

Detoxification

IS TOXIN EXPOSURE CLINICALLY RELEVANT?

As many as 80,000 commercial and industrial chemicals are now in use in the United States, with hundreds more introduced into the marketplace on a weekly basis.^{1,2} Particularly troubling is the lack of information we have for the health effects that most of these substances have at chronic low-dose exposure. Furthermore, the effect of exposure on multiple substances simultaneously, which is the norm, is essentially unknown.³ For example, a recent study by the Agency for Toxic Substances and Disease Registry (ATSDR) found that when examining the components of 15 combinations and how they may interact, they predicted that 41% of them would have additive effects, 20% would have synergistic effects, but for 24% they did not have even the minimum information necessary to make a prediction. It has been estimated that at current funding levels, it would take 1,000 years to adequately document the health effects of the chemicals commonly encountered in commerce and industry.⁴ We know that considering the effect of one chemical at a time is no longer sufficient. The Centers for Disease Control (CDC) published data on the levels of selected persistent organic pollutants (POPs)—a category of toxins which includes dioxins, phthalates, PDBEs, PCBs, etc.—and found that among a representative sample of the US population, some toxins were present in essentially every individual over the age of 12, including, for example, p,p'-DDE and hexachlorobenzene.⁵ An analysis of NHANES data found up to a 38-fold adjusted increase in risk for diabetes prevalence in those with the highest levels of 6 POPs,⁶ and increased risk has also been documented for cardiovascular disease,⁷ insulin resistance, impaired neurological development, learning and attention deficit disorders, endometriosis, and deficits in the hypothalamic-pituitary-thyroid axis^{8,9,10,11} (Figure 1 shows the increasing concentration of PBDEs (polybrominated diphenyl ethers) in breast milk).¹² While very little data for humans is available, current evidence suggests that PDBEs are likely to be developmental neurotoxins, and are likely to have synergistic effects with similar chemicals.¹³

In addition to exogenous toxins such as POPs and heavy metals, a number of endogenous substances also require efficient functioning of detoxification enzymes to prevent a build-up of harmful metabolites. For example, endotoxins from bowel flora have been associated with depression, chronic fatigue, inflammatory bowel disease, and atherosclerosis, effects partly influenced both by bacterial species as well as intestinal permeability.^{14,15,16,17,18} Also, catechol estrogens and estrogen quinones are estrogen derivatives associated with oxidative damage and reproductive tissue cancers, which accumulate due to alterations in enzymatic activity.^{19,20} Other examples are the build-up of methylmalonic acid and homocysteine—both metabolic by-products known to have vascular, renal, and neurological toxicity, consequences of genetic susceptibility and poor B vitamin status.^{21, 22, 23, 24}

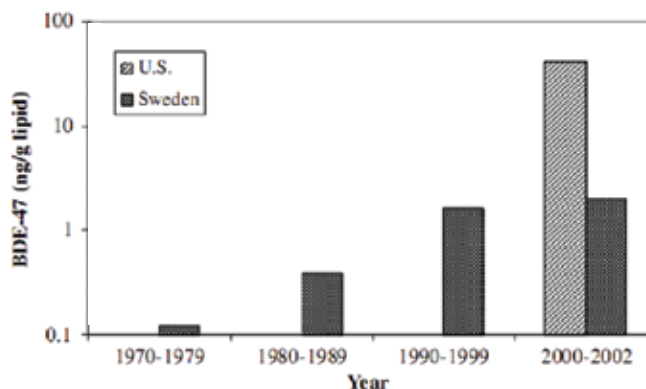


Figure 1* Increasing concentration trend of one of the most frequently-detected polybrominated diphenyl ether (PBDE) congeners for breast milk samples collected in Sweden and United States. Regulations proposing the banning of PBDE in consumer products exist in some European countries, based primarily on the results of biomonitoring studies. Proper interpretation of these data, however, requires careful consideration of dose, duration of exposure and toxicity.

HOW DO TOXINS CAUSE DAMAGE?

Damage is caused through a variety of mechanisms, but most toxins do so by increasing oxidative stress, poisoning enzymes, directly damaging DNA or cellular membranes, or acting as endocrine disruptors. For example, the toxic metal cadmium increases oxidative damage by both causing the formation of free radicals such as H_2O_2 , O_2^- , and OH , as well as by directly poisoning several enzymes which reduce oxidative stress, including catalase (CAT), glutathione reductase (GR), as well as the most abundant cellular antioxidant, glutathione (GSH).^{25, 26, 27} This is a fairly common mechanism for heavy metal toxicity (See Figure 2).

An example of enzyme poisoning is the displacement of zinc with lead in the active site of the enzyme delta aminolevulinic acid dehydratase (ALAD), leading to a variety of behavioural and neurological abnormalities.^{28,29} The toxic metal, arsenic, has been shown to disrupt a number of hormonal pathways. It disrupts the thyroid hormone and retinoic acid receptors, and data from the 2003-2004 NHANES found elevated urinary levels of arsenic to be associated with the prevalence of Type 2 diabetes, likely by influencing genes associated with insulin sensitivity.^{30,31,32}

Another example of toxins causing hormone disruption is the class of substances known as phthalates, for which exposure has been shown to be widespread and growing.³³ They also provide a good example of how our detoxification system influences the

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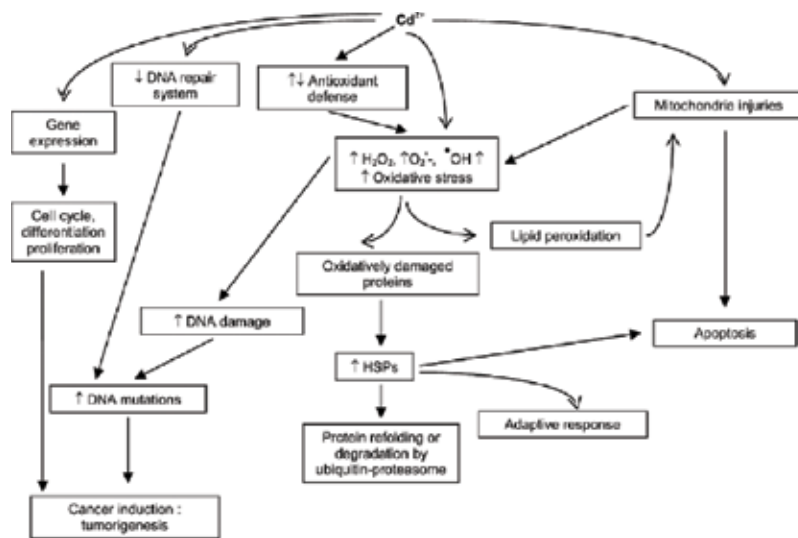


Figure 2 General scheme of biological consequence of cadmium intoxication in cells. Cadmium interferes with various important mechanisms such as gene expression, cell cycle, differentiation and proliferation. Cadmium gives rise to oxidative damage affecting DNA, proteins and membrane lipids. The induction of oxidative damage is associated with mitochondrial dysfunction, deregulation of intracellular antioxidants and apoptosis. Oxidative stress on proteins induces HSPs, associated with an adaptive response, initiation of protein refolding and/or degradation by ubiquitin proteasome. Oxidative damage to DNA leads to mutations and induction of cancer. The inhibition of some DNA repair pathways contributes to the rise in mutations and cancer.

toxicity of a substance. For many phthalates, biotransformation—the first phase in detoxification—creates metabolites (monoesters), which may be more reactive and harmful than the original substance. This is followed by phase II detoxification, in this case conjugation to glucuronic acid, which makes the monoesters less reactive and more easily excreted from the body.³⁴ For substances that follow this general pattern, it is thought that the greatest toxicity is in people who have very fast phase I enzymes, but very slow phase II enzymes, leading to greater production of reactive intermediates that are only slowly excreted from the body. Because this pattern is fairly common, broad support for phase II enzymatic reactions helps to promote healthy detoxification.

HOW DO WE TEST?

Unfortunately, no broad consensus exists for the testing of most toxins, although the availability of tests for detoxification function is increasing. And although most detoxification programs focus exclusively on the liver, the role of the GI tract is becoming increasingly recognized as crucial because the greatest portion of the toxic load on the liver comes from the bowel. For example, although the total content of the phase I family CYP3A in the entire human small intestine is only 1% of that in the liver, intestinal extraction of 3A substrates equals or exceeds that of the liver for some substances, at least partly because first-pass exposure to the intestinal enterocyte enzymes is likely to be greater, due to a slower flux through the cell.³⁵ And a bowel with healthy flora may protect the liver and stomach from injury from toxins, reduce the rate of diabetes and obesity by metabolizing endotoxins, and detoxify a number of chemicals, such as heterocyclic aromatic amines.^{36,37,38,39}

Thus, laboratory assessment should be a combination of assessing bowel health, exposure, and detoxification capacity. Small intestinal permeability is done primarily with the lactulose/mannitol test, and either culture or genomic analysis may be done to assess bowel flora. Toxic metal exposure is assessed in a variety of ways, including whole blood analysis, unprovoked and/or provoked (with a chelating agent) urine testing, and fecal testing. It is also important to distinguish acute from chronic exposure. For example, serum blood lead levels are reflective of acute exposure, but are not accurate for assessing body burden. Serum or tissue levels for many POPs are available through some laboratories, and although reference ranges are not available for toxicity for most of them, a comparison to the US average is available from the Centers for Disease Control (<http://www.cdc.gov/exposurereport/>). Lastly, a number of functional polymorphisms are known to affect function of detoxification enzymes, and probe substances may also be used to assess enzyme function. For example, caffeine administration allows for testing of the functional capacity of the phase I enzyme CYP1A2.⁴⁰

HOW DO WE TREAT?

To effectively eliminate toxins, the body goes through a series of processes that must occur in sequence. While detoxifying, it is important to support the body with adequate levels of key vitamins, minerals, amino acids, phytochemicals, and dietary fiber. The 7-Day ReduceXS™ Total Body Cleansing Program supports all of the steps involved in the body’s natural detoxification process, while at the same time nourishing and supporting the body’s systems. The first step of the 7-Day ReduceXS™ Total Body Cleansing Program involves using RestorX™ Intestinal Repair Nutritional Drink Mix—a natural functional food powdered drink mix—to help rest, heal, and restore your gut. RestorX™ helps eliminate internally-generated toxins and paves the way for the detoxification step using DetoxiCleanse™ Detoxification Nutritional Drink Mix. In Step 2 of the 7-Day ReduceXS™ Total Body Cleansing Program, DetoxiCleanse™ is used to fully support and enhance every process used by the body to transport, detoxify, and excrete heavy metals and other toxic substances from the body. This part of the week-long program is specifically designed to help eliminate toxins one has absorbed from the environment, such as heavy metals, pesticides, fumes from paints, solvents, and PCB’s. Additional liver and colon support is provided in the program.

Step 1: Support the gastrointestinal system (GI) with RestorX™ Intestinal Repair Nutritional Drink Mix

Given the importance of intestinal integrity and GI flora to efficient detoxification, support for GI health is essential to a comprehensive treatment plan. Elimination of harmful substances should be implemented as much as possible, including medications that increase intestinal permeability, as well as identifying and eliminating foods that may have the same effect. An elimination diet is often sufficient for most food sensitivities, although laboratory screening for celiac disease is warranted in

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many cases. Also, if bowel flora has been assessed, specific treatments may be needed to eradicate harmful flora before repopulation with probiotics. For more information on how to support the gastrointestinal system, refer to the *Intestinal Permeability & Rejuvenation Clinical Highlight*.

RestorX™ Intestinal Repair Nutritional Drink

A number of nutrients have been shown to repair damaged intestinal lining and regulate the integrity of tight junctions. In addition to containing many important daily vitamins and minerals, RestorX™ contains many of the nutrients shown to have specific benefit in restoring intestinal integrity:

- **L-glutamine** – long known to be the primary amino acid source for intestinal cells, glutamine has recently been shown to regulate intercellular junction integrity.⁴¹
- **Probiotics** – perhaps the greatest factor in determining intestinal integrity is the health of the microbial flora. Healthy microbial balance is essential to the maintenance of healthy digestion as well as disease prevention, the production of essential vitamins and co-factors, cidal activity against pathogenic bacteria, enhancement of intestinal barrier function through modulation of cytoskeletal and tight junctional protein phosphorylation, metabolism of toxins, reduction of GI inflammation, and the maintenance of immune homeostasis within the gut-associated lymphoid tissues (GALT).⁴²
- **N-acetyl glucosamine (NAG)** – given the breakdown of glycosaminoglycans that occurs with leaky gut, this nutrient provides a substrate for repair of these tissues. A trial in children with IBD showed significant potential for this nutrient.⁴³
- **Zinc** – zinc deficiency has been shown to disrupt tight junctions, alter membrane permeability, impair immune function, and cause intestinal ulceration.⁴⁴
- **Antioxidants** – (such as vitamin C, vitamin E, beta carotene, grape seed extract, and milk thistle extract)—not only protect the GI from oxidant damage, but also help with hepatic detoxification of compounds associated with intestinal dysfunction.
- **Quercetin** – this antioxidant appears to be critical to intestinal integrity, and acts through a number of mechanisms. These have recently been shown to include the assembly of a number of tight junction proteins zonula occludens (ZO)-2, occludin, claudin-1, and claudin-4).^{45,46}
- **Highly-digestible, low-allergy-potential protein (from organic-sprouted brown rice), and water-soluble fiber** – nutrients known to restore intestinal health, while eliminating sources of damage.

Step 2: Support detoxification with DetoxiCleanse™ Detoxification Nutritional Drink Mix

After completing Step 1 (days 1-4), the addition of broad support for detoxification pathways, particularly phase II, helps to metabolize and eliminate toxins from the body. Certainly, identification and removal of any acute exposure, such as lead or mercury, should be a part of a comprehensive treatment plan.

DetoxiCleanse™ Detoxification Nutritional Drink Mix

In addition to broad vitamin and mineral support, DetoxiCleanse™ has a number of nutrients known to support efficient detoxification.

- **Highly-digestible, low-allergy-potential protein (from organic-sprouted brown rice)** – amino acids protect and support the intensive work carried out by the liver and kidneys as they process heavy metals and other toxins for disposal.
- **N-acetyl cysteine** – because it has been shown to increase the urinary excretion of several toxic metals in proportion to body burden, especially mercury, this amino acid has been proposed for use in the biomonitoring of total load.⁴⁷ Additionally, it has been shown to increase hepatic glutathione, assisting in the detoxification of many compounds including acetaminophen.⁴⁸
- **Chlorella** – has been shown to reduce the absorption of specific toxins in the GI tract, such as dioxins, as well as the reabsorption of stored dioxins.⁴⁹ Recently, supplementation with chlorella has been shown to reduce the maternal transfer of dioxins in breast milk, as well as increasing its IgA content.⁵⁰
- **Dietary fibers (including sodium alginate, apple pectin, and guar gum)** – fiber has been found to improve postprandial glycemia and reduce absorption of endogenous and exogenous toxins.⁵¹
- **Milk thistle** – a powerful hepatoprotective agent, as well as a potent antioxidant against environmental toxins.^{52,53,54}
- **Broccoli powder** – supports several phase II metabolic pathways, and has been shown to increase 2-hydroxylation of estrogen, leading to reduced breast, prostate, and cervical cancer risk.^{55,56,57,58} Particularly important for those with specific glutathione transferase polymorphisms.⁵⁹
- **Lipoic acid** – a known antioxidant, lipoic acid is also a heavy metal chelator, and may restore glutathione levels in part by activating Phase II detoxification via the transcription factor Nrf2.⁶⁰
- **Green tea** – has been shown to protect the liver from CYP2E1-dependent alcoholic damage.⁶¹

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