Methods of Testing and Monitoring  
(Short Term and Intermediate/Long Term)

**Chemical Tools**

Mass spectroscopy  
Chromatography (HDLC)

June 1990

Source of toxin confirmed based on products provided by manufacturer

*Oct-Nov. 1990*

Toxin di-TRP identified

**Animal Models**

for assessing toxicity, side effects, etc.

*Oct-Nov. 1990*

Lewis Rat Model developed for mimicking eosinophilia-myalgia syndrome using di-TRP toxin.
IA. Medical Schools in the United States

(JAMA. 1998;280:827-831)
INVESTIGATION METHODS

TWO OPTIONS FOR THE CAUSE OF EM

CONTAMINATED TRP, tablets bear an Unidentified Substance

Causes
Accidental
Intentional

EVALUATE
1. Production methods
2. Containment
3. Shipping methods
4. Product storage and distribution
5. Product mercantile history
6. Product consumer history

PURE TRYPTOPHAN, not due to production, containment or shipping

Causes
Previously undocumented toxicity

EVALUATE
1. Samples of known contaminated product (incl. product containers)
2. "Control" versions of TRP

Focus on commerce and industry

Focus on the product and its victims
Public comments about Tryptophan, its use, and the political-economic market

"Is L-Tryptophan a magic bullet?" (1988/9)  
(Higdon, H. You lead, I'll swallow. Runner's World, Apr89, p82, 4p)

"The tryptophan tragedy; Throw it out." (5/90)  
Houck, C. The food supplement that kills. Woman's Day, 5/22/90, Vol. 53 Issue 9, p36, 5p

"We are confronted with a major public health problem" (6/90)  
HHS Secretary Louis W. Sullivan, M.D., quoted in "L-tryptophan recall broadened." FDA Consumer, Jun90, Vol. 24 Issue 5, p3

"it is possible that the contaminating material triggers a violent autoimmune reaction in susceptible people who are exposed to it" (10/90)  
Harvard Health Letter, Oct90, Vol. 15 Issue 12, p8, 1/2p

"it appears that the problem is not with the amino acid itself, but rather with the product becoming contaminated as a result of a change in the firm's manufacturing process" (6/91)  
Segal, M.; Weisheit, R. L-tryptophan recall expanded. FDA Consumer, Jun91, Vol. 25 Issue 5, p38, 2p

"As many as 10,000 people may have developed the syndrome and 31 have died. . . . These days the Food & Drug Administration is under attack for taking too long to evaluate AIDS drugs and other pharmaceuticals . . . The FDA has chosen to ignore the proliferation of health claims"

"The fault is not entirely the FDA’s . . . through a clerical error, amino acids were inadvertently included in a 1977 list of substances the agency considered "generally recognized as safe." (9/21)  

"what happened to L-tryptophan?" (1/92)  
Vegetarian Times, Jan92 Issue 173, p15, 2p
Public comments about Tryptophan, its use, and the political-economic market

"tryptophan might eventually have been approved as a drug... it didn't work out that way... tryptophan was allowed to be sold as a nutritional supplement... tryptophan in a bottle is not a nutritional supplement... Pure tryptophan in pills or in a bottle is not natural." (11/92 and 12/92)

Richard J. Wurtman, M.D., neuroscience prof. M.I.T/Harvard Medical School;
House of Representatives' Human Resources
& Intergovernmental Relations Subcommittee's hearing.
From "Hearing examines L-tryptophan regulation."
Nutrition Forum (07488165),
Nov/Dec92, Vol. 9 Issue 6, p48

"the L-tryptophan tragedy was indeed an accident waiting to happen...." (11/92)

(FDA blamed for allowing TRP to be sold)
Rep. Patsy T. Mink [D-HI]
H/R Hearing. Ibid.

"[T]he law of the land has required more precise labeling on a box of cornflakes than on the bottle they just opened."
(11/92)

Pollner, Fran. Who's minding the store?
Harvard Health Letter, Nov92, Vol. 18 Issue 1, p4

"Vitamin-sellers refuse to swallow proposed changes." (9/93)

9/20/93, Vol. 15 Issue 38,
Health Care Special... p18A

"30 years of its clinical use (at an average usage of 1.5 million people years of use), no case of EMS linked to tryptophan had been reported prior to this change of manufacturing process... [T] "the five foods and dietary supplements that the FDA has concerns about are among the most promising 'competitors' to a new generation of bioengineered 'work-a-like' medications" (4/94)


"even though it is common knowledge that it was the contamination and not tryptophan per se that made people sick, the FDA has refused to lift the ban." (7/97)

Morgenthaler, John. 5-HTP: The natural alternative to prozac.
Total Health, Jul/Aug97, Vol. 19 Issue 3, p48
The Tryptophan Nutrition Supplement Industry: from Tragedy to Success

Abstract.

During the 1970s, the amino acid tryptophan became a popular adjunct remedy prescribed by psychiatrists and family physicians for depression. Its pure form was produced either by extraction from animal products (an expensive process), or by culturing bacteria in large vats of growth medium (a fermentation process) into which they leaked large amounts of amino acid. By the early 1980s, the United States received nearly all of its tryptophan from Japanese companies which produced it using this early form of bioengineering.

From 1988 to 1989, the Bacillus cultures used to produce tryptophan were genetically altered in attempts to speed up the production process. One year into these efforts, the carbon filtration system used to purify the end-product underwent a design change. From March to April of 1989, an unknowingly contaminated tryptophan batch was extracted from active cultures, processed, and packaged for marketing.

The first cases of eosinophilia myalgia syndrome (EMS) induced by tryptophan by-products erupted in summer of 1989. Following the report of these cases to CDC on October 31st by New Mexico epidemiologists, staff of the Center for Disease Control took just seventeen days to investigate this case cluster and link it to tryptophan purchases. This in turn led to a recall of tryptophan products sold in grocery and natural food stores on November 17th, 1989, followed by a total recall of tryptophan products in March 1990. By May 1990, nearly all of the cases of EMS were traced to a set of distributors, and ultimately a single manufacturer in Japan.

The key events which followed the tryptophan recall are 1) the discovery and identification of the chemical responsible for this contamination in early 1990, 2) the initiation of lawsuits against the Japanese producer in 1991 and 1992, 3) brief discussions and some highly publicized disputes about the safety and efficacy of bioengineering in 1993, 4) the establishment of a series of guidelines and new protocols designed to control and regulate over-the-counter nutritional supplements, leading to passage of the Dietary Supplement Health Education Act in 1993, 5) a successful attempt to control the production and marketing of tryptophan once it made its way back into pharmacies as a regulated product, and 6) an attempt to market 5-hydroxy-tryptophan as a treatment for similar conditions in 1996 (withdrawn from the Over-The-Counter market by 1997).

Currently, tryptophan is marketed for therapeutic use alongside certain prescribed medicines. In 1993, the rights to produce this amino acid were given to several United States and Japanese bioengineering firms. Abbott Laboratories was allowed to produce tryptophan products for hospital use in parenteral formulas. The rights to manufacture a prescription form of tryptophan were given to a Japanese firm, with facilities housed in the United States. The largest market for tryptophan was allotted to several U.S. agritech companies, which produced and marketed it as a supplement for livestock feed.

In just ten years, the tryptophan market has gone from a state of economic failure and public health concern to a rapidly growing bioengineer industry. The current state of this market and its past legal and public health history demonstrate the impact of regulation and the global marketplace on the nutriceutical industry.
Tryptophan Facts Sheet

MINIMUM DAILY REQUIREMENTS for Tryptophan is 3.5 mg/kg. AVERAGE WESTERN DIET provides 1-3 g of Tryptophan per day.

Upon consumption, 80% of TRP is ALBUMIN-BOUND.

UNBOUND TRYPTOPHAN is capable of crossing the Blood Brain Barrier. Tryptophan rapidly diffuses into nerve cells for conversion into serotonin. Receptor research indicates that tryptophan and serotonin play important roles in the hypothalamus, forebrain and spinal cord (i.e. for mediation of pain and effect). Sedative and anti-depressant effects of Tryptophan have been inferred based on these latter findings; no serious side effects have been noted with such use, with the possible exception of manic-depression treatment.

**Chemical pathways for Tryptophan in the Body**

- Associated with NICOTINIC ACID activity
- PROTEIN SYNTHESIS Ribonucleotide activity
- SEROTONIN production
- Serotonin in turn is converted to MELATONIN, a pineal gland substance noted to influence CIRCADIAN RHYTHMS.
- INTERLEUKIN (esp. IL-5)-based autoimmune reactions
- 3-Methylindole or SKATOLE production (fecal odor substance)

A SCLERODERMA-like illness can develop in individuals unable to metabolize tryptophan; Tryptophan or its metabolite is speculated to stimulate expression of a gene that codes for fibroblast collagen synthesis beneath the skin, thereby causing tissue changes.

Similar metabolic changes are speculated to exist in blood cells, thereby resulting in EOSINOPHILIA, an indicator for this syndrome.

Serotonin and L-KYNURENINE are found in the plasma of abnormal Tryptophan metabolizers.