

## Learning the Hard Way: L-Tryptophan, the FDA, and the Regulation of Amino Acids

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# LEARNING THE HARD WAY: L-TRYPTOPHAN, THE FDA, AND THE REGULATION OF AMINO ACIDS

I sit before you helpless, broke, alone and in unyielding, relentless pain . . . . For those who have died and for those of us who live with cloudy futures, the lack of action is too little, too late. We have needed help with our orphan disease. We need help now . . . . The U.S. Government is totally ineffective, and each agonizing day we grow more fragile.

For those who appear to be in remission, we rejoice. But we cannot say with certainty that anyone is cured as long as the exact cause and cure is not found.

For many of us, it is too late. We want life again.<sup>1</sup>

— Frances L. Thompson, EMS Victim

## INTRODUCTION

Reports of a mysterious, crippling illness surfaced in New Mexico during October, 1989.<sup>2</sup> Severe muscle pain, a marked thickening of the skin, fatigue, dyspnea,<sup>3</sup> and blood counts<sup>4</sup> well out of the normal range inflicted previously healthy people.<sup>5</sup> The mystery illness, eosinophilia-myalgia syndrome (EMS), today numbers over 1500 cases and thirty-eight con-

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<sup>1</sup> *FDA's Regulation of the Dietary Supplement L-tryptophan, 1991: Hearing Before the Human Resources and Intergovernmental Relations Subcommittee of the House Committee on Government Operations*, 102d Cong., 1st Sess. 26 [hereinafter *Hearing*] (statement of Frances L. Thompson, EMS Victim).

<sup>2</sup> Mary L. Kamb et al., *Eosinophilia-Myalgia Syndrome in L-tryptophan-Exposed Patients*, 267 *JAMA* 77, 77 (1992).

<sup>3</sup> Dyspnea is an "air hunger resulting in labored or difficult breathing, sometimes accompanied by pain." *TABER'S CYCLOPEDIA MEDICAL DICTIONARY* 547 (Clayton L. Thomas ed., 16th ed. 1989) [hereinafter *TABER'S*].

<sup>4</sup> Specifically, afflicted people had abnormal eosinophil counts. *The EMS Story*, *FIBROMYALGIA NETWORK: NEWSLETTER FOR FIBROMYALGIA, FIBROSITIS/CFS SUPPORT GROUPS* (Bakersfield, Cal.), Oct. 1993, at 5. An eosinophil is a type of white blood cell which "constitute[s] 1% to 3% of [the] white blood cell count." *TABER'S*, *supra* note 3, at 1020.

<sup>5</sup> *The EMS Story*, *supra* note 4, at 5.

firmed deaths.<sup>6</sup> Many of those who survive exist in states of incapacitating pain and disability.<sup>7</sup>

How did this disease come about? Although initially a baffling puzzle, researchers now understand that EMS was caused by contaminated L-tryptophan.<sup>8</sup> L-tryptophan is an amino acid which was sold as an over-the-counter dietary supplement in health food stores and pharmacies. Manufacturers advertised L-tryptophan as a "natural" sleep aid, a remedy for premenstrual syndrome, and a cure for depression.<sup>9</sup> In reality, it was neither natural nor approved by the FDA for these proposed uses.<sup>10</sup> Yet it was readily available.

The EMS epidemic brought about an awakening in the U.S. Government. The regulation of dietary supplements became a hot topic. Members of Congress introduced three bills in 1993 aimed at altering the standards for regulating dietary supplements in the Food, Drug, and Cosmetic Act.<sup>11</sup>

This Note examines the regulatory scheme necessary to prevent future public health threats related to dietary supplements, using the L-tryptophan-related EMS outbreak as an

<sup>6</sup> Regulation of Dietary Supplements, 58 Fed. Reg. 33,690, 33,690 (1993). Although the official number of cases reported is set at 1500, the National EMS Support Group alleges that EMS afflicts more than 5000 people. See Louis Jacobson, *Washington Update*, 25 NAT'L J. 1237, 1237 (1993).

<sup>7</sup> *The EMS Story*, *supra* note 4, at 5.

<sup>8</sup> Laurence Slutsker et al., *Eosinophilia-Myalgia Syndrome Associated with Exposure to Tryptophan from a Single Manufacturer*, 264 JAMA 213, 215 (1993).

<sup>9</sup> David L. Wilson, *Tracking Down a Killer*, 22 NAT'L J. 2491, 2491 (1990).

<sup>10</sup> Malcolm Gladwell, *'72 Diet-Pill Ban Ignored Until Recent Deaths*, WASH. POST, Sept. 5, 1990, at A1.

Tryptophan in a bottle is not a nutritional supplement. Tryptophan in dietary protein is an important nutrient. When you have it in protein it comes along with 21 other amino acids and you need the pattern, all of them, in order to utilize them to make your own protein.

When you take pure tryptophan in pills or in a bottle, it's not natural. Never in man's evolutionary history did he or she take an individual amino acid of that sort. It doesn't happen; it's not natural.

*Hearing*, *supra* note 1, at 71 (statement of Richard J. Wurtman, M.D., Professor of Basic Neuroscience and Director, Clinical Research Center, Massachusetts Institute of Technology).

<sup>11</sup> H.R. 1709, 103d Cong., 1st Sess. (1993); H.R. 2923, 103d Cong., 1st Sess. (1993); H.R. 509, 103d Cong., 1st Sess. (1993).

example. Part I discusses the history of government regulation of amino acids and other dietary supplements. Part II documents the EMS outbreak and how its cause — contaminated L-tryptophan — was discovered. Part III discusses pertinent aspects of proposed regulatory frameworks for amino acid dietary supplements and analyzes their efficacy. Part IV examines the Canadian framework for the regulation of food and drugs, which effectively insulated Canada from an outbreak of L-tryptophan related EMS. Part V proposes several alternatives for the effective regulation of amino acid dietary supplements.

## I. BACKGROUND

### A. A BRIEF OVERVIEW OF AMINO ACIDS

Amino acids — components of proteins — are one of the seven materials necessary for animal life.<sup>12</sup> In their natural form, amino acids result from the breakdown of proteins in the digestive process.<sup>13</sup> Enzymes first break proteins into polypeptides,<sup>14</sup> the basic structural components of protein molecules.<sup>15</sup> Eventually, through interaction with additional enzymes,<sup>16</sup> the polypeptides break down into dipeptides and finally amino acids.<sup>17</sup> Amino acids then diffuse through the mucous membranes of the intestine and into the body to carry out their functions.<sup>18</sup>

The body uses amino acids to produce hormones such as insulin, to produce enzymes, and to produce antibodies.<sup>19</sup> In

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<sup>12</sup> PAUL B. WEISZ, *THE SCIENCE OF BIOLOGY* 447 (3d ed. 1967). The other necessary materials are water, minerals, organic carbon, organic nitrogen, vitamins, and essential fatty acids. *Id.*

<sup>13</sup> *Id.* at 454.

<sup>14</sup> *Id.* These enzymes (trypsin, chymotrypsin, and pepsin) are proteinases. *Id.* A proteinase is "an enzyme that catalyzes the breakdown of native proteins." *TABER'S, supra* note 3, at 1500.

<sup>15</sup> WEISZ, *supra* note 12, at 846.

<sup>16</sup> These enzymes are called peptidases. *Id.* A peptidase is "an enzyme promoting the liberation of individual amino acids from a peptide, that is, an amino acid complex smaller than a whole protein." *Id.*

<sup>17</sup> *Id.* at 454.

<sup>18</sup> *Id.* at 456-57.

<sup>19</sup> *THE COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS COMPLETE HOME MEDICAL GUIDE* 306 (Donald F. Tapley et al. eds., rev. ed.

nature, eighty amino acids exist; the human body has the capacity to produce all but eleven of these.<sup>20</sup> The human diet must include all eleven of these "essential" amino acids: histidine, isoleucine, leucine, lysine, methionine, cystine, phenylalanine, tyrosine, threonine, tryptophan, and valine.<sup>21</sup> The essential amino acids exist in foods as varied as milk, meat, egg whites, grains, and legumes.<sup>22</sup>

Amino acid deficiencies are rare in the United States because Americans consume excessive amounts of protein.<sup>23</sup> Although health food stores carry protein and amino acid supplements, doctors state that amino acid supplements yield no proven benefits and can lead to nutritional imbalances.<sup>24</sup> The amino acids that consumers purchase in health food stores and pharmacies are not food proteins broken down into their component amino acids; instead, health food stores sell single amino acids isolated in a way not found in nature.<sup>25</sup> Amino acid supplements are available in pills and powders, and some are genetically engineered.<sup>26</sup>

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1989) [hereinafter COMPLETE HOME MEDICAL GUIDE].

<sup>20</sup> See TABER'S, *supra* note 3, at 74.

<sup>21</sup> *Id.* at 74. The nonessential amino acids (which can be produced by the body) are alanine, aspartic acid, arginine, citruline, glutamic acid, glycine, hydroxyglutamic acid, hydroxyproline, norleucine, proline, and serine. *Id.*

<sup>22</sup> COMPLETE HOME MEDICAL GUIDE, *supra* note 19, at 306.

<sup>23</sup> *Id.*

I would hasten to say that there is not a single person in America who is tryptophan deficient. It doesn't happen that you get isolated amino acid deficiencies.

*Hearing, supra* note 1, at 71 (statement of Richard J. Wurtman, M.D., Professor of Basic Neuroscience and Director, Clinical Research Center, Massachusetts Institute of Technology).

<sup>24</sup> COMPLETE HOME MEDICAL GUIDE, *supra* note 19, at 307. Genetic anomalies in amino acid metabolism are possible. These deficiencies may be in transport (in the renal tubule or gastrointestinal mucosa) or catabolic. THE MERCK MANUAL OF DIAGNOSIS AND THERAPY 2235 (Robert Berkow et al. eds., 1992). One of the best known catabolic diseases is phenylketonuria, in which the body does not correctly excrete excess phenylalanine. If treated through regulation of phenylalanine intake, phenylketonurics may follow the normal development pattern. Children inflicted with phenylketonuria may follow a normal growth and development pattern. If left untreated, phenylketonuria leads to often severe mental retardation. Approximately one in every 16,000 persons is afflicted. *Id.* at 2235-41.

<sup>25</sup> See *Hearing, supra* note 1, at 71.

<sup>26</sup> L-tryptophan was engineered by a process called fermentation. Edward

Tryptophan<sup>27</sup>, one of the essential amino acids, occurs naturally in cottage cheese, milk, turkey, bananas, meat, dried dates, peanuts, and all other protein-rich foods.<sup>28</sup> Once ingested, the body converts tryptophan into serotonin,<sup>29</sup> a neurotransmitter "thought to be involved in neural mechanisms important in sleep and sensory perception."<sup>30</sup> Studies have shown that tryptophan induces sleep<sup>31</sup> without the side effects

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A. Belongia et al., *An Investigation of the Cause of Eosinophilia-Myalgia Syndrome Associated with Tryptophan Use*, 323 NEW ENG. J. MED. 357, 360 (1990).

<sup>27</sup> For purposes of clarity the term "tryptophan" is used when referring to the amino acid in general terms. "L-tryptophan" is used when discussing the manufactured version of the amino acid.

<sup>28</sup> EARL MINDELL, UNSAFE AT ANY MEAL 190 (1987).

<sup>29</sup> Belongia et al., *supra* note 26, at 357. Serotonin is a neurotransmitter — a biochemical used to relay nerve impulses. The breakdown route of tryptophan follows two paths. One pathway is the kynurenine pathway, the other the serotonin pathway. *See Hearing, supra* note 1, at 66 (statement of Esther M. Sternberg, M.D., Chief, Unit on Neuroendocrine Immunology and Behavior, Clinical Neuroendocrinology Branch, National Institute of Mental Health, Alcohol, Drug Abuse and Mental Health Administration). One kynurenine, quinolinic acid, is a neurotoxin linked to Huntington's Disease, temporal lobe epilepsy, hepatic encephalopathy and coma. *Id.* at 126-27 (letter of Andrew Freese et al. to Frank Young (Feb. 1, 1988)). A large neutral amino acid transport system controls tryptophan access across the blood-brain barrier. Therefore, when tryptophan is ingested alone, absent competitive amino acids, the level of tryptophan in the brain increases, as well as the amount of serotonin and kynurenes in the body. *Id.* at 126 (letter of Andrew Freese to Frank Young (Feb. 1, 1988)).

<sup>30</sup> TABER'S, *supra* note 3, at 1665.

<sup>31</sup> *See* Ernest Hartmann et al., *Hypnotic Effects of L-tryptophan*, 31 ARCHIVES OF GEN. PSYCHIATRY 394, 394 (1974) (determining that L-tryptophan, administered in doses as small as one gram, significantly decreased sleep latency, and that those who took L-tryptophan presented no more side effects than those who took a placebo); *see also* C.F.P. George et al., *The Effect of L-tryptophan on Daytime Sleep Latency in Normals: Correlation with Blood Levels*, 12 SLEEP 345, 349 (1989) (finding that L-tryptophan ingestion reduces sleep latency); Cheryl L. Spinweber et al., *L-tryptophan: Effects on Daytime Sleep Latency and the Waking EEG*, 55 ELECTROENCEPHALOGRAPHY & CLINICAL NEUROPHYSIOLOGY 652, 660 (1983) (finding that "L-tryptophan is an effective daytime hypnotic which can facilitate sleep onset at clock times which do not coincide with biological sleep times"); Arthur Yuwiler et al., *Short-Term and Repetitive Administration of Oral Tryptophan in Normal Men*, 38 ARCHIVES GEN. PSYCHIATRY 619, 619 (1981) (finding that all research subjects became drowsy 20 to 30 minutes after tryptophan ingestion); *cf.* William J. Griffiths et al., *Tryptophan and Sleep in Young Adults*, 9 PSYCHOPHYSIOLOGY 345, 345 (1972) (finding that while a 7.5 gram dose of L-tryptophan reduces

of sleeping pills.<sup>32</sup> Although health manuals discuss the benefits of tryptophan and its breakdown product, they advise that one should exercise care before ingesting L-tryptophan.<sup>33</sup> For example, *The Complete Book of Vitamins and Minerals for Health* states that tryptophan could be useful for depression, insomnia, pain relief, and maybe even mania, but adds that "[s]ince relatively little is known about the safety of amino acids, be guided by your physician in the medical use of any of these substances."<sup>34</sup>

Why the caution? Although studies have shown amino acids may provide health benefits,<sup>35</sup> scientists have associated health dangers with their unfettered use.<sup>36</sup>

### B. REGULATORY HISTORY OF L-TRYPTOPHAN AND OTHER AMINO ACIDS

In 1945, the Food and Drug Administration issued a Trade Correspondence stating that any food with added amino acids must be labelled as being intended for special dietary use.<sup>37</sup>

the wakefulness time and increased amount of slow wave sleep in experimental subjects, a 12 gram dose decreased sleep latency but increased REM sleep). *But see* J. Gila Lindsley et al., *Selectivity in Response to L-tryptophan Among Insomniac Subjects: A Preliminary Report*, 6 SLEEP 247, 253 (1983) (finding that insomniacs can be divided into groups based on tryptophan response or lack thereof); A.N. Nicholson & Barbara M. Stone, *L-tryptophan and Sleep in Healthy Men*, 47 ELECTROENCEPHALOGRAPHY & CLINICAL NEUROPHYSIOLOGY 539, 544 (1979) (finding it impossible to establish the efficacy of L-tryptophan on nighttime sleep as compared to a placebo).

<sup>32</sup> Sleeping pills not only cause sleep after ingestion but continue to cause effects the following day. "At least, L-tryptophan bears a relationship to brain serotonin and to probable natural sleep mechanisms, whereas most standard hypnotic agents are general anesthetics used in small doses." Hartmann, *supra* note 31, at 397.

<sup>33</sup> JUDITH J. WURTMAN, *MANAGING YOUR MIND AND MOOD THROUGH FOOD* 21-23 (1986); *see also* THE COMPLETE BOOK OF VITAMINS AND MINERALS FOR HEALTH 235 (Sharon Faelten et al. eds., 1988) [hereinafter COMPLETE BOOK OF VITAMINS].

<sup>34</sup> COMPLETE BOOK OF VITAMINS, *supra* note 33, at 236.

<sup>35</sup> *See generally* Hartmann et al., *supra* note 31; Yuwiler et al., *supra* note 31; Spinweber, *supra* note 31.

<sup>36</sup> *See infra* notes 46-51, 86-92 and accompanying text.

<sup>37</sup> FDA Trade Correspondence No. 2A (Nov. 5, 1945), in VINCENT A. KLEINFELD & CHARLES W. DUNN, *FEDERAL FOOD, DRUG AND COSMETIC ACT: JUDICIAL AND ADMINISTRATIVE RECORD, 1938-1949*, at 748 (1950).

The Correspondence also stated that certain amino acid preparations for oral ingestion might be subject to regulation under the drug provisions of the Federal Food, Drug, and Cosmetic Act.<sup>38</sup>

Congress further regulated amino acids in 1958 by passing the Food Additives Amendment.<sup>39</sup> The Amendment included a definition of "food additive":

The term "food additive" means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958 through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use.<sup>40</sup>

The Amendment also contained a provision allowing manufacturers to petition to establish the safety of a food additive.<sup>41</sup> Absent a petition, a food additive is considered to be unsafe unless an exemption exists covering the additive or a regulation establishing its safety is promulgated.<sup>42</sup> To establish safety, the petitioner must file: (1) the name of and information about the food additive and its composition; (2) the conditions for

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<sup>38</sup> "Amino acid preparations offered for parenteral [other than oral] use fall in the category of new drugs." *Id.* at 749.

<sup>39</sup> Food Additives Amendment of 1958, Pub. L. No. 85-929, 72 Stat. 1784 (codified as amended at 21 U.S.C. §§ 301, 321, 331, 342, 346, 348, 451 (1988)).

<sup>40</sup> *Id.* (codified as amended at 21 U.S.C. § 321(s)(1988)). For more information regarding the generally recognized as safe (GRAS) requirement, see generally Frederick H. Degnan, *Rethinking the Applicability and Usefulness of the GRAS Concept*, 46 FOOD DRUG COSM. L.J. 553 (1991).

<sup>41</sup> Food Additives Amendment of 1958, Pub. L. No. 85-929, 72 Stat. 1784, 1785 (codified as amended at 21 U.S.C. § 348(b)(1) (1988)).

<sup>42</sup> *Id.* (codified as amended at 21 U.S.C. § 348(a) (1988)).



which its use would be proposed and for which it would be labelled; (3) the technical effect or physical effect the additive would be intended to produce and the quantity required to produce that effect; (4) a description of practicable methods for determining the quantity of additives in the food; and (5) reports of investigations on the safety of the additive for use.<sup>43</sup> No petitions were filed for L-tryptophan between 1958 and 1960.

In 1961, based on information available at the time, the Food and Drug Administration listed L-tryptophan and other amino acids as "generally recognized as safe (GRAS)"<sup>44</sup> as defined under the Food Additives Amendment. According to the Amendment, "[g]eneral recognition of safety requires common knowledge about the substance throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food."<sup>45</sup> Although the FDA listed L-tryptophan as GRAS for use as a dietary supplement in 1961, scientific evidence mounted throughout the 1960s that L-tryptophan and other amino acids were not as safe as initially presumed. Scientific studies found that the injection of serotonin,<sup>46</sup> a neurotransmitter which is derived from tryptophan, would lead to skin and joint fibrosis.<sup>47</sup> Researchers expressed concerns about potential carcinogenicity of L-tryptophan because tryptophan metabolites<sup>48</sup> and aromatic bladder carcinogens have

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<sup>43</sup> *Id.* (codified as amended at 21 U.S.C. § 348(b)(2) (1988)).

<sup>44</sup> 21 C.F.R. § 121.101(d)(5) (1970).

<sup>45</sup> *Id.*

<sup>46</sup> L-tryptophan breaks down into serotonin. *See Hearing, supra* note 1, at 66 (testimony of Esther M. Sternberg, M.D., Chief, Unit on Neuroendocrine Immunology and Behavior, Clinical Neuroendocrinology Branch, National Institute of Mental Health, Alcohol, Drug Abuse, and Mental Health Administration, Figure 1).

<sup>47</sup> *See* O.B. Gum et al., *Effect of Intra-articular Serotonin and Other Amines on Connective Tissue Proliferation of Rabbit Joints*, 3 *ARTHRITIS & RHEUMATISM* 477, 477 (1960) (finding that serotonin can cause proliferation of connective tissue and enlargement of knee joints in rabbits when combined with the monoamine oxidase inhibitor iproniazid); Richard A. McDonald et al., *Dermal Fibrosis Following Subcutaneous Injections of Serotonin Creatinine Sulphate*, 97 *PROC. SOC'Y EXPERIMENTAL BIOLOGY* 334, 335 (1958) (finding that after 30 days rats receiving serotonin injections lost most of their hair in the regions of the injections and experienced visible thickening of their skin).

<sup>48</sup> Metabolites are any product of metabolism, which is the sum of all physical and chemical changes that take place within an organism. *See* TABER'S, *supra* note 3, at 115-16.

similar chemical structures.<sup>49</sup> Studies raised the possibility of hepatotoxicity<sup>50</sup> after scientists recorded liver changes in rats fed L-tryptophan.<sup>51</sup>

Coincident with these concerns about L-tryptophan's safety, researchers found potential medicinal uses for L-tryptophan. Dr. Richard Wurtman of the Massachusetts Institute of Technology's Clinical Research Center found that blood tryptophan levels control serotonin levels, affecting sleep, mood, and appetite.<sup>52</sup> Based on this discovery, Wurtman suggested that L-tryptophan may have properties making it useful to remedy insomnia, control appetite, regulate mood, and act as a painkiller.<sup>53</sup> Thus, after the FDA's 1961 designation of L-tryptophan as GRAS, research suggested new uses for L-tryptophan while, at the same time, other studies questioned its safety.

On April 6, 1972, the FDA took action in response to the mounting evidence that amino acid supplements were unsafe, proposing to remove amino acids from the list of nutrients or

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<sup>49</sup> *Hearing, supra* note 1, at 125 (letter from Andrew Freese et al. to Frank Young (Feb. 1, 1988)); see also W.F. Dunning et al., *The Effect of Added Dietary Tryptophane on the Occurrence of 2-Acetylaminofluorene-induced Liver and Bladder Cancer in Rats*, 10 *CANCER RES.* 454, 454 (1950) (concluding that tryptophan dietary supplements enhanced carcinogenic effects of 2-fluoreulacetamide in the bladder of rats); Osamu Yoshida et al., *Relationship Between Tryptophan Metabolism and Heterotrophic Recurrences of Human Urinary Bladder Tumors*, 25 *CANCER* 773, 778 (1970) (showing a correlation between the recurrence of bladder cancer and elevated tryptophan levels).

<sup>50</sup> Hepatotoxic is defined as "toxic to the liver." *TABER'S, supra* note 3, at 820.

<sup>51</sup> See Herschel Sidransky et al., *Effect of Tryptophan on Polyribosomes and Protein Synthesis in Liver*, 24 *AM. J. CLINICAL NUTRITION* 779, 783 (1971) (finding a shift toward a heavier aggregate of hepatic polyribosomes and an increase in in vitro protein synthesis from tryptophan use); Michael E. Trulson & H. Wayne Sampson, *Ultrastructural Changes in the Liver Following L-tryptophan Ingestion in Rats*, 116 *J. NUTRITION* 1109, 1114 (1986) (finding that high doses of L-tryptophan, within a range used by humans for sleep induction, produce abnormal morphology of the liver in rats).

<sup>52</sup> *Hearing, supra* note 1, at 70 (statement of Richard J. Wurtman, M.D., Professor of Basic Neuroscience and Director, Clinical Research Center, Massachusetts Institute of Technology).

<sup>53</sup> *Id.* In 1991, Dr. Wurtman, speaking in front of the House Subcommittee researching L-tryptophan, noted that his research led to the determination that L-tryptophan could have pharmacological uses in the treatment or mitigation of bodily dysfunctions. However, he did not believe that L-tryptophan had any use as a dietary or nutritional supplement. See *id.* at 71-72.

dietary supplements "GRAS without further limitation."<sup>54</sup> The FDA took the stance that the presence of amino acids in a particular food in protein form does not imply that they are safe to add in their solitary form.<sup>55</sup> When amino acids are present in such imbalanced and artificially high quantities, they can produce toxic effects, an unbalanced protein,<sup>56</sup> or an amino acid imbalance in the diet.<sup>57</sup> The FDA further acknowledged the growing body of evidence that amino acids were not harmless:

Experimental animal studies have shown that the adverse effects of these imbalances are suboptimal food intake, growth retardation, and degeneration of certain organs which can lead to the animal's early death. Excessive intakes of most of the nutritionally nonessential amino acids (for example tyrosine and glycine) will produce undesirable biochemical and pathological effects in animals. This indicates a potential health risk in man if use is not limited.<sup>58</sup>

The FDA then promulgated new regulations aimed at insuring the safe use of amino acids in foods.<sup>59</sup> These new regulations effectively removed L-tryptophan and other amino acids from the GRAS list.<sup>60</sup> The comments preceding the regulation state that there is "no reason to permit amino acid supplementation [of food] unless it will provide for a significant improvement in the protein quality."<sup>61</sup> Based on this regulation, the FDA takes the position that the marketing of amino acids — for example, L-tryptophan — as dietary supplements has been illegal since 1973.<sup>62</sup>

<sup>54</sup> 37 Fed. Reg. 6,938, 6,939 (1972) (proposed Apr. 6, 1972).

<sup>55</sup> *Id.* at 6,938.

<sup>56</sup> An unbalanced protein is "one used inefficiently for growth." *Id.*

<sup>57</sup> *Id.*

<sup>58</sup> *Id.* at 6,938-39.

<sup>59</sup> 38 Fed. Reg. 20,036 (1973).

<sup>60</sup> *See id.* at 20,038.

<sup>61</sup> *Id.* at 20,036.

<sup>62</sup> *Hearing, supra* note 1, at 105 (statement of Douglas Archer, Deputy Director of FDA Center for Food Safety and Applied Nutrition) ("[W]e wanted to . . . limit the approved food additive use of amino acids to foods that contained naturally occurring, primarily intact protein that is considered a

The dietary supplement industry argues that the regulations do not govern the use of L-tryptophan as a dietary supplement.<sup>63</sup> The industry relies on a statement in the 1972 proposal reporting that the regulations do not "cover the inclusion of amino acids in foods which do not contain original intact protein,"<sup>64</sup> and that "such uses will be the subject of separate [regulatory] actions."<sup>65</sup> The industry has therefore argued that, although the 1973 regulations expressly granted GRAS recognition to amino acids added to protein-containing foods, the regulations did not affect the status of amino acids used in other forms, such as free amino acids or those contained in dietary supplements.<sup>66</sup> Finally, the industry contends that because amino acids are GRAS for certain uses as food substances, food *additive* regulations do not apply.<sup>67</sup>

In addition, FDA inadvertence provided the supplement industry with an argument that amino acids were not food additives under the regulations. From 1974 through 1976, L-tryptophan was listed as a food additive in each year's Code of Federal Regulations.<sup>68</sup> However, during the 1977 recodification of its regulations, the FDA erroneously listed L-tryptophan as a "nutrient/dietary supplement."<sup>69</sup> The supplement industry has used this mistake as the basis for its argument that L-tryptophan was not a food additive and therefore GRAS, even though the recodification contained a blanket statement that all changes were nonsubstantive in nature.<sup>70</sup> The FDA corrected the error in a notice published in the Federal Register on October 28, 1977,<sup>71</sup> but the damage was already done.

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significant dietary source.").

<sup>63</sup> *Id.* at 291 (letter from J.B. Cordaro, President of the Council for Responsible Nutrition).

<sup>64</sup> 37 Fed. Reg. 6938, 6939 (1972) (proposed on April 6, 1972).

<sup>65</sup> *Id.*

<sup>66</sup> *Hearings, supra* note 1, at 275-76 (letter from Stanley Jacobson, President, National Nutritional Foods Association to Representative Ted Weiss (July 17, 1991)).

<sup>67</sup> *Id.* at 289-305 (letter from J.B. Cordaro, President, Council for Responsible Nutrition to Congressman Ted Weiss (July 17, 1991)).

<sup>68</sup> *See* 21 C.F.R. §§ 121.101(d)(5), 121.1002 (1974); 21 C.F.R. §§ 121.101(d)(5), 121.1002 (1975); 21 C.F.R. §§ 121.101(d)(5), 121.1002 (1976).

<sup>69</sup> 21 C.F.R. § 182.5915 (1977).

<sup>70</sup> 42 Fed. Reg. 14,306, 14,306 (1977).

<sup>71</sup> 42 Fed. Reg. 56,723, 56,728-29 (1977).

At the House Subcommittee hearing, a memorandum from the Office of the General Counsel of the Department of Health and Human Services' Food and Drug Division detailed two separate instances of the FDA's failed attempts to enforce this correction.<sup>72</sup> The FDA first seized an L-tryptophan formulation labelled as a dietary supplement on the grounds that it was an unapproved food additive, sold in violation of food additive regulations.<sup>73</sup> The manufacturer sued the FDA challenging the legality of the seizure, arguing that it could rely on the published regulation until officially changed. Although this seizure occurred prior to the issuance of the correction, the FDA argued that the seizure was valid because it recognized the printing error and had initiated efforts to publish a retraction.<sup>74</sup> The court held that the seizure was illegal under the regulations as published,<sup>75</sup> impeding the FDA's attempt to regulate amino acids as a food additive.

In 1977, prior to the October correction, the FDA implemented a second seizure of a dietary supplement formulation of L-tryptophan.<sup>76</sup> The FDA continued to insist that such a seizure was valid under the regulations.<sup>77</sup> Before trial of the second seizure's legality, the district court issued a broad statement indicating that the FDA may not have the authority to regulate the combination of *any* food ingredients, which surprised FDA attorneys.<sup>78</sup> Sure that they would lose the case, their lawyers convinced the FDA to settle it.<sup>79</sup>

As a result of these two court losses — and the concomitant expenses — the FDA stopped attempting to regulate the marketing of amino acids to consumers.<sup>80</sup> The 1976 Proxmire

<sup>72</sup> *Hearing, supra* note 1, at 155 (note from Mary Pendergast, General Counsel, Department of Health and Human Services).

<sup>73</sup> *Id.*

<sup>74</sup> *Id.*

<sup>75</sup> *Id.* (citing *United States v. An Article of Food . . . Schiff Natural L-tryptophane*, No. 77-768 (D. N.J. Nov. 30, 1977)).

<sup>76</sup> *Id.* at 156.

<sup>77</sup> *Id.* (the regulation at issue was 21 C.F.R. § 172.320).

<sup>78</sup> *Id.* at 158 (citing *United States v. An Article of Food . . . L-tryptophan*, No. 77-768 (D. N.J. Jan. 23, 1979)).

<sup>79</sup> *Id.* at 158-59.

<sup>80</sup> *Id.* at 106 (statement of Douglas Archer, Deputy Director of FDA Center for Food Safety and Applied Nutrition).

Amendment<sup>81</sup> pushed the FDA further in the direction of non-regulation. The Amendment forbade the FDA from limiting the potency of vitamin and mineral supplements.<sup>82</sup> Previously, the FDA proposed a reclassification of high dosages of Vitamins A and D, arguing that high dosages are only appropriate for drug usage.<sup>83</sup> The Proxmire Amendment prevented this proposed reclassification.<sup>84</sup> The FDA viewed the Amendment as a warning that Congress would not tolerate the regulation of supplement products unless they posed specific and immediate health danger.<sup>85</sup>

Throughout the 1980s, the FDA turned its attention to other matters despite mounting evidence that ingestion of free amino acids could have deleterious health effects.<sup>86</sup> In 1980, L-5-hydroxytryptophan, a drug very similar to L-tryptophan, was found to cause a scleroderma-like illness.<sup>87</sup> Other studies showed that quinolinic acid, an intermediary in the metabolism of L-tryptophan, was linked with Huntington's Disease,<sup>88</sup> he-

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<sup>81</sup> 21 U.S.C. § 350 (1976).

<sup>82</sup> See *id.* § 350(a)(1)(A)-(C).

<sup>83</sup> *Hearing, supra* note 1, at 171 (memorandum from Margaret Jane Porter, Chief Counsel of the Department of Health and Human Services).

<sup>84</sup> *Id.*

<sup>85</sup> See *id.* at 105 (statement of Douglas Archer, Deputy Director of the FDA Center for Food Safety and Applied Nutrition). A more recent FDA opinion, subsequent to the L-tryptophan eosinophilia-myalgia syndrome outbreak, disputes the FDA's original stance. A 1989 memo from the Chief Counsel of the Department of Health and Human Services stated that "[t]he Proxmire Amendment has no relevance, however, to what the agency would be doing with respect to L-tryptophan. The Proxmire Amendment did not change the requirements that a substance used in food must be either GRAS, prior-sanctioned, or an approved food additive." *Id.* at 171 (memorandum from Margaret Jane Porter).

<sup>86</sup> See, e.g., Michael Castleman, *The Enemy Within*, CAL. LAW., Mar. 1993, at 44 (recounting the slow regulatory response and the alleged cover up by the FDA of the dangers of silicon breast implants; from the initial disclosure of the implants' autoimmune effects in 1982, to the resulting flood of lawsuits and plaintiffs' awards during which the FDA remained ineffective, to the eventual moratorium on implant use in 1992).

<sup>87</sup> Esther M. Sternberg et al., *Development of a Scleroderma-like Illness During Therapy with L-5-hydroxytryptophan and Carbidopa*, 303 NEW ENG. J. MED 782, 782 (1980). Scleroderma is defined as a chronic disease which causes hardening of the skin and certain major organs of the human body. TABER'S, *supra* note 3, at 1644.

<sup>88</sup> M. Flint Beal et al., *Replication of the Neurochemical Characteristics of*

patic encephalopathy,<sup>89</sup> and coma.<sup>90</sup> Numerous cases appeared in which L-tryptophan, in combination with other pharmaceuticals, produced toxic effects.<sup>91</sup> Additionally, the amino acid phenylalanine — widely used in diet soft drinks and in pill form — also became suspect.<sup>92</sup>

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*Huntington's Disease by Quinolinic Acid*, 321 NATURE 168, 169 (1986) (demonstrating that quinolinic acid lesions closely resemble lesions caused by Huntington's Disease, and suggesting that quinolinic acid or a similar compound could be responsible for the neuronal degenerations characteristic of the disease). Huntington's Disease is characterized as an inherited disease causing involuntary movements and progressive dementia. TABER'S, *supra* note 3, at 846.

<sup>89</sup> Hepatic encephalopathy, also called hepatic coma, is "impaired central nervous system function due to liver disease." TABER'S, *supra* note 3, at 815-16.

<sup>90</sup> F. Moroni et al., *Increase in the Content of Quinolinic Acid in Cerebrospinal Fluid and Frontal Cortex of Patients with Hepatic Failure*, 47 J. NEUROCHEMISTRY 1667, 1668 (1986) (reporting an increased content of quinolinic acid in the frontal cortex of patients who died from hepatic coma, and extending the previous observations of quinolinic acid in the brain of rats as models of hepatic encephalopathy to humans); see also G. Curzon et al., *Plasma and Brain Tryptophan Changes in Experimental Acute Hepatic Failure*, 21 J. NEUROCHEMISTRY 137, 137 (1973) (finding abnormally high tryptophan levels in the brain of human subjects with hepatic coma); F. Moroni et al., *Content of Quinolinic Acid and of Other Tryptophan Metabolites Increases in Brain Regions of Rats Used as Experimental Models of Hepatic Encephalopathy*, 46 J. NEUROCHEMISTRY 869, 869 (1986) (finding increased levels of tryptophan in the brains of experimental rats used as models of hepatic encephalopathy).

<sup>91</sup> See W. Steiner & R. Fontaine, *Toxic Reaction Following the Combined Administration of Fluoxetine and L-tryptophan: Five Case Reports*, 21 BIOLOGICAL PSYCHIATRY 1067, 1067 (1986) (reporting the occurrence of a toxic reaction in all five cases in which L-tryptophan was combined with fluoxetine in the treatment of affective or obsessive-compulsive disorders); A.B. Levy et al., *Myoclonus, Hyperreflexia, and Diaphoresis in Patients on Phenelzine-Tryptophan Combination Treatment*, 30 CAN. J. PSYCHIATRY 434, 434 (1985) (discussing the toxicity and resulting physical effects of the combination of L-tryptophan and monoamine oxidase inhibitors in the treatment of depression).

<sup>92</sup> People with phenylketonuria must maintain a low-phenylalanine diet to prevent mental retardation. Annie Prince, *Patterns of Phenylalanine Metabolites, Vitamin B6 Status and Learning Disabilities in Phenylketonuria Children: Modeling for Diet Criteria*, in DIETARY PHENYLALANINE AND BRAIN FUNCTION 244, 245 (Richard J. Wurtman & Eva Ritter-Walker eds., 1988); see also Harvey L. Levy & Susan E. Waisbren, *Effects of Untreated Maternal Phenylketonuria and Hyperphenylalaninemia on the Fetus*, 309 NEW ENG. J. MED. 1269, 1269 (1983) (finding that the failure to maintain a low-phenylalanine diet by women with maternal phenylketonuria results in mental

During this same period of time, the dietary supplement industry grew at an astonishing pace to become a four billion dollar industry.<sup>93</sup> The supplement industry also became more bold, advertising supplements with claims that were more pharmaceutical than nutritive in nature. For example, the FDA received an anonymous package of advertisements for a variety of L-tryptophan formulations<sup>94</sup> which contained claims such as:

- [L-tryptophan is] an essential amino acid that works in the brain to make 'Serotonin' a natural tranquilizer substance that has been found to be useful as an aid for relieving depression and possibly helping to induce relaxation;<sup>95</sup>
- [L-tryptophan] relieves fatigue, wards off overexertion, prevents nervousness, and mental sluggishness;<sup>96</sup>
- [Tryptolyn (a combination of tryptophan and lysine)] reduc[es] plasma cholesterol and triglyceride levels, heart attacks, strokes, atherosclerosis, arteriosclerosis, and enlarged prostate glands;<sup>97</sup>

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retardation or other birth defects in their offspring).

Dr. Richard J. Wurtman, Professor of Basic Neuroscience and Director, Clinical Research Center, Massachusetts Institute of Technology, has published nearly 400 articles on amino acids. According to him, phenylalanine should not be on the market:

There is never, as far as I can tell, a reason ever for anyone to take phenylalanine. There are about 4 million people out there who do not know it, but their livers are not adequate at metabolizing phenylalanine. And we know that phenylalanine can be directly toxic to the brain . . . . So there's never a reason for selling phenylalanine, but its sold out there right now.

*Hearing, supra* note 1, at 72-73.

<sup>93</sup> *Senate Witnesses Say Process Needed to Balance Dietary Supplement Issue*, DAILY REP. FOR EXECUTIVES, Oct. 22, 1990, at 203.

<sup>94</sup> *Hearings, supra* note 1, at 174 (memo from Mary K. Pendergast, General Counsel of the Department of Health and Human Services).

<sup>95</sup> *Id.* at 175-76.

<sup>96</sup> *Id.* at 176-77.

<sup>97</sup> *Id.* at 177.



- [Tryptophan can be used for] dementia, insomnia, senility, hallucination, depression, heart disease, and carbohydrate craving.<sup>98</sup>

Even today, magazine articles and manufacturers' promotions make similar claims for other amino acids. L-arginine allegedly improves the immune system.<sup>99</sup> L-citrulline is "beneficial in the presence of any illness, disease, traumatic injury or wound."<sup>100</sup> L-lysine allegedly helps "to control the frequency and severity of herpes."<sup>101</sup> The list of asserted health benefits of amino acids continues.<sup>102</sup>

As the supplement industry brazenly advertised questionable claims, the FDA — believing itself to be handcuffed by current regulations — did nothing.<sup>103</sup> Then, in October, 1989, reports of a mysterious illness filtered out of New Mexico.<sup>104</sup>

## II. THE EOSINOPHILIA-MYALGIA OUTBREAK AND ITS REPERCUSSIONS

On October 30, 1989, the New Mexico Department of Health received reports that several people had developed a scarring illness, characterized by elevated eosinophil counts and severe myalgia.<sup>105</sup> The Centers for Disease Control and various state health departments began an investigation after discovering that all of the original New Mexico patients were L-tryptophan

<sup>98</sup> *Id.*

<sup>99</sup> *Id.* at 185.

<sup>100</sup> *Id.* at 186.

<sup>101</sup> *Id.* at 188.

<sup>102</sup> Products containing L-tryptophan continued to be advertised as late as 1992, three years after the FDA recall. Rossanne M. Philen et al., *Survey of Advertising for Nutritional Supplements in Health and Bodybuilding Magazines*, 268 JAMA 1008, 1009 (1992).

<sup>103</sup> See *Hearing*, *supra* note 1, at 109-12 (statement of Dr. Douglas L. Archer, Deputy Director, Center for Food Safety and Applied Nutrition) (describing executive, judicial, and legislative atmosphere of the 1970s and 1980s); *supra* notes 75-81 and accompanying text.

<sup>104</sup> Leslie A. Swygart et al., *Eosinophilia-Myalgia Syndrome: Results of National Surveillance*, 264 JAMA 1698, 1698 (1990).

<sup>105</sup> *Eosinophilia-Myalgia Syndrome — New Mexico*, 38 MORBIDITY & MORTALITY WKLY. REP. 765, 765 (1989).

users.<sup>106</sup> On November 7, 1989, the first reports of a health concern linked to L-tryptophan were filed in the FDA's New Mexico field office.<sup>107</sup> The FDA tracked the available data over the following weekend and then acted quickly. On November 11, the FDA issued a warning to the public advising the immediate discontinuation of L-tryptophan use. On November 17, the FDA requested a nationwide recall of all L-tryptophan supplements of one hundred milligrams or more. On November 21, an importation alert was ordered, cutting off all importation of L-tryptophan.<sup>108</sup> By December 6, 1989, cases were reported in forty-eight states, the District of Columbia, and Puerto Rico,<sup>109</sup> with particular clusters of the illness in the Western and Southwestern states, Minnesota, New Hampshire, New York, and South Carolina.<sup>110</sup> New reports of the illness, named eosinophilia-myalgia syndrome (EMS), rapidly dropped after the initial FDA recall.<sup>111</sup> On March 22, 1990, all products containing L-tryptophan were recalled.<sup>112</sup>

Although the number of cases dropped after the recall, the misery of those suffering from EMS did not end. The Centers for Disease Control adopted a surveillance definition for EMS, requiring that, to be counted as suffering from EMS, a patient display a systemic illness characterized by three conditions: (1) severe myalgias,<sup>113</sup> (2) eosinophilia,<sup>114</sup> and (3) absence of

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<sup>106</sup> *Id.*

<sup>107</sup> *Hearing, supra* note 1, at 97 (statement of Douglas Archer, Ph.D., Deputy Director, Center for Food, Safety and Applied Nutrition, FDA, U.S. Department of Health and Human Services).

<sup>108</sup> *Id.*

<sup>109</sup> *Update: Eosinophilia Myalgia Syndrome Associated with L-tryptophan — United States*, 38 MORBIDITY & MORTALITY WKLY. REP. 842, 842 (1989).

<sup>110</sup> Swygert et al., *supra* note 104, at 1699. These states had EMS outbreaks at a rate of 7.2 to 26.2 cases per million persons. Alaska, Arkansas, Kansas, Louisiana, and Puerto Rico reported the lowest rates, with 0.2 to 1.9 cases per million. *Id.*

<sup>111</sup> *Id.* at 61 (statement of Esther M. Sternberg, M.D., Chief, Unit on Neuroendocrine Immunology and Behavior, Clinical Neuroendocrinology Branch, National Institute of Mental Health, Alcohol, Drug Abuse, and Mental Health Administration). The epidemic peaked in November 1989. *Id.*

<sup>112</sup> FOOD AND DRUG ADMINISTRATION, 90-15 FDA ENF. REP. 1, 1990 WL 262939 (FDA).

<sup>113</sup> Myalgia is a tenderness or pain in the muscles. TABER'S, *supra* note 3, at 1164.

any infectious or neoplastic<sup>115</sup> causes accounting for the eosinophilia and myalgia.<sup>116</sup> However, EMS sufferers display a wide variety of symptoms including fatigue, generalized weakness, edema, rash, paresthesias, muscle cramps, extremity weakness, and excessive hair loss.<sup>117</sup>

EMS passes through two phases. In the acute phase, the patient suffers from eosinophilia, fever, muscle aches, cough, shortness of breath, pneumonia, skin swelling, skin rashes,<sup>118</sup> and — in some cases — paralysis of the muscles which control breathing.<sup>119</sup> The second, chronic phase includes symptoms such as fatigue, muscle weakness, aches and cramping, joint pain, scarred and tight skin, anxiety, depression, memory loss, and menstrual problems, as well as nerve, heart, and lung damage.<sup>120</sup>

Unfortunately, the majority of EMS cases do not resolve themselves over time. Two years after the EMS outbreak, although eighty percent of EMS cases showed some improvement, over sixty percent of the patients had symptoms characterized as moderately to extremely severe, and only ten percent had completely recovered.<sup>121</sup> As of June, 1993, thirty-eight people had died of EMS — largely from heart problems and paralysis of muscles surrounding the lungs — and the number

<sup>114</sup> Eosinophilia is the presence of an unusual number of eosinophils in the blood. *Id.* at 605.

<sup>115</sup> A neoplasm is a new and abnormal formation of tissue as a tumor or growth. *Id.* at 1190.

<sup>116</sup> *Eosinophilia Myalgia Syndrome and L-tryptophan Containing Products — New Mexico, Minnesota, Oregon, and New York, 1989*, 38 MORBIDITY AND MORTALITY WKLY. REP. 785, 787 (1989). The Centers for Disease Control surveillance definition may have led to underreporting of L-tryptophan-related EMS, due to the wide variations in symptoms suffered by the patients. *Underreporting of EMS Seen by CDC Doctors*, 35 FOOD CHEMICAL NEWS 36, 36 (1993).

<sup>117</sup> Katrina Hedberg et al., *Eosinophilia-Myalgia Syndrome: Natural History in a Population-Based Cohort*, 152 ARCHIVES INTERNAL MED. 1889, 1889 (1992).

<sup>118</sup> *Hearing*, *supra* note 1, at 59 (statement of Esther M. Sternberg, M.D., Chief, Unit on Neuroendocrine Immunology and Behavior, Clinical Neuroendocrinology Branch, National Institute of Mental Health Alcohol, Drug Abuse, and Mental Health Administration).

<sup>119</sup> *Id.* at 60.

<sup>120</sup> *Id.*

<sup>121</sup> *Id.*

of people injured had climbed to 1500, although there could be many more undiagnosed cases.<sup>122</sup>

Once researchers linked L-tryptophan to EMS, they questioned what aspect of the L-tryptophan caused the EMS, and why L-tryptophan-related EMS had not emerged earlier.<sup>123</sup> By the third week of November 1989, Dr. Gerald Gleich, a researcher at the Mayo Clinic, and Dr. Michael Osterholm, epidemiologist for the Minnesota Department of Health, united in an effort to find the cause of EMS.<sup>124</sup> The Oregon Health Division and the Centers for Disease Control began additional studies.<sup>125</sup>

In these studies, researchers traced the products through the distribution chain to the manufacturers, who gave the researchers the dates of production for each lot;<sup>126</sup> six foreign manufacturers had produced L-tryptophan imported to the United States.<sup>127</sup> Statistical evidence showed a strong link between manufacturer Showa Denko K.K. and the disease-causing lots.<sup>128</sup> Using High-Performance Liquid Chromatography, the researchers created a map of the chemical elements in Showa Denko L-tryptophan.<sup>129</sup> Comparing the lots of non-

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<sup>122</sup> 58 Fed. Reg. 33,690, 33,696 (1993).

<sup>123</sup> Although the EMS epidemic peaked in the fall of 1989, running a course from mid-summer 1989, to mid-winter 1990, there are documented cases of EMS that did not occur in the time frame of the epidemic. One such case is that of Paul L. Houts, who testified before the Subcommittee studying the FDA regulation of L-tryptophan, that he became a victim of EMS in February 1988, having started taking L-tryptophan in the winter of 1987. *Hearing, supra* note 1, at 30-31.

<sup>124</sup> Bob Ehlert & Lewis Cope, *Minnesota Mafia Tracked L-tryptophan Impurity*, STAR TRIBUNE (Minneapolis), July 23, 1990, at E1.

<sup>125</sup> Laurence Slutsker et al., *Eosinophilia-Myalgia Syndrome Associated with Exposure to Tryptophan from a Single Manufacturer*, 264 JAMA 213, 214 (1990).

<sup>126</sup> *Id.* at 358.

<sup>127</sup> Edward M. Belongia et al., *An Investigation of the Cause of the Eosinophilia-Myalgia Syndrome Associated with Tryptophan Use*, 323 NEW ENG. J. MED. 357, 357-58 (1990).

<sup>128</sup> *Id.* at 363. Showa Denko had a 70% market share in the production of L-tryptophan. Bob Ehlert & Lewis Cope, *L-Tryptophan's Role Revealed, But Illness Lingers for Many*, STAR TRIBUNE (Minneapolis), July 24, 1990, at E1.

<sup>129</sup> Belongia et al., *supra* note 127, at 362. HPLC creates a graph of the chemical constituents of L-tryptophan. One hundred percent pure L-tryptophan would produce one large peak on the graph. Since no substance is 100% pure, there are various smaller peaks on the graph indicating other present

implicated Showa Denko L-tryptophan and the implicated lots, a specific peak in the graph — named Peak E<sup>130</sup> — was present only in the EMS case-related L-tryptophan.<sup>131</sup>

Showa Denko representatives revealed their complex manufacturing process to the Minnesota researchers and invited them to Japan to view the L-tryptophan production plant.<sup>132</sup> Showa Denko produced L-tryptophan through a fermentation process involving bacillus amyloiquefaciens.<sup>133</sup> In December, 1988, Showa Denko began to use a new, genetically-altered strain of bacillus amyloiquefaciens called Strain V,<sup>134</sup> and in 1989, reduced the amount of activated carbon in the purification process by one-half. Between October, 1988, and June, 1989, some batches bypassed a filter which removed heavier chemicals.<sup>135</sup> These potentially contaminated batches went through the purification process with other batches.<sup>136</sup> Showa Denko shipped the finished product to the United States.<sup>137</sup>

Based on the evidence they gleaned from their research and Showa Denko's records, the Minnesota researchers hypothesized that the Peak E contaminant was a factor in causing EMS.<sup>138</sup>

chemicals. The graphs vary depending upon the company producing L-tryptophan. This way, researchers may determine the manufacturing source of an L-tryptophan pill. Ehlert & Cope, *supra* note 124, at E1.

<sup>130</sup> The Centers for Disease Control labeled this same point "Peak 97." *Analysis of L-tryptophan for the Etiology of Eosinophilia-Myalgia Syndrome*, 39 MORBIDITY & MORTALITY WKLY. REP. 589, 589 (1990).

<sup>131</sup> Belongia et al., *supra* note 127, at 360.

<sup>132</sup> Ehlert & Cope, *supra* note 128, at E1.

<sup>133</sup> Belongia et al., *supra* note 127, at 360.

<sup>134</sup> Ehlert & Cope, *supra* note 128, at E1.

<sup>135</sup> Belongia et al., *supra* note 26, at 360.

<sup>136</sup> Ehlert & Cope, *supra* note 128, at E1.

<sup>137</sup>

These findings support a hypothesis that tryptophan containing an unidentified chemical constituent contributes to the pathogenesis of the eosinophilia-myalgia syndrome. Additional support for this hypothesis is provided by the significant association between Peak E . . . and manufacturing variables — the bacterial strain used and the amount of powdered activated carbon used. The chemical constituent represented by Peak E may cause the Eosinophilia-Myalgia Syndrome or it may be a surrogate marker for another unidentified substance which triggers the syndrome.

Belongia et al., *supra* note 127, at 362.

<sup>138</sup> Although both Minnesota researchers state that Showa Denko was

Researchers at the Oregon Health Division came to a similar conclusion by comparing a group with EMS to a healthy control group, both of which had ingested L-tryptophan.<sup>139</sup> The researchers found that ninety-eight percent of EMS sufferers had taken products produced by one manufacturer — Showa Denko — while the controls had taken products produced by many different manufacturers.<sup>140</sup> The Oregon researchers further determined that neither the average daily dose nor the length of time a patient had been taking the L-tryptophan impacted the timing of the symptoms' onset or the illness' severity.<sup>141</sup> Based on these findings, they hypothesized that a contaminant in L-tryptophan formulation caused the EMS outbreak.<sup>142</sup>

Dr. Esther M. Sternberg, at the National Institute for Mental Health, developed similar findings. Dr. Sternberg determined rats fed case-related L-tryptophan developed scarring of the connective tissue surrounding the muscles, while those fed

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cooperative and wanted to find the cause of the EMS outbreak, other actions taken by the company do not corroborate this; for example, the FDA curtailed a plant inspection in May 1990, in which:

[t]he team encountered refusals to provide information, access to records and areas routinely inspected and necessary to make a comprehensive evaluation of the firm's operations and practices. However, during the limited examination of the facility, numerous structural defects and potential routes of contamination were noted, but pursuit of these areas was not possible.

*Hearing, supra* note 1, at 251 (endorsement of Peter D. Smith). Plaintiffs' attorneys have stated Showa Denko has been equally uncooperative in subsequent litigation. In several cases, Showa Denko has argued it did not have sufficient contacts with the U.S. to be brought into a U.S. court. In *DeMoss v. City Market* the court adopted a stream of commerce theory, and Showa Denko lost on that attempt. 762 F. Supp. 913, 917-19 (D. Utah 1991). Stephen Fabbro, liaison to a California judge in California litigation, states that Showa Denko's settlement strategy is based on delay, and Portland attorney Gayle Troutwine states that Showa Denko makes depositions unduly difficult by having them translated, although the deposeses speak English. *L-Tryptophan: L is for Lucrative*, THE RECORDER, Feb. 10, 1992, at 1. Rebecca Weisman suggests that if a manufacturer does not exercise good faith and diligence in turning over data, the FDA should implement economic sanctions proportional to company assets. Rebecca Weisman, *Reforms In Medical Device Regulation*, 23 GOLDEN GATE U. L. REV. 973, 995-96 (1993).

<sup>139</sup> See Slutsker et al., *supra* note 125, at 213.

<sup>140</sup> *Id.*

<sup>141</sup> *Id.* at 214.

<sup>142</sup> *Id.* at 215.

purier L-tryptophan did not.<sup>143</sup> Her research team believes either one chemical or a chemical combination in the Showa Denko L-tryptophan caused the syndrome.<sup>144</sup> To date, no one has determined the exact chemical agent triggering EMS.<sup>145</sup>

Once researchers determined the cause of the L-tryptophan EMS epidemic, Congress took action. The House of Representatives Human Resources and Intergovernmental Relations Subcommittee of the Committee on Government Operations held a hearing on the FDA's Regulation of L-tryptophan.<sup>146</sup> Representative Patsy Mink, the Committee Chairwoman, placed the blame for the epidemic squarely at the feet of the FDA.<sup>147</sup>

<sup>143</sup> *Hearings, supra* note 1, at 56 (statement of Esther M. Sternberg, M.D., Chief, Unit on Neuroendocrine Immunology and Behavior, Clinical Neuroendocrinology Branch, National Institute of Mental Health, Alcohol, Drug Abuse, and Mental Health Administration).

<sup>144</sup> *Id.*

<sup>145</sup> 58 Fed. Reg. 33,690, 33,696 (1993). The Oregon researchers found three ways a contaminant in L-tryptophan might cause EMS: (1) the contaminant has "a direct toxic effect on the tissues," (2) "a contaminant might alter normal tryptophan metabolism," and (3) "a contaminant might alter the bioavailability of tryptophan, leading to abnormal gastrointestinal absorption of tryptophan and/or bacterial luminal metabolism." Slutsker, *supra* note 125, at 217.

<sup>146</sup> *See Hearings, supra* note 1, at 1.

<sup>147</sup> Two other episodes indicate faulty FDA procedures.

*DES.* In 1947, the FDA approved the use of diethylstilbestrol (DES) to prevent miscarriages on an experimental basis. DES was widely marketed and prescribed throughout the 1950s and 1960s. However, the FDA's approval was based on research which showed neither DES's safety nor its efficacy. In 1971, DES was linked to reproductive system cancers in the children of those who had taken DES while pregnant. Only then did the FDA revoke approval of the drug. DES had been on the market for twenty-four years. Rebecca Weisman, *Reforms in Medical Device Regulation: An Examination of the Silicone Breast Implant Debacle*, 23 GOLDEN GATE U. L. REV. 971, 982 (1993).

*The Dalkon Shield.* A.H. Robins introduced the Dalkon Shield in 1971. In 1972, doctors reported to the FDA deaths caused by spontaneous septic abortion related to the Dalkon Shield. The FDA did nothing. After threats by the doctors to publish their findings in a medical journal, A.H. Robins agreed to send a warning letter to doctors distributing the device. The FDA rejected the letter, and when the head of the FDA unit regulating medical devices requested that the FDA get an injunction prohibiting the further marketing of the Dalkon Shield and recalling all of those on the market, the FDA refused. Only in 1974 did the FDA request A.H. Robins to stop selling the Dalkon Shield. Later trials revealed Robins had suppressed negative research regarding the Dalkon Shield. *Id.* at 984.

In her closing statement, Representative Mink focused on the FDA's inaction:

Throughout the 1980s, the FDA permitted all amino acids to be marketed illegally as dietary supplements. Many of these products made illegal drug claims that were also ignored by the agency.

What is perhaps most alarming, in my opinion, is the fact that all of the amino acids on the market today in supplement forms are illegal.

We fail to understand how FDA can allow the supplement industry to flaunt Federal law, and this sends a worse [sic] kind of signal, in my view, to the few unscrupulous marketers who are out there looking for an opportunity to profit over health fraud. It jeopardizes the health of all consumers and leaves honest companies at a competitive disadvantage.<sup>148</sup>

In 1990, Congress passed the Nutritional Labeling and Education Act (NLEA).<sup>149</sup> The Act, designed to expand and modernize nutritional labeling on consumer products, gave the FDA the power to regulate manufacturers' claims that products prevent disease or confer health benefits.<sup>150</sup> The FDA chose to authorize disease or health-related claims "only if the totality of publicly available scientific evidence — including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles — supports the claim, and there is significant scientific agreement among qualified experts that the claim is supported by such evidence."<sup>151</sup>

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<sup>148</sup> *Hearings, supra* note 1, at 123 (closing statement of Representative Patsy Mink, Chairwoman, House of Representatives, Human Resources and Intergovernmental Relations Subcommittee of the Committee on Government Operations).

<sup>149</sup> Nutritional Labeling and Education Act of 1990, Pub. L. No. 101-535, 104 Stat. 2353 (1990).

<sup>150</sup> Charles J. Raubicheck & Leslye B. Davidson, *Nutrition Labeling on Products Must Comply with New Statute*, DAILY REP. FOR EXECUTIVES, June 16, 1993, at A114.

<sup>151</sup> 56 Fed. Reg. 60,537, 60,537 (1991). The FDA chose to establish the same standard for health claims made on dietary supplements as those made for claims for food. *Id.* at 60,539.



In response, Congress passed the Dietary Supplement Act of 1992 to prevent the FDA from implementing these regulations.<sup>152</sup> The Act (1) placed a one-year moratorium on FDA implementation of the NLEA with respect to dietary supplements in forms other than conventional food, (2) called for additional studies on FDA regulation of dietary supplements, and (3) ordered the FDA to implement NLEA standards for dietary supplements with a new rulemaking by 1993.<sup>153</sup>

In June 1993, the FDA proposed that product labels for dietary supplements should contain the same nutritional information as labels for processed foods.<sup>154</sup> Furthermore, the FDA proposed that there should be "significant agreement among qualified experts" concerning the veracity of such claims.<sup>155</sup> In reaction, three bills were introduced into Congress during the session: The Dietary Supplement Consumer Protection Act of 1993,<sup>156</sup> the Health Freedom Act of 1993,<sup>157</sup> and the Dietary Supplement Health and Education Act of 1993.<sup>158</sup> Each outlines a unique regulatory framework for dietary supplements.

Meanwhile, Canada acted quickly to regulate amino acid marketing,<sup>159</sup> and, as a result, the EMS outbreak did not occur in Canada.<sup>160</sup> Only eleven cases of EMS were reported in Canada, ten of which were traced back to L-tryptophan purchased in the United States and later imported into Canada.<sup>161</sup> L-tryptophan became available over-the-counter in Canada in 1980.<sup>162</sup> In 1985, Health and Welfare Canada, through its Health Protection Branch, issued an Information Letter

<sup>152</sup> The Dietary Supplement Act was appended to the Prescription Drug User Fee Act of 1992. Pub. L. No. 102-571, 106 Stat. 441 (1992).

<sup>153</sup> 58 Fed. Reg. 33,690, 33,690 (1993).

<sup>154</sup> *Id.*

<sup>155</sup> *FDA Calls for Dietary Supplements to Meet NLEA Labeling Requirements*, DAILY REP. FOR EXECUTIVES, June 16, 1993, at A114.

<sup>156</sup> H.R. 2923, 103d Cong., 1st Sess. (1993).

<sup>157</sup> H.R. 509, 103d Cong., 1st Sess. (1993).

<sup>158</sup> H.R. 1709, 103d Cong., 1st Sess. (1992); S. 784, 103d Cong., 1st Sess. (1993).

<sup>159</sup> See *Hearing, supra* note 1, at 206 (Report of the Canadian Health Protection Branch Expert Advisory Committee on Amino Acids).

<sup>160</sup> See *id.* at 205.

<sup>161</sup> *Id.*

<sup>162</sup> *Id.* at 195.

which recategorized L-tryptophan as a new drug, stating that "[p]roducts containing single amino acids or mixtures of amino acids which have demonstrated pharmacological effects or for which drug claims are made or implied are considered to be drugs as defined in section 2 of the Food and Drugs Act."<sup>163</sup> Pursuant to this statement, L-tryptophan became regulated as a prescription drug in Canada.<sup>164</sup> In 1987, the Canadian Health Protection Branch established an Expert Advisory Committee on amino acids, which delivered its final report in 1990.<sup>165</sup> The Committee concluded that there is no substantial reason to allow amino acids to be readily available to the general public.<sup>166</sup>

L-tryptophan was never taken off the market in Canada, even at the height of the U.S. EMS epidemic. It is used today as a drug in Canada. Meanwhile, in the United States, the legal wrangling over L-tryptophan and other amino acids continues.

### III. THE CONGRESSIONAL BATTLE OVER DIETARY SUPPLEMENTS

By 1993, the battle over dietary supplements had become heated.<sup>167</sup> Two bills were introduced into Congress, two of

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<sup>163</sup> *Id.* at 211 (containing HPB Information Letter No. 685 (May 3, 1985)).

<sup>164</sup> The Canadian Regulations were challenged in two cases. In *Jamieson & Co. v. Attorney General of Canada*, 46 D.L.R.4th 582; 37 C.C.C.3d 193; 3 W.C.B.2d 164 (1987) (Canada), Jamieson instituted an action claiming that amino acids were not new drugs as defined in the Food and Drugs Act. *Id.* The court upheld the validity of the regulations and the status of amino acids as new drugs. *Id.* In *Regina v. Quest Vitamin Supply Ltd.*, Quest was prosecuted for continuing to sell L-tryptophan without filing a new drug submission. *Regina v. Quest Vitamin Supply Ltd.*, 354 B.C.S.C. 3 (1991) (Canada). The judge held for the plaintiff, stating that the court should respect the general deterrence provided by these regulations and that the public is entitled to rely on the integrity of health products and expect that public health standards will be maintained and offenses punished. *Id.* at 10.

<sup>165</sup> *Hearing, supra* note 1, at 85 (statement of Simon N. Young).

<sup>166</sup> *Id.* at 196 (Report of the Canadian Health Protection Branch Expert Advisory Committee on Amino Acids (1990)).

<sup>167</sup> See Kathi Gannon, *Vitamin Showdown: Who Should Control Dietary Supplements?*, DRUG TOPICS, Jan. 24, 1994, at 38 (discussing the current state of the debate over dietary supplements); *Peace on Earth? . . . Not! Supplement Battle Rages*, FOOD LABELLING NEWS, Dec. 23, 1993 (discussing tactics employed by the dietary supplement industry to prevent regulations) [herein-

which would allow dietary supplements to remain on the market with little regulation.<sup>168</sup> The third bill proposed somewhat stricter regulation.<sup>169</sup> Although none of these bills was voted on during the session, each offered an insight into legislative thought regarding amino acid dietary supplements in the United States.

Governmental efforts to control dietary supplements and to enact labeling requirements angered the supplement industry.<sup>170</sup> Through a grass-roots campaign largely centered on massive lobbying<sup>171</sup> and advertising efforts,<sup>172</sup> the industry has incited consumers against the government's control efforts. One source stated that members of Congress receive more mail from their constituents regarding dietary supplements than any other issue.<sup>173</sup>

Congress and the industry have focused on insuring that dietary supplements remain readily available.<sup>174</sup> This Part discusses several aspects of the argument between the FDA and the industry, including the debate over health claims, the scientific safety standards for dietary supplements, and the procedures the industry must follow to avoid manufacturing defects.

after *Peace on Earth?*].

<sup>168</sup> See Health Freedom Act of 1993, H.R. 509, 103d Cong., 1st Sess.; Dietary Supplement Health and Education Act of 1993, H.R. 1709, 103d Cong., 1st Sess.

<sup>169</sup> Dietary Supplement Consumer Protection Act, H.R. 2923, 103d Cong., 1st Sess. (1993).

<sup>170</sup> See *Peace on Earth?*, *supra* note 167.

<sup>171</sup> Dante E.A. Ramos, *Vitamin Makers Try a Dose of Lobbying*, 30 NAT'L J. 1879, 1879 (1993). The Nutritional Health Alliance, formed in mid-1992, hired lobbyist Anthony T. Podesta, a veteran lobbyist with close ties to the Clinton Administration and several Democratic members of Congress, to wage the battle. The alliance also sold a "health freedom kit" for \$25, which included Congress members' addresses, sample letters, and a toll-free number for inspiration. *Id.*

<sup>172</sup> Glenn Simpson, *A Raid on Your Medicine Chest?*, USA WEEKEND, Feb. 20, 1994, at 16. For example, the Health Freedom Task Force produced a television commercial, starring actor Mel Gibson, in which an FDA SWAT team overruns Gibson's home and confiscates his illegal vitamin C. *Id.*

<sup>173</sup> *Id.*

<sup>174</sup> See Mike McKee, *Odd Alliance Fights ADA Plan*, RECORDER, July 29, 1993, at 1.

## A. ADVERTISING HEALTH CLAIMS

Since the passage of the Nutrition Labeling and Education Act (NLEA),<sup>175</sup> the dietary supplement industry and the FDA have been at odds over the extent to which the FDA should regulate product claims made by the industry.<sup>176</sup> The NLEA granted the FDA discretion to determine the standards applicable to product claims for dietary supplements.<sup>177</sup> The FDA repeatedly chose to apply the same standards for health-related claims made regarding dietary supplements as those required for health-related claims regarding food.<sup>178</sup>

The supplement industry responded by making strongly anti-regulatory statements, many of which inaccurately portrayed the FDA's intended regulations.<sup>179</sup> For example, one industry statement claimed that the FDA planned to remove well-established health food staples — such as vitamin C — from the shelves of pharmacies and health food stores.<sup>180</sup> In fact, the FDA made no such threat.<sup>181</sup>

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<sup>175</sup> 21 U.S.C. § 343 (1988 & Supp. IV 1992).

<sup>176</sup> See Richard L. Frank & Michael J. O'Flaherty, *Government Regulation of Self-Care*, RECORDER, Oct. 13, 1993, at 10; *FDA Calls for Dietary Supplements to Meet NLEA Product Requirements*, DAILY REP. FOR EXECUTIVES, June 16, 1993, at 114.

<sup>177</sup> The Act provides that "a subparagraph (1)(B) claim made with respect to a dietary supplement of vitamins, minerals, herbs, or other similar nutritional substances shall not be subject to subparagraph (3) but shall be subject to a procedure and standard, respecting the validity of such claim, established by regulation of the Secretary." 21 U.S.C. § 343(r)(5)(D) (Supp. IV 1992).

<sup>178</sup> See Part I.C. *supra* (concerning FDA's implementation of the Nutritional Labeling and Education Act).

<sup>179</sup> See *Peace on Earth?*, *supra* note 167.

<sup>180</sup> See *id.*

<sup>181</sup> *Id.*

The bogus threat that ordinary daily dietary supplements, such as multi-vitamins, will be banned is a scare tactic by some in the industry who hope it will earn them a blank check from the government to make unproven health claims for mega-vitamins, amino acid products and herbal extracts.

But the government must not write that check. Instead, it should halt unproven health claims for offending products and protect consumers by getting off the market those supplements that are potentially dangerous.

Many ordinary vitamin and mineral supplements may prove useful . . . . The usefulness of ordinary substances in ordinary doses is one

The dietary supplement industry also accused the FDA of an anti-supplement bias, claiming that "the dietary supplement industry has been willing to cooperate with the FDA whenever issues of public safety are concerned . . ." <sup>182</sup> and that the "FDA has chosen to use extreme examples of products which reflect a very small segment of the dietary supplement industry to make its case against the whole industry." <sup>183</sup> However, recent industry advertising contradicts these statements of good faith. <sup>184</sup> In 1992, an advertisement for a product containing L-tryptophan appeared in a bodybuilding magazine. <sup>185</sup> The product contained one thousand milligrams of L-tryptophan (suggesting manufactured L-tryptophan). <sup>186</sup> The advertising company did not list its name and address. <sup>187</sup> Another advertisement for a product containing levodopa, a prescription drug, did not list a recommended dosage or possible side effects. <sup>188</sup> Another product listed hydrangea as an ingredient, even though the leaves and buds of the hydrangea, if consumed, can cause cyanide poisoning. <sup>189</sup> Overall, the researchers found that fifty-nine percent of the advertised products contained no toxicological information, that they made little mention of side effects or contraindications, and that they rarely stated recommended

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thing. Unsubstantiated claims for prevention, cure or treatment of specific illnesses is quite another.

*Id.* (quoting Mark Silbergeld, director of the Washington Office of Consumer's Union).

<sup>182</sup> *Opinions Collide on FDA's Supplement Advance Notice*, FOOD LABELING NEWS, Jan. 27, 1994 (quoting Nutrilite Products, Inc.).

<sup>183</sup> *Id.*

<sup>184</sup> See Philen et al., *supra* note 102, at 1009.

<sup>185</sup> *Id.* The advertisement ran even though L-tryptophan was recalled from the market in November 1989. *Id.*

<sup>186</sup> *Id.*

<sup>187</sup> *Id.*

<sup>188</sup> *Id.*

<sup>189</sup> *Id.* at 1010.

dosages.<sup>190</sup> Blatantly self-serving and misleading advertising and drug claims are not indicative of good faith.

Nevertheless, the dietary supplement industry and Congress persist in attempts to circumscribe the FDA's power to stop inappropriate health claims. The proposed Dietary Supplement Health and Education Act of 1993 would prohibit the FDA from stringently regulating dietary supplement health claims.<sup>191</sup> The Act would also allow manufacturers to set forth information about how the dietary supplement will "affect physiological processes of the body or prevent or repair damage caused by the diet or other environmental factors and does not authorize the Secretary to establish a prior restraint on the use of any labeling . . . ." <sup>192</sup>

If the FDA does not have the power to regulate manufacturers' claims, the result will be exaggerations, half-truths, and

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<sup>190</sup> The researchers reached the following conclusions:

Although our report focuses on general health and bodybuilding magazines, persons taking supplements for other reasons may be . . . vulnerable to advertising claims . . . . In particular, persons with chronic diseases such as arthritis, those with poorly understood syndromes such as chronic fatigue syndrome or premenstrual syndrome, or those with terminal diseases such as some cancers may be particularly susceptible to the alleged health benefits of nutritional supplements. These products may also be used by individuals for symptoms such as insomnia, digestive discomforts, 'nerves' or for the promotion of general well-being. The claims of beneficial health effects made for many of these products are based only tenuously, if at all, on information from peer-reviewed research. Products are promoted to the public as being 'natural' and 'organic' when in fact most ingredients in these products are from manufactured or chemically derived sources.

*Id.*

<sup>191</sup> H.R. 1709, 103d Cong., 1st Sess. § 4 (1993).

<sup>192</sup> *Id.* This information must be truthful and not misleading. Although this appears to stop the supplement industry from making outrageous claims, the scientific standards set to define when a claim is truthful and not misleading are low enough that claims could be made with ease. The bill merely provides:

A dietary supplement containing a nutrient for which the FDA has approved a given health claim, may make that claim on its label unless the Secretary determines, based on the totality of publicly available scientific evidence, that consumption of the nutrient would not tend to reduce the risk of disease or other health-related conditions in a manner similar to the consumption of such nutrient in conventional foods . . . .

*Id.*

marginally substantiated facts.<sup>193</sup> Individuals relying on marginal health claims are in danger of foregoing assistance at the onset of an illness, thereby losing valuable recovery time. If a simple, inexpensive bottle of amino acid X can cure a symptom, why go to a doctor? However, if amino acid X relieves only a symptom stemming from a serious condition, health care professionals will become involved later, perhaps at a more complex stage of the illness.

The strict regulation of manufacturers' health claims made by dietary supplement manufacturers is an admirable goal, but does not reach the heart of the problem. Certain amino acids are unsafe or useless for human consumption, even when not contaminated.<sup>194</sup> Quite simply, amino acids can be dangerous.<sup>195</sup> Therefore, attempts to regulate or deregulate health claims do not address the inherent health risks of amino acids. The pertinent question is whether amino acids should be readily available at all.

## B. THE SAFETY OF DIETARY SUPPLEMENTS

### 1. *Scientific Standards of Safety*

Another front in the battle over dietary supplement regulation is the strictness of the scientific standard manufacturers must meet before (1) they may make health claims and (2) have products deemed safe for sale to consumers. As of this writing, only one of the proposed bills gives the FDA adequate authority to protect the public.<sup>196</sup>

One proposal allows the manufacturer to determine that its product is safe.<sup>197</sup> If enacted, this proposal would replace the

<sup>193</sup> See *supra* notes 94-102, 184-190 and accompanying text.

<sup>194</sup> See *supra* notes 46-53, 86-92 and accompanying text.

<sup>195</sup> See *id.* and notes 1-10 and accompanying text.

<sup>196</sup> H.R. 2923, 103d Cong., 1st Sess. § 6 (1993).

<sup>197</sup> It specifies:

A food shall be deemed to be adulterated [i]f it is a dietary supplement and . . . (2) it contains a dietary ingredient that has not been adequately substantiated for safety by the person identified under section 403 (e)(1) or by the raw material manufacturer through— (A) evidence of a history of safe use (as part of any prior intended use) and the absence of substantial information that brings the safety of the ingredient into question; or (B) by well-designed scientific studies conducted in a manner that is consistent with

FDA's disinterested determination with that of financially interested parties, thereby reducing the consumer's assurance that a dietary supplement has been adequately proven safe. If all that is to be required of a manufacturer is proof of a history of safe use, well-designed scientific studies, or other appropriate means, the manufacturer has excessive room to maneuver. Manufacturers may rely on studies that are neither published, generally accepted within the scientific community, nor definitive. Furthermore, scientists supported by a manufacturer could easily develop a bias toward their sponsor. Using the L-tryptophan scenario as a guide, consider the following: studies show that L-tryptophan may have effective pharmacological uses if its potential is correctly developed.<sup>198</sup> However, other studies show that L-tryptophan could be dangerous if not used with extreme care.<sup>199</sup> If manufacturers retained control over the determination of safety, the studies which show L-tryptophan to have potential health benefits would be sufficient to allow it to remain on the market. Unless the FDA could meet the stringent burden of proving that the studies showing potential problems of the supplement presented "a substantial and unreasonable risk of illness or injury,"<sup>200</sup> the studies revealing potential health problems connected with the product would be ineffective evidence to prevent a manufacturer from marketing the product. The disinterested regulator should not be bound by the safety determinations of the financially interested manufacturer.

An alternative is to require general recognition of the product's safety.<sup>201</sup> This more stringent requirement would

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generally recognized scientific procedures or principles; or (C) by other appropriate means.

*Id.* § 3(f).

<sup>198</sup> *Hearings, supra* note 1, at 70 (statement of Richard J. Wurtman, M.D., Professor of Neuroscience and Director, Clinical Research Center, Massachusetts Institute of Technology).

<sup>199</sup> *See Id.* at 64 (statement of Esther M. Sternberg, M.D., Chief, Unit on Neuroendocrine Immunology and Behavior, Clinical Neuroendocrinology Branch, National Institute of Mental Health, Alcohol, Drug Abuse, and Mental Health Administration).

<sup>200</sup> H.R. 1709, 103d Cong., 1st Sess. § 3(a)(F)(1) (1993).

<sup>201</sup> The proposed Dietary Supplement Consumer Protection Act states that a dietary supplement shall be deemed unsafe unless "such ingredient is generally recognized, among experts qualified by adequate training and experience to evaluate its safety, as having been adequately shown through



give the FDA the power to keep a questionable dietary supplement off the market. By requiring general recognition of the safety of dietary supplements, the FDA could withhold approval of a supplement until the scientific community has concluded that such a supplement is safe.<sup>202</sup> Thus, this requirement would assure that no supplement manufacturer could, relying solely on a single study or a manufacturer-financed study, push an unsafe product onto the American market.

Not surprisingly, the dietary supplement industry is strongly opposed to the general recognition of safety and significant scientific agreement standards as defined by the FDA.<sup>203</sup> One industry organization, the Council for Responsible Nutrition, alleges that the FDA interprets the word "agreement" to mean "consensus" in the context of this proposal.<sup>204</sup> The industry argues that under this regulatory framework it would be nearly impossible for dietary supplements to have easy access to the market.<sup>205</sup> However, if the issue is the safety of dietary supplements, it is best to err on the side of caution. The alternative to cautionary regulations requiring product testing is to allow manufacturers to market potentially unsafe dietary supplements and place consumers at risk. As the plight of EMS victims demonstrates, the human suffering caused by reliance on unsafe products far outweighs the difficulty of meeting the requirement of general recognition of safety.<sup>206</sup>

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scientific procedures to be safe under the conditions of its intended use . . . ." H.R. 2923, 103d Cong., 1st Sess. § 6(a)(2) (1993).

<sup>202</sup> *Id.*

<sup>203</sup> *With Supplement Showdown Approaching, CRN Calls for Action*, FOOD LABELING NEWS, Jan. 20, 1994.

<sup>204</sup> *Id.*

<sup>205</sup> *See Vitamin Showdown*, *supra* note 167 (quoting Gerald Kesler, CEO of Nature's Plus, a dietary supplement manufacturer).

<sup>206</sup> The American Medical Association supports the FDA in its attempts to regulate dietary supplements: "We commend the FDA's efforts to ensure the safety of dietary supplements by increasing the responsibility of supplement manufacturers . . . . The full potential of the relationship between nutrition and health can only be realized after dietary supplements meet the standards that consumers expect and deserve of any product for human consumption." *Opinions Collide*, *supra* note 182.

## 2. *Regulating the Manufacturing Process*

Two of the current proposals seek to ensure the safety of dietary supplements by requiring manufacturers to be candid about their manufacturing processes.<sup>207</sup> One proposal deems a dietary supplement to be adulterated — and thus unmarketable — if the manufacturer does not notify the Secretary of the FDA of significant changes in the manufacturing process.<sup>208</sup> However, as this requirement only applies if the changes in the manufacturing process are substantial and produce safety risks,<sup>209</sup> the proposal does not ensure effective regulation of the manufacture of dietary supplements. This vague and open-ended loophole results in two major concerns.

First, "significant changes" in the manufacturing process remain undefined in the proposal.<sup>210</sup> Although the Secretary is given the power to promulgate regulations requiring notification of manufacturer changes, these changes must be "substantial."<sup>211</sup> The phrase "substantial changes" is highly subjective. Although the Secretary may interpret its meaning, the interpretation would have to be very complex. Is it a substantial change when a manufacturer uses a stronger strain of a bacteria which

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<sup>207</sup> S. 784, 103d Cong., 1st Sess. (1993); H.R. 2923, 103d Cong. 1st Sess. (1993).

<sup>208</sup> Under this proposal, a dietary supplement would be deemed adulterated:

(G)(1) If it is a dietary supplement and the Secretary was not notified, in accordance with regulations issued under subparagraph (2), about a significant change in the manufacturing practice which produced the supplement or of potential problems of safety or contamination affecting such practice.

(2) The Secretary shall promulgate regulations within 18 months of the date of the enactment of this subparagraph to require notification to the Secretary by manufacturers of raw materials utilized in dietary supplements of significant changes in manufacturing practices of such materials or any potential problems of safety or contamination arising from any such changes to ensure the safety of such materials.

H.R. 1709, 103d Cong., 1st Sess. § 3 (1993).

<sup>209</sup> "Subparagraphs (1) and (2) apply only to manufacturing changes that are substantial and have been shown to present adverse safety consequences. These sections do not apply to routing changes in the formulating and manufacturing of dietary supplements by dietary supplement manufacturers that utilize good manufacturing practices." *Id.* § 3(g)(3).

<sup>210</sup> *Id.* § 3.

<sup>211</sup> *Id.* § 3(g)(3).

has been used all along in a weaker form? Is it a substantial change to bypass a reverse-osmosis filtration process? Is it a substantial change to reduce the amount of activated carbon in a batch of the product? To one process any change may be substantial, to another some changes may be insubstantial.

Given the current state of affairs between the FDA, Congress, and the dietary supplement industry, the FDA may do one of two things, neither of which would effect a perfect solution. The Secretary could enact, through rulemaking, a very strict standard for "substantial changes." This rulemaking would cause a further deterioration in the relationship between the FDA and the supplement industry and circumvent the will of Congress, although it would provide a high level of protection to the public. Alternatively, the FDA could back away from regulation in this area, as they did in the 1970s.<sup>212</sup> Although the dietary supplement industry would thrive if unregulated, the American public should not be placed at such a risk.

The second source of concern regarding this proposal is that it does not require notification by the manufacturer unless the changes are not only substantial, but also "have been shown to present adverse safety consequences."<sup>213</sup> Even if the Secretary does define "adverse safety consequences" through rulemaking, the use of the phrase "have been shown" implies that there must have been past problems associated with the process. The FDA will then not have the ability to reject new manufacturing procedures which have not yet been shown to have adverse safety consequences. This requirement of adverse safety consequences would be hopelessly after-the-fact. Once a manufacturing change has produced safety problems, it is too late to require a notification of changes. The damage has already been done, and an investigation of the cause of the problem will ensue with or without a notice of changed manufacturing practices to the Secretary. All prospective manufacturing changes should be reported to the Secretary, thereby providing him or her with an opportunity to spot potential safety problems.

The second proposal considers a dietary supplement adulterated if it has not been produced in accord with good manufacturing processes and quality control procedures, as determined

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<sup>212</sup> See *supra* notes 70-80 and accompanying text.

<sup>213</sup> H.R. 1709, 103d Cong., 1st Sess. § 3(g)(3) (1993).

by the Secretary.<sup>214</sup> This proposal does not contain a provision requiring the manufacturer to notify the FDA in case of manufacturing changes. Although the proposal does require good manufacturing processes, its failure to require notification upon change of the processes — as discussed above — could be fatal to consumers and should be fatal to the proposal. The proposal contains a notification provision, but this provision applies only when someone in the chain of distribution knows that a supplement may be adulterated.<sup>215</sup> This is too after-the-fact to provide adequate protection to consumers. Once it is known that a product is adulterated, the adulteration has already occurred, and the change, maybe even the damage, is done.<sup>216</sup>

No regulation of the manufacturing process is effective unless it provides that the FDA receive notice of proposed changes in the manufacturing process. Along with that notice, the FDA should be given the power to disallow the change<sup>217</sup> or require particular testing. At a bare minimum, the FDA should receive notice of proposed manufacturing changes so that it would have a record on file in case a safety problem does arise and product tracing becomes necessary.

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<sup>214</sup> It states:

[A] dietary supplement shall be deemed to be adulterated (g)(1) If . . . it does not meet the quality factor requirements prescribed by the Secretary under this paragraph. The Secretary shall, by regulation, establish requirements for quality factors for dietary supplements as appropriate.

(h)(1) If . . . the processing of such dietary supplement is not in compliance with the good manufacturing practices and the quality control procedures established by the Secretary under subparagraph (2).

(2) The Secretary shall, by regulation, establish good manufacturing practices for dietary supplements, including quality control procedures that the Secretary determines are necessary to assure that a dietary supplement—

(A) provides the vitamin, mineral, or herb or other nutritional substance it claims to provide in its label or labeling, and

(B) is manufactured in a manner designed to prevent adulteration.

H.R. 2923, 103d Cong., 1st Sess. § 4 (1993).

<sup>215</sup> *Id.* § 6.

<sup>216</sup> For a definition of what shall be considered adulterated, see 21 U.S.C. § 342 (1988 & Supp. IV 1992).

<sup>217</sup> Such disallowance could be predicated upon previous safety problems or experimental results that indicate that the change may be unsafe.

## IV. THE CANADIAN REGULATORY FRAMEWORK

As a consequence of the Canadian Constitution's division of power between the federal government and the country's regional provinces,<sup>218</sup> the Canadian Food and Drugs Act<sup>219</sup> was enacted as a criminal statute.<sup>220</sup> The Constitution creates federal jurisdiction over trade, commerce, and criminal law,<sup>221</sup> leaving jurisdiction over things such as property and civil rights — as well as local or private matters — to the provinces.<sup>222</sup> Because the authority to regulate pharmaceuticals was not explicitly included in this division of power, Canada's federal government gained regulatory control over food and drugs in Canada through the use of criminal laws.<sup>223</sup>

The Health Protection Branch ("HPB") of Health and Welfare Canada is akin to the FDA in the United States. This agency oversees the availability of Canada's food, drugs, cosmetics, and medical devices, and is empowered to control environmental hazards.<sup>224</sup> The HPB decides whether or not to bring charges against food or drug manufacturers that fail to comply with Canadian law.

HPB compliance procedures ensure that there is very little food and drug litigation in Canada.<sup>225</sup> In order to avoid litigation when there is a compliance question, the HPB consults with manufacturers, attempts to persuade them to comply with

<sup>218</sup> CAN. CONST. art. VI (British North America Act, 1867).

<sup>219</sup> Food and Drugs Act, R.S.C., ch. F-27 (1985) (Canada).

<sup>220</sup> Robert E. Curran, *Canadian Regulation of Food, Drugs, Cosmetics, and Devices — An Overview*, 30 FOOD DRUG COSM. L.J. 644, 644 (1975).

<sup>221</sup> W. Wassenaar, *Canada: Evolution of Drug Regulation within the Health Protection Branch*, 35 FOOD DRUG COSM. L.J. 451, 453 (1980).

<sup>222</sup> *Id.*

<sup>223</sup> *Id.*

<sup>224</sup> A.B. Morrison, *The Canadian Approach to Food and Drug Regulations*, 30 FOOD DRUG COSM. L.J. 632, 632 (1975). Morrison states that the HPB's responsibilities include most of those handled in the United States by the FDA, and some of those handled by the Communicable Disease Center and the Environmental Protection Agency. *Id.* at 632-33.

<sup>225</sup> Curran, *supra* note 220, at 645. "We do not have a Food and Drug Section of the Canadian Bar Association, nor, for that matter, do we have a food and drug bar. There are relatively few lawyers in Canada who specialize in the subject . . ." *Id.* at 644.

the law,<sup>226</sup> and, only if necessary, files suit against a noncomplying manufacturer.

Some commentators have criticized the HPB's use of selective enforcement policy.<sup>227</sup> First, the procedure creates problems of selective justice.<sup>228</sup> Large corporations with abundant resources can defend against the allegations of the HPB or cure the fault found in their methods. However, small companies, when faced with the same allegations, are more likely to pay a fine or go out of business than mount a defense or institute the necessary technical renovation.<sup>229</sup> Second, a violator suffers a public relations disaster if it is listed in the HPB-authored *Protection*, a bulletin that lists all convictions under the Food and Drugs Act.<sup>230</sup> Finally, there is a problem of insufficient notice and public comment on proposed regulation. Changes in Canadian drug regulations may be spurred by elected officials, the HPB, trade associations, or consumers.<sup>231</sup> Once a regulation is proposed, the government is under no obligation to allow those affected by the regulation a period in which to make comment.<sup>232</sup> The HPB merely provides information about how the new regulations will impact manufacturers, prints administrative interpretations of the new regulations, and invites comments on the changes.<sup>233</sup>

The Food and Drugs Act itself is divided into four parts. Part I describes what is proscribed with regard to food, drugs,

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<sup>226</sup> *Id.* at 645.

<sup>227</sup> *See, e.g.,* Wassenaar, *supra* note 221, at 455-59.

<sup>228</sup> *Id.* at 456.

<sup>229</sup> *Id.*

<sup>230</sup> *Id.*; James A. Robb, *Comments and Views from the Perspective of a Canadian Food Lawyer* 30 FOOD DRUG COSM. L.J. 659, 661-62 (1975).

[W]hen a matter has reached the stage of prosecution, it is often difficult for a lawyer to give advice other than to plead guilty. The Act is, in fact, a prosecutor's act. Charges are in general terms, and distinct advantages are given departmental expertise in administration and enforcement . . . . Defense becomes difficult and, aside from the fine, the public relations consequences of this type of charge are difficult, if not impossible, to overcome. A guilty plea is often the better part of valor.

*Id.*

<sup>231</sup> Morrison, *supra* note 224, at 639.

<sup>232</sup> *Id.*

<sup>233</sup> *Id.* at 639-40.

cosmetics, and devices.<sup>234</sup> Part I of the Act prohibits the advertising of any product as a cure for a certain group of disorders,<sup>235</sup> the sale of adulterated drugs or drugs manufactured under unsanitary conditions,<sup>236</sup> and deceptive or misleading advertising of food,<sup>237</sup> drugs,<sup>238</sup> and devices.<sup>239</sup> Part II contains the Act's administrative procedures and enforcement provisions.<sup>240</sup> The Act arms drug inspectors with broad enforcement authority.<sup>241</sup> Parts III and IV of the Act cover controlled prescription drugs, "restricted" drugs, and drug trafficking.<sup>242</sup>

The Canadian Food and Drugs Act defines a drug as any substance manufactured, sold, or represented for use in (a) diagnosis, treatment, mitigation, or prevention of disease, disorder, abnormal physical state, or associated symptoms, or (b) the restoring, correcting, or modifying of organic functions, or (c) the disinfection of premises in which food is prepared or manufactured.<sup>243</sup> From 1980 through 1985, amino acids — including L-tryptophan — were sold over-the-counter in Canada.<sup>244</sup> In 1985, the HPB issued an information letter classifying as drugs products containing amino acids with demonstrated pharmaco-

<sup>234</sup> Food and Drugs Act, R.S.C., Ch. F-27, § 3(1) (1985) (Canada).

<sup>235</sup> *Id.*

<sup>236</sup> *Id.* § 8(a), (b).

<sup>237</sup> *Id.* § 6.

<sup>238</sup> *Id.* § 9(1).

<sup>239</sup> *Id.* § 20(1).

<sup>240</sup> *See id.* § 23.

<sup>241</sup> Wassenaar, *supra* note 221, at 453.

Indeed the powers of a drug inspector are much greater than [those] of a police officer. The police officer must at least obtain a search warrant before entering any premises. An inspector does not need any warrant and may enter any building and make any seizure on 'reasonable' grounds that the premises or object of seizure is subject to the Act or regulations.

*Id.*

<sup>242</sup> Parts III and IV of the Food and Drugs Act are beyond the scope of this Note.

<sup>243</sup> Food and Drugs Act, R.S.C., ch. F-27, § 2 (1985) (Can.); *see also Hearing, supra* note 1, at 196 (Memorandum from Catherine Wingfield, Legal Specialist, American-British Law Division, Library of Congress).

<sup>244</sup> *Hearing, supra* note 1, at 85 (statement of Simon N. Young, Ph.D., Professor, Department of Psychiatry and Professor, School of Dietetics & Human Nutrition, McGill University).

logical effects.<sup>245</sup> Further, products containing single amino acids or mixtures of amino acids "which have demonstrated pharmacological effects" or for which such claims were made were regarded by the HPB as "new drugs."<sup>246</sup> Regulations promulgated under the Canadian Food and Drugs Act define a new drug as: (a) a single substance which has not been sold as a drug in Canada for a sufficient time to establish that the substance is safe and effective; (b) a combination substance drug which has not been sold as a drug in that proportion in Canada for sufficient time to establish that the combination is safe and effective; or (c) a drug which the manufacturer states to have a specific use, and which has not been sold for a sufficient time in Canada to establish that the use is safe and effective.<sup>247</sup>

In order to distribute a new drug in Canada, a manufacturer must file a "New Drug Submission," obtain a "Notice of Compliance," and submit proposed packaging for the new drug.<sup>248</sup> If the HPB does not approve the New Drug Application, the manufacturer may resubmit the application to the Minister of National Health and Welfare.<sup>249</sup>

In 1986, the Bureau of Human Prescription Drugs permitted the pharmaceutical company ICN Canada to market L-tryptophan as a prescription drug for the treatment of affective disorders.<sup>250</sup> L-tryptophan continues to be available in Cana-

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<sup>245</sup> Health and Welfare Canada, Health Protection Branch, Information Letter No. 685 (May 3, 1985), *reprinted in Hearing, supra* note 1, at 209.

<sup>246</sup> *Id.* at 212; Food & Drugs Act Regulations, C.R.C., ch. 870, § C.08.001(a)-(c) (1978) (Can.).

<sup>247</sup> Food & Drugs Act Regulations, C.R.C., ch. 870, § C.08.001(a)-(c) (1978) (Can.).

<sup>248</sup> *Id.* § C.08.002(1)(a)-(d).

<sup>249</sup> *Id.* § C.08.004. The Canadian process of New Drug Applications is substantially similar to the U.S. process, even to the point that Health and Welfare Canada accepts a copy of the New Drug Application submitted to the FDA as a Canadian application. However, Canada and America do not reciprocate with regard to drug approval. Even after one country approves the application, the other conducts a separate review. Curran, *supra* note 220, at 648.

<sup>250</sup> *Hearing, supra* note 1, at 85 (statement of Simon N. Young). Affective disorders are "[a] group of disorders characterized by a disturbance of mood accompanied by a full or partial manic or depressive syndrome that is not caused by any other physical or mental disorder." TABER'S, *supra* note 3, at 48.



da, under the name "Tryptan."<sup>251</sup> No cases of EMS have been linked to patients taking Tryptan.<sup>252</sup>

In 1987, the HPB organized an Expert Advisory Committee to study the use of amino acids in pharmaceuticals.<sup>253</sup> The Committee submitted a report to Health and Welfare Canada in December 1989, during the EMS outbreak.<sup>254</sup> Among the conclusions of the Expert Advisory Committee was the determination that:

[t]here would appear to be no convincing rationale for having amino acids generally available to the public. If amino acids exert the pharmacological effects claimed, they are unsafe if not taken under medical supervision for a specific benefit; if they don't exert these effects, then there is no reason for marketing them. Furthermore, all of these amino acids were considered to have the potential for producing certain toxic effects in susceptible individuals or if consumed in large amounts for an extended duration.<sup>255</sup>

By May, 1990, only ten cases of EMS had been reported in Canada.<sup>256</sup> Eight of those who became ill had purchased single-ingredient L-tryptophan products in the United States; the ninth had ingested an L-tryptophan-containing compound formulated at a Canadian pharmacy; and the tenth had ingested L-tryptophan distributed in the United States and illegally sold in Canada.<sup>257</sup>

Classifying amino acids as drugs has worked well in Canada. Although legislation pending in the U.S. Congress eschews classification of all dietary supplements as drugs, regulating the

<sup>251</sup> *Hearing, supra* note 1, at 85.

<sup>252</sup> *Id.* at 86.

<sup>253</sup> *Id.* at 81 (statement of Simon N. Young, Ph.D., Professor, Department of Psychiatry and Professor, School of Dietetics & Human Nutrition, McGill University).

<sup>254</sup> *Id.* at 204 (referring to HEALTH AND WELFARE CANADA, REPORT OF THE EXPERT ADVISORY COMMITTEE ON AMINO ACIDS (1990)).

<sup>255</sup> *Id.*

<sup>256</sup> *Eosinophilia Myalgia Syndrome — Canada*, 39 MORBIDITY & MORTALITY WKLY. REP. 326, 326 (1990).

<sup>257</sup> *Id.*

subcategory of amino acids as drugs would offer viable protection for the American people.<sup>258</sup>

## V. WHAT SHOULD BE DONE?

### A. REGULATE AMINO ACIDS AS DRUGS

At the House Subcommittee Hearing on the FDA's Regulation of L-tryptophan, Dr. Richard J. Wurtman, Professor of Neuroscience and Director of the Clinical Research Center at the Massachusetts Institute of Technology, enumerated several reasons why amino acids such as L-tryptophan should be regulated as drugs. First, it is not natural for a human to ingest any amino acid individually. Tryptophan in pill form is not a nutritional supplement and cannot be used by the body.<sup>259</sup> Second, since administering tryptophan in pill form changes the chemistry of the brain,<sup>260</sup> it is a drug. Third, drugs have to be proven safe and efficacious and must contain package inserts listing contraindications and side effects,<sup>261</sup> both of which greatly benefit potential consumers of L-tryptophan. In addition, when L-tryptophan is marketed as a nutritional supplement, pharmaceutical companies have less incentive to determine whether it could be a useful drug.<sup>262</sup> Finally, more

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<sup>258</sup> In the U.S., a New Drug Application must include substantial evidence of safety and efficacy of the drug, based on animal and human research. In addition, the applicant must include literature on the use of the drug in the U.S. and foreign countries. Jeffrey N. Gibbs & Bruce F. Mackler, *Food and Drug Administration Regulation and Products Liability: Strong Sword, Weak Shield*, 22 TORT & INS. L.J. 194, 204 (1987).

<sup>259</sup> *Hearings, supra* note 1, at 71 (statement of Richard J. Wurtman, M.D., Professor of Neuroscience and Director, Clinical Research Center, Massachusetts Institute of Technology).

<sup>260</sup> *Id.*

<sup>261</sup> *Id.* at 71-72. For example, patients taking cardiovascular or psychiatric drugs should not take L-tryptophan concurrently. Furthermore, one side effect of L-tryptophan is tiredness; therefore, one should never drink alcohol or drive after its ingestion. *Id.*

<sup>262</sup> *Id.* at 72. When Dr. Wurtman first researched tryptophan and discovered it had an effect on the serotonin levels of the brain, he hoped that a pharmaceutical company might do more research and invest the money to do safety and efficacy studies before bringing it to the market as a drug. As long as it remains a dietary supplement, he states, no pharmaceutical manufacturer will take the time or effort to do these studies because a consumer can get the substance more quickly and without a prescription through health

accidents occur when amino acids are sold over the counter. It is not just impurities that make amino acids unsafe; these compounds can cause dangerous reactions when sensitive people ingest them.<sup>263</sup> A Canadian researcher, Dr. Simon Young of McGill University's School of Dietetics & Human Nutrition, agreed with Dr. Wurtman on similar grounds, stating that although L-tryptophan in its unadulterated form is one of the safer drugs on the market, it is not without its risks.<sup>264</sup>

Questions remain as to whether the contaminated L-tryptophan would have entered the American market even if it were regulated as a drug. Dr. Wurtman thinks not. If L-tryptophan had been classified as a drug, the FDA would have been able to oversee changes in the manufacturing process and ensure that impurities were not introduced.<sup>265</sup>

Even if amino acids were regulated as drugs, the government would not be able to catch every problem associated with their ingestion. Some people would suffer allergic reactions, as they do to drugs currently on the market. It is even conceivable that contaminants would slip by since they are in such small amounts.<sup>266</sup> However, the federal government, including the FDA, is against regulating particular amino acids as drugs.

After the L-tryptophan-related EMS outbreak, the FDA received a study about amino acids by the Life Sciences Research Office of the Federation of American Societies of Experimental Biology (LSRO), and commissioned a Dietary Supplement Task Force to study the problems related to amino acid dietary supplements.<sup>267</sup> Both studies support regulation of amino acid dietary supplements as drugs. The LSRO listed concerns about the continued unregulated use of amino acids.

food stores and catalogs. *Id.* at 70.

<sup>263</sup> *Id.* at 72. For example, tyrosine may be hazardous when taken in combination with anti-depressants. Phenylalanine can be deadly when taken by those persons who are unaware that their livers cannot adequately metabolize it. *Id.* at 72-73.

<sup>264</sup> *Id.* at 81 (statement of Simon N. Young, Ph.D., Professor, Department of Psychiatry and Professor, School of Dietetics and Human Nutrition, McGill University).

<sup>265</sup> Changes in the drug manufacturing process require FDA approval. *Id.* at 92 (statement of Richard J. Wurtman, M.D., Professor of Neuroscience and Director, Clinical Research Center, Massachusetts Institute of Technology).

<sup>266</sup> The Show Denko L-tryptophan implicated in EMS was 99.6 percent pure. Belongia et al., *supra* note 127, at 363.

<sup>267</sup> Regulation of Dietary Supplements, 58 Fed. Reg. 33,690, 33,691 (1993).

First, the LSRO could not identify a safe level of intake for amino acids.<sup>268</sup> Second, the LSRO identified certain segments of the healthy population that had a higher risk of experiencing negative effects due to amino acid consumption.<sup>269</sup> Third, it stated that D-amino acids have no known nutritional function in humans and thus should not be used.<sup>270</sup> Fourth, the LSRO recommended that dietary supplements' labels list the chemical composition, isomeric identity, shelf life, dose, and contraindications.<sup>271</sup> Finally, the LSRO concluded "that the safety of unrestricted use of amino acids in dietary supplements cannot be assumed."<sup>272</sup>

The Dietary Supplement Task Force recommended that dietary supplements containing amino acids be regulated as drugs.<sup>273</sup> From studies of amino acid supplements, the Task Force concluded that the "primary intended use of these products is for therapeutic rather than nutritional purposes."<sup>274</sup> As such, the amino acids should be regulated as drugs. By regulating amino acids as drugs, the government would create a hurdle for manufacturers to clear before placing their products on the market. New drugs would have to meet two conditions before clearance: (1) safety, and (2) efficacy for use under the conditions recommended on their labels.<sup>275</sup> Therefore, any amino acid manufacturer attempting to get its product onto the market must prove not only that the product is safe, but also that it effectively treats the condition they claim it treats. The latter requirement would force more studies to determine the beneficial uses of amino acids and might uncover positive proof of their medicinal uses as well.

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<sup>268</sup> *Id.*

<sup>269</sup> *Id.*

<sup>270</sup> *Id.*

<sup>271</sup> *Id.*

<sup>272</sup> *Id.* at 33,692.

<sup>273</sup> *Id.* at 33,697.

<sup>274</sup> *Id.*

<sup>275</sup> 21 U.S.C. § 321(p) (1988) provides that a "new drug" is

(1) Any drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labelling thereof . . . .

In August 1990, a memo from the Director of the Center for Food Safety and Applied Nutrition, a branch of the FDA, discussed and quickly rejected the possibility of regulating amino acids as drugs.<sup>276</sup> The Center for Drug Evaluation and Research, another FDA branch,<sup>277</sup> determined that the FDA would have to declare that amino acids have no nutritional value in order to succeed in a case challenging the definition of amino acids as drugs.<sup>278</sup> The agency would not contend that amino acid supplements had no nutritional value, although experts such as Dr. Wurtman and Dr. Young both stated that any use of a single amino acid supplement would be pharmacological and not nutritional.<sup>279</sup>

Canada has had good results regulating amino acids as prescription drugs. None of the proposed U.S. Acts would regulate amino acids as stringently. To protect people from dietary supplement-related diseases in the future, the U.S. government should assure the safety and efficacy of every supplement on the market by regulating amino acids as drugs. Current Congressional actions, however, combined with the U.S.'s heavy emphasis on consumer freedom, indicate that regulating amino acids as drugs may not be politically or socially viable, even though it may be the best way to insure public safety.

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<sup>276</sup> *Hearing, supra* note 1, at 222-31 (draft memorandum from the Director of the Center for Food Safety and Applied Nutrition to the FDA Commissioner (Aug. 30, 1990)).

<sup>277</sup> *Id.* at 227. The Center for Drug Evaluation and Research is another component branch of the FDA which researches both investigational new drugs and new drug applications involving bioengineered products. Linda Maher, *The Environment and the Domestic Regulatory Framework for Biotechnology*, 8 J. ENVTL. L. & LITIG. 133, 144 (1993).

<sup>278</sup> *Hearing, supra* note 1, at 227. The Center only grants drug status to "(1) those products being clinically studied following submission of an [investigational new drugs] or [new drug applications], and (2) those products labeled with obvious statements regarding mitigation of disease or direct claims of an effect on the structure or function of the human body." *Id.* at 226.

<sup>279</sup> *Id.* at 71 (statement of Richard J. Wurtman, M.D., Professor of Neuroscience and Director, Clinical Research Center, Massachusetts Institute of Technology); *id.* at 81 (statement of Simon N. Young, Ph.D., Professor, Department of Psychiatry and Professor, School of Dietetics & Human Nutrition, McGill University).

B. REGULATE AMINO ACIDS AS NON-DRUG ITEMS, BUT INCLUDE STRICT STANDARDS FOR PUBLICLY MARKETED SUPPLEMENTS

Since the U.S. government does not appear ready to regulate amino acid dietary supplements as drugs, Congress should enact laws that clearly indicate the status of dietary supplements on the U.S. market. Although the supplements would remain easily obtainable, the inclusion of particular requirements in the regulations would reduce the chances for widespread future outbreaks of dietary supplement-related illnesses.

(1) *Include amino acids explicitly in the regulations*

Amino acids are not mentioned by name in most current dietary supplement regulations, and that has caused problems. Supplement manufacturers should no longer be able to argue that, since amino acids are not mentioned by name, they do not come within the scope of the regulations. Including amino acids in the regulation would prevent further litigation and grant the FDA clear-cut authority over the sale of amino acid dietary supplements in the United States.

(2) *Explain where amino acids fit under the Food, Drug, and Cosmetic Act so there will not be bureaucratic or legal tussles over whether amino acids are food additives or drugs*

A statement that amino acids are either drugs or food additives would clarify the standing of amino acids. In this way, someone taking amino acid X for bronchitis and another taking it for an X deficiency would no longer be using the same substance classified in two different ways — the former classified as a drug, but the latter as a dietary supplement.

Amino acids also could be differentiated on a case-by-case basis, regulating them as drugs for use in disease prevention or control<sup>280</sup> or for their ability to change bodily structure or function,<sup>281</sup> and also regulating them as either food additives or nutritional supplements, assuming non-pharmacological, non-harmful nutritive uses of certain amino acids are discovered. Case-by-case decisions regarding in which category each amino

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<sup>280</sup> 21 U.S.C. § 321(g)(1)(B) (1988 & Supp. IV 1992).

<sup>281</sup> *Id.* § 321(g)(1)(C).

acid supplement belongs would take time and use FDA resources; however, such decisions could be used to document the fact that most amino acids are used for pharmacological, not nutritive, uses. Proof that amino acids are used for predominantly pharmacological purposes would bolster the currently unpopular idea that amino acids are potentially dangerous and should be regulated as drugs.

- (3) *Require substantial scientific agreement, based on research done by independent parties, that an amino acid is safe before it is placed on the market*

One study, conducted by the manufacturer or a manufacturer-supported researcher, should never be sufficient to endorse a supplement as safe. A supplement should be considered safe and effective only after multiple research trials produce positive results and relatively few negative outcomes. Such a standard could have prevented the L-tryptophan EMS outbreak.

- (4) *Arrange a system providing for strict FDA supervision of the manufacturing process*

Establishing quality controls and purity standards would minimize contamination of amino acid supplements. This alone, however, will not prevent all supplement-related illnesses: Some contaminants exist in small enough quantities to be acceptable under most quantity control standards, but are powerful enough to create illness.<sup>282</sup> Manufacturers should be required to obtain FDA approval of their manufacturing procedures by filing a report with the agency. The FDA can reject supplements if it finds that the manufacturing process used creates an unreasonable risk of contamination. The FDA will also have reports of the manufacturing processes on file if any illnesses related to the supplement do occur.

- (5) *Require manufacturers to report any changes in their manufacturing process*

The FDA should require manufacturers to file notice of any change in the manufacturing of their product, and a detailed

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<sup>282</sup> The Showa Denko L-tryptophan implicated in EMS was 99.6 pure. Belongia et al., *supra* note 127, at 363.

description of (1) the changes made, (2) the expected results of the change, and (3) any potential, unintended effects of the change which were noticed in the corporation's testing of its new procedure. Such notice would highlight potential problems before they occur and alert the FDA to reject the intended changes in production methods to the extent that it deems them unsafe or inconsistent with good manufacturing procedures. For example, if the FDA had knowledge of the new methods Showa Denko was using to manufacture L-tryptophan, it could have required Showa Denko to maintain a higher amount of carbon in the filtration process and prohibited the bypassing of the membrane filter before allowing shipment of the drug into the United States. This would probably have prevented the EMS outbreak. At the very least, the FDA would have a record of the change in the manufacturing process. If an outbreak of a supplement-related disease occurs, having information about changes in manufacturing process would allow the FDA to act more quickly to minimize the damage.<sup>283</sup>

(6) *Require inclusion of literature in the packaging stating contraindications and side effects related to the amino acids*

All drugs come with warnings to those who should avoid the drug, as well as information about the drug's potential side effects.<sup>284</sup> If such literature were required to accompany the products containing amino acids, consumers would be able to exercise informed consent before ingesting them rather than relying solely on advertising claims indicating their good effects. Manufacturers may truthfully advertise that amino acid X

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<sup>283</sup> The FDA did not have the opportunity to inspect the L-tryptophan manufacturing plant until May 1990, almost a year after the EMS epidemic began. By that time, the plant had been shut down and some of the equipment had been removed from the plant. *Hearing, supra* note 1, at 252 (memorandum from Ronald F. Tetzlaff et al. to Richard R. Klug (June 29, 1990)).

<sup>284</sup> Gibbs & Mackler, *supra* note 258, at 212 (1987). The FDA requires product literature to be included with all prescription drugs. This information is used "to allow the physician to make an informed risk/benefit assessment for the individual patient, to inform the patient of what risks a product may have, and to reduce the risks of using the product." There are three basic sources of this information. First, it must be included as a package insert with the product. Second, the Physician's Desk Reference contains product labeling for approved products. Third, any advertisements for prescription drugs must contain a summary of product information. *Id.* at 212-13.



relieves heartburn. However, if fifty percent of those taking amino acid X experience mild nausea from taking it, consumers have a right to be told.

(7) *The FDA should conduct random testing of dietary supplements for contamination*

At random intervals, the FDA should test supplements for contamination. If the supplements exhibit unacceptable impurities, the FDA should fine the manufacturer and, in the case of repeat offenders, recall the product pending FDA review of the manufacturing process. This would encourage manufacturers to control strictly the quality of their products and to monitor continually the safety of their products.

## CONCLUSION

Protecting consumers' rights to choose health-related products is a noble goal, but protecting the consumers' health is paramount. With new scientific advances in medical manufacturing technology taking place at a breathtaking rate, it is of the utmost importance to protect an uninformed public from the hidden risks that lurk in products found on the shelves of local health-food stores. Manufacturers can and will take unjustified risks with the public's health unless they are regulated strictly. None of the three bills proposed in Congress give the FDA enough regulatory power to keep the dietary supplement industry from playing Russian roulette with the public's health. Both the Health Freedom Act of 1993 and the Dietary Supplement Health and Education Act sacrifice consumer safety for consumer choice. The Dietary Supplement Consumer Protection Act, although more consumer-protective than the other bills, still fails to accord the consumer adequate safeguards.

Regulating dietary supplements as drugs will assure consumer safety and might produce other benefits. Regulation might motivate pharmaceutical companies to research these amino acids and discover safe, effective, and health-improving uses for them, without fear that supplement manufacturers will appropriate their expensive research and produce inexpensive supplements. Consumer choice may suffer slightly from diminished access to supplements, but the gains in consumer safety outweigh the costs of requiring consumers to purchase a drug rather than an unregulated dietary supplement. However, since Congress and the FDA have refused to seriously consider the

option of regulating amino acids as drugs, the regulatory scheme Congress enacts should be strict and well-enforced, placing the health of the American public above the pecuniary interests of the supplement manufacturers.

If the U.S. fails to take any action to regulate amino acid manufacturers, additional crises will certainly arise. Somewhere a contaminant will slip into a manufacturing process and become part of a gelcap. People will take amino acids in toxic doses in light of publicized reports that they prevent certain illnesses. Combinations of amino acids will result in unintended drug interaction because the potential for such problems was never adequately studied before sale. It is not a matter of if, why, or how. If amino acids remain unregulated, it is only a matter of when.

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