Food Safety and Quality Assurance of Food Products

Yoko OBAYASHI

Quality Assurance & External Scientific Affairs Dept.
Ajinomoto Co., Inc.

Presentation outline

1. The international food code to protect public health

   ------ Codex Alimentarius

2. Industry's effort to guarantee the safety of the substance

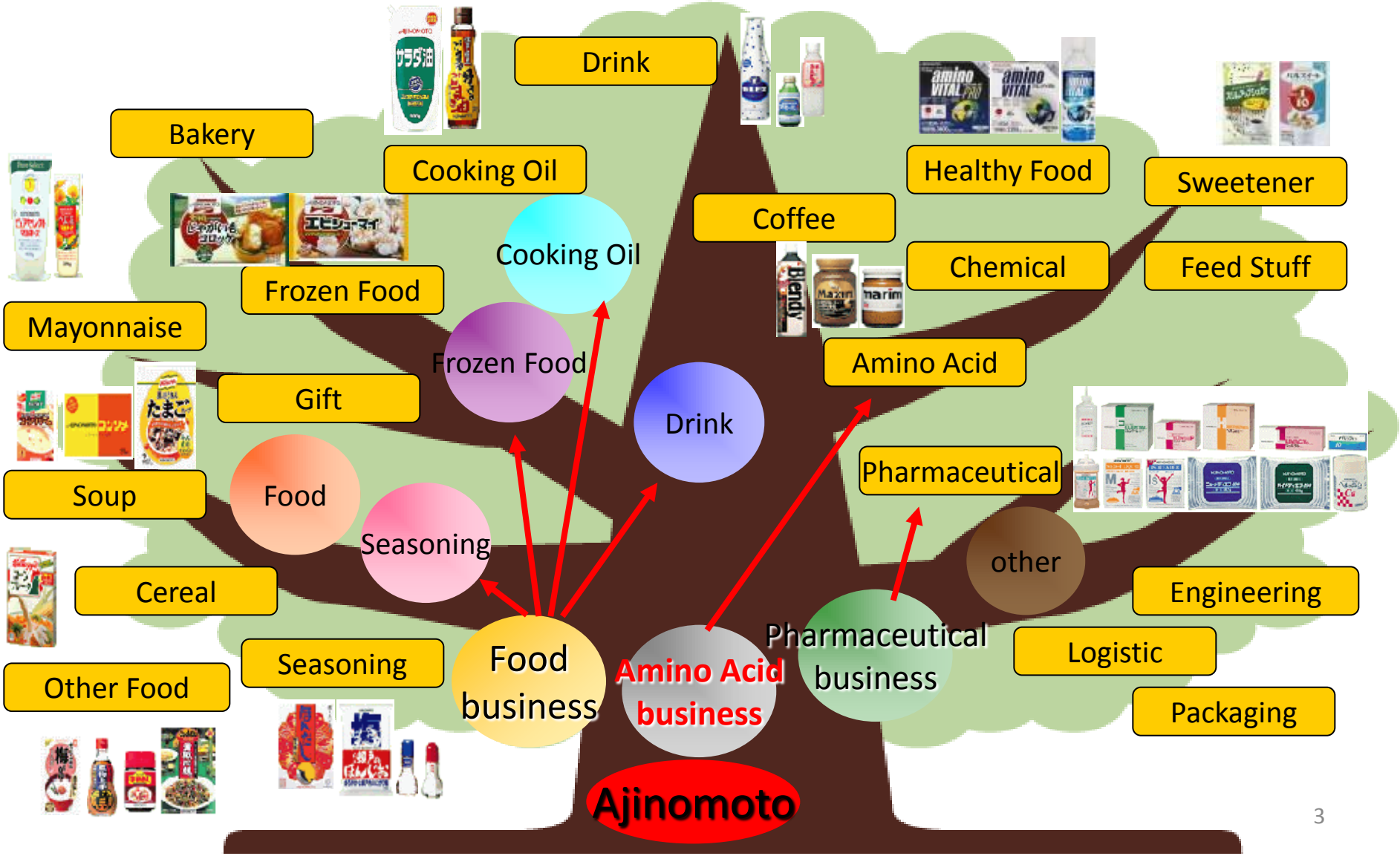
   ------ in case of fermentation product, MSG

3. The importance of setting an appropriate specification of food compounds ---- in case of fermentation product, L-tryptophan

4. GMP and the management of quality assurance of our company

Products of Ajinomoto Group

Net sales including overseas affiliates (FY2011) : 1,197 billions of yen



What is Codex Alimentarius?

Codex = collection of statutes Alimentarius = nourishment

- Food and Agriculture Organization of the United Nations (FAO) and the World Health Organizaion (WHO) determined to formulate **international food standards** in 1962.
- Codex Alimentarius Commission was established by FAO and WHO to develop food standards and ensure their global implementation.
- The food standards are called Codex Alimentarius.
- Codex Alimentarius contributes to the protection of public health and fair practices in the food trade.
- Codex standards are the reference for food trade under WTO Agreements (SPS & TBT agreement).
- Codex Alimentalius Commission advises that each nation should adopt Codex standards as far as possible, when formulating national policies regarding food.
- Codex Alimentarius Commission consists of more than 180 countries, as of 2012.

Codex standards, guidelines and codes of practice

	Number of codes
Commodity standards	186
Food Labelling	9
Food Hygiene	5
Food safety risk assessment	3
Sampling and analysis	15
Inspection and certification procedures	8
Animal food production	6
Contaminants in foods (maximum levels, detection and prevention)	12
Food additives provisions	1112, covering 292 FAs
Maximum limits for pesticide residues	2930, covering 218 pesticides
Maximum limits for veterinary drugs in foods	441, covering 49 drugs
Regional Guidelines	3

Regulatory system for ensuring the safety of food additives

Whether or not the substance is natural, the following **official approvals** are required.

1. The safety assessment of the substance

The safety assessment and the setting of ADI (acceptable daily intake) by JECFA (Joint FAO/WHO Expert Committee on Food Additives)

ADI = NOAEL / 100 (safety coefficient)

NOAEL : no observed adverse effect level

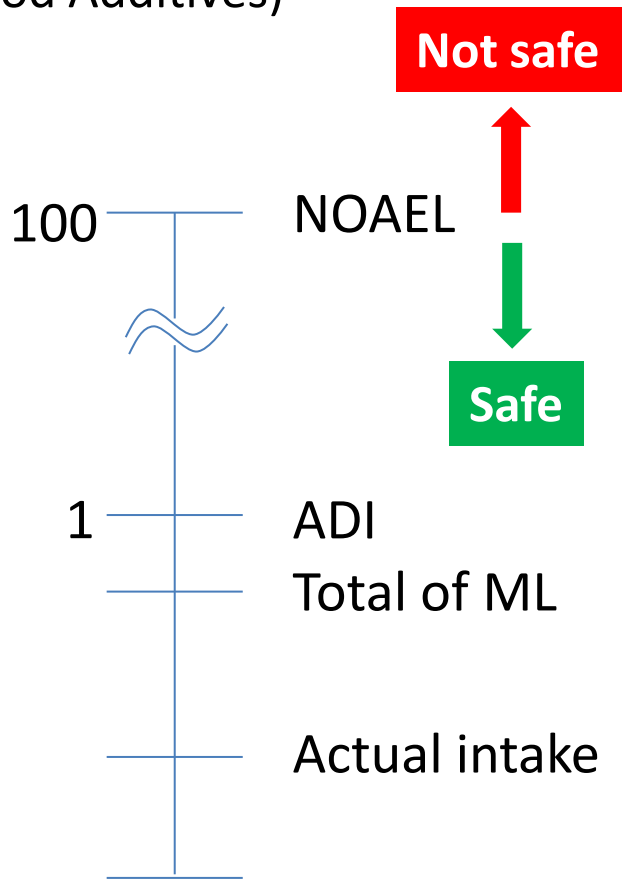
2 . The setting of the criteria for use

Setting of maximum limit (ML) on each food category

"Codex General Standard for Food Additives" (GSFA)

3 . Setting the specification

The maximum concentration of purity, impurity, contaminants, and the analytical methods to quantify these amounts must be standardized for the purpose of preventing low-quality products from going on sale.



Industry's effort to guarantee the safety of the substance

----- in case of fermentation product, MSG -----

MSG : monosodium glutamate

Safety assessment of monosodium glutamate(MSG) over the world

MSG: A sodium salt of glutamic acid, which is one of amino acids composing proteins. Free glutamic acid is a natural umami substance contained at relatively high level in seaweed, fish sauce, cheese, tomato, etc..

Organization	Year of assess.	Comments
JECFA Joint FAO/WHO Expert Committee on Food Additives	1987	ADI not specified
EC/SCF European Commission Scientific Committee on Food	1990	ADI not specified
US FDA Food and Drug Administration	1980, 1995	**GRAS status(Generally Recognized as Safe)** has been acknowledged since 1958.
FSANZ Food Standards Australia New Zealand	2003	Safety of MSG was reaffirmed through the review of data.

ADI not specified : the total dietary intake of the substance at the levels necessary to achieve the desired effect in food does not cause a health hazard. A term applicable to a food substance of very low toxicity.

The first report about so-called Chinese Restaurant Syndrome (CRS)

Dr. Kwok's report

The New England Journal of Medicine, April 4(1968)

After a meal in Chinese restaurant;

- Transient & subjective symptoms:
  burning, numbness, tight sensation
- Candidates of causing agents:
  Cooking wine, MSG, High sodium salt

Multicenter Clinical Study was conducted in late 1990s.

Publication:

Multicenter, double-blind, placebo-controlled, multiple-challenge evaluation of reported reactions to monosodium glutamate,

Geha R.S., et al. Journal of Allergy and Clinical Immunology, 106(5): 973-980(2000)

Multicenter Clinical Study --- Methods

Protocol A (130)
- 5g MSG
- Placebo
- in beverage

Placebo : positive MSG : negative	Placebo : negative MSG : positive	Positive to both	Negative to both
17(13.1%)	50(38.5%)	19(14.6%)	44(33.8%)
Eligible for protocol B			Ineligible for pro-B

Protocol B (70/86)
- 1.25, 2.5, 5g MSG
- placebo
- in beverage

[Reproducibility of symptoms in protocol A and B]

Placebo : positive MSG : negative Completed protocol B	Placebo : negative MSG : positive In both protocol A & B	Reproducible reactions Across A & B
37	19	14
Ineligible for protocol C	Eligible for protocol C	

Prot. C(12/19)
- 5g MSG x 2 times
- Placebo(sucrose)
- in capsule

Only 2 out of the 12 subjects reported symptoms after 5g MSG challenges

Prot. D(2)
- 5g MSG x 3 times
- Placebo
- in capsules with meal.

subject	Placebo challenges Symptoms reported	MSG challenges Symptoms reported	Reproducible response
B	0 0 0	0 0 3	0
C	0 0 1	2 0 1	0

Multicenter Clinical Study

Conclusion

- Large doses of MSG given without food may elicit more symptoms than a placebo.
- Neither persistent nor serious effects from MSG ingestion were observed, and the frequency of the response was low.
- The responses reported were inconsistent and were not reproducible.
- The responses were not observed when MSG was given with food.

FASEB recommend as follows,

In order to confirm the MSG symptom complex, three DBPC challenges on separate occasions must reproduce symptoms with the ingestion of MSG and produce no response with placebo.

The importance of setting an appropriate specification of food compounds

---- in case of fermentation product, L-tryptophan ----

Health hazard caused by L-Tryptophan which followed the official specification

The outline of the health hazard

- Place & time : US, 1989 - 1992
- What happened : Pathogenesis of Eosinophilia-Myalgia Syndrome (EMS) was reported.
- How many cases : 1511 cases from 52 states, 38 cases were fatal.
- The symptoms of EMS :
  1. Severe inflammation including severe eosinophilia (>1000/mm^3), muscle pain, Joint pain, edema, leukocytosis, etc..
  2. Complication of nerve system, heart, and lung causes death.

The cause of pathogenesis

- 95% of the patients regularly ingested L-Trp as health foods, which was produced by Company S (Japanese company) during the specific period (mid-1989) and derived from the specific lots.
- The daily intake of the patients was 0.15-17g/day, with the average of 2.6g/day.

The countermeasures taken by FDA

- In Feb.1990, FDA ordered the recall of all L-Trp-fortified products.
- In Mar.1990, FDA prohibited the import of L-Trp-containing products and L-Trp as drug substance.

No further case was reported after the actions above.

Investigation into the cause of EMS by L-Trp ingestion

The research organizations in charge

◆USA : Cooperatively performed by FDA , CDC (Centers for Disease Control and Prevention), and NIAMS(National Institute of Arthritis and Musculoskeltal and Skin Disease).

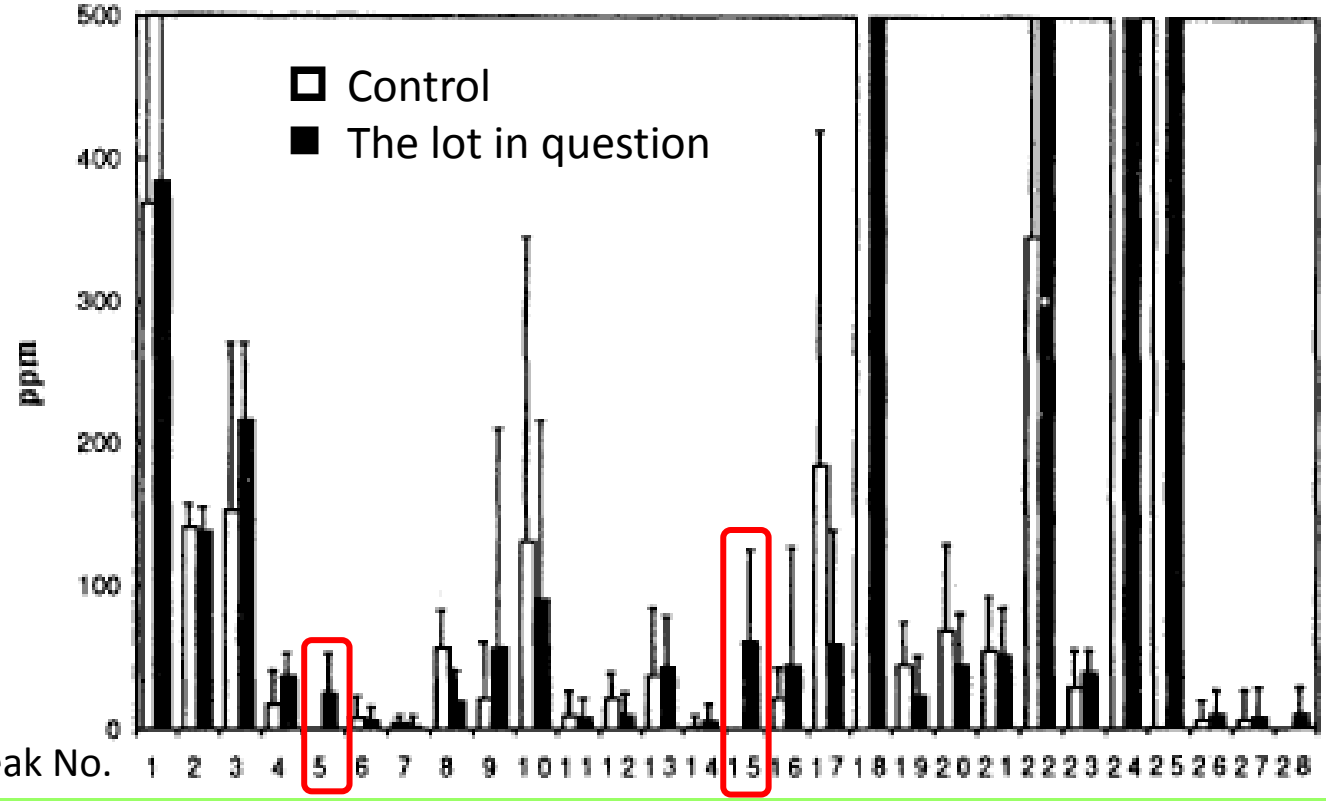
◆Japan : In May 1990, the task force was established in Ministry of Health, Labor and Welfare.
It involved National Institute of Health, Tokyo Univ., Ohsaka Univ., Institute for Protein Research, Ajinomoto Co. Inc., etc..

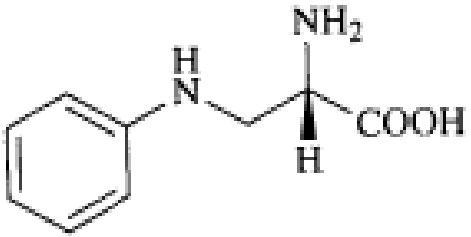
What was studied

1. The identification of impurities in the lot in question, along with the investigation of pharmacokinetics of the substance.
2. Efforts to establish the animal model of EMS caused by L-Trp
3. Elucidating the mechanism of development of EMS using L-Trp and the impurities in in vitro and in vivo experiment.
4. The research of food hygienics to prevent recurrence.

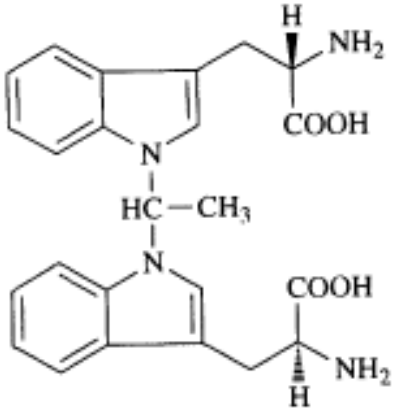
Investigation into the cause of EMS by L-Trp ingestion

The content of impurities of the lot in question





Peak5 : PAA



Peak15 : EBT

- 6-7 peaks were found to statistically correlate with the onset of EMS. Among them, peak 5 and 15 are contained at relatively high level.
- The purity of the lot in question was more than **99.6%. This is in accordance with the official specification for pharmaceuticals and food additives** over the world.
- **The amount of the activated carbon** used on the process of purification was lower than usual.

reference: Toyo'oka T, Yamazaki T, Tanimoto T, Sato K, Sato M, Toyoda M, Ishibashi M, Yoshihira K, Uchiyama M. Chem Pharm Bull (Tokyo). 1991 Mar;39(3):820-2.

Investigation into the cause of EMS by L-Trp ingestion

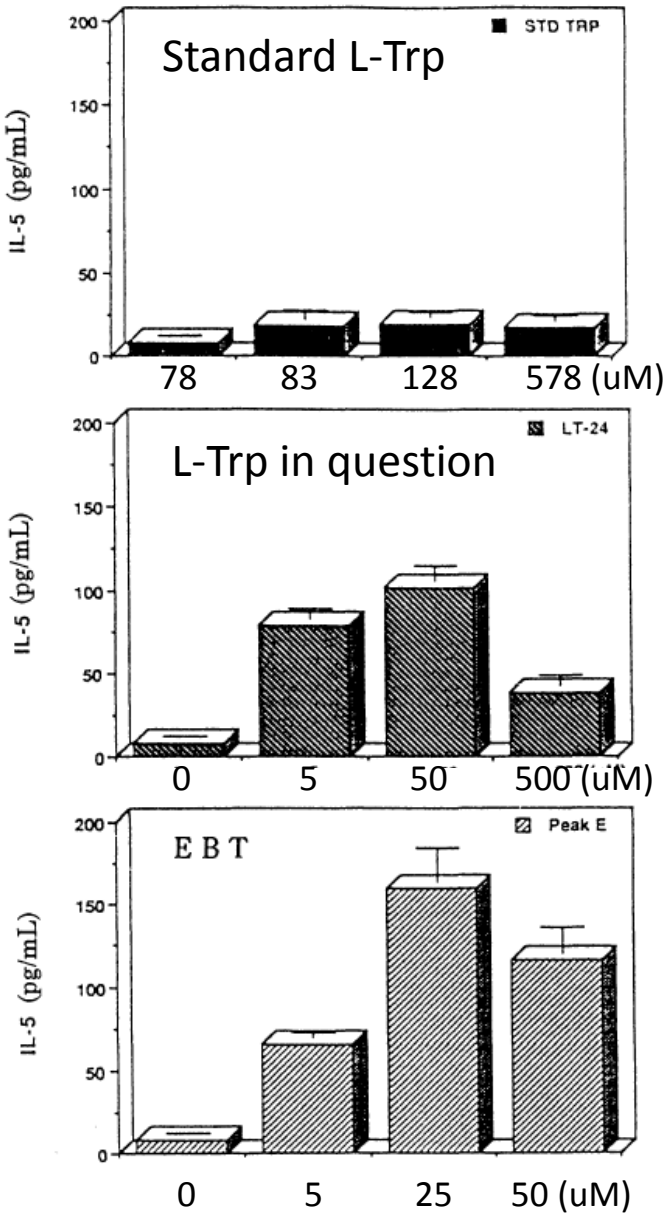
The attempt to mimic EMS in animal experiment

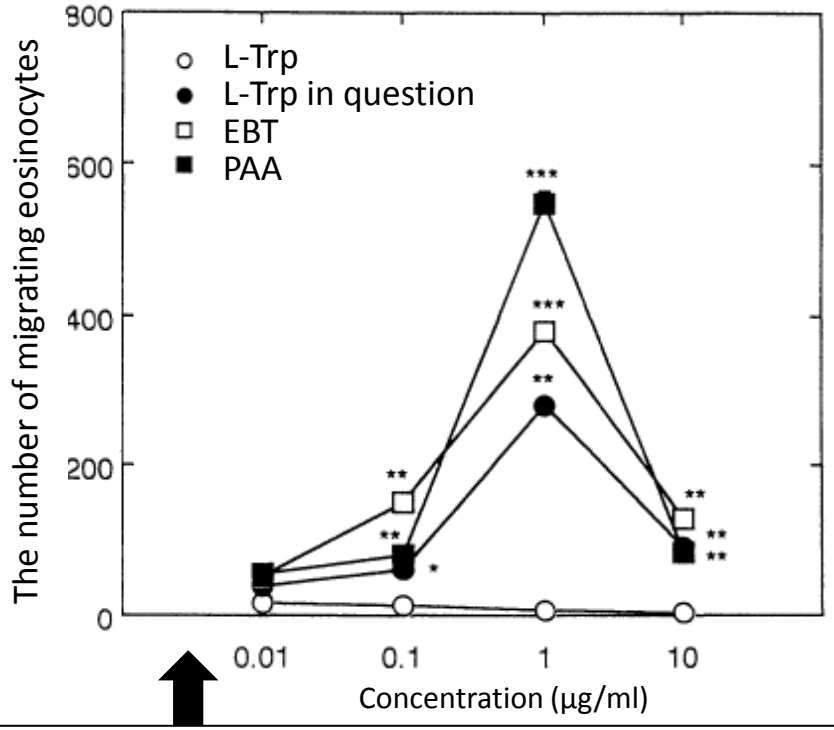
The all symptoms of EMS could not be completely reproduced by the administration of standard L-Trp, impurities including EBT, or L–Trp in question. The symptoms were just partially reproduced.

EMS could not be completely mimicked in animal experiment.

Investigation into the cause of EMS by L-Trp ingestion

The activation of eosinocytes in in vitro experiment





The activity to promote migration of eosinocytes

Seemed to be the mechanism of massive accumulation of eosinocytes on the surrounding tissue of myocardium.

IL-5 in culture of human spleen T cells after 72-hr incubation with L-Trp or EBT

The induction of IL-5 seemed to be the cause of eosinophilia.

The cause of EMS pathogenesis --- Conclusion

Although they didn't reach a clear conclusion, it was thought that the multiple factors cooperatively worked to cause EMS.

(1) Excessive consumption of L-Trp.

(2) The ingestion of the specific impurities contained in the specific lots produced by Company S

(3) The specific diathesis of the patients.

The issues on the manufacturing management

◆ Manufacturing process varied between lots.

- Starting materials (from anthranilic acid, PAA arose on the purification process.)
- **B**acterial strains for fermentation.
- **The amount of activated carbon** used on the purification process was changed based on megascopic judgment on decoloration, etc..

◆ **Impurity-profile analysis** was not conducted.

The concept of GMP was not applied.

GMP: Good Manufacturing Practice

GMP and the management of quality assurance of our company

What is GMP?

◆GMP : Good Manufacturing Practice

◆The rule and the system for maintaining the safety of production and the standardized quality of products on the entire process including the storage of raw materials and the shipping of products.

The establishment of the system for implementing GMP

Software side	Governing structure	◆Clarification of responsibility ◆Training & education
	Working management	◆Management of manufacturing process/quality/hygiene ◆Checking and recording system
Hardware side	Facilities	Appropriate working environment

The following documentations are required.

(1) Product master formula
(2) Statement of manufacturing management
(3) Statement of hygiene management
(4) Statement of quality control

ASQUA
(Ajinomoto System of Quality Assurance)

Quality management system

ISO 9001

◆International standards for quality assurance by manufacturers.

◆Only the manufacturers which can produce products above a certain standard can be certified.

Hygiene management system

HACCP

Management criteria by which the manufacturer can cope with any hygienic problems on all the process including the arrival of raw materials, production and shipping, based on the prediction of hygienic risk.

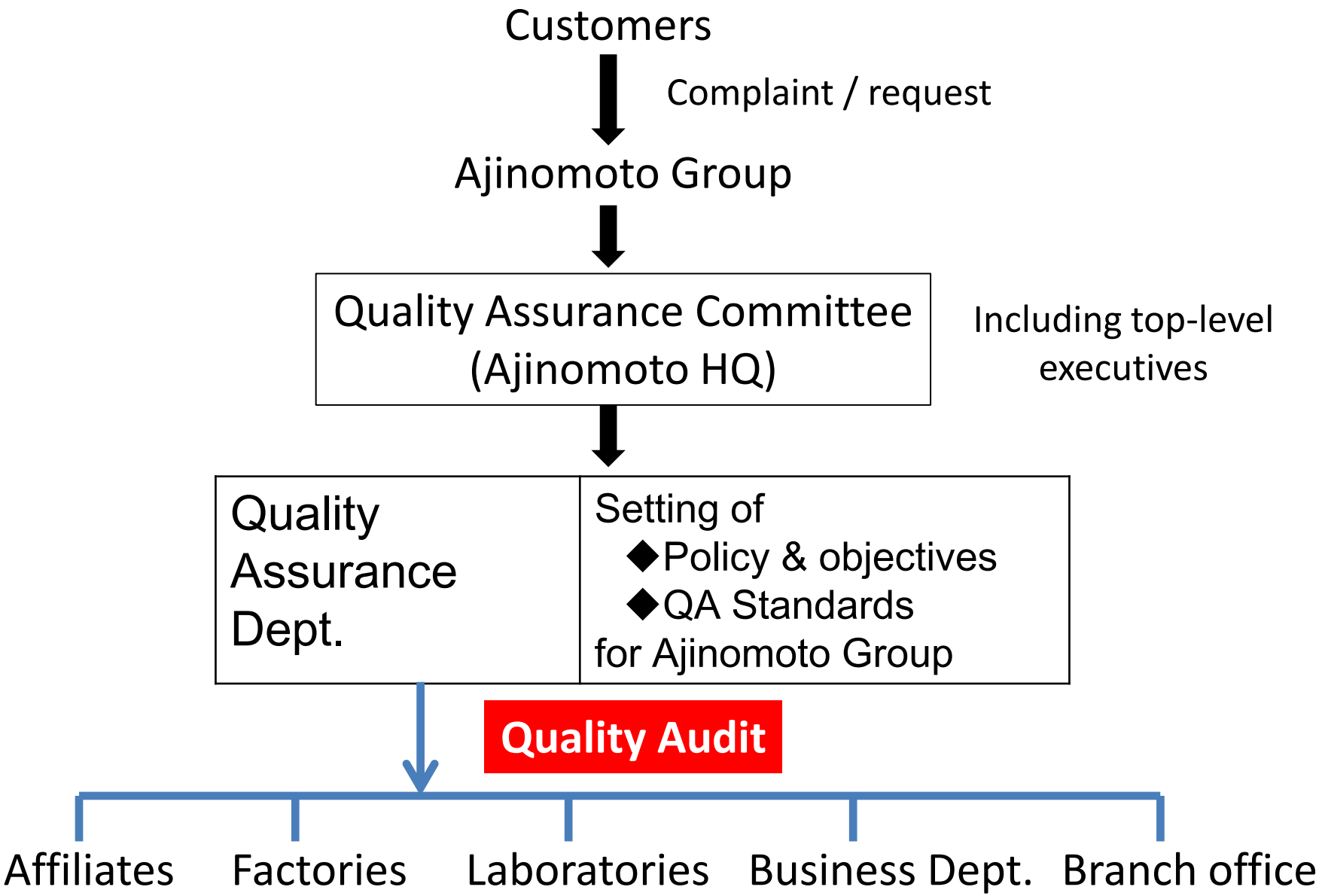
Quality Standards for Ajinomoto Group

◆Company-specific standards to maintain the quality standards for Ajinomoto brand.

◆Comprehensive strict criteria for raw material, packaging, labeling, etc.

ASQA = ISO9001 + HACCP + Quality Standards for Ajinomoto Group

Implementation system of ASQA



Improvement of products based on customer's complaint

The case of 50% reduced-sodium salt

Complaint

The warning label of inclusion of **potassium** is so small that a patient with renal disease didn't realize to buy.

Countermeasures

- The warning label was enlarged.
- The letters of "potassium" was emphasized by color and size.

Before improvement

After improvement

This product is a salt in which 50% of sodium was replaced by potassium -----

Since this product contains **potassium**, the patient with renal disease should consult with doctor before use. ----

Thank you for your attention.

Kawasaki factory　Ajinomoto Co, Inc.