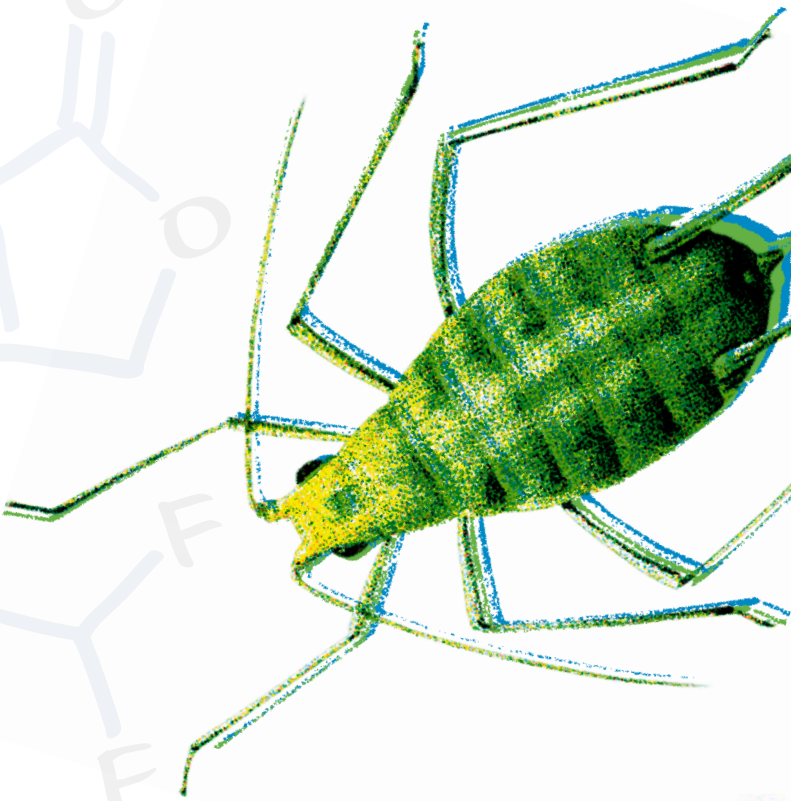
Insecticide

Flupyradifurone



Technical Information

Flupyradifurone

Contents

1. General information

Sivanto™ (active substance flupyradifurone) is a new insecticide with a distinct spectrum of activity belonging to Bayer CropScience´s own chemical class of Butenolides. Sivanto will be developed, registered and sold throughout the world in all major climatic zones allowing agriculture, the key markets being Brazil, USA, Europe, Ghana, India, and China.
The basic formulations are currently a 200 SL for foliar and drench/drip use and a 480 FS for seed treatment. Mixtures with other active substances are under development.

When compared to other insecticides, Sivanto exhibits a very promising safety profile.

Crops and Pests
Sivanto is intended to be used as an insecticide in agriculture on a wide range of crops such as vegetables, fruits, grapes, date palm, coffee and cocoa as foliar spray or soil drench, and as a seed treatment product for broad acre crops, e.g. soybean.

Sivanto is a systemic insecticide, flexible in application and mainly intended for sucking pest control such as aphids, hoppers and whiteflies. Spectrum extension to mealybugs, leafminer, soft scales, weevils, flea beetles and psyllids is under examination. Sivanto is most effective, when used as a foliar application, as a threshold treatment as well as with water amounts providing good crop coverage.

Mode of Action
Flupyradifurone, the active substance of Sivanto, interacts with insect nicotinic acetylcholine receptors, a class of neurotransmitter-gated cation channels which are involved in excitatory neurotransmission. These are also the target sites for neonicotinoid insecticides. The compound acts as an agonist, i.e., the binding of flupyradifurone to the receptor protein induces a depolarising ion current and subsequent excitation of the nerve cell. In contrast to natural acetylcholine, flupyradifurone cannot be inactivated by acetylcholinesterase resulting in a disorder of the nervous system of the insect and subsequent death of the treated insects.

Resistance Management
Despite having the same mode of action as neonicotinoids, Sivanto can effectively be used for the control of several pests' species which became resistant to commercially available insecticides in this chemical class, because it belongs to a different chemistry. Sivanto is a new tool in resistance management, particularly of whiteflies, jassids, and the damson hop aphid; and it does not exhibit significant cross-resistance to insecticides from other chemical classes.

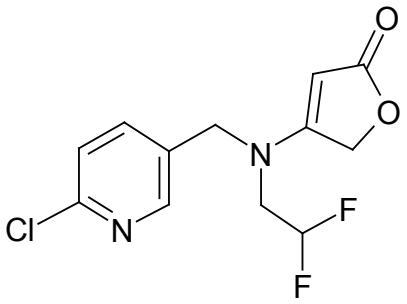
IPM Considerations and safety to beneficial insects

Selectivity towards beneficial insects and predatory mites is a requirement for a modern IPM-compatible product. Side effects of Sivanto on beneficial arthropods have been tested in various semi-field and field trials. In practical conditions, Sivanto can be considered safe to most beneficial insects (with the exception of predatory bugs), and specifically to pollinators.

Sivanto will provide significant benefits to the growers

- High level of efficacy with pronounced adulticidal effects, and excellent speed of action.
- Efficacy, IPM fit and versatile application systems allow use during a wide application window, where Sivanto can be directed against adults and larvae, or nymphs.
- Speed of activity on virus vectors prevents secondary spread of viruses.
- Protection of new plant growth after seed treatment and soil application.
- Despite the same MOA as neonicotinoids, Sivanto is an excellent tool for resistance management – notably for whiteflies – being different in its chemical structure. It is also a good rotation partner for ketoenols (Movento; Oberon).
- Minimal risk to natural enemies and non-target insects, making it an ideal addition to IPM programs.
- Extended residual activity due to the complementary effects with natural enemies, in cases in which beneficial insects are present in relevant populations.

2. Identity of the active substance

Name (common name, ISO):	Flupyradifurone
Development code:	BYI 02960
Chemical name (IUPAC):	4-[[(6-chloropyridin-3-yl)methyl](2,2-difluoroethyl) amino]furan-2(5H)-one
Chemical name (CAS):	2(5H)-furanone, 4-[[(6-chloro-3-pyridinyl)methyl] (2,2-difluoroethyl)amino]-
CAS-No.:	951659-40-8
Structural formula:	
Empirical formula:	$C_{12}H_{11}Cl\ F_2N_2O_2$
Molecular weight:	288.68 g/mol

3. Physico-chemical properties

Appearance:	Solid (powder)
Colour:	White to beige
Odour:	distinct, solvent-like odour (TGAI), weak, not characteristic (pure AI)
Melting point:	69° C (pure a.i.), 67,1° C for TGAI at atmospheric pressure
Boiling point:	no boiling point at atmospheric conditions, pure a.s. decomposed at 270° C, TGAI at 245° C
Vapour pressure:	9.1 x 10-7 Pa (20° C)
Density:	D=1.43 (purity 99.4%), D= 1.52 (TGAI)
Solubility (at 20° C):	• in water: 3.2 g/L (pH 4, 20° C) • in organic solvents:

Solvent	**[g/L]**
• n-heptane	• 0.0005
• toluene	• 3.7
• 1,2-dichloromethane	• > 250
• ethyl acetate	• > 250
• methanol	• > 250

Partition coefficient:	log P = 1.2 (at 25°C and pH 7)

4. Behaviour in the environment

The behaviour of flupyradifurone in plants, animals, soil and water was investigated by mainly using [pyridinylmethyl-^{14}C] and [furanone-4-^{14}C]-labelled compound. Additionally for selected studies the [ethyl-1-^{14}C] and the [pyridine-2,6-^{14}C]-labels have also been used to fully elucidate the metabolic pathways.

In plants:
The behaviour and metabolism of flupyradifurone was investigated in five diverse target crops (tomato, apple, potato, cotton, and rice) for foliar, soil or seed/tuber treatment applications, and in confined rotational crops (Swiss chard, turnip, and wheat) after application of flupyradifurone onto bare soil and cultivating of succeeding crops at three plant-back intervals. Sivanto 200 SL was used for foliar and soil applications and Sivanto 480 FS for seed/tuber treatments. The plant metabolism studies have shown a reasonably consistent metabolic profile across both foliar and soil application, and as well for seed/tuber treatment. The only residues of flupyradifurone that were consistently observed at significant levels across all target and succeeding crops were the parent compound and difluoroacetic acid (DFA), both of which are specific to the use of flupyradifurone. On the basis of these results, parent compound and DFA are the proposed constituents (expressed as their sum, in parent equivalents) for the residue definition for *enforcement* for primary (target) plants and rotational crops.

For *data collection and risk assessment,* metabolite BYI 02960-difluoroethyl-amino-furanone (DFEAF) was added to the residue definition since it was a major metabolite found in the Swiss chard RACs in all rotations of the confined rotational crop study and was not observed in the rat ADME studies. For the sake of consistency, the samples of all supervised residue trials on target plants and rotational crops were analysed for these three compounds.

In animals:
The absorption, distribution, metabolism, and excretion (ADME) of flupyradifurone have been studied in rats following a single oral or i.v. administration of [^{14}C]flupyradifurone labelled in the furanone ring, the pyridinylmethyl bridge or the difluoroethyl side chain.

The biokinetic behavior of flupyradifurone was characterized by a rapid absorption reaching peak plasma concentrations (C_{max}) between 1 and 4 hours after oral administration; in total, >80% of the orally administered dose was absorbed independent of the label position. Plasma level decline in male rats receiving [^{14}C]flupyradifurone by *i.v.* injection was essentially identical from 8 to 72 hours after administration to that of males that were dosed orally.

Excretion of radioactivity was also rapid, being nearly complete within 24-48 hours of administration. The main route of excretion was renal. Female rats had slightly higher renal excretion rate than male rats. Comparison of the excretion patterns in male rats from oral vs. *i.v.* experiments shows equivalent urinary excretion levels and rates; as expected, faecal excretion was somewhat higher in rats after oral administration.

As expected for a compound with a log P_{OW} of 1.2, overall retention in tissues was low. The radioactivity remaining in the tissues from the low dose experiments following oral dosing were negligible.

In urine, the parent compound was the predominant component, representing 36 – 74 % of the administered dose. Metabolites identified in urine were BYI 02960-OH and its conjugates BYI 02960-OH-gluA and BYI 02960-OH-SA, and the cleavage products BYI 02960-hippuric acid, BYI 02960-des-difluoroethyl, 6-chloronicotinic acid (6-CNA), difluoroacetic acid (DFA), and BYI 02960-difluoroethyl-amino-furanone (DFEAF). Additionally BYI 02960-iso-OH was identified at minor amounts. BYI 02960-OH and parent compound were the major components found in faeces. Additionally, organ metabolism studies with [furanone-4-^{14}C] and [ethyl-1-^{14}C]flupyradifurone were conducted. In the study with [furanone-4-^{14}C]flupyradifurone, parent compound was by far the largest component detected in all samples of plasma, organs and tissues, accounting for more than 72% of the total radioactivity. In the second organ metabolism study, parent compound was the main constituent observed in urine at all time-points as in the corresponding study with the [furanone-4-^{14}C]-label. In organs, plasma and tissues taken 24 hours after administration, difluoroacetic acid (DFA) was by far the dominant metabolite, accounting for more than 50% of the radioactivity.

The livestock metabolism of flupyradifurone was investigated in laying hens as a model for poultry and lactating goats as a model for ruminants following oral administration of [pyridinylmethyl-^{14}C]flupyradifurone and [furanone-4-^{14}C]flupyradifurone for both species.

The overall recovery of radioactivity was high in all livestock metabolism studies; the predominant amount of radioactivity was detected in excreta. Less than 5% of the administered dose was present in eggs, milk and in tissues and organs. In eggs, a plateau level was reached six to nine days after the first administration and in milk a plateau level was reached one to two days after the first administration.

The unchanged parent compound is a significant, if not the dominating constituent of the residues in milk, eggs and edible tissues of both species. Other metabolites determined in comparable concentrations are the natural compound lactose in the milk of goats after administration of [furanone-4-^{14}C]flupyradifurone, and BYI 02960-acetyl-AMPC in eggs and tissues of poultry after administration of [pyridinylmethyl-^{14}C] flupyradifurone. Difluoroacetic acid (DFA) was determined in selected livestock samples by high resolution LC-MS subsequently to the metabolism studies since rat studies conducted with [ethyl-1-^{14}C]flupyradifurone showed major amounts of this metabolite in organs and tissues. Extrapolation of rat data suggested high DFA levels in livestock tissues which was confirmed in the poultry and cattle feeding studies. In the poultry feeding study, BYI 02960-acetyl-AMCP was included in the analytical method for data collection, as well.

With the exception of one muscle sample in which a concentration of 0.003 mg/kg was determined, the residue levels of BYI 02960-acetyl-AMCP were in all cases below the LOD of 0.003 mg/kg. Considering the results of the livestock metabolism studies and as well the results of the feeding studies, the sum of parent compound and DFA are the proposed constituents (expressed as their sum, in parent equivalents) for the residue definition for *enforcement, data collection* and *risk assessment.*

In soil:

From the laboratory and field dissipation studies conducted with flupyradifurone it can be concluded that parent substance degrades at a moderate rate in soil. Under aerobic conditions extensive mineralization to CO_2 occurs (up to 59 %), and moderate levels of non-extractable residues were observed (up to 34 %). Non-extractable residues have been shown to be formed by biological processes and were strongly bound to the solid (humin) fractions of soil.
Two major non-volatile metabolites, difluoroacetic acid (DFA) and 6-chloronicotinic acid (6-CNA), were also formed, both of which degrade and are therefore not expected to accumulate in the environment.
Degradation under anaerobic or photolytic conditions is not expected to significantly contribute to the overall environmental dissipation of flupyradifurone.

Rate of Degradation

Degradation in laboratory aerobic soil (in the dark at 20° C)

BYI 02960	DT_{50} lab.	73 days (geomean US and EU) soils; range 33 – 371 days (all soils)
DFA	DT_{50} lab.	61 days (geomean); range 44.9 to 73.6 days
6-CNA	DT_{50} lab.	5.3 days (geomean); range 2.9 to 36.6 days (including Nisso protected data)

Degradation under field conditions

BYI 02960	DT_{50} field	8.3 to 251 days

Mobility in soil

The adsorption constants, K_{oc}, for flupyradifurone determined by batch equilibrium indicated medium mobility in soil. Desorption constants, K_{doc}, were higher indicating significantly stronger sorption. In time dependent sorption studies the sorption of flupyradifurone was shown to increase over time with an ageing factor of 2.6 to 4.4.
According to the K_{oc} values the major metabolite DFA is potentially of high mobility while 6-CNA is of medium mobility.

BYI 02960	mean K_{oc} 98.4 mL/g (EU and US soils), 331mL/g (Brazilian soils) + pronounced time dependant sorption
DFA	mean K_{oc} 6.8 mg/L
6-CNA	mean K_{oc} 88 mL/g (Soils only, Nisso data – protected)

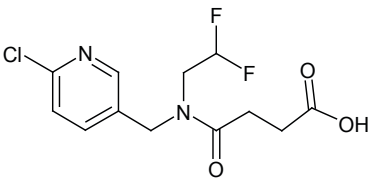
In aquatic systems:

The fate and behaviour of flupyradifurone in aquatic systems was investigated under standardized laboratory conditions and additionally under outdoor conditions in a pond system. Under laboratory conditions, in biotic systems, in the dark, flupyradifurone was moderately degraded under aerobic conditions with mineralisation to carbon dioxide and the formation of non-extractable residues. No major metabolites were formed; DFA was detected at a maximum of 7% in the total system. The DT50 was calculated to be 9.2 to 53.5 days in the water phase and 201 to 259 days in the total system. In an outdoor pond study performed in Germany, the rate of degradation was similar (DT50 80.6 days in the water). Under anaerobic laboratory conditions flupyradifurone was stable.

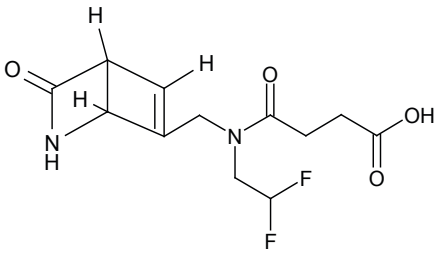
In abiotic systems flupyradifurone was stable to hydrolysis but rapidly degraded by photolysis. In photolysis studies in buffer solution and in natural water two major degradates were formed, BYI 02960- succinamide and BYI 02960-azabicyclosuccinamide.

Photolysis degradates

BYI 02960-succinamide
maximum 40%



BYI 02960-azabicyclosuccinamide
maximum 26%



Rate of Degradation under laboratory conditions, due to photolysis

Aqueous buffer photolysis:	DT_{50} 13.8 experimental hours (equivalent to 1.75 day (Pheonix AZ), 2.7 days (Athens, Greece)
Natural water photolysis:	DT_{50} 14 experiment hours (equivalent to 3.8 days (Tokyo, Japan), 1.8 day (Pheonix AZ), 2.7 days (Athens, Greece)

5. Effects on organisms in the environment

Aquatic organisms:
The toxicity of flupyradifurone and the major environmental metabolites was tested against a range of aquatic organisms. For the metabolites limit tests confirmed that the metabolites are less toxic than the parent and are not of environmental concern. Amongst aquatic species flupyradifurone is of low toxicity to algae, aquatic plants, fish and amphibians. Aquatic invertebrates showed some sensitivity to flupyradifurone, aquatic insects are most sensitive. The formulation Sivanto SL200 was not more toxic than the active substance.

BYI 02960 technical a.s.
Freshwater organisms

Fish	Acute	*Pimephales promelas*	LC_{50}	> 70.5 mg/L
	Acute	*Cyprinus carpio*	LC_{50}	> 100 mg/L
	Acute	*Oncorhynchus mykiss*	LC_{50}	> 74.2 mg/L
	Chronic	*Pimephales promelas*	NOEC	4.4 mg/L
Amphibian	Acute	*Xenopus laevis*	LC_{50}	> 80 mg/L
Algae		*Pseudokirchneriella subcapitata*	EC_{50}	> 80 mg/L
Plants		*Lemna gibba*	EC_{50}	> 67.7 mg/L
Invertebrates	Acute	*Daphnia magna*	EC_{50}	> 77.6 mg/L
	Chronic	*Daphnia magna*	NOEC	3.2 mg/L
	Acute	*Chironomus riparius*	EC_{50}	0.062 mg/L
	Chronic	*Chironomus riparius*	NOEC	0.0105 mg/L

Marine organisms

Fish	Acute	*Cyprinodon variegatus*	LC_{50}	> 83.9 mg/L
Invertebrates	Acute	*Americamysis bahia*	EC_{50}	0.26 mg /L
	Chronic	*Americamysis bahia*	NOEC	0.0132 mg./L
Oyster	Acute	*Crassostrea virginica*	EC_{50}	> 29 mg a.i./L

Metabolites 6-CNA

Algae		*Pseudokirchneriella subcapitata*	EC_{50}	> 100 mg/L
Invertebrates	Acute	*Daphnia magna*	EC_{50}	> 95.5 mg/L[#]
	Acute	*Chironomus tentans*	EC_{50}	> 1 mg/L
	Chronic	*Chironomus riparius*	NOEC	100 mg/L

[#] Nisso data - protected

DFA

Fish	Acute	*Oncorhynchus mykiss*	LC_{50}	> 10 mg/L
Algae		*Pseudokirchneriella subcapitata*	EC_{50}	> 10 mg/L
Invertebrates	Acute	*Daphnia magna*	EC_{50}	> 10 mg/L
	Chronic	*Chironomus riparius*	NOEC	100 mg/L

BYI 02960-succinamide

Fish	Acute	*Oncorhynchus mykiss*	LC_{50}	> 100 mg/L
Algae		*Pseudokirchneriella subcapitata*	EC_{50}	> 10 mg/L
Invertebrates	Chronic	*Daphnia magna*	NOEC	43.3 mg/L
	Acute	*Chironomus riparius*	EC_{50}	> 100 mg/L

BYI 02960-azabicyclosuccinamide

Invertebrates	Acute	*Chironomus riparius*	EC_{50}	> 100 mg/L

Sivanto SL200

Fish	Acute	*Oncorhynchus mykiss*	LC_{50}	> 105 mg a.i./L
Algae		*Pseudokirchneriella subcapitata*	EC_{50}	> 250 mg product/L
Invertebrates	Acute	*Daphnia magna*	EC_{50}	684 mg product/L
	Chronic	*Chironomus riparius*	NOEC	0.012 mg a.i./L

Birds:

The toxicity of flupyradifurone and the formulation Sivanto SL200 was tested for a number of bird species, there is no indication that birds are at risk.

BYI 02960 technical a.s.

Acute	*Colinus virgianus*	LD_{50}	232 mg a.i./kg bw
	Serinus canaria	LD_{50}	330 mg a.i/kg bw
	Gallus gallus domesticus	LD_{50}	> 2000 mg a.i/kg bw
Dietary	*Colinus virgianus*	LC_{50}	> 4876 mg a.i./kg diet (> 470 mg a.i/kg bw/day)
	Anas platyrhynchos	LC_{50}	> 4741 mg a.i./kg diet; (> 825 mg a.i/kg bw/day)
Reproduction	*Colinus virgianus*	NOAEL	302 mg a.i./kg diet (40 mg a.i/kg bw/day)
	Anas platyrhynchos	NOAEL	>845 mg a.i./kg diet (>81 mg a.i/kg bw/day)

Sivanto SL200

Acute	*Colinus virgianus*	LD_{50}	431 mg a.i./kg bw
	Gallus gallus domesticus	LD_{50}	>2000 mg formulation/kg bw (> 343 mg a.i./kg bw)

Soil earthworms and macro-organisms:

The effects of flupyradifurone, the major soil metabolites and the formulation Sivanto SL200 were tested on earthworms and soil macro-organisms in a series of laboratory and field studies. The results do not indicate that the organisms are at risk following the use of flupyradifurone. The metabolites were less toxic than the active ingredient.

BYI 02960 technical a.i:

Earthworms	Acute	*Eisenia foetida*	LC_{50}	192.9 mg a.i/kg dws

Sivanto SL200:

Earthworms	Acute	*Eisenia foetida*	LC_{50}	709 mg product/kg dws
	Chronic	*Eisenia foetida*	NOEC	8.9 mg product/kg dws
Soil macro-organisms	Chronic	*Folsomia candida*	NOEC	8.47 mg product/kg dws
	Chronic	*Hypoaspis aculeifer*	NOEC	1000 mg product/kg dws
Earthworms	Field study	Earthworm population	No effects at 300g a.i/ha Full recovery at 600 and 1500 g/ha after 11 months	

Metabolites DFA

Earthworms	Acute	*Eisenia foetida*	LC_{50}	> 1000 mg /kg dws
	Chronic	*Eisenia foetida*	NOEC	62 mg/kg dws
Soil macro-organisms	Chronic	*Folsomia candida*	NOEC	100 mg/kg dws
	Chronic	*Hypoaspis aculeifer*	NOEC	1000 mg/kg dws

6-CNA

Earthworms	Acute	*Eisenia foetida*	LC_{50}	> 1000 mg /kg dws[#]
	Chronic	*Eisenia foetida*	NOEC	95 mg /kg dws
Soil macro-organisms	Chronic	*Folsomia candida*	NOEC	90 mg/kg dws
	Chronic	*Hypoaspis aculeifer*	NOEC	100 mg/kg dws

[#] Nisso data - protected

Soil microorganisms:
Flupyradifurone, Sivanto SL200 and the metabolite 6-CNA were shown to have no influence on soil micro-organisms.

Effects on bees
The toxicity to bees of flupyradifurone (BYI 02960), Sivanto SL200, Sivanto FS480 and plant metabolites of flupyradifurone, to which bees could potentially be exposed, have been tested in laboratory studies. For the metabolites, limit tests confirmed that plant metabolites of flupyradifurone are virtually non-toxic to bees.

The favourable bee safety profile has been confirmed in a number of semi-field (tunnel) and field studies performed in highly bee attractive surrogate crops. The results indicate that there is low risk to bees, even when the flupyradifurone is applied to bee-attractive, flowering crops, while honey bees are actively foraging.

Laboratory Studies

Acute oral toxicity

BYI 02960 (tech.)	LD_{50}	1.2 µg a.i./honey bee
Sivanto SL200	LD_{50}	3.2 µg a.i./honey bee
Sivanto FS480	LD_{50}	3.4 µg a.i./honey bee
Plant metabolites	LD_{50}	≈ 100 µg pure metabolite/ honey bee

Acute contact toxicity

BYI 02960 (tech.)	LD_{50}	122.8 µg a.i./honey bee
Sivanto SL200	LD_{50}	15.7 µg a.i./honey bee
Sivanto SL200	LD_{50}	> 100 µg a.i./bumble bee
Sivanto FS480	LD_{50}	68.6 µg a.i./honey bee
Plant metabolites	LD_{50}	> 100 µg pure metabolite/bee

Chronic feeding studies in honey bees

BYI 02960 (tech.)	NOEC	≥10000 µg a.i./L diet
Plant metabolites	NOEC	≥10000 µg a.i./L diet

Chronic honey bee larvae study

BYI 02960 (tech.)	NOEC	≥10000 µg a.i./kg diet

SEMI-FIELD STUDIES

Tunnel studies under forced exposure conditions	**Application to Phacelia tanacetifolia, a highly bee attractive surrogate crop**	**Result**
Six independent studies, conducted in Germany, Italy and Denmark	Up to 200 g a.i./ha during full bloom (bees actively foraging during application)	No adverse effects

FIELD STUDIES

Long-term field studies, evaluating bee health aspects and over-wintering performance	**Application in winter oil-seed-rape (OSR, canola), a highly bee attractive (surrogate) crop**	**Result**
Two independent studies, conducted in France and Germany	205 g a.i./ha during full bloom (bees actively foraging during application)	No adverse effects
Honey bee colony feeding study, comprising exposure to fortified diet during two complete honey bee brood cycles	Fortified carbohydrate- and protein diet at 600, 2500 and 10000 µg a.i./kg diet	No adverse effects at levels of up to and including 10000 µg a.i./kg diet

Effects on other non-target arthropods

The toxicity of flupyradifurone to non-target arthropods has been tested in laboratory studies and field studies for a range of species. Some sensitivity of insects, as represented by *Aphidius rhopalosiphi*, was observed in the laboratory studies. Two full-fauna off-crop field studies indicate that there are no unacceptable effects on the off-crop populations expected following the use of the formulation Sivanto SL200 under practical use conditions.

Glass plate Lab. Tests:

Aphidius rhopalosiphi	LR_{50}	< 0.5 g a.i./ha
Typhlodromus pyri	LR_{50}	17.3 g a.i./ha

Extended Lab. Tests

Aphidius rhopalosiphi	LR_{50}	2.02 g a.i/ha
	ER_{50}	>0.89 g a.i/ha
Typhlodromus pyri	LR_{50}	177 g a.i./ha
	ER_{50}	>142g a.i./ha
Aleochara bilineata	ER_{50}	>300 g a.i./ha
Coccinella septempunctata	LR_{50}	273.9 g a.i./ha
	ER_{50}	ER_{50} > 250 g a.i./ha

Aged residue tests (2 x 250 g/ha)

Aphidius rhopalosiphi No significant effects 56 days after 2nd app.

Orius laevigatus No significant effects 28 days after 2nd app.

Full fauna off-crop field studies

Sivanto SL200 Population NOEAER 21 g a.i/ha (max. tested rate)

6. Toxicological properties of the technical active substance

6.1 Acute oral toxicity

Flupyradifurone (BYI 02960) is of low acute oral toxicity.
The LD_{50} in rats was equal to 2000 mg/kg body weight. 4/6 mortalities were observed at 2000 mg/kg bw, whereas no mortality was seen at 300 mg/kg bw.

6.2 Acute dermal toxicity

Flupyradifurone is of low acute dermal toxicity. The LD_{50} in rats was > 2000 mg/kg body weight.

6.3 Inhalation toxicity

Flupyradifurone is of low acute inhalation toxicity. The LC_{50} in rats was > 4671 mg/m^3.

6.4 Skin irritation

Flupyradifurone is not irritating to the skin.

6.5 Eye irritation

Flupyradifurone is not irritating to the eyes.

6.6 Sensitizing effects

Flupyradifurone is not a sensitizer after dermal exposure in a modified LLNA in NMRI mice.

6.7 Subacute/subchronic toxicity

Flupyradifurone was administered to rats, mice and dogs continuously over 28-day or 90-day periods. The liver and the thyroid were the target organs in rats. In the mice, the target organs were the liver and the kidney and in the dogs, the target organs were the liver, the kidney and the skeletal.

In the 90-day studies, the NOAEL were as follows:

NOAEL rat (male/female)	30.2/38.3 mg/kg bw/day
NOAEL mouse (male/female)	80.6/98.1 mg/kg bw/day
NOEL dog (male/female)	12/12 mg/kg bw/day

6.8 Chronic toxicity

Flupyradifurone was administered to rats and dogs continuously over a 1-year period. The liver was a common target organ in both species. In the rats effects were also observed in both sexes in the thyroid. In the dogs the kidneys were affected only in the males.

NOAEL rats (male/female)	18.5/25.3 mg bw/day
NOAEL dogs (male/female)	7.8/7.8 mg bw/day

6.9 Carcinogenicity

Flupyradifurone was administered to rats and mice continuously over a 2-year period or a 78-week period. No treatment-related tumours were observed in either study. In the rats, the target organs were the liver and the thyroid in both sexes and the lung in the females. In mice, the liver was a common target organ in both sexes and the kidney was affected in the males only.

NOAEL rat (male/female)	15.8/22.5 mg/kg bw/day
NOAEL mouse (male/female)	43/53 mg/kg bw/day

6.10 Effects on reproduction

Flupyradifurone was administered to rats continuously over two generations. A slight decrease in cycle number, litter size and number of implants was observed in the F1 generation at maternal toxic doses. The liver and the thyroid were target organs in males only. In the pups, decreased body weight and body weight gain conducted to decreased organ weights in brain, thymus and spleen.

NOAEL parent (male/female)	32.3/7.8 mg/kg bw/day
NOAEL reproduction (male/female)	32.3/39.2 mg/kg bw/day
NOAEL pups (male/female)	7.8/7.8 mg/kg bw/day

6.11 Embryonic and teratogenic effects

Flupyradifurone was orally (by gavage) administered to rats and rabbits during the gestation period. Reduced ossification of a few skull bones was observed in the rat pups at a concentration conducted to decreased fetal body weight. No treatment-related effects were observed in the rabbit pups.

NOAEL maternal rat	30 mg/kg bw/day
NOAEL developmental rat	50 mg/kg bw/day
NOAEL maternal rabbit	15 mg/kg bw/day
NOAEL developmental rabbit	40 mg/kg bw/day

6.12 Mutagenic effects

Flupyradifurone did not show any potential for genotoxicity in an *in vitro* prokaryotic test system or in *in vitro* or *in vivo* eukaryotic systems.

Flupyradifurone is devoid of any genotoxic effect.

6.13 Neurotoxic effects

In an acute neurotoxicity study piloerection and dilated pupils were observed at 50 mg/kg bw and lower muscle tone, rapid respiration, gait incoordination, tremors, reduced motor activity, impaired righting reflex, impaired flexor and tail pinch responses were observed at 200 and 800 mg/kg bw. There were no histopathological findings. In a dietary 90-day neurotoxicity

study, there were no neurotoxic treatment-related findings apparent at any dietary level in either sex.

NOAEL acute neurotoxicity (male/female)	35 mg/kg bw
NOAEL 90-day neurotoxicity (male/female)	143/173 mg/kg bw/day

6.14 Immunotoxic effects

Flupyradifurone was administered to female rats continuously in the diet over a 28-day period. No immunotoxic effects were observed up to the highest dose tested of 230 mg/kg bw/day.

- Acute oral rat : (4/6 mortalities at 2000 mg/kg; none at 300 mg/kg) (GHS category 4)
- Acute dermal rat : LD_{50} >2000 mg/kg (GHS category 5)
- Eye irritation rabbit : not irritating, no label (the only effect observed was redness of the conjunctivae : 1/3 score 2 and 2/3 score 1 at 24h)
- Skin irritation : not irritating, no label (no effects)
- Acute inhalation : LC_{50} > 4671 mg/m3
- LLNA : not sensitizing in mice after dermal application up to a 50 % concentration

6.15 Proposed endpoints for human and dietary risk assessment:

AOEL:

- The dog provides the lowest NOEL in the subchronic studies: NOEL of 12 mg/kg/day
- The developmental studies have slightly higher NOELs : 15 mg/kg/day
- No need for correction for oral absorption

AOEL = 12/100 = 0.12 mg/kg/day

ADI:

The lowest NOAEL was observed in rats and dogs. The lowest NOAEL of 7.8 mg/kg bw/day was observed in the rat 2-generation reproduction study based on body weight effects in females and in the one-year dog study based on histopathological effects in skeletal muscles. Based on the toxicological profile of flupyradifurone, a margin of safety of 100 is appropriate.

ADI = 7.8 /100 = 0.078 mg/kg/day

ARfD:

Only slight body weight gain effects were observed at the top dose in the developmental toxicity studies in both rats and rabbits. Acutely toxic effects were seen only in the acute neurotoxicity study, where typical signs of nicotinergic insecticides have been observed. Therefore it seems appropriate to set up the ARfD using the NOAEL of the acute neurotoxicity study, dividing by a 100-fold margin of safety.

ARfD = 35/100 = 0.35 mg/kg

7. Maximum Residue Limits

Proposed Maximum Residue Limits (MRLs) for flupyradifurone (Sivanto) – based on primary and rotational EU uses as well as on residue data from "global" uses for import-relevant crops.

Proposed EU MRLs based on envisaged uses of flupyradifurone

Commodity	**Harmonized MRL Proposal (mg/kg*)**
PLANT matrices	
Citrus fruit	3.0
Tree nuts	0.15
Pome fruit	1.5
Grapes	3.0
Blueberries	4.0
Prickly pear	0.7
Root vegetables	0.3
Bulb vegetables	0.4
Tomatoes/eggplants	3.0
Peppers	1.0
Chili peppers	3.0
Cucumbers/zucchini	1.5
Watermelons	1.0
Sweet corn/maize	0.4 (1.5) †
Brassica vegetables	0.3
Lettuces/spinach	9.0
Endive (scarole)	0.3
Legume vegetables	2.0
Stem vegetables	0.6 (general) 40 (celery)
Pulses - dry beans - dry peas	6.0 (general) 8.0 (peas)

Commodity	**Harmonized MRL Proposal (mg/kg*)**	
Oilseeds - peanuts - soybean - cotton	 0.15 (peanuts) 4.0 (soybean) 0.9 (cotton)	
Potatoes (tuber veg.)	0.7	
Hops	20	
Coffee	2.0	
Cereals - barley - corn/maize - sorghum - wheat	4.0 (general) 1.5 (corn)	
ANIMAL matrices		
eggs	0.15	(0.3) ‡
poultry meat (muscle)	0.20	(0.5) ‡
poultry fat	0.07	(0.2) ‡
poultry liver/offal	0.30	(0.5) ‡
milk	0.07	(0.3) ‡
bovine meat (muscle)	0.20	(1.0) ‡
bovine fat	0.15	(0.5) ‡
bovine liver	0.30	(n.a.) ‡
bovine kidney	0.40	(n.a.) ‡
other bovine offal	0.40	(2.0) ‡

* total residues of flupyradifurone + DFA, expressed in parent equivalents† proposal depends on whether sweet corn is covered by EU rotational crop value for "cereals" or not

‡ values based on Australian feeding calculations

n.a. not applicable (no MRLs are set in Australia for these commodities)

8. Special instructions/advice

8.1 Protecting the user:
Avoid unnecessary contact with the product. Severe misuse can result in damage to health. Flupyradifurone-containing products have to be stored under lock and key, in a cool but frost-free place, away from food for human or animal consumption, out of the reach of children and only in the original sales container.
Wear protective clothing and protective gloves when handling the product.
After working with the product wash your hands with soap and plenty of water.

8.2 First aid measures:
In case of skin contact wash with polyethylenglycol-300if not available flush with copious amounts of water. Remove contaminated clothing.
In case of contact with eyes, rinse eyes with lukewarm water for 15 minutes.
In case of actual or suspected swallowing, the patient should be kept strictly at rest. Decontamination and first aid should be performed. The patient should be seen by a doctor. This bulletin or the safety data sheet should be provided to the doctor.

8.3 For the doctor:
There is no known antidote. Treatment after appropriate decontamination should be symptomatic and supportive.

In case of emergency, please contact:
Bayer AG
D - 41539 Dormagen
Tel. +49 (0) 21 33 51 42 33

8.5 Protecting water catchments:
Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment. Do not empty into drains; dispose of this material and its container in a safe way. Do not allow this product and/or its container to get into the aquatic environment. Do not clean application equipment in the direct proximity of surface waters; prevent direct entry via yard and street drains. Do not use on areas where there is the danger of it being washed away, especially as a result of rain or watering.

8.6 Disposal of waste:
Dispose of any leftover product and empty containers and packaging in an orderly manner.

9. Formulations

Key product brand name	**Formulation type**	**Active substance content**	**Remark**
Sivanto™ 200	SL Soluble liquid	Flupyradifurone 200 g/L	basic formulation
Sivanto™ 480	FS (flowable concentrate for seed treatment)	Flupyradifurone 480 g/L	for seed treatment

Further mixture formulations with ketoenols, pyrethroids and others active substances and *also other formulation types are under development.*

Based on the acute toxicity profile, the formulation Sivanto SL 200 is classified in EU and should be labelled as follows:

Symbols of danger	Xn, Harmful Xi, Irritant
Risk phrases	R20, Harmful by inhalation R43, May cause sensitization by skin contact

Thus far, the formulation Sivanto FS 480 is only used for seed treatment in soybean in the USA and therefore no classification is needed in the EU.

10. Recommendations for use

Sivanto (Flupyradifurone SL 200) is very effective against whiteflies, aphids, hoppers and selected scales, mealybugs, psyllids, and *Sciriothrips sp.*; depending on rate and species. It has a very good initial and sufficient residual activity and acts against adults and immature stages. It works after oral ingestion or direct contact. In many cases it outperforms current standards, as used for the control of the whiteflies *(Bemisia sp.)* on vegetables, control of the citrus pest complex, or control of certain aphids and scales.
Sivanto is intended to be used as an insecticide in agriculture on a wide range of crops such as citrus, pome and stone fruits, tree nuts, grapes, coffee, cocoa, fruiting and leafy vegetables (indoor and outdoor), brassica vegetables, and hops, but also on tuber vegetables and broad acre crops such as cotton and soybean. The use the product on ornamentals and flower bulbs is also being considered, as well as in date palm for the control of the red palm weevil *(Rhynchophorus ferrugineus)*.

After intensive and thorough field development, the use rates indicated below are recommended for a very good control of the particular target pests. All results have been derived from the SL 200 or FS 480 formulations.

Crop	Pest	Application rate [g a.i./ha] per treatment	Appli-cation method	Pre-Harvest Interval PHI [days]	Region, Countries
Alfalfa	Aphids Leafhopper *Lygus sp.*	100 – 150 / 205	foliar	7	CAN/USA
Animal feed, non-grass, clover seed forage	Aphids Leafhopper *Lygus sp.*	102 - 205	foliar	7 (lespedeza, saint foin) 14 (all others)	USA
Brassica vegetables	Whitefly aphids leafhoppers	100-205	foliar	1	USA/CAN/EU
				3 (proposed)	Brazil
Blueberry Bushberry	Aphids, flies (maggots)	102 - 205	foliar	3	USA/CAN/MEX/EU
Raspberry	Aphids, flies (maggots)	100 g mCH*	foliar (G)	3	EU
Cactus	Aphids Mealybugs, scales	102 – 205	foliar	14	MEX/USA
Cereal grain	Aphids Leafhopper	102 - 205	foliar	7 (sweet corn) 21 (dried grain, stovers or straw)	USA/CAN
Citrus	Asian Citrus Psyllid *(Diaphorinia citri)* Citricola scale *(Coccus pseudo-magnoliarum)* Thrips *(Scirothrips citri)* Whiteflies Hopper Aphids	100-205	foliar	1	USA/MEX
	Asian Citrus Psyllid *(Diaphorinia citri)*	600 – 1000	drench	0 (proposed)	Brazil
	Asian Citrus Psyllid *(Diaphorinia citri)*	100 – 160	foliar	0 (proposed)	Brazil
	Asian Citrus Psyllid *(Diaphorinia citri)*	100 – 150 / 205	drench	30	CAN/USA
Coffee	Coffee leaf miner *(Leucoptera cof-feela)*	100 – 200	foliar	0	Brazil
		300 – 600	drench	0	
Corn (field, sweet, pop, seed)	Aphids	100 - 150	foliar	7 (sweet corn, forage, silage, hay cutting) 21 (dried grain)	CAN

Crop	Pest	Application rate [g a.i./ha] per treatment	Appli-cation method	Pre-Harvest Interval PHI [days]	Region, Countries
Cotton	Cotton aphid *(Aphis gossypii)* Lygus Bugs *(Lygus sp.)*	102-205	foliar	14	USA
Flower bulbs	Aphids	100	foliar	na	EU
Foliage of Legume vegetables	Aphids Whitefly Leafhopper	102 - 205	foliar	7	USA/CAN
Fruiting vegetables *Solanaceous*	Whitefly *(Bemisia tabaci)* Greenhouse whitefly *(Trialeurodes vaporariorum)* Green peach aphid *(Myzus persicae)* Leafhopper Silverleaf whitefly *(Bemisia argentifolii)* Potato Psyllid *(Bactericera cockerelli)*	100 – 150	foliar	1	Australia
		112.5 g mCH	foliar G	3	EU
		102-205	foliar	1	USA/CAN Latin America
		307-410	drench	45	USA/CAN/MEX
Fruiting vegetables *Cucurbits*	Silverleaf whitefly *(Bemisia tabaci)* Greenhouse whitefly *(Trialeurodes vaporariorum)* Green peach aphid *(Myzus persicae)* Potato psyllids *(Bactericera cockerelly)* Cotton aphid *(Aphis gossypii)* Leafhopper whitefly *(Bemisia argentifolii)*	100 – 150	foliar	1	Australia
		112.5 g mCH	foliar G	3	EU
		102-205	foliar	1	USA/CAN/ MEX
		307-410	drench	21 - 30	USA/CAN MEX
Grape	Leafhoppers *(Empoasca vitis, Scaphoideus titanus, Erythroneura sp.)* Vine mealybug *(Planococcus ficus)*	48-100	foliar	14	EU
		102-205	foliar	0	USA/CAN
		307-410	drench	30	USA/CAN/MEX

Crop	Pest	Application rate [g a.i./ha] per treatment	Application method	Pre-Harvest Interval PHI [days]	Region, Countries
Green beans	Whitefly Aphids	100 – 150	foliar	7	Australia
Hops	Hop aphid *(Phorodon humuli)*	102-154	foliar	21	EU/USA/CAN
Leafy vegetables	Silverleaf whitefly *(Bemisia tabaci)* Green peach aphid *(Myzus persicae)* Lettuce aphid *(Nasonovia ribisnigri)* Leaf hoppers	102-205	foliar	1	USA/CAN
		125	foliar	3 (F) 3 (G)	EU
Low growing berries	Aphids Whiteflies	102 – 205	foliar	0	USA/CAN
Olive	Olive Fly *(Bactrocera oleae)*	120-180	foliar	tbd	EU (proposed)
Ornamentals	Aphids Whiteflies	150	foliar	n.a.	EU
Peanut	Aphids Whitefly Leafhopper	102 - 205	foliar	7	USA/CAN
Peas	Aphids Seed beetle	75	foliar	3 (green peas) 7 (dried peas)	EU
Potato	Green peach aphid *(Myzus persicae)* Silverleaf whitefly *(Bemisia tabaci)* Leafhoppers Potato Psyllid *(Bactericera cockerelli)*	100	foliar	7	EU
		100-150	foliar	7	Australia
		102-205	foliar	7	USA/CAN/MEX
		307-410	drench	7	MEX
Pome fruit	Aphids *(Dysaphis plantaginea, Aphis pomi)* Sawfly *(Hoplocampa testudinea)* Leafhopper Psyllids Scales	102 - 205	foliar	14	USA/CAN
		24 – 60 g mCH	foliar	14	EU

Crop	Pest	Application rate [g a.i./ha] per treatment	Appli-cation method	Pre-Harvest Interval PHI [days]	Region, Countries
Root vegetables (except Sugar-beet)	Aphids Whitefly Leafhopper	102 - 205	foliar	7	USA/CAN
Small fruits (vine climbing subgroup)	Leaf hopper Mealybugs	102 – 205	foliar	0	USA/CAN
		307 - 410	drench	30	USA/CAN
Soybean	Aphids Bean leaf beetle	30 – 45 g a.i./100 kg seed	seed treatment	Earliest commercial harvest	USA
Legume vegetables	Aphids Whiteflies Leafhoppers	102 - 205	foliar	7 (21 days for soy-bean dry seed)	USA/CAN
Strawberry	Aphids	125	foliar (G)	3	EU
Tobacco	Aphids *(Myzus nicotianae)*	100 200 - 300	foliar drench	n/a n/a	EU/Brazil Brazil
Tree nuts	Aphids Whiteflies	102 - 205	foliar	7	USA/CAN

* g/mCH: grams of active ingredient per meter canopy high

11. Product compatibility

Sivanto (Flupyradifurone SL 200) is generally well miscible with conventional crop protection products. No miscibility problems have been observed thus far with any formulation type, i.e. EC, EW, SC, OD or WG.

In particular cases, miscibility tests should be performed prior to application.

After foliar application, the product generally shows good plant compatibility at recommended rates on a wide range of crops.
In a limited number of trials on some rock melon varieties (cantaloupe) and on greenhouse cucumbers, phytotoxicity symptoms in the form of necrotic spots or, mainly, leaf margin burn were observed on foliage.

It has been demonstrated that these symptoms remain within the range of commercial acceptability, but please always refer to local product labels and warning language for details.

To maintain the favourable bee safety profile of flupyradifurone, plant protection products containing flupyradifurone must not be tank-mixed with azole fungicides (ergosterol biosynthesis inhibiting fungicides) when applied to flowering crops.

12. Analytical methods

Methods for residue analysis and for the determination of the active ingredient content in products are available on request.

13. References

To be published soon

14. Disclaimer

Before using this product read and carefully observe directions, cautionary statements and other information appearing on the product label. Our technical information, whether given verbally or in writing, is based on extensive testing. It is, to the best of our current knowledge, true and accurate, but given without warranty in as much as the conditions of use and storage are beyond our control. Descriptions and property data of the product do not contain any statement as to liability for possible damage. In other respects our conditions of sale apply.

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