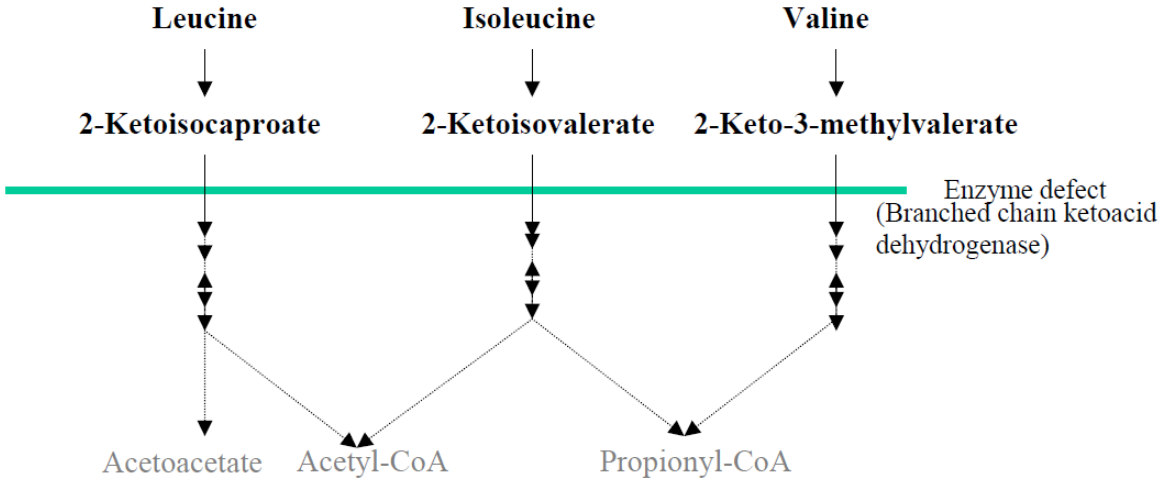
LONG TERM MANAGEMENT MAPLE SYRUP URINE DISEASE (MSUD)

OMIM# 248600

Definition:

- Aminoacidopathy involving the branched chain amino acids **Leucine, Isoleucine** and **Valine** metabolism.
- Enzyme defect: branched chain ketoacid (alpha-oxoacid) dehydrogenase complex (BCKD) multi-enzyme complex similar to PDH complex
- Consequence: increased ketoacids (BCKA) and BCAA (leu, ile, val)
- Toxic metabolic component: 2-oxoisocaproic acid (from leucine breakdown)
- Treatment must optimize the transport of the seven amino acids (Tyr, Trp, His, Met, Thr, Gln, Phe) that compete with branched-chain amino acids for entry into the brain via a common transported (LAT1).(1-3)

Pathway:



Clinical Presentation:

5 phenotypes:

Classic**,** severe form:

- Progressive encephalopathy from 3rd-5th days of life
- Lethargy, feeding problems, somnolence, cerebral edema, coma
- Fincing and bicycling abnormal movement
- Maple syrup odor of cerumen
- Enzyme activity 0-2%

Intermediate form:

- Similar presentation but usually later onset and onset is variable.
- Psychomotor retardation
- Fluctuating/progressive neurological disease
- Recurrent ketoacidotic decompensation
- Biochemically same as classical
- Enzyme activity: 3-30%

Intermittent

- Transient neurologic disorder with elevation of BCAA and BCKA
- Recurrent episodic ataxia, lethargy, cyclic vomiting.
- Patient has normal development and normal biochemical parameters between the episodes

Thiamine-responsive

- Thiamine hydrochloride 10 mg/kg/day (50-300 mg/day)

Dihydrolipoyl dehydrogenase (E3) deficient

- Lactic acidosis, ketosis (combined deficiency of BCKD, PDH and alpha-KGD complexes).(1-3)

Genetics:

- AR, several proteins ($E_{1\alpha}$, $E_{1\beta}$, E_2, E_3)
- E_3 deficiency: combined deficiency of several mitochondrial dehydrogenases
- Incidence:1:200000
- Frequency: 1:185,000 in newborns
- No exact incidence in Saudi Arabia.(1-3)

Diagnosis:

- Plasma amino acids: ↑valine, ↑↑leucine, isoleucine, alloisoleucine (diagnostic)
- UOA: ↑branched-chain keto (oxo) and hydroxyacids (2-OH-isovalerate, 2-OH-caproate , 2-keto-isocaproate, 2keto-3-methylvalerate, 2 ketoisovalerate,).
- BCKAD enzyme activity can be measured in skin fibroblasts, lymphocytes, or biopsied liver tissue but is of variable accuracy and may not be necessary.
- Confirmatory DNA sequencing of genes encoding BCKAD subunits.(1-3)

Treatment:

1. **Acute episode treatment guidelines (Emergency)(1-4):**
   - ABC or now CAB
   - Stop all source of protein central and parenteral nutrition.
   - If patient not tolerating orally within 12 hours after presentation start enteral BCAA-free amino acid until Leucine levels are at the clinic's upper treatment range of 250 umol/L
   - Check GlucoChecks
   - Insert an IV line and take bloods for the following: blood gas, Chem 1, Ammonia, and urine analysis to check ketones. In addition to plasma amino acids.
   - Call Biochemical Genetics lab (Metabolic) lab for urgent processing of plasma aminoacids at 40195, 40196, 40197
   - Start one and half to double maintenance I.V.F as 10% Dextrose + KCL 20 Meq/l. Re-adjust according to lab results (Keep GlucoChecks 5-8mmol/L). Consider start insulin if hyperglycemia develop at dose of 0.01-0.05 unit/kg/hour and titrAate up until blood glucose controlled.
   - Start IV intralipid 20% at 2-3 g/kg/day to provide additional calories.
   - Ensure enough caloric intake covering 110% of the recommended daily allowance (RDA) in order to shut down endogenous protein breakage (120-140 kcal/kg/day for neonates and 110 to 120% of RDA for older children (Note :RDA for infant: 110 kcal/kg/day, for 1-3 yrs:100, for 4-6yrs: 90, for 7-10yrs: 70, for 11-14 yrs: 50-55).
   - Give prophree or polycose (non-protein calorie source) P.O/NGT as tolerated.
   - Identify and treat the infection or other cause of the metabolic stress
   - When there is nausea or vomiting give Granisetron 10 to 40 microgram / kg, infused over 3 to 5 minutes.
   - Call metabolic dietician on-call to help with dietary management.
   - Begin enteral therapy if tolerated with a metabolic formula containing all required amino acids except for limited BCAA (Ketonex®-), 2.5-3.5 g/kg/day.
   - Maintain phenylalanine, tyrosine, histidine, methionine, tryptophan, and threonine within normal.

- Begin 1% solutions of Isoleucine and Valine when levels approach upper treatment range (105umol/l, 318 umol/l). Start supplements at 20-30 mg/kg/day (1.5 to 3.0 mL/kg). Dose range between 20-120 mg/kg/day and adjust based on Plasma amino acids results.
- It is important to realize that isoleucine and valine levels may drop rapidly and that very low levels (isoleucine < 100 umol/L and valine < 200 umol/L) will keep the leucine level from dropping by limiting protein synthesis. Low levels will also allow more leucine to enter brain by providing less transport competition and thus will produce or enhance brain edema and neurological complications.
- Start Glutamine and alanine. Total intake: 150-400 mg/kg/day each, depending on plasma amino acids result.
- Monitor plasma amino acids and urine for ketones and ammonia daily until patient improved clinically and leucine came back to upper treatment range.

Metabolic variables	
Total caloric intake	120-140 kcal/kg/day for neonate and 110 to 120% of normal energy needs for older children
Intralipid 20%	40-50% of calories can be achieved through 2-3 gram/kg/day
Dextrose solution	10 mg/kg/min
Protein as essential and nonessential AA	3-4 g/kg/d
Isoleucine and valine supplements	• Begin 1% solutions when levels approach upper treatment range. • Start supplements at 20-30 mg/kg/day (1.5 to 3.0 mL/kg). Dose range between 20-120 mg/kg/day and adjust based on PAA results
Whern there is nausea or vomiting Granisetron	10 to 40 microgram / kg, infused over 3 to 5 minutes
Control of brain edema (for details please see appendix 1)	
Furosemide	0.5-1 mg/kg q6h to prevent water retention, monitor serum Na, K, osmolarity (urine specific gravity should be below 1.010)
Sodium added to keep serum Na conc.>140 mEq/L	Formula to calculate sodium deficit for replacement if patients sodium <135: (135-patient's sodium)x0.6x weight in kg give in 24 hours Formula to calculate sodium needs if patients sodium <140 or between 135-140: (145-patient's sodium)x0.6x weight in kg give in 24 hours
Mannitol	0.5 g/kg IV prn
Dialysis (details see appendix 2)	
• Persistently high plasma leucine despite above measures • Leucine encephalopathy • If hyperammonemic	Hemodialysis or continuous venovenous hemofiltration, with the help of Nephrologist and PICU specialists
Goals of therapy	
Rate of decrease of plasma Leu conc.	Aim for >750 umol/L-24 hr
Plasma Leucine	100-250 umol/L
Plasma isoleucine	150 - 300 umoL/L
Plasma valine	200-400 umoL/L
Serum Na	138-145 mEq/L
Serum osmolality	290-300 mosm/L. Avoid osmolarity changes of greater than 5 mosm/L per day or 0.25 mosm/L per hour
Urine output	2-4 ml/kg/hr
Urine osmolality low	300-400 mosm/L
Weight gain	30-40 g/day
Soft fontanelle, stable OFC and VS	
Carefully observe for pancreatitis	Occurs on 2nd or 3rd day of hospitalization as leucine levels return to normal

2. **Transition to long term management (Wards protocol)(1-4)**

- Continue on above measures including high calorioc intake, Ketonex® formula) with close monitoring of plasma aminoacids until target ranges of plasma leucine (100-250), Isoleucine (150-300) and Valine (200-400) are achieved.
- Ensure appropriate caloric intake and medication dosages by calculating calories and medication dosages/ kg daily and document it in the chart.
- Discontinue IV lipid 20% when target caloric intake can be achieved through other sources because long administration of lipid may cause fatty liver.
- Patient need daily evaluation from metabolic dietician with gradually introduction of natural protein 50% of normal intake at home then upgrade to 100% if patient improve clinically and target plasma levels of leucine, Isoleucine and Valine achieved.
- Titrate IVF according to PO intake until discontinue. Measure electrolytes and urine analysis once before discharge.
- Discharge the patient if the following parameters achieved:
    1. Normal clinical status as home before crises.
    2. Target plasma level of Leucine, Isoleucine, Valine achieved.
    3. Normal eletrolytes and no ketones in the urine.
    4. For new diagnosed case: parents educated about the disease natural history, formula, medications and sick day protocol.
    5. For new diagnosed case: Emergency card provided to the parents
    6. Family are comfortable with preparation of formula and sick day protocol
    7. Calculate the dosage of medications and ensure that had appropriate dosages / kg.

- Give appointment with General Metabolic Genetics Clinic 2 week after discharge with plasma aminoacids and electrolytes, prealbumin prior to appointment.

3. **Long term management (home and out patient visits)**

a. Nutritional management:

The aim of dietary management includes:

- Normal weight gain, linear growth, and head growth
- Normal psychomotor development, as assessed by serial examinations and valid developmental screening tools (e.g., Denver Developmental Screening Test II)
- Age-appropriate tolerance of leucine, isoleucine, and valine, with stable plasma BCAA concentrations and BCAA concentration ratios
- Avoidance of essential amino acid, fatty acid, and micronutrient deficiencies

b. Metabolic dietitian should ensure the following:

- Home formula supplies include BCAA-free powder (Ketonex-1 (for infant and toddler), Ketonex-2 (for children; adolescents, and adults).
- For infant: Breast milk or regular formula as a natural protein source. For older children: the source of natural protein from regular diet.
- Supplementation with 10-mg/ml (1%) solutions of isoleucine, valine, and leucine and fortified formula with glutamine and alanine. The dose adjusted according to plasma amino acids result.
- Monitoring of amino acid concentrations. The frequency of amino acid monitoring varies by age, metabolic stability, compliance, and regional clinical practice. For rapidly growing infants, monitoring weekly is recommended.

Suggested clinical parameters for the asymptomatic infant or young child include the following:

- Normal age- and weight-adjusted energy intake
- Protein as essential and non-essential amino acids: 2-30 g/kg/day (see table 2)
- Appropriate leucine tolerance. The dietary requirement for BCAAs varies as a function of age, growth rate, calorie intake, illness, and residual in vivo BCKAD enzyme activity. In persons with classic MSUD (0%-2% enzyme activity), leucine tolerance in mg/kg/day is 65-85 for neonates, 20-40 for children, and 10-15 for adults [Strauss, Puffenberger, Morton, unpublished observations].
- Isoleucine and valine supplements as needed to maintain a plasma valine to leucine concentration ratio (mol:mol) of 2 or greater, and an isoleucine to leucine ratio of 0.5 to 1. Isoleucine supplements can periodically be suspended based on plasma amino acid monitoring, but continuous valine supplementation is prudent, because its low affinity for the blood-brain barrier

  LAT1 transporter makes it especially vulnerable to competitive inhibition by leucine [Smith & Takasato 1986].

Table 1: Treatment Ranges for Target Amino Acids in MSUD(5)

Amino Acid	(2-4 hr postprandial)
ALA	150-500 umol/L
GLUT	400-800 umol/L
ALLO	0
ILE	150-300 umol/L
LEU	100- 250 umol/L
VAL	200-400 umol/L

Table 2: recommended daily nutrient intake:(5)

Age	Nutrient					
	ILE (mg/kg)	LEU (mg/kg)	VAL (mg/kg)	Protein(g/kg	Energy (Kcal/kg)	Fluid (ml/kg)
Infants						
0 to <3 mo	36-60	60-100	42-70	3-3.5	120 (95-145)	125-150
3 to <6 mo	30-50	50-85	35-60	3-3.5	115 (95-145)	130-160
6 to <9 mo	25-40	40-70	28-50	2.5-3	110 (80-135)	125-145
9 to <12 mo	18-33	30-55	21-38	2.5-3	105 (80-135)	120-135
Girls and Boys	ILE (mg/day)	LEU (mg/day)	VAL (mg/day)	Protein (g/day)	Energy (Kcal/day)	Fluid (ml/day)
1 to <4 yr	165-325	275-535	190-400	≥30	1,300 (900 - 1800)	900- 1,800
4 to < 7 yr	215-445	360-695	250-490	≥35	1,700 (1300 - 2300)	1,300-2,300
7 to < 11 yr	245-470	410-785	285-550	≥40	2,400 (1650 - 3300)	1,650-3,300

Normal target aminoacids references by age:

Amino Acid	(2-4 hr postprandial)			
	Newborn	1-3 m	3m-6y	6-18y
LEU	61-183	43-165	40-158	79-174
ILE	27-80	32-87	13-81	38-95
VAL	78-264	96-291	85-334	156-288
GLU	243-822		475-746	360-740
ALA	132-455	134-416	148-475	193-545

Supportive measures:

- Neuropsychiatric morbidity is first addressed with strict and consistent metabolic control. Adolescents and adults with MSUD and ADHD, depression, or anxiety respond favorably to standard psychostimulant and antidepressant medications.

- Thiamine treatment. The existence of "thiamine-responsive" BCKAD mutants is controversial. Nevertheless, for any person with MSUD in whom the functional consequences of the mutation(s) are unknown, a four-week trial of enteral thiamine (50-100 mg/day, divided twice a day) is reasonable. However, it should be noted that significant changes in dietary therapy (e.g., BCAA or calorie intake) during the treatment period confounds interpretation of a specific thiamine effect.(3)

Look for complications of MSUD which includes(3):

- **Iatrogenic essential amino acid deficiency.** Anemia, acrodermatitis, hair loss, growth failure, arrested head growth, anorexia, and lassitude valine.(6)
- **Iatrogenic nutritional deficiencies**. Commercially available MSUD synthetic formulas provide marginal intakes of certain minerals and micronutrients, and utilize vegetable oils that contain little or no omega-3 fatty acid (linolenic, EPA, DHA). Zinc, selenium, and omega-3 fatty acid deficiency were common among patients with classic MSUD [Strauss & Morton 2003]. Other studies have documented deficiencies of folic acid and selenium in persons treated with MSUD formula.(7, 8)
- **Osteoporosis.** In 90% of adolescents with classic MSUD (n=10), bone mineral density of the radius and femoral neck, but not lumbar spine, were low compared to unaffected age-matched siblings [Strauss, Puffenberger, Morton, unpublished observations]. Bone fractures commonly cause transient leucinosis.
- **Recurrent oroesophageal candidiasis**. Candida infections are common in hospitalized persons with MSUD and may result from T-cell inhibitory effects of elevated plasma leucine(9) iatrogenic immunodeficiency as a result of inadequate BCAA intake.

Monitoring:

Suggested monitoring schedule includes

Age	PAA	Electrolytes, urine dipsticks for ketones	CBC, total protein, albumin, prealbumin, Se, Zn, ferritine, Ca, Mg, 25-hydroxy vitamin D, Growth parameters	Clinic visits
0-3 months	weekly	weekly	2 months	2 months
3-18 months	2 weeks	2 weeks	3 months	3 months
18 month – 10 years	monthly	monthly	4 month	4 months
10-18 years	monthly	monthly	6 months	6 months

Maintain records of food intake for 3 days immediately before each plasma amino acids.

Goals of laboratory monitoring:

- Plasma leucine concentration: 150-300 µmol/L with an age-appropriate intake.
- Plasma isoleucine concentration approximately equal to plasma leucine concentration.
- Plasma valine concentration at least twofold plasma leucine concentration.
- Indices of calcium, magnesium, zinc, folate, selenium, and omega-3 essential fatty acid sufficiency.
- Normal growth parameters.

Management of feeding problems:

1. General recommendations:
   - Monitor growth and intake of essential nutrients with every 200 gram change in weight
   - Consider overnight tube feeding or limited nocturnal fasting times
2. Children with mild to moderate feeding problems
   - use a combination of pureed foods and commercial enteral feeds to meet the nutritional prescription in addition to the medical protein and other energy modules
   - increase the frequency of meals and reduce quantity per feed
3. Children with severe feeding problems
   - G-tube feeding consisting of an enteral product to the natural protein in addition to the medical protein and other energy modules
   - if severe vomiting: use pharmacotherapy, consider fundoplication or J-tube feeding

Sick day management:

- At the first sign of illness start sick day formula.
- Sick-day diet to provide 120-130 kcal/kg/day for neonates or 110 to 120% of normal energy needs in older individuals
- Minor illness like URTI can normally be managed with a sick day formula providing 50% of normal protein intake and high in calories and meeting or exceeding CHO requirements
- Give prophree or polycose as tolerated
- Give ibuprofen (10 mg/kg/dose q 6 h) when fever >38 C
- give ondansetron (0.15 mg/kg/dose q 8 h) to manage vomiting

Management with immunizations:

Give sick day formula 50% for 24 hours

- manage fever >38 C with ibuprofen
- give double dose of carnitine (200 mg/kg/day)
- If not improved within 24 hours bring to ER

Management with surgical procedure:

- Ensure that the patient on his usual state of health prior to procedure
- Ensure stability of metabolic parameters including leucine, isoleucine and valine prior to procedure.
- Plasma aminoacids, chem1, urine for ketones prior to procedure
- High caloric intake with IVF D10 and 20% intralipid which provide 110 to 120% of normal energy needs starting 12-24 hours prior to procedure
- After surgery follow the guidelines mentioned in Transition to long term management (Wards protocol)

Orthotopic liver transplantation:

Is an effective therapy for MSUD patients. 37 individuals with classic MSUD (age 1.9-20.5 years) underwent elective orthotopic liver transplantation between 2004 and 2009. Plasma leucine, isoleucine, and valine concentrations were normal within six hours after transplantation in all individuals and remained so, on an unrestricted diet. Metabolic cure was reflected by a sustained increase in weight-adjusted leucine tolerance from 10-40 mg/kg/day to more than 140 mg/kg/day, normalization of plasma concentration relationships among branched-chain and other essential and non-essential amino acids, and metabolic and clinical stability during protein loading and intercurrent illnesses.(10)

Appendix 1:

Control of brain edema(3):
A decrease in blood osmolarity of more than 8 mosm/L per day can precipitate fatal brain herniation in an ill infant or child with MSUD. Close monitoring (preferably in an intensive care unit) is warranted.

Neurologic assessments to be performed on a frequent basis to monitor for brain swelling include the following:

- Measure head circumference and fontanel size in neonates
- Watch for signs of increased intracranial pressure including:
    - Papilledema
    - Disorientation, combativeness
    - Depressed level of consciousness
    - Refractory vomiting
    - Extremity hyperreflexia
    - Bradycardic hypertension
- Watch for signs of impending brain herniation including:
    - Hyperactive gag
    - Pupillary asymmetry
    - Ophthalmoplegia
    - Decorticate posturing
    - Methods to minimize the possibility of brain swelling:
    - Elevate the individual's head
- Assess total body sodium, potassium, and water balance at 12-hour intervals. The following clinical formula is useful for managing the serum sodium concentration [Rose & Post 1994; Strauss, Puffenberger, Morton, unpublished observation]:
    - Serum Na concentration equals ~[(total body Na + total body K)/ total body water]
    - Assume total body water equals ~70% body weight, 2/3 of which is intracellular and has sodium and potassium concentrations of 14mEq/L and 140 mEq/L,respectively [Guyton & Hall 1996].
    - Minimize osmotic variation of the extracellular fluid in hospitalized patients, by assessing weight trend, urine output, and serum and urine

electrolytes every 12 hours and adjusting electrolyte and water intake accordingly [Strauss, Puffenberger, Morton, unpublished observation].

- Give Furosemide (0.5-1.0 mg/kg/dose) as needed every six to 12 hours to oppose the urinary concentrating action of vasopressin and maintain urine osmolarity at a ceiling value of 300-400 mosm/L. This allows for brisk output of isotonic urine to compensate for the large infused volume associated with hypercaloric feeding.

Methods to manage brain swelling:

- For weight gain, hyponatremia, or deepening encephalopathy, administer [Strauss, Puffenberger, Morton, unpublished observation]:
- Furosemide: 1 mg/kg, followed by
- Mannitol: 0.5-1.0 g/kg over 60 minutes, followed by
- Hypertonic (3%-5%) saline: 2.5 mEq/kg over 60 minutes

Neuroimaging:

During episodes of acute encephalopathy, individuals with MSUD are typically too unstable for magnetic resonance imaging. Cranial CT scan is used to look for major indices of cerebral edema, such as decreased volume of cerebral ventricles and basal fluid spaces, or reduced gray-white discrimination [Strauss, Puffenberger, Morton, unpublished observation].

If there is clinical evidence of evolving brain herniation, elevate the individual's head, hyperventilate by face mask or endotracheal tube, give mannitol 1-2 g/kg and hypertonic saline 3 mEq/kg, and transfer the individual emergently to a pediatric or neurologic intensive care unit.

Hemodialysis/hemofiltration. Nutritional therapy alone can effectively reduce even extremely elevated plasma concentrations of leucine in persons with MSUD of any age and under a wide variety of clinical circumstances [Morton & Strauss 2002, Strauss & Morton 2003]. However, numerous publications have shown that renal

replacement methods can achieve rapid corrections of BCAAs and BCKAs during the acute phase of MSUD crisis [Jouvet et al 1997, Schaefer et al 1999, Yoshino et al 1999, Jouvet et al 2001, Puliyanda et al 2002].

Appendix 2:

Dialysis:

As methods of invasive leucine removal, peritoneal dialysis and venovenous hemofiltration are less effective and more dangerous than short courses of continuous hemodialysis [Schaefer et al 1999]. When hemodialysis is used to treat MSUD it must be coupled with effective nutritional management to constrain the catabolic response and prevent recurrent clinical intoxication. A combined approach to therapy, using hemodialysis with simultaneous anabolic nutritional therapy, was shown to be highly effective in one neonate with classic MSUD [Puliyanda et al 2002]. Dialysis without simultaneous management of the underlying disturbance of protein turnover is analogous to treating diabetic ketoacidosis with invasive removal of glucose and ketones rather than insulin infusion. In both conditions, effective treatment depends not only on lowering concentrations of pathologic metabolites, but also on controlling the underlying metabolic derangement.

Appendix 3:

Table 3: Ketonex formula compositions:

Nutrient	Ketonex-1		Ketonex-2	
	(per 100 g pwd)	(per g protein equiv)	(per 100 g pwd)	(per g protein e
Energy, kcal	480	32	410	13.7
Protein equiv, g	15.00	1.000	30.00	1.000
Nitrogen, g	2.40	0.160	4.80	0.160
Amino acids, g	14.45	0.963	28.90	0.963
Cystine, g	0.15	0.010	0.30	0.010
Histidine, g	0.42	0.028	0.84	0.028
Isoleucine, g	trace	0.000	trace	0.000
Leucine, g	trace	0.000	trace	0.000
Lysine, g	1.00	0.067	2.00	0.067
Methionine, g	0.30	0.020	0.60	0.020
Phenylalanine, g	0.88	0.059	1.76	0.059
Threonine, g	0.70	0.047	1.40	0.047
Tryptophan, g	0.17	0.011	0.34	0.011
Tyrosine, g	0.89	0.059	1.78	0.059
Valine, g	trace	0.000	trace	0.000
Other Nitrogen-Containing Compounds				
Carnitine, mg	100	6.67	200	6.67
Taurine, mg	40	2.67	50	1.67
Carbohydrate, g	53.0	3.53	35	1.17
Fat, g	21.7	1.45	14	0.47
Linoleic acid, g	2.00 [4]	0.133	1.50 [5]	0.050
α-Linolenic acid, g	0.36 [6]	0.024	0.17 [7]	0.006
Minerals				
Calcium, mg	575	38	880	29
Chloride, mg/mEq	325/9.17	21.7/0.61	940/26.51	31.33/0.8
Chromium, µg	11	0.73	27	0.90
Copper, mg	1.10	0.073	1.00	0.033
Iodine, µg	65	4.33	100	3.33
Iron, mg	9.0	0.60	13	0.43
Magnesium, mg	50	3.33	225	7.50
Manganese, mg	0.50	0.033	0.80	0.027
Molybdenum, µg	12	0.80	30	1.00
Phosphorus, mg	400	27	760	25
Potassium, mg/mEq	675/17.26	45/1.15	1,370/35.04	45.7/1.17
Selenium, µg	20	1.33	35	1.17
Sodium, mg/mEq	190/8.26	12.7/0.55	880/38.28	29.3/1.28
Zinc, mg	8.0	0.53	13	0.43
Vitamins				
A, µg RE	420	28	660	22
D, µg	7.50	0.50	7.50	0.25
E, mg α-TE	10.10	0.67	12.10	0.40
K, µg	50	3.33	60	2.00
Ascorbic acid, mg	50	3.33	60	2.00
Biotin, µg	65	4.33	100	3.33
B_6, mg	0.75	0.050	1.30	0.043
B_{12}, µg	4.90	0.327	5.00	0.167
Choline, mg	80	5.33	100	3.33
Folate, µg	230	15	450	15
Inositol, mg	40	2.67	70	2.33
Niacin equiv, mg	12.80	0.850	21.7	0.72
Pantothenic acid, mg	6.90	0.460	8.00	0.267
Riboflavin, mg	0.90	0.060	1.80	0.060
Thiamin, mg	1.90	0.127	3.25	0.108

[1] Designed for infants and toddlers. [2] Designed for children, adolescents, and adults.

[3] Approximate **packed** weight of Ketonex in level, dry US standard household measures:

		Ketonex-1	Ketonex-2
1 Tbsp	=	7 g	8 g
1/4 cup	=	26 g	32 g
1/3 cup	=	35 g	41 g
1/2 cup	=	53 g	61 g
1 cup	=	105 g	117 g

[4] Analytical data at manufacture = 4.32 g/100 g powder. [5] Analytical data at manufacture = 2.66 g/100 g powder.

[6] Analytical data at manufacture = 0.40 g/100 g powder. [7] Analytical data at manufacture = 0.28 g/100 g powder.

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