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# FLONICAMID (F1785, IKI220): NOVEL INSECTICIDE CHEMISTRY FOR COTTON AND OTHER CROPS

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## Abstract

Although flonicamid is structurally similar to nicotine and several neonicotinoids, it has been mistakenly classified with the neonicotinoid insecticides. Whereas nicotine and the neonicotinoids, as a group, function as agonistics of the nicotinic acetylcholine receptor, flonicamid's mode of action is dissimilar. This unique mode of action confers on flonicamid the lack of cross-resistance with not only neonicotinoids but also the major insecticide classes including the organophosphates (OP), carbamates and pyrethroids, among others. Therefore, classification of flonicamid as a neonicotinoid functionally is, in our opinion, erroneous.

Flonicamid is a superlative aphicide. In the mounting field efficacy database, a wide range of species has demonstrated susceptibility to low application rates. This is significant not only in the direct injurious effects of aphids but also in the reduction of spread of plant pathogens by aphid vectors. Promising results continue to build for non-aphid species as well. Plant bugs (*Lygus* spp.) appear well controlled by flonicamid and early work indicates that other agronomically important Hemiptera may well be susceptible. Very favorable toxicological and environmental profiles round out what will become a very effective, useful and safe pest management tool for cotton and other growers.

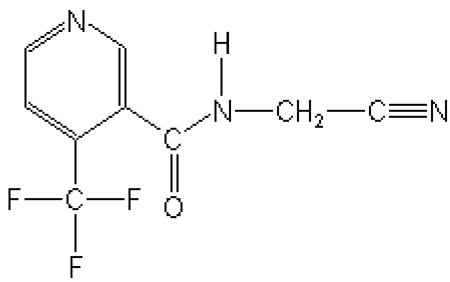
## Introduction

In late 2001, FMC Corporation obtained the exclusive rights to develop, market and distribute Ishihara Shangyo Kaisha, Ltd.'s (ISK) insecticide, flonicamid (F1785) in North America, much of Latin America, the United Kingdom, Spain and Portugal. Under this agreement, FMC and ISK will jointly develop flonicamid in the European Union.

Currently, several structural groups are recognized among the neonicotinoids including the nitroguanidines, nitromethylenes, and pyridylmethylamines. It is not uncommon for a neonicotinoid to be classified in one or more categories (e.g. nitenpyram). Since its discovery in 1993, flonicamid has been incorrectly considered in the class of neonicotinoids. It is our contention that flonicamid, a trifluoromethylpyridine derivative, is grouped or classified with the neonicotinoids due solely to its structural similarity with nicotine and the insecticides traditionally considered as neonicotinoids. From the outset, flonicamid has demonstrated significant insecticidal effects not typical of the neonicotinoids. More recently, additional evidence suggests that its mode of action is sufficiently distinct to warrant separate classification. This evidence is presented as a basis to distinguish flonicamid from chemistry of similar structure.

## Technical and Chemical Properties

Structural Formula:



Chemical Name: N-cyanomethyl-4-trifluoromethyl nicotimamide
Common Name: Flonicamid (proposed)
Code Names: F1785, IKI-220
Trade Names: to be announced
Molecular Formula, Weight: $C_9H_6F_3N_3O$, 229.16
Physical Description: White crystalline solid (ai)
Tan solid (50DF, WDG)

Solubility: 5.2 g /L (20°C)
Vapor Pressure: 9.43 x $10^{-4}$ kPa @25°C
Melting Point: 157.5°C
Odor: Odorless
Log $P_{ow}$: 0.3 @25°C
Hydrolysis pH 5, 7: Stable
pH 9: $t_{½}$ =204 days

## Toxicology

Acute Oral (rat) $LD_{50}$ = 884 mg/kg male, 1768 mg/kg female
Acute Dermal (rat) $LD_{50}$ >5000 mg/kg
Acute Inhalation (rat) $LC_{50}$ >4.9 mg/L
Eye Irritation: Minimally irritating

Dermal Irritation: Non-irritating
Dermal Sensitization: Non-sensitizing
Mutagenicity / Genotoxicity: Negative

## Ecotoxicology

| | | | |
|---|---|---|---|
| Bobwhite Quail | Acute Oral $LD_{50}$ >2000 mg/kg | Mallard Duck | Acute Oral $LD_{50}$= 1591 mg/kg |
| | Dietary $LC_{50}$ >5000 mg/kg | | Dietary $LC_{50}$ >5000 mg/kg |
| Bluegill Sunfish | $LC_{50}$ >100 mg/L (96hr) | Algal Toxicity | |
| Rainbow Trout | $LC_{50}$ >100 mg/L (96hr) | | 96 hr $EC_{50}$ = 119 mg/L |
| Daphnia magna | $LC_{50}$ >100 mg/L (48hr) | | NOEC = 119 mg/L |

## Environmental Fate Parameters

Aqueous Photolysis: $t_{½}$ =267 days

Soil Photolysis: $t_{½}$ = 22 days

Aerobic Soil: $t_{½}$ =1-2 days

Aerobic Aquatic: $t_{½}$ =34 days (aqueous phase)
$t_{½}$ =40 days (total system)

Anaerobic Aquatic: $t_{½}$ =61 days (aqueous phase)
$t_{½}$ =121days (total system)

Terrestrial Field Dissipation: $t_{½}$ =3-10 days

Flonicamid exhibits little tendency to persist, due to its short half-life, and its moderate soil mobility is negated by rapid metabolism and mineralization. Neither bioaccumulation nor any other significant hazard is expected to occur.

## Biochemistry and Mode of Action

Morita, et.al. (2000) first described the unique activity of flonicamid. While demonstrating the complete cessation of aphid feeding, flonicamid exhibited no effects common to other neonicotinoids. Whereas pymetrozine and another GABA antagonist promoted the spontaneous contractions of the foregut of *Locusta migratoria,* similar treatment with flonicamid failed to do so. This research also showed a concomitant reduction in aphid honeydew production and salivation with the cessation in feeding. Other behavioral changes noted in aphids following intoxication with flonicamid were pronounced sensitivity to light, random or irregular leg movement, altered righting response, and uncoordinated locomotion. Most noteworthy is increased and erratic antennal movement. These particular behavioral effects were very different from those displayed by aphids treated with imidacloprid (Staetz and Argentine, FMC, unpublished.)

The most recent research (unpublished), that addresses the structure versus mode of action issue, has provided additional evidence that flonicamid does not bind to the nicotinic acetylcholine receptor as directly compared to nicotine and imidacloprid. This information, when fully disclosed, could provide the basis for a separate insecticide classification for flonicamid.

## Systemicity

The extent of flonicamid's systemic movement is becoming more fully understood. Initially indirect methods (e.g. bioassays) were used (Morita, et.al. 2000). Root uptake and subsequent redistribution was demonstrated in eggplant using *Myzus persicae* caged on upper leaves 5 days after a soil drench treatment. Similarly, these researchers demonstrated translaminar movement by spotting one leaf surface with a dilute flonicamid solution and caging aphids on either side of the leaf. In both types of experiments, flonicamid exhibited complete mortality of *Myzus persicae.*

## Biological Activity

Since 2001, when FMC acquired the development rights, flonicamid has undergone expanded biological evaluation in both controlled laboratory conditions and replicated field trials across a range of crops in the Americas and Europe. This work, in combination with that completed by ISK and ISK BioSciences, portrays the robust and diverse pest spectrum of this chemistry.

### Aphids

Flonicamid has exhibited excellent activity in numerous species of agronomically important aphids (Table 1). Aphid mortality is generally seen as a linear response to flonicamid dose rate under controlled conditions. This response has been observed in numerous species. In the field, flonicamid rates required to provide commercially acceptable control typically range from 0.036 to 0.054 lb ai /a. Application rates increase (0.054 to 0.071 lb ai/a) for greater plant volume, higher pest populations and/or longer residual activity.

### Non-Aphid Species

In a relative sense, less definitive evaluative work has been completed on non-aphid pests versus aphids. However, a reasonably clear picture of flonicamid's activity in this spectrum is beginning to emerge. Significant activity among the Plant Bugs (*Lygus* spp.) adds much to the insect spectrum, particularly in cotton.

Good to excellent activity against greenhouse whitefly (*Trialeurodes vaporariorum*) has been observed as well. Promising activity against onion thrips (*Thrips tabaci)* and, in preliminary work, excellent ovicidal activity against Pear Psylla (*Cacopsylla pyricola*) has been recorded with flonicamid.

### Research in Cotton

Among the ever-expanding compliment of field efficacy work with flonicamid, cotton has remained a central part of the development program. This work has been jointly developed by FMC and ISK in-house researchers as well as university and contract cotton entomology researchers.

From 2000 to 2002, cotton aphid evaluations were conducted under a wide set of environmental conditions ranging from drought to excessive rainfall and extremes of temperature in both North America and in Brazil. The results (Table 2) indicate that flonicamid provides good to excellent control of cotton aphid (*Aphis gossypii*) at exceptionally low application rates. Flonicamid's performance generally exceeded that of neonicotinoid and other chemistries being introduced in cotton.

Another example of its potential utility in cotton was produced in a limited set of trials conducted against Tarnished Plant Bug (*Lygus lineolaris*). Flonicamid exhibited very good activity on adult and nymph plant bugs versus the standards while maintaining comparable levels of square retention (Table 3). Activity against Western Plant Bug (*Lygus hesperus*) also appeared to differentiate adults and nymphs with somewhat better control of the latter (Table 4). Under severe pest pressure (Table 5), flonicamid exhibited acceptable, albeit lower reductions, of Green (*Nezara hilare*) and Southern Green Stink Bugs (*Nezara viridula*).

## Cross-Resistance and Resistance Management

Extensive laboratory research, including *in vivo* and *in vitro* methodology, as well as field observations has shown that flonicamid does not exhibit cross-resistance to OP, carbamate, pyrethroid nor neonicotinoid insecticides. Furthermore, resistance to flonicamid was not observed to develop in an OP, carbamate-resistant population of *Myzus persicae* after continuous exposure for 71 generations. However, field use recommendations will be structured to limit the potential for development of flonicamid resistance.

## Effects on Beneficial Species

Flonicamid appears to elicit little if any negative effects on beneficial insects in laboratory evaluations and field observations made to date. Among the arthropods evaluated, were honey bee (Apis mellifera) Pirate bugs (*Orius* spp.), Big-eyed bugs (*Geocoris* spp.), nabids (*Nabis* spp.), lacewings *(Chrysoperla spp.),* mantids *(Tenodera* spp.*),* fire ant (*Solenopsis invicta*), parasitic wasps (*Trichogramma* spp.), parasitoids (*Aphidius* spp.), predacious mites (*Typhlodromus* spp.) and spiders. In direct comparison studies, flonicamid exhibited significantly less negative effects to the various beneficial species than organophosphate, carbamate and pyrethroid insecticides, and usually much less injurious effect than neonicotinoid compounds.

## Registration Status

Flonicamid was granted OP alternative status by the US EPA in April 2002 for use on ornamentals grown in indoor greenhouses and is scheduled for review during the third quarter of the US EPA's FY03. Similarly, OP replacement status will be sought for agricultural use as well. The first US agricultural use registrations are anticipated in 2004. Besides cotton, flonicamid is expected to be registered in a diverse array of row crops and tree fruit and nut crops in the Americas and European Union.

## Conclusions

Despite the structural similarities of flonicamid with the 'neonicotinoids', evidence has been offered that suggests the structure – mode of action relationship, with respect to classification, does not necessarily apply in this case. Complete and full details of this research will be published imminently and, perhaps, result in the proper reclassification of flonicamid.

Irrespective of the current nomenclature, flonicamid exhibits numerous qualities of an efficient, effective and environmentally safe insecticide. Its low application rates (0.036 to 0.089 lb ai/a) represent a major reduction in pesticide load; combined with its ecotoxicology and environmental fate profile makes flonicamid a significant improvement over 'hard' chemistries. Its lack of cross-resistance with existing OPs, carbamates, pyrethroids and the apparently growing group of neonicotinoids, further adds to its overall utility especially in resistance management.

## Acknowledgements

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Table 1. Current aphicidal spectrum of flonicamid.

| | | | |
|---|---|---|---|
| Bird Cherry Oat aphid | *Rhopalosiphum maidis* | Hops aphid | *Phorodon humuli* |
| Black Bean aphid | *Aphis fabae* | Leafcurling Plum aphid | *Anuraphis helichrysi* |
| Black Cherry aphid | *Myzus cerasi* | Lettuce aphid | *Nasonovia ribis-nigri* |
| Blue Alfalfa aphid | *Acyrthosiphon kondoi* | Mealy Plum aphid | *Hyalopterus pruni* |
| Brown Citrus aphid | *Toxoptera citricida* | Pea Aphid | *Acyrthosiphon pisum* |
| Cabbage aphid | *Brevicoryne brassicae* | Potato aphid | *Macrosiphum euphorbiae* |
| Corn Leaf aphid | *Rhopalosiphum maidis* | Rose Aphid | *Macrosiphum rosae* |
| Cotton / Melon aphid | *Aphis gossypii* | Rosy Apple aphid | *Dysaphis plantaginea* |
| Cowpea aphid | *Aphis craccivora* | Russian Wheat aphid | *Diuraphis noxia* |
| English Grain aphid | *Sitobion avenae* | Soybean aphid | *Aphis glycines* |
| Foxglove aphid | *Aulacorthum solani* | Spirea aphid | *Aphis spiraecola* |
| Grain aphid | *Sitobion avenae* | Spotted Alfalfa aphid | *Therioaphis maculata* |
| Green Apple aphid | *Aphis pomi* | Tobacco aphid | *Myzus nicotianae* |
| Green Peach aphid | *Myzus persicae* | Turnip aphid | *Lipaphis erysimi* |
| Greenbug | *Schizaphis graminum* | Wooly Apple aphid | *Eriosoma lanigerum* |

[a] Confirmed efficacy in replicated field trials.

Table 2. Efficacy of flonicamid versus competitive chemistries against cotton aphid (*Aphis gossypii*) in cotton.[a]

| | | | Brazil 2001 | | N. America 2000-01 | | N. America 2002 | |
|---|---|---|---|---|---|---|---|---|
| **Treatment[b]** | **g ai/ha** | **lb ai/a** | **% Control** | **(n)[c]** | **% Control** | **(n)** | **% Control** | **(n)** |
| Flonicamid 50 DF | 40 | 0.036 | | | | | 80.2 | (3) |
| | 50 | 0.044 | 93.5 | (4) | 98.0 | (1) | | |
| | 60 | 0.053 | | | 85.0 | (9) | 82.1 | (8) |
| | 75 | 0.066 | 85.0 | (4) | 98.0 | (1) | | |
| | 80 | 0.071 | | | 88.8 | (9) | 84.1 | (8) |
| Thiamethoxam 40WP | 53 | 0.047 | | | | | 79.1 | (8) |
| Acetamiprid 70WP | 20 | 0.02 | 98.8 | (4) | | | | |
| | 56 | 0.05 | | | | | 87.0 | (6) |
| Pymetrozine 50WG | 140 | 0.125 | | | | | 20.8 | (1) |
| Imidacloprid 4F | 53 | 0.047 | | | 72.3 | (4) | | |
| | 100 | 0.089 | | | | | 56.9 | (3) |
| Thiacloprid 480SC | 72 | 0.064 | 72.7 | (4) | | | | |
| Untreated[d] | | | 47.9 | (4) | 78.8 | (10) | 112.2 | (8) |

[a] Data are from 7 days after application in replicated FMC and ISK in-house and university field trials conducted in North and Latin America during 2000 to 2002.
[b] Treatments applied as foliar applications at local threshold.
[c] Number of trials per mean.
[d] Average number of aphids per leaf.

Table 3. Efficacy of flonicamid against tarnished plant bug (*Lygus lineolaris*) in cotton. [a]

| | | | % Control – Adults | | |
|---|---|---|---|---|---|
| **Treatment[b]** | **lb ai/a** | **g ai/ha** | **5DAT[c]** | **8DAT** | **12DAT** |
| Flonicamid 50DF | 0.053 | 60.0 | 0.0 | 100.0 | 100.0 |
| Thiamethoxam 40WP | 0.047 | 53.0 | 0.0 | 50.0 | 64.7 |
| | 0.063 | 70.0 | 62.5 | 0.0 | 0.0 |
| Acetamiprid 70WP | 0.05 | 56.0 | 0.0 | 0.0 | 0.0 |
| Imidacloprid 4F | 0.047 | 53.0 | 0.0 | 0.0 | 64.7 |
| Untreated[d] | | | 8.0 | 6.0 | 17.0 |
| | | | **% Control - Adults + Nymphs** | | |
| Flonicamid 50DF | 0.053 | 60.0 | 74.0 | 71.9 | 87.8 |
| Thiamethoxam 40WP | 0.047 | 53.0 | 69.0 | 61.9 | 67.6 |
| | 0.063 | 70.0 | 75.6 | 68.7 | 71.9 |
| Acetamiprid 70WP | 0.05 | 56.0 | 47.3 | 51.8 | 67.6 |
| Imidacloprid 4F | 0.047 | 53.0 | 44.6 | 28.1 | 11.5 |
| Untreated[d] | | | 258.0 | 278.0 | 139.0 |
| | | | **%Square Retention** | | |
| Flonicamid 50DF | 0.053 | 60.0 | 80 | 72 | 76 |
| Thiamethoxam 40WP | 0.047 | 53.0 | 76 | 88 | 78 |
| | 0.063 | 70.0 | 92 | 94 | 86 |
| Acetamiprid 70WP | 0.05 | 56.0 | 88 | 84 | 70 |
| Imidacloprid 4F | 0.047 | 53.0 | 84 | 76 | 76 |
| Untreated | | | 73 | 70 | 56 |

[a] Data from one, replicated trial in North America 2002.
[b] Foliar application at local threshold.
[c] Days after treatment.
[d] Values are pests per 100 ft. of row

Table 4. Efficacy of flonicamid against western plant bug (*Lygus hesperus*) in cotton. [a]

| Treatment[b] | lb ai/a | g ai/ha | % Control - Adults 1-4 DAT[c] | 6-10 DAT | 13-16 DAT | 20-22 DAT |
|---|---|---|---|---|---|---|
| Flonicamid 50DF | 0.036 | 40 | 43.0 | 67.9 | 71.9 | 71.3 |
| | 0.053 | 60 | 59.7 | 46.7 | 39.4 | 58.0 |
| | 0.071 | 80 | 67.6 | 57.1 | 64.0 | 31.3 |
| Acetamiprid 70WP | 0.05 | 56 | 60.6 | 71.5 | 58.2 | 51.8 |
| Thiamethoxam 40WP | 0.063 | 70 | 62.6 | 57.4 | 53.1 | 29.2 |
| Untreated[d] | | | 5.5 | 6.7 | 6.3 | 7.8 |
| | | | % Control -Nymphs | | | |
| Flonicamid 50DF | 0.036 | 40 | 67.0 | 75.4 | 60.8 | 93.2 |
| | 0.053 | 60 | 80.8 | 77.0 | 59.4 | 71.7 |
| | 0.071 | 80 | 72.5 | 68.2 | 64.0 | 84.3 |
| Acetamiprid 70WP | 0.05 | 56 | 57.5 | 72.4 | 78.2 | 74.8 |
| Thiamethoxam 40WP | 0.063 | 70 | 50.0 | 46.5 | 34.9 | 57.9 |
| Untreated[d] | | | 2.6 | 4.6 | 3.8 | 6.9 |

[a] Data from two replicated trials in North America, 2002.
[b] Foliar application at local threshold.
[c] Days after treatment.
[d] Values are pests per 50 sweeps.

Table 5. Efficacy of flonicamid against green (*Nezara hilare*) and southern green stink bugs (*Nezara viridula*) in cotton. [a]

| Treatment[b] | lb ai/a | g ai/ha | % Control: Green Stink Bug Adults & Nymphs 8 DAT[c] | Southern Green Stink bug Nymphs 8 DAT | Southern Green Stink bug Adults & Nymphs 12 DAT |
|---|---|---|---|---|---|
| Flonicamid 50DF | 0.053 | 60.0 | 78 | 75 | 65 |
| Thiamethoxam 40WP | 0.063 | 70.0 | 100 | 100 | 29 |
| Acetamiprid 70WP | 0.05 | 56.0 | 100 | 100 | 100 |
| Imidacloprid 4F | 0.047 | 53.0 | 100 | 100 | 100 |
| Untreated[d] | | | 50 | 44 | 17 |

[a] Data from one, replicated trial in North America 2002.
[B] Foliar applications at local threshold.
[c] Days after treatment
[d] Data are pest counts per 100 ft of row.