agitation	0	1	0	4	5
fainting	1	0	0	3	4
dizzy	1	1	0	1	3
nervous	0	0	1	2	3
sleepy	0	0	1	1	2
backache	1	0	0	1	2
dipmenorrhea	2	0	0	0	2
rhinitis	0	0	1	1	2
dipurea	0	0	1	0	1
hot and cold feeling	0	0	1	0	1
sweating	0	0	1	0	1
arthralgia	0	1	0	0	1
dry mouth	0	1	0	0	1
polyuria	0	0	0	1	1
respiratory distress	0	0	0	1	1
sore throat	0	0	0	1	1
cough	0	0	0	1	1
depression	0	0	0	1	1

[a] There were three washout periods: (1) before first test period, (2) after the first test period, and (3) after the second test period (total of 12 days).

As in study II, body weights were monitored daily and all subjects maintained body weight within ±3 lb throughout the course of the study.

Table 22. Reported Symptoms

	no. of reports[a]								
	all			female			male		
report	C60	T30	T60	C60	T30	T60	C60	T30	T60
gastrointestinal	8	5	33	5	5	28	3	0	5
all	19	13	47	15	10	38	4	3	9

[a] Severity = 1.

Study IV. Single Dose. It was proposed that the symptoms reported by subjects in studies II and III might be related to ketone bodies, which are likely products of acetate metabolism. Therefore, this study was conducted to determine if consumption of SALATRIM 23SO caused increases in serum acetoacetate or β-hydroxybutyrate.

In study IV, fasting subjects were given single doses of various levels of SALATRIM, hydrogenated soybean oil, or MCT, and the serum levels of acetate, acetoacetate, β-hydroxybutyrate, and glucose were monitored for 4 h after the exposure. The results are reported in Table 24. A slight increase in serum acetate was seen in subjects receiving 15 g of SALATRIM. No increases were observed in serum ketones at any level of SALATRIM feeding. As expected, slight increases in acetoacetate and β-hydroxybutyrate were observed in subjects receiving MCT (Greenberger and Skillman, 1969; Allee et al., 1972; Wiley and Leveille, 1973).

It is therefore concluded that, at the levels studies, SALATRIM is not ketogenic. Thus, ketogenesis does not appear to be involved in the clinical symptoms observed.

DISCUSSION

The results of these studies do not suggest any metabolic disruption as a result of SALATRIM consumption. Body weight was steady and the biochemical parameters measured showed no clinically relevant changes throughout any of the studies.

Table 23. Enzyme Levels Observed in Subjects with or without Gastrointestinal Symptoms (Study III)

	no. of subjects reporting symptoms		enzyme activity (milliunits/mL) mean level		
treatment	subjects with no symptoms	subjects with symptoms	subjects with no symptoms	subjects with symptoms	diff (no symptoms – with symptoms)
C60					
ALT	19	5	17	13	4
AST	19	5	27	26	1
GGT	19	5	13	12	1
T30					
ALT	20	4	17	14	3
AST	20	4	27	24	3
GGT	20	4	13	13	0
T60					
ALT	9	15	24	22	2
AST	9	15	33	35	-2
GGT	9	15	14	13	1

Table 24. Serum Constituents at Various Times after Ingestion of Beverages

			averaged values at						
response	oil	level	0 min	15 min	30 min	60 min	120 min	180 min	240 min
acetate (μmol/dL)	soy	7.5	33	34	37	31	32	34	35
	soy	15	39	37	40	39	39	35	41
	SALATRIM	7.5	38	39	39	39	34	33	38
	SALATRIM	10	36	34	32	34	38	36	39
	SALATRIM	12.5	35	37	36	35	35	33	40
	SALATRIM	15	30	36	37	42	40	39	34
	MCT	15	30	36	36	36	36	33	34
acetoacetate (μmol/dL)	soy	7.5	3	2	3	2	2	4	5
	soy	15	4	5	3	2	3	6	7
	SALATRIM	7.5	4	3	3	3	3	4	4
	SALATRIM	10	2	2	2	1	2	3	5
	SALATRIM	12.5	3	1	2	1	2	4	4
	SALATRIM	15	4	4	4	2	1	3	5
	MCT	15	4	5	5	4	8	7	6
β-hydroxybutyrate	soy	7.5	10	8	9	6	7	12	18
	soy	15	10	13	11	6	7	16	20
	SALATRIM	7.5	13	10	9	6	7	12	15
	SALATRIM	10	9	8	8	7	7	14	19
	SALATRIM	12.5	10	9	8	6	5	12	16
	SALATRIM	15	17	14	10	6	5	8	18
	MCT	15	9	22	17	12	33	27	23
glucose (mg/dL)	soy	7.5	96	103	110	101	84	90	92
	soy	15	92	102	111	97	87	86	87
	SALATRIM	7.5	95	100	110	86	89	91	89
	SALATRIM	10	87	94	105	89	83	85	85
	SALATRIM	12.5	90	95	112	90	82	82	85
	SALATRIM	15	87	97	113	82	82	90	88
	MCT	15	88	98	91	75	77	84	88

Serum enzymes, indicative of hepatic function, did not change at a clinically significant level, although in both study II and study III there was an initial increase in the activity of these enzymes which was followed by a return to baseline after SALATRIM ingestion ceased. These changes were not observed when SALATRIM was consumed at 30 g/day in study III. The AST and ALT levels generally increased less than 50% in individual subjects for whom an increase was observed. According to Kaplan (1987), changes of less than 100% are not usually considered to be clinically significant. Porikos and Van Itallie (1983) reported increases in AST and ALT of 80–100% when subjects were fed high-sucrose diets. Other reports show increases in serum aminotransferase activity in subjects receiving parenteral nutrition (Lindor et al., 1979; Mercer et al., 1984; Chang and Silvis, 1974; Dudrik et al., 1972).

The changes in AST and ALT were observed at high levels of SALATRIM (45–60 g/day), whereas subjects fed 30 g/day SALATRIM did not exhibit changes. The 30-g level is equivalent to the 90th percentile of anticipated of SALATRIM exposure. The results suggest that diet can cause minor variations in serum transaminase activity in some individuals but that values remain within normal ranges.

Consideration of the hematological profiles reveals no significant statistical trends. Clinically, the data are remarkably stable and reflect no clinically significant abnormalities. Care was taken in designing the study to avoid excessive blood sampling. As evidenced by consistent values in Tables 15 and 20, there was excellent maintenance of overall circulating red cell mass and volume. When one considers the hematopoietic system overall, the statistical and clinical data are best summarized as representing no discernible impact of SALATRIM ingestion on the formed elements of the blood.

In study II, there was an anticipated significant difference between test and control groups in week 2 (treatment period) of the study in fecal lipid. The highly significant increase in fecal stearate was found in subjects ingesting SALATRIM. The increased lipid was mostly accounted for as stearic acid, which was poorly absorbed. The limited absorption of stearic acid is a significant contributor to the reduced caloric nature of SALATRIM.

This result is discussed in detail by Finley et al. (1994). The fecal stearic acid supports the rationale that SALATRIM provides fewer calories because the stearic acid hydrolyzed from the triacylglycerols is poorly absorbed.

In study III fecal stearic acid showed trends similar to those observed in study II. Due to the short duration of the study, stearic acid in the collected feces was carried over into the posttreatment period and data could not be related to test materials.

Two sets of data were obtained for serum lipid levels in study II. One set, total cholesterol and triglycerides, was reported with the routine safety chemistry values (Table 15). Another set, including total cholesterol and VLDL, LDL, and HDL cholesterol, was obtained by centrifugation (Table 16). The data suggest that mean serum HDL cholesterol, total cholesterol, and LDL cholesterol decreased significantly in subjects ingesting SALATRIM.

In studies II and III some subjects reported gastrointestinal discomfort and headaches. The incidence was much greater in female subjects, who were receiving more SALATRIM on a body weight basis. It is possible that, since the short-chain fatty acids are rapidly hydrolyzed from the triacylglycerols, the level of short-chain fatty acids might temporarily overwhelm the ability to utilize acetate. This is, however, purely speculative.

CONCLUSIONS

In 1-day acute and 4- or 7-day human clinical studies, SALATRIM, a low-calorie fat, was consumed at levels as high as 60 g/day. At the 60 g/day exposure, slight increases were observed in AST, ALT, and LDH, but all values were within normally expected ranges. All changes were less than 50% of baseline values. These increases are not believed to be clinically significant. No changes in the activity of these enzymes were observed when 30 g/day SALATRIM was consumed.

No other clinical parameters were affected by the ingestion of SALATRIM. Fecal fat and fecal stearic acid increased in proportion to SALATRIM in the diet, as expected from the limited absorption of stearic acid.

Several subjects reported gastrointestinal discomfort when 45 and 60 g/day SALATRIM was consumed, whereas consumption of 30 g/day did not result in any gastrointestinal effects. The 30 g/day consumption of SALATRIM exceeds the projected 90th percentile consumption of SALATRIM for the intended uses. The lack of significant clinical changes at levels of about 2.5 times the projected mean consumption led to the conclusion that SALATRIM can be safely consumed at a level of at least 30 g/day.

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