

# The Role of Detoxification in the Maintenance of Health

## Research Review

### TOXINS, TOXICANTS & TOXIC SUBSTANCES

The word "toxin" itself does not describe a specific class of compounds, but rather something that can cause harm to the body. More specifically, a toxin or toxic substance is a chemical or mixture that may injure or present an unreasonable risk of injury to the health of an exposed organism. The National Cancer Institute defines "toxin" as a poisonous compound made by bacteria, plants, or animals; it defines "toxicant" as a poison made by humans or that is put into the environment by human activities.<sup>1</sup> Each toxic substance has a defined toxic dose or toxic concentration at which it produces its toxic effect.

Environmental pollutants (referred to as exogenous toxicants) present at variable levels in the air, drinking water, and food supply. Toxicants in the environment include a wide range of compounds, such as heavy metals, organic pesticides, drugs, and industrial materials. Exposure to environmental toxicants has been associated with many types of serious diseases, such as cancers and neurodegenerative disorders—as well as other health ailments characterized by fatigue, muscle weakness, and cognitive dysfunction. It is important to note that besides environmental pollutants, the human body generates toxins (referred to as endogenous toxins) as part of daily normal function.

To avoid confusion, the word "toxin" in this review will be used to indicate either toxins (biological source) or toxicants (chemical source). One of the most important biochemical processes attending to toxin removal in our bodies is the biotransformation process, also called the detoxification system, which is comprised of Phase I, Phase II, and Phase III pathways. The detoxification system is highly dependent on nutrient support for optimal functioning.

### TOXIN EXPOSURE & CHRONIC DISEASE

A growing body of literature suggests an association between toxicant exposure and the etiology of a number of chronic conditions, such as chronic fatigue syndrome (CFS), multiple chemical sensitivities (MCS), fibromyalgia (FM), and atherosclerosis. Symptoms including unremitting and debilitating fatigue, myalgias, arthralgias, and cognitive dysfunction are common amongst these syndromes. Associations between environmental toxicant exposure and the development of many other chronic degenerative diseases have been reported as well (Table 1).<sup>2,11</sup>

Exposure to environmental toxicants can occur from air pollution, food supply, and drinking water, in addition to skin contact. For example, epidemiological studies have identified associations between symptoms of Parkinson's disease and prolonged exposure to pesticides through farming or drinking well water; proximity in residence to industrial plants, printing plants, or quarries; or chronic occupational exposure to manganese, copper, or a combination of lead and iron.<sup>12</sup> While the mechanisms of these toxic exposures are not known, an individual's ability to excrete toxins has been shown to be a major factor in disease susceptibility.<sup>13,14</sup>

**Table 1.** Clinical Symptoms and Conditions Associated with Environmental Toxicity

Abnormal pregnancy outcomes
Atherosclerosis
Broad mood swings
Cancer
Chronic fatigue syndrome
Chronic immune system depression
Contact dermatitis
Fatigue
Fertility problems
Fibromyalgia
Headaches
History of increasing sensitivity to exogenous exposures, odors, or medications
Joint pain
Kidney dysfunction
Learning disorders
Memory loss
Mineral imbalances (particularly zinc and calcium)
Multiple chemical sensitivities
Muscle pain and weakness
Nonresponsive or recurrent yeast infections
Panic attacks
Parkinson's disease
Tinnitus
Unusual responses to medications
Worsening of symptoms after anesthesia or pregnancy

### COMMON CLASSES OF TOXINS

- **Industrial chemicals and combustion pollutants.** This is one of the largest categories of toxicants. Virtually everyone is exposed to halogenated hydrocarbons, such as polychlorinated biphenyls (PCBs), at some level during an average day.<sup>15</sup>

- **Pesticides.** Many of the industrial chemicals are developed for their toxic effects on certain organisms and then sold as pesticides, insecticides, and herbicides. Most pesticides are in some way toxic to humans.<sup>16</sup>
- **Endocrine disruptors.** Common endocrine disruptors include phthalates found in plastics, PCBs, bisphenol A (BPA), some pesticides, synthetic steroids in meat, and dichlorodiphenyltrichloroethane (DDT).<sup>17</sup> Biologists have long noted problems with sterility and malformation of sex organs in many animal species that have been linked to the presence of these contaminants in the environment.
- **Toxic metals.** Lead, mercury, cadmium, arsenic, and other toxic metals are ubiquitous in the environment and often have delayed effects because they accumulate in the body. For example, lead can be sequestered in bones, replacing calcium, where it has a half-life of 62 years.<sup>18</sup> Lead toxicity includes DNA damage, depressed immune system function, anemia, hypertension, kidney disease, and increased tooth decay.<sup>19,20</sup>
- **Food additives, preservatives, and drugs.** The greatest toxin exposure by far is through oral intake of foods, drugs, and water containing toxic substances that can be absorbed in the gastrointestinal (GI) tract.

## TOXIC LOAD & STORAGE OF TOXINS

It is becoming apparent that toxin exposures cannot be considered individually, because humans are not exposed to individual toxins exclusively. Moreover, toxins can act in an additive manner if they exert their toxic effects through the same pathway(s). Further, the majority of toxic substances are fat-soluble, so they can sequester in tissues and remain there for many years.<sup>21,22</sup> In this way, toxins can continue to accumulate so that body tissues are exposed to much higher doses than environmental concentrations would suggest are present.

## REMOVAL OF TOXINS FROM THE BODY

In order to remove these diverse toxins, the body has a complex, integrated system designed to convert fat-soluble toxins to water-soluble molecules, after which they can be directly excreted through renal or biliary routes. This system is called the detoxification or biotransformation system, including Phase I and Phase II metabolizing enzymes and Phase III transporters. Toxin-metabolizing enzymes are predominantly expressed in the liver, GI tract, lungs, and kidneys, although most cells have some detoxification capacity. Biotransformation reactions occur in concert, working together to remove toxins.

**Phase I Bioactivation.** Fat-soluble toxins do not have a reactive site that will easily attach to the water-soluble moiety; therefore, a reactive site must be made first on the toxin before the water-soluble piece can be attached. This is accomplished by the Phase I enzymes.<sup>23</sup> Phase I reactions are catalyzed by a number of different enzymes, primarily from the cytochrome P450 (CYP) superfamily of enzymes. Eighteen families of CYP enzymes have been identified in humans, and each of these contains several subfamilies.

Phase I enzymes are localized to the cytosol of the cell and are regulated by receptor mediated gene transcription. CYPs have broad specificity and use the reduced form of nicotinamide adenosine dinucleotide (NADH) as a cofactor in converting oxygen to a hydroxyl group on the fat-soluble toxin. The result of this reaction is the generation of a reactive site on the transformed toxin. This reactive hydroxyl site is very much like that of a reactive oxygen species (ROS), and can readily bind to other molecules, such as DNA and proteins.

On occasion, the product from this part of the detoxification process becomes soluble in water after the addition of the hydroxyl group and can be directly excreted. This is the case with caffeine, which undergoes only Phase I activation before excretion. This direct, one-step excretion is not common, however, and most activated toxins (*reactive intermediates*, see below) require conjugation with a larger, more water-soluble moiety to effectively alter their lipid characteristics.

Many dietary ingredients support CYP reactions (**Figure 1**), including niacin, which is required for generation of NADH. In addition, the activation reaction often generates ROS. Dietary antioxidants, therefore, may help protect tissue from damage that may occur by this reaction.<sup>23,24</sup>

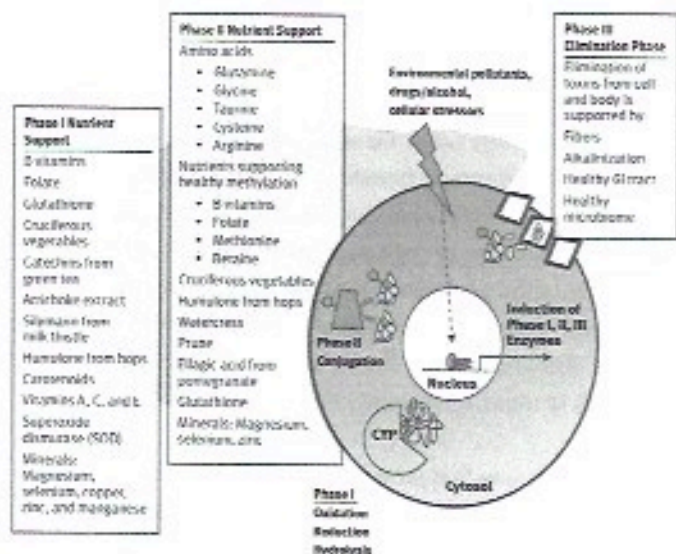
**Phase II Conjugation.** Phase I activation results in the generation of reactive intermediates that are often more reactive—and potentially more toxic—than the parent molecule. This molecule should be converted to a non-toxic, water-soluble molecule at the site of production as soon as possible. Conjugation of the reactive intermediate to a water-soluble molecule is accomplished by Phase II conjugation enzymes, which consist of many enzyme superfamilies—including sulfotransferases (SULT), UDP-glucuronosyl-transferases (UGT), glutathione S-transferases (GST), and N-acetyltransferases (NAT).<sup>24</sup>

Conjugation reactions not only require the water-soluble moiety that will be attached to the toxin—such as sulfate in the case of sulfation or glucuronic acid in the case of glucuronidation—but also use a large amount of energy in the form of adenosine triphosphate (ATP). In addition to energy depletion, Phase II reactions require an abundance of cofactors.<sup>23</sup> Multiple nutrients and phytonutrients may help support Phase II reactions (Figure 1).

**Phase III Transport.** Phase III proteins are transmembrane-spanning proteins that transport substrate out of the cell.<sup>24</sup> Depending on the membrane localization of the transporter, water-soluble toxins are exported from the cell to the circulation for eventual elimination by the kidneys or exported into the bile and then excreted via the feces.<sup>24</sup>

Phase I metabolizes a toxin and Phase II conjugates a water-soluble group to the toxin, promoting its excretion in Phase III. These activities work in concert and thus must be balanced. In particular, Phase II activities must keep up with the Phase I generation of reactive intermediates or an imbalance in the production of reactive substances occurs.

Figure 1. Liver Cell Detoxification Mechanisms



Detoxification occurs primarily in the liver, but also throughout the GI tract, kidneys, lungs, and brain. Nutrient support is vital for optimal functioning of detoxification pathways.

## ENERGY PRODUCTION & OXIDATIVE STRESS IN TOXICITY

As noted earlier, ATP is vital for adequate biotransformation. Generation of adequate ATP requires healthy, nutrient-supported mitochondria. Unfortunately, many toxins can inhibit mitochondrial function, which can lead to a decreased biotransformation capacity of other toxins.<sup>25</sup> Production of ROS is also a consequence of energy production, and excess presence of these damaging molecules—a state referred to as oxidative stress—is associated with toxicity.<sup>26</sup>

**Nutrients that support mitochondrial function** include the essential cofactors for energy production: thiamin, riboflavin, niacin, pantothenic acid, and magnesium. Also, nutrients that help protect the body from oxidative stress, such as vitamins C and E, zinc, selenium, and copper, are beneficial.<sup>27,28</sup>

## DIGESTION, EXCRETION & DIET IN TOXICITY

Gastric emptying, intestinal transit, and bile secretion are part of healthy digestion and can have a profound effect on detoxification. Toxins that are conjugated in the intestinal tract and during first pass metabolism in the liver are primarily excreted via bile, which requires healthy fecal production. Dietary fiber supports healthy excretion—which is important for removing biotransformed toxins—and has been shown to bind some toxins directly, thereby facilitating their removal before significant absorption occurs.<sup>29</sup>

Human urinary pH can range from 4.6 (acidic) to 8.0 (alkaline),<sup>30</sup> which may affect the elimination of toxins. For example, urine alkalization increases the urine elimination of methylchlorophenoxypropionic acid and 2,4-dichlorophenoxyacetic acid (herbicides).<sup>31</sup> In the event of acute poisoning or overdose of toxins, alkalization of urine to pH  $\geq 7.5$  is a method for the enhanced elimination of toxins under acute medical settings.<sup>31</sup> Clinical studies have shown that alkaline minerals commonly found in fruits and vegetables increase urinary pH.<sup>32,33</sup> Thus, progressive alkalization of urine via dietary agents may assist metabolic detoxification by enhancing urinary excretion of weak acids.<sup>34</sup> In addition, adequate intake of water is essential to maintaining healthy kidney function and promoting urinary excretion of toxins.

## NUTRITION & THE DETOXIFICATION SYSTEM

In addition to support for excretion, overall nutrition influences biotransformation in many other ways. Support for energy production, as well as generation of new enzymes (protein production), are vital during detoxification. Therefore, adequate intake of complex carbohydrates, energy-supportive fats, and high quality protein are essential for providing protective mechanisms against toxic damage.<sup>35</sup> Fats can be problematic, since many people consume too many unhealthy fats. Moreover, individuals undergoing toxic exposure may not efficiently absorb nutrients through the intestinal tract if they are also experiencing altered intestinal permeability. Therefore, provision of a highly bioavailable source of fats that can be used directly to support energy production is beneficial. The medium-chain triglycerides (MCTs) are fats that fit this profile.<sup>36</sup>

## PHYTONUTRIENT SUPPORT FOR BALANCED DETOXIFICATION ACTIVITIES

Nutrient support for all detoxification activities is essential to achieving healthy, balanced detoxification. Phytonutrients support detoxification through multiple mechanisms. Antioxidant activity supports Phase I specifically. Modulation of enzyme activity directly and induction of gene transcription of Phase I and II enzymes and Phase III proteins are additional mechanisms of phytonutrient regulation of detoxification.

Some phytonutrients support Phase I activity, such as indole-3-carbinol from broccoli, which provides modest support for the CYP1A enzymes. Overactivation of Phase I is a concern, however, and is associated with high, continuous levels of toxins that are known to be particularly effective at inducing Phase I activities. For example, smoked meats (heterocyclic amines formed on charbroiled beef) and dioxins have all been shown to over-induce CYP1A enzymes, and even low doses of these compounds induce CYP1A much more effectively than the modest support provided by indole-3-carbinol.<sup>37-39</sup>

Many phytonutrients also act as antioxidants and bind reactive intermediates and ROS from Phase I reactions. Therefore, nutrient modulators minimize damage caused by reactive intermediates, which may be one reason for the association between diets high in fruits and vegetables and reduced susceptibilities to many health conditions.<sup>40</sup>

Phytonutrients particularly beneficial for Phase II activities include catechins (from green tea and grapes), ellagic acid (from pomegranate and many berries), xanthohumol (from

hops), and glucosinolates (found in crucifers, such as watercress and broccoli).<sup>41</sup>

## NUTRIENTS THAT SUPPORT DETOXIFICATION

Provision of macronutrients is extremely important in a detoxification program. Water fasting has many adverse health effects, including decreased energy production, catabolism of lean tissue, upregulation of Phase I activities with a concomitant increase in oxidative stress, and decreased levels of Phase II cofactors. Detoxification is an energy-dependent process that puts a metabolic burden on the body. Instead of decreasing nutrient support, a focused, high impact source of nutrients is essential. However, this source of nutrients should have a low allergenic potential so as to minimize inflammation due to food allergen reactions.

An 8-week study in women with fibromyalgia demonstrated that a diet low in food allergens supplemented with a phytonutrient-rich powdered supplement produced increased elimination of heavy metals and improved fibromyalgia symptoms compared to a standard American diet supplemented with rice protein powder.<sup>42</sup> A nutrient base that includes protein, carbohydrate, fiber, and fat is important to maintaining healthy metabolism during a detoxification program.

**Fiber.** Dietary fiber, such as isomalto-oligosaccharides (IMO), citrus pectin, and apple fiber, can benefit a detoxification program in many ways. Fiber supports intestinal mucosal cell barriers and improves beneficial colonic microbiota and bowel movements, which decrease toxic burden on the body and provide a first line of defense against toxins. Fiber promotes removal of the conjugated toxins that are excreted via bile and may decrease the absorption of some toxins.<sup>43-45</sup> Most notably, some fibers have been shown to directly bind toxins, thereby helping to remove potentially damaging toxins.<sup>45</sup>

**Protein.** Protein that provides methionine and cysteine in a highly absorbable form is of benefit to Phase II conjugation, as these amino acids can be used to generate the sulfation and glutathione cofactors. A high quality protein may also benefit those with toxic mercury burdens, since mercury exposure is associated with the depletion of specific amino acids that are precursors to neurotransmitters.<sup>46</sup> Methionine is also a component of S-adenosylmethionine (SAM), and is required for methylation (see page 5).

**N-Acetylcysteine (NAC).** NAC is a precursor of L-cysteine,

and L-cysteine is a substrate and the rate-limiting factor in glutathione synthesis. Glutathione is an important antioxidant, plays a major role in the detoxification of both endogenous and xenobiotic compounds, and is a chelating agent for heavy metals.<sup>19</sup> In the presence of a toxic load of metals or oxidative stress, the demand for glutathione increases and L-cysteine could be depleted.<sup>46</sup> Orally administered glutathione is poorly absorbed, and direct supplementation of glutathione does not seem to improve glutathione status and biomarkers of oxidative stress in humans.<sup>47</sup> On the other hand, supplementation of NAC replenishes L-cysteine and has been shown to boost the endogenous synthesis of glutathione.<sup>48</sup>

**Methionine, Choline, Vitamin B<sub>12</sub> & Folate.** Methylation is one of the conjugation reactions of Phase II detoxification.<sup>49</sup> The methyl donor SAM is a cofactor required to form methyl conjugates. Thus, nutrients that are involved in 1-carbon metabolism and the production and recycling of SAM are essential to support balanced biotransformation. These nutrients include, but are not limited to, methionine, choline, vitamin B<sub>12</sub>, and folate. Methionine is essential for the synthesis of SAM. Vitamin B<sub>12</sub>, folate, and choline provide support for homocysteine metabolism, which drives re-methylation of SAM.<sup>50</sup>

**Super Oxide Dismutase (SOD).** SOD is an endogenous antioxidant enzyme present in nearly all cells exposed to oxygen. It neutralizes the highly reactive radical superoxide (O<sub>2</sub><sup>-</sup>) to oxygen or hydrogen peroxide (which is further degraded by other endogenous enzymes such as catalase), thereby protecting cells from oxidative stress and superoxide toxicity. Different forms of SOD exist in humans, including cytosolic (Cu, Zn-SOD), mitochondrial (Mn-SOD), and extracellular (EC-SOD).<sup>51</sup>

SOD can be extracted from dietary sources. Cantaloupe melon (*Cucumis melo* L), for example, is rich in multiple forms of SOD (Fe-SOD; Cu, Zn-SOD; and Mn-SOD). However, SOD via oral consumption is denatured by gastric acid in the stomach. Encapsulating SOD using microencapsulation technology may enable the enzyme to reach the intestinal tract. Interestingly, oral consumption of the encapsulated melon SOD concentrate in animal models has been shown to increase endogenous antioxidant enzymes (SOD, glutathione peroxidase, and catalase) in the liver, adipose tissue, and heart tissue.<sup>52-55</sup> This suggests that this specially formulated SOD may potentially boost the body's endogenous antioxidant capacity.

**Ellagic Acid.** Ellagic acid, a phenol antioxidant found in many plant foods (e.g., pomegranate), may act directly against some metal toxicity (e.g., nickel) by chelating the metal and promoting its excretion, thereby providing protection from liver damage and oxidative stress.<sup>56</sup>

Ellagic acid promotes balanced detoxification via several mechanisms. It induces expression of glutathione synthesizing enzymes, GST, and other Phase II enzymes.<sup>57-59</sup> Reports that ellagic acid modulates CYP enzymes suggest a role for the compound in Phase I detoxification pathways as well. Ellagic acid has demonstrated direct binding to toxins, such as benzo[a]pyrene-related compounds from air pollution, rendering them non-toxic and promoting their excretion.<sup>60,61</sup>

**Green Tea Catechins.** A large body of literature studying the health benefits of catechins is available. These data suggest that catechins—a class of flavonoids found in high concentrations in green tea extracts—are bifunctional modulators that provide many beneficial activities, including induction of Phase I CYP enzymes and Phase II glucuronidation and glutathione conjugation enzymes.<sup>62</sup> Cell-based assays demonstrated that catechins induce receptor-mediated gene expression of enzymes involved in metabolic detoxification.<sup>63</sup> Interestingly, some catechins have been shown to induce Phase I activities while others selectively inhibit Phase I activities.<sup>64-66</sup> A cell-based study showed that catechins inhibited the over-induction of Phase I activities by a toxic substance, but were able to moderately induce Phase I activity themselves when the toxin was not present.<sup>67</sup> This capacity of catechins to regulate expression and activity of Phase I enzymes suggests that this natural compound is effective for supporting a balanced detoxification system.

The molecular structure of catechins enables these compounds to act as chelators, binding to reactive intermediates produced by Phase I that are not immediately conjugated by a Phase II reaction, which is another mechanism by which this class of flavonoids may promote balanced detoxification.<sup>68,69</sup>

A cup of tea contains between 100 mg to 200 mg catechins, which is suggested to account for at least 90% of the observed beneficial effects of green tea.<sup>60,67</sup> Green tea catechins also have been shown to promote healthy intestinal microbiota and pH and to support healthy bowel function—qualities that further support detoxification.<sup>68</sup>

**Glucosinolates.** Glucosinolates are sulfur-containing glycosides found in cruciferous vegetables. Intact plant cells contain the enzyme myrosinase that is physically separated from glucosinolates.<sup>69</sup> When the plant cells are damaged as a result of chopping or chewing, myrosinase is released and interacts with glucosinolates, forming the biologically active compounds termed isothiocyanates.<sup>70</sup> Different types of glucosinolates form different types of isothiocyanates. For example, watercress (*Nasturtium officinale*) contains high levels of gluconasturtiin that is converted into phenethyl isothiocyanate (PEITC), and broccoli (*Brassica oleracea*) is rich in glucoraphanin that is metabolized to sulforaphane. These isothiocyanates have been shown to be potent inducers of antioxidant and Phase II detoxification enzymes via the Keap1/Nrf2 pathway.<sup>71-73</sup> Plant myrosinase is inactivated by heat (e.g., cooking) and thus cooked cruciferous vegetables are devoid of myrosinase activity. However, research has shown that the human gut contains myrosinase-producing bacteria capable of converting some glucosinolates to isothiocyanates.<sup>74,75</sup>

**Xanthohumol.** Xanthohumol is the most abundant prenylated flavonoid in the flowers of hops. Preclinical studies have found that xanthohumol exhibits a broad spectrum of biological activities, including suppression of nitric oxide production, down-regulation of IL-12, and inhibition of lipopolysaccharide-induced responses.<sup>76,77</sup> Further, xanthohumol upregulates antioxidant and Phase II detoxification enzymes via the Keap1/Nrf2 pathway.<sup>78</sup> Xanthohumol has also been shown to act as a selective kinase response modulator (SKRM) and inhibit NF- $\kappa$ B signaling pathways.<sup>79-81</sup>

**Silymarin.** Silymarin (from milk thistle) has been used in traditional medicine throughout the world as a hepatoprotectant, and recent studies demonstrate effective liver-protectant functions of silymarin.<sup>84,85</sup> Randomized, controlled clinical trials have demonstrated a beneficial effect of 420 mg silymarin per day on indices of liver function in patients with various etiologies of acute hepatitis. Other studies have found similar benefits for patients with liver disease—including those exposed to toxic levels of industrial phenolics, such as loloene.<sup>85,86</sup> Silymarin has also been shown to increase serum glutathione and glutathione peroxidase in patients with liver disease and induce glutathione transferase activity in animals.<sup>82,83</sup> Silymarin glycosides exhibit potent antioxidant activity, and therefore silymarin may act as a bifunctional modulator.<sup>68</sup>

**Artichoke.** Traditional medicine has long used artichoke extract (*Cynara scolymus*) for liver support, and several bioactives have been identified, including chlorogenic acid, cynarin, caffeic acid, and luteolin.<sup>80,70</sup> Results from cell-based studies suggest that artichoke has potent antioxidant activity and attenuates toxin-induced reduction of glutathione reserves.<sup>71,72</sup> Artichoke leaf extract administration for two weeks protected rats against oxidative stress-induced hepatotoxicity.<sup>73</sup> Consumption of encapsulated artichoke extract has been shown to increase the absorption of these bioactives in humans, resulting in the production of beneficial metabolites such as ferulic acid.<sup>84</sup> Ferulic acid, chlorogenic acid, and cynarin provide strong antioxidant protection, which may account for some of their health-promoting activities.<sup>80,70</sup>

## CLINICAL APPLICATIONS

Optimizing the body's ability to manage and excrete toxins is essential for optimal health. Several recent reviews have discussed targeted, nutrient-based detoxification intervention therapies for patients with CFS, FM, MCS, and Parkinson's disease, as well as in apparently healthy individuals.<sup>37,75-80</sup>

Decreasing exposure to toxins is extremely important in all programs. However, minimizing toxin exposure is only one part of a successful strategy to decrease susceptibility to toxicity-related conditions. Low-allergy-potential, targeted nutrition that provides the full spectrum of cofactor precursors, support for excretion, and bifunctional inducers for balanced Phase I and Phase II biotransformation may promote balanced detoxification and health throughout life.

**Table 2.** Clinical Considerations for Programs to Support Biotransformation

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| <ul style="list-style-type: none"><li>• Decrease exposure to toxins</li><li>• Provide nutritional support for biotransformation and conjugation reactions</li><li>• Provide nutritional support for energy production during detoxification programs</li><li>• Support endogenous antioxidant mechanisms for biotransformation and heavy metal detoxification</li><li>• Provide methyl donors to promote methylation pathways</li><li>• Support healthy digestion and excretion</li></ul> |
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