Toxic L-tryptophan: Shedding Light on a Mysterious Epidemic

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PDF creator's note:
Formatting in this PDF version varies slightly from the original; there is a whole other sequence of perhaps more-technical articles, to the references of which I have added URLs; and Part 8 here is one of those articles, which I have inserted into the original sequence as being directly relevant.

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Part 1

Introduction:

Was Genetic Engineering the Cause of Contaminated L-tryptophan and the EMS Epidemic?

http://www.responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/introduction

Knowing my long-standing interest in food purity issues, a friend in California suggested in 1996 that I look into the cause of the tragic eosinophilia-myalgia syndrome (EMS) epidemic that had struck seven years earlier. The outbreak was traced to consumption of L-tryptophan food supplements produced by a Japanese company using genetically engineered (GE) bacteria. Exactly what role biotechnology played in the contamination of the supplement was hotly debated. After thousands of hours of self-sponsored research, I believe I can shed some light on that issue.

I began by interviewing representatives of all the interested parties, including many EMS patients, scientists, attorneys involved in the litigations, the Food and Drug Administration (FDA) and the Centers for Disease Control (CDC). I was generally met with courtesy and cooperation. I discovered sincere differences of opinion among scientists about the possible causes of the contamination that led to the EMS epidemic, and some interesting facts about biotechnology. My follow-up questions — particularly to government agencies about its own findings and about the "problem with the purification process" — generated obvious discomfort. Suddenly, agency personnel to whom I had spoken were "out of the country," would not reply to my emails and/or letters, and in one instance I was told that a CDC spokesperson refused to talk to me and had "referred the matter to their attorney."

Similarly, my several Freedom of Information Act requests were essentially denied, sending me irrelevant information or saying the information requested was proprietary, i.e., trade secret of the manufacturer. Later, I learned from an attorney that the proprietary period had expired, so again I made an FOIA request for specific agency reports. Again I came to a stonewall. An FOIA spokesperson told me that the authors of the reports were no longer with the agency. I listed at least four scientists who were still there, but the FOIA representative simply repeated they were "no longer there" — as if unable to deviate from following a script. This left me with the distinct feeling that FOIA requests are a waste of time on closely guarded issues unless you are a major media journalist or otherwise have the clout to back them up. No matter, in this case, that scores had died from EMS and thousands had been left in various degrees of debility.

I quickly realized that the government agencies were caught between two conflicting mandates: both regulating and promoting biotechnology — and that the latter seemed to have the higher priority.

This review covers both the results of my research and the process of getting to those results. The FDA's and CDC's sudden stonewalling made my work more difficult than it needed to be — and made it clear that they preferred to leave all this "a mystery" rather than to investigate seriously all of the factors that led to the epidemic. I invite a careful reading of the facts that I was able to extract from the parts of the L-tryptophan mess that they weren't able to completely sweep under the carpet.

Part 2

Background Information:

The EMS Epidemic, Initial Research Studies and News of Biotech Link
http://www.responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/background-information

During the summer and autumn of 1989, an outbreak of a tragic and mysterious disease swept across the U.S. First scores, then hundreds of people fell seriously ill with a rare blood and muscle disorder. Doctors and hospital staffs were baffled by the unusual cluster of symptoms and were largely ineffective in treating the victims.

The disease was characterized by an overproduction of white blood cells called eosinophils (1000 or more cells per mm[3]) and severe and often debilitating myalgia (muscle pain). Hence, it was called eosinophilia-myalgia syndrome or EMS.[1] In addition to elevated eosinophils and severe muscle pain, EMS patients exhibited a variety of other symptoms including physical weakness, leg and arm swelling (edema), fever, breathing difficulties, skin rashes, arthralgia, and pneumonia. In some instances, patients displayed signs of congestive heart failure and complete paralysis. An initial report showed that as many as half of EMS patients were hospitalized.[1-3] (Refer also to comments by patients and physicians, Part 8, below.)

By late October of 1989, three physicians in New Mexico discovered a connection between the disorder and patients who had been taking food supplements of L-tryptophan.[1]

On November 11, the U.S. Food and Drug Administration (FDA) issued a nationwide warning that advised consumers to discontinue use of L-tryptophan after 30 potential cases of EMS had been identified in New Mexico. Within a few days of this first publicity alert, the Center for Disease Control (CDC) in Atlanta received reports of 154 potential cases of a similar illness from public health agencies, physicians and the general public in 17 states and the District of Columbia.[1] The FDA quickly issued a recall of all dietary supplements of L-tryptophan sold in doses of 100 mg. or more.

By early December of that same year, reports of EMS cases had soared to 707 in 48 states. One death had been reported and several others were under investigation. Expanding its constraints, FDA imposed an automatic detention at U.S. ports on all L-tryptophan products coming into the country.[2]

For the next few months researchers and epidemiologists traced the multiple retail brands of L-tryptophan involved with the disease back through hundreds of wholesalers, distributors, tablet makers, encapsulators and importers.

On March 22, 1990, the FDA expanded its recall of L-tryptophan to include any dosages of the dietary supplement after it was discovered that one person with EMS had taken less than 100 milligrams a day. Meanwhile, the number of EMS cases linked to use of L-tryptophan had risen to 1,411, including 19 deaths.[3]

In late April, the first preliminary scientific data on the outbreak was reported in meetings at the CDC that linked victims of EMS to L-tryptophan produced by a single Japanese company, Showa Denko K.K. In two separate studies virtually all EMS-case patients whose L-tryptophan

consumption could be reliably traced had taken product that came wholly or in part from this one manufacturer.[4]

L-Tryptophan: A Key Amino Acid

L-tryptophan is known to play a key role in the functioning of the human body as a constituent of protein. It is important for the production of serotonin, a neurotransmitter in the brain that helps regulate sleep, mood, and perception of pain.[5] For years, it was used by many Americans to treat insomnia, depression, premenstrual syndrome and other disorders. The FDA classified it as a food nutrient rather than a drug. Most people obtain sufficient amounts of natural tryptophan in dietary sources contained in high protein foods such as mother's milk, cow's milk, cheese, soybeans, fish, poultry and meat.[1,2,6,7]

All L-tryptophan marketed in the U.S. was manufactured by six companies in Japan. It was available by mail order and through a wide variety of retail outlets including pharmacies, grocery stores and health food stores. It was sold in tablet, capsule, powder and liquid form as a dietary supplement.[8-10]

Showa Denko Altered Manufacturing Process

On July 11, 1990, the *Journal of the American Medical Association* (*JAMA*)[7] published a study showing that 98 percent, and possibly 100 percent, of the EMS cases in Oregon had taken L-tryptophan product made by one manufacturer, Showa Denko, and that there was a significant correlation between these case patients and product manufactured by the company between January and June 1989. The *JAMA* study also noted that Showa Denko produced L-tryptophan by bacterial fermentation using a genetically engineered Bacillus species that had been introduced in its manufacturing process in December 1988.

The following month, a study published in *The New England Journal of Medicine* (*NEJM*),[10] reported that shortly after Showa Denko introduced the newest strain of Bacillus (Strain V) in its manufacturing process, it reduced the amount of carbon powder used in the filtration of L-tryptophan from 20kg. to 10kg. in most batches.

The final product still exceeded the standards specified by the United States Pharmacopoeia, of 98.5 percent purity. The NEJM study's coauthors noted, "Although the powdered carbon may have contributed to the removal of the etiologic agent, it does not explain how the agent was introduced into the product." They said that the newly introduced Strain V bacterium "may have produced larger quantities of the etiologic agent than earlier strains."

High performance liquid chromatography (HPLC) analysis of Strain V samples revealed a number of peak trace contaminants, but only one, Peak E, was initially found to be significantly associated with the EMS epidemic. The researchers observed that because the change in carbon used during manufacturing happened at about the same time as the introduction of the new bacterial strain, it was difficult to assess the contribution of the bacterial strain to the onset of EMS.

Hence, the authors concluded, "The outbreak of eosinophilia-myalgia syndrome in 1989 resulted from the ingestion of a chemical constituent that was associated with specific tryptophan-

manufacturing conditions at one company. The chemical constituent represented by Peak E may contribute to the pathogenesis of eosinophilia-myalgia syndrome or it may be a surrogate to another chemical that induces the syndrome."

News of Biotech Link to Epidemic

A few days later, on August 14, 1990, *Newsday*[11] ran a story that linked genetic engineering to the EMS epidemic. In the article, Dr. Michael Osterholm, coauthor of the *NEJM* study on EMS and epidemiologist at the Minnesota Health Department, said, "Strain V was cranked up to make more L-tryptophan and something went wrong. This obviously leads to that whole debate about genetic engineering."

A flurry of newspaper headlines ensued on genetic engineering gone awry.

In late August, *Science* magazine published an article[12] in which Sam Page, chief of natural products and instrumentation branch at FDA, "blasted Osterholm for 'propagating hysteria.' The whole question: Is there any relation to genetic engineering? is premature-especially given the impact on the industry."

According to the article, Osterholm seemed somewhat bewildered by Page's response. "Anyone who looks at the data comes to the same conclusion," he said, namely, that genetic engineering could be involved. "I think FDA doesn't want it to be so because of the implications for the agency."

The article said that the FDA knew for months that the batches of L-tryptophan implicated in EMS were produced by a genetically engineered organism, but government officials had withheld the information from the public "apparently hoping to keep the recombinant link quiet until they could determine whether it in fact did play a role in the outbreak."

The article also reported that researchers had identified the chemical structure of the contaminant Peak E as a "dimer" — essentially, two tryptophan molecules linked together.

FDA Knew of the Danger

The FDA knew that genetic engineering could potentially promote toxicity in a plant or organism. According to its 1992 Statement of Policy: Foods Derived From New Plant Varieties:

> Plants are known to produce naturally a number of toxicants and anti-nutritional factors… which often serve the plant as natural defense compounds against pests and pathogens… Many of these toxicants are present in today's foods at levels that do not cause acute toxicity… Plants, like other organisms, have metabolic pathways that no longer function due to mutations that occurred during evolution. Products or intermediates of some such pathways may include toxicants. In rare cases, such silent pathways may be activated by mutations, chromosomal rearrangements, or new regulatory regions introduced during breeding, and toxicants hitherto not associated with a plant species may thereby be produced. Similarly, toxicants ordinarily produced at low levels in a plant may be produced at high levels in a new variety as a result of such occurrences (e.g., using recombinant DNA techniques, also known as genetic

engineering).[13]

Four years later in a telephone interview, James Maryanski, FDA biotech policy coordinator, had a different view. I asked him whether the genetically engineered bacteria used by Showa Denko during fermentation could have created toxic impurities in their L-tryptophan product.

"We have no evidence of that, none whatsoever that the technique causes those kind of effects, differently from other methods of modifying organisms," he said.[14]

Apparently Maryanski was unaware that a year earlier, in 1995, a study by scientists at Japan's Research Institute for Food Science, reported that genetically engineered yeast produced an accumulation of a highly toxic compound in yeast cells, compared to non-transformed control cells. The authors concluded, "These results illustrate that careful thought should be given to the potential metabolic products and their safety when a genetically engineered yeast is applied to food-related fermentation processes.[15]

Michael Antoniou, PhD., Reader in Molecular Genetics in the U.K., commented, "[This example] illustrates that a product derived from a GE organism can be devoid of genetic material, but can still unexpectedly contain potentially harmful alterations to a GE product, a novel toxin or elevated levels of a known hazardous substance.[16]

Later in my interview with Maryanski, he said that while theoretically genetic engineering could have played a role in causing EMS, it was not likely the cause:

> We can not rule it (genetic engineering) out. However, close to two dozen cases of L-tryptophan linked EMS (cases) occurred before Showa Denko began using their engineered strain. So, there would have to be a cause other than just the mere engineering of the strains. I can't say that definitively because we don't have a lot of information on these earlier cases.
>
> We can not say definitely that the engineering strains were not a contributing factor. However, we do have enough information that suggests that there are probably other factors involved, that either L-tryptophan itself, or L-tryptophan in combination with something that was the result of the purification process, was the more likely cause. Until the science advances far enough, we really can't say.[14,17]

That was before new information surfaced regarding the pre-epidemic cases (next section).

See also:
- Part 8: The Severity of the Disease — Comments by Victims and Physicians

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Part 3

Pre-epidemic Cases:

A Key to the EMS Puzzle?

http://www.responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/pre-epidemic-cases

> "The existence of cases prior to those that constituted the great bulk of the epidemic is one of the most peculiar and interesting aspects of the EMS outbreak."
>
> — Edwin M. Kilbourne,[1] epidemiologist, Center for Disease Control

For more than a decade now, researchers have been puzzled by cases of EMS that occurred for several years prior to the epidemic.

The Center for Disease Control (CDC) surveillance data revealed nearly 100 cases with onset of illness prior to May 1989, the beginning of the epidemic period.[2] This represented about 7% of the patients for whom complete information was available.[3] CDC estimated that the number of actual EMS cases could be about four times what was reported. This is because of the agency's passive surveillance system and its surveillance case definition, which stressed specificity over sensitivity. The definition was not sensitive enough to recognize the broad spectrum of EMS symptoms and excluded milder cases.[3,4]

CDC researchers calculated that with a more sensitive case definition there could be as many as 5,000 to 10,000 EMS cases in the U.S.4 Using the 7% figure from CDC surveillance data, this would mean that there could be as many as 350 to 700 pre-epidemic cases of EMS. These early EMS victims would have consumed L-tryptophan (LT) pills that were contaminated prior to the manufacturing changes attributed to the etiology of the epidemic. In that scenario, Showa Denko's introduction of the Strain V bacterium and their reduction in activated carbon powder in the filtering process could not have been solely responsible.

Some researchers suggested that a low level of contaminants may have always been present in L-tryptophan-containing products,[5] while others suggested that Showa Denko L-tryptophan might have contained the etiologic agent in lower concentrations or in fewer lots before the manufacturing changes were implemented.[6,7]

Evidence Points to Showa Denko

While limited data has been available on pre-epidemic EMS, findings from product trace-back studies on epidemic cases have been unambiguously clear.

In four epidemiological studies (Oregon, Minnesota, New York and South Carolina) 96-100 percent of epidemic cases traced to Showa Denko.[6] In the two cases that didn't initially appear to trace to Showa Denko, tablets from one (in Minnesota) were analyzed and found to have a chromatographic pattern that was characteristic of Showa Denko L-tryptophan. The other victim (in Oregon) had consumed two different brands, one of which was untraceable and therefore could have been from Showa Denko.[1] CDC researchers concluded, "Of 6 manufacturers of LT, only LT manufactured by Showa Denko KK was clearly associated with illness."[8]

Surprisingly little trace-back data is available on the pre-epidemic EMS cases. In the Minnesota

study on the epidemic, four 1988 cases (September to November) were excluded from the analysis because they were pre-epidemic. Two of these cases were traced to Showa Denko and two were untraceable.[6] In a CDC study, two case patients were found to have consumed pills manufactured by Showa Denko in April 1988, but they also had consumed pills from 1989 lots. Again, only Showa Denko product was found to be case-associated; no other manufacturer's product was linked to EMS.[9]

Curious if pre-epidemic or epidemic EMS cases were linked to other manufacturers' L-tryptophan, I faxed and called about a dozen law firms who had handled Showa Denko cases. None had handled or knew of any definite case associated with another manufacturer.

Stephen Sheller, a Philadelphia attorney whose firm handled over 100 EMS cases, including about 10 pre-epidemic, commented,

> "We have always been suspicious that there were EMS cases caused by other L-tryptophan…. However, we have never had a case that we could confirm that with. All cases that we've had (have) been traced to Showa Denko.
>
> "I thought I had a case with Ajinomoto.... We went through hoops in certain tracing. We had affidavits from companies who insisted they had no Showa Denko product. A diet food, for example, put out by some companies, we traced.... product to a time when Hormel had a strike and they sub-contracted out the work to another company that used Showa Denko L-tryptophan. We were able to confirm direct shipments of Showa Denko product to that company in 1986."[10]

In response to how many EMS victims claimed early onset of illness, Don Morgan, an attorney representing Showa Denko in the litigations, replied in a phone interview, "I don't have a good idea of that... See, there have been thousands of cases... My general impression is that there have been a good number of those cases of pre-epidemic onset of symptoms... more and more cases came up that involved onset before 1989." He said that SDKK has settled some EMS claims related to such tryptophan, and many epidemic-period claims, without admitting causation or legal liability.[11]

Gerald Gleich, M.D., a leading researcher on L-tryptophan/EMS at the Mayo Clinic, recently summed up the matter, saying, "Tryptophan itself clearly is not the cause of EMS in that individuals who consumed products from other companies, other than Showa Denko, did not develop EMS. The evidence points to Showa Denko product as the culprit and to the contaminants as the cause."[12]

Intrigued by the elusive pre-epidemic cases, I contacted a woman with the National EMS Network, a nonprofit organization composed of EMS victims and their families. She put me in touch with several pre-epidemic EMS victims, some with onset of illness dating back to 1984-85. I also found two early cases who had given testimony at the Congressional Committee Hearings on EMS.[13] All of these had received settlements from Showa Denko (except for two who were offered settlements but declined them and then later lost their cases on statutes of limitation).

One case was particularly striking, because the man had onset of illness in November 1987 and stopped using L-tryptophan in February 1988. In his legal proceedings, his pills were tested and

identified as from Showa Denko.[14] His tablets had to have been from lots manufactured about a year and a half before October 1988, — the alleged date when L-tryptophan product became contaminated.[15] (It took several months for product to be packaged in Japan, shipped to the U.S., pass through the distribution chain, and then be consumed for a few weeks before onset of symptoms.)

Birth of a New Disease: A Problem with Diagnosis

In late October 1989, when three physicians in New Mexico first linked L-tryptophan ingestion to patients with debilitating myalgia (muscle pain) and elevated eosinophil levels, the EMS epidemic had already been six months in progress. Prior to that time, no medical classification existed to accommodate the cluster of symptoms associated with EMS.[1] Consequently, physicians were either baffled by this new disease and gave no clear diagnosis, or they gave a diagnosis that fit only one of the patient's predominant symptoms.

In addition to severe myalgia and elevated eosinophils, EMS patients often exhibited fasciitis, scleroderma, rashes, perimyositis, peripheral edema (swelling), and/or other symptoms.14Before news of the epidemic emerged in November 1989, patients seeking medical treatment were sometimes diagnosed with one of these illnesses. Of the eleven pre-epidemic cases on whom I collected information, two were initially diagnosed with eosinophilic fasciitis (EF), one with fibromyalgia, one with scleroderma, and one with neuritis and fibromyalgia. Six had no clear diagnosis, though their physicians had considered some of the above diseases. All were re-diagnosed with EMS after news of epidemic emerged.

One woman who had onset of illness in October 1988 told me she was initially diagnosed as having eosinophilic fasciitis "even though some of the symptoms didn't quite match." A man with onset in March 1989 said that he was not given a diagnosis though "fibromyalgia was tossed around." And a woman who testified at the Congressional Committee Hearings on L-tryptophan stated that her doctor noted elevated eosinophils, but gave no diagnosis because "he knew of no illness which had this cluster of symptoms."

Other Diseases Linked to L-Tryptophan Ingestion

I started searching the medical literature for L-tryptophan-related illnesses other than EMS, and found several studies and a few isolated case reports.

A study at the University of Miami School of Medicine reported (1991) that 65% of EF cases (11 of 17) and 20% of scleroderma patients (2 of 10) had ingested L-tryptophan prior to onset of disease. Eight of the eleven EF cases and both scleroderma patients had pre-epidemic onset, with one scleroderma case dating back to 1985.[15]

A study at the University of Pennsylvania reported (May 1990) that all eight patients with EF had taken L-tryptophan before the onset of their disease. All had myalgias and high peripheral eosinophil counts. Only one of 40 patients with scleroderma had used L-tryptophan preceding illness.[16]

An article on the Los Alamos Conference on EMS (1990) stated, "It is of interest that since 1986, one-half of the patients diagnosed with EF at the Mayo Clinic had been exposed to L-tryptophan;

and 9 of 45 patients in the ARAMIS database with EF (1985-1986) remembered using L-tryptophan before onset of EF."[4]

EF is a rare disease with unknown cause, characterized by scleroderma-like skin changes and peripheral eosinophilia, two common symptoms of EMS. It was first diagnosed in 1974 by Shulman and by 1988 some 200-plus cases had been reported worldwide.[17]

Other studies on L-tryptophan-related EF reported similar findings.[18,19] Some commentators have concluded that L-tryptophan products are the first agents to be implicated as a cause of EF in some patients.[5] Others have suggested that L-tryptophan-related EF and EMS are the same disease.[15] One 1988 case of EF was contacted after news of the EMS epidemic and it was found that she had used L-tryptophan before onset of her illness; she was re-diagnosed as having EMS.[1]

Isolated cases of other diseases have also been linked to L-tryptophan ingestion, including eosinophilic perimyositis20 and lichen sclerosus et atrophicus and acanthosis nigricans.[15]

Although L-tryptophan usage is also associated with cases of these other diseases, researchers never conducted trace back studies to determine whose product was causing all this damage. Commentators assumed that L-tryptophan-containing products in general were probably responsible, but no one did follow-up research to verify this.

To date, the available evidence, from both L-tryptophan trace back studies and EMS legal proceedings, appears to point to Showa Denko product as the source of the problem.

In retrospect, these pre-epidemic L-tryptophan-related illnesses may provide vivid demonstration of the mechanics of the birth of a disease, and how medical science grapples with diagnosing and accommodating a new entity into its medical repertoire. For several years, cases of the new disease were occurring unbeknownst to the manufacturer, government regulators and medical authorities. It took a tragic epidemic in 1989 to bring EMS into focus. For more than a decade since then, scientists have been trying to fit the pieces of the EMS puzzle together. These puzzle pieces fit together only one way, namely, when the scientific model and understanding are correct. The pre-epidemic EMS and other L-tryptophan-related diseases appear to be a key piece in solving the puzzle.

According to attorney Sheller, there is a huge lesson in all this. Because EMS cases went unrecognized for so many years, he said, "One has to wonder about a lot of different things that are in the food supply, because no one has really tested it to find out. The biggest problem is that most of the testing is done for short periods of time."[10]

For more information on the pre-epidemic cases of EMS, see:

- 1987 EMS Victim — Initially Diagnosed with Fibromyalgia
  http://www.responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/1987-ems-victim
- Summary Profiles of 11 Pre-epidemic EMS Cases
  http://www.responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/summary-profiles
- Excerpt from Attorneys Frank Silvestri and John Massicot article on 'EMS Lawsuits'
  http://www.responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/attorney-excerpt

With respect to Showa Denko's L-tryptophan, the next piece in the puzzle is to address the question, Where did the contaminants come from?

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Part 4

Contaminants: Where Did They Come From?

http://www.responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/contaminants

> "Although the [20kg/batch] powdered carbon may have contributed to the removal of the etiological [causal] agent, it does not explain how the agent was introduced into the product."
>
> — Edward Belongia, M.D., et al., *The New England Journal of Medicine* [1]

It's been more than a decade since Belongia and his colleagues raised this salient point about what created the contaminants that caused EMS. Surprisingly, few researchers have addressed it.

Instead, scientists have largely focused on identifying the contaminants in Showa Denko L-tryptophan and trying to replicate EMS in bioassay (test tube) and animal feeding experiments. Unfortunately, their experiments have not yielded satisfactory results.[2]While solid epidemiological evidence supports the conclusion that Showa Denko L-tryptophan caused the EMS epidemic, it is unclear precisely which compound(s) in the implicated product caused the illness.[3]

A leading EMS researcher, Gerald Gleich at the Mayo Clinic, said in an interview, "It doesn't really make a difference where they [the contaminants] came from. The fact of the matter is the thing is contaminated."[4]

This has been the prevailing view of many scientists and regulatory officials, but it misses the big picture.

Baseball analogy: The pitcher's or catcher's fault?

An analogy from baseball may help clarify this crucial issue:

If a new pitcher enters a baseball game in the late innings and throws a pitch that gets by the catcher, causing the winning run to score, who's responsible: the pitcher or the catcher?

If the pitch was what the catcher had called for and/or was thrown within the batting zone or a reasonable distance outside of it, an umpire would probably call it a "passed ball" and it would go against the catcher's record. The catcher should have caught the pitch because it was within a normal range of performance.

On the other hand, if the pitcher throws a ball that was not anticipated by the catcher and/or was significantly outside his normal range, perhaps a knuckleball that bounces in the dirt, then even a good catcher may not have adequate time to react and catch the ball. Thus, the umpire would rule it a "wild pitch" and it would go against the pitcher's record.

Of course, this is an oversimplification of Showa Denko's manufacturing process. Nevertheless, it illustrates the key roles of both bacterial fermentation, which produced the L-tryptophan, and purification, which was supposed to "catch" and remove the impurities.

Anyone familiar with baseball knows that it would be foolish for someone to say that it doesn't matter who the pitcher is, the catcher should be able to catch anything that he throws.

With respect to Showa Denko's manufacturing process, scientists have largely avoided this critical issue involving the role that the genetically engineered (GE) bacteria played in creating impurities in the product. The whole question surrounding Showa Denko's use of GE bacteria appears to have been downplayed or dismissed outright by researchers and government agencies, especially here in the United States — where the biotech industry would stand to lose the most if GE was implicated in, or linked to, a major epidemic like EMS.

Showa Denko's genetically modified bacteria

Showa Denko K.K. is the fourth largest petrochemical manufacturer in Japan. In December 1981, at its Oita complex, the company began construction of a new plant to manufacture L-tryptophan food supplement.

On December 14, 1982, Showa Denko received a U.S. patent (#4,363,875) for its L-tryptophan production process using a novel mutant microorganism, Bacillus amyloliquefaciens strain IAM 1521, obtained from the Institute of Applied Microbiology, University of Tokyo.[5] A mutant of this parent strain was developed by Showa Denko as Strain I, and was used from the start of production on December 16, 1982 to October 22, 1984, when Strain II was introduced.[5]

Strain II was the first of several genetically engineered — recombinant DNA — strains of the parent bacterium used by the company to bolster L-tryptophan yields (see table of genetic modifications -- http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/gm-table).[6] Strain III was used in commercial production from February 23, 1986 to November 21, 1988; Strain IV from November 22 to December 25, 1988 and Strain V from December 26, 1988 until November 21, 1989,[7] when production ceased following news of the L-tryptophan-linked epidemic in America.

Showa Denko, like most Japanese manufacturers of L-tryptophan at that time, used a fermentation process, where a selected bacterial strain was grown from specific precursors under specific conditions.[8] Showa Denko's bacteria were fed intermittently with sterilized glucose (sugar) and anthranilic acid to produce a broth containing L-tryptophan and impurities. The liquid broth was then heat treated and sent to a cell separator. From there it was sent to the purification process, including ion exchange resin columns, a membrane for removal of high molecular weight substances, and towers with activated and granulated carbon powder to remove trace impurities.[9]

Don Morgan, an attorney representing Showa Denko in the legal proceedings in the U.S., commented about the purity of the company's product:

"Showa Denko assured that its LT [L-tryptophan] was at least 98.5% pure, and generally the purity was around 99.5%, and purchasers were advised of the purity."[5]

In the summer of 1988, a German company, A.S. Biologische, tested Showa Denko L-tryptophan and found impurities, one of which was called Peak D. According to internal Showa Denko documents, when Showa Denko was questioned about the Peak D impurity, they admitted that

they couldn't determine a lack of toxicity of the impurity because they couldn't figure out what the impurity was.[10,11]

John Baker, a Denver-based attorney who represented many EMS victims and was a member of the National Steering Committee for litigation against Showa Denko, commented:

"After reviewing the company documents and the depositions of company employees, expert scientists retained by Plaintiffs in the EMS litigation in the United States have opined that Showa Denko appears to have destroyed some of the serial chromatograms that showed contaminants in their L-tryptophan product in 1988."[12]

1988 was nearly a year before the U.S. epidemic began.

However, all L-tryptophan preparations contain various minor impurities, which vary with different manufacturing processes. The high performance liquid chromatography (HPLC) "fingerprint" profiles of impurities[13] are relatively consistent from lot to lot for each manufacturer. The chromatograms from EMS patient-related L-tryptophan (i.e., Showa Denko's product) showed many more small peaks of impurities and much higher levels of several impurities than other manufacturers' products.[14]

The search to identify contaminants

Using HPLC, researchers have found as many as 60-69 trace contaminants in Showa Denko L-tryptophan. Six of these were associated with EMS cases[15] [http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/six-ems-contaminants]. The chemical structures of five of these case-associated contaminants have been identified, and the sixth, Peak AAA, still has not been identified. Four of the case-associated contaminants were tryptophan derivatives and one was an aniline derivative.[16,17]

According to Showa Denko attorney Don Morgan,

> "There is no evidence to suspect that any external materials got into the production process and 'contaminated' the product. The manufacturing process was carefully controlled to assure, among other things, that contaminants did not get into the process. All fermentation products contain a number of impurities. For example, beer contains numerous impurities, most of which I believe have never been identified or isolated."[5]

If the contaminants did not get into the product externally, where did they come from?

One of the world's leading authorities on the biosynthesis of L-tryptophan, Charles Yanofsky, PhD, with the Department of Biological Sciences at Stanford University, said that impurities could be created in several ways:

> "If you significantly overproduce a natural substance, such as tryptophan, it is likely that one or more enzymes of the bacterium will modify tryptophan and produce an unnatural product or products [during fermentation]. Furthermore, tryptophan is unstable at extreme pH's and therefore during purification it is possible that under the conditions used some other compounds produced by the bacterium, or that are used during purification, modify

the tryptophan at some step in purification.

> "Thus depending upon the organism used for overproduction, the level of expression, and the conditions of growth, some fraction of the synthesized tryptophan could be modified. In addition, during purification modification is also possible. In fact there is also a third possibility, namely that a modified form of tryptophan produced during bacterial growth is further altered during purification, i.e., toxic forms of tryptophan could be generated by a two-stage process. It should be possible to determine exactly what happened from analysis of a typical bacterial preparation of tryptophan, before purification, and what contaminants are present before and at different stages of purification."[18]

Yanofsky raises a key point, which suggests that if contaminant(s) are formed at some stage of purification, it doesn't necessarily eliminate what happened during bacterial fermentation as a possible cause or contributing factor.

In an article in the *Medical Post* in 1990 [http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/ems-deaths], Yanofsky explained that the more L-tryptophan that is produced in the fermentation cell, the greater the chance that some side reaction will occur at a greater rate, producing more of some contaminant: "It's possible that one purification scheme may be quite adequate when producing low levels of tryptophan, but at higher levels, it might not be good enough."[19]

Showa Denko's genetically modified strains (II-V) were used to increase the biosynthesis of L-tryptophan through bacterial fermentation. Interestingly, the introduction of these higher yielding GE strains over several years prior to the EMS epidemic appears, on the surface, to correspond directly to the gradual increase in the incidence of EMScases reported by researchers.[20]

Regarding overproduction of L-tryptophan through bacterial fermentation, Yanofsky said (emphasis added):

> "If Showa Denko engineered the bacterium to overproduce tryptophan [which Showa Denko did], then there are many unknowns that would be associated with its overproduction. They probably engineered the strain to overproduce chorismate [which they did], the common aromatic precursor of tryptophan, as well as overproduce all the enzymes of the tryptophan biosynthetic pathway. *Overall this would mean that the bacterium is producing large amounts of about 10-15 metabolites that are not normally produced in excess. The accumulation of these metabolites would, in some cases, lead to the modification by other enzymes, to give products that normally are never produced by the bacterium. One or more of these products could be a compound toxic to man.*
>
> *"Similarly the production of enzymes of the aromatic and tryptophan biosynthetic pathwayscould lead to the synthesis of unnatural products by side reactions that normally do not occur. Again, toxic products could be produced*...."[21]

In fact, in an unpublished study[7] Showa Denko scientists reported that in Strain V, genetic engineering was used to increase and amplify genes for two enzymes used in the biosynthesis of L-tryptophan:

> "The principal difference between strains III and V is that the prs and serA genes for two enzymes required for the biosynthesis of tryptophan PRPP [5-phosphoribosyl-1-pyrophosphate] and serine were increased and their expression amplified in Strain V by standard genetic engineering techniques."

Dr. Yanofsky continued:

> *"Genetic engineering results in the formation of higher than normal concentrations of certain enzymes and products; these could provide the basis for the synthesis of higher levels of toxic substances."*[21]

Thus, from a theoretical perspective, genetic engineering could have played a role in creating metabolites, enzymes and other compounds during fermentation that directly or indirectly caused increased toxins in Showa Denko's product.

Is there any evidence to support this view? Unfortunately, there's very little, because researchers have not been able to study samples of the genetically engineered (GE) bacteria used in Showa Denko's fermentation.

FDA officials say that Showa Denko never gave them samples of their GE bacterial cultures.[22,23] but an attorney representing the manufacturer claims that FDA never followed up on the manufacturer's offer to supply the GE bacteria to FDA via a trained courier rather than by shipping. (Shipping could cause mutations, creating impurities not present in Showa Denko's cultures — see Discrepancy Over Genetically Engineered Cultures [http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/ge-cultures]).[24] The manufacturer eventually destroyed the cultures in 1996.

In the absence of the GE cultures, researchers have studied how the case-associated contaminants could have been formed during the purification process.

One case-associated contaminant that has received significant attention is 3-phenylamino-L-alanine (3-PAA,[25] also referred to as Peak I or UV-5 [26,1]5). 3-PAA is remarkably similar to 3-PAP (3-phenylamino-1, 2-propanediol), an impurity implicated in the 1981 toxic oil syndrome (TOS) that seriously injured 20,000 people (causing 839 deaths) in Spain with an EMS-like disease.[17,6] Both 3-PAA and 3-PAP are aniline derivatives.[6]

Showa Denko used anthranilic acid in the biosynthetic pathway during fermentation to create L-tryptophan:[9] Anthranilic acid + 5-phosphoribosyl-1-pyrophosphate (PRPP) + serine = LT.

According to an *Asahi News Service* report (1992: http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/asahi-news), Showa Denko said that it "did not use any aniline compounds anywhere in the manufacturing process."[27] But an article in the *Journal of the American Medical Association* (*JAMA*) reported that the chemical structures of anthranilic acid and aniline are similar.[20] Could anthranilic acid, which has a similar structure to aniline, get modified to form an aniline-derived compound, 3-PAA?

The Asahi News Service article states, "Showa Denko genetically altered the Bacilli to increase The *Asahi News Service* article states, "Showa Denko genetically altered the Bacilli to increase

the bacteria's production of the serine used to manufacturer L-tryptophan."[27] Serine is a non-toxic, natural amino acid, but its overproduction via the genetically engineered bacteria could have created the contaminant 3-PAA, according to Yanofsky:

> "It is conceivable that by overproducing serine the manufacturer [Showa Denko] caused, or increased, the production of [3-] PAA."[28]

So, theoretically, Showa Denko's genetically engineered bacteria, which were used to overproduce serine in the biosynthesis of L-tryptophan, could quite feasibly have created the toxic aniline derivative 3-PAA by modifying anthranilic acid during fermentation.

However, a study by Toyoda, et al., found that 3-PAA could be formed under the purification conditions used by Showa Denko from anthranilic acid and serine through a 2-step process: Aniline was made first by the heat degradation of anthranilic acid under acidic conditions, and this aniline subsequently reacted with L-serine under basic conditions to produce 3-PAA. The authors stated that formation of 3-PAA from anthranilic acid and serine had not yet been investigated (i.e., during fermentation) and cautioned, "more precise experiments are needed before any quantitative statements can be made regarding the formation of PAA under fermentation and purification conditions."[29]

Interestingly, in the paper's abstract, it states, "These results suggest that PAA could be formed under the *fermentation* and purification conditions used to produce L-tryptophan on an industrial scale."(emphasis added). Why did the authors include "fermentation" in the abstract, if the conditions of their experiment pertained to Showa Denko's purification procedures?

This appears confusing, but a description of Showa Denko's manufacturing process may offer clarification. It states that the fermentation broth — containing anthranilic acid, serine, L-TRP, glucose, anti-foaming agent and impurities — underwent "heat treatment" immediately following fermentation, while the broth was still in the vat, and before it went to the cell separator and onto the filtration system.[9] Technically, the results of the study would suggest that aniline and case-associated contaminant 3-PAP were formed between fermentation and filtration.

Is there evidence of other steps in the process where the case-associated contaminants may have been formed?

A study by Thomas Simat and colleagues at the University of Hamburg, Germany, reported that two case-associated contaminants, IMT and HIT, were 2-tryptophan derivatives formed by the reaction of excess L-tryptophan during purification.[30]

Showa Denko used GE bacteria specifically to produce excess L-tryptophan, i.e., to amplify the biosynthetic pathway of tryptophan to increase yields. This suggests that the GE bacteria did, in fact, play a role in creating case-associated contaminants IMT and HIT, because if excess L-tryptophan had not been produced during fermentation in the first place, then IMT and HIT would not have been formed, or at least not to the same extent, in the downstream processing (filtration).

From the foregoing discussion it is apparent that the formation of these and other contaminants associated with EMS (i.e., EBT and PIC) were the result of specific features of Showa Denko's

manufacturing process — both during fermentation and purification.

Simat and his colleagues reported, "All results indicate that the purification process, not the fermentation, governs the pattern of contaminants in biotechnologically derived Trp."[16]But this claim is contrary to findings of a CDC priority case lot study, which showed "peaks predictive of case status reflected principally the differences in trace components between the bacterial strain V (and IV2) fermentation processes and bacterial strain III fermentation processes."[15]

This contradiction in reports is clarified by Yanofsky's earlier point, that contaminants in SDK product could have formed in two-step processes, where the overproduction or excess of L-tryptophan produced from the GE bacteria during fermentation subsequently reacted to some condition during purification. At first glance, some researchers may fault Showa Denko's purification process. But the two aspects of the manufacturing process — fermentation and purification — are not as separate as some have suggested. Contaminants formed during purification could have been directly influenced by what happened during the GE-enhanced fermentation, which created the initial conditions for the reactions.

Coming back to the baseball analogy, the unbiased umpire must decide whether or not the pitcher threw the ball in the normal range of the catcher, such that he should have caught it. Similarly, unbiased observers must query, Did Showa Denko's GE bacteria create an unexpected situation during fermentation that made proper filtration more difficult and/or out of the normal range of catching impurities?

The view of many scientists has been that it doesn't matter where the contaminants came from — the manufacturer should be able to clean up its product. From that perspective, the problem was due to defective filtration.[3]0 This is similar to saying that it doesn't matter what the pitcher did, a good catcher should be able to catch any ball thrown to him — which anyone familiar with baseball knows is ludicrous.

Nevertheless, let's assume for the time being that their logic is correct. This raises several important questions: Why didn't Showa Denko have proper filtration in place to purify its L-tryptophan? Why were these contaminants so toxic at such low concentrations — well within the U.S. Pharmacopoeia limit — that they caused EMS, a seriously debilitating disease? And, why didn't FDA have more strict regulatory standards in place to prevent such a public health tragedy?

These questions and related issues are addressed in the subsequent sections.

For more on this subject, see also:

- Discrepancy Over Genetically Engineered Cultures
  http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/ge-cultures
- Table of Genetic Modifications of the different strains of Bacillus amyloliquefaciens used [by Showa Denko] to manufacture L-tryptophan, *TIBTECH*, Sept. 1994 (Vol. 12), p. 348
  http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/gm-table
- Six EMS case-associated L-tryptophan contaminants
  http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/six-ems-contaminants

- Comments by Charles Yanofsky, PhD, Stanford University
  http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/yanofsky
- "EMS deaths: Is recombinant DNA technology involved?" *The Medical Post*, Nov. 6, 1990
  http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/ems-deaths
- "Japanese Identify Second Impurity in L-Trypt.," Asahi News Service, June 23, 1992
  http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/asahi-news

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Part 5

Problems with Identifying and Testing for Trace Contaminants

http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/identify-test

> "I must emphasize that the presence of the contaminants in the [Showa Denko] L-tryptophan is astonishingly small and so you require very sophisticated instrumentation and a lot of hard work to even come close to determining the structures."
>
> — Stephen Naylor, Mayo Clinic[1]

Researchers have had enormous difficulty identifying the specific micro contaminant(s) in Showa Denko L-tryptophan that caused EMS.

In June 1990, the Los Alamos National Laboratory hosted a research conference on EMS in cooperation with the CDC, FDA, NIH and the New Mexico Department of Health and Environment. Phillip Hertzman, one of three New Mexico physicians who discovered the link between EMS and L-tryptophan consumption, summarized the conference proceedings in a paper published in the *Journal of Rheumatology*. Regarding toxicity tests on Showa Denko L-tryptophan, he and his colleagues stated:

"Radio-chemical studies have found no contamination. Analyses for 37 inorganic elements and for gross chemical contamination have been negative. Microbiological analyses have detected no significant contamination. While endotoxin has been detected in some lots, this contamination has not been associated with the illness. Several toxicological studies have been unable to produce the syndrome [EMS] in an animal model. Although the L-tryptophan was generally greater than 98.5% pure, high performance liquid chromatography analysis of material from the implicated manufacturer indicates the presence of more than 30 trace contaminants.[2]

Other analyses such as ion chromatography and gel-permeation chromatography identified no case associated contaminants in Showa Denko product from the comparison of batches of control and case-associated L-tryptophan.[3]

Using high performance liquid chromatography (HPLC), researchers have identified six case-associated contaminants in Showa Denko L-tryptophan.[4] Two of these were novel amino acids: EBT[5] (also called Peak 97 and Peak E) and 3-PAA (also called Peak I and UV-5). EBT and 3-PAA were significantly correlated to each other and patients with EMS ingested significantly greater amounts of both (10 and 15 times respectively) than did control L-tryptophan users.6Others reported, "The quantities of the known EMS case-associated contaminants, EBT and 3-PAA, were remarkably small, of the order of .01%, and could easily escape detection.[7]; EBT and 3-PAA levels were 105 and 220 parts per million (ppm) respectively in one Showa Denko (SDK) L-tryptophan lot.[8] Others reported 3-PAA levels at 89 ppm[5] and 100 ppm,[9] while EBT levels varied widely from zero to nearly 300 ppm.[10]

In one study, Center for Disease Control (CDC) researchers found contaminant EBT in case-associated L-tryptophan lots dating back to August 19, 1986,[10] more than two years before the alleged date of contamination.[11] High levels of EBT were positively associated with EMS, but the association lacked statistical significance. The CDC researchers wrote: "While these findings do not rule out the possibility that EBT is the etiologic agent in EMS, they raise the possibility

that other chemical contaminants in manufactured tryptophan modify the effects of EBT or that the causal agent of EMS is an entirely distinct compound.[10]

Still, epidemiological data showed that EBT was the impurity most strongly associated with EMS[12] and the Wilcoxon rank-sum test showed Peak 97 (EBT) was the single most predictive peak of case associated L-tryptophan lots.[13]

Researchers said, "It is also possible that the causative agent (1) may not absorb in the UV [ultraviolet] range [used in chromatography] or (2) may be present in a peak that is hidden beneath another peak (e.g., the large L-tryptophan peak) on HPLC.[2]

Rossanne Philen and Robert Hill at CDC commented on the biological potency of Showa Denko L-tryptophan trace contaminants:

> "The L-tryptophan associated with EMS met the standards for purity established by the United States Pharmacopoeia (USP). Nevertheless, more than 60 micro contaminants have been found in L-tryptophan in amounts of 10 or fewer parts per million. *This finding implies that if one of these 60 or more contaminants is the etiologic agent for EMS, the contaminant must be a biologically potent compound to cause such a serious disease at such a low dosage* (emphasis added).[14]

Animal Studies Fail to Reproduce Full EMS Pathology

An early study of implicated L-tryptophan (L-TRP) in Lewis rats produced encouraging results, replicating many of the pathological features of human EMS.[15]

In late 1990, FDA and NIH researchers reported that Lewis rats treated with implicated L-TRP, but not USP grade L-TRP or vehicle control, developed many of the specific features of L-TRP EMS, including perimyositis, fasciitis, and perivascular inflammation. However, peripheral blood eosinophilia, a common feature of human EMS, was not observed. The large dosage of L-TRP given to the animals was equivalent to human consumption of about 5 grams/day of L-TRP (a recommended human dosage was 1-2 grams/day[16]) and treatment was for 38 days.[15]

"Our study provides evidence that the female Lewis rat is a suitable animal in which to study the effects of implicated L-tryptophan as well as the complex factors involved in the pathogenesis of inflammatory, fibrosing syndromes of muscle and fascia," the researchers concluded.

Douglas L. Archer, Ph.D., the deputy director of FDA's Center for Food Safety and Applied Nutrition, testified before a subcommittee hearing of the House of Representatives on July 18, 1991: "One of the most significant scientific breakthroughs was the development of an animal model for EMS…. After suspect LT [L-tryptophan] was fed to a special stain of rats, several pathological changes that were comparable to those in the EMS patients were observed."[17]

But FDA's initial enthusiasm for an animal model of EMS was short lived.

In March 1993, government researchers led by Laurie Love, M.D., Ph.D., reported that while all animals (Lewis rats) treated with case-associated L-TRP or EBT developed significant myofascial thickening, compared with two control groups, even those animals receiving the

control L-TRP showed a mild but significant increase in the thickness of the myofascia, compared with vehicle-treated control animals. The basic difference between this study and the previous one was that it was with a higher dosage (approx. 5-6 grams/day) of implicated L-TRP for a slightly longer period (42 days).[12]

The study demonstrated for the first time the pathological effects of the EBT contaminant, but the results did not rule out the possibility that other impurities in the EMS-case-associated L-TRP might also contribute to some of the features of EMS. "Our study implicates EBT as one compound found in case-associated L-TRP that can cause some pathological changes in Lewis rats that are similar to some pathological features of L-TRP-associated EMS," according to the researchers.[12]

Myofascial thickening and immune cell changes were most prominent in test animals after administration of case-associated L-TRP, but EBT when combined with control L-TRP was also found to cause immune cell activation in the peripheral blood.

The researchers stated, "This study also strongly suggests that control L-TRP alone [in high doses] plays an important role in this [EMS] and possibly other fibrosing illnesses, because it is associated with mild but significant myofascial thickening and alterations in peripheral mononuclear cell phenotypes, as well as with significant pancreatic pathology."[12]

Edwin Kilbourne, M.D., a CDC epidemiologist, commented, "The meaning of the experimental findings in Lewis rats is not yet clear. The histopathologic changes produced by implicated tryptophan and by EBT mimic a part of the pathology of human EMS but fall short of reproducing the illness."[18]

In 1998, a leading EMS researcher at the Mayo Clinic, Gerald Gleich, MD, updated the status of EMS research [*http://www.nemsn.org/Articles/Gleich%20summary%2098.htm*] after scores of studies:

> "The failure of both the bioassay and the animal feeding experiments to yield robust and reproducible results has been a major disappointment…. As a consequence of the investigations by public health authorities, L-tryptophan produced by Showa Denko KK has been implicated as a cause of EMS. Certain contaminants present in the L-tryptophan have been implicated as candidates for causation. However, we do not know the exact structures and without this knowledge one fears that another epidemic will occur at some time."[19]

For more information on this subject, see also:

- "Current Status of Research on EMS" by Gerald J. Gleich, M.D., Mayo Clinic
  http://www.nemsn.org/Articles/Gleich%20summary%2098.htm

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Part 6

Government Agencies Disagree on Cause of EMS

http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/govt-agencies

The FDA's finding that control L-tryptophan itself was a contributing factor to the syndrome is surprising, because it is inconsistent with the epidemiological evidence linking production lots of implicated L-TRP to cases of EMS. Earlier studies by leading researchers, including those at the Center for Disease Control (CDC), clearly suggested that L-tryptophan itself was not responsible for EMS and that the disease was caused by contaminant(s) in a single manufacturer's L-TRP.[1-3]

In August 1989, researchers headed by Edward A. Belongia, M.D., from CDC, reported in *The New England Journal of Medicine* on a study of EMS cases in Minnesota, "Our data suggests that the syndrome is not produced by tryptophan itself."[2]

Steven Auerbach, M.D., and Henry Falk, M.D., at CDC's Center for Environmental Health and Injury Control, reported, "Even at the time of the initial reports, the epidemiological pattern suggested that EMS was not caused by tryptophan per se, but was probably due to a contaminant. Further research linked LTCP's [L-TRP containing products] ingested by EMS case-patients to specific lots of a single manufacturer of bulk L-tryptophan."[4]

A CDC study by Mary L. Kamb, M.D., and associates clearly established a dose relationship in South Carolina patients who consumed varying dosages of one particular brand (i.e., Showa Denko's). Eighty-four percent had definite or possible EMS from taking more than 4 grams/day of implicated L-TRP, "suggesting that a contaminant and not tryptophan itself was the etiological [casual] agent, since persons in this cohort who took [high doses of] non-implicated brands of tryptophan were not similarly affected."[5, 6]

Gerald J. Gleich, M.D., at the Departments of Immunology and Medicine, Mayo Clinic and Foundation, summed it up: "The issues are twofold: 1. Tryptophan itself clearly is not the cause of EMS in that individuals who consumed product from companies other than Showa Denko did not develop EMS. 2. The evidence points to Showa Denko product as the culprit and to the contaminants as the cause."[7]

But FDA interpreted these findings differently.

In policy statement letters and Congressional Hearings following the epidemic, FDA officials seemed to ignore the consistent epidemiological evidence, in favor of shifting the focus of blame away from Showa Denko's product to include all sources of the food supplement L-tryptophan.

David Kessler, FDA Commissioner, in testimony before a Congressional subcommittee in July 1991, said that FDA was not convinced that the impurities in the bad batches of Showa Denko L-tryptophan were the total answer. Some cases of eosinophilia-myalgia syndrome occurred prior to the 1989 epidemic and had been linked to other batches and to other sources of L-tryptophan. "For that reason, the FDA continues to keep L-tryptophan off the market, although a number of other amino acids continue to be available…."[8]

An FDA letter on L-tryptophan-related EMS mailed to a U.S. Senator stated, "Both initial and subsequent epidemiological studies on the EMS epidemic have identified cases of EMS, and another related disease, eosinophilic fasciitis, that occurred before the 1989 epidemic that appear to be related to other batches or sources of L-tryptophan…. 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 contaminant in a single source of L-tryptophan…."[9]

Stuart L. Nightingale, M.D., FDA Associate Commissioner for Health Affairs, stated,

> "Although *no other company's product has been definitely linked to EMS* [emphasis added], in some instances the source of LT could not be fully ascertained. However, several observations have caused FDA not to eliminate other brands of LT, or LT itself, as causal or contributing to the development of EMS:
>
> - Three to five percent of the EMS cases have not been definitely linked to Showa Denko's product.
> - At least eight cases with EMS-like symptoms have been associated with 5-hydroxy-tryptophan a compound related to LT, but produced from botanical sources.
> - Surveillance for EMS has demonstrated that "non-epidemic" cases were occurring prior to the epidemic in 1989-90…."
>
> "[T]hese findings raise serious questions regarding the safety of high dose levels of 'uncontaminated' LT."[10]

Let's examine these observations and reasons used by FDA to justify its ban on over-the-counter L-tryptophan sales:

1. Three to five percent of the EMS cases have not been definitely linked to Showa Denko's product

The 3-5 percent figure cited by FDA apparently represents EMS cases that were untraceable to an L-TRP manufacturer. However, because any epidemiological study involves a reconstruction of events that led to an outbreak, such a failure to determine all of the facts is hardly unusual. Three to five percent ambiguity is rendered even more insignificant by the FDA's own admission, "No other company's product has been definitely linked to EMS."[11]

The combined results from three trace-back studies (in Oregon, Minnesota and New York) are compelling: Out of 189 EMS cases, pills from all but two traced unambiguously to Showa Denko L-TRP. Of those two, one patient's pills were initially traced to another manufacturer but were later tested by high performance liquid chromatography (HPLC) and found to have a "signature" (pattern of contaminant peaks) similar to Showa Denko product and dissimilar to the L-TRP produced by the company to which it was initially traced. The other case patient whose L-TRP pills were traced to another manufacturer had consumed two different brands before onset of illness, and the second brand was untraceable — which meant it could have come from Showa Denko.[1]

"Taken together, the Oregon, Minnesota, New York, and FDA/CDC product-tracing studies provide strong evidence implicating the tryptophan produced by one company, Showa Denko, as

the cause of the EMS outbreak. All of the exceptions (traces to other companies) are easily attributable to the 'noise' expected in following a product through the multiple levels of its distribution system," stated Kilbourne, a CDC epidemiologist.[1]

Thus, in three major trace-back studies published on the EMS epidemic, 99.5 percent of the cases were traced to Showa Denko's L-TRP, and only one case (out of 189) was not clearly traceable. So it is unclear what FDA's source is for the 3-5 percent of EMS cases that it claimed didn't trace to Showa Denko.

2. At least eight cases with EMS-like symptoms have been associated with 5-hydroxytryptophan a compound related to LT, but produced from botanical sources

If eight 5-hydroxytryptophan [5-HTP]-related cases with EMS-like symptoms are relevant to FDA's policy questioning the safety of L-tryptophan, then why does FDA still allow 5-HTP to be sold over-the-counter as a food supplement?[11]

"No EMS cases have ever been proven to be caused by 5-HTP (or, for that matter, uncontaminated L-tryptophan)," reported Joshua H. Beisler, in Rutgers Law Journal.[11] 5-HTP is not synthetically produced, which is significant because the tainted batches of EMS-implicated L-TRP were attributed to changes in the manufacturing process.[11,2] As an extraction from the seed of an African plant (Griffonia simplicifolia), 5-HTP "avoids the contamination problem,"[12] which bacteriologically-produced L-TRP is subject to. "Consequently, the chance of 5-HTP ever being associated with an outbreak of EMS is extremely small, if not non-existent," said Beisler.[11]

These isolated, non-referenced cases of 5-HTP are a separate issue. Otherwise, FDA would have to include the 20,000 cases in Spain of Toxic Oil Syndrome (TOS), which also exhibited clinical features similar to EMS.[2]; (TOS was linked to consumption of an aniline-derived contaminant, 3-PAP, in denatured canola oil. Implicated L-TRP also contained an aniline-derived impurity, 3-PAA.)[14]

3. Surveillance for EMS has demonstrated that "non-epidemic" cases were occurring prior to the epidemic in 1989-90

As previously explained, the non-epidemic cases of EMS and eosinophilic fasciitis (EF) that occurred for several years prior to the epidemic also appear to be linked to batches of Showa Denko's L-TRP, manufactured using genetically engineered strains II-IV (see *Part 3: Pre-epidemic Cases of EMS* and *Part 4: Where Did the Contaminants Come From?*). FDA has assumed that these cases were associated with other manufacturers' L-TRP, but the scientific literature is quite clear that all traceable EMS cases, whether epidemic or pre-epidemic, were linked to Showa Denko's product.[15,1];The trace-back data on pre-epidemic EMS cases is limited, but still no other manufacturer's L-TRP was clearly associated with the disease,[15,16] and no other company was sued over the EMS tragedy.[11]

Regarding the L-TRP-related EF cases, surprisingly, no trace-back studies have been done. The scientific literature cites one case of L-TRP-related EF that was rediagnosed as having EMS after news of the epidemic.[1] *This suggests that other pre-epidemic L-TRP-related EF cases may also have been misdiagnosed, which would not be surprising because at that time (before the*

clinical discovery of EMS in late October 1989), no medical definition existed for the syndrome, so physicians could not make a proper diagnosis.[13] To clarify this key issue of cases of pre-epidemic EF — and other pre-epidemic L-TRP related diseases that shared common symptoms with EMS, such as scleroderma, fibromyalgia, and perimyositis — I searched and identified eleven such early victims, including two which were EF cases, and all eleven had been rediagnosed as having EMS following the epidemic (see articles referenced at end of this part).

FDA has assumed that these pre-epidemic L-TRP-related EF and other early cases of EMS were caused by other manufacturers' L-TRP. However, the scientific data, albeit limited, combined with information on these early cases traced in legal proceedings, clearly suggests that they were also linked to Showa Denko product, which apparently was contaminated in much lesser degrees and/or in few batches for several years prior to the epidemic.[17]

A study by CDC researchers found varying levels of contaminant EBT in case-associated Showa Denko L-TRP production lots dating back to August 19, 1986.[17]

> "The amount of EBT present in Showa Denko tryptophan varied markedly in the period 1987-1989, presumably reflecting alterations in the manufacturing process," said Arthur Mayeno and Gerald Gleich, researchers at the Mayo Clinic and Foundation. "It is likely that all of the contaminants varied with time. These data are consistent with the hypothesis that a contaminant in tryptophan is responsible for EMS and the sporadic cases of EF between 1986 and 1988."[18]

[T] hese findings raise serious questions regarding the safety of high dose levels of 'uncontaminated' LT — The epidemiological evidence clearly does not support this conclusion by FDA, because the South Carolina study of L-tryptophan users showed that people who consumed high doses (i.e. more than 4 grams/day) of uncontaminated L-tryptophan — from other brands than Showa Denko — were not similarly affected with EMS.[5,6]

In summary, FDA has presented no substantial or compelling evidence to support its position that uncontaminated L-TRP was a causal factor in EMS. All of FDA's reasons and/or observations mentioned above are based on unverified assumptions, including the agency's interpretation of finding in the Lewis rat animal study by Love, et al. (see *Part 5: Problems Identifying and Testing for Trace Contaminants*).

On this latter point, Charles Yanofsky, at Stanford University, commented:

> "If they [toxic products] were produced during purification then it is very unlikely that they would be produced in animals from tryptophan itself. In any event testing high doses of tryptophan (or anything) for long periods in experimental animals is hardly an adequate test. Tryptophan is metabolized by man and important products like serotonin, niacin, and others, are derived from it.
>
> "Over-administration of any natural metabolite is likely to generate byproducts, which may or may not be toxic. Unless you know exactly how a toxin works, and can perform a valid functional test, it is scientifically unsound to claim that an animal shows what could be the same symptoms from over-administration, and therefore conclude erroneously that the same toxin is produced from tryptophan in animals."[19]

"*Administering a natural metabolite at high doses for an extended period is not a valid test of safety*. This procedure might be appropriate for foreign substances which are not known to be metabolized and for which there is no knowledge of the normal levels that are established in the body, but it makes no sense for natural substances that are metabolized.[20]

Any natural metabolite if taken in excessive doses or if improperly purified could conceivably be a source of toxic substances that cause serious health problems. In addition, high levels of a metabolite may influence other metabolic pathways. However, administering sensible levels of natural compounds based on known features of metabolism is very unlikely to cause any medical problem, otherwise that problem would exist naturally."[20]

The EMS problem doesn't exist naturally, evidenced by the epidemiological data clearly linking EMS only to contaminated Showa Denko L-TRP. Therefore the EMS pathological features caused by implicated L-TRP must be fundamentally different from the side effects produced in laboratory animals from over administration (i.e., high doses) of uncontaminated L-TRP, a natural metabolite. FDA appears to have confused the real issue, using the side effects from high doses of control L-tryptophan in animals to divert attention from Showa Denko's contaminated L-TRP — and its genetically engineered bacteria.

Otherwise, if tryptophan, an essential amino acid, were unsafe, why would current FDA policy permit L-TRP usage for medical purposes and in infant formulas?

"It makes no sense at all," said Hans Fisher, Ph.D., who has conducted several animal studies on L-TRP at Rutgers University. "However, if people consume large amounts of LT, the conversion products, serotonin, kynurenine, etc., could have harmful effects. Thus there is reason to suggest care as to LT administration. Too much aspirin causes stomach bleeding!"[21]

But aspirin is not banned from the over-the-counter market — and L-tryptophan is.

This has caused alarm among some public health policy organizations and professionals questioning FDA's real motives.[11]

"Through efforts to increase its regulatory control over dietary supplements, the FDA has exploited this unfortunate [EMS] tragedy and often cites to the incident when recommending greater regulatory control over dietary supplements…. The FDA's ban of L-tryptophan… illustrates that the FDA's motivations for increasing its regulatory power include an unacknowledged political element that exists independently of any desire to protect and preserve the public health," wrote Beisler. [11]

Dennis Mackin, an attorney who represented an EMS victim at trial, commented, "The FDA had a political agenda that truth was not going to deter. Dr. Kessler of the FDA wanted to get control of food supplements in addition to drugs. Therefore it would not behoove his situation to lay the blame on an impurity in Showa Denko's LT product...[H]e testified before the U.S. Congress that it wasn't proven that Showa Denko was the culprit because the 'etiological' agent had not been identified." Mackin said that the judge at his client's trial would not admit Kessler's testimony as

evidence on Showa Denko's behalf because the judge agreed with the plaintiff that Kessler had an agenda in testifying before Congress and had not been subjected to cross-examination.[22]

"At bottom, the FDA public ban of safe, uncontaminated L-Tryptophan is uneven, expensive, and biased in favor of the pharmaceutical industry," said Dean Wolfe Manders, in *Social Policy*. "It is time for appropriate congressional committees to review openly and aggressively the entire matter of L-tryptophan."[23]

Uncontaminated L-tryptophan is safely used today in the United States in infant formulas, medical foods, weight loss products, and animal feed; has never been associated with EMS in any of the many other countries that allow its over-the-counter sale; and may be the only effective treatment for EMS. (It's true: The US Government issued patent number 5185157 on February 9, 1993, to use L-tryptophan to treat and cure EMS.)[11]

See also:

- 1987 EMS Victim–Initially Diagnosed with Fibromyalgia
  http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/1987-ems-victim
- Summary Profiles of Eleven Pre-epidemic EMS Cases
  http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/summary-profiles
- Excerpt from "EMS Lawsuits"
  http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/ems-lawsuits

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Part 7

Unanswered Letters to Government Officials

http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/govt-letters

This section includes three letters sent to government regulatory authorities and researchers concerning:

(1) key information and/or data that appears to have been concealed from the public regarding L-tryptophan and the EMS epidemic, and
(2) discrepancies in the interpretation of research data and in the procurement of samples of Showa Denko's (SDK) genetically engineered strains of bacteria.

After several months, and now years, no one from either the National Centers for Disease Control or the Food and Drug Administration has answered several key, material questions.

1. Dr. Rossanne Philen, at the National Centers for Disease Control (CDC) in Atlanta, did not reply to either a letter or to two follow-up phone messages. At issue is an obvious missing correlation in the CDC epidemiological data, between the known dates of onset of 97 pre-epidemic EMS cases (Swygert, JAMA, 1990) and the reported levels of EBT contaminant in "case-associated" production lots dating back to August 19, 1986 (Philen,American Journal of Epidemiology, 1993). This is more than two years before the manufacturer's product allegedly became contaminated, according to the agency's reports.
   Read letter: http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/philen

2. James Maryanski, PhD, Biotechnology Coordinator at FDA, and Joseph A. Levitt, Director of the Center for Food Safety and Applied Nutrition at FDA, did not reply to a letter that raised several key discrepancies concerning the agency's interpretation of research data used in FDA's Position Statement on L-Tryptophan Dec. 17, 1997. Copies of my letter were sent to both FDA officials by Certified Mail.

   In question is the validity of the arguments used by FDA in its position on L-tryptophan to exonerate the GE strains used by Showa Denko and to implicate L-tryptophan itself as a possible cause of EMS. The latter suggested that consuming any manufacturer's L-tryptophan can cause EMS and led to FDA's banning L-tryptophan as an over-the-counter food supplement. However, on close inspection, this view is not substantiated either by leading EMS researchers (non-FDA), including CDC's (Kilbourne, Philen, et al,J. Rheumatology Suppl, 1996), or from the information available on pre-epidemic EMS cases, which also appear to be unambiguously linked to Showa Denko product made from earlier GE strains.
   Read letter: http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/maryanski

3. Dr. Sam Page, Scientific Director, Center for Food Safety and Applied Nutrition at FDA, returned one call and left a phone message after receiving a letter, but a few days later he was assigned to WHO in Geneva, Switzerland, for two years. Via email correspondence, he said that he had forwarded the letter to someone else at FDA. No one ever responded. A follow-up email to Dr. Page asked him for the name of the person at FDA that he forwarded the letter to. Dr. Page never replied.

The key discrepancy here is that FDA claims that Showa Denko never provided them with samples of the bacteria/GE strains, while an attorney representing the company claims that the FDA never followed up on the manufacturer's offer to provide them with samples. Read letter: http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/page

In addition, several Freedom of Information (FOI) requests were sent to the FDA and CDC, one series in 1998 and another in 2001. In 1998, responses were received from FDA and CDC, but none of the specific documents and/or information requested were supplied. In 2001, FDA FOI staff said that the information requested either "was lost" or "could not be found," and that the people who were involved at that time (1989-90) had all left FDA. I mentioned that Dr. Sam Page is still at FDA and that Dr. Rossanne Philen, Dr. Henry Falk, and Dr. Edwin Kilbourne are all still at CDC, to which the requests related among others, but the FDA FOI staff person repeated that the people involved had left.

This lack of response to key questions is perplexing. Why wouldn't representatives of FDA and CDC have the common courtesy to answer some pretty simple questions? Are they trying to hide something, hoping that the questions will go just away by ignoring them? Their failure to respond suggests that the questions may, in fact, be on target. For more than a decade the whole question of whether Showa Denko's genetically engineered bacteria were a causal factor in EMS has been downplayed or denied outright by these agencies. Now, it appears that both agencies knew critical information about the GE strains, including their link to pre-epidemic cases, but concealed it to protect the US biotech industry. If they did not intentionally hide information, then it would suggest serious blundering in these agencies.

Part 9

The Severity of the Disease: Comments by EMS Victims and Physicians

http://www.responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/background-information

Janet O'Brien, an EMS patient living in California, was prescribed L-tryptophan in 1987 by her gynecologist to treat premenstrual syndrome. Janet said that the food supplement really helped her and that she took it faithfully without a problem until the summer of 1989. Then her symptoms appeared:

"During the acute stage (of EMS), I was in so much pain— joints, bones, skin, everything—that I could barely stand to be touched. I lost about 60 percent of my hair, had no energy, and was usually asleep. At various times, I have had mouth ulcers, nausea, shortness of breath, severe muscle spasms, itching and painful rashes all over, edema (swelling of extremities), concentration and memory difficulties, handwriting problems, balance problems, irritable bowel syndrome, weight gain, visual perception problems, just to name a few symptoms!"[1]

In an interview, Harry Schulte,[2] an EMS victim who is an ordained Catholic deacon living in Cincinnati, said that his physician suggested that he take L-tryptophan to help him sleep better. In March 1989, he purchased the food supplement from a local pharmacy and started taking 2000 milligrams, or 4 pills, a day. Within just a few days he recalls feeling the first effects of the toxic L-tryptophan:

"One night I was sitting, watching TV after I had taken the medicine, and it literally sounded like a shotgun went off in my head. I thought I was going crazy."

In the weeks following, Schulte said that his condition gradually worsened:

"The pain was so intense in my body that if I were to lay on the mattress at nighttime when I went to bed, it would hurt too bad. I would sit up on the side of the bed and try to sleep sitting up because of the intensity of the pain.

"My legs became—you wouldn't believe it unless you saw it—they became as big as a telephone pole. They split and water oozed from them. No amount of medicine they gave me... calmed the pain."

After six years of severe EMS symptoms, Schulte started work again in the fall of 1995. He settled with Showa Denko, and, although he has had some improvement in his stamina, he still lives with constant muscle pain and physical disabilities.

"There is just no amount of money that Showa Denko could have given me that would ever make up for what I lost in all of this. I lost my job. I lost my health. My family broke up. Every day since my illness has come about is tentative."

Bruce Freundlich, M.D., Chief, Division of Rheumatology, The Graduate Hospital, Philadelphia, Pennsylvania, says, "The EMS pain has been the severest I have seen in my rheumatology practice over the years." Most of his (EMS) patients have improved, some substantially. However, the neurological dysfunction of his EMS patients appears to have been persistent and

"some of the worst cases early on still remain very debilitated."[3]

"EMS can cripple. It can cause great pain. It can kill," said Louis W. Sullivan, M.D., Secretary of Health and Human Services in 1990.[4]

One woman, who took L-tryptophan to help her sleep, had consumed no more than 15 pills. She became very sick in September 1989 and was bedridden, and died on Christmas morning, 1990.[5]

According to a study by researchers at CDC (Center for Disease Control), at least 36 people died from EMS as of August 10, 1991. But the authors acknowledged "the true number of deaths related to this disease is probably greater than the number that has been reported."[6]This is because CDC uses a passive surveillance system where physicians and patients voluntarily report cases. Also, the cause of some deaths related to EMS was unclear when pre-existing conditions were involved. CDC stopped monitoring deaths shortly after resolution of the epidemic.

Another study by CDC researchers found that the mortality rate of those with definite EMS was more than three times higher than the general population and of L-tryptophan users in the practice who were not ill.[7]

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Part 10

Conclusion:

Who's Responsible?

http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/conclusion

What created the biologically potent trace contaminants in Showa Denko L-tryptophan that inflicted a seriously debilitating disease at such low dosages of a food supplement?

Researchers still do not know. Some, like Gleich [http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/gleich] and Maryanski, have stated that genetic engineering can't be ruled out as a causal factor, though they favor other scenarios, usually the manufacturer's inadequate purification system.

Showa Denko clearly had a filtration problem, as scientists and government regulatory agencies concur. But this is only clear in hindsight. In 1984, when Showa Denko introduced its first genetically engineered bacterial strain to bolster yields, no one was able to anticipate that novel impurities would appear, which might require more filtration (than does standard bacterial fermentation) to obtain a safe product.

Showa Denko daily monitored the levels of impurities in their L-tryptophan product and kept their product above the USP standard of 98.5% purity. A company position paper stated, "The cause of EMS remains unknown. Showa Denko had every reason to believe its product was safe. L-tryptophan manufactured by Showa Denko met all the purity standards of the United States, and had been extensively tested in animals.[1] An attorney representing the firm said that to his knowledge none of the tests showed any adverse effect on animals or humans, and that prior to the 1989 EMS outbreak, "no complaint of any adverse reaction had been received, and there thus was no reason to believe that the product was ever capable of causing any harm…."[2]

How was Showa Denko to know that their product had been, in fact, contaminated to varying degrees, even before the epidemic, and was silently causing harm that eventually would lead to over 2000 US litigation cases, representing more than $2 billion in settlements? If they had detected a problem, they would have had more filtration in place. But they didn't know, at least for several years, until the EMS outbreak tragically revealed that something was amiss.

Hundreds of studies by researchers worldwide since 1989 have not been able to clearly identify the trace contaminant(s) in Showa Denko's L-tryptophan that caused EMS, and bioassay and animal feeding models have failed to reproduce the disease. How could the manufacturer have done differently in testing their product to prevent the early cases of EMS and the epidemic?

Outdated Regulatory Standards

Sam Page, PhD, Scientific Director at FDA's Center for Food Safety & Applied Nutrition, said that if he had been asked to verify the purity of the [Showa Denko] product, he would not have found anything wrong with it either. *This suggests that no existing regulatory procedure could have caught this problem in advance.*[3]

According to CDC researchers, "Although the tryptophan associated with the epidemic of 1989

was US Pharmacopoeia grade [98.5% pure], the presence of 60 micro contaminants, at least one of which can apparently cause disease at very low concentrations, raises the issue of purity standards for dietary supplements and other bacterial fermentation products as well."[4]

"Other bacterial fermentation products" includes products manufactured via genetically engineered bacteria, which are used to increase yields but simultaneously increase impurities during the fermentation process. Regulators have yet to address the issue of purity standards for GE-manufactured products.

FDA did not require Showa Denko or any other manufacturer to notify it of the use of genetically engineered bacteria to produce a product marketed as a dietary supplement, i.e., a "food." The agency has imposed no new regulatory requirements to deal with the use of genetic engineering in the production of food products. Even after the EMS epidemic, a revised policy statement did not specify any additional safety testing for foods, including dietary supplements, produced using genetic engineering.[5]

Like any business enterprise, Showa Denko simply responded to its regulatory environment. Companies are always looking for new ways to increase yields and reduce costs, without violating regulatory standards. But government regulators did not (and do not) regard genetically engineered (GE) foods or GE-produced food supplements as potentially different from conventional ones — so why would the manufacturers?

Page said that everything that FDA requested from Showa Denko with regard to records and samples of product — even beyond what was requested — had been supplied, with one exception: the genetically engineered material.[5]

Why did Showa Denko withhold from FDA the five genetically engineered cultures/strains, which it eventually destroyed in 1996? (See *Discrepancy over Genetically Engineered Cultures* [http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/ge-cultures].) Was the company trying to hide something that it knew would have negative repercussions on biotechnology or on itself as a manufacturer? These questions may never be answered. Key evidence, possibly the "weapon" itself in this tragic disease and epidemic, has been destroyed, making the case much more difficult to solve than it need be.

In mid-1988, a German company tested Showa Denko L-tryptophan and discovered an impurity, called Peak D,[1] and notified the manufacturer's headquarters (in Tokyo). The headquarters in turn corresponded on the issue with its Oita plant, where L-tryptophan was manufactured, and with Showa Denko Europe (SDE). *One communication from headquarters to SDE reportedly stated, "The issue of genetic engineering is not a kind of information to be disclosed outside the company. We will convince the German company by explaining that we simply changed the refining process.*[8] Changing the refining process implied changing the pattern of contaminants, which would include the Peak D impurity.

Showa Denko had in fact made several changes in their manufacturing process from October 1988 to January 1989, including the introduction of three new GE strains (IV-1, IV-2, and V);[7] a 50% reduction in the amount of activated carbon powder used in filtration of most batches; and the fermentation broth of some batches partially bypassed the ROM filter.[8] CDC researchers later found that the contaminant "peaks predictive of case status reflected principally the

differences in trace components between the bacterial strain V (and IV-2) fermentation processes and bacterial strain III fermentation process."[7] Showa Denko apparently resolved the Peak D issue, but subsequent events would indicate that they created a far more serious contamination problem.

In EMS litigations with Showa Denko in the US, some three hundred thousand pages of Showa Denko internal documents were turned over to a Steering Committee of leading attorneys representing the victims. Paul Rheingold, an attorney on the committee, whose New York firm handled about 270 cases, gave me a copy of his personal notes (70 pages) from the discovery process. He agreed that I could make general use of them so long as I explained "there is no proof it was more than suspicions at the time and subsequent events have undoubtedly proved many of the statements incomplete or inaccurate." Nevertheless, one note said that *Showa Denko recalled all pamphlets mentioning gene technology on December 13, 1989*,[9] just a few weeks after FDA and CDC officials had visited the manufacturer's Oita plant. (The visit was in response to the discovery by physicians and regulators in the US that L-tryptophan consumption was linked to the EMS epidemic then in progress.)

Interestingly, US scientists and government regulators appear to have used the same tactic as the implicated manufacturer, namely, that the issue of genetic engineering is not something to be disclosed outside (to the public). Instead, they offer a vague explanation that the contaminants linked to the EMS tragedy were caused by changes in the manufacturing process. But, from 1984 to 1989, genetically engineered bacteria were a key part of Showa Denko's manufacturing process.

In the absence of clear evidence either way, however, government regulators have acted on the assumption that GE wasn't at fault and that Showa Denko's filtration and/or L-tryptophan itself are to blame (see FDA Policy Statement on L-tryptophan). Hence, Showa Denko has borne the responsibility for EMS, because they had inadequate filtration and marketed batches of a contaminated product that resulted in thousands of consumers being seriously injured — even though the product met the USP standard for purity. This last point — that the regulatory environment was inadequate to assure consumers sufficient purity of the final product — indicates that regulatory agencies should shoulder at least a share of the responsibility. They, along with the manufacturer and biotech scientists, all may have grossly underestimated the power of genetically engineered bacteria to create biologically potent micro contaminants linked to EMS — and still do to this day.

Did a Novel Gene Technology Create a Novel Epidemic?

Assigning blame to the manufacturer's filtration problem is, in my view, only partially correct, because it disregards two crucial elements: the powerful new GE technology that Showa Denko introduced, and the regulatory environment at the time. All three factors — filtration, GE bacteria, and purity standards/regulations — appear to have contributed to creating a contaminated L-tryptophan product.

In the baseball analogy mentioned in Section 4, *Where Did the Contaminants Come From?*, it's easy at first glance to fault the catcher (filtration) when a ball gets by him, but to completely disregard the pitcher (GE bacteria) who threw the ball, as well as the context or rules of baseball within which the ball was thrown (regulatory environment), is absurd — and unscientific. But,

that's precisely what scientists and regulators appear to have done.

This demonstrates a breakdown in scientific and regulatory logic. Regulators continue to claim that biotechnologically-produced foods are substantially equivalent to their natural counterparts, even though they have no clear evidence exonerating Showa Denko's GE strains as a causal factor in creating EMS. To say that the cause of a major disease/epidemic linked to GE technology is "unclear," and that there is no evidence of health risk associated with that technology, flies in the face of scientific logic, common sense, and regulators' mandate to safeguard public health. And it places consumers at risk for another tragic, mysterious GE-related disaster in the future.

Is the EMS tragedy a mystery? Or are biotech scientists downplaying the consequences of their genetic manipulations?

The late George Wald (d. 1997), Nobel Laureate in Medicine or Physiology in 1967 and Higgins Professor of Biology at Harvard University, was one of the first scientists to speak out about the potential dangers of genetic engineering.

In his essay "The Case Against Genetic Engineering: The Recombinant DNA Debate," published in 1976, Professor Wald wrote (emphasis added):

> "Recombinant DNA technology [genetic engineering] faces our society with problems unprecedented, not only in the history of science, but of life on the Earth.... Now whole new proteins will be transposed overnight into wholly new associations, with consequences no one can foretell, either for the host organism or their neighbors.... It is all too big and is happening too fast.... For going ahead in this direction may not only be unwise but dangerous. Potentially, it could breed new animal and plant diseases, new sources of cancer, novel epidemics."[10]

"Novel epidemics" indeed. Wald sounded the alarm thirteen years before the EMS outbreak occurred. Today, after more than 100 studies, scientists know that only Showa Denko's L-tryptophan was clearly associated with EMS. They still do not know the specific contaminant(s) in the product that created the disease.

Something clearly went wrong that Showa Denko, government regulators and biotech scientists did not anticipate. Genetic engineering looms as one of the few possible remaining etiologies for creating the novel trace impurities that caused the disease.

See also:

- Gerald J. Gleich, M.D., Mayo Clinic researcher, position statement for National EMS Network, May 25, 2000
  http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/gleich

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Part 11

Acknowledgments

http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/acknowledgments

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--William E. Crist, July 21, 2005

Part 12

Addendum:

Comments by Scientists and Other Professionals

http://responsibletechnology.org/gmo-dangers/health-risks/L-tryptophan/scientists-comments

Includes:

- "A different perspective on GM food," by David Schubert, M.D., professor, Salk Institute of Biological Studies, published by, and reprinted with permission of, *Nature Biotechnology*, October 2002 (Volume 20)
- Section on L-tryptophan from "Dietary Supplements and Their Discontents: FDA Regulation and the Dietary Supplement Health and Education Act of 1994," by Joshua H. Beisler, *Rutgers Law Journal*, Winter 2000
- 'Is GM Food Devoid of DNA Safe?' by Dr. Michael Antoniou, Reader in Molecular Genetics, UK, published by *Nutritional Therapy Today*, 1996
- "EMS Lawsuits" by Frank Silvestri and John Massicot, published by the *National EMS Network Newsletter*, June 2001 (Vol. 11, Issue 2, p. 6)
- "The FDA Ban of L-tryptophan: Politics, Profits and Prozac," by Dean Wolfe Manders, *Social Policy*, Winter 1995 (Vol. 26, No. 2)
- "Deaths and Crippling from Genetically Engineered L-tryptophan," website article by Philip J. Regal, PhD, University of Minnesota
- Richard Strohman, PhD, University of California at Berkeley, comment on genetic engineering
- Author's letter to Dr. William Rolleston, chairman, The Life Sciences Network, New Zealand, May 15, 2005
- Emails from Dr. Hans Fisher, professor of nutritional biochemistry, Rutgers University, April 27 & 30, 2001