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Vitamin B

Updated: May 9, 2016.

OVERVIEW

Introduction

Vitamin B refers to several water soluble vitamins often found together in foods, all of which are necessary for normal growth and metabolism, but none of which are synthesized in adequate amounts by humans. The common forms of vitamin B include vitamin B1 (thiamine), B2 (riboflavin), B3 (niacin), B6 (pyridoxine) and B12 (cyanocobalamin). Except for niacin (when given in high doses), there is no evidence that the other B vitamins, in physiologic or even super-physiologic, high doses, cause liver injury or jaundice. The major forms of vitamin B and selected other water soluble vitamins (biotin, pantothenic acid, choline) are discussed briefly in this record.

Vitamin B1, Thiamine

Thiamine (or thiamin) (thye' a min) is a water soluble B vitamin found in whole grains, legumes, yeast, beef and pork. Thiamine was the first B vitamin to be discovered and was designated vitamin B1. Thiamine is required in amino acid and carbohydrate metabolism and is active in energy generation reactions. Thiamine deficiency is rare, but can occur in malnourished patients due to chronic alcoholism or cancer chemotherapy with poor dietary intake. Populations and cultures that rely heavily upon rice based diets are at increased risk of thiamine deficiency. Classic thiamine deficiency causes the symptom complex known as beriberi ("weak, weak"), marked by variable degrees of weight loss, nausea and vomiting, diarrhea, irritability, apathy, muscle weakness and painful peripheral neuropathy. Cardiac dysfunction with right sided heart failure and peripheral edema can also occur and is called "wet" beriberi. Thiamine deficiency can also present with prominent central nervous system symptoms (Wernicke-Korsakoff syndrome), particularly in malnourished patients with chronic alcoholism or on cancer chemotherapy. Wernicke's encephalopathy is characterized by mental deterioration, nystagmus, ophthalmoplegia and ataxia; Korsakoff's syndrome by memory loss, confabulation and psychosis. Acute thiamine deficiency can also cause lactic acidosis. Thiamine is highly water soluble and body stores are not great, for which reason deficiencies can develop rapidly (within weeks to months). The recommended dietary allowance is 1.2 mg in adult men and 1.1 mg in adult women, amounts that are provided in the average American diet. Thiamine is available generically in many over-the-counter forms and is included in virtually all multivitamin preparations (typically in concentrations of 0.3 to 1.5 mg). Parenteral thiamine is available (100 mg/mL) and used in parenteral nutrition and to treat suspect thiamine deficiencies, often given routinely to hospitalized patients admitted with complications of chronic alcoholism. Oral forms of thiamine have not been associated with adverse events, ALT elevations or liver injury even when given in high doses. Parenteral administration of thiamine can be associated with immediate hypersensitivity reactions including anaphylaxis, but these are extremely rare.

Likelihood score: E (unlikely cause of liver injury).

Vitamin B2, Riboflavin

Riboflavin (rye' boe flay vin) is a water soluble B vitamin found in milk and dairy products, whole grains, legumes, lean meat and fish. Riboflavin is important in fat, carbohydrate and protein metabolism and is a central component in flavin adenine dinucleotide (FAD), a component of many enzymes that require electron transfer. Riboflavin deficiency is rare, but can occur with severe malnutrition and chronic alcoholism and usually presents with nonspecific symptoms including weakness, sore throat, mucositis, cheilosis, glossitis, dermatitis and anemia. Several foods are fortified with riboflavin including bread, cereals and milk. The recommended dietary allowance is 1.3 mg for adult men and 1.1 mg for women, which are well within the amounts found in a typical American diet. Riboflavin is available over-the-counter in multiple forms and is included in most multivitamin preparations in typical concentrations of 0.3 to 1.7 mg. Riboflavin is yellow in color, has natural fluorescence and is inactivated by light. Oral forms of riboflavin have not been associated with adverse events, ALT elevations or hepatotoxicity even when given in high doses. One reason why high doses of riboflavin are well tolerated is that oral doses above 30 mg are not absorbed, and what riboflavin is absorbed is rapidly excreted and body stores are generally limited.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Vitamin B3, Niacin

Niacin (nye' a sin) is a water-soluble B vitamin found in many foodstuffs, particularly fresh vegetables, milk, meat and eggs. Cereal grains and bread are often fortified with niacin. Chemically niacin is known as nicotinic acid and its amide as nicotinamide, both of which are precursors of two important co-enzymes, nicotinamide adenine dinucleotide (NAD) and its phosphate (NADP), which are important in oxidative and reductive reactions and in DNA repair. Niacin deficiency is the cause of pellagra which is now found largely among malnourished alcoholics, but was previously epidemic in populations dependent upon corn based diets. Symptoms of pellagra (“sour skin”) include dermatitis, diarrhea, depression, seizures and dementia. The recommended daily allowance of niacin for adults is 16 mg in men and 14 mg in women. Unlike other B vitamins, niacin has been linked to instances of clinically apparent liver injury, but only when given as niacin and in very high doses. Doses of niacin and nicotinamide used in multivitamins and as vitamin supplements (typically ~20 mg) and the higher doses used to treat pellagra (100-200 mg of nicotinamide three times daily) have not been linked to ALT elevations or to clinically apparent liver injury. Niacin (nicotinic acid) in high doses causes a decrease in serum cholesterol and is used to treat dyslipidemia, using concentrations in the range of 1.5 to 6.0 grams daily (100 to 400 times the RDA). Niacin at these dose levels and particularly the long activing formulations have been linked to a distinctive and severe form of liver injury typically presenting after several months of therapy with marked elevations in serum aminotransferase levels and with early features of hepatic failure. The latency to onset can be quite long (6 months to several years), but there is often a history of recent increase in dose or change in niacin formulation (to a sustained release form). Recovery upon withdrawal is rapid. Further discussion and examples of liver injury due to high dose niacin are provided in the section on niacin which can be reached using the link below.

Likelihood score: A[HD] (well known cause of clinically apparent liver injury but only when given in high doses).

Vitamin B6, Pyridoxine

Pyridoxine (pir" i dox' een) is a water soluble B vitamin found in many foodstuffs, but in highest concentrations in meat, legumes and nuts. Pyridoxine actually represents a family of related compounds including pyridoxine, pyridoxal, pyridoxamine and their phosphates, which are the active coenzyme forms of vitamin B6. Pyridoxine

acts as a cofactor in many enzyme systems, particularly in amino acid metabolism and heme synthesis. The recommended dietary allowance for pyridoxine is 1.3 to 2.0 mg for adults, a level that is well within that provided in typical American diets. Pyridoxine deficiency is rare, but can occur with severe malnutrition and chronic alcoholism. Symptoms of deficiency include weakness, fatigue, dermatitis, cheilosis and anemia. Certain medications including isoniazid, L-dopa, penicillamine and cycloserine interact with vitamin B6 and can cause deficiency. For that reason, these drugs are often given with pyridoxine supplementation (10 to 25 mg daily). Pyridoxine is available over-the-counter in multiple forms and concentrations and is included in virtually all multivitamin preparations, typically in concentrations of 2 to 3 mg. High doses of pyridoxine (50 to 500 mg daily) have been recommended to treat carpal tunnel syndrome, schizophrenia, autism and diabetes, but the efficacy in these conditions is not proven. Oral forms of pyridoxine (below 100 mg daily) have not been associated with adverse events, ALT elevations or hepatotoxicity. Prolonged use of high doses has been linked to sensory neuropathy and to occasional symptoms of nausea, gastrointestinal upset and dermatitis, but not to liver injury.

Likelihood score: E (unlikely cause of liver injury).

Vitamin B12, Cobalamin

Cyanocobalamin (sye" an oh koe bal' a min) is a water soluble B vitamin found in dairy products and meat. The cobalamins are complex organometallic compounds with a central cobalt atom within a porphyrin-like corrin ring. Cobalamins act as essential cofactors for several enzymes including methionine synthase and methylmalonyl-coenyzme A-mutase. The activities of these enzymes are important in RNA, protein and lipid metabolism and in hemoglobin synthesis. Cobalamin cannot be synthesized by humans and its presence in meat and eggs is due to its synthesis by microorganisms in the intestines of animals. Vitamin B12 absorption from the diet requires a cofactor (intrinsic factor) produced by parietal cells of the stomach. The major cause of cobalamin deficiency in humans is lack of intrinsic factor due to gastric atrophy caused by autoimmune destruction of parietal cells. Classic vitamin B12 deficiency causes profound anemia and symptoms of anorexia, irritability, apathy, weakness and a distinctive neurologic syndrome with paresthesias in the hands and feet, unsteady gait, moodiness, confusion and memory loss. The recommended daily dietary allowance of vitamin B12 is 2.4 µg in adults which is well within the concentrations found in the average American diet. Normal serum levels range from 200 to 900 pg/mL (150 to 660 picomoL). Vitamin B12 is available in multiple over-the-counter oral forms and it is included in most multivitamin preparations in typical concentrations of 1 to 6 µg. Parenteral formulations are available by prescription and treatment of vitamin B12 deficiency usually requires parenteral administration, typically in doses of 1000 µg intramuscularly once monthly. Neither oral nor parenteral forms of vitamin B12 have been linked to significant side effects or toxicity. The parenteral forms can cause local injection reactions and hypersensitivity and should be given intramuscularly or by deep subcutaneous injection and not intravenously. Vitamin B12 therapy has not been linked to ALT elevations or to clinically apparent acute liver injury.

Likelihood score: E (unlikely cause of liver injury).

Biotin

Biotin (bye' oh tin) is a water soluble vitamin (also known as vitamin B7, formerly vitamin H) and is found in liver, soy, beans and egg yolks. Egg whites, however, contain the protein avidin that binds to biotin and reduces its availability. Biotin acts as a carrier of carbon dioxide and plays a role in carboxylase enzymes involved in gluconeogenesis and fatty acid metabolism. The recommended daily dietary allowance for biotin has not been formally established, but the amounts needed are small and biotin is found in many foods and is produced by intestinal bacteria. An adequate intake for biotin has been estimated as 30 µg daily. Thus, most diets provide adequate amounts of biotin and its deficiency is rare. Biotin deficiency has occurred in humans on parenteral nutrition. Symptoms include hair loss, seborrheic dermatitis, depression, hallucinations and paresthesias. Biotin

is available generically in many over-the-counter forms in doses of 5 to 10 mg and is included in most multivitamin preparations, usually in concentrations of 30 to 300 µg. Biotin is typically added to parenteral nutrition and the doses for deficiencies is in the range of 10 mg daily. Biotin supplements have no known adverse events and have not been linked to ALT elevations or hepatotoxicity.

Likelihood score: E (unlikely cause of liver injury).

Pantothenic Acid

Pantothenic acid (pan" toe then' ik as' id) is a water soluble vitamin (also known as vitamin B5) that is found in many foods including vegetables, eggs, liver and yeast. Pantothenic acid is a component of coenzyme A and is involved in fatty acid and cholesterol metabolism and synthesis of steroid hormones. Pantothenic acid deficiency has been produced experimentally and causes gastrointestinal disturbance, muscle cramps, paresthesias, ataxia, depression and hypoglycemia. It may be the cause of burning feet syndrome, experienced by prisoners of war. Pantothenic acid deficiency occurs largely as a component of mixed, severe malnutrition with combined vitamin deficiencies. The recommended dietary allowance of pantothenic acid has not been formally established, but the dietary reference adequate intake is 5 mg daily in adults. Pantothenic acid is available generically in many over-the-counter forms and is included in most multivitamin preparations, typically in concentrations ranging from 1 to 10 mg. Pantothenic acid supplementation has not been associated with adverse events, ALT elevations or liver injury even when given in high doses.

Likelihood score: E (unlikely cause of liver injury).

Choline

Choline (koe' leen) is a precursor of acetylcholine, phospholipids and betaine and is necessary for the structural integrity of cell membranes and cholinergic neurotransmission. Choline is not considered a vitamin because it is synthesized in the mammalian liver. However, the amounts derived from de novo synthesis are not thought to be adequate for normal nutrition. Choline is widely distributed in many foodstuffs and particularly liver, milk, eggs and peanuts. The recommended adequate intake was been estimated to be 550 mg daily in men and 425 mg in women, levels which are regularly met by typical American diets. Choline deficiency can be created in experimental animals and causes fatty liver, which is often used as an experimental model for alcoholic and non-alcoholic fatty liver disease. Whether choline deficiency is an important cause of fatty liver disease in humans is not known, but severe protein-calorie malnutrition is often accompanied by marked fatty liver and choline supplementation of total parenteral nutrition decreases fat accumulation in the liver. High levels of choline intake (above 3.5 grams daily) can cause hypotension, diarrhea, salivation, sweating and a fishy body odor. However, there have been no reports of liver injury or ALT elevations associated with high oral supplement of choline.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Drug Class: Vitamins

Other Drugs in the Class: Vitamin A, Vitamin C, Vitamin D, Vitamin E, Vitamin K, Folate, Niacin

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Vitamin B1, Thiamine – Generic, Combination Products

Box continues on next page...

Box continued from previous page.

Vitamin B2, Riboflavin – Generic, Combination Products

Vitamin B6, Pyridoxine – Generic, Combination Products

Vitamin B12, Cyanocobalamin – Generic, Combination Products

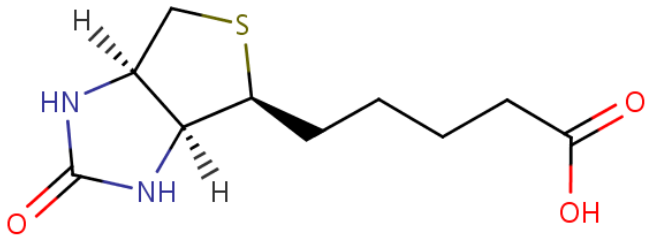
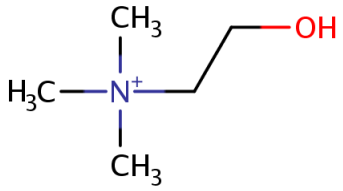
DRUG CLASS

Vitamins

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Biotin	58-85-5	C10-H16-N2-O3-S	
Choline	62-49-7	C5-H14-N-O	

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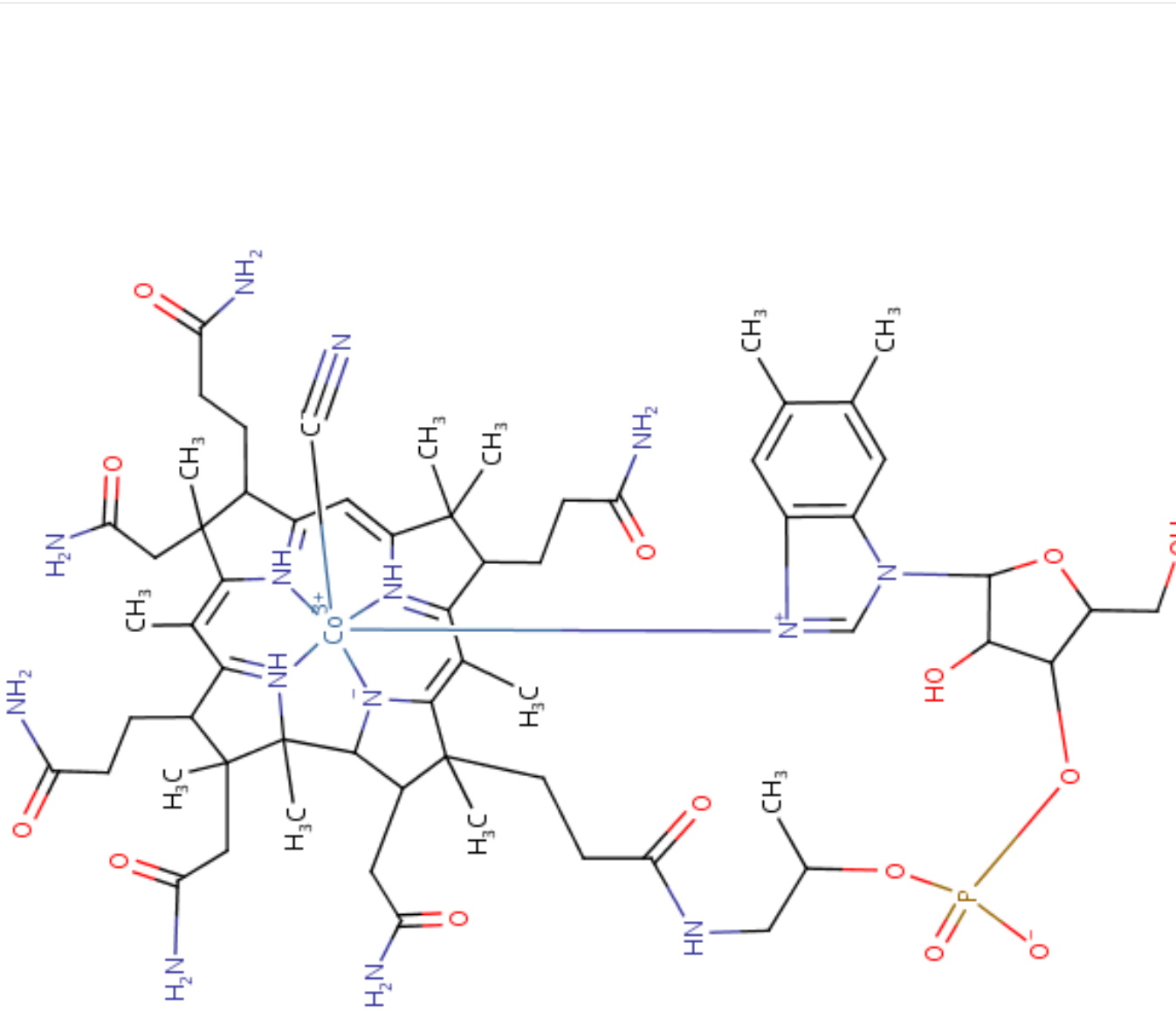
DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Cyanocobalamin	68-19-9	C63-H88-Co-N14-O14-P	

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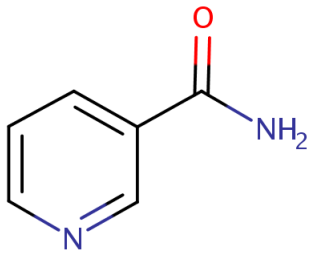
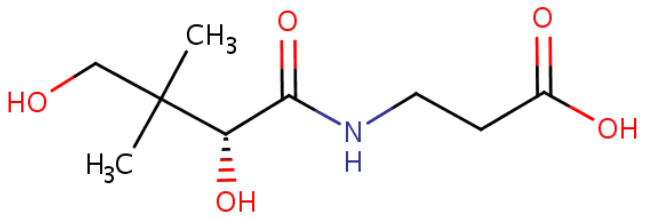
DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Nicotinamide	98-92-0	C6-H6-N2-O	
Pantothenic Acid	79-83-4	C9-H17-N-O5	

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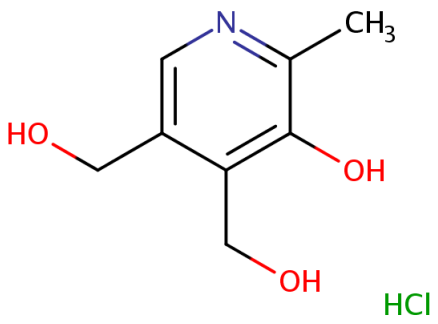
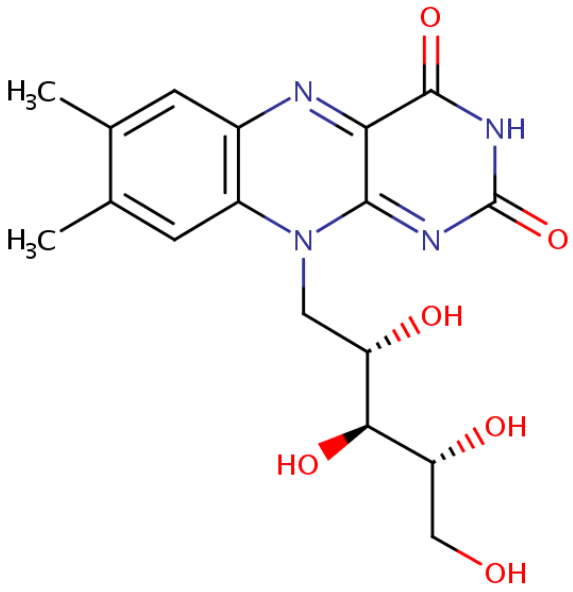
DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Pyridoxine HCl	58-56-0	C8-H11-N-O3.Cl-H	
Riboflavin	83-88-5	C17-H20-N4-O6	

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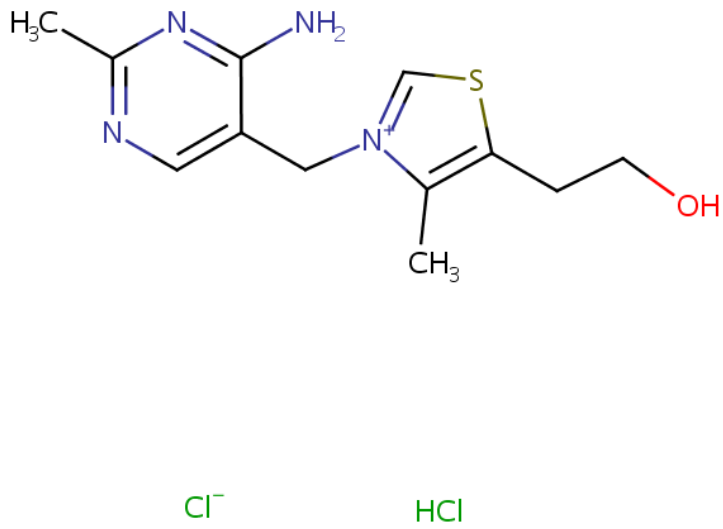
DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Thiamine HCl	67-03-8	C12-H17-N4-O-S.Cl-H.Cl	

ANNOTATED BIBLIOGRAPHY

References updated: 09 May 2016

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Expert review of hepatotoxicity published in 1999, does not discuss vitamin B or water soluble vitamins other than niacin).

Seeff L, Stickel F, Navarro VJ. Hepatotoxicity of herbals and dietary supplements. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013: pp, 631-57.

(Review of hepatotoxicity of dietary supplements; does not discuss vitamins and minerals).

Kaushansky K, Kipps TJ. Hematopoietic agents: growth factors, minerals and vitamins. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1067-1100.

(Textbook of pharmacology and therapeutics).

Shils ME, Olson JA, Shike M, Ross AC. Modern nutrition in health and disease. 9th ed. Baltimore: Williams & Wilkins, 1998.

(Textbook of nutrition with separate chapters on each of the B vitamins).

Food and Nutrition Board, Institute of Medicine. DRI dietary reference intakes: for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin and choline. Washington DC: National Academy Press, 1998.

(Reports from the Food and Nutrition Board of the Institute of Medicine on reference values for vitamin intake, replacing the previously published Recommended Dietary Allowances).

Available at: https://ods.od.nih.gov/factsheets/list-all/

(Fact sheets on dietary supplements including B vitamins maintained and regularly updated by the Office of Dietary Supplements, National Institutes of Health).

(Fact sheets on dietary supplements including B vitamins maintained and regularly updated by the Office of Dietary Supplements, National Institutes of Health).

Schaumburg H, Kaplan J, Windebank A, Vick N, Rasmus S, Pleasure D, Brown MJ. Sensory neuropathy from pyridoxine abuse. A new megavitamin syndrome. N Engl J Med 1983; 309: 445-8. PubMed PMID: 6308447.

(27 year old woman developed difficulty walking and peripheral neuropathy 2 years after starting increasing doses of pyridoxine [to 5 g daily], resolving slowly and incompletely upon stopping; no mention of liver test results or hepatotoxicity).

Stephen JM, Grant R, Yeh CS. Anaphylaxis from administration of intravenous thiamine. Am J Emerg Med 1992; 10: 61-3. PubMed PMID: 1736919.

(32 year old man developed nausea, diffuse skin erythema, shortness of breath and wheezing within minutes of receiving intravenous thiamine [100 mg], responding to corticosteroids, epinephrine and antihistamines).

Wrenn KD, Slovis CM. Is intravenous thiamine safe? Am J Emerg Med 1992; 10: 165. PubMed PMID: 1586415.

(Letter in response to Stephen [1992] mentioning the safety of intravenous thiamine, the authors estimating that among 10,000 injections given for alcoholism and malnutrition, they had not seen any significant allergic reactions or other side effects).

Johri S, Shetty S, Soni A, Kumar S. Anaphylaxis from intravenous thiamine--long forgotten? Am J Emerg Med 2000; 18: 642-3. PubMed PMID: 10999594.

(51 year old woman with confusion and alcoholism developed shock requiring intubation after receiving intravenous thiamine [100 mg] with recurrence on reexposure two days later).

Bendich A, Cohen M. Vitamin B6 safety issues. Ann N Y Acad Sci 1990; 585: 321-30. PubMed PMID: 2192616.

(Review of the safety of pyridoxine in high doses including reports of neuropathy which is typically reversible upon stopping and associated with use of more than 100 mg daily; no mention of ALT elevations or hepatotoxicity).

Gdynia HJ, Müller T, Sperfeld AD, Kühnlein P, Otto M, Kassubek J, Ludolph AC. Severe sensorimotor neuropathy after intake of highest dosages of vitamin B6. Neuromuscul Disord 2008; 18: 156-8. PubMed PMID: 18060778.

(75 year old man developed gait disturbance and sensory neuropathy two years after starting high doses of pyridoxine [9.6 g daily] along with 100 other supplements with marked, but not complete recovery upon stopping).

Bender DA. Non-nutritional uses of vitamin B6. Br J Nutr 1999; 81: 7-20. PubMed PMID: 10341670.

(Review of the non-nutritional uses and toxicity of pyridoxine mentions neuropathy, which arises usually with doses in excess of 200 mg daily; no mention of ALT elevations or hepatotoxicity).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, but none were attributed to water soluble vitamins including niacin).

Sriram K, Manzanares W, Joseph K. Thiamine in nutrition therapy. Nutr Clin Pract 2012; 27: 41-50. PubMed PMID: 22223666.

(Review of thiamine in nutrition, history of its discovery and complications of its deficiency).

Steinberg A, Gorman E, Tannenbaum J. Thiamine deficiency in stem cell transplant patients: a case series with an accompanying review of the literature. Clin Lymphoma Myeloma Leuk 2014; 14 Suppl: S111-3. PubMed PMID: 25486948.

(49 year old woman with acute leukemia underwent hematopoietic cell transplantation and developed diarrhea, weight loss, headaches and encephalopathy, responding to intravenous thiamine).

Stroh C, Meyer F, Manger T. Beriberi, a severe complication after metabolic surgery - review of the literature. Obes Facts 2014; 7: 246-52. PubMed PMID: 25095897.

(Review of 255 published cases of thiamine deficiency after bariatric surgery).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 7 were attributed to niacin, but none were attributed to any other vitamin).

Isenberg-Grzeda E, Alici Y, Hatzoglou V, Nelson C, Breitbart W. Nonalcoholic thiamine-related encephalopathy (Wernicke-Korsakoff Syndrome) among inpatients with cancer: a series of 18 cases. Psychosomatics 2016; 57: 71-81. PubMed PMID: 26791514.

(Over an 18 month period, 18 hospitalized patients receiving cancer chemotherapy were diagnosed with Wernicke-Korsakoff Syndrome, many with nausea, vomiting, weakness and lactic acidosis).