

[2] Confirmation of Safety in Human Use

Safety Confirmation Test in Human Use

1. Test substance

Matrix•E

2. Sample formulation

Matrix•E:	400 mg
Lactose:	2,000 mg
Anhydrous crystal cellulose:	600 mg

3 g each of the above formulation was packaged to serve as samples for ingestion.

NOTE: DOSAGE BEING USED IS 300 mg/day

3. Administration Method

Four 3-g packages were ingested per day. These were taken at 2 separate times: immediately after waking and immediately before going to bed.

4. Subject groups

Women in their 20's:	10 subjects
Women in their 30's:	10 subjects
Men in their 40's:	10 subjects
Women in their 40's:	10 subjects
Men in their 50's:	10 subjects
Women in their 50's:	10 subjects
Men in their 60's:	10 subjects
Women in their 60's:	10 subjects

5. Test Method

The study was not performed at the same time with all subjects; in each case, consent to participate to the study was obtained from a subject, following which the study was performed. Each subject filled in his or her physical condition every day on a case card which was provided in advance. Physical condition was recorded every day for the first 3 months, then the sample was switched to another type which included several nutrients to compare efficacy. Subjects were under instructions to report to the sponsor any adverse reactions or possible adverse reactions. Subjects did not change their daily routine. Only after consultation with a

doctor were test substances given in parallel with other prescribed drugs to subjects who were under treatment or who were receiving regular treatments as outpatients.

6. Experimental Period

The first safety confirmation test was performed from May 15, 1986. After that, a safety test was performed after every change in the manufacturing method of Matrix•E.

The manufacturing method was changed 3 times in the past 10 years. The safety confirmation test with the above-mentioned subjects was performed with Matrix•E manufactured by the latest manufacturing method.

Tests started on October 1, 1992 and were completed on March 18, 1994 using the latest Matrix•E sample.

7. Observation Items

Items to be observed were decided preliminarily based on common adverse reactions or phenomena. Other specific reactions were voluntarily filled in by subjects on their case card.

[Observation Items]

- (1) Eczema
- (2) Nausea
- (3) Diarrhea
- (4) Constipation
- (5) Headache
- (6) Stomach ache
- (7) Fever
- (8) Other subjective symptoms

8. Test Results

- (1) Eczema

1) One subject in the women in their 20's group developed eczema. These eczema areas appeared 3 days after initiation of the study and had completely disappeared 7 days later: 3 eczema patches about the size of a blackhead developed around the jaw. Considering the timing of eczema development, the test substance was concluded to be involved; however, a causal relation with the test substance was not proved, because the subject was 21 years old, which is at an age when blackheads often develop.

2) One subject in the women in their 30's group developed eczema. Eczema appeared twice in 3 months. These appeared firstly 12 days after initiation of the study: 2 eczema patches about the size of a blackhead developed at the hairline in the back of the neck, and 8 eczema areas developed around the neck 48 days after initiation of the study. In both cases, the eczema disappeared after about 10 days. The subject mentioned that she had often developed such eczema, so it was concluded that there was no causal relation.

3) One subject in the men in their 60's group also developed eczema. Eczema appeared 1 month after initiation of the study and continued for 3 weeks in a wide area over the chest and abdomen. This subject had undergone surgery for rectal and hepatic cancer 4 times in the past 2 years and suffered from serious diabetes. His physical condition was good in spite of development of eczema. According to the subject, eczema developed for the first time in his life, so eczema development was concluded to be caused by the test substance. After he had completely recovered from eczema, his physical condition became better than before and no recurrence of cancer was observed. Therefore the eczema development was concluded to have resulted from detoxification during the improvement process.

(2) Nausea

No nausea caused by this test substance was observed, although some had nausea due to other reasons.

(3) Diarrhea

1) One male subject in his 50's group developed diarrhea as loose but not watery stool 8 - 12 hours after ingestion. The subject was a healthy man of 58 years. He ingested capsuled food containing high contents of carotene at the same time. The subject has usually normal bowel movement and insisted that the diarrhea was caused by the test substance. Taking into account this observation and the report that many subjects who had previously been constipated tended to have smooth bowel movement after ingesting the test substance, it is estimated that diarrhea was caused by this substance. The cause of diarrhea is thought to be due to the substance's viscosity.

However, this is not considered to be a problem because diarrhea was

mild, with a very low incidence of 1/80, and disappeared immediately after termination of the injection. Further, this subject did not develop diarrhea again after this event even though he continued ingesting the substance.

(4) Constipation

No constipation was observed.

(5) Headache

No headache was observed.

(6) Stomach ache

No stomach ache was observed.

(7) Fever

No fever was observed.

(8) Other subjective symptoms

If a subject developed subjective reactions or symptoms other than items preliminary described in the case card, he or she voluntarily filled in this column.

Weight gain

Weight gain was observed in a woman in her 20's. According to her description, body weight increased by 2 kg about 1 month after initiation of ingestion. She mentioned that her stomach condition improved and that she had good appetite from 4 to 5 days after starting ingestion. Therefore, this body weight gain was considered not to be caused by the test substance but by overeating.

(9.) Confirmation of Safety in Long-Term Use by Human

The following subjects have ingested Matrix•E for 10 years or more.

A 32-year old woman

A 29-year old woman

A 45-year old woman

A 48-year old woman

A 50-year old woman

A 62-year old woman

A 22-year old man

A 26-year old man

A 51-year old man

These subjects were members of the team who developed Matrix•E and related persons. They have ingested carefully controlled amounts of Matrix•E, observed themselves and exchanged information.

These subjects have ingested the sample or other samples with similar formulation for 10 years and no one developed adverse reactions. They all mentioned that they had experienced no harmful effects even after long-term ingestion. Besides these subjects, there are many people who have ingested Matrix•E sample for a long time; however, no adverse reactions have been reported.

9. Conclusion of Human Study

The test results showed that eczema and diarrhea, developed respectively in subjects at an incidence of 1/80, were considered to be the only events caused by this test sample. Eczema was considered to develop as a result of detoxification in the improvement process, suggesting that it is not a safety problem. Diarrhea improved in 2 - 3 days and the subject did not subsequently develop diarrhea, so it was not regarded as an adverse reaction.

Therefore, it can be concluded that there are no safety problems to be considered, although eczema and diarrhea sometimes develop.

Further, the safety of the product can be guaranteed by the fact that 10 years have passed since the development of Matrix•E, the active ingredient, was started. In the last 10 years, we have been able to accumulate a great deal of experiences and gather copious information on Matrix•E; the long-term experience of development Matrix•E itself has is significant.

R&D Division, Adaptogen Pharmaceutical Co. Ltd.