

## Technical Information

### Summary of Toxicological Studies on Acequinocyl

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(Accepted September 25, 2001)

#### INTRODUCTION

Acequinocyl, active ingredient of Acequinocyl 15% SC, is a novel naphthoquinone derivative which was synthesized in the 1970s for use in control of plant parasitic mites in the agricultural field. This novel chemical has a unique mode of action in mite species, namely inhibition of the electron transfer system by binding hydroxy Acequinocyl with the Qo center at complex III in mitochondria after hydrolysis in mite body (Y. Koura et al., 1997), and has excellent miticidal activity against a wide range of plant mite species at all development stages including the egg stage without any cross resistance towards other commercial miticides. After expending many years in developing formulation which would ensure optimum biological activity, official efficacy trials were initiated in a wide range of crops in co-operation with the Japan Plant Protection Association. Acequinocyl 15% SC is used widely in Japan to control plant mite species incorporated into IPM program since it was first registered here in 1999, and maintains excellent efficacy without any sign of developing miticide resistance. This product is also registered in Korea and Taiwan, and many field trials are being conducted with this product in the US and European countries for the purpose of registration in these countries.

Chemical properties and toxicological information of Acequinocyl are summarized below:

#### PHYSICAL AND CHEMICAL PROPERTIES

Common name: Acequinocyl (ISO)

Chemical name: 3-dodecyl-1,4-dihydro-1,4-dioxo-2-naphthyl acetate (IUPAC)

Chemical structure:

CAS No.: 57960-19-7

Molecular formula: C<sub>24</sub>H<sub>32</sub>O<sub>4</sub>

Molecular weight: 384.5

Appearance: yellowish crystalline powder

Melting point: 59.6° C

Vapor pressure (25° C): 1.69 × 10<sup>-6</sup> Pa

Water solubility (25° C):  $6.7 \times 10^{-6}$  g/l

Solvent solubility (20° C): n-hexane 44g/l, dichloromethane 620g/l, methanol 7.8g/l, n-octanol 31g/l, acetone 220g/l

Partition coefficient (25° C):  $\log P_{ow} = >6.2$

### **ACUTE TOXICITY STUDIES**

Acute LD 50 values for Acequinocyl and the 15% SC formulation were determined using rats and mice. LD 50 values are presented in the following tables.

No clinical signs or gross pathological findings were observed in any of the animals in all studies except that diarrhea was observed for a few hours after oral dosing.

### **IRRITATION AND SKIN SENSITIZATION STUDIES**

#### **1. Primary Eye Irritation Study**

Eye irritation potential of Acequinocyl 15% SC formulation was evaluated using 9 female Japanese White rabbits. All rabbits were treated with 0.1ml of Acequinocyl 15% SC formulation in their left eyes. Right eye of each rabbit was remained untreated and served as a control. Both eyes of 3 rabbits were washed with warm water 2 min after the treatment. Following treatment, changes for cornea, iris and conjunctiva of all rabbits were observed and scored for 72 hr according to the criteria described by Draize. Slight redness and discharge in conjunctivae were observed in the unwashed eyes at 1 hr after the treatment, but disappeared within 24-hr observation period. No changes were observed in any of the washed eyes during the observation period. Under the conditions of this study, Acequinocyl 15% SC formulation is considered to have minimal irritation potential to eyes of rabbits.

(Bozo Research Center, 1995)

#### **2. Primary Skin Irritation Study**

Skin irritation potential of Acequinocyl 15% SC formulation was evaluated using 6 female Japanese White rabbits. All rabbits were treated with 0.5ml of Acequinocyl 15% SC formulation in their clipped dorsal skin sites for 4 hr by the closed patch method. Following treatment, treated skin sites of all rabbits were observed and scored for signs of erythema and edema for 72 hr according to the criteria described by Draize. No changes were observed in any of the rabbits during the observation period. Under the conditions of this study, Acequinocyl 15% SC formulation is considered to have no irritation potential to the rabbit skin.

(Bozo Research Center, 1995)

### 3. Skin Sensitization Study (Buehler Test)

Skin sensitization potential of Acequinocyl 15% SC formulation was evaluated using 10 male and 10 female Dunkin-Hartley guinea pigs according to the Buehler's method. At days 1, 8 and 15 of the induction phase, undiluted Acequinocyl 15% SC formulation was applied topically to the clipped skin site of the left flank for 6 hr. Two weeks after the final induction application, a challenge application was conducted with undiluted Acequinocyl 15% SC formulation on the clipped skin site of the right flank topically for 6 hr. Following the challenge application, all guinea pigs were observed and scored for signs of erythema in treated skin sites for 48 hr. No changes were observed in any of the guinea pigs during the observation period. Positive control animals treated with chlorodinitrobenzene or hexyl cinnamic aldehyde in the same manner showed erythema during the observation period. Under the conditions of this study, Acequinocyl 15% SC formulation is considered to have no sensitization potential to the skin of the guinea pig.

(Huntingdon Life Sciences, 1996)

## **SUBCHRONIC TOXICITY STUDIES**

### 1. 13-Week Oral Toxicity Study in Rats

Acequinocyl was administered in the diet to 5 groups of Fisher rats (10 rats/sex/group) at a concentration of 0, 100, 400, 1600 or 3200 ppm for 13 weeks. Clinical condition, body weight, food consumption and ophthalmoscopic findings were recorded during the dosing period. At the end of the study, hematology, blood chemistry, urinalysis and organ weight data were recorded on survivors. Histopathological findings were recorded on all rats in this study.

All rats at 3200 ppm were dead or sacrificed between weeks 1 and 3 of dosing due to deteriorated clinical condition, severe body weight loss and decreased food consumption. No deaths or clinical signs were observed in the lower dose levels. Hematological examination with survivors revealed prolonged PT and APTT values at 1600 ppm. Neither organ weight changes nor histopathological changes were observed at 1600 ppm and lower dose levels. Based on the results of this study, NOAEL for Acequinocyl is considered to be 400 ppm (30.4 mg/kg/day for males and 32.2 mg/kg/day for females).

(Biosafety Research Center, 1994)

### 2. 13-Week Oral Toxicity Study in Dogs

Acequinocyl was administered orally to 5 groups of beagle dogs (4 dogs/sex/group) daily at a dose level of 0, 40, 160, 640 or 1000 mg/kg for 13 weeks. Clinical condition, body

weight, food consumption and ophthalmoscopic findings were recorded during the dosing period. Hematology, blood chemistry and urinalysis data were recorded on survivors at weeks 4, 8 and 12 of dosing. At the end of the study, organ weights were recorded on survivors. Histopathological findings were recorded on all dogs in this study.

All dogs at 1000 mg/kg and 2 females at 640 mg/kg were dead or sacrificed between weeks 1 and 4 of dosing due to deteriorated clinical condition, severe body weight loss and decreased food consumption. At the end of the dosing period, cumulative body weight gain was decreased at 160 mg/kg and higher dose levels. Slight decrease of cumulative body weight gain was also observed at 40 mg/kg mainly in males, which suggested effect of administration. Hematological examination revealed increased platelet counts at 160 and 640 mg/kg. Blood chemistry analysis revealed decreased cholesterol, phospholipid, ALT, glucose and/or total protein values at 640 mg/kg. Neither organ weight changes nor histopathological changes were observed at all dose levels. Based on the results of this study, NOAEL in this study is considered to be less than 40 mg/kg/day for both sexes.

(Huntingdon Research Centre, 1995)

## **CHRONIC TOXICITY AND CARCINOGENICITY STUDIES**

### **1. 104-Week Combined Chronic Toxicity/Carcinogenicity Study in Rats**

Acequinocyl was administered in the diet to 5 groups of Fisher rats (80 rats/sex/group) at a concentration of 0, 50, 200, 800 or 1600 ppm for 104 weeks. Ten rats per sex per group were sacrificed at weeks 26, 52 and 78. Clinical condition, body weight, food consumption and ophthalmoscopic findings were recorded during the dosing period. At the end of the dosing period, hematology, blood chemistry, urinalysis and organ weight data were recorded on survivors. Histopathological findings were recorded on all rats in this study.

At 1600 ppm, food conversion ratio decreased during the first 52 weeks of the study, and body weight gain decreased between weeks 26 and 78. Hematological changes such as higher platelet counts and prolonged PT and/or APTT values were observed at 800 and/or 1600 ppm. Blood chemistry analysis revealed increased creatinine values and decreased triglyceride and sodium values at 1600 ppm. No changes were observed at 50 and 200 ppm. Neither organ weight changes nor histopathological changes were observed at all dose levels. No increased incidence of particular non-neoplastic/neoplastic lesions that may be correlated to the administration was observed at any of the dose levels. Based on the results of this study, NOAEL for Acequinocyl is considered to be 200 ppm (9.0 mg/kg/day for males and 11.6 mg/kg/day for females). Acequinocyl is considered to have no carcinogenic potential in rats.

(Biosafety Research Center, 1996)

## 2. 80-Week Carcinogenicity Study in Mice

Acequinocyl was administered in the diet to 5 groups of ICR mice (70 mice/sex/group) at concentrations of 0, 20, 50, 150 or 500 ppm for 80 weeks. Twenty mice per sex per group were sacrificed at week 55. Clinical condition, body weight, food consumption and water consumption were recorded during dosing period. At the end of the dosing period, hematology, blood chemistry, urinalysis and organ weight data were recorded on survivors. Histopathological findings were recorded on all mice in this study.

During the dosing period, no changes were observed in respect of mortality, clinical signs, body weight, and food and water consumption at all dose levels. Hematological examination revealed increased platelet counts and/or hematocrit values at 150 and 500 ppm. Blood chemistry analysis revealed increases in ALP, AST and/or ALT levels at 50 ppm and higher dose levels. Total protein values decreased in males at 500 ppm. Neither organ weight changes nor histopathological changes were observed at all dose levels. No increased incidence of particular non-neoplastic/neoplastic lesions that may be correlated to the treatment was observed in any of the dose levels. Based on the results of this study, NOAEL for Acequinocyl is considered to be 20 ppm (2.7 mg/kg/day for males and 3.5 mg/kg/day for females). Acequinocyl is considered to have no carcinogenic potential in mice.

(Huntingdon Life Sciences, 1997)

## 3. 52-Week Chronic Toxicity Study in Dogs

Acequinocyl was administered orally to 5 groups of beagle dogs (4 dogs/sex/group) daily at dose levels of 0, 5, 20, 80 or 320 mg/kg for 52 weeks. Clinical condition, body weight, food consumption and ophthalmoscopic findings were recorded during the dosing period. Hematology, blood chemistry and urinalysis data were recorded on survivors in weeks 6, 13, 26, 39 and 52 of dosing. At the end of the dosing period, organ weights were recorded on survivors. Histopathological findings were recorded on all dogs.

One male and 1 female at 320 mg/kg were sacrificed in weeks 6 and 22, respectively due to severe inappetence and body weight loss. No other changes were observed in these 2 dogs in any of the parameters recorded during their lifetime. Survivors at 320 mg/kg showed decreased food consumption and body weight values in the early stage of the study. Hematological changes such as increased platelet counts and/or reticulocyte counts were observed at 20 mg/kg and higher dose levels. Blood chemistry analysis revealed decreased total protein value and increased cholesterol value at 320 mg/kg. No changes were observed at 5 mg/kg. Neither organ weight changes nor histopathological changes were

observed at all dose levels. Based on the results of this study, NOAEL for Acequinocyl is considered to be 5 mg/kg/day for both sexes.

(Huntingdon Life Sciences, 1996)

## **REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDIES**

### **1. 2-Generation Reproduction Toxicity Study in Rats**

Acequinocyl was administered in the diet to 4 groups of SD rats (25 rats/sex/group) over 2 successive generations at concentrations of 0, 100, 800 or 1500 ppm. Clinical condition, body weight and food consumption were recorded during the study period. At the end of both generations, major organs including reproductive organs/tissues were subjected to weight determination and microscopic examination. Data on reproductive ability were recorded during the course of study. Offspring were evaluated for their physical and functional development.

No changes were observed in any of the dose levels on parental mating, pregnancy and parturition performances, female estrus cycle and male sperm morphology for both generations. At 1500 ppm, spleen weights in the P females and liver and lung weights in the F1 females were underwent statistically significant increases but no findings that may be related to these weight changes were observed in any of the parameters. No changes were observed in the parental animals at 100 and 800 ppm. In pups, incidence of hemorrhagic body parts and/or swollen body parts increased at 800 and 1500 ppm soon after weaning for both generations. Some of them showed subcutaneous hemorrhage on the body parts at necropsy. Physical development of the F2 pups at 800 and 1500 ppm was affected by the administration as indicated by slight delay in eye opening, opening of vagina, descent of testes and/or preputial separation. No changes were observed in the pups at 100 ppm. Based on the results of this study, NOAEL for Acequinocyl is considered to be 800 ppm for the parental animal (P: 58.9 mg/kg/day for males and 69.2 mg/kg/day for females, F1: 65.5 mg/kg/day for males and 70.4 mg/kg/day for females) and 100 ppm for the offspring (P: 7.3 mg/kg/day for males and 8.7 mg/kg/day for females, F1: 8.2 mg/kg/day for males and 8.9 mg/kg/day for females). No adverse effects on reproductive ability are observed at all dose levels.

(Corning Hazleton, 1996)

### **2. Teratogenicity Studies**

#### **2.1. In rats**

Acequinocyl was administered orally by gavage to 5 groups of SD rats (25 females/group) from days 7 to 17 of pregnancy at dose levels of 0, 50, 150, 500 or 750 mg/kg. Day zero of

pregnancy defined the day insemination was confirmed. Clinical condition, body weight and food consumption were recorded from days 0 to 20 of pregnancy. Gravid uterus weights and data on implantation were recorded at cesarean section conducted on day 20 of pregnancy. Fetal examination was also conducted at the cesarean section.

One female at 500 mg/kg and 4 females at 750 mg/kg were sacrificed between days 13 and 17 of pregnancy due to deteriorated clinical condition and red discharge from the vagina. Necropsy of these sacrificed females revealed intra-uterine hemorrhage and blood stained contents of stomach and/or intestine at 750 mg/kg. During the course of the study, body weight gain slightly decreased at 750 mg/kg. Cesarean section conducted on day 20 of pregnancy revealed decreased gravid uterus weights, decreased numbers of live fetuses and increased post-implantation loss at 750 mg/kg. No other maternal changes were observed at all dose levels. No effect on fetal sex ratio, individual weight and incidence of external and visceral abnormalities were observed at all dose levels. Increased incidences of minor skeletal variations that are considered to be related to maternal toxicity were observed in fetuses at 750 mg/kg. No other fetal changes were observed at any of the dose levels. Based on the results of this study, Acequinocyl is considered to have no teratogenic potential in rats. NOAEL for Acequinocyl is considered to be 150 mg/kg/day for the pregnant female and 500 mg/kg/day for the fetus.

(Toxicol Laboratories, 1995)

## 2.2. In rabbits

Acequinocyl was administered orally by gavage to 4 groups of New Zealand White rabbits (18 females/group) from day 6 to 18 of pregnancy at dose levels of 0, 30, 60 or 120 mg/kg. Day zero of pregnancy defined the day insemination was confirmed. Clinical condition, body weight and food consumption were recorded from day 0 to 28 of pregnancy. Gravid uterus weights and data on implantation were recorded at cesarean section conducted on day 28 of pregnancy. Fetal examination was also conducted at the cesarean section.

Five females at 120 mg/kg were sacrificed between days 15 and 20 of pregnancy due to deteriorated clinical condition and red discharge from the vagina. Necropsy of these females revealed uterine hemorrhage and/or fluid cecal contents. During the course of the study, body weight gain and food consumption values were slightly decreased at 120 mg/kg. Cesarean section conducted on day 28 of pregnancy revealed discolored amniotic fluid at 120 mg/kg. No other maternal changes were observed at all dose levels. No effect on fetal sex ratio, individual weight and incidences of external and visceral abnormalities were observed at all dose levels. Increased incidence of a minor skeletal variation that is considered to be related to maternal toxicity was observed in fetuses at 120 mg/kg. No other fetal changes

were observed at any of the dose levels. Based on the results of this study, Acequinocyl is considered to have no teratogenic potential in rabbits. NOAEL for Acequinocyl is considered to be 60 mg/kg/day for both pregnant females and fetuses.

(Toxicol Laboratories, 1995)

## **GENETIC TOXICITY STUDIES**

### **1. Bacterial Reverse Mutation Test**

Acequinocyl was evaluated for its potential to induce reverse gene mutations according to the Ames method. Assay was conducted using 4 strains of *Salmonella typhimurium* (frame shift type of TA98 and TA1537, and base pair substitution type of TA1535 and TA100) and 1 strain of *Escherichia coli* (base pair substitution type of WP2uvrA) in the presence or absence of rat liver metabolic activation system (S-9 Mix). Acequinocyl dissolved into DMSO was preincubated with each test strain for 20 min at 37° C in the presence or absence of S-9 Mix. These solutions were then mixed with agar to prepare plates, which were incubated for 48 hr at 37° C. Acequinocyl was tested up to cytotoxic concentration or 5000 µg/plate. On completion of incubation, the number of revertant colonies in the Acequinocyl treated plates did not increase in any of the strains tested in the presence or absence of S-9 Mix at all dose levels. Based on the results of this study, Acequinocyl is considered not to be mutagenic in the tested strains of *Salmonella typhimurium* and *Escherichia coli*.

(Biosafety Research Center, 1992)

### **2. Chromosome Aberration Assay**

The potential of Acequinocyl to induce chromosome aberration was evaluated using Chinese hamster lung fibroblast cells (CHL) in the presence or absence of rat liver metabolic activation system (S-9 Mix). Acequinocyl dissolved into 1% aqueous methylcellulose was mixed with cell suspension and culture medium to prepare cell culture. Four test doses were selected for Acequinocyl in the range of 481~3850 µg/ml in the presence of S-9 Mix and 150~1200 µg/ml in the absence of S-9 Mix based on the cell toxicity test. Cell cultures were incubated at 37° C for 24 or 48 hr without S-9 Mix and for 6 hr with S-9 Mix. At the end of the incubation period, cell cultures were harvested, fixed and put on microslides to prepare chromosome spreads. Each slide was examined microscopically to analyze metaphase cells for the presence of structural and/or numerical aberrations in chromosomes, as well as mitotic index. Decreased mitotic indices that are indicative of cell toxicity were observed at the highest dose levels in both presence and absence of S-9 Mix. Acequinocyl caused no statistically significant increase in the number of cells with chromosome aberration or polyploidy at all dose levels in the presence or absence of S-9 Mix.



Based on the results of this study, Acequinocyl is considered not to induce any type of chromosome aberration even at the highest dose that caused cell toxicity in CHL.

(Biosafety Research Center, 1993)

### 3. Spore Rec-Assay in *Bacillus subtilis*

Acequinocyl was evaluated for its DNA damaging effect using DNA repair deficient strain (M45 rec<sup>-</sup>) and DNA repair proficient strain (H17 rec<sup>+</sup>) of *Bacillus subtilis* in the presence or absence of rat liver metabolic activation system (S-9 Mix). Each test strain was incubated for an appropriate period to form spores. The spores were collected and then mixed with agar to prepare a test plate. Acequinocyl dissolved into DMSO was placed on a filter disc and put on the surface of the agar plate. Acequinocyl was tested up to maximum soluble concentration (i.e., 550  $\mu$ g/disc in the presence of S-9 Mix and 1100  $\mu$ g/disc in the absence of S-9 Mix). Following incubation for 24 hr at 37° C, all plates were measured for diameters of growth inhibition zones. Acequinocyl caused no growth inhibition in the presence or absence of S-9 Mix at all dose levels. Based on the results of this study, Acequinocyl is considered not to induce any damage on DNA of tested strains of *Bacillus subtilis*.

(Biosafety Research Center, 1992)

## PHARMACOLOGY STUDIES

To obtain useful information on acute toxicity in humans when they are exposed to massive Acequinocyl accidentally, acute responses in animals were evaluated in respect of their central and peripheral nervous systems, cardiovascular system, respiration, blood, digestive tract, uterus and urinary system.

Rats given 600 or 2000 mg/kg single oral doses of Acequinocyl showed prolonged blood clotting time and increased fibrinogen level. Other rats given the same dosages of Acequinocyl showed decreased urine volume and electrolyte excretion levels. Hemolytic change was observed in in vitro assay when 3% suspension of rabbit RBC was treated with 1.0 mg/ml of Acequinocyl. No other changes were observed in any of the experiments.

(Huntingdon Life Sciences, 1996)

## SUMMARY

Safety evaluation of Acequinocyl was conducted via comprehensive studies. Acute toxicity is very low in every exposure route for both Acequinocyl and the 15% SC formulation. Primary irritation potential of Acequinocyl 15% SC formulation is minimal for eyes and nil for skin. Acequinocyl 15% SC formulation has no skin sensitization potential. In long term

studies, hemorrhagic changes and/or prolonged blood clotting time were observed in rats treated with high doses of Acequinocyl. Similar changes were also observed in pharmacology studies in which rats dosed with a single high dose of Acequinocyl showed increased fibrinogen level and prolonged blood clotting time. As Acequinocyl has a chemical structure similar to that of vitamin K, it is assumed that Acequinocyl competes against vitamin K in the mechanism of blood coagulation in rats. No effect on reproductive ability was observed in rats. In teratogenicity studies, no teratogenic effect was observed even in the highest doses that induced embryotoxic changes. No mutagenic effect was observed in genetic toxicity studies, and no specific non-neoplastic/neoplastic lesions were observed in chronic studies. ADI value for Acequinocyl was established at 0.027 mg/kg/day based on the NOAEL in the 80-Week Carcinogenicity Study In Mice. Maximum residue levels on crops established by the Japanese Ministry of Health and Welfare are 1 ppm for eggplants, 0.5 ppm for cucumbers and gherkins, 0.1 ppm for watermelons and melons, 0.2 ppm for mandarin oranges, 2 ppm for natsudaidai, 1 ppm for lemons and other citrus fruits than mandarin oranges and natsudaidai, 1 ppm for apples, 2 ppm for pears and Japanese pears, 0.1 ppm for peaches, 1 ppm for plums and prunes, 2 ppm for cherries and 0.5 ppm for grapes. Acequinocyl 15% SC formulation is considered to be a useful agent in the agricultural field on account of its excellent acaricidal effect and minimal risk to humans and the environment when used in accordance with the instructions.

## 要 約

### アセキノシルの毒性試験の概要

アグロ カネショウ株式会社

アセキノシルは新規開発されたナフトキノン骨格の殺ダニ剤で、各生育ステージのダニに対して速やかに活性を発現する。本剤はミトコンドリアの電子伝達系の酵素阻害により殺ダニ活性を示すが、その作用点が他の薬剤とは異なるため、薬剤抵抗性ダニにも活性を示すことが確認されている。本剤の原体及び15%フロアブル製剤の安全性試験の結果、アセキノシル及び製剤は急性毒性、並びに眼及び皮膚に対する刺激性が非常に弱く、皮膚感作性もないことが確認された。また発がん性、変異原性及び催奇形性は認められず、繁殖性への影響もなかった。ラットに本剤を大量に経口投与した場合、血液凝固時間の延長がみられた。アセキノシルの化学構造がビタミンKと似ていることから、アセキノシルを投与されたラット体内では、アセキノシルがビタミンK依存性血液凝固系に介在し、血液凝固能の低下が誘発されると推測された。これらの変化はイヌには認められなかった。

ここに要約した安全性試験結果に基づき、アセキノシルのADIは0.027 mg/kg/dayに設定された。残留農薬基準はなす1 ppm、きゅうり(含ガーキン)0.5 ppm、すいか0.1 ppm、メロン類0.1 ppm、みかん0.2 ppm、なつみかんの果実全体2 ppm、レモン1 ppm、その他

のかんきつ 1 ppm, りんご 1 ppm, 日本なし 2 ppm, 西洋なし 2 ppm, すもも (含ブルー  
ン) 1 ppm, おうとう 2 ppm, ぶどう 0.5 ppm に設定された.

本剤は, 農薬の一般的な安全使用上の注意事項を遵守して使用する限り作業者に対する  
安全性が高く, 有用な農業資材と考えられる.

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Table 1 Results of acute toxicity studies with Acequinocyl.

Dosing Route	Species	Sex	LD50 (mg/kg)
Oral a)	Rat	♂♀	>5000
	Mouse	♂♀	>5000
Dermal a)	Rat	♂♀	>2000
Inhalation b)	Rat	♂♀	>0.84 (mg/l) c)

a) Bozo Research Center, 1993. b) Huntingdon Life Sciences, 1994. c) LC50  
value.

Table 2 Results of acute toxicity studies with Acequinocyl 15% SC formulation.

Dosing Route	Species	Sex	LD50 (mg/kg)
Oral a)	Rat	♂♀	>5000
	Mouse	♂♀	>5000
Dermal a)	Rat	♂♀	>2000
Inhalation b)	Rat	♂♀	>4.56 (mg/l) c)

a) Huntingdon Life Sciences, 1996. b) Huntingdon Life Sciences, 1997. c) LC 5 0 value.