FOOD BIOTECHNOLOGY

TRYPTOPHAN PRODUCTION QUESTIONS RAISED

WASHINGTON, D.C.—Researchers have tentatively traced the cause of eosinophilia-myalgia syndrome (EMS), a rare but sometimes deadly disease affecting blood cells and muscle tissues, to contaminants found in several lots of L-tryptophan. Some of the researchers as well as biotechnology critics, noting that Showa Denko KK (Tokyo) produced the contaminated amino acid by a fermentation process, say that genetic engineering of the producer strains might be the source of the problem.

Representatives from Showa Denko, biotech companies, and the U.S. Food and Drug Administration (FDA, Bethesda, MD), which is one of several federal agencies investigating the EMS incident, say the situation is complex and that the full explanation is not in. With sizable lawsuits now pending against Showa Denko, some of the missing details undoubtedly will be disclosed in courtrooms as well as by laboratories.

By now, EMS has affected more than 1,500 individuals in the U.S. and caused several dozen deaths. Symptoms include overproduction of eosinophils, fatigue, skin rashes, fever, and severe and sometimes debilitating muscle pain. Last year, epidemiologists began associating the EMS cases in the U.S. with the consumption of products containing the amino acid L-tryptophan. Because of the tryptophan connection, FDA officials early this year banned most tryptophan-containing diet supplements.

EMS is being investigated by researchers from the Centers for Disease Control (CDC, Atlanta, GA), FDA, the Mayo Clinic (Rochester, MN) and the Minnesota Department of Health (Minneapolis), and elsewhere. Investigators in Minnesota and New Mexico concluded in 1989 that use of specific lots of L-tryptophan—typically as a nutritional supplement to treat insomnia and depression—was closely associated with cases of EMS. However, according to the Minnesota-based research team, the data show that "the syndrome is not induced by tryptophan itself" and the underlying cause of EMS "remains speculative." Most speculation now centers around two contaminant peaks—one an unusual tryptophan dimer molecule, called Di-L-tryptophan aminal of acetaldehyde, and the other a beta-carboline derivative of the amino acid—found in several lots of L-tryptophan produced by Showa Denko.

The presence of the contaminant molecules in bulk tryptophan products has touched off controversy about how the product is manufactured. According to Showa Denko, several changes in the amino acid manufacturing process were introduced during a 10-year development program, including genetic enhancements of a high-tryptophan producing strain of *Bacillus amyloliquefaciens* and changes in the product recovery and purification steps—specifically, in steps involving use of activated charcoal to remove trace impurities. According to Showa Denko scientists, the dipeptide derivative identified in company batches of L-tryptophan is "unlikely [to be] a secondary metabolite formed during the biosynthesis of L-tryptophan." The company says that it is "very premature to conclude that genetic engineering is in any way related to EMS."

The data so far "in no way prove" but "do leave open the possibility that genetic manipulations played a causal role in the toxicity," says Margaret Mellon of the National Biotechnology Policy Center at the National Wildlife Federation (Washington, DC).

The FDA points out that a causal relationship between use of tryptophan and EMS still is unproved, let alone proof that bioengineering plays a significant part. "A great number of products, medicines and foods, continue to be made by fermentation processes, many involving bioengineered organisms, with no apparent deleterious effects," an agency spokesman says. The correlation of EMS cases with the product purification steps "means we should home in on that," says another FDA official. "However, we can't overlook genetic engineering either."

Several months ago, the International Food Biotechnology Council (IFBC, Washington, DC) issued a report saying that current federal laws and regulatory practices are an "adequate" foundation for evaluating new food products and processes (*Bio/Technology* **8**:822, Sept. '90). Could the IFBC principles, if applied in time, have prevented the EMS incident? "Until we know more of what was done by Showa Denko...we can't say whether the IFBC procedures would have picked it up," says David Glass of the Massachusetts-based biotechnology company Biotechnica International (Cambridge), who was one of the authors of the IFBC report. The IFBC principles "say a lot about detecting unexpected components and conducting toxicology. But until we know all the facts, it's impossible to know what's the cause of EMS." **—Jeffrey L. Fox**

REGULATORY MECHANISMS

FEDERATION STILL FRAGMENTED

LONDON—October 3rd may have seen East and West Germany unified, but the picture for the regulation and approval of biotechnological production and products is far from uniform. Indeed, by occupying center stage in the thoughts and actions of German politicians and administrators, reunification may slow progress towards a truly integrated and coherent framework for the development of recombinant DNA products.

The Gene Law enacted on July 1st has eased the way for companies to obtain approval for production processes. Generally, most systems envisaged for production will fall under the lowest safety level defined by the Law; applications will not, therefore, need to come before a public hearing (as was the case under the Federal Emissions Act). The mere existence of the Gene Law has removed the legal objection to Hoechst's (Frankfurt) production system for recombinant insulin. Consequently, according to Diter Brauer at Hoechst, the company will finalize construction of its plant in Frankfurt next spring and later in the year will start pilot-scale production and apply for a license for the production plant. Gruenenthal (Stolberg) is also going ahead with the construction of its plant for recombinant pro-urokinase, Saruplase, following an approval granted under the Federal Emissions Act in August. Contrary to expectations, Gruenenthal's opponents will not appeal against that decision: Katrine Gruber of the Green Party, who had led the opposition, conceded that an appeal would be very expensive and time consuming and that the chances of success were low.

Instead, Gruber and colleagues plan to direct their resources to opposing the approval of the product itself on the ground that "[Saruplase] is really no better than other products." And if Hoechst's experience is anything to go by, they may find that they have unexpected allies within the Federal Health Authority (BGA). Hoechst is expected to submit a registration application for recombinant