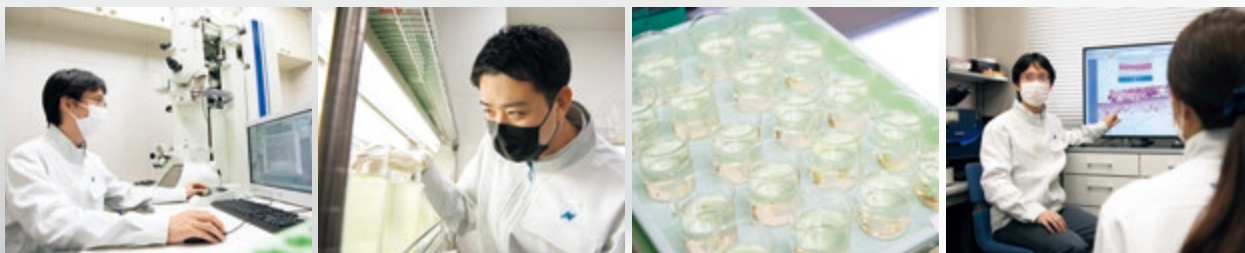


## Feature

# Contributing to Maintaining the Food Supply by Correctly Evaluating Safety Toxicology & Environmental Science Department

Safety evaluations are indispensable during the development of agrochemicals. We asked Dr. FURUKAWA, General Manager of Toxicology & Environmental Science Department, about the process of commercialization of agrochemicals through strict inspections and the role that agrochemicals play in solving the social issue of stable food supply.



### FURUKAWA Satoshi, PhD, DVM

Associate Executive Officer and Deputy Head of Biological Research Laboratories, and General Manager of Toxicology & Environmental Science Department

#### —Please tell us about the process behind how agrochemicals are released to the market.

Generally speaking, it takes about 11 years from the start of agrochemical development to the launch of the product with the development cost for a product being around 50 billion yen.

After product screening, it takes three years for initial development to evaluate whether selected substance has any toxicologic problems in releasing to the market, and takes another eight years until the product is launched, through a full-scale development decision, tests for registration application, and various examinations (see Figure A).

The development process for agrochemicals is similar to that for pharmaceuticals. In the case of pharmaceuticals, however, safety for the patients are considered important. Whereas, in the case of agrochemicals, we must ensure the safety of three parties, the farmers who use agrochemicals, the consumers who eat crops, and the aquatic organisms and safety tests are mandatory.

For the safety inspection of applications, the Food Safety Commission of Japan evaluates the risks based on the safety test data we submit, the Ministry of Agriculture, Forestry and Fisheries sets standards on the use of pesticides for farmers, the Ministry of Health, Labour and Welfare sets maximum residue limits for agrochemicals for consumers, and the Ministry of the Environment sets standards to withhold registration for aquatic organisms (see Figure B). Once these standards are met, crops to which the agrochemical was applied will be allowed to be sold on the market.

#### —Please tell us about the role of the Toxicology & Environmental Science Department.

The Toxicology & Environmental Science Department consists of the Toxicology Group, which evaluates toxicity of chemical substances, and the Environmental Science Group, which evaluates the environmental dynamics of agrochemicals. The Toxicology Group investigates the toxic impact of agrochemicals with *in vivo* and *in vitro* studies. The Environmental Science Group investigates the quantity of residual

Development Period, Development Cost, and Probability of Success of Agrochemicals

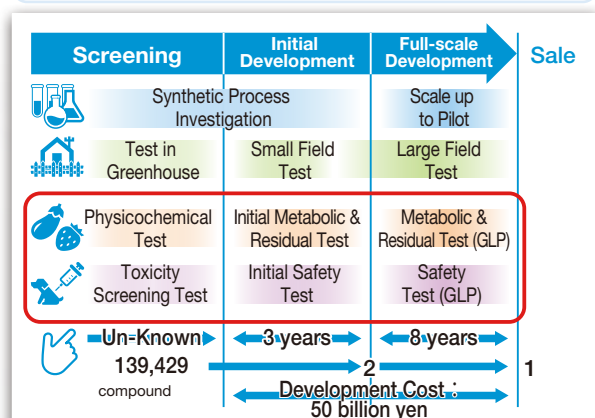


Figure. A

Review of Agrochemical Safety

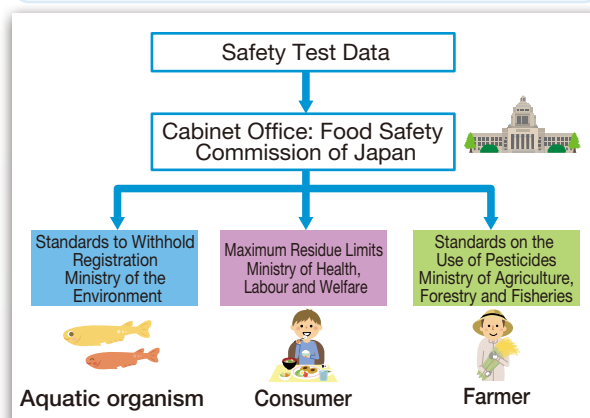


Figure B

agrochemicals in crops and in the soil and water, and how they are metabolized (broken down).

The safety of an agrochemical cannot be evaluated simply by its toxicity. It is difficult to say which is safer: a highly toxic agrochemical but hardly residual in crops, or a less toxic agrochemical but remains in large amount. In other words, it is necessary to make a comprehensive risk assessment based on the strength of the toxicity (hazard assessment) and the amount of residual agrochemical (exposure assessment). Therefore, for our company, the Toxicology & Environmental Science Department conducts risk assessments with the Toxicology Group in charge of hazard assessments and the Environmental Science Group is in charge of exposure assessments.

Since safety test is common to both pharmaceuticals and chemicals, the Toxicology Group conducts safety evaluations for the entire corporate research. The Environmental Science Group specializes in agrochemicals development and is inspected by the Ministry of Agriculture, Forestry and Fisheries once every three years as a GLP-compliant facility that can submit materials for agrochemicals applications.

**—You conduct safety evaluations in-house. What is the advantage of having a specialized in-house section performing safety evaluations rather than outsourcing?**

We conduct all the initial safety tests and some of the tests for registration applications in-house.

There are three advantages in doing so. First, we can confirm and understand the nature of the toxicity with our own eyes, and determine accurately whether it is safe or not though it's hard to get the image of expressed toxicity since the test results are received in paper simply in the case of using outsource.

The second is the ability to conduct tests flexibly. In the case of outsourced testing, testing is conducted according to the convenience of the client, whereas in-house testing allows us to prioritize the magnitude of the issue and respond quickly. In addition, we can conduct additional test if necessary.

Third, we can accumulate experience and know-how within the Company by conducting the tests that require skill. This also leads to the development of human resources as experts.

**—What are the future plans of the Toxicology & Environmental Science Department?**

This is partly my personal wish, but I would like to spread a greater understanding of the safety of agrochemicals. I sometimes see theories that emphasize the risks of agrochemicals, but most of them are overlook the risk assessment. If agrochemicals are used to increase the yield per unit area in areas where food shortages are serious, many lives can be saved. We hope to correctly inform the world about the role and safety of agrochemicals.

As for the Toxicology & Environmental Science Department, we will focus on human resource development so that each of our researchers can form an intellectual group with a high level of expertise with the goal of becoming a research department that possesses the ability to make rapid, accurate, and highly precise decisions related to product development. We will continue to contribute to the R&D of all Nissan Chemical businesses by conducting safety evaluations of chemical substances from the perspective of regulatory science, and by managing the organization with a sense of unity in cooperation with each business division.



## Two Groups Work in Tandem to Ensure the Safety of Agrochemicals

In order to ensure the safety of newly developed agrochemicals, the Toxicology & Environmental Science Department conducts a variety of tests using the latest equipment and advanced technologies. We interviewed the leaders of the Toxicology Group and the Environmental Science Group to find out about their work and the challenges they face.

### —First of all, please tell us about your work and backgrounds.

**Takeuchi** The main job of the Toxicology Group is to determine types of toxicity that agrochemicals cause to farmers, consumers who eat the crops, and aquatic organisms, and intakes at which they occur. The group consists of three teams: A general toxicity team that evaluates various types of toxicity by *in vivo* experiments, a mutagenicity team that evaluates genetic damage, and an aquatic toxicity team that evaluates toxicity to aquatic organisms.

**Kusakari** Our job in the Environmental Science Group is to investigate the degradability of agrochemicals in plants, animals, soil and water, their residue level in crops, and their persistence in the environment such as soil and water. Agrochemicals sprayed on crops decompose over time, but sometimes a small amount remains on them. In addition to confirming the degree of agrochemical remaining, the Environmental Science Group also conducts research on the degradability of agrochemicals on crops and evaluates the residue of agrochemicals themselves and their degradation products.

**Takeuchi** After joining the Company, I worked in the Pharmaceutical Research Department and was in charge of research on drug metabolism and disposition that occur in the body when people take medicine. At that time, I had opportunities to be involved in safety evaluation, which is similar to what I am doing now. I thought I could make use of the skills and various

knowledge I had accumulated, so I agreed to be transferred to the Toxicology & Environmental Science Department and am working in my current position. In passing, Mr. Kusakari was actually my junior at university.

**Kusakari** That's right. We were students in the pharmaceutical department of the same university. When I was a student, I was engaged in research to determine the structure of new antibacterial compounds contained in extracts of bacteria. When I was looking for a job, Mr. Takeuchi, one of my seniors, told me that the work of investigating degradability of agrochemicals in plants and animals was similar to my university research. I thought I could make use of my structural analysis skills cultivated in university and I was attracted to the work, so I joined Nissan Chemical.

### —What are some of the difficulties you face in conducting safety evaluations?

**Takeuchi** The Toxicology Group must strictly determine whether the products we are developing are really safe, so I feel that this job is very responsible. Our job would be easy if we can decide to discontinue development immediately if even the slightest toxicity is found in a safety test. However, that would not allow us to develop anything, would it? One of the hardest parts of this job is that we have to determine from scientific data whether or not the toxicity found in the safety test poses a risk to humans or aquatic organisms. To avoid making biased decisions, we review the test results with the entire group and have in-depth discussions before deciding whether the found toxicity poses a risk.

**Kusakari** The Environmental Science Group analyzes and evaluates the amount of residual agrochemicals in crops. It is easy to say "Analyze the amount of residual agrochemicals" in words, but the residue level of agrochemicals is extremely low. For example, 1 liter of a soft drink contains about 100 grams of sugar is here. We can express it as a concentration of 100 grams per liter. The residue level of agrochemicals in crops is 0.01mg/L, which is about the same concentration as one drop of this soft drink in a bath. In order to accurately determine the amount of this extremely small amount of residual agrochemical, we have to use a variety of technologies to purify and concentrate



**TAKEUCHI Kazuya, PhD.**

Toxicology Group,  
Toxicology & Environmental  
Science Department





samples for analysis, and derive reliable data. I feel a lot of pressure since there is much involved.

**Takeuchi** One of the hardest things about this job is we have to stop a project if we determine that the found toxicity poses a safety risk. This is a very discouraging decision for those in charge of development, who believe in the potential of a new agrochemical. That's why we need to communicate with the people in charge of development and provide them with explanations so that they will understand the situation.

**Kusakari** I understand your feeling very well. Since we make decisions based on the residue level, we have to consider the overall safety of the agrochemical and decide whether or not to develop it, even if the toxicity of the agrochemical itself is not so strong, if the residue level in crops or the environment is high. There are times when we have to make painful decisions, but that is the most important thing we can do to ensure the safety of agrochemicals.

### —Please tell us about your job satisfaction and dreams for the future.

**Takeuchi** In the Toxicology Group, we are able to work not only with staff involved with agrochemicals but also with those from various business units within the Company, such as pharmaceuticals, performance materials, chemicals, and cosmetics and so on. So, I can come into contact with various ideas and have the opportunity to learn new things. It's rewarding for me.

**Kusakari** In order to correctly judge the safety of agrochemicals, I will make full use of analytical techniques to clarify the amount of residual agrochemicals that can never be seen with the naked eye. It's rewarding for me.

**Takeuchi** The Toxicology Group will continue to actively introduce new technologies and strive to improve the level of skills to elucidate the mechanism of toxicity. The world is moving in the direction of reducing the use of chemical agrochemicals, and there is a possibility of a shift to more environmental-friendly agrochemicals, such as biological agrochemicals and RNA-based agrochemicals. In anticipation of such future trends, I would like to take on the challenge of establishing safety evaluations that are suitable for new types of agrochemicals.

**Kusakari** The Environmental Science Group is working on the introduction of a method to evaluate the concentration of agrochemicals not only in crops and soil, but also in water bodies such as ponds and rivers, and in groundwater. In addition, the technology for simulating the concentration of agrochemicals in the environment is evolving day by day, and I would like to contribute to the development of safer agrochemicals by using these technologies to clarify the previously unknown dynamics of agrochemicals in the environment.

