Research and Development of a Novel Insecticide “Oxazosulfyl”

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Oxazosulfyl is a novel insecticide originally discovered and developed by Sumitomo Chemical Co., Ltd. It belongs to a new chemical class, the “Sulfyl” group, structurally characterized by its ethylsulfonyl moiety. In nursery box application, it exhibits excellent control against a broad range of major rice insect pests, including Hemiptera, Coleoptera, Lepidoptera and Orthoptera. Field studies in in-house and contracted rice paddy fields demonstrate that Oxazosulfyl is highly effective against local populations of planthoppers and rice leaf beetles that have developed high resistance to existing insecticides. Oxazosulfyl was registered as “ALLES® granule”, which contains 2.0%(w/w) Oxazosulfyl, in April 2021.

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Introduction

The rice acreage in Japan is 1,469,000 ha in 2019 and is larger than the cropping acreages of barley, wheat, soybeans, vegetables, and fruit trees, accounting for 37% of the total cropping acreage1). Although the rice acreage has been decreasing after peaking at approximately 3.17 million ha in 1969, rice is still the most important cultivated crop in Japan, and technology to control rice insect pests is still required for its stable production and supply.

For rice cultivation in Japan, there are a broad range of important insect pests, which include small brown planthoppers as well as rice leaf beetles and rice water weevils that occur in the early period of cultivation in eastern Japan, and migratory insect pests, such as white-backed planthoppers, brown planthoppers, and rice leafrollers, in western Japan. In general, these insect pests are controlled primarily by nursery box application. It is the method to control insect pests by applying insecticides to the soil in the box from sowing until transplanting, or by mixing insecticides with the nursery soil before sowing. In the 1990s, imidacloprid and fipronil have been developed and have spread rapidly as long-lasting insecticides for nursery box application performing effectively even against migratory planthoppers in addition to other insect pests. As a result, the number of insecticide applications in paddy fields has been reduced, providing a dramatic labor saving.

However, insect pests have developed insecticide resistance since around 2005, and the reduction in the efficacy of representative insecticides by nursery box application has become a concern. For example, brown planthoppers are resistant to neonicotinoid insecticides such as imidacloprid2), white-backed planthoppers to fipronil2), small brown planthoppers to neonicotinoid insecticides and fipronil3), and rice leaf beetles to neonicotinoid insecticides4) and fipronil5),6). As countermeasures against these resistances, insecticides containing diamide insecticides (*e.g.*,

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chlorantraniliprole, cyantraniliprole and tetraniliprole) and triflumezopyrim (which is effective against planthoppers) have been used for nursery box application in recent years. In the mode of action classification by the Insecticide Resistance Action Committee (IRAC), however, the former belongs to Group 28, and the latter belongs to Group 4, which is the same as neonicotinoid insecticides. Thus, the control measures against rice insect pests is still dependent on insecticides with the limited modes of action.

Oxazosulfyl (the ISO common name registered in November 2017) is a novel insecticide originally developed by Sumitomo Chemical Co., Ltd. By nursery box application, oxazosulfyl exhibits excellent control against a broad range of important rice insect pests. It has a novel chemical structure (**Fig. 1**) different from conventional insecticides and is highly effective also against the insect pests resistant to existing insecticides. In Japan, oxazosulfyl was registered as ALLES® granule, which contains 2.0% (w/w) oxazosulfyl, on April 21, 2021. In this article, we report the discovery and development background, manufacturing method, mode of action, and biological effects of oxazosulfyl, as well as its formulation and mammalian and environmental safety.

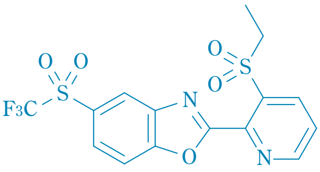


Fig. 1 Chemical structure of Oxazosulfyl

Discovery and Development Background

We previously found that Compound 1 shown in **Fig. 2** had insecticidal activity against planthoppers. Because Compound 1 had a unique chemical structure, it was also expected to have a mode of action different from those of existing insecticides. We started the structural optimization with Compound 1 as the lead compound to explore a family of compounds with a more desirable property[7),8)]. First, we focused on the methylsulfanyl moiety (1→2), which was a characteristic of this family of compounds. Then, for the structures of both sides of aromatic rings, we investigated many conversions to heterocycles and combinations in detail (2→3→4). Finally, we found that a family of compounds with the structure of trifluoromethylthio group at the 5-position of the benzoxazole ring was promising (4→5, 6, and Oxazosulfyl).

These benzoxazole compounds have a potent insecticidal activity against a wide variety of insect pests, as well as systemic action, thus we further compared their performances in detail. Against insect pest species (field populations) resistant to each of the major existing insecticides, such as neonicotinoids, phenylpyrazoles, pyrethroids, and diamides, these compounds showed similar activities to those against each susceptible strain, indicating no cross-resistance. Because these compounds also showed a high activity against major rice insect pests, we focused on their development as an insecticide for rice nursery box application. In laboratory pot studies replicating nursery box application, the sulfinyl compound (n = 1, Compound 6) and the sulfonyl compound (n = 2, Oxazosulfyl) had a higher

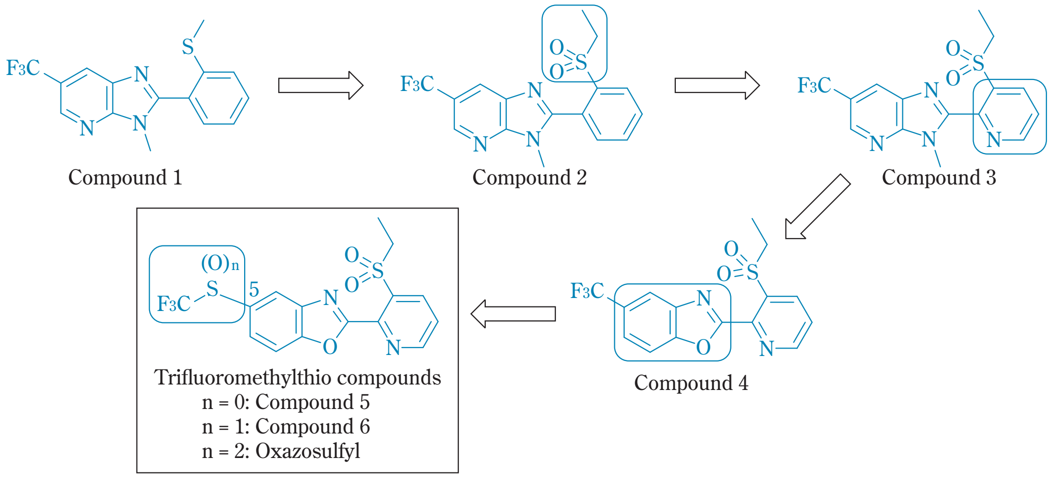


Fig. 2 Optimization of lead compound 1

activity against insect pest species that damage the aerial part of rice plants. We selected the two compounds as promising compounds and compared their practical efficacy in field studies. As a result, the sulfonyl compound more strongly suppressed the insect pests of Hemiptera, Lepidoptera, and Coleoptera, to a lower density, showing its higher efficacy. The difference was more prominent when the granules of the compounds were applied at sowing. Therefore, we selected the sulfonyl compound, oxazosulfyl, as a development compound.

Manufacturing Method

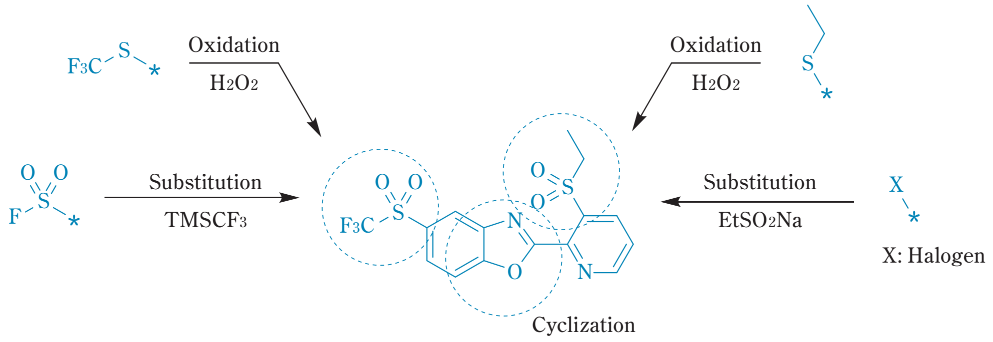
Oxazosulfyl has a pyridine ring and a benzoxazole skeleton. The key to developing the production method was how to introduce 2 different types of sulfonyl moieties. In the initial method, 2 sulfur atoms were oxidized together to obtain oxazosulfyl[9]. Because the introduction of an ethylsulfonyl moiety by oxidation method uses ethanethiol, which has a strong odor, it is essential to take odor control measures. To avoid it, we developed a substitution reaction with sodium ethanesulfinate. We also developed the Ruppert - Prakash reagent method to introduce a trifluoromethanesulfonyl moiety in the final step, because it had a larger cost impact than the other moieties. With further research in an energetic way, we established the industrial manufacturing method of oxazosulfyl that satisfied industrial requirements at a high level, including safety, quality, and robustness (**Fig. 3**).

Mode of Action

To clarify the mode of action of oxazosulfyl in insect, we conducted symptomology tests with large insect pest species because it was easy to observe poisoning symptom. When oxazosulfyl (10 µg) was injected to American cockroaches, staggering gait and a decreased responsiveness to external stimuli were observed within 1 h after treatment. Subsequently, the cockroaches were unable to walk and eventually developed general paralysis. The paralysis persisted at least 7 days after treatment. When oxazosulfyl (1 to 10 µg) was injected to common cutworms, a large Lepidopteran pest, cutworms paralyzed in 10 to 15 min after treatment. However, the treated larvae recovered from paralysis 24 h after treatment. Because those results suggested that oxazosulfyl acted as an anesthetic in insect pests, we injected lidocaine, a voltage-gated sodium channel blocker anesthetic, in both species. As a result, lidocaine similarly induced reversible paralysis in both species.

Because it was suggested that oxazosulfyl acted on the nervous system of insect pests, we evaluated its action on the central nervous system of American cockroaches with extracellular recording. In cockroaches treated with oxazosulfyl, the spontaneous discharge of the central nerve was inhibited (**Fig. 4**). The inhibitory action was dose-dependent and was consistent with the speed of the onset of poisoning symptom. In American cockroaches treated with lidocaine, the central nerve activity was also suppressed.

Based on the results of the symptomology observation and extracellular recording, we investigated the possibility that oxazosulfyl may act on voltage-gated sodium channels in insect pests, with the two-electrode voltage clamp method. Voltage-gated sodium channels transit four states of resting, activation, fast inactivation, and slow inactivation depending on the membrane potential. The resting state and two inactivated states are non-conductive. The resting state is present under the hyperpolarized condition and can be activated by depolarization, whereas two inactivated states occur after activation and are changed to the resting state by



Oxazosulfyl

Fig. 3 Synthetic route of Oxazosulfyl

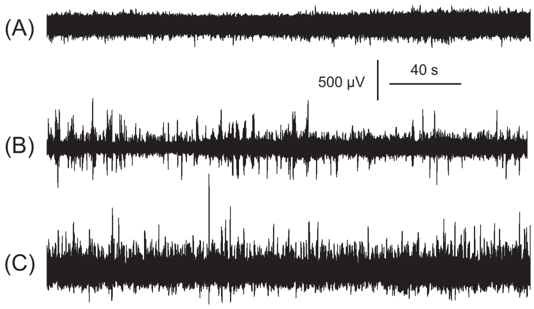


Fig. 4 Representative trace of the nerve activity in a cockroach 2 h after injecting 10 μg (A) and 0.3 μg (B) Oxazosulfyl, and (C) Control (DMSO). The electrodes were set at the connective tissue between the first and second abdominal ganglia.
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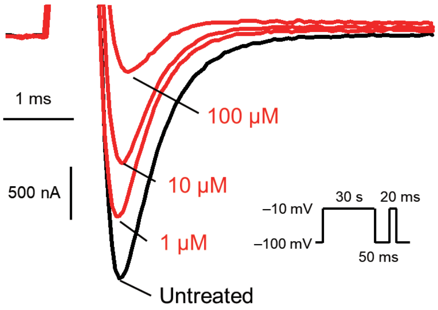

Fig. 5 Inhibitory concentration response of Oxazosulfyl on the slow inactivation of German cockroach voltage-gated sodium channels. Sodium channels were inactivated by depolarization from −100 to −10 mV for 30 s and allowed to recover from fast inactivation by repolarization at −100 mV for 50 ms.
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repolarization. The fast inactivation occurs after depolarization on the millisecond timescale, whereas the slow inactivation is induced by depolarization on hundreds of milliseconds to second timescale. By transiting these four states, sodium channels regulate action potential generation on the cell membrane. Generally, sodium channel agonists are known to act selectively to the state of the channels. We evaluated the action of oxazosulfyl, focusing on the dependence on the channel state. As a result, oxazosulfyl selectively acted on sodium channels in the slow-inactivated state, to inhibit the Na^+ current (**Fig. 5**).

Based on the above, it is suggested that oxazosulfyl fixes sodium channels in the slow-inactivated state to inhibit the nerve activity of insect pests, resulting in the induction of paralysis.

Biological Effects

1. Insecticidal characteristics

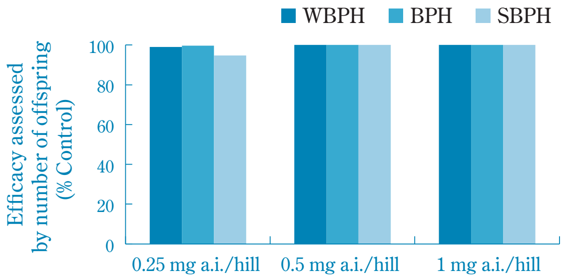
We investigated the insecticidal characteristics of oxazosulfyl against major insect pests in laboratory pot studies replicating rice nursery box application (by treatment at transplanting of young seedling). Representative study results are shown below.

(1) Activity against adult planthoppers

Among planthoppers damaging rice plants, brown planthoppers and white-backed planthoppers infest only rice plants and are non-diapausing, so they cannot overwinter in Japan, where rice cannot be cultivated all year. Every year, the planthoppers migrate from the north central part of Vietnam, where they occur constantly, to the south part of China, where several generations pass on, then flying into western Japan, especially to Kyushu region, along with the low-level jet stream developing in the rainy season in June and July. Macropterous adult males and females of both planthoppers fly to paddy fields to suck rice plants, mate, lay eggs, and reproduce. In particular, brown planthoppers have a high reproduction potential and are considered the most important rice pest species in Japan. When the massive outbreak of this species occurs, they cause "hopper burn," where rice plants were intensively and totally killed, just before harvest (**Fig. 6**). On the other hand, small brown planthoppers can overwinter widely in Japan because they can diapause and infest not only rice but also barley, wheat, and other gramineous weeds. After their overwintering on gramineous weeds in ridges between rice fields and bottom weeds in orchards, they fly mainly to barley and wheat fields. Thereafter, in the harvest season of barley and wheat in May and June, macropterous adults fly into rice paddy fields, where they suck rice plants to lay eggs and reproduce. Because the damages caused by these planthoppers starts at the time adult planthoppers fly into paddy fields, the key points to control them are the insecticidal activities to kill adult insects and to reduce the density of their offspring, thereby blocking their lifecycle.

Thus, we evaluated the activity of oxazosulfyl against adult planthoppers how it reduces the density of

Fig. 6 “Hopper burn” caused by feeding of brown planthopper, *Nilaparvata lugens* in rice.



Insect: WBPH (White-backed planthopper, *Sogatella furcifera*)
BPH (Brown planthopper, *Nilaparvata lugens*)
SBPH (Small brown planthopper, *Laodelphax striatellus*)
Method: Soil drench application onto rice seedlings before transplanting

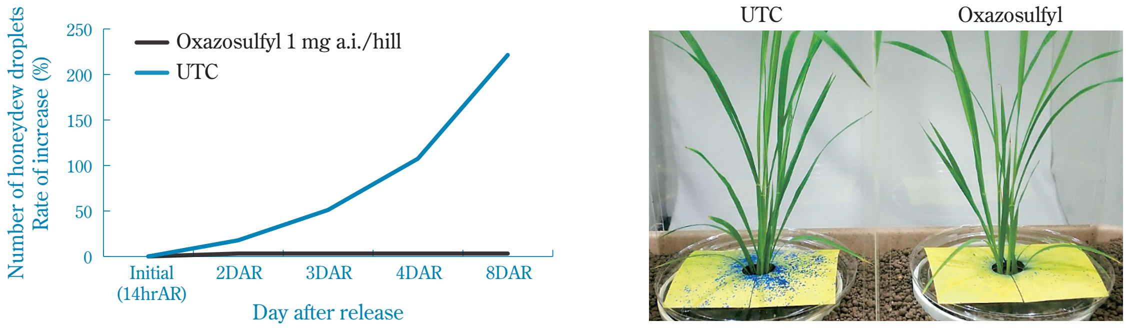
Fig. 7 Insecticidal activity of Oxazosulfyl against three rice planthopper species by soil application.

offspring in white-backed planthoppers, brown planthoppers, and small brown planthoppers (the field populations collected in paddy fields in Kagoshima Prefecture). In this study, various doses of oxazosulfyl were applied and thereafter macropterous adult males and females were released in the same timing of their infestation as in the practical situation. In all of the three planthopper species, oxazosulfyl showed a high efficacy in reducing the density of offspring even at a low dose of 0.25 mg a.i./hill (one-fourth of the calculated dose [1.0 mg a.i./hill] of the rice nursery box application of granules containing 2.0% oxazosulfyl) (**Fig. 7**).

(2) Activity against adult small brown planthoppers (inhibitory effect on sucking behavior)

Small brown planthoppers mentioned above are especially considered problematic because they transmit rice stripe virus to cause rice stripe disease. To control them in the practical situation, therefore, it is necessary to inhibit sucking behavior of invading adult planthoppers in addition to reducing the density of their offspring.

We evaluated the inhibitory activity of oxazosulfyl on sucking behavior of adult small brown planthoppers (the field population collected in paddy fields in Ibaraki Prefecture). In this study, oxazosulfyl was applied at 1.0 mg a.i./hill and macropterous adult males and females were released in the same timing of their infestation as in the practical situation. Because planthoppers excrete honeydew from the anus after sucking plants, we



Insect: Small brown planthopper (*Laodelphax striatellus*)
Method: Soil application of granules onto rice seedlings before transplanting
(Blue spots on water-sensitive paper are honeydew droplets excreted by *L. striatellus*.)

Fig. 8 Inhibitory action of Oxazosulfyl on honeydew excretion by small brown planthopper, *Laodelphax striatellus*.

quantified the amount of honeydew excreted after sucking by the number of honeydew droplets on water-sensitive paper, to evaluate the extent of sucking behavior. After releasing insects, the number of honeydew droplets rapidly increased over time in the untreated check, whereas the number did not increase after the initial counting in the treatment of oxazosulfyl (**Fig. 8**). The number of surviving adults in the treatment of oxazosulfyl was similar to that in the untreated check at the initial counting, however the mortality increased afterwards. Therefore, oxazosulfyl rapidly stopped the sucking behavior of adult planthoppers, and they did not recover from the intoxicated state leading to death.

(3) Activity against adult rice leaf beetles

Rice leaf beetles occur mainly in cold areas, such as Hokkaido, Tohoku, and Hokuriku regions, in one generation a year and overwinter as adults. The overwintered adults start exploratory activities at the beginning of May at the earliest and fly into paddy fields to lay eggs just after rice planting. Both adults and larvae of this species damage the leaf blade of rice plants.

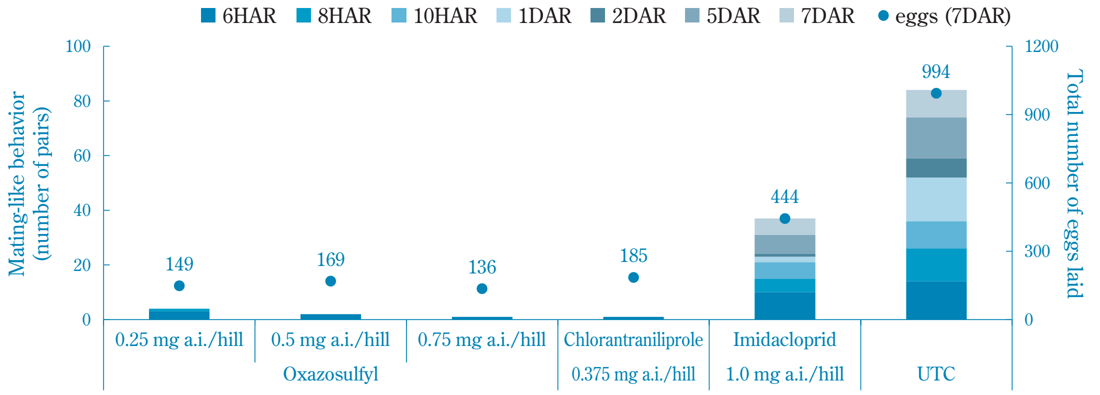
To control rice leaf beetles, the key point is also the insecticidal activity against the adults, and we evaluated how oxazosulfyl acts on adults of this species (the field population collected in paddy fields in Hokkaido). In this study, various doses of oxazosulfyl were applied and adult males and females were released in the same timing of their infestation as in eastern Japan. Even at a low dose of 0.25 mg a.i./hill, the insects showed intoxicated symptoms and slow movement and did not exhibit mating-like behavior at 6 h after releasing. Because the adults used in this study had mated before releasing, a certain number of eggs were laid in all treatments. However, even in the treatment of oxazosulfyl at 0.25 mg a.i./hill, the number of eggs was obviously lower than that in the untreated check and was similar to that in the conventional treatment of chlorantraniliprole at the registered dose (0.375 mg a.i./hill) (**Fig. 9**). Oxazosulfyl is known to have a high insecticidal activity against the young larvae of this species, and in this study we found dead larvae just emerged from egg hatch in the treatment of oxazosulfyl.

(4) Comparison with competitors in efficacy against various insect pests

We compared the efficacy between oxazosulfyl and competitors against various insect pests, by using the granules containing 2.0% oxazosulfyl and commercial products of granules of competitors, at the respective registered doses of 50 g/nursery box. In all studies, we released adult insects at appropriate time points after transplanting to be consistent with the actual timing when each species moves into paddy fields in the practical situation.

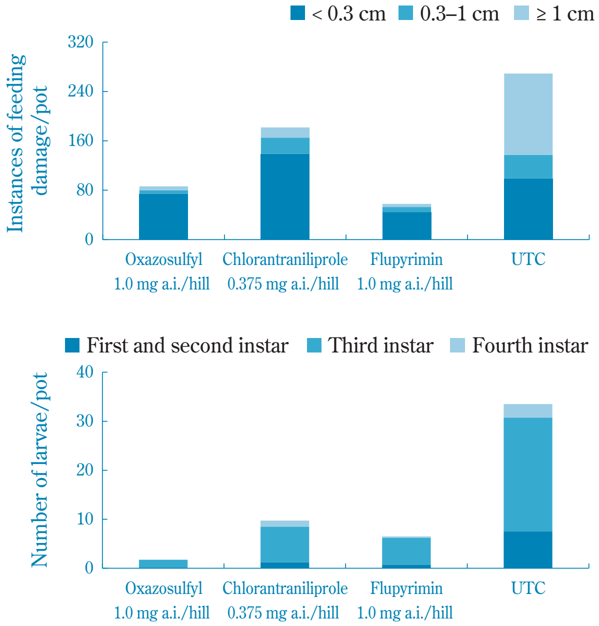
In a study of rice water weevils (the field population collected in paddy fields in Hyogo Prefecture), we evaluated the extent of feeding damage caused by the adults on rice leaf blades and the number of offspring on rice roots. Oxazosulfyl showed a high efficacy in reducing the density of offspring and was superior to competitors, although the feeding damage by adults was not completely suppressed (**Fig. 10**).

In a study using white-backed planthoppers resistant to fipronil and brown planthoppers resistant to imidacloprid (the field populations collected in paddy fields



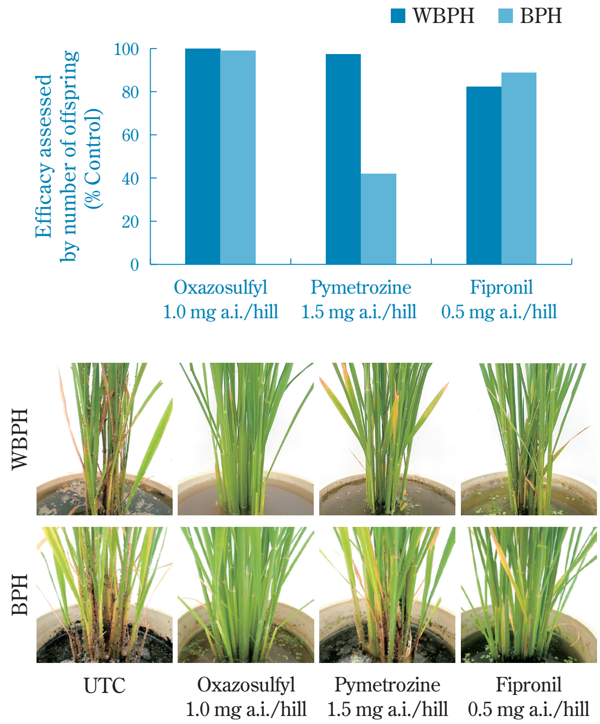
Insect: Rice leaf beetle (*Oulema oryzae*)
Method: Soil drench application onto rice seedlings before transplanting

Fig. 9 Inhibitory action of Oxazosulfyl on mating-like behavior and reproduction of rice leaf beetle, *Oulema oryzae*.



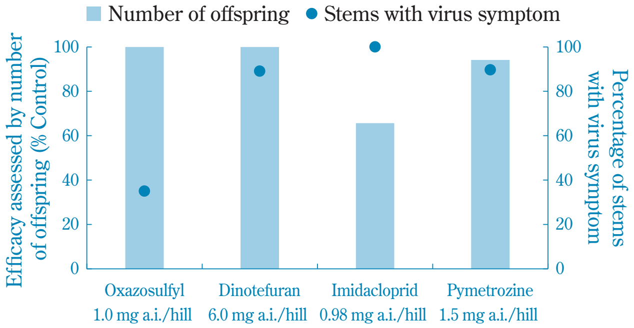
Insect: Rice water weevil (*Lissorhoptrus oryzophilus*)
Method: Soil application of granules onto rice seedlings before transplanting

Fig. 10 Anti-feeding activity and insecticidal efficacy of Oxazosulfyl against rice water weevil, *Lissorhoptrus oryzophilus*.



Insect: WBPH (White-backed planthopper, *Sogatella furcifera*)
BPH (Brown planthopper, *Nilaparvata lugens*)
Method: Soil application of granules onto rice seedlings before transplanting

Fig. 11 Insecticidal efficacy of Oxazosulfyl against two rice planthopper species.



Insect: Small brown planthopper (*Laodelphax striatellus*)
Virus: Rice stripe virus
Method: Soil application of granules onto rice seedlings before transplanting

Fig. 12 Insecticidal efficacy and inhibitory action of Oxazosulfyl on virus transmission vectored by small brown planthopper, *Laodelphax striatellus*.

in Kagoshima Prefecture), oxazosulfyl was superior to competitors in reducing the density of offspring in both species (**Fig. 11**). White-backed planthoppers sometimes cause the browning damage on leaf sheaths called “oviposition scars” when many adult insects fly to paddy field. In this study, however, no sign of it was observed in the treatment of oxazosulfyl. The result suggested that oxazosulfyl rapidly suppressed their action before they initiate oviposition behavior.

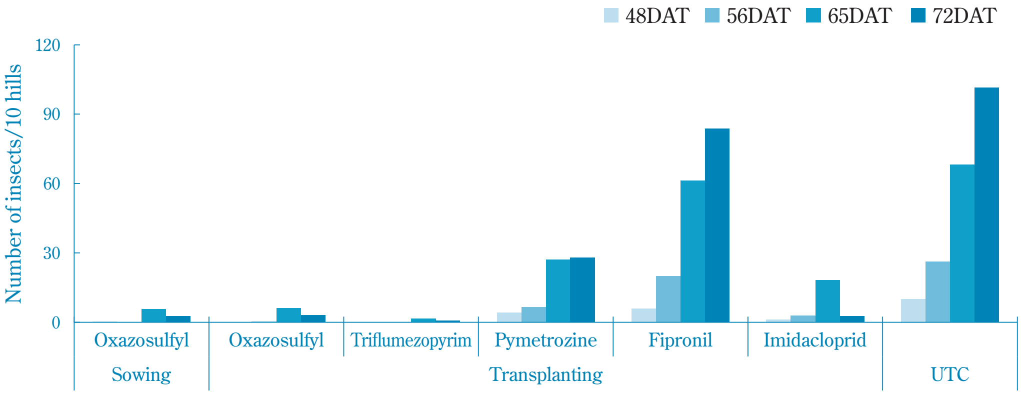
In a study of small brown planthoppers, we selected and used a strain that carried rice stripe viruses (RSV) at a high rate of 93%. The infection pressure of RSV was very high, and the percentage of affected stems was 100% in the untreated check. Under such severe condition, oxazosulfyl was obviously superior to competitors in inhibiting RSV transmission (**Fig. 12**). Notably, the incidences of the disease were clearly different among the treatments, even though the efficacy of reducing the density of offspring was observed in all treatments. This distinction was probably attributed to the difference in the inhibitory activity on sucking behavior and in the speed of action, suggesting that oxazosulfyl was superior to competitors in these activities.

A set of the above studies on the insecticidal characteristics demonstrated that oxazosulfyl acted on various insect pests to cause intoxicated symptoms and affect their behaviors, such as sucking, oviposition, and mating. These unique actions should result in the insecticidal action and the efficacy of reducing the density of offspring, contributing to a high efficacy of pest control in practical use. The examples of practical efficacy evaluation are shown below.

2. Practical efficacy evaluation

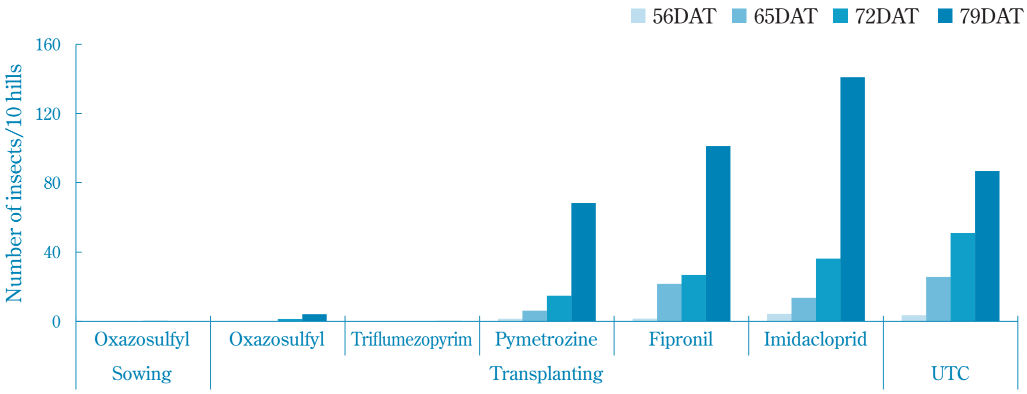
(1) Control effects against insect pests resistant to existing insecticides

We evaluated the control effects against insect pests resistant to existing insecticides, in paddy fields across Japan, by nursery box application of granules containing 2.0% oxazosulfyl. Oxazosulfyl showed a high efficacy against white-backed planthoppers resistant to fipronil (**Fig. 13**), brown planthoppers resistant to imidacloprid (**Fig. 14**), small brown planthoppers resistant



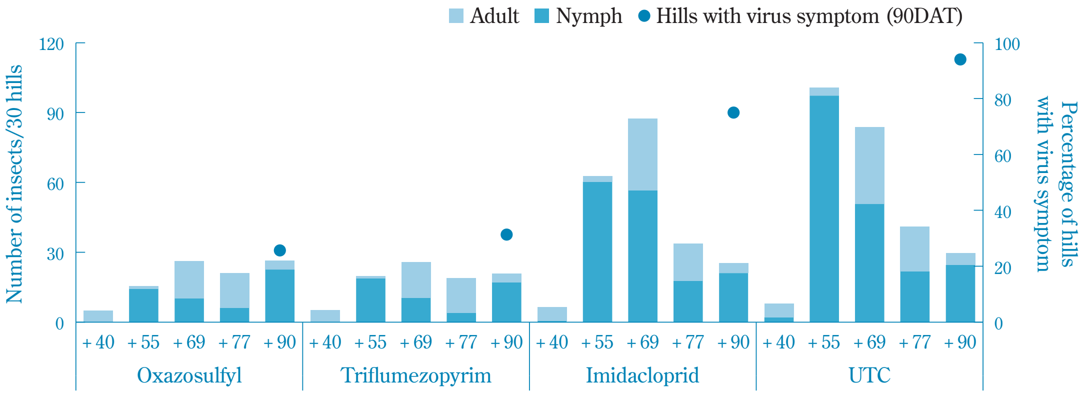
∗ "Sowing" means application after sowing before cover with soil and "transplanting" means application at one day before transpraniting.

Fig. 13 Efficacy of Oxazosulfyl granules against white-backed planthopper, *Sogatella furcifera*, in rice paddy field (Kagoshima).



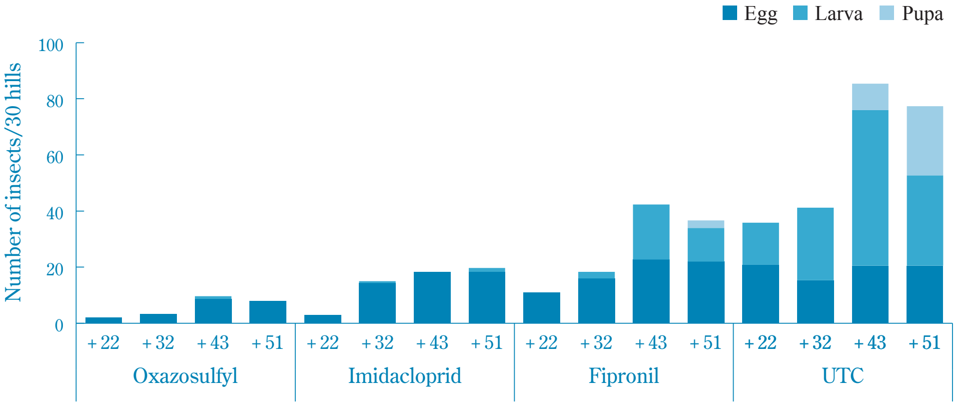
∗ "Sowing" means application after sowing before cover with soil and "transplanting" means application at one day before transpraniting.

Fig. 14 Efficacy of Oxazosulfyl granules against brown planthopper, *Nilaparvata lugens* in rice paddy field (Kagoshima).



∗ Application timing : on the day of transpraniting

Fig. 15 Efficacy of Oxazosulfyl granules against small brown planthopper, *Laodelphax striatellus*, in rice paddy field (Ibaraki).



∗ Application timing: on the day of transpraniting

Fig. 16 Efficacy of Oxazosulfyl granules against rice leaf beetle, *Oulema oryzae*, in rice paddy field (Hokkaido).

Table 1 Summary of trials of Oxazosulfyl 2.0% granules conducted by the JPPA (Japan Plant Protection Association) in 2016–2020

Order	Target pests		Efficacy*
Coleoptela	Rice leaf beetle	*Oulema oryzae*	+++
	Rice water weevil	*Lissorhoptrus oryzophilus*	+++
Lepidoptera	Rice stem borer	*Chilo suppressalis*	+++
	Rice green caterpillar	*Naranga aenescens*	+++
	Rice skipper	*Parnara guttata*	+++
	Rice leafroller	*Cnaphalocrocis medinalis*	+++
Hemiptera	Brown planthopper	*Nilaparvata lugens*	+++
	Small brown planthopper	*Laodelphax striatellus*	+++
	White-backed planthopper	*Sogatella furcifera*	+++
	Green rice leafhopper	*Nephotettix cincticeps*	+++
	Black rice bug	*Scotinophara lurida*	+++
Orthoptera	Rice grasshopper	*Oxya yezoensis*	+++
Diptera	Smaller rice leaf miner	*Hydrellia griseola*	++
	Rice stem maggot	*Chlorops oryzae*	++

∗: Average of indexed values of the trial results conducted by the JPPA (Excellent = 3, Good = 2, Inferior = 1, No efficacy = 0)
+++ : 2 ≤ average value, ++ : 1 ≤ average value < 2
Application timings : Before sowing (Mixture with bed soil or cover soil), Sowing (before covering with soil) -Transplanting.

to imidacloprid (**Fig. 15**), and rice leaf beetles resistant to fipronil and insensitive to imidacloprid (**Fig. 16**).

(2) Insecticidal spectrum

In the official efficacy evaluation for the registration of plant protection products conducted by the Japan Plant Protection Association between 2016 and 2020, the granules containing 2.0% oxazosulfyl also showed a high efficacy for the control of locusts and lepidopteran pests such as rice stem borers and rice leafrollers. It was highly effective in any of the application timings before sowing (mixture with bed soil or cover soil), at sowing, and at transplanting (**Table 1**). In addition, there was no case of crop injury in practical use, which indicates that it is very safe for rice plants.

Formulation

As mentioned above, the product containing oxazosulfyl has been developed for rice plants in Japan. It has been registered as ALLES® granule, which contains 2.0% (w/w) oxazosulfyl, in April 2021 and will be launched in the first quarter of 2022 (**Fig. 17**, left). In addition to ALLES® granule, STOUT® ALLES® granule, which contains 2.0% isotianil (a fungicide effective against rice blast) and 2.0% (w/w) oxazosulfyl, has been registered and will be launched at the same time (**Fig. 17**, right). These products can be used in a wide range of application time from before-sowing until at-transplanting. Further, ALLES® MONGALESS® granule, which contains 2.0% oxazosulfyl and 2.0%

Fig. 17 ALLES® granule & STOUT® ALLES® granule

(w/w) inpyrfluxam (a fungicide effective against rice sheath blight disease) granules, and STOUT® ALLES® MONGALESS® granule, which contains 2.0% isotianil, 2.0% oxazosulfyl, and 2.0% (w/w) inpyrfluxam, are under development. Both products will be registered as insecticides and be launched in the first quarter of 2022.

With the formulation design techniques cultivated in our company, the formulations of ALLES® granule and STOUT® ALLES® granule were optimized with respect to the combination of inert ingredients and their amounts, considering the efficacy, crop injuries, and ease of manufacturing at a factory. The main physical and chemical properties of ALLES® granule and STOUT® ALLES® granule are shown in **Table 2**. Both products showed favorable physical and chemical properties.

Toxicity, Metabolism, and Residual Property

1. Mammalian toxicity

(1) Acute toxicity, irritation, and skin sensitization

The LD_{50} values of oxazosulfyl Technical Grade (TG) were > 300 mg/kg body weight (bw) and < 2000 mg/kg bw in rats for oral administration, > 2000 mg/kg bw in rats for dermal application, and > 2030 mg/m^3 in rats for inhalation exposure. The main clinical signs observed in rats after oral administration and inhalation exposure included tremor, mydriasis, and vocalization. No notable changes were observed after dermal application. Acute toxicity of 3.0% granules (3.0% GR) was extremely low and there were no mortality and toxic signs at 2000 mg/kg bw in rats for oral administration and dermal application. The skin irritation potential of oxazosulfyl TG was minimal. The eye irritation potential of oxazosulfyl TG and the 3.0% GR was minimal and reduced by washing. 3.0% GR did not show skin irritation potential. For skin sensitization, oxazosulfyl TG was positive in the maximization test, whereas the 3.0% GR was negative in the Buehler test (**Table 3**).

Table 2 Physical and chemical properties of ALLES® granule & STOUT® ALLES® granule

Properties	ALLES® granule	STOUT® ALLES® granule
Oxazosulfyl content	2.0%	2.0%
Isotianil content	–	2.0%
Appearance	Fine whitish granule	Fine whitish granule
Bulk density	0.95 g/mL	0.92 g/mL
Moisture	0.2%	0.2%
Hardness	0.8%	0.6%
pH	9.2	9.1
Number of granules per gram	537/g	446/g
Granularity (500–1700 mm)	100%	100%

Table 3 Acute toxicity summary of Oxazosulfyl

Test type	Oxazosulfyl	Oxazosulfyl 3.0%GR
Rat acute oral (LD_{50})	300 mg/kg < LD_{50} < 2000 mg/kg	> 2000 mg/kg
Rat acute dermal (LD_{50})	> 2000 mg/kg	> 2000 mg/kg
Rat inhalation (LC_{50})	> 2030 mg/m^3 (4 hours, nose only exposure)	–
Eye irritation (Rabbit)	Minimally irritant	Minimally irritant
Skin irritation (Rabbit)	Minimally irritant	Non-irritant
Skin sensitization (Guinea pig)	Sensitizer	Non-sensitizer

(2) Subacute and chronic toxicity and carcinogenicity

In the subacute and chronic toxicity and carcinogenicity studies in rats, dogs, and/or mice, repeated administration of oxazosulfyl TG caused decreases in body weight gain and food consumption. The main toxic effects included an increase in liver weight, hepatocyte hypertrophy, and changes in blood biochemical parameters. Tremor, mydriasis, and vocalization in rats and vocalization in mice were also observed. No carcinogenicity was observed in rats or mice (**Table 4**).

(3) Reproductive and developmental toxicity

In the developmental toxicity studies in rats and rabbits, no teratogenicity was observed in fetuses. In the two-generation reproductive toxicity study in rats, there was no effect on the reproductive performance and nursing behavior (**Table 5**).

(4) Neurotoxicity

In the acute neurotoxicity study in rats, tremor, mydriasis, decrease in locomotor activity, and flaccidity were observed. In functional tests, decrease in body temperature and decrease in hindlimb grip strength were observed. In the subacute neurotoxicity study in rats, tremor and mydriasis were observed. In functional tests, increase in score of pain response, decrease in forelimb grip strength, and decrease in landing foot splay were observed (**Table 6**).

Table 4 Subacute and chronic toxicity summary of Oxazosulfyl

Species	Administration route and duration	Dose	NOAEL (mg/kg/d)
Rat	Oral (in diet), 13 weeks	150, 550, 2000 ppm	Male: 32.7 (550 ppm) Female: 39.5 (550 ppm)
Rat	Oral (in diet), 24 months	Male: 100, 300, 1000 ppm Female: 100, 300, 1000/600 ppm*	Male: 11.7 (300 ppm) Female: 15.6 (300 ppm)
Dog	Oral (in capsule), 13 weeks	Male: 3, 10, 50, 150 mg/kg/d Female: 3, 10, 50, 150/100 mg/kg/d*	Male: 10 Female: 10
Dog	Oral (in capsule), 12 months	1, 5, 30 mg/kg/d	Male: 5 Female: 5
Mouse	Oral (in diet), 18 months	70, 700, 7000/5000 ppm*	Male: 76.9 (700 ppm) Female: 74.0 (700 ppm)

*: The highest dose was reduced during the treatment period due to severe effects.

Table 5 Developmental and reproductive toxicity summary of Oxazosulfyl

Study	Species	Administration route and duration	Dose	NOAEL (mg/kg/d)	
Developmental toxicity	Rat	Oral (gavage) Days 6–19 of gestation	6, 20, 60 mg/kg/d	Maternal Fetal	20 60
	Rabbit	Oral (gavage) Days 6–27 of gestation	2, 6, 20 mg/kg/d	Maternal Fetal	6 6
Two-generation reproductive toxicity	Rat	Oral (in diet)	50, 200, 700 ppm	Parental	Male: 12.3 (200 ppm) Female: 15.4 (200 ppm)
				Offspring	Male: 12.3 (200 ppm) Female: 15.4 (200 ppm)
				Reproductive	Male: 43.1 (700 ppm) Female: 53.4 (700 ppm)

Table 6 Neurotoxicity summary of Oxazosulfyl

Study	Species	Administration route and duration	Dose	NOAEL (mg/kg/d)
Neurotoxicity	Rat	Acute oral (gavage)	25, 200, 400 mg/kg/d	25
	Rat	Oral (in diet), 13 weeks	150, 550 2000 ppm	Male: 35.2 (550 ppm) Female: 41.3 (550 ppm)

Table 7 Mutagenicity summary of Oxazosulfyl

Study	Study design	Results
Reverse mutation (Ames test)	*S. typhimurium*: TA100, TA98, TA1535, TA1537 *E. coli*: WP2*uvrA* −/+ S9 mix: 156–5000 µg/plate	Negative
in vitro chromosomal aberration	CHL/IU cells −/+ S9 mix: 31.3–125 µg/mL (6 hours) − S9 mix: 32.5–75.0 µg/mL (24 hours)	Negative
Bone marrow micronucleus	Rat 125, 250, 500 mg/kg/d	Negative

(5) Mutagenicity

In the reverse mutation study in *Salmonella typhimurium* and *Escherichia coli*, the chromosomal aberration study in Chinese hamster lung CHL/IU cell line, and the micronucleus study in rats, the results were all negative (**Table 7**).

2. Animal and plant metabolism

(1) Metabolism in animals

Following a single oral administration of ^{14}C-labeled oxazosulfyl to rats, it was rapidly absorbed and distributed throughout the body. Then, it was rapidly metabolized and excreted primarily in feces. The oral absorption rate was estimated to be at least 80%. No significant residue or accumulation of radioactivity was observed in tissues.

The main metabolic reactions of oxazosulfyl were hydroxylation of the pyridyl group followed by glucuronidation, hydrolysis and cleavage of the oxazole ring, and glutathione conjugation of the ethylsulfonyl group followed by generation of cysteine conjugate, thiol metabolite, and mercapturic acid conjugate.

(2) Metabolism in plants

The metabolism of ^{14}C-labeled oxazosulfyl was investigated in rice plants. The primary metabolic pathway of oxazosulfyl was the hydrolysis and cleavage of the oxazole ring. The generated metabolites were considered to be further degraded and incorporated into the constituents of plants.

3. Environmental behavior and residual property

(1) Degradation in water

In the hydrolysis study, ^{14}C-labeled oxazosulfyl was stable in buffer solutions at pH 4 and 7 with a half-life of ≥ 1 year (25 °C). In the buffer solution at pH 9, its degradation was proceeded by the cleavage of the oxazole ring with the half-life (25 °C) of 281 days. The degradation half-life of oxazosulfyl under light irradiation was 331 days in the buffer solution (pH 7), whereas degradation was slightly accelerated by light irradiation in natural water with a half-life of 156 days (equivalent to the natural sunlight at Tokyo in spring).

(2) Metabolism in soils

In the flooded aerobic soil and aerobic soil metabolism studies, the degradation half-life of ^{14}C-labeled oxazosulfyl (25 °C) was approximately 1000 days and ≥ 2000 days, respectively. The primary degradation pathway in soils was considered to be the cleavage of the oxazole ring.

(3) Residues in soils

Paddy field dissipation studies with an application of oxazosulfyl 3.0% GR at a rate of 3 kg/10 a in Ibaraki and Chiba demonstrated that the dissipation half-life was estimated to be 3 to 8 days with the maximum residual concentration of 1.42 to 1.92 mg/kg.

(4) Transfer into soils

The adsorption constant $K_{Foc(ads)}$ and the desorption constant $K_{Foc(des)}$ of oxazosulfyl corrected with the organic carbon content were calculated using Freundlich adsorption isotherm and were 207.9 to 2348.1 and 192.9 to 2489.1, respectively.

(5) Residues in water

Rice plants in the nursery boxes in which oxazosulfyl 3.0% GR had been applied at 1 kg/10 a were transplanted in paddy fields in Ibaraki and Tochigi. Paddy lysimeter studies in the fields demonstrated that the residual concentrations were up to 0.024 to 0.042 mg/L in paddy water and were below the limit of quantification (< 0.001 mg/L) in percolating water with the exception of 0.004 mg/L at 14 days after transplanting in Ibaraki.

(6) Residues in crops

In residue trials using rice with an application of 50 g of oxazosulfyl 3.0% GR in a rice nursery box, the residual concentration was below the limit of quantification (< 0.01 mg/kg) in hulled rice, below the limit of quantification (< 0.01 mg/kg) to 0.06 mg/kg in unhulled rice, and 0.08 to 0.46 mg/kg in rice straw.

(7) Residues in succeeding crops

It is unlikely that residual oxazosulfyl will affect succeeding crops, because its elimination half-life was 3 to 8 days in the study of residual oxazosulfyl in soils.

4. Effects on non-target organisms

The test results in aquatic organisms, honeybees, and birds are summarized in **Table 8**.

(1) Effects on aquatic organisms

The acute toxicity values (LC_{50}/EC_{50}/EC_{50}/ErC_{50}) of oxazosulfyl Technical Grade (TG) in fish, *Daphnia magna*, *Chironomus yoshimatsui*, and freshwater green alga were > 7.9, > 8.0, 0.036, and 2.2 mg/L, respectively. The acute toxicity values (LC_{50}/EC_{50}/ErC_{50}) of oxazosulfyl 3.0% GR in fish, *D. magna*, and freshwater green alga were > 1000, > 1000, and 100 mg/L, respectively. These values were sufficiently higher than the concentrations in environmental water expected from the practical use. Therefore, it is unlikely that oxazosulfyl will affect aquatic organisms.

(2) Effects on honeybees

When oxazosulfyl Technical Grade (TG) was administered orally and by contact to Western honeybees, the LD_{50} was 0.015 and 0.077 µg/bee, respectively. In the registered usage, there is no risk of exposing honeybees to oxazosulfyl, and it is unlikely that oxazosulfyl will affect honeybees.

(3) Effects on birds

When oxazosulfyl Technical Grade (TG) was administered orally to bobwhite quails, the LD_{50} was > 2250 mg/kg. The toxicity to birds was low. In the registered usage, it is unlikely that oxazosulfyl Technical Grade (TG) will affect birds.

Based on the above, the acute mammalian toxicity of oxazosulfyl 3.0% GR is very low, although that of oxazosulfyl Technical Grade (TG) is relatively high when it is orally administered. It is unlikely that oxazosulfyl will cause adverse effects on offspring including carcinogenicity, teratogenicity, and reproductive toxicity, even if oxazosulfyl TG is ingested for a long time. The evaluation on the environmental behavior and effects on non-target organisms suggests that oxazosulfyl does not affect the environment as long as it is used according to the registered methods.

Conclusions

Oxazosulfyl is characterized by the following 3 points: (1) a broad range of target insects controlled (a single active ingredient oxazosulfyl is effective against various insect pests including the species whose infestation varies largely in a year and those that occur locally), (2) a wide range of application window (it is very safe for rice plants and can be applied before sowing and during nursery periods from sowing to transplanting with a high efficacy in any of these application timings), and (3) unique insecticidal characteristics (it rapidly induces intoxicated

Table 8 Ecotoxicological summary of Oxazosulfyl on non-target organisms

Test substance	Test species		Test type	Results
Oxazosulfyl	Aquatic organisms	*Cyprinus carpio*	Acute (96 hours)	$LC_{50} > 7.9$ mg/L
		Daphnia magna	Acute (48 hours)	$EC_{50} > 8.0$ mg/L
		Chironomus yoshimatsui	Acute (48 hours)	$EC_{50} = 0.036$ mg/L
		Green alga*1	Acute (72 hours)	$ErC_{50} = 2.2$ mg/L
	Honeybee	*Apis mellifera*	Acute oral (96 hours)	$LD_{50} = 0.015$ µg/bee
		Apis mellifera	Acute contact (72 hours)	$LD_{50} = 0.077$ µg/bee
	Bird	*Colinus virginianus*	Acute oral	$LD_{50} > 2250$ mg/kg
Oxazosulfyl 3.0%GR	Aquatic organisms	*Cyprinus carpio*	Acute (96 hours)	$LC_{50} > 1000$ mg/L
		Daphnia magna	Acute (48 hours)	$EC_{50} > 1000$ mg/L
		Green alga*1	Acute (72 hours)	$ErC_{50} = 100$ mg/L

*1: *Raphidocelis subcapitata* (Formerly known as *Pseudokirchneriella subcapitata*) symptoms in insect pests to inhibit their behaviors, such as sucking, oviposition, and mating; also it does not exhibit cross-resistance and is highly effective against insect pests resistant to existing insecticides as well). Because oxazosulfyl is a long-lasting insecticide by nursery box application, it can reduce the number of insecticidal components applied and the number of applications, resulting in the reduction of environmental impacts. With these characteristics, this product is the next-generation insecticide having unique and attractive profiles that can meet various needs from farmers and customers, such as countermeasures against insecticide resistance, preference for low input of agricultural chemicals, labor-saving trend, and large-scale cultivation. We hope that it will become a core insecticide to yield a new value for rice cultivation in Japan. We will promote the effective use of this product and further deepen our research and investigation to find new technologies to control insect pests in rice cultivation.

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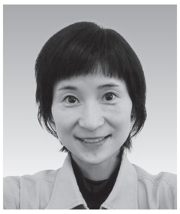
PROFILE



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