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THIAMINE

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THIAMINE

Summary

Thiamine, as thiamine pyrophosphate, functions as a coenzyme in animal carbohydrate metabolism; hence, a sufficient quantity must be present in the diet to insure good health. In the late 19th century, Eykman correlated thiamine-deficiency with nerve degeneration in fowl. Thirty years later, Peters demonstrated that the central nervous system was involved in thiamine deficiency, as well as the peripheral nerves. Lameness, convulsions, anorexia, emaciation, and "biochemical lesions" are also symptoms of thiamine deficiency (3599). Accordingly, most of the research on thiamine has been directed toward clarifying the effects of vitamin B_1 deficiency, not excess.

Based on tests with 60 normal humans, Thomson and Leevy (4012) revealed that the intestinal absorption of thiamine hydrochloride was rate-limited and appeared to follow Michaelis-Menton kinetics. The maximum amount of thiamine absorbed in a single dose was 8.3 mg; a dose of 12 mg produced half-maximum absorption.

While studying the resorption of thiamine, Gassman (1215) determined that the walls of the duodenum and small intestine were enriched with thiamine; resorption efficiency depended on thiamine supply.

As early as 1944, Williams and Bissel (4385) found that when thiamine hydrochloride was ingested by man, it was rapidly absorbed and converted to diphosphothiamine (cocarboxylase). Twenty years later, Rindi et al. (3327) concurred in their experiments with rats.

In several animals, including man, the heart, kidney, liver, and brain have the highest thiamine concentration; the spleen, lung, adrenals, and muscle contain lesser amounts (3599). Balaghi and Pearson (191) reported that the mitochondrial plus soluble fraction of the liver, brain, kidneys, and testes of rats contained 60-70% of the labelled thiamine administered.

Burkholder and McVaigh (516) have demonstrated that thiamine can be produced by certain intestinal bacteria.

The method of thiamine administration exerted a marked effect on the metabolic pattern of ^{35}S-thiamine in rats. After intravenous injection, 65.0% of the radioactivity was excreted in the urine as intact thiamine, but when given orally, only 6.5% was excreted intact. Eighty-four percent of the urinary activity came from 4-methyl-5-beta-hydroxyethylthiazole (HT) (2509). According to Fujita et al. (1158) HT is a product of hydrolytic cleavage by a specific bacterial thiaminase. After oral dosing of ^{35}S-thiamine, the concentration of HT was highest in the portal venous blood and lowest in the intestinal wall; Meshi and Sato (2509) suggested that this transport is quite rapid. The production of HT was much slower in the mouse, rabbit, and guinea pig than in the rat.

Baker et al. (179) determined the biological half-life of thiamine to be approximately 18 days in man. Most of the ingested thiamine was excreted in the urine; 3.8% was excreted in the feces. Verrett and Cerecedo (4177) recovered 77% of the activity from oral administration of ^{35}S-thiamine to rabbits in their urine and feces over a 4-6 day period.

Balaghi and Pearson (189) and Neal and Pearson (2777) isolated more than 20 urinary metabolites of thiamine given i.p. to rats. Five to ten percent of the radioactivity in the urine was found to be 2-methyl-4-amino-5-pyrimidinecarboxylic acid (2778). Balaghi and Pearson (189) reported that 29-42% of the activity from i.p. administration of ^{14}C-thiamine was excreted in the rat's urine; 17.5% was excreted daily in the feces. A significant amount was excreted as respiratory carbon dioxide.

Thiamine pyrophosphate (TPP) is the active coenzyme form of thiamine which participates in carbohydrate metabolism. In vivo studies have shown that TPP functions in the decarboxylation of pyruvic acid, alpha-ketoglutaric acid, and their degradation products (4389).

Nakada and Sund (2741) determined that TPP is involved in the oxidative decarboxylation of glyoxylate to N-formylglutamic acid and carbon dioxide in rat liver mitochondria. Van Eys (4138) indicated that thiamine pyrophosphate may act as a cofactor for alpha-glycerophosphate dehydrogenase and lactic dehydrogenase. Racker et al. (3226) found that TPP enhanced the activity of a transketolase from E. coli.

Because thiamine-deficient rats didn't excrete the normal metabolites of tryptophan, Dalgliesch (744) surmised that thiamine must be necessary for the conversion of tryptophan to nicotinic acid.

The feeding of 10 and 50 mg/kg thiamine hydrochloride to Wistar rats stimulated the biosynthesis of protein bound lipoic acid (a coenzyme in the TCA cycle) in the liver mitochondria (1886).

Sorrell et al. (3783) found the intravenous injection of 60 mg thiamine hydrochloride in a multivitamin solution increased the thiamine concentration in man's red blood cells.

After performing numerous tests, Zbinden (4562) reported that thiamine had no strong pharmacological properties; but some weak cardiovascular effects were noted.

Oral doses of 20 or 100 mg of thiamine to man decreased the number of correct responses in a test of artificial conditioned speech connections (1638).

According to Fancher et al. (1038), thiamine slightly increased the acidity of human saliva.

Grosse and Wade (1371) found that feeding 2 mg thiamine daily to rats depressed the in vitro metabolism of aniline and zoxazolamine.

The feeding of excessive amounts of thiamine (100 mcg/day) to rats on an iodine-deficient diet caused a moderate hypertrophy of the thyroid (2735); iodine content increased, also. Slingerland and Sullivan (3743) found feeding thiamine to have an inhibitory effect on the formation of organic radio-iodine compounds in the thyroid.

Several studies have examined the effects from ingesting excess levels of thiamine in pigeons, mice, rats, dogs, monkeys, and man. A table of acute toxicity can be found on page 12. Tables listing the minimum daily requirement of vitamins for man and many animals are provided on pages 40 and 41.

Ostrovskii (2938) found excessive fat deposition in the subcutaneous tissues, omentum, and heart of pigeons fed 100-150 mcg thiamine daily for 20-30 days; the normal amount fed is 10 mcg.

Male Swiss mice were dosed orally with 0.06 mg or 0.4 mg thiamine daily for one week with no untoward effect (708).

Thiamine hydrochloride (0, 500, or 1500 mg/kg) was administered by stomach tube five days a week for 6 weeks to groups of 8 rats. Extensive blood, urine, and liver function tests and a histological examination of the heart, liver, kidneys, and testicles were performed. At 1500 mg/kg growth was slightly depressed for both males and females; at 500 mg/kg growth was even more depressed, but only for the females (4004).

Three generations of rats were maintained from weaning to 6 months on rations containing 300 mg thiamine hydrochloride or thiamine mononitrate per kg diet. Although this was a three to four-hundred-fold increase over the rat's daily requirement, growth, reproductive performance, and autopsy reports were normal (2767).

Brown (477) fed rats up to 10,004 mg thiamine/kg diet (3000 times the requirement) for up to 6 weeks with no deleterious effects.

Kidney lesions developed in 60% of the rats given 10 mcg/ml of thiamine in their drinking water but fed a thiamine deficient diet. Rats provided with the same diet and regular drinking water suffered no such lesions (4139).

Kato (1886) fed 45-day-old male Wistar rats 0, 1, 10, or 50 mg/kg body weight thiamine hydrochloride in addition to a basal diet; after 4 weeks growth was comparable for all groups. When groups of 12 female rats were fed a basal diet with or without additional thiamine hydrochloride (3.6 g/kg diet), riboflavin, and nicotinic acid, growth was comparable for all groups during the 20-week period. Blood tests were normal, as well (495).

The conditioned reflex was slightly decreased in dogs given 500 mg thiamine per os daily for 6-10 days, but no other effects were reported (4572).

Rhesus monkeys received 1-100 mg/kg thiamine hydrochloride for 2-17 days with no ill effects (2271).

Thirty-six patients with Korsakoff psychosis were provided with a basal diet plus 3.3 mg thiamine for 6-53 days; twenty-one subjects also received 10-50 mg daily parentally. No untoward effects were mentioned (431).

After 4 color blind students were given 8 mg thiamine daily for 10 weeks, LeGalley and Harris (2193) reported a 20% improvement of color vision.

Headache, irritability, and general weakness befell a 47-yr-old female who consumed 10 g of thiamine hydrochloride daily for two and a half weeks (2544).

Researchers have investigated the possible effects of excess thiamine in the fields of teratology and carcinogenicity, as well as on reproductive performance. Injection of thiamine (10-20 times the normal level) into chicken eggs increased the incidence of embryo deformity and raised the hemoglobin content of the embryo (3983). Kobayashi (2018) introduced 1-18 mg of thiamine hydrochloride into Leghorn eggs and found a reversible granular degeneration in the renal tubules; no change in the heart was observed. Sakiya (3608) did not find any malformations with 10 gamma thiamine in a similar study.

The protective effect of thiamine administration against transplanted and induced tumors ranged from slight to none at all. Taylor et al. (3983) found 10-15% of the dba mice fed an increased level of the B vitamins (34 mcg/g of thiamine) to be resistant to tumor transplants. Subcutaneous injection of vitamin B_1 into the mammary adenocarcinomas of mice decreased tumor growth and prolonged survival (881). Paratumoral injections of 0.5 mg thiamine/day into male NMRI mice with Crocker sarcoma accelerated tumor growth, but 1.5 mg/day retarded tumor growth (239). In a similar study by DiGrazia (875), thiamine prolonged the time required for papilloma cancerization, but reduced the survival period of rats.

Scott (3589) observed that rats fed 0.5 mg thiamine hydrochloride per week did not develop definite tumors from the topical application of DMBA, but 44% of the control animals did. Thiamine given in the drinking water (0.2%) plus 2.5 mg s.c. twice a week did not protect "101" mice from 3-, 4-benzopyrene-induced skin papillomas (3366). Daily intraperitoneal injections of excess thiamine (100-200 mcg) had no effect on transplanted sarcoma 298 growth or on the development of La hemocytoblastosis in $C_{57}B_1$16 mice (947).

Cerecedo and Vinson (593) fed 250 mg thiamine per kg of diet to three generations of albino mice resulting in normal growth and reproduction. Seventy-day-old female Wistar rats were fed diets containing either 2.5 or 5.0 mg thiamine per kg diet; sacrifice on the 22nd day of gestation revealed normal serum parameters and a normal number of resorptions for the higher level (480).

Morrison and Sarett (2662) found neither growth nor reproduction to be affected by the addition of 50 times the normal amount of thiamine to the diets of McCollum-Wisconsin rats. Schumacher (3581) reported that the feeding of 100 mg/kg diet of thiamine to dams throughout gestation did not affect the vitamin requirement of the offspring.

Groups of 6-9 female rats were given 0.156 mg thiamine daily as Brewer's yeast or as thiamine concentrate; Perla (3069) observed a severe disturbance of lactation. A second study indicated that this was a result of a manganese deficiency (3071).

Several papers documented the occurrence of sensitivity to thiamine of individuals. When a 50-yr-old woman, previously sensitized by daily consumption of B-complex capsules, consumed a few slices of vitamin enriched bread, severe dermatitis erupted (2793). Contact dermatitis has been reported in women employed by pharmaceutical firms; patch tests for sensitivity to thiamine were positive (691; 1579). One sensitized woman died from ingestion of a 100 mg tablet of thiamine (18). Oral administration of vitamin B_1 was thought to be responsible for encephalitis in one young man (2397).

Thiamine is generally added to foods as a vitamin supplement. In a summary of the effects of storage and processing on thiamine loss in foods, Sebrell and Harris (3599) stated that losses during canning depended on acidity, temperature, and time. Roasting beef involved a thiamin loss of 36-53%. Frozen fish and vegetables lost far less thiamine during storage than frozen meats and liver. Thiamine mononitrate was found to be far more stable in flour than the hydrochloride (1595). Sebrell and Harris (3599) declared thiaminase, a thiamine-destructive enzyme found in certain freshwater fish and shellfish, to be an insignificant factor in human nutrition unless large quantities of these foods are consumed raw.

THIAMINE HYDROCHLORIDE

Chemical Information

I. Nomenclature

A. Common Names

1. Vitamin B_1 hydrochloride
2. Thiamine chloride hydrochloride
3. Thiamine dichloride
4. Aneurine hydrochloride
5. Thiaminium chloride hydrochloride
6. Antineuritic vitamin
7. Antiberiberi vitamin

B. Chemical Name

3-(4-amino-2-methylpyrimidyl-5-methyl)-4-methyl-5(beta-hydroxyethyl)thiazolium chloride hydrochloride

C. Trade Names

1. Apate Drops
2. Beatine
3. Begiolan
4. Bedome
5. Benerva
6. Bequin
7. Berin
8. Betabion Hydrochloride
9. Betalin S
10. Betaxin
11. Bethiazine
12. Beuion
13. Bevitex
14. Bevitine
15. Bewon
16. Biuno
17. Bivatin
18. Bivita
19. Clotiamina
20. Eskapen
21. Eskaphen
22. Lixabeta
23. Metabolin
24. Slowten
25. THD
26. Thiadoxine
27. Thiaminal
28. Thiamol
29. Thiavit
30. Tianidon
31. Tiaminal
32. Trophite
33. Vetalin S
34. Virothiam
35. Vitaneuron

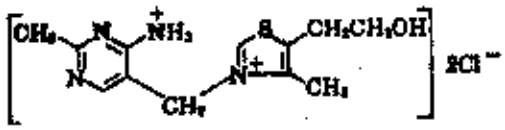
D. Chemical Abstracts Registry Number

000067038

II. Empirical Formula

$C_{12}H_{17}ClN_4OS \cdot HCl$

III. Structural Formula



IV. Molecular Weight

337.27

V. Specifications

Food Chemicals Codex

Assay	Not less than 98.0% and not more than the equivalent of 102.0% of $C_{12}H_{17}ClN_4OS \cdot HCl$, calculated on the dried basis.
pH of a 1 in 100 solution	Between 2.7 and 3.4
Limits of Impurities	
Color of solution	Passes test
Loss on drying	Not more than 5%
Nitrate	Passes test
Residue on ignition	Not more than 0.2%

VI. Description

A. General Characteristics

Thiamine hydrochloride occurs as white monoclinic plates in rosette-like clusters, with a slight thiazole odor and a bitter taste.

B. Physical Properties

Thiamine hydrochloride decomposes at 248 degrees C. One gram dissolves in approximately 1 ml water, 18 ml glycerol, 100 ml 95% alcohol, 315 ml absolute alcohol, and is more soluble in methanol. It is soluble in propylene glycol. It is practically insoluble in ether, benzene, hexane, and chloroform. The pH of a 1% w/v solution in water is 3.13 and the pH of a 0.1% w/v solution is 3.58. On exposure to air of average humidity, the vitamin absorbs an amount of water corresponding to nearly one mole, forming a hydrate. Generally, the vitamin contains 4% water which is removable by drying at 100 degrees. One gram of crystalline vitamin B_1 hydrochloride is equivalent to 333,000 international units.

C. Stability

Thiamine hydrochloride should be stored in tight, light resistant containers.

VII. Analytical Methods

The official method for the determination of thiamine in food involves the oxidation of thiamine to thiochrome and the measurement of thiochrome fluorescence. This method fails if materials that absorb thiamine or extraneous materials which affect thiochrome flourescence are present. Substances containing thiamine pyrophosphate are hydrolyzed enzymatically and purified prior to oxidation to thiochrome by potassium ferricynamide. Flourescence of the oxidized sample is compared to flourescence of a standard solution for a quantitative determination (4607).

VIII. Occurrence

A. Plants

Thiamine occurs in rice husk, cereal grains, green leaves, roots, and tubers.

B. Animals

It is naturally occurring in animal tissues, eggs, milk, and yeast.

C. Synthetic

Practically all vitamin B_1 sold is synthetic. Thiamine can be synthesized by several methods. The pyrimidine nucleus and the thiazole nucleus can be synthesized separately and then linked. Alternatively, one nucleus with an extra side branch can be synthesized and the other ring built onto it (3599).

D. Natural Inorganic Sources

None

THIAMINE MONONITRATE

Chemical Information

I. Nomenclature

A. Common Names

1. Thiamine mononitrate
2. Vitamin B_1 mononitrate
3. Aneurine mononitrate

B. Chemical Name

3-(4-amino-2-methyl-pyrimidyl-5-methyl)-4-methyl-5(beta-hydroxyethyl)thiazolium nitrate

C. Trade Names

Betabion mononitrate

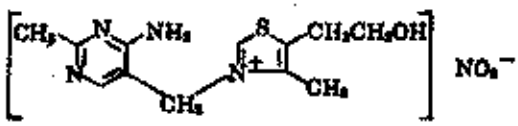
D. Chemical Abstracts Registry Number

000532434

II. Empirical Formula

$C_{12}H_{17}N_5O_4S$

III. Structural Formula



IV. Molecular Weight

327.36

V. Specifications

Food Chemicals Codex

Assay	Not less than 98.0% and not more than the equivalent of 102.0% of $C_{12}H_{17}N_5O_4S$, calculated on the dried basis.

V. Specifications Con't.

pH of a 1 in 50 solution	Between 6.0 and 7.5
Limits of Impurities	
Chloride	Not more than 600 ppm (0.06%)
Loss on drying	Not more than 1%
Residue on ignition	Not more than 0.2%

VI. Description

A. General Characteristics

Thiamine mononitrate occurrs as white crystals or crystalline powder, usually having a slight, characteristic odor.

B. Physical Properties

Thiamine mononitrate decomposes between 196 and 200 degrees C. It is practically nonhygroscopic, with a pKa equal to 4.8. It is soluble in water 2.7 g/100 ml at 25 deg. and 30 g/100 ml at 100 deg. The pH of a 2% aqueous solution is 6.5-7.1. One gram is equal to 343,000 international units.

C. Stability

Thiamine mononitrate should be stored in tight, light-resistant containers. Solutions of pH 4 show greater stability than nuetral solutions. The mononitrate is more stable than thiamine hydrochloride.

VII. Analytical Methods

See Thiamine Hydrochloride

VIII. Occurrence

A. Plant

See Thiamine Hydrochloride

B. Animal

See Thiamine Hydrochloride

C. Synthetic

The mononitrate is prepared by removing all chloride ions from thiamine hydrochloride by treatment with alkali and reconstituting the half salt by treatment of the free base with a stoichiometric amount of nitric acid.

D. Natural Inorganic Sources

None

Biological Data

I. Acute Toxicity

Substance	Animal	Sex	Route	Dosage (mg/kg Body Weight	Measurement	Ref.
Thiamine	Mice	Male	i.v.	125	LD_{50}	3502
Thiamine	Mice	--	i.p.	400	LD_{0}	2248
Thiamine	Mice	--	i.p.	495	LD_{50}	2248
Thiamine	Mice	Male	i.p.	185	LD_{50}	3502
Thiamine	Mice	--	i.p.	600	LD_{100}	2248
Thiamine	Mice	--	p.o.	2,450	LD_{50}	3502
Thiamine	Mice	--	p.o.	5,000	LD_{50}	2609
Thiamine	Rats	--	i.v.	170	LD_{50}	2609
Thiamine	Rats	--	i.p.	300	LD_{0}	2247
Thiamine	Rats	--	i.p.	390	LD_{50}	2247
Thiamine	Rats	--	i.p.	500	LD_{100}	2247
Thiamine	Rats	--	s.c.	500	LD_{0}	2609
Thiamine	Rats	--	s.c.	700	LD_{0}	2247
Thiamine	Rats	--	s.c.	840	LD_{50}	2247
Thiamine	Rats	--	s.c.	1400	LD_{50}	2609
Thiamine	Rats	--	s.c.	1000	LD_{100}	2247
Thiamine	Rats	--	p.o.	6000	LD_{0}	2609
Thiamine	Rats	--	p.o.	9500	LD_{50}	2609
Thiamine	Rabbits	--	i.p.	40	LD_{0}	2248
Thiamine	Rabbits	--	i.p.	115	LD_{50}	2248
Thiamine	Rabbits	--	i.p.	200	LD_{100}	2248

Substance	Animal	Sex	Route	Dosage (mg/kg Body Weight	Measurement	Ref.
Thiamine hydrochloride	Mice	--	i.v.	85	LD_{50}	2767
Thiamine hydrochloride	Mice	Male	i.v.	89.2	LD_{50}	4419
Thiamine hydrochloride	Mice	Male	i.v.	74*	LD_{50}	588
Thiamine hydrochloride	Mice	--	i.p.	329.8	LD_{50}	1427
Thiamine hydrochloride	Mice	Male	i.p.	268*	LD_{50}	588
Thiamine hydrochloride	Mice	--	p.o.	6000	LD_{50}	2767
Thiamine hydrochloride	Mice	Male	p.o.	8224	LD_{50}	4419
Thiamine hydrochloride	Mice	--	p.o.	3000	LD_{50}	2505
Thiamine hydrochloride	Mice	--	p.o.	3000	LD_{50}	4562
Thiamine hydrochloride	Mice	--	p.o.	$>$ 5000	LD_{50}	4004
Thiamine hydrochloride	Rats	Male	i.v.	175*	LD_{50}	588
Thiamine hydrochloride	Rats	--	i.v.	140	LD_{50}	2767
Thiamine hydrochloride	Rats	--	i.v.	125	LD_{50}	1220
Thiamine hydrochloride	Rats	Male	i.p.	481*	LD_{50}	588
Thiamine hydrochloride	Rabbits	Male	i.v.	850	LD_{50}	392
Thiamine mononitrate	Mice	--	i.v.	75	LD_{50}	2767
Thiamine mononitrate	Mice	--	i.v.	84.2	LD_{50}	1427

Substance	Animal	Sex	Route	Dosage (mg/kg Body Weight	Measurement	Ref.
Thiamine mononitrate	Mice	--	i.p.	387.3	LD_{50}	1427
Thiamine mononitrate	Mice	--	p.o.	7000	LD_{50}	2767
Thiamine mononitrate	Rats	--	i.v.	140	LD_{50}	2767
Thiamine mononitrate	Rats	--	i.v.	160	LD_{50}	2767

* mg thiamine radical per kg body weight

Mice

The acute lethal dose of thiamine in mice was found to be 125 mg/kg upon intravenous injection and 750 mg/kg subcutaneously. Per os, a dose of 5000 mg/kg via a 20% solution was lethal in 10-15 minutes. Shock, muscle tremors, occasional clonic cramps, and respiratory disturbances preceded death (2610).

Malachovskis injected i.v. into groups of 10 (5 male and 5 female) white mice doses of 30, 60, 90, 120, 150, 200, and 250 mg thiamine per kg. The maximum tolerant dose was about 100 mg/kg; the absolute lethal dose was 200 mg/kg (2355).

Rats

Moliter and Sampson reported that doses of thiamine of up to 100 mg/kg subcutaneously and 10 mg/kg intravenously were tolerated by rats (95-100 g; mostly males) without reaction. The acute lethal dose was 250 mg/kg i.v. Symptoms demonstrated were shock, muscle tremors, occasional clonic cramps, and respiratory disturbances; respiratory arrest preceeded cardiac arrest (2610).

Guinea Pigs

Eckler and Chen determined the minimum lethal dose of thiamine hydrochloride administered i.v. to guinea pigs (210-265 g). Doses are presented in the following table:

Toxicity of Natural and Synthetic Vitamin B_1 Hydrochloride.

Vitamin B_1.HCl	Dose mg. per kg.	No. of Pigs Died Over No. Used	M. L. D. mg. per kg.
Synthetic	300	1/1	180
	200	1/1	
	180	2/3	
	160	0/2	
	150	0/1	
	100	0/1	
Natural	180	2/2	180
	160	1/3	

Doses of 150 mg/kg or more produced clonic convulsions. Surviving animals recovered within 1½-5 min., with no obvious effects (960).

Rabbits

Haley established the average intravenous lethal dose of thiamine hydrochloride in rabbits at 117.45 mg/kg; it was 112.58 mg/kg for thiamine mononitrate. The dose rate was 1 ml (50 mg/ml/minute).

Rabbit	Mononitrate	Intravenous	Animal wt, kg	Total dose, mg	Intrav. lethal dose, mg/kg	Avg intrav. lethal dose, mg/kg
			3.66	500	136.61	112.58
			4.20	475	110.46	
			3.32	375	110.46	
			4.44	437.5	98.83	
			4.60	470	100.95	
"	Hydrochloride	"	1.704	180	105.63	117.45
			1.818	220	121.01	
			1.591	200	125.70	

The symptoms of toxicity observed were: restlessness, labored respiration, vasodilatation, cyanosis, muscular twitching, clonic convulsions and death by respiratory paralysis. This respiratory paralysis was of central origin because electrical stimulation of both the muscle of the diaphragm and the phrenic nerve showed that the muscle was still capable of contraction. Anorexia and cardiac arrhythmia were also seen (1427).

In a second study with over 100 unanesthetized rabbits, clonic convulsions were produced by intravenous injection of over 300 mg thiamine hydrochloride per animal but few fatalities occurred (1427).

The acute lethal dose of thiamine in rabbits was 300 mg/kg upon intravenous administration. Some of the animals were anesthetized (2610).

Dogs

In dogs (3-3.7 kg), the intravenous acute lethal dose of thiamine was 350 mg/kg. Urethane anesthesia was used on some of the animals (2610).

II. Short-Term Studies

Pigeons

Pigeons received a husked rice diet plus 10 mcg (normal) or 100-150 mcg (excess) thiamine daily for 20 to 30 days. Compared to the normal group, the hypervitaminotic group exhibited excessive fat deposition in the subcutaneous tissues, omentum, and heart. The myocardium was firmer and often thicker than normal. The relative heart weight increased, too. Transketolase, thiamine dehydrase, aldolase, and transaminase activity increased (2938).

Mice

Groups of 10 male Swiss mice were given by gavage 0.0, 0.06, or 0.4 mg of thiamine daily for 1 week with no untoward effect (708).

Rats

Groups containing 4 male and 4 female white rats (80-90 g) received 0, 500, or 1500 mg/kg thiamine hydrochloride by stomach tube 5 days per week for 6 weeks. Hemoglobin content, hematocrit value, reticulo-, thrombo-, and leukocyte counts, and a differential white blood count were made. Urine sediments were examined microscopically. The following liver function tests were performed: serum glutamate-oxalacetate transaminase (SGOT); serum glutamate-pyruvate transaminase (SGPT); lactic acid dehydrogenase (LDH); sorbite dehydrogenase (SDH); and the thymol turbidity test. The heart, liver, kidney, and testicles were submitted to a histological examination. For males and females, 1500 mg/kg caused a slight growth depression. For the females, weight was depressed even more at the 500 mg/kg level. Three rats died from the accidental insertion of the tube into the lungs. No organ changes were reported (4004).

Short term feeding studies were performed on rats (5-30 of each sex per group) for 3 generations; 300 mg thiamine hydrochloride or thiamine mononitrate per kg of diet were added to a basal ration. This was a 300 to 400 fold increase over the rats' daily requirement. Animals were maintained from weaning to 6 months on their respective diets. Rats receiving the mononitrate or hydrochloride were indistinguishable both in growth and reproductive performance from controls. Autopsy finding were identical for all groups (2767).

Brown fed groups of male weanling Sprague-Dawley rats a basal diet containing 12, 21, 39, 74, 1004, 2004, 3004, 4004, 5004, and 10,004 gamma of thiamine/gm of ration. Four gamma of thiamine per gm of ration was accepted as the requirement for the rat. Eight to thirty animals were used per group. The amount of choline, thiamine, and casein as well as carbohydrate source were varied in experiments which lasted from 2-6 weeks. Brown concluded that the addition of as much as almost 3000 times the requirement of thiamine had no effect on growth. High levels of thiamine didn't contribute to the deposition of fat in the liver, nor did they alter the concentration of liver nitrogen and moisture. The thiamine level was increased in all tissues save the adrenals with the greatest concentration in the heart, kidneys, liver, and testes (477).

"When Wistar rats are maintained on a thiamine deficient diet, supplemented with 10 microgram/ml of thiamine in their drinking water, a kidney lesion develops in about 60% of the animals. The same diet, without thiamine, does not provoke such lesions. The most reasonable hypothesis at present is that the lesions are caused by a breakdown product of thiamine in the drinking water. However, thiochrome is ineffective in provoking the lesions (4139)."

Kato fed 45 day old male Wistar rats (50 g) a basal diet plus 0, 1, 10, and 50 mg/kg body weight thiamine hydrochloride for 4 weeks. Growth was more favorable for the experimental groups than controls for the first two weeks, but returned to normal by 4 weeks (1886).

For 20 weeks groups of 12 female rats (90 days old; 170 g) were fed 2 complete basal rations, one (diet B) with the B-complex vitamins supplied by yeast and one (diet A) with an equivalent amount of each vitamin provided synthetically. Both diets A_2 and B_2 were supplemented with additional thiamine hydrochloride (3.6 g/kg of diet), riboflavin (0.45 g/kg diet), and nicotinic acid (3.0 g/kg diet). In one series rats were fed ad lib, but in a second series rats could only consume 6 g/day. Growth data was computed for the top 10 rats of each group. The table below revealed no significant differences between controls and test groups. However, the ad lib controls weighed slightly more than the ad lib supplemented group.

Effects of massive doses of thiamine hydrochloride, riboflavin and nicotinic acid on the body weight of rats fed ad libitum and under conditions of reduced caloric intake

DIETARY GROUP	NO. OF ANIMALS	INITIAL BODY WT. GRAMS	AVERAGE CHANGE IN BODY WT. IN GRAMS AFTER		
			4 weeks	12 weeks	20 weeks
6 gram per day series					
A_1	10	172.6	−38.0	−48.0	−39.3±4.1*
A_2	10	168.0	−33.0	−44.6	−40.7±3.0
B_1	10	170.5	−39.2	−50.2	−43.2±3.4
B_2	10	168.0	−45.5	−59.0	−51.0±3.7
Ad libitum series					
A_1	10	168.4	+26.9	+28.1	+42.1±7.2
A_2	10	169.0	+16.2	+21.9	+23.4±4.1
B_1	10	170.5	+37.0	+49.0	+60.6±5.4
B_2	10	171.1	+19.8	+28.0	+41.9±5.2

Red blood cell, hemoglobin, and white blood cell determinations were normal for the ad lib supplemented groups. However, these test groups had a lower basal metabolism and a high granulocyte count. In the 6 g/day series, control and test animals compared favorably (495).

Dogs

In a study of the conditioned reflex activity to light and sound in dogs, 500 mg of thiamine was given orally over a period of 26 days. After 10 days, the conditioned reflex was slightly decreased. Doses of 500 mg/day for 6 days also weakened the conditioned reflex reactions (4572).

Monkeys

Rhesus monkeys received 1-100 mg/kg thiamine hydrochloride for 2-17 days without ill effects (2271).

Man

In a study by Bowman et al. 36 patients with Korsakoff psychosis were provided with a basal diet plus 18 g of vegex (estimated to contain 1,066 IU or 3.3 mg thiamine) daily. This supplied 4 times the thiamine requirement for a 60 kg human. Twenty-one of these subjects received an additional 10-50 mg daily by parenteral administration. The observation period varied from 6 to 53 days; the average recovery time was 24 days. No untoward effects were mentioned (431).

Le Galley and Harrison studied the effect of increased thiamine hydrochloride intake on color blind students. Groups of 4 were arranged so as to provide approximately the same degree of color blindness per group. For 10 weeks groups received 30,000 U.S.P. units of vitamin A, 8 mg of thiamine, or 16 mg of vitamin B_2 (riboflavin) daily corresponding to 6, 8, and 8 times the minimum daily requirement. One group received no supplement. Weekly testing of color vision revealed an improvement of 22.3% for the thiamine group and 20.7% for the vitamin A group, compared to 2.2% for the controls. After 10 weeks, the vitamin A group and the thiamine group reversed supplements, and an additional increase of 10.8-11.8% was discovered during this second 10-week period. Vitamin B_2 showed no effect. Tests were designed to avoid "learning" as a source of error (2193).

Mills reported a case of thiamine overdosage in man. A 47 year old female consumed 10 g thiamine hydrochloride daily for 2.5 weeks and consequently suffered from headache, irritability, insomnia, rapid pulse, and general weakness. The symptoms dissolved within 2 days of discontinuation of treatment. One week later the patient started taking 5 mg thiamine hydrochloride daily; after 4.5 weeks the toxic symptoms reoccurred (2544).

III. Long-Term Studies

None available

IV. Special Studies

Teratology

Chickens

Taylor et al. incubated groups of 65 white Leghorn eggs for 11-13 days. Four days after incubation, enough thiamine was injected into one group to raise the vitamin level by 10-20%. The heart, brain, liver, and feet were examined microscopically. Thiamine raised the hemoglobin content and brain size by 10% and 9%, respectively. Feet size decreased 12%. Incidence of embryo deformity was raised to an index of 277, given the control group a value of 100 (3983).

Groups of 100 fresh white Leghorn eggs were injected with 1, 3, 5, 8, 10, 13, 15, or 18 mg of thiamine hydrochloride in a gum arabic suspension and incubated for 12, 15, and 18 days. Eighty eggs were used as the

control. The heart and kidneys of five embryos from each group were examined histologically. No change in the heart was observed. In the kidneys, thiamine caused reversible granular degeneration and necrobiotic or necrotic change with loss of nucleus in the renal tubules at an early stage of incubation with large doses and at a later stage with small doses (2018).

Injection of 100 gamma of thiamine to chicken eggs on the 5th day of incubation produced no malformations (3608).

Carcinogenicity

Mice

Taylor et al. found mice to be slightly resistant to tumor transplants when fed higher than normal levels of B vitamins. Groups of 20 dba mice (male and female) were fed for 3 weeks Purina dog chow with or without the supplements shown in the following table:

Vitamin Content of Various Diets Used
γ/gm.

	Thiamin	Riboflavin	Niacinic Acid	Pantothenic Acid	Pyridoxin	Biotin	Inositol	Folic Acid*	Choline
Group I Purina (Control)	3.7	5.7	89	14	2.1	0.19	1600	0.71	
Group II Purina + 7 vitamins	34	45	290	74	10	0.19	4800	0.71	600
Group III Purina + 7 vitamins + yeast extract	34	45	290	80	10	0.50	4800	0.81	600
Group IV Purina + spleen extract	3.8	6.6	43	14	1.9	0.22	1700	1.4	
Group V Purina + 8 vitamins	3.7	45	290	74	2.1	0.19	1600	0.71	
Group VI Rice-Carrot	3.4	0.22	17	7.1	0.26	0.016	140	0.05	
Group VII Purina + raw egg white	3.3	7.2	32	13	1.7	0.18	1400	0.63	

*Calculated on basis of material with "potency" 40,000.

Prior to this each animal had received tumor tissue (from a spontaneous mammary carcinoma) subdermally in the dorsal area posterior to the cervical vertebrae. Ten to fifteen percent of the mice fed raised levels of B vitamins were tumor resistant compared to the complete susceptibility of the control mice (3983).

Dobrovolskaia-Zavadskaia determined that subcutaneous injection of vitamin B_1 into 19 mice with mammary adenocarcinomas decreased tumor growth and prolonged their survival. Animals were observed for as long as 1000 days (881).

Male NMRI mice were implanted with Crocker sarcoma 180; after 6 days paratumoral injections of 0, 0.5, or 1.5 mg thiamine per day were begun. Tumor growth was monitored for a total of 24 days. Injection of 0.5 mg/day thiamine accelerated tumor growth from the 11th day after implantation, but 1.5 mg/day retarded tumor growth. Although X-ray therapy caused tumor regression, the addition of thiamine did not prolong life (239).

Groups of "101" strain mice, (males and females) were fed a basal diet plus 0 or 0.2% thiamine in their drinking water. After 4 weeks, skin papillomas were induced by a single application of DMBA followed in 3 weeks by applications of croton oil weekly for 15 weeks. It was concluded that thiamine may have protected mice slightly (3366).

In a second study mice received 0.2% thiamine in their drinking water plus 2.5 mg thiamine s.c. twice a week. After 4 weeks 3,4-benzopyrene was applied twice weekly; at 20 weeks all treatment ceased except for thiamine in their water. Thiamine exerted no protective effects (3366).

Groups of C57 Bl/6 mice were fed a thiamine-deficient diet but administered i.p. 10, 100, or 200 mcg of thiamine daily. D'yachkova et al. had previously found that 10 mcg thiamine guaranteed optimal growth, tissue thiamine concentration, and transketolase activity. After 17 days either sarcoma 298 or La hemocytoblastosis was transplanted. Selected mice were sacrificed on the day of transplantation, 2-3 weeks after sarcoma transplantation, and 6 days after La hemocytoblastosis transplantation. Excess thiamine had no effect on sarcoma 298 growth, transketolase activity, or tissue thiamine concentraiton. The development of La hemocytoblastosis was not influenced by extra thiamine (947).

Rats

Di Grazia treated 40 white rats 3 times a week with a topical application of 1,2-benzopyrene to the sacral region. Twenty animals received 0.2 mg of thiamine simultaneously. The latent period between the beginning of treatment with benzopyrene and the appearance of the warts and papillomas was shortened by thiamine treatment. Thiamine prolonged the time required for papilloma cancerization, but reduced the survival period from 231 to 207 days (875).

Scott determined that feeding as little as 0.5 mg of thiamine hydrochloride per week reduced the irritating effects of dimethyl-benzanthracene applied topically to a clipped backs. Fourteen black and white rats (70-150 g) were fed hospital scraps plus 0.5 mg thiamine per week before treatment with the carcinogen commenced. Half were treated with DMBA for 3 months, the others for 5 months. Eighteen rats served as controls. None of the thiamine-fed rats developed definite tumors but 44.5% of the controls did. Six thiamine rats and one control rat remained lesion-free (3589).

Reproduction

Mice

The effect of high dietary level of thiamine was investigated over 3 generations of albino mice. A basal diet of ground Purina dog chow plus 0 or 250 mg/kg diet thiamine and 0 or 1 mg/kg diet manganese chloride was given when the mice were 21 days old. The following table provides specific reproduction information:

Data on Reproduction and Lactation in Albino Mice Kept on a Basal Diet of Purina Dog Chow Supplemented with (a) Thiamine, (b) Thiamine + $MnCl_2$, and (c) $MnCl_2$.

Generation	Supplement	No. of mice	No. of litters born	No. of litters weaned
Parent	None	10	10	8
	Thiamine	10	7	7
	" + $MnCl_2$	5	5	4
	$MnCl_2$	5	5	5
F_1	Thiamine, 1st mating	5	5	0
	" 2nd "	5	3	3
	" + $MnCl_2$	5	4	4
	$MnCl_2$	5	4	4
F_2	Thiamine	5	5	4
	" + $MnCl_2$	5	3	3
	$MnCl_2$	5	4	4

The average daily intake in the test groups was 625-750 micrograms for the growing mice. During lactation the intake was 2000 micrograms. Growth and reproduction were normal for the test groups (593).

Rats

Female Wistar rats were fed a basal diet containing either 2.5 mg thiamine/kg diet (adequate) or 0.5 mg/kg diet (low). This low level was gradually raised to 1.0 mg/kg by the sixth week. At 70 days of age, females were mated. Each initial group was divided and given either adequate thiamine (2.5 mg/kg diet) or extra thiamine (5.0 mg/kg diet). Other vitamins were doubled as well at this 5.0 mg/kg level. Six to thirteen litters per group were produced. On the 22nd day of gestation, rats were sacrificed and the hematocrit, hemoglobin, serum protein, and liver thiamine content were determined. Weight of young and the number of resorptions were not significantly different between groups (480).

Morrison and Sarett studied the effects of excess dietary thiamine, pyridoxine, or both on growth and reproduction in McCollum-Wisconsin rats. Four groups of 12 female weanling rats were fed a basal diet containing 150 micrograms/100 g of diet of thiamine hydrochloride and pyridoxine hydrochloride plus 0 or 50 times this amount of thiamine, pyridoxine, or both for 12 weeks. They were then mated and continued on these diets

until the offspring were weaned. At this time the dams and representative young were sacrificed and the livers, kidneys, and adrenals were weighed. Livers were assayed for solids, total lipid, thiamine, riboflavin, pyridoxine, pantothenate, and vitamin B_{12}. Excess dietary thiamine increased the liver thiamine levels in both mothers and young. Neither growth nor reproduction was affected by the vitamin excesses; reproductive information is tabulated below (2662).

Data on reproductive performance of female rats fed diets containing various levels of thiamine and pyridoxine

No. and description of diet	No. of animals	No. of litters	No. of young	Av. birth weight of young	Survival data				Av. weight of young, 21 days
					3 days		21 days		
				gm	no.	%	no.	%	gm
1. Adequate thiamine, pyridoxine	10	6	44	6.5	43	93	32	73	37
2. Excess thiamine	12	11	75	6.3	72	96	57	76	43
3. Excess pyridoxine	11	9	75	6.1	67	89	56	75	41
4. Excess thiamine, pyridoxine	10	9	87	6.2	76	96	56	64	39

Shumacher et al. studied the effects of high dietary thiamine on reproduction in rats and the vitamin requirements of offspring. Fifteen female Long Evans rats were fed a basal diet containing adequate amounts of vitamins and 5 females consumed a high thiamine diet (10 mg/100 g diet or 25 times the normal amount). After 2 weeks on these diets, the females were mated, and the diets were continued throughout gestation and lactation. The average birth weight, number of young per litter, and average weight of the young at weaning were not significantly different for the two groups. At weaning the offspring of females fed the high thiamine diet had almost twice as high a level of liver thiamine as did controls. It was also determined that the feeding of an excessive amount of thiamine to dams did not affect the vitamin requirement of the young (3581).

Perla studied the effects of excess dietary thiamine in rats as regards growth and reproduction. For several generations, groups of 6-9 females 4 weeks old received a basal diet containing 2 I.U. (6 ug) thiamine per day plus 0, 50 I.U. (.15 mg) thiamine/day in the form of brewer's yeast, or 50 I.U. thiamine concentrate. The concentrate was later replaced by synthetic thiamine. Although the rats fed brewer's yeast had improved growth over controls, a severe disturbance in lactation and a loss of the nursing instinct (neglect and cannibalism) were reported. Synthetic thiamine produced similar but somewhat less toxic results (3069).

In a similar study, Perla and Sandberg determined that the toxic effects of excess thiamine feeding to rats stemmed from a manganese deficiency. No interference in lactation or rearing of the young was observed for 3 generations when rats received both excess thiamine (400 gamma/day) and manganese (2 mg/day) (3071).

Four groups of female Wistar rats received 10, 100, 200, or 400 microgram thiamine daily in addition to a basal diet estimated to contain 330 mcg/100 g diet. Rats were bred and the reproductive abilities examined for 3 generations. The dose was increased for subsequent

generations as shown in the following table:

Influence of massive doses of vitamin B_1 on fertility and lactation

Group Vitamin B_1 daily dose	Generation	Females	Litters	Young born	Young allowed to be reared	Young weaned	Per cent young weaned	Remarks
A								
10 μg.	First	4	4	37	24	23	96	
10 μg.	Second	6	6	49	32	30	94	
800 μg.	Third	6	6	59	36	15	41	One female was sterile after 161 days of mating. Another female resorbed twelve embryos.
B								
100 μg.	First	4	4	36	24	24	100	
100 μg.	Second	4	2	21	12	12	100	Two females were sterile.
400 μg.	Third	6	7	64	42	0	0	One female was sterile after 110 days of mating.
C								
200 μg.	First	6	4	43	24	24	100	Two females were sterile.
200 μg.	Second	2	2	12	12	12	100	
600 μg.	Third	6	2	25	12	0	0	Four females were sterile 120 days after mating. One female resorbed fourteen embryos.
D								
400 μg.	First	4	6	61	34	32	94	
400 μg.	Second	6	6	60	36	30	83	
800 μg.	Third	6	14	147	76	10	12	

In group A, the lactation efficiency dropped from 95 to 41% in the third generation. In group D, the infant mortality was 88% of the third generation (3875).

Groups of 10-11 female rats were fed a synthetic diet (flour, casein) that was approximately equal in caloric value and calcium content to a poor human diet, plus low (198 i.u./1000 cal.), medium (554 i.u./1000 cal.), and high (3756 i.u./1000 cal.) amounts of thiamine. These groups were repeated in a second series in which chalk was fed, raising the calcium intake from 0.33 g to 0.81 g per 1000 cal. "In the growth tests, which lasted from weaning till the rats were mated at about 115 days of age, the chalk group at each level of B_1 intake showed a higher weight increase than the corresponding group without chalk, but these differences were not great. The groups receiving high B_1, both with and without added chalk, were somewhat lower in weight than the corresponding groups on medium B_1, but there was no noticeable difference between the animals in their general condition."

However, signs of severe pyridoxine deficiency were revealed during lactation. Milk supplements (10-20 ml) did little to relieve the symptoms. "Comparison of the groups showed that at lactation performance deteriorated as the level of B1 increased, and that conditions were made worse by the addition of chalk. At each level of B_1 the group receiving chalk was worse than the corresponding group without chalk. Thus the best group was Group I-the basal group with low B_1 and no added chalk. The litters were approximately normal in their weight curves, whether the milk supplement was 10 or 20 ccm and convulsions were not observed in any of the litters." Only 6 litters out of 11 from the high thiamine-high chalk diet survived to weaning; representatives of all litters on the high thiamine-no chalk diet lived, but many from each litter had died and the survivors were in poor condition. Death and convulsions were reported in the other groups. The authors stated that feeding extra pyridoxine to rats on these diets relieved the symptoms in the young (3297).

Sensitivity

Man

Dermatitis was triggered by consumption of a few slices of enriched bread (thiamine, riboflavin, and niacin) in a 50 year old woman previously sensitized by daily consumption of "B-complex" capsules. One or two "B complex" capsules were consumed daily, inducing a severe pruitic dermatitis. Discontinuance of this medication eliminated symptoms within 24 hours. However, lesser erruptions could be provoked by eating several slices of white bread made from enriched flour (2793).

Combes and Groopman reported 2 cases of contact dermatitis in women (35 and 36 years old) who filled ampuls and vials with thiamine solutions daily. Dermatitis appeared after 3 and 8 months of the first handling of the substance; protective clothing was not used. Patches of an erythematovesicular dermatis covered with fine scales were present on the fingers, hands, wrists, and forearms. One woman had inflammatory edema of both eyelids. Patch tests for sensitivity to pure vitamin B_1 and thiamine hydrochloride were positive (691).

Hjorth reported a case of occupational dermatitis in a 17 year-old girl who worked at a pharmaceutical firm. A positive patch test for thiamine was found. Relapses of the eczema occurred after ingestion of 200 mg thiamine and intracutaneous injection of 10 mg thiamine (1579).

Acharya et al. reported a case of sensitization in a 55 year-old female. She had taken a tablet of 100 mg of thiamine hydrochloride daily for 15 days, and two months later she ingested one 100 mg tablet. The patient was admitted to a hospital with rash and itching all over her body, chest pain, dyspnoea, and a choking sensation in the throat. Treatment with noradrenaline, hydrocortisone, antazoline-HCl, and adrenaline relieved the symptoms for a day. However, she died the next day (18).

"Post-mortem examination revealed depigmented patches ranging from a pin point to a pin head in size all over the skin. The lungs revealed

marked pulmonary oedema." "There were minimal atheromatous changes in the coronary arteries. Histopathology revealed epidermal basal cell hyperplasia of the skin. The lungs showed dilated bronchioles. Intervening lung parenchyma showed fibrosis and infiltration with a large number of chronic inflammatory cells. One of the arteries showed evidence of a recent thrombus. The examination of the liver, brain, kidney, heart did not reveal any abnormality" (18).

Oral administration of vitamin B_1 was thought to be responsible for encephalitis in a 25-year-old man. A severe skin rash accompanied fever and other symptoms (2397).

Biochemical Aspects

I. Breakdown

The effects of storage on thiamine were summarized by Sebrell and Harris. Frozen fish and vegetables lost little thiamine as did refrigerated meats and vegetables. However, the losses for frozen muscle meats and liver are between 20-40% for 2-8 months storage (3599).

Losses during canning depend on the acidity, temperature, and time. Canned fruit juices retain far more thiamine than do most canned meats and vegetables. Dehydration is not too destructive unless sulfite has been used. Dehydrated nonfat milk retains much of its thiamine. Little is lost from the curing of meats (3599).

"The milling of cereal grains removes a large proportion of their thiamine, wheat flour extraction of less than 80% resulting in a marked drop in thiamine and the degerming of corn involving a one-third loss. Parboiling of rice and drying before milling conserves the bulk of the thiamine (3599)."

"Cooking processes are costly in terms of thiamine. Roasting of beef and pork involve thiamine losses of 36-53%. Pressure and steam cooking of vegetables involve considerably less loss of thiamine than boiling (about 40%). Electronic cooking destroys little thiamine in several meats. Ionizing radiation destroys 53-88% of thiamine in meats, yet, in certain poultry, fish, and vegetable samples, losses were only 5-37% (3599)."

"The stability of vitamin B_1 in dry products is generally excellent; e.g., losses in cocoa powder containing added vitamins B_1, C, D_3 and iron were 13% and 21% after 12 months at 75 degrees F and 98 degrees F, respectively. Degradation during operations requiring heat depends on pH, oxygen content and other factors. Experimental work is generally required to determine the necessary overages for a given heating step. Vitamin B_1 can be added to the dough in preparing toasted cereal products, in some cases. Losses may be as low as 15% in this type of process, but even small losses may cause undesirable flavors and odors. Thiamine degradation odors are objectionable in some cereals and almost unnoticeable in others. The degradation incurred during heating may be avoided by adding thiamine via solution spray after the heating operation. This may cause flavor problems also since the thiamine is concentrated on the surface of the product (1170)."

"In general, heating in solution at pH 5.5-7.0 is undesirable, but pasteurization of multivitamin milk has no effect on vitamin B_1. Stability is excellent in low pH fruit drinks; e.g. losses in drinks are 6% after 12 months at room temperature. Flavor may be a problem at levels above 4 mg/liter. Drink concentrates containing high levels of vitamin B_1 and C may be less stable than ready-to-serve drinks. The stability problem of vitamin B_1 in solution with vitamin C has already been discussed. Stability in frozen drink concentrates is excellent (1170)."

Thiamine is quite sensitive to sulfite treatment, being readily split into the pyrimidine and thiozole moieties (1170).

Hollenback and Obermeyer performed storage tests on flour samples enriched with thiamine mononitrate and thiamine hydrochloride under normal and harsh conditions. In general, increased temperature and flour moisture decreased thiamine stability in storage. However, the mononitrate was far more stable than the hydrochloride which was attributed to its low hygroscopicity compared to the hydrochloride (1595).

Rice et al. reported that storage of vacuum-packed dehydrated pork at temperatures above 27 degrees C (80.6 degrees F) for 7 days or more resulted in significant destruction of thiamine; dehydrated eggs showed a similar loss. When the pork was mixed with 53% cereal (wheat, barley, and soya flour mix) and then dehydrated, the pork retained much of its thiamine activity. Dehydrated milk showed no loss from high storage temperatures, and exerted a protective effect when mixed with pork. Thiamine stability was found to be roughly proportional to the moisture content of the dehydrated pork, with a maximum loss of activity at 6% moisture (3296).

Thiaminase, a thiamine-destructive enzyme, has been found in certain freshwater fish, shellfish, crustacea, ferns, and the cockscomb but not in higher plants or land animals. This enzyme catalyzes an exchange reaction in which the thiazole portion of thiamine or thiamine pyrophosphate is displaced by a base, giving off a hydrogen ion. Another type of thiaminase has been found in bacteria which hydrolytically cleaves thiamine only into its pyrimidine and thiazole parts. According to Sebrell and Harris, thiaminase has little significance in human nutrition unless large quantities of raw fish, clams, or processed foods in which ground fish was incorporated prior to heating are consumed (3599).

II. Absorption-Distribution

A recent study by Thomson and Leevy on 60 normal humans revealed that the intestinal absorption of thiamine hydrochloride is rate limited and appears to follow Michaelis-Menton kinetics. After ingestion of a single dose, the maximum absorbed is 8.3 mg. The dosage required to produce half-maximum absorption is 12.0 mg. According to the authors, a comparison of the absorbtive ability of various areas of the intestine has not been performed, nor is the influence of intestinal motility known (4012).

Gassman et al. determined that the gastrointestinal tract of the rat resorbs thiamine. After enteral application, thiamine was enriched primarily in the walls of the duodenum and small intestine. Resorption efficiency of the individual intestinal sections depended on thiamine supply. The resorption efficiency of the distal sections was 20% of that found in the duodenum and small intestine (1215).

When 15 mg of thiamine hydrochloride was administered orally to normal humans, it was rapidly absorbed and converted to diphosphothiamine

(cocarboxylase) within a few minutes. When the same amount was given intravenously, an immediate increase in the diphosphothiamine blood level was found. However, the thiamine level returned to normal within 6 minutes and the diphosphothiamine blood level never exceeded 5% of the injected dose (4385).

Rindi et al. reported that a significant amount of thiamine hydrochloride was phosphorylated upon in vivo absorption in rats. More thiamine diphosphate than thiamine monophosphate was formed (3327).

In a review of the literature, Sebrell and Harris found the heart, kidney, liver, and brain to have the highest thiamine concentration in several animals, including man. Lesser amounts are present in the spleen, lung, adrenals, and muscle (3599).

The distribution of radioactive thiamine in intracellular fractions of the liver, brain, kidney, and testes of rats was examined by Balaghi and Pearson. The mitochondrial plus soluble fractions of all these tissues contained 60-70% of the radioactivity. About 20% was found in the nuclear fractions from liver, kidney, and testes but only 9% in the brain. Liver and kidney microsomal fractions had 7-8% but the microsomal fraction of the brain had 20-24% (191).

Burkholder and McVeigh have demonstrated that thiamine can be produced by the intestinal bacteria, E. coli, P. vulgaris, B. aerogenes, A. fecalis, B. mesentericus, and B. vulgatus. Age of culture and other factors affect the distribution of the vitamin between the cells and medium (316).

III. Metabolism-Excretion

Meshi and Sato reported a marked difference in the metabolic pattern of ^{35}S-thiamine in rats, depending on the method of administration. After intravenous injection, 65.5% of the radioactivity was excreted in the urine as intact thiamine, but when given orally, only 6.5% of the radioactivity was excreted as intact thiamine, and 84.0% was 4-methyl-5-beta-hydroxyethylthiazole (HT). The authors referred to a study by Fujita et al. (1158) which revealed that HT is a product by hydrolytic cleavage by a specific bacterial thiaminase. Because parental administration produced different metabolites, it was suggested that the formation of HT occurs in the gut. Chromatographic analyses of radioactivity in portal venous blood, intestinal wall, liver, and kidney one hour after the oral dosing of ^{35}S-thiamine indicated that ^{35}S-HT was highest on the portal venous blood and lowest in the intestinal wall. This fact supported the idea that HT is only formed in the gut and that transport from the intestinal wall into portal blood occurs extremely fast compared to thiamine. The cleavage of thiamine was much slower in the mouse, rabbit, and guinea pig than in the rat (2509).

Baker et al. administered 2-^{14}C-thiazole labelled thiamine (0.592 mg) orally to a normal man and examined the excretion of radioactivity

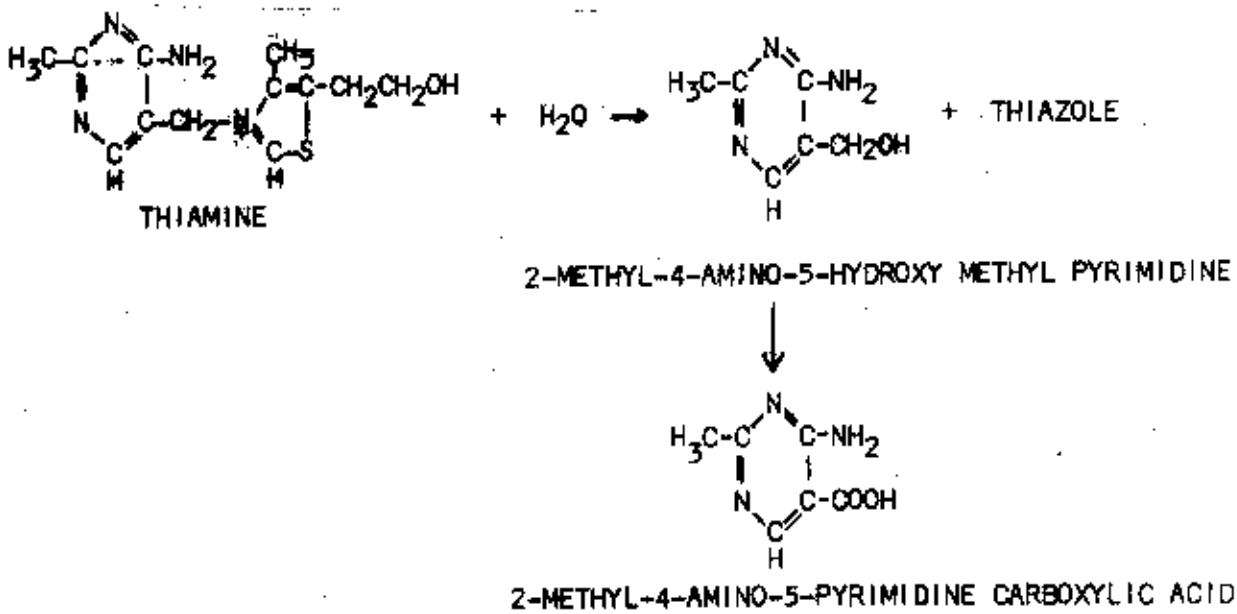
in the urine, feces, and respiratory air. The man was maintained on a normal diet for 17 days. The daily urinary excretion for 10 days was 9.7, 6.7, 2.9, 2.5, 2.2, 2.0, 1.4, 1.5, 1.3, and 1.6% of the dose. After 3 days, 3.8% of the dose was excreted in the feces. Radioactivity in respiratory carbon dioxide was undetectable. The biological half-life of thiamine was estimated to be 18 days (179).

Verratt and Cerecedo studied the fate of ^{35}S-thiamine in adult Chinchilla or Dutch rabbits after oral, intravenous, and intramuscular administration of 50-100 gamma (physiological range). Analysis of excreted urine and feces showed an averaged total recovery of radioactivity (after 4-6 days) of 77% for oral, 86% for intramuscular, and 54% for intravenous administration. After oral dosing the feces contained 8-14% of the activity. The fractions examined were inorganic sulfate, ethereal sulfate, and nuetral sulfur, with the largest amount of radioactivity occurring in the last fraction. Isolation of the main metabolites following oral dosage revealed that unchanged ^{35}S-thiamine and the ^{35}S-thiazole moiety accounted for roughly 95% of the activity of the nuetral sulfur fraction in the first 24-hour period and are excreted in a ratio of 2:1, respectively (4177).

Using column and paper chromatography, Balaghi and Pearson discovered more than 20 urinary metabolites of thiazole-2-C^{14} labeled thiamine injected i.p. into Sprague-Dawley rats. A half-life of about 9 days was determined for thiamine sufficient rats (6 days for deficient rats). Breakdown of the thiazole ring was indicated by the production of respiratory $^{14}CO_2$. Because the metabolites resembled those obtained from previous studies using pyrimidine-^{14}C-labeled thiamine, the authors suggested that most of these metabolites are derived from the entire thiamine molecule. They stated that the 2-position of the thiazole ring is the active metabolic site (189).

Neal and Pearson found at least 22 different urinary metabolites of thiamine after injecting ^{14}C-pyrimidine-labeled thiamine into rats. Three of these could have resulted from the breakdown of thiamine in the urine, but the authors stated that the bulk of the stability studies indicated otherwise. The exact mechanism of breakdown was unknown, but appeared to result from the action of thiamine as a coenzyme or from the action of thiaminases (2777).

From studies in which thiamine-^{14}C or HMP(2-methyl-4-amino-5-hydroxymethylpyrimidine) were injected in rats, Neal and Pearson reported 2-methyl-4-amino-5-pyrimidinecarboxylic acid to be a metabolite of thiamine. It represented 5-10% of the total activity excreted in the urine of rats given 100 microcuries thiamine-^{14}C daily. A possible mechanism is presented below:

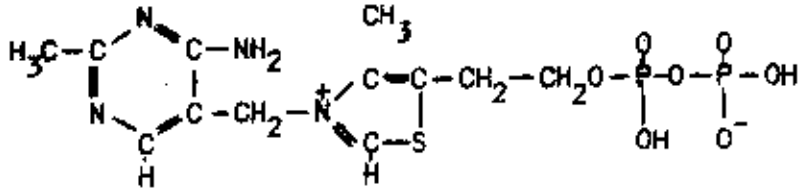


This metabolite was also present in the urine of rabbits and humans (2778).

The excretion of thiamine in rats' urine, feces, and respiratory carbon dioxide was investigated by Balaghi and Pearson. Thiamine depleted rats were given intraperitoneal injections of thiazole-2-^{14}C labelled thiamine (30-100 mcg) daily for 4 weeks. When injections of 30 mcg thiamine per day were begun, only 3.1% of the radioactivity appeared in the urine during the first 24 hours; this increased to 43.7% by the twelfth day. The larger the daily dosage of the thiamine, the more radioactivity was found in the urine. The percentage of activity in the urine ranged from 29-42% injected activity for all groups. An average daily fecal excretion of 17.5% was found for rats given 30 mcg over a 9-week period. Intakes of 30, 50, and 100 mcg/day had values of 24.0, 13.6, and 17.5% activity excreted as respiratory carbon dioxide (189).

IV. Effects on Enzymes and Other Biochemical Parameters

Thiamine pyrophosphate (TPP) is the active coenzyme form of thiamine; other names include cocarboxylase, diphosphothiamine (DPT), and anuerin pyrophosphate (APP). The structure is given below:



In vivo studies have shown that thiamine pyrophosphate functions in the decarboxylation of pyruvic acid, alpha-ketoglutaric acid, and their degradation products. Several different processes require TPP but are involved in only two types of reactions:

1) Simple decarboxylation of either pyruvic or alpha-ketoglutaric acid; or

2) Oxidative decarboxylation of one of these two metabolites (4389).

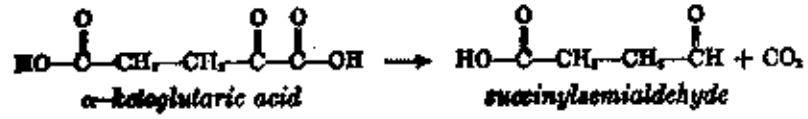
The reactions of pyruvic acid catalyzed by TPP require a divalent cation (Mg^{++} or Mn^{++}) as well. The simplest reaction is the direct decarboxylation of pyruvic acid to yield acetaldehyde and carbon dioxide. Yeast cultured anaerobically utilize this step to form ethanol from glucose. A second reaction involves the condensation of pyruvate and acetaldehyde to give acetoin and CO_2; this has been demonstrated in animal tissues. A third reaction (aerobic) involved the production of a phosphoryl acetyl intermediate from pyruvate (4389).

pyruvic acid + H_3PO_4 + riboflavin-containing enzyme + pantothenic acid coenzyme $\longrightarrow$ CO_2 + reduced flavoprotein + phosphoryl acetyl intermediate associated with pantothenic acid coenzyme

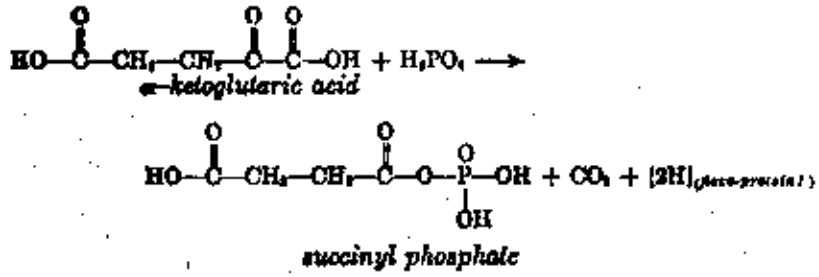
This phosphoryl acetyl intermediate has many biochemical functions: acetylating choline; acetylating aromatic amines; forming acetoacetic acid and its homologues (intermediates in fatty acid synthesis); condensing with oxalacetate to form cis-aconitic acid (precursor of citric acid); alpha-ketoglutaric acid, etc. A fourth reaction is the oxidation of pyruvic acid in the absence of phosphate to give acetic acid and CO_2; this has been demonstrated in cell-free preparations of animal tissue. Other reactions are developed in detail in the text (4389).

Alpha-keotglutarate has been shown to the enzymatically decarboxylated by the 3 following mechanisms, each requiring TPP (4389).

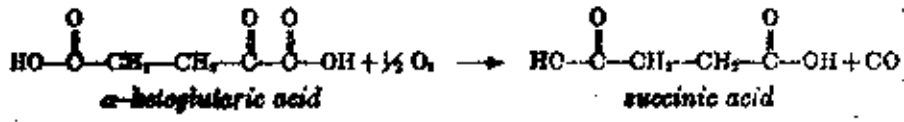
(1) *Simple decarboxylation*[100]



(2) *Aerobic oxidation requiring phosphate*[61]



(3) *Aerobic oxidation independent of phosphate*[66]



From in vitro preparations of rat liver mitochondria, Nakada and Sund determined that thiamine pyrophosphate is involved in the oxidative decarboxylation of glyoxylate to N-formylglutamic acid and carbon dioxide. L-glutamate, DPN (diphosphopyridine nucleotide), and magnesium, calcium, and manganese ions were also required by the enzyme system. Because thiamine pyrophosphate, DPN, and the metal ions stimulated this reaction, the mechanism for glyoxylate catabolism was compared to the oxidative decarboxylation of other alpha-keto acids, e.g., pyruvate or alpha-ketoglutarate. Possible mechanisms are discussed (2741).

Thiamine may act as a cofactor for alpha-glycerophosphate dehydrogenase and lactic dehydrogenase. Van Eys reported that thiamine-deficient rats showed a decrease in liver and muscle alpha-glycerophosphate dehydrogenase activity. When the deficiency was caused by feeding oxythiamine or pyrithiamine (thiamine antimetabolites) concurrently, the decreased activity was proportionate to the dose given. Similar though slightly lesser results were found for lactic dehydrogenase (4138).

Racker, de la Haba, and Leder isolated a transketolase from bakers yeast that catalyzed the cleavage of ribulose-5-phosphate to form D-glyceraldehyde-3-phosphate. An acceptor aldehyde must be present such as ribose-5-phosphate, glycoaldehyde, or glyceraldehyde. The addition of thiamine pyrophosphate enhanced the activity of a transketolase from E. coli (3226).

Dalgliesh reported that thiamine-deficient rats did not excrete any of the normal metabolites of tryptophan. He stated that thiamine must be necessary either for the conversion of tryptophan to formylkynurenine or for the conversion of formylkynurenine to kynurenine, most likely the former. These are the first steps involved in the conversion of tryptophan to nicotinic acid (744).

The feeding of 1, 10, and 50 mg/kg body weight of thiamine hydrochloride to Wistar rats stimulated growth and the biosynthesis of protein bound lipoic acid in liver mitochondria. However, after 3 and 4 weeks these effects subsided. The effect of thiamine on lipoic acid is not direct, evidenced by the fact that the addition of thiamine to liver mitochondria of control animals produced no specific change. Lipoic acid is a coenzyme required for the oxidative decarboxylation of alpha-ketogularate to succinyl-SCoA, in the citric acid cycle (1886).

Sorrell et al. reported that intravenous multivitamin injection (60 mg thiamine HCl, ascorbic acid, riboflavin, nicotinamide, etc.) into healthy adult male volunteers resulted in a striking increase in concentration of thiamine in red blood cells. Other volunteers received 60 mg thiamine pyrophosphate (cocarboxylase) i.v. or 60 mg of thiamine propyldisulfide orally. The thiamine HCl induced the least rise and the propyldisulfide the greatest rise in activity (3783).

Zbinden reported that thiamine possessed no strong pharmacological properties. There were some weak cardiovascular effects, such as a transient blood pressure fall, improved sympathetic compensation following postural tilting, negative inotropic effects on isolated auricular tissue, temporary block of bradycardial response to serotinin, and a possible prolongation of the vascular recovery following histamine. The screening tests performed were: acute toxicity, muscle relaxant effect, fighting mouse test, anti-inflammatory effects, analgesic effect, diuretic effect, anticonvulsant effect, effect on appetite, gastric secretion in Heidenhain pouch, antiulcer effect, intestinal tone and motility, effect on bile flow, antitussive effect, sialoschesis, mydriasis, antihypertensive action, cardiovascular tests, effect on nictitating membrane, effect on isolated auricle, avoidance behavioral test, antiparkinsonism test, monoamine oxidase inhibition, DOPA decarboxylase inhibition, effect on serum cholesterol, effect on blood sugar, potentiation of 5-hydroxytryptophan, and potentiation of DOPA (4562).

The method of artificial conditioned speech connections was used to study the effects of thiamine administered orally (20 and 100 mg) to 16 healthy subjects (male and female; 17-18 yr.). One hour after administration no significant effect on the number of necessary repetitions was reported at the 100 mg level, but the number of correct responses was decreased. Responses improved at 2 hours (1638).

An in vitro study by Fancher et al. indicated that thiamine slightly increased the activity of human saliva (1038).

V. Drug Interaction

The effect of thiamine consumption on the metabolic rates of various drugs in vitro was investigated by Grosse and Wade. The metabolism of aniline and zoxazolamine was depressed by high dietary consumption of thiamine (2 mg/day) in rats; aminopyrine was depressed only in males. The

hydrolysis of alpha-napthol acetate was significantly increased. These effects were due to factors in the microsomal liver fraction, as opposed to the soluble fraction (1371).

Nagina fed groups of 9-23 white male rats a starch-casein diet deficient in iodine supplemented by 0, 20, or 100 mcg thiamine/day per os for three series of 10, 15, and 30 days. The highest dose caused a moderate hypertrophy of the thyroid gland and an increase in its iodine content as compared to the 20 mcg/day group (physiological range). Thiamine avitaminosis led to similar hypertrophy, but decreased the concentration of iodine in the thyroid (2735).

Based on both in vitro and in vivo studies, Slingerland and Sullivan found thiamine to have an inhibitory effect on the formation of organic radioiodine compounds in the thyroid. One gram thiamine hydrochloride per kg was fed to rats for 4 to 15 days; ^{131}I was injected prior to sacrifice. When 20-60 mg extra thiamine was injected i.p., the uptake of ^{131}I in the thyroid was inhibited consistently. Thiamine and ^{131}I were incubated with calf thyroid, resulting in inhibition of ^{131}I uptake (3743).

VI. Consumer Exposure

Thiamine is generally added to food as a vitamin supplement. Tables 2, 3, 11, and 13 were compiled from data submitted by user firms. Food consumption values for each food category were derived from the Market Research Corporation of America (MRCA) data on the frequency of eating, and from the USDA data on mean portion size of foods in each category. The food consumption values thus derived were coupled with the usage level data obtained in the surveys to calculate the daily intake of the substance.

Table 12 from "Dietary levels of households in the United States, Spring 1965", a U.S. Dept. of Agriculture publication, correlated thiamine intake with family income.

Included for comparison are Tables on pages 41 and 42 which provide the recommended daily vitamin requirements for a variety of animals and man as established by the NAS/NRC (2767). Merck (2505) suggests that a sedentary 70 kg male ingesting 2400 cals/day requires 1.2 mg thiamine per day.

TABLE 2 -- USAGE LEVELS REPORTED FOR NAS APPENDIX A SUBSTANCES (GROUP I) USED IN REGULAR FOODS(R)

SUBSTANCE NAME (SURVEY NO.)	FOOD CATEGORY NO.	NAME	# FIRMS REPORTING	*** USUAL USE *** WTD MEAN, %	*** MAXIMUM USE *** WTD MEAN, %
THIAMINE HYDROCHLORIDE NAS 0221 FEMA 3400	01	BAKED GOODS(R)	14	.00130	.00327
	02	BREAK CEREALS(R)	8	.00145	.00475
	03	OTHER GRAIN(R)	*	.00059	.00065
	05	MILK PRODS(R)	9	.00333	.00422
	07	FROZEN DAIRY(R)	*	.00508	.01000
	08	PROCSD FRUT(R)	4	.00029	.00054
	10	MEAT PRODS(R)	8	.01037	.02192
	11	POULTRY(R)	*	.04080	.04080
	13	FISH PRODS(R)	*	.04080	.04080
	15	CANDY MELTS(R)	*	.00474	.00952
	16	SOFT CANDY(R)	*	.00500	.01000
	20	GELATIN PUD(R)	*	.00064	.00132
	22	SNACK FOODS(R)	*	.00020	.00040
	23	BEV TYPE I(R)	5	.00033	.00038
	24	BEV TYPE II(R)	*	.00020	.00040
	25	HOT PROMS(R)	*	.00240	.00240
	27	GRAVIES(R)	*	.00120	.00240
	30	HARD CANDY(R)	*	.00102	.00102
	31	CHEWING GUM(R)	*	.00240	.00240
THIAMINE MONONITRATE NAS 0222	01	BAKED GOODS(R)	13	.00053	.00083
	02	BREAK CERLS(R)	11	.00208	.00401
	03	OTHER GRAIN(R)	13	.00041	.00067
	05	MILK PRODS(R)	4	.00076	.00378
	08	PROCSD FRUT(R)	*	.00030	.00100
	19	SWEET SAUCE(R)	*	.00100	.00100
	22	SNACK FOODS(R)	*	.00020	.00040
	23	BEV TYPE I(R)	*	.00012	.00012
	28	INIT DAIRY(R)	*	.00200	.00200

TABLE 3 -- USAGE LEVELS REPORTED FOR NAS APPENDIX A SUBSTANCES (GROUP II) USED IN INFANT FORMULA PRODUCTS & BABY FOODS(B)

0221 THIAMINE HYDROCHLORIDE	02	CEREALS(B)	*	.00400	.00400
	23	FORMULAS(B)	7	.00012	.00045
	93	COMB DINNER(B)	*	.00030	.00030
0222 THIAMINE MONONITRATE	01	BAKED GOODS(B)	*	.00100	.00120
	02	CEREALS(B)	*	.00018	.00100

TABLE 11. PART A -- ANNUAL POUNDAGE DATA FOR NAS APPENDIX A SUBSTANCES (GROUPS I & II)

THIAMINE HYDROCHLORIDE NAS 0221 FEPA 3408	28/ 32	63,000	73,896	74,836	16	6,421	83,257
THIAMINE MONONITRATE NAS 0222	21/ 25	106,100	127,173	133,527			133,527

TABLE 13. PART A -- POSSIBLE DAILY INTAKES OF NAS APPENDIX A SUBSTANCES (GROUPS I & II), PER FOOD CATEGORY AND TOTAL DIETARY, BASED ON FOOD CONSUMPTION BY TOTAL SAMPLE - - - SEE EXPLANATORY NOTES IN EXHIBITS SECTION

THIAMINE HYDROCHLORIDE NAS 0221	01	BAKED GOODS(R)	14	0-5 MO.	.044200	.058500	.111180
				6-11 MO.	.330200	.673400	.830580
				12-23 MO.	.708500	1.167400	1.782150
				2-65+ YR.	1.783600	2.649400	4.488440
THIAMINE HYDROCHLORIDE NAS 0221	02	BREAK CEREALS(R)	5	0-5 MO.	.008940	.025330	.028500
				6-11 MO.	.332270	.891020	1.059250
				12-23 MO.	.388890	.758410	1.239750
				2-65+ YR.	.298000	.771820	.950000
THIAMINE HYDROCHLORIDE NAS 0221	03	OTHER GRAIN(R)	9	0-5 MO.	.002950	.010030	.003250
				6-11 MO.	.097230	.168740	.063050
				12-23 MO.	.096760	.223610	.106600
				2-65+ YR.	.164020	.362260	.180700
THIAMINE HYDROCHLORIDE NAS 0221	05	MILK PRODS(R)	9	0-5 MO.	.179820	.133200	.227880
				6-11 MO.	2.077920	9.993330	2.632280
				12-23 MO.	1.814850	5.807520	2.295900
				2-65+ YR.	1.315350	4.015980	1.666900
THIAMINE HYDROCHLORIDE NAS 0221	07	FROZN DAIRY(R)	9	0-5 MO.	.050000	.205000	.100000
				6-11 MO.	.475000	1.320000	.950000
				12-23 MO.	.720000	1.690000	1.440000
				2-65+ YR.	1.380000	3.085000	2.560000
THIAMINE HYDROCHLORIDE NAS 0221	08	PROCSD FRUT(R)	4	0-5 MO.	.013630	.036540	.026320
				6-11 MO.	.150220	.374100	.290080
				12-23 MO.	.291740	.579130	.563360
				2-65+ YR.	.343070	.726740	.642480

TABLE 13, PART A — POSSIBLE DAILY INTAKES OF NAS APPENDIX A SUBSTANCES (GROUPS I & II), PER FOOD CATEGORY AND TOTAL DIETARY, BASED ON FOOD CONSUMPTION BY TOTAL SAMPLE - - - SEE EXPLANATORY NOTES IN EXHIBITS SECTION

SUBSTANCE NAME (SURVEY NO.)	FOOD CATEGORY NO. NAME	# OF FIRMS	********** POSSIBLE DAILY INTAKE, MG. ********** (AGE)	AVERAGE	HIGH A	HIGH B
THIAMINE HYDROCHLORIDE NAS 0221	10 MEAT PRODS(R)	9	0-5 MO.	.114070	.300730	.241120
			6-11 MO.	2.146590	5.786460	4.537440
			12-23 MO.	3.131740	5.382030	6.619840
			2-65+ YR.	8.130080	13.491370	17.185280
THIAMINE HYDROCHLORIDE NAS 0221	11 POULTRY(R)	*	0-5 MO.	.245000	1.127000	.245000
			6-11 MO.	1.911000	4.468000	1.911000
			12-23 MO.	3.234000	9.016000	3.234000
			2-65+ YR.	6.321000	16.072000	6.321000
THIAMINE HYDROCHLORIDE NAS 0221	13 FISH PRODS(R)	*	0-5 MO.	.049000	.147000	.049000
			6-11 MO.	.637000	2.401000	.637000
			12-23 MO.	2.646000	6.615000	2.646000
			2-65+ YR.	6.076000	15.141000	6.076000
THIAMINE HYDROCHLORIDE NAS 0221	15 CONDM RELSH(R)	*	0-5 MO.	**********	.004760	**********
			6-11 MO.	.038080	.184720	.076160
			12-23 MO.	.133280	.361760	.266560
			2-65+ YR.	.418880	1.009120	.837760
THIAMINE HYDROCHLORIDE NAS 0221	16 SOFT CANDY(R)	*	0-5 MO.	.010000	.100000	.020000
			6-11 MO.	.110000	.340000	.220000
			12-23 MO.	.175000	.465000	.350000
			2-65+ YR.	.290000	.880000	.580000
THIAMINE HYDROCHLORIDE NAS 0221	20 GELATIN PUD(R)	*	0-5 MO.	.013200	.017820	.026400
			6-11 MO.	.084480	.256080	.168960
			12-23 MO.	.091080	.221760	.182160
			2-65+ YR.	.134640	.346500	.269280
THIAMINE HYDROCHLORIDE NAS 0221	22 SNACK FOODS(R)	*	0-5 MO.	**********	.000200	**********
			6-11 MO.	.000800	.002200	.001600
			12-23 MO.	.002200	.008200	.004400
			2-65+ YR.	.002600	.007400	.005200
THIAMINE HYDROCHLORIDE NAS 0221	23 BEV TYPE I(R)	5	0-5 MO.	.007920	.011880	.009120
			6-11 MO.	.074910	.256410	.086260
			12-23 MO.	.178860	.536250	.205460
			2-65+ YR.	.343200	.916410	.395200
THIAMINE HYDROCHLORIDE NAS 0221	24 BEV TYPE II(R)	*	0-5 MO.	.000800	.000000	.000000
			6-11 MO.	**********	.000200	**********
			12-23 MO.	**********	.000400	**********
			2-65+ YR.	.065000	.188800	.130000

TABLE 13. PART A — POSSIBLE DAILY INTAKES OF NAS APPENDIX A SUBSTANCES (GROUPS I & II), PER FOOD CATEGORY AND TOTAL DIETARY, BASED ON FOOD CONSUMPTION BY TOTAL SAMPLE - - - SEE EXPLANATORY NOTES IN EXHIBITS SECTION

SUBSTANCE NAME (SURVEY NO.)	FOOD CATEGORY NO. NAME	# OF FIRMS	POSSIBLE DAILY INTAKE, MG. (AGE)	AVERAGE	HIGH A	HIGH B
THIAMINE HYDROCHLORIDE NAS 0221	29 NUT PRODS(R)	*	0-5 MO.	**********	.004800	**********
			6-11 MO.	.088200	.321600	.129500
			12-23 MO.	.064200	.216000	.094500
			2-65+ YR.	.124800	.372000	.182000
THIAMINE HYDROCHLORIDE NAS 0221	27 GRAVIES(R)	*	0-5 MO.	.001200	.003600	.002500
			6-11 MO.	.016800	.046800	.034000
			12-23 MO.	.043200	.122400	.090000
			2-65+ YR.	.096600	.255600	.207500
THIAMINE HYDROCHLORIDE NAS 0221	30 HARD CANDY(R)	*	0-5 MO.	.000000	.000000	.000000
			6-11 MO.	.001020	.003060	.001020
			12-23 MO.	.003060	.009180	.003060
			2-65+ YR.	.006120	.017340	.006120
THIAMINE HYDROCHLORIDE NAS 0221	31 CHEWING GUM(R)	*	0-5 MO.	**********	**********	**********
			6-11 MO.	.002400	.002400	.002400
			12-23 MO.	.002400	.007200	.002400
			2-65+ YR.	.004800	.009600	.004800
THIAMINE HYDROCHLORIDE NAS 0221	32 CEREALS(R)	*	0-5 MO.	.540000	.932000	.540000
			6-11 MO.	.368000	.464000	.368000
			12-23 MO.	.080000	.360000	.080000
THIAMINE HYDROCHLORIDE NAS 0221	83 FORMULAS(B)	7	0-5 MO.	.402840	.738000	18.295650
			6-11 MO.	.082080	.391080	3.727800
			12-23 MO.	.026400	.007440	1.199000
THIAMINE HYDROCHLORIDE NAS 0221	93 CORN DINNER(B)	*	0-5 MO.	.089000	.235200	.089000
			6-11 MO.	.152400	.426900	.152400
			12-23 MO.	.044500	.177000	.046800
THIAMINE HYDROCHLORIDE NAS 0221	ALL CATEGORIES **********	47	0-5 MO.	1.751770	4.091990	19.994920
	**********		6-11 MO.	9.137200	31.191500	17.880780
	**********		12-23 MO.	19.879240	33.729690	22.456140
	**********		2-65+ YR.	27.200760	60.315340	42.706600
THIAMINE MONONITRATE NAS 0222	01 BAKED GOODS(R)	13	0-5 MO.	.016820	.023850	.020220
			6-11 MO.	.134620	.274540	.210620
			12-23 MO.	.288850	.475940	.492350
			2-65+ YR.	.727160	1.080140	1.138760
THIAMINE MONONITRATE NAS 0222	02 BREAK CERLS(R)	11	0-5 MO.	.012460	.035360	.024060
			6-11 MO.	.463840	1.243840	.894250
			12-23 MO.	.542880	1.058760	1.048610
			2-65+ YR.	.416000	1.077440	.602000

TABLE 13, PART A — POSSIBLE DAILY INTAKES OF NAS APPENDIX A SUBSTANCES (GROUPS I & II), PER FOOD CATEGORY AND TOTAL DIETARY, BASED ON FOOD CONSUMPTION BY TOTAL SAMPLE -- SEE EXPLANATORY NOTES IN EXHIBITS SECTION

SUBSTANCE NAME (SURVEY NO.)	FOOD CATEGORY NO. NAME	# OF FIRMS	POSSIBLE DAILY INTAKE, MG. (AGE)	AVERAGE	HIGH A	HIGH B
THIAMINE MONONITRATE NAS 0222	03 OTHER GRAIN(R)	13	0-5 MO.	.002050	.006970	.005850
			6-11 MO.	.039770	.117260	.044990
			12-23 MO.	.067240	.156390	.1[illegible]
			2-65+ YR.	.118980	.251740	.1[illegible]
THIAMINE MONONITRATE NAS 0222	05 RICE PROCS(R)	4	0-5 MO.	.041050	.030400	.2[illegible]
			6-11 MO.	.474240	2.260760	2.3[illegible]
			12-23 MO.	.414260	1.325440	2.0[illegible]
			2-65+ YR.	.300290	.916560	1.4[illegible]
THIAMINE MONONITRATE NAS 0222	08 PROCSD FRUIT(R)	*	0-5 MO.	.014100	.037600	.047000
			6-11 MO.	.155400	.387000	.510000
			12-23 MO.	.301500	.599100	1.006000
			2-65+ YR.	.354900	.751200	1.183000
THIAMINE MONONITRATE NAS 0222	19 SWEET SAUCE(R)	*	0-5 MO.	.003000	.004000	.00[illegible]
			6-11 MO.	.004000	.031000	.005000
			12-23 MO.	.026000	.076000	.036000
			2-65+ YR.	.068000	.179000	.068000
THIAMINE MONONITRATE NAS 0222	22 SNACK FOODS(R)	*	0-5 MO.	**********	.000200	**********
			6-11 MO.	.000000	.002200	.001600
			12-23 MO.	.002200	.006200	.004400
			2-65+ YR.	.002600	.007400	.005200
THIAMINE MONONITRATE NAS 0222	23 BEV TYPE I(R)	*	0-5 MO.	.002880	.004320	.002880
			6-11 MO.	.027240	.093240	.027240
			12-23 MO.	.065040	.195000	.065040
			2-65+ YR.	.124800	.333240	.124800
THIAMINE MONONITRATE NAS 0222	28 IMIT DAIRY(R)	*	0-5 MO.	.000000	.000000	.000000
			6-11 MO.	.020000	.046000	.020000
			12-23 MO.	.016000	.060000	.016000
			2-65+ YR.	.018000	.030000	.018000
THIAMINE MONONITRATE NAS 0222	81 BAKED GOODS(R)	*	0-5 MO.	.001000	.003000	.001200
			6-11 MO.	.003000	.003000	.003600
			12-23 MO.	**********	**********	**********
THIAMINE MONONITRATE NAS 0222	82 CEREALS(R)	*	0-5 MO.	.024300	.041940	.216000
			6-11 MO.	.010600	.049320	.147200
			12-23 MO.	.003600	.016200	.032000
THIAMINE MONONITRATE NAS 0222	ALL CATEGORIES **********	31	0-5 MO.	.118870	.187840	.529830
			6-11 MO.	1.357470	4.522720	4.263400
			12-23 MO.	1.727810	3.975990	4.818380
			2-65+ YR.	2.125640	4.627320	5.019120

Table 12.--Thiamine: Household diets providing specified amounts per nutrition unit per day

Region, urbanization, 1964 money income after taxes (1)	Thiamine, in milligrams: All households 14/ (2)	Under 0.80 (3)	0.80-1.19 (4)	1.20-1.79 (5)	1.80-2.39 (6)	2.40-2.79 (7)	2.80 and over (8)
	Percent	Percent	Percent	Percent	Percent	Percent	Percent
United States:							
All urbanizations 6/	100	1	7	28	32	13	19
Under $3,000	100	2	8	27	28	13	22
$3,000-$4,999	100	1	7	26	31	14	20
$5,000-$6,999	100	1	7	27	33	14	18
$7,000-$9,999	100	1	5	28	36	13	1[illegible]
$10,000 and over	100	1	5	32	34	13	1[illegible]
Urban 6/	100	2	7	29	32	13	17
Under $3,000	100	2	9	29	28	13	18
$3,000-$4,999	100	2	8	28	30	14	19
$5,000-$6,999	100	1	7	27	34	13	18
$7,000-$9,999	100	1	5	29	36	13	16
$10,000 and over	100	1	6	34	33	13	14
Rural nonfarm 6/	100	1	6	26	32	14	22
Under $3,000	100	2	7	25	27	12	28
$3,000-$4,999	100	*	6	25	33	16	20
$5,000-$6,999	100	1	6	29	32	14	18
$7,000-$9,999	100	0	6	25	35	14	20
$10,000 and over	100	0	2	26	41	12	18
Rural farm 6/	100	1	3	21	32	15	28
Under $3,000	100	1	4	20	28	15	31
$3,000-$4,999	100	1	2	20	33	14	29
$5,000-$6,999	100	1	4	18	32	18	27
$7,000-$9,999	100	0	3	20	34	14	30
$10,000 and over	100	1	2	25	40	16	17
Northeast:							
All urbanizations	100	2	7	30	32	12	17
Urban	100	2	8	30	31	12	18
Rural nonfarm	100	1	7	31	35	13	13
Rural farm	100	0	7	23	35	14	21
North Central:							
All urbanizations	100	1	7	28	33	13	17
Urban	100	1	8	29	34	13	14
Rural nonfarm	100	1	6	27	32	12	23
Rural farm	100	*	2	23	34	16	2[illegible]
South:							
All urbanizations	100	1	6	25	32	14	23
Urban	100	1	6	27	33	13	2[illegible]
Rural nonfarm	100	1	5	22	30	15	27
Rural farm	100	1	4	18	29	15	32
West:							
All urbanizations	100	2	8	32	30	14	15
Urban	100	2	7	33	30	14	15
Rural nonfarm	100	0	9	27	33	17	15
Rural farm	100	1	3	23	35	14	24

Two-thirds NRC allowance

NRC allowance

*0.5 or less.

See footnotes at end of tables.

Vitamins—(Continued)

TABLE 3. ANIMAL REQUIREMENTS (per kilo ration) (NAS-NRC)

Animal	Purpose	A (IU)	D (IU)	E (IU)	K (mg)	AA (mg)	Bi (μg)	Ch (mg)	Cy (μg)	FA (mg)	Ni[a] (mg)	Pa (mg)	Py (mg)	Ri (mg)	Th (mg)
Cat (1962)	Growing	25,000	1,000	34-136	-	*	—	3,000	-	*	40	5	2	4	4
Dog (1962, revised)	Growing	5,000	250	50[b]		—	—	1,200	22	0.18	10	2.2	1	2.2	0.7
Fox[c] (1955)	Growing	2,410	*	*	—	—	*		*	0.2	10	8	2	2.6	1.8
Guinea pig (1962)	Growing	16,000	*	60	10	200	—	1,500	-		50	20	4	16	6
Hamster (1962)	Growing	13,000	*	25	*	*	*	*	*		*	40	6	6	6
Mink[c] (1966)	Growing	3,500	*	25	—	—	*	*	30	0.5	20	6	1.1	1.5	1.2
Monkey	Growing	*	*	*	—	25	250		25	1.3	38	*	1.2	0.8	0.8
Mouse (1962)	Growing	500	150	20	*	*	*	570-1,140	5	*	30	8.5	1	4	2.9
	Pregnancy and lactation	500	*	*	*	*	*	*	4.5	*	*	10.2	*	7	5
Rat (1962)	Growing	2,000	*	60	1	*	*	750	5	*	15	8	1.2	2.5	1.3
	Gestation	12,000	*	30	*	*	*	<1,000	5	*	*	8	0.6	4	4
	Lactation	12,000	*	20	*	*	*	<1,000	5	*	*	10	0.6	4	4
Poultry															
Chicken (1966)	Growing 0-8 weeks	2,000	200	*	0.5	—	90	1,300	9	1.2	27	10	3	3.6	1.8
	Growing 8-16 weeks	2,000	200	*	*	—	*	*	*	*	11	10	*	1.8	*
	Laying	4,000	500	*	*	—	*	*	*	0.25	*	2.2	*	3.2	*
	Breeding	4,000	500	*	*	—	150	*	3	0.35	*	10	4.5	3.8	0.8
Duck (1966)	Growing	*	220	*	*	—	*	*	*	*	55	11	2.6	4	*
Pheasant (1966)	Growing	*	1,200	*	*	—	*	*	*	*	60	*	*	3.5	*
Quail (1966)	Growing	13,000	*	*	*	—	*	*	*	*	*	*	*	*	*
Turkey (1966)	Growing 0-8 weeks	4,000	900	*	0.7	—	*	1,900	3	0.9	70	11	3	3.6	*
	Growing 8-16 weeks	4,000	900	*	*	—	*	*	*	*	*	*	*	*	*
	Breeding	4,000	900	*	*	—	*	*	*	0.8	*	16	*	3.8	*
Swine (1968)	Growing 5-10[d]	2,200	220	*	*	—	*	1,000	22	0.5-1	22	13	1.5	3	1.3
	Growing 10-20	1,750	200	*	*	—	*	900	15	0.5-1	18	11	1.5	3	1.1
	Growing 20-35	1,300	200	*	*	—	*	*	11	*	14	11	1.1	2.6	1.1
	Growing 35-60	1,300	125	*	*	—	*	*	11	*	10	11	*	2.2	1.1
	Growing 60-100	1,300	125	*	*	—	*	*	11	*	10	11	*	2.2	1.1
	Breeding 110-160	4,100	275	*	*	—	*	*	13.8	*	22	16.5	*	4.4	1.4
	Lactating 140-200	3,300	220	*	*	—	*	*	11	*	17.6	13.2	*	3.3	1.1
	Boars 110-180	4,100	275	*	*	—	*	*	13.8	*	22	16.5	*	4.1	1.4

Compiled by J. C. Bauernfeind and E. DeRitter.

[a] AA, Ascorbic acid; Bi, Biotin; Ch, Choline; Cy, Cyanocobalamin; FA, Folic acid; Ni, Niacin; Pa, Pantothenic acid; Py, Pyridoxine; Ri, Riboflavin; Th, Thiamine.

[b] Required but specific needs not established. AA only a dietary essential for monkey and guinea pig.

[c] NAS-NRC publications also exist for the vitamin requirements of large animals.

[d] Kilograms

[e] Not a dietary essential.

[f] From 7-31 weeks of age, male body wt. goes from 690 to 2,070 g with consumption of 27 to 75 g of dry food daily; female body wt. goes from 560 to 1,110 g with consumption of 32 to 60 g of dry food daily.

[g] From 7-31 weeks of age, male body wt. goes from 1.4 to 5.7 kg with consumption of 39 to 160 g of dry food daily; female body wt. goes from 1.3 to 4.7 kg with consumption of 36 to 118 g of dry food daily.

[h] Growing.

FOOD AND NUTRITION BOARD, NATIONAL ACADEMY OF SCIENCES–NATIONAL RESEARCH COUNCIL
RECOMMENDED DAILY DIETARY ALLOWANCES,[a] Revised 1968
Designed for the maintenance of good nutrition of practically all healthy people in the U.S.A.

	Age[b] (years)		Weight		Height				Fat-Soluble Vitamins			Water-Soluble Vitamins							Minerals				
	From	Up to	(kg)	(lbs)	cm	(in.)	kcal	Protein (gm)	Vitamin A Activity (IU)	Vitamin D (IU)	Vitamin E Activity (IU)	Ascorbic Acid (mg)	Folacin[c] (mg)	Niacin (mg equiv)[d]	Riboflavin (mg)	Thiamin (mg)	Vitamin B_6 (mg)	Vitamin B_{12} (μg)	Calcium (g)	Phosphorus (g)	Iodine (μg)	Iron (mg)	Magnesium (mg)
Infants	0	1/6	4	9	55	22	kg × 120	kg × 2.2[e]	1,500	400	5	35	0.05	5	0.4	0.2	0.2	1.0	0.4	0.2	25	6	40
	1/6	1/2	7	15	63	25	kg × 110	kg × 2.0[e]	1,500	400	5	35	0.05	7	0.5	0.4	0.3	1.5	0.5	0.4	40	10	60
	1/2	1	9	20	72	28	kg × 100	kg × 1.8[e]	1,500	400	5	35	0.1	8	0.6	0.5	0.4	2.0	0.6	0.5	45	15	70
Children	1	2	12	26	81	32	1,100	25	2,000	400	10	40	0.1	8	0.6	0.6	0.5	2.0	0.7	0.7	55	15	100
	2	3	14	31	91	36	1,250	25	2,000	400	10	40	0.2	8	0.7	0.6	0.6	2.5	0.8	0.8	60	15	150
	3	4	16	35	100	39	1,400	30	2,500	400	10	40	0.2	9	0.8	0.7	0.7	3	0.8	0.8	70	10	200
	4	6	19	43	110	43	1,600	30	2,500	400	10	40	0.2	11	0.9	0.8	0.9	4	0.8	0.8	80	10	200
	6	8	23	51	121	48	2,000	35	3,500	400	15	40	0.2	13	1.1	1.0	1.0	4	0.9	0.9	100	10	250
	8	10	28	62	131	52	2,200	40	3,500	400	15	40	0.3	15	1.2	1.1	1.2	5	1.0	1.0	110	10	250
Males	10	12	35	77	140	55	2,300	45	4,500	400	20	40	0.4	17	1.3	1.3	1.4	5	1.2	1.2	125	10	300
	12	14	43	95	151	59	2,700	50	5,000	400	20	45	0.4	18	1.4	1.4	1.6	5	1.4	1.4	135	18	350
	14	18	59	130	170	67	3,000	60	5,000	400	25	55	0.4	20	1.5	1.5	1.8	5	1.4	1.4	150	18	400
	18	22	67	147	175	69	2,800	60	5,000	400	30	60	0.4	18	1.6	1.4	2.0	5	0.8	0.8	140	10	400
	22	35	70	154	175	69	2,800	65	5,000	—	30	60	0.4	18	1.7	1.4	2.0	5	0.8	0.8	140	10	350
	35	55	70	154	173	68	2,600	65	5,000	—	30	60	0.4	17	1.7	1.3	2.0	5	0.8	0.8	125	10	350
	55	75+	70	154	171	67	2,400	65	5,000	—	30	60	0.4	14	1.7	1.2	2.0	6	0.8	0.8	110	10	350
Females	10	12	35	77	142	56	2,250	50	4,500	400	20	40	0.4	15	1.3	1.1	1.4	5	1.2	1.2	110	18	300
	12	14	44	97	154	61	2,300	50	5,000	400	20	45	0.4	15	1.4	1.2	1.6	5	1.3	1.3	115	18	350
	14	16	52	114	157	62	2,400	55	5,000	400	25	50	0.4	16	1.4	1.2	1.8	5	1.3	1.3	120	18	350
	16	18	54	119	160	63	2,300	55	5,000	400	25	50	0.4	15	1.5	1.2	2.0	5	1.3	1.3	115	18	350
	18	22	58	128	163	64	2,000	55	5,000	400	25	55	0.4	13	1.5	1.0	2.0	5	0.8	0.8	100	18	350
	22	35	58	128	163	64	2,000	55	5,000	—	25	55	0.4	13	1.5	1.0	2.0	5	0.8	0.8	100	18	300
	35	55	58	128	160	63	1,850	55	5,000	—	25	55	0.4	13	1.5	1.0	2.0	5	0.8	0.8	90	18	300
	55	75+	58	128	157	62	1,700	55	5,000	—	25	55	0.4	13	1.5	1.0	2.0	6	0.8	0.8	80	10	300
Pregnancy							+200	65	6,000	400	30	60	0.8	15	1.8	+0.1	2.5	8	+0.4	+0.4	125	18	450
Lactation							+1,000	75	8,000	400	30	60	0.5	20	2.0	+0.5	2.5	6	+0.5	+0.5	150	18	450

[a] The allowance levels are intended to cover individual variations among most normal persons as they live in the United States under usual environmental stresses. The recommended allowances can be attained with a variety of common foods, providing other nutrients for which human requirements have been less well defined. See text for more-detailed discussion of allowances and of nutrients not tabulated.

[b] Entries on lines for age range 22–35 years represent the reference man and woman at age 22. All other entries represent allowances for the midpoint of the specified age range.

[c] The folacin allowances refer to dietary sources as determined by *Lactobacillus casei* assay. Pure forms of folacin may be effective in doses less than ¼ of the RDA.

[d] Niacin equivalents include dietary sources of the vitamin itself plus 1 mg equivalent for each 60 mg of dietary tryptophan.

[e] Assumes protein equivalent to human milk. For proteins not 100 percent utilized factors should be increased proportionately.

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