FACT 1 SHEET

The Tryptophan Incident

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EFB

This series of "Fact Sheets" aims to clarify recurring issues that are often invoked inaccurately in the biotechnology debate. They are intended to provide the reader with the essential information and references resulting from the combined contributions of scientists, journalists, industrialists, and governmental, consumer and environmental organisations across Europe.

Allegation

In 1989 over thousand people became severely ill with a new disease called EMS (Eosinophilia-Myalgia-Syndrome), 38 of them died. This new disease was caused by some preparations of the amino acid L-tryptophan, widely used at that time in the US as a non-prescription medication. Since the specific batches of L-tryptophan associated with EMS had largely been industrially produced by genetically modified bacteria, this incidence of disease was ascribed by some people to the genetic modification of the producer bacteria.

Analysis

Between 1980 and 1989 L-tryptophan had been used extensively in the USA as a freely available substance in pills and capsules of 100 mg or more against insomnia, pre-menstrual syndrome and depression, sold largely in health food stores as "natural" inducer of serotonin, a neurotransmitter. It was marketed as a food supplement, not as a drug, a distinction which is important from a regulatory standpoint. Humans take up 1-3 grams of L-tryptophan in dietary proteins. In the autumn of 1989 clinicians observed a few patients with a disease showing a combination of symptoms they had not seen before. Within weeks and with the help of epidemiologists at the Center of Disease Control and Prevention (Atlanta GE) the incidence of this new disease could be traced to the consumption of L-tryptophan made by one specific company, Showa-Denko K.K. of Japan, the major producer of L-tryptophan world-wide. Over 1000 people became sick in a dose dependent manner and 38 died[1, 2]. Some sporadic cases of EMS are believed to have occurred also in users of L-tryptophan preparations made earlier or by other companies. The Showa-Denko K.K. product and other preparations of L-tryptophan were removed from the market and in the intervening period of over ten years no new cases of EMS have occurred. Some of those who had contracted EMS recovered, but there was still higher mortality in those with EMS than in control groups. There was no evidence of delayed onset of EMS in tryptophan users who were not already ill in 1989[3]. L-tryptophan was subsequently banned by the FDA as an over-the-counter drug, while 5-Hydroxy-L-tryptophan is still freely available. The latter compound has for many years been suspected to be associated with some sporadic EMS-like cases[4].

Most of the preparations of L-tryptophan associated with EMS were made in a transgenic strain of *Bacillus amyloliquefaciens,* strain V, which had been developed to increase the yield of tryptophan. However, already previously used strains (III and IV) were transgenic, and, what is more important, at the same time as strain V was introduced, the purification scheme of the product was radically shortened. The amount of active charcoal used to filter was halved and in several batches another purification step, called ROM filtration (reverse osmosis membrane filtration), was left out altogether. The new L-tryptophan preparations, although still over 99% pure, were less pure than previous preparations.

It is obvious that the L-tryptophan preparations in question contained one or more toxic contaminant which could have arisen either during processing, purification and/or fermentation. Several contaminants, present in the order of 0.01%, have been identified, for instance 1,1'-ethylidenebis (tryptophan) = EBT. Batches of the tryptophan derivative 5-Hydroxy-L-tryptophan, whether natural or synthetic, contain similar, but not identical contaminants. The amount of EBT in the many Showa Denko K.K. preparations of L-tryptophan was followed over a period of several years and showed a

highly marked peak in early 1989. This is consistent with the hypothesis that EBT or another contaminant of L-tryptophan was responsible for EMS and sporadic cases of a similar disease called EF which occurred between 1986 and 1988[5]. Showa-Denko K.K. claimed that the contaminants were not present at the end of the fermentation, but arose during the purification process. The company apparently does not have the producer strains any longer. Several litigation cases against Showa Denko K.K. were settled out of court and no published compensation figures are available[6]. It is plausible that the high yields during fermentation led to chemical or enzymatic reactions resulting in minute amounts of toxic contaminants during processing of fermentation products. In animal experiments none of these compounds caused the symptoms of EMS and clinical studies also did not lead to the definitive identification of the etiological agent. There have not been any new outbreaks of EMS since 1989.

Conclusion

The EMS incidence of 1989 was clearly caused by contaminating substances in some batches of the amino acid L-tryptophan, which had been sold as a food supplement. This incidence highlights the importance of checking for pharmacological and toxicological effects of known compounds when their mode of production is changed. There is no evidence that the producer strain being transgenic had any relevance to the EMS outbreak.

References

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INFORMATION

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