



# TECHNICAL BULLETIN

## DETOXIFICATION CLINICAL PERSPECTIVE

### INTRODUCTION

The human detoxification system is driven by a complex network of enzymatic reactions and is regulated by a large number of mechanisms. Since these mechanisms are affected or modulated by numerous external and internal factors, it is now recognized that each individual has a particular “detoxification profile” defined by his/her own specific environmental and genetic conditions. The variability in individual detoxification capacity could explain why, in a large population exposed to the same levels of carcinogens, some persons develop cancer while others do not.<sup>1</sup>

The steady developments in the field of toxicology and detoxification continue to provide the clinician additional tools for the identification of factors that affect the individual’s detoxification pattern. They also continue to expand the healthcare provider’s ability to apply programs that improve the outcome of diseases affected by dysfunctional detoxification.<sup>2,3</sup>

This Technical Bulletin discusses clinical aspects of detoxification, clinical tools, and the nutrition support of the detoxification process. More in-depth reviews on the subject are recommended.<sup>4,5</sup> The biochemical principles of detoxification are described in the first Technical Bulletin of this series: Detoxification - Biochemistry.

### CLINICAL PERSPECTIVE

The extensive research in the past few years on the individual’s ability to detoxify multiple xenobiotics has significantly increased our clinical understanding of detoxification.<sup>6,7</sup> For example, it has provided information about the damaging effect(s) of alcohol and smoking, which result in an increase of highly reactive compounds and free radical formation. Most significantly, it has pointed out the key role that nutrition has in the multiple mechanisms involved in detoxification, both as a source of the essential cofactors and conjugation moieties, and providing support for the production of the energy required by those mechanisms.

## CLINICAL PRESENTATION OF TOXICITY

Several warning signs may be indicative of toxicity in an individual, including:

- A history of increasing sensitivity to exogenous exposures, odors, or medications
- Abundant use of medications or potentially toxic chemicals in the individual's environment
- Musculoskeletal symptoms (similar to fibromyalgia)
- Cognitive dysfunction
- Unilateral paresthesia
- Autonomic dysfunction
- Recurrent patterns of edema
- Worsening of symptoms after anesthesia or pregnancy
- Unusual responses to medications or supplements.

## CONDITION ASSOCIATED WITH IMBALANCED DETOXIFICATION

The conditions mentioned below are just some examples of those in which improper detoxification of exotoxins and/or endotoxins has been found to be involved.

### CHRONIC FATIGUE and RELATED SYNDROMES

Researchers have suggested the existence of a relationship between the symptoms presented by Chronic Fatigue Syndrome (CFS) patients and impaired detoxification resulting from toxic exposure.<sup>8</sup> In two separate studies, reducing toxic insults through diet and lifestyle modification, along with nutritional support of detoxification pathways, achieved significant improvement of symptoms in patients affected by CFS.<sup>9,10</sup>

### MULTIPLE CHEMICAL SENSITIVITY (MCS)

MCS is an acquired disorder characterized by fatigue and a wide range of other symptoms resembling CFS and Fibromyalgia (FM), which occur as a result of low-level chemical exposure.<sup>11,12</sup> Although MCS is a controversial and complex condition with no specific diagnostic tests or criteria, it appears to be related to the ability of the individual to manage the low-level exposure to environmental compounds.<sup>13</sup>

### ENCEPHALOPATHY and PANCREATITIS

These two syndromes share a commonality: patients' histories include exposure to xenobiotics, typically various organic solvents and/or their fumes. Chronic toxic

encephalopathy, resulting in lowered detoxification capacity, is more likely to occur in individuals with a genetic defect in one of the glutathione transferase enzymes.<sup>14</sup> In many patients who have been exposed to diesel fumes, paint solvents, or trichloroethylene, idiopathic pancreatitis can be associated with upregulation of the Phase I cytochrome P450 enzymes.<sup>15</sup>

#### NEUROLOGICAL DISEASES

The combination of genetic susceptibility, reduced detoxification capacity, and increased exposure to neurotoxins creates the right situation, over time, for development of a clinical disease. As an example, the impaired ability of some individuals to metabolize sulfur-containing xenobiotics may leave them at higher risk for neurotoxicity when exposed to these types of compounds.<sup>16</sup> In fact, this connection has been demonstrated in some cases of Alzheimer's, Parkinson's, and other motor neuron diseases.<sup>17,18</sup> Moreover, a detoxification intervention approach with strong nutritional support was beneficial in cases of early onset Parkinson's Disease.<sup>19</sup>

#### AUTOIMMUNE DISEASES

Research in recent years suggests a possible role of impaired detoxification in Lupus erythematosus and rheumatoid arthritis.<sup>20</sup>

#### GENETICALLY INDUCED DISORDERS

Gilbert's Syndrome (GS) is a genetically induced, nutritionally exacerbated metabolic disorder caused by a malfunction of a key enzyme involved in glucuronidation, a major Phase II conjugation reaction. Recent observations indicate that patients affected by GS may be predisposed to bioactivation and potential drug toxicity.<sup>21</sup> Some studies have shown improvement in GS symptomatology through the use of a nutritional support approach.<sup>22</sup>

### OTHER FACTORS ASSOCIATED WITH IMPAIRED DETOXIFICATION

#### DYSBIOSIS

The many species of beneficial bacteria that reside in the human large intestine produce endotoxins as the end result of their metabolic activity. In cases where colonic bacteria become imbalanced, undesirable species that produce damaging metabolites may appear. The state of imbalance of beneficial organisms in the colon – or dysbiosis –

may be caused by the presence of bacterial species such as *Klebsiella pneumoniae*, *Escherichia coli*, and *Candida albicans*. Studies have suggested the association between metabolites of fungi and undesirable bacteria residing in the intestine and conditions such as autism,<sup>23</sup> multiple sclerosis, depression, and psychosis.<sup>24</sup>

#### HEAVY METAL EXPOSURE

Heavy metals such as lead, mercury, cadmium, arsenic, nickel, and aluminum accumulate in the body primarily as a result of exposure to a contaminated environment.<sup>25</sup> Toxic metals may be present in industrial waste spreading to water, air, and soil. Pipes, pesticides and cigarette smoke are also common sources of toxic metals. The presence and consequential accumulation of toxic metals has been demonstrated to result in neurological impairment, influence neurotransmitter production and utilization, as well as affect the kidneys and the immune system. Metals can be stored in various tissues and most likely cause damage to the depot structures of the affected areas.<sup>26,27</sup> Additionally, the presence of these heavy metals may lead to impairment of other detoxification pathways, causing poor elimination of xenobiotics that use these pathways, and thus intensify their damaging effects. Metals that have nutritive roles in the body, such as iron, copper, and manganese, may also become toxic at high levels.

## CLINICAL TOOLS

### TOOLS TO ASSESS DETOXIFICATION IMPAIRMENTS

#### CHALLENGE TESTING

Challenge methods are valuable to assess the “detoxification ability” of an individual, that is, to evaluate his/her functional capacity to detoxify or respond to a toxic compound. While these tests are very useful, it is important to remember that:

- no one single test by itself is capable of assessing functional detoxification status,
- the level of toxin and the individual’s unique biochemistry are the two most important factors in interpreting the results of these determinations.

Challenge tests are ideal non-invasive tests and are currently the most accepted clinical tools used to assess functional detoxification. These tests measure the individual’s metabolic capacity of various detoxification pathways as he/she is challenged with particular compounds called probe substances.

A challenge test involves the oral ingestion of a defined amount of the probe substance, usually a drug with a well-known detoxification pathway, and the measurement of its metabolites in two or three samples of blood, urine, or saliva taken at specified times.<sup>28</sup>

Some examples of probe substances are:

Caffeine – used to measure the activity of the CYP1A2 enzyme, which is key for the detoxification of many environmental toxins such as polyaromatic hydrocarbons in pesticides, pro-carcinogens in cigarette smoke, and polyaromatic amines in charbroiled beef.<sup>29,30</sup>

Acetaminophen – used to assess the functionality of the glucuronidation and sulfation conjugation reactions.<sup>31</sup> If these pathways are compromised, the acetaminophen is metabolized through an alternate pathway with the formation of acetaminophen mercapturate as the end product.

Aspirin – is detoxified by conjugation with glycine (considered to be one of the most important amino acids in humans),<sup>32</sup> and is used to assess the functionality of this amino acid conjugation reaction. Alternatively, benzoic acid can be used with the same purpose in subjects with salicylate sensitivity.<sup>33</sup>

#### IMPORTANT COFACTORS IN DETOXIFICATION

Cofactor	Role
Sodium sulfate	Provides inorganic sulfate necessary for sulfation conjugation (Phase II). This pathway is important in the detoxification of many drugs.
Amino acids: Glycine	Considered to be one of the most important amino acids in humans. One of the cofactors used in Phase II amino acid conjugation reactions. Also used in the synthesis of glutathione.
Methionine, cysteine N-acetylcysteine	Sulfate donors for sulfation reaction (Phase II). Contributes to glutathione synthesis, which protects against reactive oxygen species such as hydrogen peroxide.
Glutathione	Tripeptide that has a key role in detoxification and excretion of many xenobiotics (such as toxic metals) and metabolically produced oxidizing agents. Also acts as an antioxidant by scavenging free radicals.
Vitamins and minerals: Carotenoids Vitamin C Vitamin E Zn, Mn, Cu, Se	These vitamins and minerals act as antioxidants, and thus help prevent cellular damage caused by oxidizing agents such as free radicals. An example is inflammation, which results in an increase of free radical production that, if not adequately controlled, can react with polyunsaturated fatty acids of the cell membrane and lead to cellular damage.

## TOOLS TO ASSESS INCREASED TOXIC LOAD

### ORGANIC COMPOUNDS EXPOSURE

Assessment of exposure to organic compounds can be made by simply using a patient questionnaire. Questions about working and living conditions, as well as lifestyle habits, often unveil clues about possible sources of direct contact with solvents or exposure to solvent fumes.

Several types of laboratory tests are available to assess specific toxic compounds. For example, immunological methods are used to test volatile organic compounds such as formaldehyde, since their hapten-like actions induce tissue-specific autoimmune reactions.<sup>34</sup>

### HEAVY METAL ASSESSMENT

Some of the most used tests for presence of toxic metals are:

**Hair Analysis** – Hair acts as a depot of toxic metals, therefore, its analysis provides information of element storage over time. Studies have demonstrated correlation between element hair concentration, environmental exposure, and pathological effects.<sup>35,36</sup> Hair analysis is an excellent indicator of long-term risk as well as a barometer for early, chronic exposure, often reflecting excess exposure before symptoms appear. Hair analysis is a low cost, non-invasive procedure; the fact that concentrations of elements in hair are often up to 300 times higher than those of serum or urine make this an excellent medium for analysis. However, this is still considered a “screening test” and should be followed by confirmatory testing in blood or urine.

**Blood analysis** – Due to the effective clearance mechanisms in the blood, the level of toxic metals in it are usually transient in nature. Therefore, measurement of metal levels in blood is only informative about what has been recently absorbed (hours or days). Metals may be analyzed in plasma, serum, or red blood cells.

**Urine analysis** – Urine is a good indicator of recent exposure to metals (days-weeks), showing what the body is currently excreting. “Provocative urine testing” is a special technique useful to determine toxic element deposition and to monitor its excretion as a response to treatment. The procedure consists of obtaining a urine sample before and after administration of a strong excretory inducer, and calculating the amount of stored toxic elements from the resulting analytical measurements.

### BACTERIAL/YEAST/FUNGAL IMBALANCES

Several laboratory techniques are used to determine the presence of abnormal amounts of potential pathologic bacteria and other organisms. The most commonly used include:

- microbiological identification of potentially pathogenic bacteria and yeast in stool,
- identification of bacterial by-products: the urine indican (Obermeyer) test estimates bacterial activity in the small and large intestines by measuring the amount of indole generated by the bacterial degradation of tryptophan,
- immunological methods to quantify bacterial and yeast antibodies.

## THERAPIES to OPTIMIZE DETOXIFICATION

The primary therapies employed to improve detoxification may be used individually but most frequently are used together to complement one another. They include:

- Decrease the exposure to the toxin source. This is a straightforward approach once the toxin(s) is identified, and it usually involves lifestyle changes.
- Maximize excretion of the toxin. For example, metal chelation with various agents is used to treat chronic metal intoxication (such as mercury).<sup>37,38</sup>
- Provide nutritional support, either generally or for specific detoxification pathways. More information on this approach is provided in the next section.
- Re-establish balance in cases of bacterial flora imbalance, through the use of probiotic and prebiotic supplementation. More information on this approach may be found in another Technical Bulletin: Remove, Replace, Reinoculate, Repair: The 4R Gastrointestinal Support Program.

## NUTRITIONAL SUPPORT for DETOXIFICATION

### BASIC NUTRITIONAL INTERVENTION

The basic intervention to support detoxification consists of a nutritional program that ensures provision of factors required by the detoxification pathways, plus supplementation with antioxidant nutrients. The diet should meet the following requirements:

- Provide the daily nutritional needs of the patient, including high-biological-value protein.
- Provide increased amounts of those nutrients directly involved in the enzymatic transformation of toxins (detoxification steps), such as cofactors and conjugation moieties.
- Provide adequate hydration to promote the excretion of the biotransformed toxins.
- Exclude foods containing potential toxins, such as food allergens.

- Optimize body composition to eliminate the toxins accumulated in adipose tissue, especially advisable in cases of overweight individuals. Generally, this intervention should only proceed after other basic nutritional needs are met.

## SPECIFIC NUTRITIONAL INTERVENTION

The decisions about intervention to support specific dietary insufficiencies and/or impaired detoxification pathways are made based upon diagnosis. Diagnosis is based on patient's symptomatology, physical examination, and laboratory results as well as on the insight provided by patient's history and environment.

Signs and symptoms of impaired detoxification may suggest:

- Nutritional insufficiencies, as assessed by patient's history, physical exam, and/or direct laboratory measurement, may result in the impairment of one or more detoxification pathways. This may be improved by supplementation with specific nutrients or cofactors:
  - Impaired sulfation, requiring adequate amounts of dietary sulfur-containing compounds such as sulfur-containing amino acids and inorganic sulfate.<sup>39</sup>
  - Impaired glucuronidation, requiring magnesium, and abstention from smoking, fasting, possibly high fructose intake.
  - Impaired glutathione conjugation, requiring vitamins B6 and B12, magnesium, and folate.
  - Impaired amino acid conjugation, requiring specific amino acids such as glycine or taurine.
- Inadequate antioxidant support – e.g., in individuals with increased detoxification Phase I to Phase II ratios. This results in an increased generation of reactive intermediate metabolites (which are normally generated by the reactions of Phase I pathways but are readily transformed into soluble molecules by the conjugation reactions in Phase II pathways).
- Inadequate phytonutrient support for upregulation of Phase II detoxification activities. For example, the cruciferous vegetable family may provide protection against carcinogen exposure by inducing glutathione S-transferase activity.<sup>40</sup> Below is a list of phytonutrients that have a modulatory effect on detoxification activities.

## IMPORTANT PHYTONUTRIENTS IN DETOXIFICATION

Compound	Action mechanism	Plant Sources
Naringenin	Powerful inhibitor affecting the activity of Phase I cytochrome P450 enzymes: CYP1A2 and CYP3A4. A single glass of grapefruit juice is capable of decreasing up to 30 percent of these activities for a 12- to 24-hour period. <sup>41</sup> This inhibitory capability can be beneficial to enhance the availability and clinical activity of some drugs, but can also increase the toxicity of some other compounds that use the same enzymes.	Grapefruit, watermelon
Rutin, Quercetin	Chemically related compounds that inhibit Phase I cytochrome P450 activities. They also act synergistically with ascorbic acid and tocopherol, and protect against oxidation injury induced by glutathione deficiency. <sup>42,43</sup>	Tea, onions, some citrus foods, buckwheat
Tangeretin, Nobiletin	Flavonoids shown to induce the Phase I cytochrome P450 enzyme CYP3A4. <sup>44</sup>	Orange juice
Rosmanol, Ursolic Acid, Carnosol, Carnosic Acid	Polyphenolic compounds with high antioxidant activity. They have been shown to scavenge inflammation-induced nitric oxide and peroxynitrite radicals. <sup>45</sup>  Carnosol and carnosic acid also stimulate the glutathione-S-transferase and quinone reductase activity in Phase II detoxification, and suppress DNA damage from xenobiotics. <sup>46</sup>	Rosemary (Rosemarinus officinalis)
d-Limonene, Mormilin	These compounds induce the glutathione conjugation and glucuronidation activities of Phase II detoxification. The support of glucuronidation may account for their ability to improve resistance to glutathione depletion by prolonged use of acetaminophen. Their support of both Phase II activities may explain their ability to inhibit tumorigenesis in animal studies. <sup>47</sup>	Citrus foods, especially lemon
Curcuminoids	These compounds have a wide range of biological activities: they are potent antioxidants, anti-inflammatory agents and anti-mutagens. They can also act as inducers of glutathione production and glutathione-S-transferase activity, and may inhibit some of the Phase I cytochrome P450 activities. <sup>48,49</sup>	Turmeric (Curcuma longa)
Indole-3-carbinols	These compounds inhibit the Phase I cytochrome P450 CYP1A1 and CYP1A2 activities. <sup>50</sup> They also have the capability of enhancing Phase II glutathione pathways, thus providing a more efficient means to clear xenobiotics.	Vegetables of the Brassica family: cabbage, broccoli, brussel sprouts

In conclusion, our increased exposure to exogenous toxins from the environment and to a larger number of endogenous toxins from drug metabolism and dysbiosis has emphasized the significance of the human detoxification system. Differences among individual detoxification capacities based upon genetic makeup, environmental exposure, and nutritional status can have a tremendous effect upon susceptibility to a wide range of diseases. Therefore, the ability to measure an individual's detoxification capability, and apply a nutritional approach to detoxification, are key elements in assessing and improving overall health.

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