U. S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Nutritional Products, Labeling, and Dietary Supplements
February 2001

Information Paper on L-Tryptophan and 5-hydroxy-L-tryptophan

Background | Current policy | Reporting problems

Background on L-Tryptophan and 5-hydroxy L-Tryptophan and the eosinophilia myalgia syndrome

FDA took action to limit the availability of dietary supplements containing the amino acid that is the biological precursor of L-5-hydroxytryptophan, that is, L-Tryptophan, because of the association between dietary supplements containing L-Tryptophan and the 1989 epidemic outbreak of eosinophilia-myalgia syndrome (EMS) in the United States. In the summer and fall of 1989, an epidemic outbreak of eosinophilia-myalgia syndrome (EMS) occurred in the United States. This illness is associated with the use of dietary supplements containing L-Tryptophan. In all, more than 1500 cases of EMS, including at least 37 deaths, have been reported to the national Centers for Disease Control and Prevention (CDC), although the true incidence of the disorder is thought to be much higher. Some individuals suffering from L-Tryptophan-related EMS have recovered, while other individuals' illnesses have persisted or worsened over time.

In certain epidemiological studies, more than 95 percent of the cases of EMS were traced to L-Tryptophan supplied by Showa Denko K.K. of Japan. However, many people who consumed Showa Denko L-Tryptophan did not develop EMS and cases of EMS and a related disease, eosinophilic fascitis, have occurred prior to and after the 1989 epidemic. EMS and related disorders are also reported to be associated with exposure to L-5-hydroxytryptophan, which is not made in the same manner as L-Tryptophan (e.g., via fermentation processes). Based on these observations, FDA concluded that other brands of L-Tryptophan, or L-Tryptophan itself, regardless of the levels or presence of impurities, could not be eliminated as causal or contributing to the development of EMS. The serious nature of this disease necessitates that caution be exercised.

Numerous trace level impurities have been identified in the L-Tryptophan implicated in many of the EMS cases. Based on the epidemiologic data, several of these impurities, including 1,1'-ethylidenebis[L-Tryptophan] (EBT), have been associated with EMS. However, the role, if any, of these impurities in EMS is unclear. Animal studies in the Lewis rat showed that EBT caused some, but not all, of the pathologic effects associated with EMS. In addition, these studies showed that significant myofascial thickening and pancreatic fibrosis occurred in rats treated with the control L-Tryptophan that did not contain EBT. These data, as well as data from a number of experiments employing different strains or species of animals indicate that L-Tryptophan, when ingested by susceptible individuals either alone or in combination with some other component in the product, results in the pathological features in EMS. These findings raise serious questions regarding the safety of high dose levels of "uncontaminated" L-Tryptophan. EBT and the other impurities epidemiologically associated with the EMS epidemic cases may only be markers for a yet unidentified substance(s) which trigger(s) EMS in a susceptible host. Other environmental factors could also act as "triggers."

Taken together, these findings support previous suggestions that the L-Tryptophan-associated EMS was caused by several factors and is not necessarily related to a impurity in a single source of L-Tryptophan. Based on the scientific evidence that is available at the present time, we cannot determine with certainty that the occurrence of EMS in susceptible persons consuming L-Tryptophan supplements derives from the content of L-Tryptophan, an impurity contained in the L-Tryptophan, or a combination of the two in association with other, as yet unknown, external factors. Furthermore, results from published studies suggest that the risk of developing EMS may be linked in part to different patterns of xenobiotic metabolism and immune response genes in patients with EMS. Consequently, FDA cannot determine that oral dosage forms of L-Tryptophan and related compounds such as L-5-hydroxytryptophan can be safely used as dietary supplements.

Current policy on the marketing of dietary supplements containing L-Tryptophan and related compounds

Although FDA continues to enunciate its concern about the safety of dietary supplements containing L-Tryptophan and related compounds such as L-5-hydroxytryptophan, this does not mean that FDA prohibits the marketing of dietary supplements that contain L-Tryptophan. Under the Food, Drug and Cosmetic Act (the Act), as amended by the Dietary Supplement Health and Education Act of 1994 (DSHEA), the manufacturer is responsible for ensuring that its products are safe. A firm is not required to obtain premarket review or approval from the FDA of its products before marketing them as dietary supplements. Moreover, a firm is not required to submit scientific evidence to FDA of the safety of its products or ingredients. While we are unaware of conclusive scientific data that would establish that a dietary supplement L-Tryptophan would be safe, if a firm has information that it believes establishes that a product containing L-tryptophan is safe within the meaning of the Act, it could market such a product as a dietary supplement. The burden and responsibility for assuring that such a product is not adulterated under the Act is with the firm and not FDA.

At the present time, an import alert remains in force which limits the importation of L-Tryptophan into the United States, except if it is intended for an exempted use. FDA has provided for the use of manufactured L-Tryptophan for special dietary purposes. Manufactured L-Tryptophan is a lawful and essential component of foods, such as infant formulas, enteral products and approved parenteral drug products, in compliance with Title 21 of the Code of Federal Regulations (21CFR) Part 172.320. L-Tryptophan may also be added as a nutrient to special dietary foods, which are intended for use under medical supervision. FDA continues to permit the use of L-Tryptophan in accordance with the provisions of 21 CFR 172.320(f) in these types of foods, that are intended for use sole under medical supervision to meet nutritional requirements in specific medical conditions, since removal of L-Tryptophan from this permitted use could result in a life-threatening situation for infants or other patients dependent on these products for sustenance.

Reporting of problems associated with the use of L-Tryptophan or 5-hydoxy L-Tryptophan containing dietary supplements:

- Adverse Event Reporting
- Reporting Unlawful Sales of Medical Products on the Internet
- Med Watch

This document was issued in February 2001.
For more recent information on Dietary Supplements
See http://www.cfsan.fda.gov/~dms/supplmnt.html

http://aminoacidbotanicalandsupplementsource.net/Tryp_FDA_Statement.htm