# MCS®-2

### Nutrition Designed to offer constancy to the Liver Detoxification Pathways

The liver is regarded as the major organ controlling metabolic homeostasis. It serves as the body's main route for "metabolic clearing," and functions as the body's primary pathway for detoxification, and subsequent elimination of harmful substances.<sup>(1)</sup> Metabolic homeostasis is defined as "the maintenance of a constant supply of substrates, which can be oxidized to provide energy."(2) This process, in which the liver plays a vital role, requires both the capability to build up reserves, and the ability to break down these stores during times of need. Since the liver functions at the core of these mechanisms, via its role in both the regulation and control of these actions, it is crucial that optimal liver function be maintained, as the body is constantly exposed to a wide variety of potentially damaging substances, which if left unchecked can result in suboptimal liver function.

Toxic substances, being either endogenously produced molecules arising from metabolism itself or exogenously encountered ones, are processed by the liver on a continual basis, primarily via the mechanisms of the Cytochrome P450 (P450) enzymes. P450 enzymes are a superfamily of hemoproteins, which catalyze the Phase I biotransformation of various substrates, oxidizing these compounds into forms which are easily eliminated by the body. The reaction catalyzed by these enzymes is displayed by the general reaction;

> $NADPH + H^+ + R + O2 \rightarrow NADP^+ + H2O + RO$ where (R = substrate, RO = product)

The enzymes associated with Phase I and Phase II are typically classified into two broad categories; those that are involved in steroid anabolism and those that have a generalized function of removing accumulated waste material from the body, (1) subsequently referred to as steroidogenic or xenobiotic enzymes. In humans the P450 system is a ubiquitous enzyme system that catalyzes oxidative reactions of both steroidogenic and xenobiotic enzymes, whose products are removed almost exclusively by these enzymes. These "waste" compounds consist of both endogenously



produced and exogenously encountered ones. Compounds produced endogenously include cholesterol, fat soluble vitamins, sterols, including bile acids, prostaglandins, thromboxane A2,<sup>(4)</sup> as well as both products of microbial metabolism and bacterial produced lipopoly-saccharides, while exogenously encountered substances include chemicals and drugs, naturally occurring toxins or synthetic chemicals in food, food additives, plasticizers, organic solvents, drugs, pesticides, along with industrial waste contaminates. (5) Both types of components have a potentially negative impact on bodily functions, unless properly dealt with by the liver P450 enzymes.

It is for this reason that the liver and also the small intestines contain high concentrations of P450 enzymes. (6) The highest concentration of human xenobiotic P450s is located in the smooth endoplasmic reticulum of the liver cells, the hepatocytes.<sup>(7)</sup> Other tissues contain these enzymes as well, albeit at significantly lower levels than that of the liver. (8) These tissues include the intestine, lungs, kidneys and brain.

### Phase I and Phase II Detoxification Pathways

Despite the body's elaborate means of detoxification, certain aspects may contribute to the suboptimal functioning of these pathways, resulting in a less than adequate means of eliminating harmful substances, including foreign chemicals and drugs. The presence of foreign proteins and



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other toxins can overwhelm the immune system's ability to respond effectively, increasing susceptibility to infection and disease. In our current environment, the range of toxic chemicals is found at an ever escalating rate, and these chemicals are accumulating in all sectors of the environment, making exposure more prevalent. In Phase I intermediate metabolites are formed via the addition of functional groups. Phase II involves conjugation by a variety of enzymes, which in turn renders the metabolite less harmful and more readily excretable. Efficient functioning of both phases is necessary for the adequate removal of bodily toxins. Other factors also play important roles in these processes. For example, adequate oxygen and exercise generally results in enhancing the normal function of phase I and II.<sup>(9)</sup> In addition, it is well known that nutritional deficiencies, including deficiencies in glutathione, magnesium, calcium, copper, zinc, niacin, riboflavin, vitamin B6, and vitamins C and E, can result in impaired liver function. (10,11) Conversely, certain dietary nutrients offer support to the detoxification process, making it more efficient and accelerating the healing process.

### $\label{thm:continuous} \textbf{Vitamins and Their Role in the Detoxification Processes}$

### Vitamin A

Vitamin A, along with vitamins C and E, serve as cofactors for Phase II enzymes. In addition, numerous gene products and receptor binding proteins are influenced by vitamin A. These genes include, among others, those that code for the peroxisomal proliferators-activated receptors (PPARs) and the retinoid X receptors (RXR). Formation of the PPARy/RXR dimer results in the binding of the peroxisome proliferator response element (PPRE), which in turn functions in the modulation of gene transcription. (12) PPARy and the RXR ligands have been demonstrated to cooperatively induce cellular differentiation and apoptosis via the PPARy/RXR interaction. (13,14,15,16) Retinoids have also been associated with a reduction in local inflammatory response via their inhibitory action on TNF- $\alpha$ and IFN-y.(17) Activation of the PPAR genes are unregulated in inflammation, and vitamin A may serve as an important factor given this scenario.

Vitamin A is also essential for the normal functioning of the immune system,<sup>(18)</sup> and acts as an important antioxidant, via its ability to scavenge reactive oxygen species, which left unchecked may potentially result in oxidative DNA damage. Carotenoids, specifically, exhibit an extraordinary capacity to quench singlet oxygen molecules.<sup>(19)</sup> Their action has been attributed to their 'chain-breaking' effect, resulting in a protective effect against free radical attack.<sup>(20)</sup>

### Vitamin C

Vitamin C is a powerful water-soluble antioxidant, and serves as excellent quencher of free radicals, acting as a barrier against lipid oxidation. Due to its water soluble properties, vitamin C it aids in protecting other non-water soluble compounds, such as polyunsaturated fatty acids and vitamin E, from peroxidation and/or oxidative damage. It is also a necessary component for the production of several P450 oxidases, as well as for the production of flavin-containing monooxygenases (FMOs). PMOs are an important component in detoxification as they consist of a number of genes, which code for drug metabolizing enzymes as well as for enzymes that metabolize other encountered foreign compounds (xenobiotics). (23)

### Vitamin E

A significant side effect to metabolic activity during the transformation of toxins is the production of free radicals, resulting in oxidative stress. As the premier lipid antioxidant, Vitamin E, along with other antioxidant vitamins such as vitamins C and E, selenium and copper, functions to aid in protecting the cell from oxidative stress. A diminished erythrocyte lifespan, (24,25) and an increased susceptibility to hemolysis have been demonstrated in populations with both marginal and severe vitamin E deficiency. (26) As a localized membrane component, vitamin E also functions to reduce alkoxyl and peroxyl radicals, as well as to neutralize intermediate toxins. Additionally, in humans, vitamin E administrations have been demonstrated to augment both red blood cell glutathione levels(27) and reduced/oxidized glutathione (GSH/GSSG) ratios. (28) A low plasma GSH/GSSG ratio is associated with an increased production of free radicals.(29)

### Thiamin (B<sub>1</sub>)

Thiamin, along with other B vitamins, functions to support bodily energy production. *In vivo*, thiamin is an incredibly active vitamin, functioning as a dynamic component in many aspects of energy metabolism, including the oxidation of glucose. Thiamin diphosphate (TPP), the active form of thiamine, comprising over 80% of the body stores, functions as a co-factor in enzymatic reactions that cleave alpha-keto acids (decarboxylation reactions), which includes transketolase, pyruvate dehydrogenase,  $\alpha$ -oxoglutarate dehydrogenase and the branched-chain  $\alpha$ -oxoacid dehydrogenase complex, as well as enzymes of both the pentose phosphate pathway and the citric acid cycle. Depleted tissue stores of TPP and thiamin

deficiency are interconnected, and in animal studies thiamin deficiency is correlated with large reductions in the level of mitochondrial, plasma and liver TPP, resulting in a major influence on the activities of the keto acid dehydrogenase complexes. (30) These multienzyme complexes catalyze the irreversible oxidative decarboxylation of various reactions in the mitochondria. (31) The oxidation of glucose as part of the citric acid cycle is highly dependent upon TPP.(32) Additionally, the inhibition of thiamine-dependent enzymes in both the pentose phosphate pathway and citric acid cycle have been correlated with elevated levels of glyoxal compounds, which are endogenously originating reactive forms of  $\alpha$ -oxoaldehydes. The pathological ramifications of increased glyoxal levels have been demonstrated to result in increased cellular cytotoxicity, increased oxidative stress, and a decreased efficiency of metabolic detoxification. (33)

Interestingly, it has also been reported that thiamin deficiency can manifest as symptoms of congestive heart failure (CHF), and in patients diagnosed with CHF an increased risk of thiamin deficiency exists, primarily due to either medications that increase thiamin excretion, malnutrition, or advanced age.<sup>(34)</sup> Increased stressors, both emotional and physical, can result in an accelerated loss of B vitamins, including thiamin. Additionally, Western diets are typically high in sugars and poor in thiamine, which has been associated with the predisposition for advanced glycation end-products (AGE) related conditions.<sup>(33)</sup>

### Riboflavin

Riboflavin is needed for normal cell function and growth, and is a necessity for energy production. Upon cellular entry, riboflavin is converted to the coenzymes flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). Both FMN and FAD are important components of intermediary metabolism, as a consequence of their participation as coenzymes in reactions that involve oxidation-reduction,(35) including reactions that are vital to normal tissue respiration, pyridoxine activation, tryptophan to niacin conversion, fat, carbohydrate, and protein metabolism, and glutathione reductase mediated detoxification. (36) Riboflavin and its flavin cofactors have also been implicated in the modulation of polypeptides involved in both fatty acyl-CoA and amino acid metabolism, with an alteration of these enzymatic pathways demonstrated in deficient situations. (37) Additionally, in certain individuals, supplemental riboflavin may be extremely important, as a

genetic polymorphism in the flavin-containing molecule flavin monooyxgenase (FMO3) has been associated with a decreased ability to detoxify drugs,<sup>(38)</sup> implicating a general inadequacy in the detoxification ability in these individuals.

### Niacin

Niacin, like riboflavin, has two main coenzymes-NAD<sup>+</sup> and NADP<sup>+</sup>, both of which function in the maintenance of the redox state of the cell. As a substrate for the enzyme poly ADP-ribose polymerase, an enzyme required in DNA repair, niacin plays an important role in the maintenance of DNA integrity. Deficiency, when accompanied by an increase in oxidative damage, increases the susceptibility of DNA to strand breaks, and produces an additive effect with respect to cellular damage and resultant tissue pathology. (35) Cellular detoxification can put added stress on these mechanisms, thus supplementation offers a curtailing effect to ensuing DNA damage.

### Vitamin B<sub>6</sub>

Vitamin B6, in its active form (pyridoxal 5-phosphate), participates in well over one hundred enzymatic reactions. It supports the synthesis of phospholipids, the conversion of methionine to cysteine, and is required for the production of nonessential amino acids. It also provides a supportive role in the maintenance of both a healthy immune response and healthy nerve function. Both hydrazides and hydrazines, environmental chemicals known to occur in food additives and cigarette smoke, among others, interfere with the functions of vitamin B6,<sup>(39)</sup> thus necessitating its use with increased environmental burdens.

### **Pantothenic Acid**

Pantothenic acid plays a vital role in the production of energy from protein, fat, and carbohydrates, and forms the core of Coenzyme A (CoA). CoA functions as an acyl group carrier in enzymatic reactions involving fatty acid oxidation, fatty acid synthesis, pyruvate oxidation, as well as other acetylation reactions in the body, including that of choline and sulfonamides. Other reactions that CoA participates in include the oxidation of fatty acids, pyruvate,  $\alpha$ -ketoglutarate and acetaldehyde, and the synthesis of fatty acids, cholesterol, citrate and other sterols. (35)

### **Folic Acid**

As another member of the B family of vitamins, folic acid plays an important role in the synthesis of purines and pyrimidines, both essentials in DNA synthesis. It also plays a vital role in red blood cell formation, as a necessary component for the formation of heme. In cell-mediated immunity, a decrease in folate is correlated to a decreased blastogenic response of T-lymphocytes to specific mitogens, while its impact upon humoral immunity is correlated to a decreased response to multiple antigens. (40) Both result in immune alterations with deficiency. Folate deficiency has also been correlated to changes in gene expression, including gene-specific methylation/demethylation (41) and altered cellular function. (42) Due to its instability in food, intake may be insufficient to meet dietary needs, thus not surprisingly it is one of the most common deficiencies worldwide. (39) Added to insufficient intake, a variety of drugs interfere with folic acid uptake and utilization, including glucocorticoids, antacids, and aspirin, further necessitating the need for supplementation.

### Vitamin B<sub>12</sub>

Of the B vitamins, B<sub>12</sub> is considered the most potent. It is required for both cellular division and growth, albeit in very minute quantities. Functionally, it acts as both a coenzyme and a substrate in the attachment of a methyl group to cobalt in the formation of methylcobalamin, and is a required component in nucleic acid synthesis. In fact nucleic acid synthesis is arrested with suboptimal cellular concentrations of B<sub>12</sub>. A number of other enzymes also require B<sub>12</sub> as a participating coenzyme, including methylmalonyl-CoA mutase, which is involved in the conversion of succinyl coenzyme A, and acetate synthetase. (35) In addition to its role in DNA and RNA synthesis, it also functions in both fatty acid synthesis and energy production, making it a crucial ingredient in liver support and detoxification.

### Choline

Choline is a natural amine found in lipids that make up cell membranes, as well as in the neurotransmitter acetylcholine. By nature of its makeup, it plays an essential role in the structural integrity of the cell, and is involved in cellular signaling and neurotransmission, which includes the synthesis of acetylcholine. It also participates in the synthesis of S-adenosyl-methionine (SAMe),<sup>(43)</sup> which has hepatoprotective properties.<sup>(44)</sup> Additionally, as the major dietary source of methyl groups, it participates directly in nerve signaling and in both the transport and metabolism of lipids and cholesterol.<sup>(45,46)</sup>

### **Trace Minerals and Detoxification**

Various trace minerals are known to play an important role in both detoxification and metabolic support. The enzyme superoxide dismutase (SOD) plays a critical role in

endothelial function, and is considered the key enzymatic defense system for converting the oxygen radical (O2<sup>-</sup>) to hydrogen peroxide (H2O2) and molecular oxygen (O2). (47) As the cytochrome P450 enzymes act to break down toxins, superoxide radicals are formed, along with other reactive type species know as epoxides. As implicated by the name, the copper/zinc SOD (CuZnSOD), commonly referred to as SOD-1, (48) requires both **zinc** (Zn) and **copper** (Cu), both as a structural component as well as a participating cofactor. (49) This enzyme is active in the cytoplasm of eukaryotic cells, (50) and acts to neutralize the superoxide radicals. The CuZnSOD has been correlated with a critical role in the protection of the blood vessels in response to oxidative stress during aging. In addition to Cu and Zn, manganese also participates in this action. (51)

**Zinc** is also classified as a pivotal component in the antioxidant defense network, functioning as a defensive component in protecting the membrane from cellular oxidation. (52) Additionally, both MnSOD and extracellular SOD (EC-SOD) play crucial roles in the regulation of the oxidant status in the mitochondria and vascular interstitium (spaces between cells), respectively. (53)

**Molybdenum** (Mb) functions as a detoxifying agent, and is a component of the liver enzyme sulfite oxidase, whose task is to destroy sulfite. The degradation of purines in the production of uric acid requires molybdenum as a cofactor. Molybdenum is also a cofactor for aldehyde oxidase as well as sulfite oxidase. Thus impaired sulfoxidation and/or sulfite toxicity is aided with Mb intake. A diet high in refined or processed foods minimizes the intake of Mb, and may result in an additional need for this trace mineral.

Dietary **selenium** intake is correlated to the activity of the selenoproteins, specifically that of the glutathionie peroxidases (GSH-Px), a family of enzymes that functions in the destruction of both hydroperoxides, and that of peroxides formed via the polyunsaturation of fatty acids. Both of these actions support the integrity of cellular membranes. (54) Additionally, cells that have a high turnover rate, such as those of the gastrointestinal tract quickly show signs of deficiency, which is rapidly reversed with supplemental intake.

## Other Ingredients which offer support to the Metabolic Processes

### L-Methionine

Methionine is an essential sulfur containing amino acid. It functions as a critical building block for cellular proteins, and plays other vital roles in bodily functions. For example it is the raw material for the amino acid cysteine, for the neurotransmitter acetylcholine, and for both epinephrine and choline. In the liver methionine is converted to sulfate, which is utilized by the liver to solubilize toxic chemicals and wastes, thus necessitiating its role in detoxification. Additionally, taurine, a component of bile salts, important for fat digestion, is manufactured by the body from methionine.<sup>(39)</sup>

### N-Acetyl-L-Cysteine (NAC)

Oxidative stress, simply defined by Sen and Packer, is 'an imbalance favoring prooxidants over antioxidants'. (55) Certain circumstances, including detoxification, can inherently lead to the production of an excessive quantity of reactive oxygen species (ROS), which can overwhelm the body and ultimately result in oxidative stress. Documented evidence implicates that an increase in the circulating levels of antioxidants aids in preventing free radical accumulation within the cells, thus reducing oxidative stress. In the cell, NAC is utilized to produce the powerful cellular antioxidant glutathione (GSH), which functions in the delivery of cysteine to cells. (39) In animal studies, NAC administration was demonstrated to inhibit the loss of mitochondrial membrane potential and to inhibit glucocorticoid-induced cytochrome C release. (56) In human studies oral administration of NAC has been demonstrated to elevate the level of GSH in both plasma and the fluid bronchoalveolar lavage. (57) Adding to its cellular antioxidant action, NAC is attributed with promoting a positive cellular redox balance, (58) and has been shown to modulate both gene expression and anti-inflammatory activity, via its ability to block NF-kappaB activation. (59)

### Alpha Lipoic Acid

Like methionine, alpha lipoic acid is a sulfur containing compound. It functions primarily as an antioxidant and in the degradation of carbohydrates. As a result of its ability to deactivate both fat and water soluble free radicals, it is sometimes referred to as the universal antioxidant. It can also facilitate the blood-brain barrier. (39) In vitro experiments have demonstrated its ability to alter the cellular redox status, and to interact with thiols and antioxidants, thus may offer cellular support, specifically where oxidative stress is

implicated. (60) A separate study corroberated this action, indicating that supplemental alpha-lipoic acid resulted in decreased oxidative stress, thus may offer a protective effect on the preventing oxidative protein damage. (61)

### **Taurine**

Taurine is a sulfur-containing compound, produced in the liver. It is utilized by the body in the conversion of cholesterol to bile salts, and is a required component for normal functioning of multiple tissues, including the heart, brain, eyes, liver, kidney, intestine, adrenal glands and vascular system. Functionally, it is associated with the protection of tissues from damage resulting from inflammatory reactions, via a reaction with HOCl/OCl to form taurine chloramines, which confers cellular protection via the regulation of pro-inflammatory mediators, including TNF- $\alpha$  and NF-kappaB (64,65,66,67,68) Studies have also associated its use with other forms of cellular protection, including the inhibition of leukocyte apoptosis. (69)

### L-Glutathione

In the cytoplasm of the cell the concentration of glutathione is very high, as it functions in the maintenance of the internal cellular redox environment. It also functions as a critical component in cellular maintenance and repair via the reduction of proteins. It has the capacity to directly quench free radicals (reactive oxygen species), and functions in the reduction of cytoplasmic peroxidases and peroxides. It has also been suggested that glutathione may be an important factor in the induction of nitric oxide synthase in macrophage activation. Furthermore, a separate study noted glutathione's action in immunity, concluding that "low intracellular glutathione levels in antigen-presenting cells correlate with defective processing of antigen with disulfide bonds, indicating that this thiol may be a critical factor in regulating productive antigen processing." (71)

### **Botanical Support of Detoxification Pathways**

Herbal components are known to possess hepatoprotective actions, thus serve an important role in liver support during metabolic clearing and detoxification. MCS®-2 supplies a unique blend of herbs to support these processes, including Milk Thistle, Lycium berries, Cleavers, Culvers, Burdock, and Red Clover.

### Milk Thistle

Milk thistle (*Silybum marianum*) has documented hepatoprotective actions, which are typically attributed to its molecular components and their respective

isomers, including silybin, isosilybin, cis-silybin, silydianin, and silvchristine. (72) In animal studies, intake has been associated with an increase in both the redox state and the total glutathione content of multiple organs, including the liver. (73) In addition to protection against glutathione depletion, studies indicate that its mechanism is in the promotion of protein synthesis, and it acts as an aide in liver tissue regeneration. It has also been demonstrated to control inflammation and to enhance glucuronidation, (74) which is a critical step for phase II enzymes, responsible for conjugating glucuronic acid to a variety of endogenous and exogenous nucleophilic substrates. For example, bilirubin and estrogen. (75) In fact, glucuronidation accounts for 33% of all drugs metabolized by phase II detoxification enzymes, (76) thus demonstrating its importance in liver support. In one study, silymarin's ability to attenuate the recruitment of mast cells and to downregulate the expression of matrix metalloproteinases, which are correlated with cellular invasion and angiogenesis, was demonstrated. (77) Its use has also been associated with the downregulation of COX-2 expression, (78) anti-inflammatory activities, and the modulation of cellular survival and apoptosis, via active interference in both the expression of the cell cycle regulator and in the proteins involved in apoptosis. (79)

### Lycium berries

In the Chinese tradition, Lycium is noted as a kidney strengthener and that also nourishes the liver and aids vision. (80) This berry, also known as Goji Berry, is said to be a very rich source of vitamins and minerals, especially in vitamins A, C and E, flavonoids, and other bio-active compounds. It is also quite a good source of essential fatty acids, which is noted as rather unusual for a fruit. (81) The plant has a long history of medicinal use, both as a general energy restoring tonic and for a wide range of ailments, including skin rashes, eyesight problems, and blood sugar issues. (82) Its consumption in Asia as both food and medicine has been noted for over 2,000 years. (83,84)

### Cleavers

Cleavers (*Galium aparine*) is used in traditional homeopathy for cleansing of the kidneys, blood and lymph systems, as well as for its diuretic properties. It is considered a good lymphatic and blood purifying tonic. (85)

### **Culvers Root**

In modern herbalism, Culvers Root (*Veronicastrum virginicum*) is used mainly for its effect upon both liver and bile production. The root properties are noted as being anodyne,

cathartic, emetic, hepatic, laxative and tonic, (86,87,88,89,90,91) as well as a gentle liver excitant, which serves to increase bile flow. (86,92)

### Burdock

Burdock (*Arctium lappa*) root contains complex volatile oils which include polyynes, caffeic acid derivates, triterpenes and phytosterols. Preparations are generally used for its diuretic, diaphoretic (increasing perspiration) and blood purifying properties.<sup>(93)</sup>

### **Red Clover**

Red Clover's (*Trifolium pretense*) active compounds include volatile oil, isoflavonoids, coumarin derivates and cyanogenic glycosides. It is noted as having antispasmodic and expectorant effects and promotes the skin's healing ability. (93)

In addition to the above ingredients, glandular support can also provide aide in the detoxification process. Parotid tissue (bovine), for example, serves as a functional aide for the saliva glands. These glands serve to lubricate and bind, as well as to solubilize food.

The environment in which we live has become increasingly polluted and toxic. Even very low levels of toxins can result in serious health consequences. Added to this is the fact that toxin exposure is ubiquitous in the external environment. Toxin exposure, however, is not only external. It can also result as a consequence of normal (or abnormal) bodily processes. Poisons enter the body from the external environment through air, water, food, and other places, as well as from inside the body due to normal and abnormal processes involving our cells, genes, and more. As a consequence, the physical body is affected, resulting in sub-optimal performance and function. To overcome the ramifications of the ensuing suboptimal bodily functions, a comprehensive support for metabolic clearing and detoxification, incorporating key ingredients to assist the body in toxin elimination, enables the body to naturally regain optimal function and health.

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Vitamin E (as d-alpha tocopheryl acetate)	13 mg	87%	L-Methionine	100 mg	*
Thiamin (B1) (as thiamin mononitrate)	1 mg	83%	N-Acetyl-L-Cysteine	60 mg	*
Riboflavin (B2)	1 mg	77%	Taurine	50 mg	*
Niacin (as niacinamide)	8 mg	50%	L-Glutathione (reduced)	20 mg	*
Vitamin B6 (as pyridoxal-5-phosphate,			Alpha-Lipoic Acid	20 mg	*
pyridoxine HCI)	1 mg	59%	Proprietary Blend	180 mg	
Folate (as calcium folinate)	100 mcg DFE	25%	Milk Thistle (Silybum marianum) (root & aeri	al part) (extract)	) *
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Choline (as choline bitartrate)	20 mg	4%	Dandelion (Taraxacum officinale) (root) (extra	act)	*
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