

Summary of Toxicological Studies on Acrinathrin

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DESCRIPTION OF THE TEST CHEMICALS

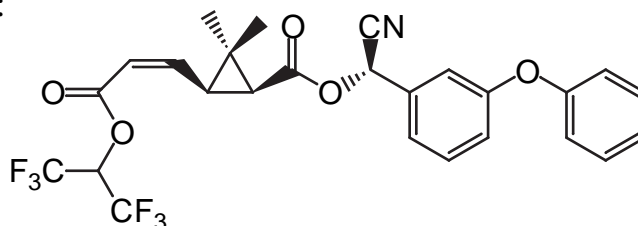
Acrinathrin is a new active ingredient which belongs to the family of Synthetic Pyrethroids and possesses high insecticidal activity against a wide range of insect pest together with miticidal activity. It has been discovered and synthesized by Roussel Uclaf in 1980s. In Japan, acrinathrin has been developed for application on various crops including vegetables, fruits, tea and ornamentals as the formulation product of the compound, ARDENT[®] 3% WP (acrinathrin 3% wettable powder, hereafter as WP formulation) and was registered in 1995 as a insecticide for the control of these crops.

The chemical structure and physico-chemical properties of acrinathrin are given as below.

Common name: Acrinathrin (BSI, draft ISO)

Chemical name: (*S*)- α -cyano-3-phenoxybenzyl (*Z*)-(1*R*, 3*S*)-2,2-dimethyl-3-[2-(2,2,2-trifluoro-1-trifluoromethylethoxycarbonyl)vinyl]cyclopropane-carboxylate (IUPAC)

Structural formula:



Molecular formula: C₂₆H₂₁F₆NO₅

Molecular weight: 541.4

Physical state: Whitish powder

Melting point: 81.5°C

Vapor pressure: 3.9 x 10⁻⁴ mPa (25°C)

Solubility in water (mg/l at 25°C): <0.02 mg/l

Solubility in organic solvents (g/l at 25°C): xylene 400, toluene 550, dichloroethane 650, acetone 700, ethanol 61, *n*-octanol 13

Partition coefficient (*n*-octanol/water): log *P* = 5.24

Stability: Stable under heat or acidic condition, unstable under diffused light and alkaline condition

ACUTE TOXICITY STUDIES

The results of acute toxicity studies *via* various routes are summarized in Table 1.

In these studies *via* routes of oral or respiratory tract, dosing of acrinathrin technical or WP formulation caused non-specific signs of toxicity, which were reversible during

Table 1 Acute toxicity studies.

Test substance	Route	Species	LD ₅₀ (mg/kg)	Laboratory (year)
Technical	Oral	Rat	M, F ^{a)} > 5,000	Centre International de Toxicologie (1987)
		Mouse	M, F > 5,000	
	Dermal	Rat	M, F > 2,000	Huntingdon Research Centre Ltd. (1987)
		Inhalation (4 hr)	Rat	
Formulation (3% WP)	Oral	Rat	M, F > 5,000	Biosafety Research Center, Foods, Drugs and Pesticides (1989)
		Mouse	M, F > 5,000	
	Dermal	Rat	M, F > 2,000	

^{a)} M, F: Value each for male and female.

^{b)} M+F: Value combined male and female.

the observation period of 14 day. No toxic signs were observed in dermal toxicity studies.

Acute oral LD₅₀ was considered to be 5000 mg/kg or more in rats and in mice.

IRRITATION STUDIES

1. Primary Eye Irritation Studies on Rabbits

A dose of 100 mg of acrinathrin technical was placed into the left eye of 6 New Zealand White rabbits. Untreated right eye served as a control.

One hour after the instillation, slight ocular reactions were observed in all of the animals. No ocular reactions were noted at 24, 48 and 72 hr.

Under this test conditions, acrinathrin was considered to be non-irritant.

(Centre International de Toxicologie, 1989)

A dose of 100mg of WP formulation or 0.1 ml of 1000 x diluted solution of the formulation (1 g/l water) each was instilled into the right eye of 9 New Zealand White rabbits consisting of 6 unwashed and 3 washed eye animals. The eyelids were gently held together for 1 sec, then the right eye of each rabbit was washed with physiological saline at 2-3 min after instillation. The eyes were examined after 1, 24, 48, 72 hr and after 7 and 14 days.

In the rabbits treated with the undiluted formulation, although slight to moderate irritation was noted in the unwashed eye, the irritation reaction was reduced and recovered to normal within shorter period in the eyes washed after installation of the

test substance compared to the unwashed eyes. In the rabbits treated with 1000 x diluted solution of the formulation, no irritation was observed.

(Biosafety Research Center, Foods, Drugs and Pesticides, 1989)

2. Primary Dermal Irritation Studies on Rabbits

A single application of 500 mg of acrinathrin technical or WP formulation each was applied to the clipped area of 6 New Zealand White rabbits. The test substance was held in contact with the skin for 4 hr by a occlusive dressing.

The cutaneous reactions were observed 1 hr after the removal of the dressing and then daily, up to 3 days. No irritation was observed in the rabbits treated with acrinathrin technical, while very slight and reversible irritation was noted in the animals treated with WP formulation.

(Technical: Centre International de Toxicologie, 1989;

WP formulation: Biosafety Research Center, Foods, Drugs and Pesticides, 1990)

DERMAL SENSITISATION STUDIES ON GUINIA PIGS

The potential of acrinathrin technical or WP formulation to induce delayed contact hypersensitivity were evaluated according to guinea pig Maximization method.

At any scoring time, following the removal of the occlusive dressing of the cutaneous challenge application of each test substance, no reaction of cutaneous sensitisation was recorded for both acrinathrin technical and WP formulation. On the other hand, positive reactions were apparently noted in positive control group of 2,4-dinitrochlorobenzen.

It was concluded, therefore, neither acrinathrin nor WP formulation have any evidence of cutaneous sensitisation potential.

(Technical: Centre International de Toxicologie, 1993;

WP formulation: BOZO Research Center Inc., 1991)

THE DELAYED NEUROTOXICITY STUDY

Oral administration of a single dose of acrinathrin technical at a dose level of 5000 mg/kg, followed by a repeat dose after 21 days, did not produce any clinical signs of neurotoxicity in adult hens used. This results was confirmed by histological examination, which showed no treatment-related changes in the nerve tissue.

(Huntingdon Research Centre Ltd., 1988)

SUBCHRONIC TOXICITY STUDIES

1. Rats Study by Dietary Repeat Dose for 90 Days Followed by a 28-Day Recovery Period

Group of 20 male and 20 female CD (SD) rats were fed diet containing 0, 30, 100 or 300 ppm of acrinathrin for 90 days. The animals were housed two per cage of the

same sex and the same group in metallic cages.

At doses of 100 and 300 ppm, several animals of both sexes showed skin lesions with scabs, sores and alopecia which sometimes persisted with an itching phenomenon. During the recovery period all of the skin lesions (except only for one female in 100 ppm group) seen in the treatment period regressed and disappeared in the high levels of 100 ppm or more.

Overall, the mortality was not marked, except in the 300 ppm group where deaths recorded in females could be treatment related and/or due to malnutrition. A body weight decrease and a reduction in food consumption each related to the concentration were observed in both sexes of the 100 and 300 ppm groups.

Those effects were gradually reversible during the recovery period. The microscopic examinations showed skin lesions recorded in 1 male and 1 female from the 100 ppm group and 7 animals of 300 ppm group. Other microscopic findings observed were lymphoid deletion in the spleen and thymus in 5 females of the 300 ppm group and medullar atrophy in 2 females of the 300 ppm group.

No other treatment related changes were observed in hematological and blood biochemical examinations, urinalysis and organ weight. The No Observed Effect Level (NOEL) for this study was considered to be 30 ppm (male: 2.4 mg/kg/day; female: 3.1 mg/kg/day). (Centre International de Toxicologie, 1988)

2. Dogs Study by Repeated Oral Dose for 90 Days Followed by a 4-Week Recovery Period

Groups of 8 male and 8 female Beagle dogs were dosed daily for 90 days in gelatin capsules at 0, 1, 3 and 10 mg/kg/day.

The main treatment-related clinical signs observed were vomiting and diarrhea. They occurred sporadically and sometimes repeatedly (only for diarrhea) in almost all the treated animals with dose-related incidence and Intensity. They did not impair the general condition of the animal and were still present during the first day of the recovery period, but not thereafter. No deaths occurred during the study.

At 10 mg/kg/day, a slight body weight loss which did not exceed 6% in the males and 3% in the females was recorded only in the first month of treatment.

In conclusion, acrinathrin dosed daily for 90 days at 1, 3 and 10 mg/kg/day did not induce overt signs of systemic toxicity. Except vomiting and diarrhea clinically recorded with a dose-relationship in the treated dogs, no test substance-related changes were seen in this study.

Under these experimental conditions, because of the slight digestive intolerance seen at 1 mg/kg/day, a true NOEL was not clearly established; however, considering the absence of impairment on the clinical condition of the dogs, it had been ascertained that 3 mg/kg/day was a true No Observed Adverse Effect Level (NOAEL).

(Centre International de Toxicologie, 1989)

3. 13 Week Complementary Toxicity Study in Dogs

This study was carried out as the complementary to the 90 day and 52-week toxicity studies in Beagle dogs previously performed by the oral route and in gelatin capsule. The objective of this study was to evaluate, on a clinical basis, the potential toxicity and determine the NOEL of acrinathrin when administered daily by oral route, capsules, to female dogs for 13 weeks at the dose levels of 0, 0.1, 0.3, 0.6, 1 and 3 mg/kg/day.

The conclusion was that no treatment-related effect on diarrhea and vomiting could be demonstrated at any doses up to 3 mg/kg/day. No treatment-related effects were also observed both on body weight change and food consumption.

Consequently, the digestive findings in the 90 day and 52 week studies are considered to be of no toxicological importance at doses up to 3 mg/kg/day.

(Centre International de Toxicologie, 1994)

4. Mice Study by Dietary Repeat Dose for 8 Weeks

Group of 10 male and 10 female Swiss (CD-1) mice were fed diet containing 0, 5, 50, 150 and 450 ppm of acrinathrin for 8 weeks. The animals were housed individually in polycarbonate cages.

Increase of skin lesions was noted at higher dose levels of 150 and 450 ppm.

No other treatment related changes were observed in hematological and blood biochemical examinations and in organ weight. Some signs of cutaneous reactions were seen in the two high dose levels.

Thus, the highest dose level for a carcinogenicity study had been ascertained as lower than 150 ppm.

(Centre International de Toxicologie, 1988)

CHRONIC TOXICITY/ONCOGENICITY STUDIES

1. Combined Dietary Chronic Toxicity and Oncogenicity Study in Rat

Groups of 90 male and 90 female SD rats each were fed diet containing 0, 5, 15 and 45 ppm of acrinathrin for 104 weeks. A fourth treated group of 40 male and 40 female rats were fed diet containing highest concentration of 90 ppm of the test substance for 104 weeks.

The highest dose for this study was ascertained to be lower than 100 ppm based on the findings observed in the 90 day rats subchronic toxicity study; at the dose levels of 100 and 300 ppm, acrinathrin induced signs of cutaneous toxicity and decreased body weight gain and food consumption.

The animals were housed two per cage of the same sex and the same group in suspended wire-mesh cages.

No treatment-related clinical signs were observed. The palpable masses in animals of both sexes of all groups did not indicate any treatment or dose-relationship, either

in frequency, time of onset, location, size or morphological type. There was no difference in mortality between the treated and control groups and any treatment-related effects could not be seen. No treatment-related body weight and food consumption changes were observed. Efficiency of food utilization was similar in control and treated groups of both sexes. No treatment-related changes were observed in water consumption and ophthalmological examination.

Upon hematological examination, a slight decrease in total white cell count and lymphocyte number observed in both sexes of the 15 ppm or more without a dose and time-relationship were considered unlikely to be treatment-related.

No treatment-related changes were noted in biochemistry, urinalysis and organ weight.

At the microscopic examination, after 52 weeks of treatment, the changes encountered were recognized as those commonly occurring in the laboratory rat, furthermore similar in incidence, severity and morphological character between the control and treated animals, therefore they were considered irrelevant to the treatment.

After 104 weeks, the non-neoplastic changes encountered were commonly recorded findings in the aged rat. In addition, these changes were of similar incidence, severity, and morphological character in control and treated animals and were considered as not treatment-related.

All neoplastic lesions reported in all organs were recognized as those commonly occurring in the aged rat and showed no variations in incidence or morphological types that were considered to be related to the treatment with the test substance.

In conclusion, the oral administration by dietary mixture of the test substance for 104 weeks to rats at the dose levels of 5, 15, 45 and 90 ppm did not show any treatment-related abnormalities in all parameters evaluated and any evidence indicating the carcinogenic potential of the test substance.

Under conditions of this study, therefore the NOEL is considered to be 90 ppm (4.6 mg/kg/day for males and 6.1 mg/kg/day for females).

(Centre International de Toxicologie, 1991)

2. Oncogenicity Study in Mice

Groups of 50 male and 50 female Swiss (CD-1) mice were fed diet containing 0, 3, 15 and 75 ppm of acrinathrin for 78 weeks. The animals were housed individually in polycarbonate cages.

In the highest dose group of 75 ppm, cutaneous lesions (weeping wounds and crusts) were observed with a higher frequency and led to a poor physical condition of some animals.

The palpable masses found among mice of both sexes of all groups showed no indication of treatment or dose-relationship either in frequency, time of onset, size, or histological type.

Except the animals prematurely sacrificed for humane reasons due to severe cutaneous lesions, the mortality rate and the factors contributing to death or premature sacrifice showed no indication of a treatment or dose-relationship.

No changes in body weight, food consumption, hematological parameters and organ weight which could be related to the treatment were observed.

At the macroscopic examination, only non-neoplastic lesions such as subcutaneous swellings were observed in some animals at the highest dose of 75 ppm. The mass found in some organs at the macroscopic examination among mice of control and treated groups, showed no indication of treatment or a dose-relationship either in frequency, size or multiplicity.

At the microscopic examination, skin ulcerations and chronic inflammations were observed in some animals of the highest dose of 75 ppm and were considered to be treatment-related.

The neoplastic lesions found among control and treated animals, were recognized as those occurring commonly in mice and were not modified by treatment either in incidence, morphological type or multiplicity.

In conclusion, the oral administrations by dietary mixture of the test substance for 78 weeks to mice at the concentration of 3, 15 and 75 ppm had neither carcinogenic potential nor caused an increase in the incidence of spontaneously occurring tumors. The highest dose of 75 ppm induced severe skin lesions (ulceration and chronic inflammations) among the animals with high frequency which could be treatment-related.

Thus, the NOEL in this study is determined to be 15 ppm (or 2.49 and 3.00 mg/kg/day in males and females, respectively).

(Centre International de Toxicologie, 1990)

3. 52 Week Oral Study in Dogs

Group of 6 male and 6 female Beagle dogs were dosed by oral route, in gelatin capsules for 52 weeks at the levels of 0, 1, 3 and 10 mg/kg/day. Control animals received empty capsules only.

Slight to moderate, soft or liquid diarrhea were observed sporadically throughout the study in the treated animals.

A loss of weight was observed until week 3 or 4 in both sexes treated at 10 mg/kg/day and the mean body weight of the males of this group remained inferior to that of the other males thereafter (with a statistical significance for weeks 5 to 35 and 43 to 46), while it was similar to that of the other groups in the females.

The food consumption of the animals was not influenced by the treatment.

The ophthalmological and neurological examinations of the animals did not reveal any test substance-related abnormality. The results of the laboratory investigations (hematology, blood chemistry and urinalysis) failed to indicate any test substance-

related change.

The organ weight, macroscopic and microscopic examinations of the animals at the end of the study did not show any abnormality which could indicate a treatment relationship concerning the few observations made.

Based on the transient body weight loss observed until weeks 3-4, then a body weight retardation throughout the study for the males only, at 10 mg/kg/day, the NOAEL in this 52 week study is considered to be 3 mg/kg/day. The animals showed occasionally mild diarrhea with a very slight occurrence, however a clear dose response could not be observed. (Centre International de Toxicologie, 1990)

In conclusion, the dose of 3 mg/kg/day is confirmed to be the NOEL of acrinathrin through above three studies in dogs.

(Centre International de Toxicologie, 1989-1994)

REPRODUCTION AND TERATOGENICITY STUDIES

1. Rat Two-Generation Study

Acrinathrin was administered to SD rats in the diet at concentrations of 0, 5, 20 and 80 ppm. After about 8 weeks of treatment, groups of 25 male and 25 female rats from the F₀ generation were paired to produce the F₁ litters. Mated F₀ females were then treated during pregnancy and lactation.

The only observed clinical signs were transient cutaneous lesions in F₀ adult animals of the 20 and 80 ppm groups during the first 6 weeks of treatment; the cutaneous lesions were not observed either in F₁ pups or in F₁ adult animals or F₂ pups.

The treatment did not induce any effect in the reproductive parameters of both parents and offspring. In particular, the mating and fertility indices, the length of gestation of F₁ and F₂ animals as well as the birth index and viability of pups on day 4 and 21 post-partum of the F₁ and F₂ litters were comparable in treated and control groups.

In the parents, the highest dose level of 80 ppm induced a slight and transient reduction in body weight gain and food consumption of F₀ and F₁ animals.

In conclusion, the NOEL in terms of reproductive performance is defined as 80 ppm corresponding to 9.4 mg/kg/day for males and 10.6 mg/kg/day for the females. And the NOEL for parental generations is 20 ppm corresponding to 2.5 mg/kg/day for the males and 2.8 mg/kg/day for the females.

(Centre International de Toxicologie, 1989)

2. Rat Teratology Study

Acrinathrin suspended in corn oil was administered at the dose levels of 0, 2, 6 and 18 mg/kg/day to groups of 25 mated females in SD rats from days 6 to 15 of pregnancy. On day 20 of pregnancy, females were sacrificed and fetuses were removed by caesarean section. Litter values were determined and fetuses were subsequently

examined for external, visceral and skeletal abnormalities.

The following findings were observed:

Maternal findings: At 6 mg/kg/day or more, the body weight gain of the females had stopped or decreased between days 9 and 15. At 18 mg/kg/day, piloerection were observed in high frequency and three females were found dead. At this highest dose level, the body weight still remained lower through days 20, and furthermore the decrease in the rate of live fetuses and the increase in the rate of fetal loss were noted.

Litter findings: At 18mg/kg/day, the mean body weight of fetuses was decreased. The incidence of minor skeletal abnormalities was increased at the highest dose level but these abnormalities were essentially represented by a delay in the ossification process. The rate of fetuses affected with external, skeletal or visceral abnormalities was comparable between the control and the 2 and 6 mg/ kg/day groups.

In conclusion, the dose of 2 mg/kg/day was considered to be the NOEL in terms of maternal toxicity. The dose of 6 mg/kg/day was considered as the NOEL in terms of embryofetal development. Acrinathrin revealed no evidence of teratogenicity even at the highest dose level of 18 mg/kg/day. (Centre International de Toxicologie, 1988)

3. Rabbit Teratology Study

Acrinathrin suspended in corn oil was administered at the dose levels of 0, 15, 45 and 135 mg/kg/day to groups of 16 mated females in New Zealand White rabbits from days 6 to 18 of pregnancy. On day 28 of pregnancy, females were sacrificed and fetuses were removed by caesarean section. Litter values were determined and fetuses were subsequently examined for external, visceral and skeletal abnormalities.

The following findings were observed:

Maternal findings: At 45 mg/kg/day or more, a transient decrease in body weight gain from days 5 to 12 was observed slightly. At 135 mg/kg/day, the rate of live fetuses was lower and the rate of fetal losses was higher. On general symptoms, reduced food consumption and anorexia were observed animals of the highest dose level.

Litter findings: The delay in ossification was observed at the highest dose of 135mg/kg/day. The rate of fetuses affected with external, skeletal, or visceral abnormalities were quite comparable between control and treated groups.

In conclusion, the dose of 15 mg/kg/day was considered to be the NOEL in terms of maternal toxicity. The dose of 45 mg/kg/day was considered as the NOEL in terms of embryofetal development. Acrinathrin revealed no evidence of teratogenicity even at the highest dose level of 135 mg/kg/day.

(Centre International de Toxicologie, 1988)

MUTAGENICITY STUDIES

Acrinathrin has been the subject of numerous studies in the field of mutagenicity. The possible mutagenic potential of acrinathrin has been studied at three possible levels of genotoxic action:

- (1) Detection of gene mutation
- (2) Detection of chromosomal aberration (*in vitro* and *in vivo*)
- (3) DNA damage repair test

While a very weak positive reaction was noted only *in vitro* cytogenic assay with Chinese hamster CHO cell with metabolic activation system, both *in vivo* cytogenic assay and micronucleus assay were negative.

Acrinathrin was also negative in other test systems, therefore it is not considered that this test substance is mutagenic. All the test results are summarized in Table 2.

Table 2 Mutagenicity studies.

Method	Species, cell type	Concentrations of acrinathrin	Test conditions	Results	Laboratory (year)
Ames test <i>in vitro</i>	<i>S. typhimurium</i> ; TA 98, 100, 1535, 1537, 1538 <i>E. coli</i> , WP2uvrA	100 to 5000 µg/plate	Without S-9 mix	Negative	CIT ^{b)} (1989)
			With S-9 mix	Negative	
Gene mutation test <i>in vitro</i>	HPRT locus in V79 Chinese hamster cell	3 to 300 µg/ml	Without S-9 mix	Negative	CIT (1990)
			With S-9 mix	Negative	
Metaphase chromosome analysis <i>in vitro</i>	Chinese hamster ovary (CHO) cell	30 to 300 µM	Without S-9 mix With S-9 mix	Negative Positive ^{a)}	CIT (1987)
Metaphase chromosome analysis <i>in vivo</i>	Chinese hamster bone marrow cell	50 to 200 mg/kg per os	Hamsters sacrificed, 6, 24, 48 hr after dosing	Negative	CIT (1989)
Micronucleus test <i>in vivo</i>	Swiss Cr1 mouse bone marrow cell	2000 mg/kg per os	Mice sacrificed, 24, 48, 72 hr after dosing	Negative	CIT (1987)
DNA repair test <i>in vivo</i>	<i>E. coli</i> ; pol A ⁺ , pol A ⁻	50 to 5000 µg/plate	Without S-9 mix	Negative	CIT (1987)
			With S-9 mix	Negative	

^{a)} Statistically significant slightly enhanced number of aberrations was observed at the highest level of 300 µM Which is the limit of solubility in culture medium.

^{b)} CIT: Centre International de Toxicologie.

RAT METHABOLISM STUDIES

Absorption, distribution, excretion and metabolism in rats were tested using [¹⁴C-benzyl] and/or [¹⁴C-dimethyl]acrinathrin.

In the study in SD rats given by gavage at single dose of 1 mg/kg, it was measured in plasma that T_{max} is 4-6 hr and C_{max} is 0.5-0.8 µg eq./ml.

At the 48 hr after dosing, 48-52% dose in bile, 33-45% dose in urine and 55-67% dose in feces each was excreted. Thus, acrinathrin in rats was rapidly absorbed and excreted. At the T_{max} after dosing of the compound, a relatively higher concentration of radioactivity in liver when compared to that in plasma was detected, but it was decreased rapidly with time. There was no indication of preferential accumulation of radioactivity in any specific tissue. Major metabolites identified in feces were unchanged parent compound and cis-deshexafluoroisopropyl acrinathrin.

Major metabolic reactions were hydrolysis of ester bonds, oxidation of cyano-3-phenoxybenzyl alcohol group and production of conjugates.

(Huntingdon Research Centre Ltd., 1990)

SUMMARY

The results of studies showed that acrinathrin demonstrated low mammalian toxicity following acute oral, dermal or inhalation exposure. The results obtained support those already known for other pyrethroids in particular the cyano-pyrethroids.

No irritation was observed in the skin and eye of rabbits treated with acrinathrin technical, while very slight and reversible irritation was noted following treatment with WP formulation. No ocular irritation was observed with the diluted solution of WP formulation. Both acrinathrin technical and WP formulation were negative in skin sensitisation studies conducted by Maximization method.

Acrinathrin did not show mutagenic potential, was not oncogenic in rats and mice and did not affect reproduction of two generations in rats.

Acrinathrin exhibited no teratogenic potential in rats and rabbits.

Main effects observed in subchronic toxicity studies through chronic toxicity studies were the decrease of body weight gain and food consumption, and skin lesions seen at high dose levels in rats and mice dietary studies. The skin lesions persisted with an itching and scratching phenomenon due to paresthetic changes, which were considered to be related to the pharmacological property of acrinathrin and it seems probable that it is brought about by an action of the substance on sodium channels and depolarisation of the sensory nerves. The findings in the reproduction study indicate that the effects are reversible and result in no permanent changes.

Through these long term studies, the overall NOAEL for acrinathrin was determined to be 15 ppm (2.49 mg/kg/day) in the oncogenicity study in mice. ARDENT[®] 3% WP was registered by Japanese MAFF in 1995 as the insecticide with miticidal activity for various crops including vegetables, fruits, tea as well as ornamental. When used in accordance with label directions, acrinathrin and its formulation will not adversely

affect human health.

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