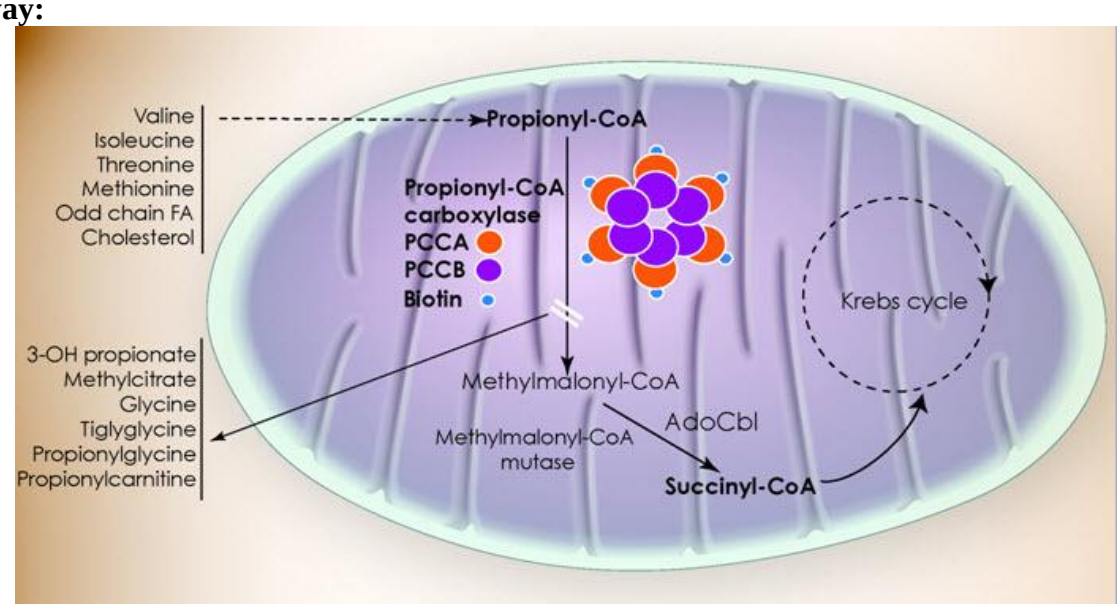
LONG TERM MANAGEMENT PROPIONIC ACIDEMIA (PA)

OMIM# 606054

Definition:

- Autosomal recessive disorder, one of the most common organic acidemia.
- Caused by deficiency of propionyl Co-A carboxylase (PCC), the enzyme that catalyzes the conversion of propionyl-CoA to methylmalonyl-CoA.
- Sources of propionyl CoA from catabolism of isoleucine, valine, methionine, threonine (50%), odd-chain fatty acids (25%), cholesterol side chains, thymine, and uracil (and gut bacterial activity 25%).(1-3)

Pathway:



Clinical Presentation:

- Neonatal-onset PA, the most common form, is characterized by poor feeding, vomiting, and somnolence in the first days of life in a previously healthy infant, followed by lethargy, seizures, coma, and death. It is frequently accompanied by metabolic acidosis with anion gap, ketonuria, hypoglycemia, hyperammonemia, and cytopenias.
- Late-onset PA includes developmental regression, chronic vomiting, protein intolerance, failure to thrive, hypotonia, and occasionally basal ganglia infarction (resulting in dystonia and choreoathetosis) and cardiomyopathy. Affected children can have an acute decompensation that resembles the neonatal presentation and is precipitated by a catabolic stress such as infection, injury, or surgery.
- Isolated cardiomyopathy and arrhythmia can be observed on rare occasion in the absence of clinical metabolic decompensation or neurocognitive deficits.
- Manifestations of neonatal and late-onset PA over time can include growth impairment, intellectual disability, seizures, basal ganglia lesions, pancreatitis, and cardiomyopathy. Other rarely reported complications include optic atrophy, hearing loss, premature ovarian insufficiency (POI), and chronic renal failure. (1-3)

Diagnosis:

- By clinical presentation and lab finding: hyperammonemia, hyperlactacidemia, hypoglycemia or hyperglycemia, metabolic acidosis,ketosis, hypocalcemia, leukothrombocytopenia, +/-liver dysfunction.
- Acylcarnitine profile (MS/MS): Increase propionyl carnitine in acylcarnitine profile measured by MS/MS (increase C3, C3/C2 ratio).

- Urine organic acids: Increase propionylcarnitine, 3-hydroxypropionate, methylcitrate, and intermediates of the isoleucine pathway: tiglic acid, tiglylglycine, 2-methyl-3-hydroxybutyrate, 3-hydroxybutyrate, propionylglycine.
- Secondary metabolic disturbances: inhibition of the pyruvate dehydrogenase complex, N-acetyl-glutamate synthetase, and glycine cleavage system, result in hypoglycemia, hyperlactacidemia, hyperammonemia, hyperglycinemia, hyperalaninemia.
- Plasma aminoacids: increase glycine
- Carnitine N-acylase can remove accumulating propionyl-CoA from mitochondria results in elevated acylcarnitines (propionylcarnitine) in blood and urine and this can cause a relative carnitine deficiency.
- Propionyl-CoA carboxylase (PCC) enzyme activity can be determined in peripheral blood leukocytes or cultured skin fibroblasts by assaying the substrate-dependent fixation of 14C from NaH14CO3 or 1-14C-propionate.
- Confirmed by DNA molecular testing.(1-3)

Genetics:

- Autosomal recessive disorder.
- Parents of affected child are obligate carriers. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier
- PCC enzyme composed of alpha (which bind biotin) and beta subunits.
- Mutations occur in the PCCA and PCCB gene.(1-3)

Treatment:

1. <u>Acute episode treatment guidelines (Emergency):</u>

- ABC (or now CAB).
- Stop all source of protein central and parenteral nutrition.
- Check GlucoChecks.
- Insert an IV line and take blood for blood gases, chem 1, Ammonia (NH3), & CBC, liver enzymes, lactic acid and blood C/S (peripheral and central if patient has central line) as **STAT** order.. Other labs as needed.
- Ammonia blood sample should be taken with precaution because of high false positive rate (without tourniquet, in green-top tube, put on ice to the laboratory, separated within 20 minutes of collection and analyzed immediately).
- After taking the blood give Carbaglu® 100-250mg/kg by NGT or oral then continue on 100-250mg/kg/day q6.
- High caloric intake is the main stay of therapy. Therefore, Start 1 1/2 to double maintenance I.V.F as D10 1/2NS + Kcl 30meq/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 titrate up until blood glucose controlled.
- If ammonia > 100 umol/l. Start intralipid 20% at 2-3 g/kg/day to provide additional calories.
- DO NOT DECREASE DEXTROSE RATE or amount and DO NOT STOP calorie delivery in the acute stage for any reason (e.g. medications**,** addition required fluid bolus, or hyperglycemia) as this can precipitate hypoglycemia and catabolism which will further worsen the patient's condition.
- If Ammonia elevated >100 umol/l and Carbaglu not available:
    1. If the patient has central line give ammonul® 250mg/kg IV over 90 minute as loading dose then maintenance dose 250mg/kg/day over 24 hours.
    2. If there is no central line gives the patient sodium benzoate 250mg/kg PO/NGT as loading dose then maintenance dose 250mg/kg/day over 24 hours.
- Call pharmacy to expedite the intralipid20% and medications.
- If ammonia < 100umol/l start 50% natural protein and propiomex formula.
- Give polycose or prophree PO/NGT as tolerated.
- According to clinical evaluation, empirical antibiotics may be started.

- In case of refractory acidosis, give bolus of NaHCO3 and start NaHCO3 infusion as 0.5-2 meq/kg/h.(5)
- Continue on metronidazole at 10–20 mg/kg per day divided Q8.
- Increase Carnitine dose to 300-400 mg/kg/day divided Q8 hours IV, orally or NGT.
- For Nausea and vomiting give serotonin receptor-blocking agent Granisetron 10 to 40 microgram / kg, infused over 3 to 5 minutes.
- Continue on same Biotin dose (if patient still on it)
- For constipation give glycerin suppositories, Dulcolax or Docusate by NGT.
- Consider hemodialysis:
    1. Hyperammonemic coma.
    2. Dilated pupils.
    3. Failure to improve or deterioration within 4 hours of initial treatment
    4. Ammonia more than 500micromol/l.
    5. Extreme acidosis or electrolytes imbalances.
- Ammonia, electrolyte and blood gases need to be followed at regular intervals during this acceleration of management stage. The frequency is dictated by the patient's condition and the speed at which results can be obtained.
- DO NOT STOP other oral chronic medications.
- Proteins should be reintroduce within 24 hours-36 hours of initiation of therapy even if the patients on dialysis.

1. <u>Transition to long term management (Wards protocol):</u>

- Continue on above measures including high caloric intake, aminoacids mixture eg. Propimex® formula with close monitoring of ammonia level, blood gas and electrolytes until normalization of their levels.
- Ensure appropriate caloric intake and medication dosages by calculating calories and medication dosages/ kg daily and document it in the chart.
- Provide remaining prescribed energy with Polycose® or Pro-Phree ®.
- Discontinue IV lipid when target calori intake can be achieved through other sources because long administration of lipid may cause fatty liver.
- Patient need daily evaluation from metabolic dietitian with gradually introduction of natural protein 50% of normal intake at home then upgrade to 100% if patient improve clinically and normalization of ammonia level, blood gas and electrolytes.
- Titrate IVF according to PO intake until discontinue. Measure electrolytes and urine analysis for ketones, blood gas and CBC once before discharge.
- Discharge the patient if the following parameters achieved:
    1. Normal clinical status as home before crises.
    2. Normal plasma level ammonia 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. <u>Long term management (home and outpatient visits)</u>

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).
- Protein is restricted in the diet to provide limited amounts of isoleucine, methionine, threonine, valine and odd chain fatty acids and the further

supplemented with aminoacids mixture to provide additional amino acids without the offending amino acids (see table 1 and 2).

- Avoidance of essential amino acid, fatty acid, and micronutrient deficiencies.

b. Metabolic dietitian should ensure the following:

- Home formula supplies include aminoacids mixture eg: Propimex-1® (for infant and toddler), Propimex-2® (for children; adolescents, and adults) see appendix 1.
- For infant: Breast milk or regular formula as a natural protein source. For older children: the source of natural protein from regular diet.
- Compliance of the mother with weighing skills, appropriate preparation of formula and 3-days diet records prior to clinic visit.
- 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 (see monitoring section).
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Table 1: Treatment Ranges for Target Amino Acids in PA:

(2-4 hr postprandial)				Amino Acid
6-18y	3m-6y	1-3 m	Newborn	
158-302	125-318	105-222	106-254	GLY
38-95	13-81	32-87	27-80	ILE
16-37	5-34	4-39	6-36	MET
74-202	40-139	64-225	65-147	THR
156-288	85-334	96-291	78-264	VAL

Note: the optimal levels should be near the lower limit of normal ranges.(7)
These levels based on BC Children Hospital reference ranges.

Table 2: Recommended daily nutrient intakes:(8)

Total protein (g/kg/day)	Amino acids mixture(g/kg/day)	Natural protein (g/kg/day)	Age
1.8–2.2	1.5–1 –0.7	0.7–1 –1.5	0–12 months
1.5–2	1 –0.5	1 –1.5	1 year–4 years
1.2–1.5	0.5–0.2	1 –1.5	4–7 years
1.2–1.5	0.4–0.0	0.8–1.2	> 7 years

Table 3: proposed nutrient intake when prescribing nutrition support in patients with Propionic Acedemia: (9)

11<19y	7<11y	4<7y	1<4y	5m-1y	0-5m	Nutrients
956–1470/day	715–1090/day	630–960/day	485–735/day	90-40/kg	110-60/kg	ISL
550–780/day	410–580/day	360–510/day	275–390/day	40–15/kg	50-20/kg	MET
830–1200/day	610–885/day	540–780/day	415–600/day	75–20/kg	125-50/kg	THR
1105–1655/day	815–1225/day	720–1080/day	550–830/day	80–40/kg	105/60/kg	VAL
50/day	40/day	≥35/day	≥30/day	2.5/kg	2.5/kg	Protein
100-125% of RDA for age						Energy

Chronic medications for life:

Comments	Route	Dose	Medication
	PO	200-300mg/kg/day divided 2-3 times /day	Carnitine
Discontinue if no reduction in plasma C_3	PO	5 -10 mg daily	Biotin
	PO	10-20 mg/kg/day, one week on drug with three weeks off	Metronidazole
	PO	Daily use of laxatives at age/weight-appropriate doses	Laxative agents

Other supportive measures:

- **Sodium benzoate:** There is no evidence that would support a role for benzoate in chronic treatment.
- **Growth hormone:** only considered if there is low level of growth hormone/IGF1 and normal nutritional parameters.
- **Gastrostomy tube insertion:** recommend consideration be given to the placement of GT tube particularly in infants and young children with PA at the time of diagnosis.
- **Placement of a port-a-cath** (totally implantable central venous access device): may be considered when unreliable peripheral venous access is significantly compromising patient care but should be balanced by the increased risk of destabilizing infection.(10).
- **Carbaglu®:** There is no current published evidence for its use in chronic management, although ongoing studies suggest a utility for PA associated chronic hyperammonemia.(10)
- **Antiepileptic drugs:** as needed.(1)
- **Therapy for arrhythmia** as needed.(1)
- **Anti-emetics** such as ondansetron may be used on individual bases.(1) Dose:(body weight 8 to 15 kg) 2 mg, (body weight 15 to 30 kg) 4 mg, and (body weight over 30 kg) 8 mg (0.13 to 0.26 mg/kg), dissolved ORALLY on the tongue usually as a single dose.
- **Alkali therapy:** There are no published evidence for the use of alkali therapy like polycitra or sodium bicarbonate on chronic bases.

Look for complications of PA which includes(1, 7, 10):

1. **Iatrogenic essential amino acid deficiency**:
    a. **ILE deficiency: Weight loss or no weight gain; redness of buccal mucosa; fissures at corners of mouth; tremors of extremities; decreased plasma cholesterol and ILE; increased concentrations of plasma lysine, phenylalanine (PHE), serine (SER), tyrosine (TYR), and VAL; skin desquamation, and corneal de-epithelialization.**
    b. **MET deficiency: Decreased plasma MET and cholesterol and increased plasma PHE, proline, SER, THR, and TYR concentrations.**
    c. **THR deficiency: Arrested weight gain; glossitis and redness of buccal mucosa; and decreased plasma THR and globulin concentrations.**
    d. **VAL deficiency: Poor appetite, drowsiness; excessive irritability and crying in infants; weight loss or decrease in weight gain; and decreased plasma albumin concentration.**
2. **Intellectual and developmental delay:** to maximize patients intellectual-developmental outcome patients need the following:
    a. Early initiation of physical, occupational and speech therapy services, to continue throughout childhood
    b. Optimize nutrition.
    c. Avoid acute metabolic decompensation.
    d. Treat episodes of metabolic decompensation swiftly and aggressively.
3. **Stroke like episodes and cerebellar haemorrage:**
    a. Ensure adequate fluid and caloric intake during the episode.

b. Symptomatic treatment of focal neurological deficits and altered mental status (supportive care primarily).

4. **Seizures:** occur in 50% of patients:
   a. EEG at diagnosis and then yearly
   b. Referral to child neurology if epileptiform activity detected.
5. **Radiological brain abnormalities:** basal ganglia changes, cerebral volume loss , signal abnormalities in the caudate and putamen and delayed myelination. MRS showed increase lactate peak. Routine MRI/MRS not recommended unless there are neurological deterioration.
6. **Cardiomyopathy:**
   a. Echocardiogram at presentation and yearly afterwards to evaluate for cardiomyopathy.
   b. Echocardiogram as needed to evaluate shortness of breath, tachycardia or other signs and symptoms of cardiac failure.
7. **Long QT syndrome:**
   a. ECG yearly.
   b. 24-hour Holter yearly
   c. ECG and 24-hour Holter for syncope, fainting or other signs and symptoms of Long QT.
8. **Immune defects:**
   a. CBC with differential at diagnosis annually, and as needed to follow abnormalities.
   b. If neutropenia present, institute infection control precautions isolation, gown and glove, etc.), as indicated by hospital policy.
   c. Expectant management with judicious use of colony stimulating factors only in cases where neutropenia is not resolving or there is evidence of bacterial infection with neutropenia.
9. **Pancreatitis:**
   a. Episodes of acute pancreatitis in PA should be managed like any other case of acute pancreatitis (i.e. fluids, judicial short term bowel rest, jejunal feeds, pain management).
   b. When necessary, total parenteral nutrition can be used safely, provided the amount of protein provided is not excessive (at or near the RDA for patient's age).
   c. Intravenous carnitine at 200–300 mg/kg/day to maintain propionylcarnitine excretion.
10. **Optic neuropathy:**
    a. Annual examination by an ophthalmologist to include visual acuity as well as visual examination of the anterior chamber and dilated evaluation of the fundus.
    b. Treatment of decreased visual acuity, as indicated.
11. **Dermatologic manifestations** : resembling acrodermatitis enteropathica are frequently associated with deficiency of essential amino acids, particularly isoleucine, which is excessively restricted in the diet of persons with PA.
12. **Osteoporosis and osteopenia and failure to thrive**:(11)
13. **Hearing loss,premature ovarian insufficiency and chronic renal failure** (rarely).

Monitoring:

Clinic visit and dietitian visit	Plasma aminoacids, ammonia, urine dipsticks for ketones, acylcarnitine profile	Age
Monthly	**weekly**	**0-3 months**
Every 3 months	**Every 2 weeks**	**3-18months**
Every 3 months	**monthly**	**18months-10years**
Every 6 months	**Every 3 months**	**10-18years**

Time	Test/action
Prior to each clinic visit	CBC, albumin, prealbumin, Se, Zn, ferritine, Ca, Mg, 25-hydroxy vitamin D, Growth parameters, chem1, bone profile, liver ezymes, urine for organic acids (quantitate Methylcitrate/ Citrate ratio), thiamine,lactic acid and cholesterol.
At diagnosis and then Yearly	ECG, Echocardiogram, 24-hour Holter monitoring
At diagnosis and then yearly	EEG
At diagnosis and then yearly	Ophthalmology exam
At 18 months and continue throughout child hood	Referral to physical, occupational and speech therapy services
At diagnosis, 6 months, 1 year then yearly	Detailed developmental assessment
At diagnosis and then if there is neurological detorioration	MRI brain and MRS
At diagnosis	Hearing test
At 3 years and then every 2 years	Bone age
When osteoporosis suspected	X-ray of long bones

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 granisterone (10-40 m/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 ammonia, plasma aminoacids, chem1, urine for ketones prior to procedure.
- High caloric intake with IVF D10 and lipid 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).

Liver transplantation:

- May be considered in individuals with recurrent episodes of hyperammonemia or acidosis that are not adequately controlled with medical therapies outlined above.
- Recipients of living-related donor livers from carriers (i.e. haploinsufficient livers) seem to have similar results to Orthotopic Liver Transplant(OLT)recipients.

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Appendix 1:

Table 4: Propiomex formula composition:

Nutrient	Propimex-1		Propimex-2	
	(per 100 g pwd)	(per g protein equiv)	(per 100 g pwd)	(per g protein equiv)
Energy, kcal	480	32	410	13.7
Nitrogen, g	2.40	0.160	4.80	0.160
Protein equiv, g	15.00	1.000	30.00	1.000
Amino acids[5], g	16.17	1.078	32.34	1.078
Cystine, g	0.45	0.030	0.90	0.030
Histidine, g	0.42	0.028	0.84	0.028
Isoleucine, g	0.12	0.008	0.24	0.008
Leucine, g	1.38	0.092	2.76	0.092
Lysine, g	1.00	0.067	2.00	0.067
Methionine, g	trace	0	trace	0
Phenylalanine, g	0.88	0.059	1.76	0.059
Threonine, g	0.10	0.007	0.20	0.007
Tryptophan, g	0.17	0.011	0.34	0.011
Tyrosine, g	0.89	0.059	1.78	0.059
Valine, g	trace	0	trace	0
Other Nitrogen-Containing Compounds				
Carnitine, mg	900	60	1,800	60
Taurine, mg	40	2.66	50	1.67
Carbohydrate, g	53.0	3.53	35.0	1.17
Fat, g	21.7	1.45	13.0	0.43
Linoleic acid, g	2.00 [4]	0.133	2.00 [5]	0.07
α-Linolenic acid, g	0.36 [6]	0.024	0.17 [7]	0.006
Minerals				
Calcium, mg	575	38	880	29
Chloride, mg/mEq	410/11.56	27/0.77	1,160/32.72	38.7/1.09
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	0.6	13.0	0.43
Magnesium, mg	50	3.33	225	7.5
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	1370/35.04	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	4.3	100	3.33
B_6, mg	0.75	0.05	1.30	0.043
B_{12}, µg	4.90	0.33	5.00	0.167
Choline, mg	80	5.3	100	3.33
Folate, µg	230	15	430	14.33
Inositol, mg	40	2.7	70	2.33
Niacin equiv, mg	12.8	0.85	21.7	0.72
Pantothenic acid, mg	6.90	0.46	8.00	0.267
Riboflavin, mg	0.90	0.06	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 Propimex-1 and Propimex-2 in level, dry US standard household measures:

Propimex-1		Propimex-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.