In the Spotlight

Initiatives for Discovering a Bee-Friendly Insecticide

A new insecticide that contributes to global agriculture and the environment

GRACIA®

GRACIA® is an insecticide that is effective against a wide range of pests yet safe, and also has limited impact on honeybees. We interviewed MIYAKE Toshiro, Head of Biological Research Laboratories, about the product's special features and development process.

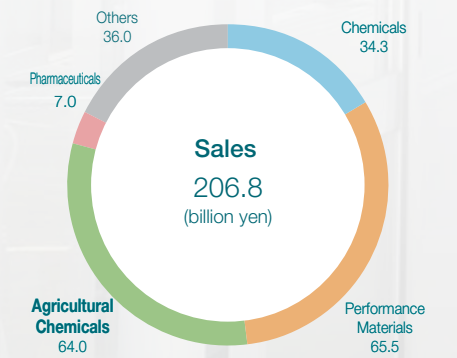
MIYAKE Toshiro

Managing Executive Officer
Head of Biological Research Laboratories

— At first, please tell us about the special features of GRACIA®.

GRACIA® is a high-performance insecticide for vegetables and tea that contains active ingredient fluxametamide consisted of isoxazoline-structure developed by our company. This product has three main features. Firstly, GRACIA® acts fast against a wide range of pests. Generally speaking, insecticides produced in recent years have high selectivity and are effective only against a specific group of insects to ensure their safety to humans and low impact on the environment. In contrast, GRACIA® is an excellent insecticide that acts on a wide variety of pests and is highly safe for humans and non-pest organisms. The second feature is its new chemical structure and mode of action, so it can effectively control pests such as diamondback moths and thrips, which are resistant to conventional insecticides. The third feature is that it has limited impact on honeybees or bumblebees, which play important roles in the pollination of crops. As the mass deaths of European honeybees continue in Europe and the United States and regulations on neonicotinoid pesticides become more stringent, GRACIA® is attracting attention as a "bee-friendly insecticide".

Agricultural Chemicals Business Positioning (FY2019)



Changes in Organic Synthetic Agrochemical Regulations

1939	Discovery of DDT's* insecticidal action	
1940s/1950s	Quality Control Standards Agricultural Chemicals Regulation Act (1948)	Manufacture
1960s/1970s	Major Revision to the Agricultural Chemicals Regulation Act focusing on human safety and environmental persistence (1971)	Mammalian Toxicity
1980s/1990s	Standards for proper implementation of agricultural chemical toxicity testing Good Laboratory Practice (GLP) for Agricultural Chemicals (1984)	Experimental Facilities
2000s/2010s	High level of safety environmental fate for the environment/Environmental biological effects	Environment

* Dichlorodiphenyltrichloroethane




— What prompted the development of GRACIA®? Could you please also explain about its commercialization background?

Since long ago, as one of our pesticide creation policies, we had the idea of creating a versatile insecticide that could be used for a wide range of crops. From the end of 2003, we started a research on isoxazoline compounds. By creating completely new compounds and combining partial structures of known active compounds of insecticides, we were able to obtain compounds with insecticidal activity close to those of our current GRACIA® as early as 2005. However, at this point, the only positive attribute was the effect, and it was completely useless in terms of safety to mammals and environmental organisms, soil persistence, etc. The synthesis cost was high as well, so it was far away from practical use. From that time until around 2010, it took about five years to solve each issue, including safety, and we were the first in Japan to verify its effects on honeybees. Eventually, as a result of various experiments and verifications at internal and external evaluation facilities, we succeeded in commercializing GRACIA® and started selling the product in South Korea (2018) and in Japan (2019).

— Why is GRACIA® a safe insecticide that has little impact on honeybees?

To be precise, there are some parts that are still unknown about it, but this is my idea: Insecticides are absorbed through the mouth and skin of insects and affect on the target site in the body, causing pests to die. This is also true for bees, but GRACIA® (fluxametamide) showed different result. We speculate that honeybees have the ability to metabolize (decompose) GRACIA® in the body from the results of our research. I also imagine that the reason why it does not work on bumblebees, which are used for pollination of tomatoes, is the same as for honeybees.

— What are the benefits of using GRACIA® for farmers? Also, in what way does it contribute to society?

For the farmers who are using it, it is effective against pests associated with a wide range of crops. It is also gentle on honeybees and there is no issues regarding resistance to it, so I think that it is a very easy-to-use insecticide for pest management. After GARCIA® was put on the market, I hear that it is very popular and there are few complaints from farmers. Also, this is a common tendency among pesticides in recent years, but since it works even in low concentration, so GRACIA® contributes to society by reduction of amount of chemical and burden on environment. Sales are also strong and it is a product that greatly contributes to our business.

— Please tell us about future development policies at Biological Research Laboratories.

While having an awareness of the top share of the domestic market in Japan, we will closely examine the situation of overseas markets, especially the Asian market, consider the needs of the region, and move ahead with the development of agrochemicals that are suitable for the environment while coordinating with our Agricultural Chemicals Division.

In addition, research is being carried out globally for “biopesticides” that utilize the action of microorganisms, insects, etc. as agrochemicals that are friendlier to the environment than conventional agrochemicals. Our laboratories would also like to contribute to the development of agriculture in the world by working on the research and development of “biopesticides” while making use of the experience and technology cultivated in conventional agrochemical development.

Unraveling the Mysterious Power of Living Things Through Experiments

We interviewed two researchers of Biological Research Laboratories who struggled on the mode of action analysis of fluxametamide and the elucidation of the factors of selectivity in order to elucidate the safety for honeybees, which is an important feature of GRACIA®.

— Please give us an overview of the mode of action analysis and elucidation of the factors of selectivity that you were involved in.

ASAHI In regard to the mode of action analysis work that I was involved in, at the stage of observing the biological activity of fluxametamide, it became known that pests die in a very unusual excitatory symptom, which is different from how they die using conventional insecticides.

INADA There are several types of excitatory symptom, such as leg cramps and violent shaking, but in the case of fluxametamide, it was different from the previous patterns in that pests started shaking their heads firstly. The phenomenon that the intense excitatory symptom sustained for a long duration was also unique.

ASAHI So, in order to visualize symptoms that haven't been felt to this extent before, we made charts of contraction pattern of the insect body surface using a device called a transducer.

Looking at this chart, I noticed that it resembles the pattern of existing agents that act on GABA (gamma-aminobutyric acid) receptors. Fortunately, we had a relationship with a university professor who is studying GABA receptors in insects, so we requested to conduct joint research. From that, we were able to clarify that fluxametamide acts on GABA receptors as expected and binds different position compared to existing GABA inhibitors. As next step, we investigated whether fluxiametamide acts same or differently on GABA receptor of different species using artificially expressing GABA receptors in frogs oocytes.

— As the next step in the mode of action analysis, you moved on to elucidating the factors of selectivity as to how it affects honeybees, right?

ASAHI Yes. As we proceeded with development, somehow we found out the effect on honeybees was minimal. It means that fluxametamide is actually bee-friendly. When developing it as a new insecticide, we thought the explanation why the mechanism of the insecticide has limited impact on honeybees would be selling point, so I proceeded with research to clarify related factors.

INADA Before commercialization, we also had the responsibility to explain properly to consumers the reason why it has minimal impact on honeybees.

ASAHI At first, I thought that fluxametamide would not act on the GABA receptors of honeybees. When I tested it, however, I found that it acts as strongly on them as on other pests. So this time I decided to use honeybees and common cutworms to investigate how fluxametamide was actually taken into the body and how it was metabolized (decomposed).

ASAHI Miho
Agricultural Chemicals Research & Development Department
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INADA At first, it was confirmed that treatment with a metabolism inhibitor added to fluxametamide increased the insecticidal effect on honeybees but did not change it with common cutworms. Therefore, I thought that metabolism may have an effect on this difference. When we analyzed the metabolites in the insect body, we found that honeybees often metabolized fluxametamide whereas common cutworms did not.

ASAHI As a specific experimental method, we prepared insects treated with agents and froze them after 1 hour, 2 hours, and 24 hours. After each insect was homogenized, an extract was obtained and component analysis was performed to analyze what kind of metabolite was contained in the extract. From the analysis pattern, we speculated how fluxametamide is metabolized in the insects' bodies.

INADA From those results, we came to the conclusion that, unlike pests, honeybees metabolize fluxametamide in the body. This means that fluxametamide does not reach GABA receptors in honeybee and hence they are less likely to be affected.

— What were the really difficult points in regard to conducting research and development?

ASAHI There were many difficult points. It took much time to clarify mode of action. In particular, it took a considerable amount of time to assemble a test system using insect GABA receptors.

The series of tests to evaluate agents that act on the nerves of insects was a test that I had no experience with, so I went to an external research institute to learn the method and set up the equipment. It took time at the stage.

As to insect metabolite analysis, since compounds obtained from one small insect, such as honeybee or common cutworms was very small, so it was very difficult to determine the analysis conditions. In addition, in the analysis of honeybees, there are many impurities such as honey, so it took time to examine the conditions for pretreatment of the sample until only the target fluxametamide and its metabolites could be analyzed.

— Please tell us if you have any products that you would like to develop in the future, work dreams, etc. as you continue your R&D work.

ASAHI Although GRACIA® is a bee-friendly insecticide, I am concerned that it acts on their GABA receptors. Therefore, I would like to find a compound that can create appeal for complete selectivity at the mode of action level.

INADA In recent years, technological advances have made it possible to design compounds with AI (artificial intelligence). In addition, next-generation sequencers have made it easier to obtain genetic information, and I hope to utilize these latest technologies for efficient research.

ASAHI Me too. I also want to make full use of these technologies to aim for agrochemical developement that is more versatile, safe, and secure. The development of GRACIA® took more than 15 years. By the time I joined, the compound itself had been discovered and some research had been done. I am very grateful that I was able to take part in such project while feeling the thoughts of many people who had been involved in its development until then. I hope this experience will be used as an important source of future research.

INADA Makoto

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