

Meeting Report of the Special Committee for the Safety of Protein Hydrolysates in Cosmetics

4th Meeting

Date and Time: 13:00-16:00, March 9, 2012

Venue: Meeting Room of the Japanese Society of Allergology Office

Attendee: 12 committee members, 9 observers

Kayoko Matsunaga (Chair), Michiko Aihara, Yoshiro Ikezawa, Yasuharu Itagaki, Atsuo Urisu, Zenichiro Kato, Mitsuru Sawa, Yuko Chinuki, Shinichi Sugiura, Michihiro Hide, Eishin Morita, Akiko Yagami

Absentee: Reiko Kishikawa, Hiroyuki Tanaka, Reiko Teshima, Atsuki Fukushima, Yuma Fukutomi (presence by proxy), Kazuo Akiyama (president)

Witness: Kenji Hanno, Haruhiko Aoki, Hiroo Kumagai from Katayama Chemical Inc.

Norio Takeda, Norio Sakaki from Yuuka Co., Ltd.

Observer: Masashi Nakamura (Fujita Health University); Katsuhiro Takano, Hitoshi Sasa, Mariko Sugiyama (Japan Cosmetic Industry Association)

Minutes:

1. Progress of research by each member, current situation of treatment

Discussion was made concerning each member's report on applicable cases, things to be considered and challenges.

2. Matsunaga group research report

Mr. Nakamura reported on the study conducted at Fujita Health University with the participation of Katayama Chemical Inc. and the Japan Cosmetic Industry Association, which had submitted ingredient specimen for the study.

Progress of ELISA test (analysis for 192 cumulative cases) :

[Diagnostic criteria] Positive: 5 units or more; Quasi-positive: 3 to 5 units;

Negative: less than 3 units

[Sensitivity] There were no SPT-negative patients who tested positive in ELISA. ELISA is extremely useful method for patients who cannot undergo SPT due to mechanical urticaria or other disorders.

[ELISA-negative but SPT-positive case] It was estimated that there was no allergic reaction due to wheat intake, but allergic reaction to hydrolyzed wheat powder might remain.

Correlation between ELISA result and severity : ELISA level correlated with severity. It is considered ELISA level of 100 units or more relates to severe symptoms. Further research is required to prove that negative reaction in ELISA indicates remission.

Validation research progress : Sera of 20 patients are being analyzed at five institutions (Hiroshima University, Shimane University, Yokohama City University, Fujita Health University).

Possibility of antigen expression during Gluperal 19S manufacturing process : Specimen submitted by Katayama Chemical Inc. was analyzed by means of ELISA and Western blotting. Acid and heat treatment eliminated conventional wheat allergy patients' reaction but enhanced "Cha no Shizuku" allergy patient reaction. Therefore, acid and heat treatment process is considered the main factor to let Gluperal 19S have a property as antigen.

Cross-reactivity between other HWP's and Gluperal 19S : ELISA test of all the HWP's submitted by the Japan Cosmetic Industry Association revealed that Croda Japan's ingredients have high cross-reactivity. If Croda Japan discloses its manufacturing process, which employs enzyme treatment, and provides samples, more information will be obtained.

The Committee plans to request Croda Japan to hold a hearing session.

Time required for Gluperal 19S-specific IgE antibody to decrease by half : About 5.1 months excluding some exceptions.

3. Explanation by Mr. Hanno from Katayama Chemical Inc.

The following materials were presented:

Attachment 1: Gluperal 19S Manufacturing Process Chart

Attachment 2: Literature for Water-soluble Polymer

Attachment 3: Japanese Standards for Quasi-drug Ingredients (JSQI) 2006 (nature and standard for "hydrolyzed wheat powder")

Attachment 4: Gluperal 19S Analytic Test Results

The company considers Katayama Chemical's Gluperal 19S, which is hydrolyzed with acid and equivalent to water-soluble polymer defined in Attachment 2, a water-soluble substance conforming to "hydrolyzed wheat powder" stipulated in the Japanese Standards for Quasi-drug Ingredients (2006).

Gluperal 19S have also gained approval from the Japan Food Research Laboratories.

Sensitization-inducing property gained through the manufacturing process is being investigated to clarify the mechanism.

4. Action taken by the Japan Cosmetic Industry Association

1) To identify causes, the Association is publicly seeking researchers for the following themes
(12/22/2012-01/21/2013)

(1) Likelihood for all the hydrolyzed wheat proteins contained in the cosmetics and pharmaceutical cosmetics to be causative substances for systemic allergy

(2) Mechanism of systemic allergy induced by hydrolyzed wheat proteins

Study results submitted by March 31, 2013 will be utilized by the cosmetic industry for safe products supply and also presented to responsible authorities including MHLW so that applicable safety measures can be taken.

Applications are now coming and research will start on April 1.

2) Measures to be taken if health problems should occur in relation to cosmetics (including

quasi-drugs/cosmetics)

Apart from the notification duty based on the Pharmaceutical Affairs Act, the Association has asked Dr. Sugiura (Nagoya University) to establish the system to collect and share health hazard information under the cooperation of medical institutions in order to prevent the proliferation of damages.

- 3) The Association posted message (dated December 16, 2012) on its website to call attention of individuals who developed wheat allergy after using “Cha no Shizuku” soap bar (old product name).

4) Submission of ingredients

Hydrolyzed wheat proteins and derivative ingredients (Hydrotritricum WQ, Crodason W, Tritisol, Cropeptide W) were submitted to the Committee.

As hydrolyzed wheat gluten might be contained besides hydrolyzed wheat, effort is underway to obtain ingredients. (Cognis Japan has already submitted ingredients. As to imported hydrolyzed wheat gluten powder, Provital is being asked for submission.)

Croda, which declined to participate in the Committee Meeting, will be requested to join again.

5. Report by Yuuka Co., Ltd.

Number of cases as of February 24 collected from May 20, 2011 through Feb. 10, 2012

- (1) Medical certificates submitted by customers: 1567 in cumulative total (256 cases were diagnosed as positive)
- (2) Notification from healthcare professionals (through the Pharmaceutical and Medical Devices Agency): 214 in cumulative total (27 cases were diagnosed as positive)

*Cumulative total includes overlapped data as notification is sometimes offered by both customers and medical institutions.

6. Case registration site

Case collection site has been completed for grasping accurate number of patients.

List of institutions providing support: List was posted to show institutions that had reported the cases to MHLW (Ministry of Health, Labour and Welfare) and had been admitted to the system as registered institutions. Dr. Matsunaga is uploading the data (more than 292 cases were reported and 204 institutions requested provision of Glupearl 19S).

Registration system is scheduled to be open to the public on March 12 after approved by the Committee. MHLW will provide the link to the Japanese Society of Allergology, through which the system is accessible. Doctors are encouraged to register.

Dr. Sugiura explained how to operate the site for providing information to the public and for collecting applicable data as follows:

Every case must be registered by a physician who actually examined a patient.

Confirmation, addition and modification of data may be conducted only by a physician who registered the applicable data.

The system is established on groupware applications and allows only the authorized members to upload the data, and only the administrator can control the entire system to assure security.

Case data collected will be open to the public and the Committee members will be provided with the information about how to use the site.

7. Progress report presented by absentees

Dr. Teshima: “Study on Hydrolyzed Wheat’s Sensitization and Elicitation Property using Animal and Cell Models”

Dr. Tanaka: “Effect of Oral Hydrolyzed Wheat on Percutaneously Sensitized Mice”

The above studies are under the sponsorship of the Japan Cosmetic Industry Association.

8. Joint research of reported cases including prognosis investigation

Dr. Matsunaga suggested that problematic cases be chosen at the next meeting so that they could be further studied through challenge test or other means, and this suggestion was agreed. There was an opinion that risk, reproducibility and others should be investigated after authorized by the Ethical Review Board at each institution.

9. English version of the diagnostic criteria

Regarding the diagnostic criteria translated into English by MHLW, Dr. Matsunaga requested the members to make suggestions, if any, as to medical terms and others.

10. Research and activity scheduled for the following year

Apart from the ongoing activities, such as identifying “Cha no Shizuku” allergy causes, developing animal model and establishing health hazard report system, it was proposed to expand research to various hydrolysates contained in cosmetics (e.g. rice, silk) and also analyze epitope and other antigen determinant construction so that results can be applied to other health problems.

11. Next meeting schedule

Sunday, May 13, 11:45~12:45 at Osaka International Convention Center (10-2)