Summary of Toxicological Studies on Cyproconazole

Regulatory Affairs Department, SDS Biotech K.K.
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TEST CHEMICAL

Cyproconazole has been developed by Sandoz Agro Ltd. (now Novartis Crop Protection Inc.) since 1982. Cyproconazole is a new broad spectrum triazole fungicide classified in the group of fungicides known as ergosterol-biosynthesis inhibitors. In Japan, the chemical was registered as a fungicide for Powdery mildew (*Erysiphe graminis*), Leaf rust (*Puccinia recondita*) on wheat and Cercospora leaf spot (*Cercospora beticola*), Ramularia leaf spot (*Ramularia beticola*) on Sugar beet.

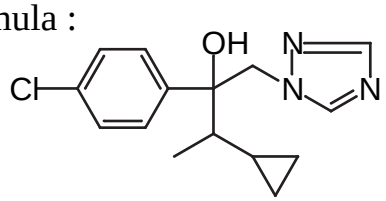
Identity, physical and chemical properties, solubility and stability are as follows.

Common name : Cyproconazole (lSO)

Trade name : ALTO®

Chemical name : (2*RS*, 3*RS* ; 2*RS*, 3*SR*)-2-(4-Chlorophenyl)-3-cyclopropyl-1-(1*H*-1, 2, 4-triazol-1-yl)butan-2-ol

Structural formula :



Molecular formula : $C_{15}H_{18}ClN_3O$

Molecular weight : 291.78

Appearance : Colorless crystalline solid

Specific gravity : 1.259

Melting point : 106-109˚C

Vapor pressure : 2.6 X 10^{-7} Torr (20˚C)

Solubility : Water, 0.093 g/*l* (22˚C) ; organic solvent (w/w% 25˚C); *n*-hexane, 0.28 ; acetonitrile, >23.0 ; xylene, 12.1 ; dichloromethane, >15.0 ; toluene, 11.7 ; diisopropylether, 2.8 ; methanol, >23.0 ; ethyl acetate, >20.0 ; ethanol, >23.0 ; polyethylene glycol, 17.0 ; acetone, >23.0 ; dimethyl sulfoxide, 18.0

Partition coefficient (*n*-octanol/water) : log P_{ow}=2.91

Stability : Heat, acid, alkali, photo ; stable

ACUTE TOXICITY STUDIES

The result of acute toxicity studies are summarized in Table 1.

The oral toxicity of cyproconazole appears to be moderate in rats and roughly equally toxic to both sexes. Cyproconazole technical and its 100SL formulation were more toxic to mice than rats.

Table 1 Results of acute toxicity studies.

Test substance	Route	Species	Sex[g)]	LD_{50} (mg/kg)
Technical	Oral[b)]	Rat	M	1115
			F	1342
	Oral[c)]	Mouse	M	352
			F	355
	Dermal[b)]	Rat	M	> 2000
			F	> 2000
	Inhalation[d)]	Rat	M	> 5645[h)]
			F	> 5645[h)]
100SL[a)] formulation	Oral[e)]	Rat	M	> 5000
			F	> 5000
	Oral[c)]	Mouse	M	3306
			F	2732
	Dermalf)	Rat	M	> 4496
			F	> 4496

[a)] 100SL: 9% soluble liquid formulation. [b)] Sandoz Ltd., 1984. [c)] Bozo Research Center, 1992. [d)] Research & Consulting Company AG, 1985. [e)] Sandoz Ltd., 1986. [f)] Sandoz Ltd., 1988. [g)] M : male, F : female. [h)] LC_{50} (mg/m^3).

Overt signs of toxicity in rats administered the technical were fairly non-specific and included weakness, dis-orientation, rough coat, decreased movement, flaccidity, exophthalmus, lacrimation and respiratory disturbances. In rats administered the 100SL formulation, there were no overt signs of toxicity during the 14-day observation period. At post mortem there were no gross histological effects in the studies with the technical and formulated product.

Clinical signs of toxicity in mice administered the technical or the 100SL formulation were staggering gait, decreased spontaneous movement, deep breathing, tonic convulsions or prone position and oligopnea. At post mortem dark red patches in the grandular stomach were observed in more than half of the mice administered technical or 100SL formulation, and dark reddening of the lungs were observed in a few mice administered 100SL formulation.

No signs of systemic toxicity were observed in the rat administered dermally the

technical and the 100SL formulation. In the inhalation toxicity study in the rat, slight sedation, dyspnoea and ruffled fur were observed during and after exposure oftechnical in all animals but resolved within 24 hr.

IRRITATION STUDIES

l. Primary Eye Irritation

Six New Zealand White rabbits were used in each cyproconazole technical or 100SL formulation study. A 0.06 g of the technical or 0.1 ml of the 100SL formulation was placed into the lower everted lid of one eye of each animal. The eyelids were then gently held together for one second before releasing. The contralateral eye remained untreated and served as a control. Examination of the eyes was made after 1 hr and 1, 2, 3, 4, 7 days after instillation.

Instillation of cyproconazole technical or its 100SL formulation resulted in conjunctival reaction only in all 6 animals. The eyes were normal 3 days after instillation. Based on the result, cyproconazole technical and lOOSL formulation are slight eye irritants. (Huntingdon Research Centre Ltd., 1988, 1989)

2. Primary Skin Irritation

Six New Zealand White rabbits were used in each cyproconazole technical or 100SL formulation study. A 0.5 g of the technical was applied under a 2.5 cm square gauze moistened with 0.5 ml distilled water to one intact skin site on each animal. In the case of 100SL formulation, 0.5 ml of the formulation was applied under the same experimental conditions as in the technical study. After 4 hr the bandages were removed and the application sites were washed. Observations were made on day 1 (*i.e*. 30 min after removal the bandages) and days 2, 3, 4.

Following removal of the bandages after application of cyproconazole technical or its 100SL formulation, no evidence of erythema or oedema could be found. None of the animals showed any observable response to treatment during the following 3 days. Based on the result, cyproconazole and 100SL formulation are not skin irritants. (Huntingdon Research Centre Ltd., 1988, 1989)

DERMAL SENSITIZATION STUDIES

The Maximization method was employed for a dermal sensitization study. Cyproconazole technical or its 100SL formulation was applied to 20 guinea pigs. A negative control group of 20 animals and a positive control, 1-chloro-2, 4-dinitrobenzene (DNCB), group of 20 animals were provided.

Following challenge application of cyproconazole technical or its 100SL formulation, no dermal reactions were observed in any of the test or control animals. According to these results, cyproconazole technical and its 100SL formulation were considered to be not a skin-sensitizer.

In addition the positive control, DNCB, produced evidence of delayed contact hypersensitivity in both studies. (Sandoz Ltd., 1985, 1986)

SUBCHRONIC TOXICITY STUDIES

1. 13-Week Feeding Study in Rats

A main group of each 15 male and 15 female Han Wistar rats per dose level was given diet containing cyproconazole technical at concentration of 0, 20, 80 or 320 ppm for 13 weeks. In a parallel study 15 animals of each sex were given diet containing cyproconazole technical at concentration of 0 or 320 ppm for 13 weeks followed by a 4-week recovery period.

All animals survived until termination of the study. The only overt sign of toxicity was piloerection in male rats receiving 80 or 320 ppm. Body weight was not affected except for a significant decrease in female rats at 320 ppm. Food consumption was not affected by the treatment except the consumption of satellite male rats at 320 ppm was reduced in the first week. There were no treatment related changes in haematology or urinalysis values. The clinical biochemistry parameters were not affected by the treatment except aspartate aminotransferase activity in female rats at 80 or 320 ppm which was increased in the last week of the study.

In post mortem examination, liver weights in both sexes receiving 320 ppm were increased but not in those of the recovery group. Histopathological examination revealed vacuolated hepatocytes, predominantly centrilobular, in male rats at 320 ppm. Individualization of hepatocytes lobular distinct pattern occurred in both sexes at 320 ppm. These hepatic effects were reversible, they were not found in the recovery group.

Based on the result of this study, the no observed effect level was 20 ppm (male 1.5, female 1.9 mg/kg/day). (Sandoz Ltd., 1986)

2. 13-Week Feeding Study in Dogs

Groups of 4 male and 4 female Beagle dogs were fed diets containing cyproconazole technical at concentration of 0, 20, 100 or 500 ppm for 13 weeks.

All animals survived until termination of the study. Apart from reduced muscle tone and subdued behavior in male and female dogs at 500 ppm, no other overt sign of toxicity were observed. Body weight gain in male dogs and female dogs receiving 500 ppm was slightly reduced and food consumption in male dogs receiving 500 ppm was reduced.

Cyproconazole affected clinical biochemistry parameters in animals receiving 500 and 100 ppm. Dogs receiving 500 ppm, creatinine levels, alkaline phosphatase activity, gamma-glutamyl transferase activity and glutamate dehydrogenase activity were significantly increased in both sexes, triglycerides levels, albumin levels, calcium levels and inorganic phosphate levels were significantly decreased in both sexes,

total-cholesterol and high density lipoprotein-cholesterol levels were significantly reduced in male dogs. Because of the reduction in muscle tone seen in animals receiving 500 ppm, creatinine phosphokinase levels were measured and found to be elevated in male dogs receiving 500 ppm. Total protein levels were significantly decreased in female dogs receiving 500 ppm. Animals receiving 100 ppm, creatinine levels were increased in both sexes, gamma-glutamyl transferase activity was increased in female dogs. There were no treatment related effects in urinalysis values.

Post mortem examination revealed significantly increased liver weights in both sexes at 500 ppm and a slight increase in male dogs at 100 ppm. Histopathological examination showed centrilobular hepatocyte hypertrophy in both sexes receiving 500 or 100 ppm.

Based on the result of this study, the no observed effect level was 20 ppm (male 0.77, female 0.70 mg/kg/day). (Sandoz Ltd., 1986)

CHRONIC TOXICITY AND ONCOGENICITY STUDIES

1. Combined Chronic Toxicity/Oncogenicity Study in Rats

Seventy male and 70 female Wistar rats were fed diets containing cyproconazole technical at concentration of 0, 20, 50 or 350 ppm for 118 and 121 weeks, respectively. Approximately 60% of the animals, including 72% (male) and 64% (female) of the control, died or were killed *in extremis* before the end of the study. These effects were not treatment related. There were no overt signs of toxicity and opthalmoscopy revealed no treatment related findings. Body weight gain was significantly reduced in both sexes at 350 ppm. Food consumption was not affected by treatment except the food efficiency in male rats at 350 ppm was reduced.

Laboratory investigations were performed at 14, 26, 52, 78, 105 weeks and at termination. Haemoglobin values in females rats at 50 or 350 ppm were significantly reduced. Alanine aminotransferase and aspartate aminotransferase activities in male rats receiving 350 ppm were significantly increased. Total cholesterol, total protein and globulin levels in female rats at 50 or 350 ppm were increased. Gamma-glutamyl transferase activity in both sexes at 50 or 350 ppm were increased, but did not achieve statistical significance at any sampling period. The other parameters of clinical biochemistry were not affected by treatment. There were no treatment related effects in urinalysis values.

Post mortem examination revealed significantly increased liver weights in both sexes at 350 ppm. In histopathological examination hepatocellular fatty changes in male rats at 350 ppm and hepatocellular hypertrophy in female rats at 350 ppm were found as treatment related effects. Lipoproteinosis in lung was found in male rats at 350 ppm. The incidence of neoplastic lesions was not affected by the treatment at the terminal or interim sacrifice.

Based on the above mentioned result, the no effect levels for this study was 20

ppm (male 1.0, female 1.2 mg/kg/day). (Sandoz Ltd., 1988)

2. Oncogenicity Study in Mice

Groups of 50 male and 50 female ICR mice were given cyproconazole technical at concentration of 0, 5, 15, 100 or 200 ppm in the diet for 81 and 88 weeks respectively.

Mortalities of control, 5, 15, 100 and 200 ppm groups were 65, 60, 50, 42 and 28% respectively in male rats and 60, 52, 60, 28 and 46% respectively in female rats. There were no overt signs of toxicity. Food consumption was not affected by treatment although reduced body weight gains were found in both sexes at 100 and 200 ppm. Blood smears drawn after 52, 79 weeks and prior to female terminal sacrifice (90 weeks) from mice were evaluated for differential white blood cell count. White blood counts at interim sacrifice or terminal investigation were not affected by treatment.

At post mortem liver weight were significantly increased in both sexes receiving 100 or 200 ppm. In macroscopic examination an increased incidence of liver nodules was found among male and female rats treated with 100 or 200 ppm. In histopathological examination single-cell hepatocytic necrosis and diffuse hepatocytic hypertrophy were found in male rats at 100 or 200 ppm and in female rats at 200 ppm. Other changes that were associated with treatment included testicular germinal epithelial deficit and possibly an increase in skin wounds in male rats at 200 ppm. An incidence of hepatocytic neoplasia was increased in males rats at 100 or 200 ppm and in females at 200 ppm. The mechanism leading to the observed hepatocytic neoplasia is tumour promotion as a result of hepatic enzyme induction, a non-genotoxlc event. This mechanism was supported by a "Cell proliferation study" and an "Enzyme induction study." Additionally, it should also be noted that a comprehensive array of tests, both *in vivo* and *in vitro*, with and without metabolic activation, did not show any genotoxic activity of cyproconazole.

Based on the above mentioned result, the no effect levels for this study was 15 ppm (male 1.84, female 2.56 mg/kg/day). (Sandoz Ltd., 1989)

3. Chronic Toxicity Study in Dogs

Groups of 4 male and 4 female beagle dogs were fed diets containing cyproconazole at concentration of 0, 30, 100 or 350 ppm for 52 weeks. All animals survived until the end of the study. Female dogs of the 100 and 350 ppm treatment groups showed subdued behavior for 4 and 1 week respectively, otherwise there were no overt signs of toxicity. Ophthalmoscopy revealed no treatment related effects. Body weight gain in male dogs at 350 ppm was slightly reduced in the first 9 weeks. Food consumption was not affected by treatment in both sexes.

Blood samples were obtained from all dogs before commencement of treatment. During the treatment period, blood samples were obtained at 13, 26, 38 weeks and prior to termination. Laboratory investigation showed elevated platelet counts in both

sexes at 100 or 350 ppm. However, prothrombin time at the same dose were not affected by treatment. Cholesterol and albumin levels were reduced in both sexes at 350 ppm, total protein was reduced in male dogs at 350 ppm. Alkaline phosphatase activity and percentage globulin were increased in both sexes at 350 ppm, alanine aminotransferase activity was increased only in male dogs at 350 ppm. Cytochrome P-450 activities were increased in both sexes at 350 ppm and in female dogs at 100 ppm. Urinalysis revealed no dose related effects.

At post mortem examination, liver weights of both sexes at 350 ppm were significantly increased. In macroscopic examination, the livers of 2 male dogs at 350 ppm appeared enlarged with pronounced lobular patterning. In histopathological examination, treatment-related lesions were confined to the liver. Laminar eosinophilic intrahepatocytic bodies were present in all male dogs at 350 ppm and in one male dog at 100 ppm. They were also present in 2 female dogs at 350 ppm.

Based on the above mentioned result, the no effect levels for this study was 30 ppm (male, female 0.99 mg/kg/day). (Sandoz Ltd., 1988)

REPRODUCTION AND TERATOLOGY STUDIES

l. 2-Generation Reproductive Study in Rats

In a 2-generation study groups of Wistar rats were fed diets containing cyproconazole technical at concentration of 0, 4, 20 or 120 ppm and the effect of treatment on the reproductive function was assessed. One litter per generation was produced, 26 animals of each sex of the F0 and F1 generation were used in the study. The test material was administered to the parental F0 during the premating (10 weeks), mating, the resulting pregnancy and through weaning of their offspring. The F1 parents were treated in the same way except the premating period which covered a period of 12 weeks.

There were no overt sign of toxicity and no treatment related deaths. Body weight gain and food consumption were not affected by treatment in both sexes and both generations. There were no effect of treatment on the reproductive function of the two generations.

At post mortem, histopathological examination revealed increased hepatocellular fatty changes in the F0 males at 120 ppm. No treatment related changes were seen in the F1 or F2 pups on histopathological examination.

Based on the above mentioned result, the no effect level in males was 20 ppm and that in females was 120 ppm (male 1.39, female 9.88 mg/kg/day).

(Sandoz Ltd., 1987)

2. Teratology Study in Rats

Groups of 25 pregnant female Wistar rats were dosed cyproconazole technical orally at dose levels of 0, 6, 12, 24 or 48 mg/kg/day on days 6-15 of pregnancy. Distilled water containing 4% carboxymethyl cellulose sodium salt was used as the

vehicle.

There were no overt signs of toxicity. Body weight gain was reduced during from first to third treatment days in female rats at 48 mg/kg/day and from day 12 post coitum to day 21 post coitum in female rats at 24 mg/kg/day. Food consumption was reduced during treatment in females receiving 24 or 48 mg/kg/day. A dose-related, significantly increased postimplantation loss in females at 24 or 48 mg/kg/day was observed. The significantly reduced body weights of fetuses at 24 or 48 mg/kg/day as well as the effects on skeletal development were considered to be caused by the primary maternal toxicity. A hydrocephalus and palatoschisis were observed in fetuses at 48 mg/kg/day.

Based on the above mentioned result, the no effect level was 12 mg/kg/day (maternal and embryo/teratogenicity). (Research & Consulting Company AG, 1986)

3. Teratology Study in Rabbits

Groups of 16 females Chinchilla rabbits were dosed cyproconazole technical by orally at dose level of 0, 2, 10 or 50 mg/kg/day on days 6-18 of pregnancy. Distilled water containing 4% carboxymethyl cellulose sodium salt was used as the vehicle.

There were no overt signs of toxicity. Body weight gain and food consumption were reduced in females at 50 mg/kg/day. Pre-implantation loss was not affected by treatment however postirnplantation losses were significantly increased at 50 mg/kg/day. Examination for external, skeletal and visceral abnormalities revealed no treatment related effects.

Based on the above mentioned result, the no effect level was 10 mg/kg/day (maternal and embryo/teratogenicity). (Research & Consulting Company AG, 1986)

MUTAGENICITY STUDIES

1. Reverse Mutation Assay

Five strains of *Salmonella typhimurium*, TA 1535, TA 1537, TA 1538, TA 98 and TA 100 and *Escherchia coli* WP2 *uvrA* were used to evaluate the mutagenic potential of cyproconazole technical. The study of 5 strains of *S. typhimurium* was carried out at a dose level of 0, 1, 5, 10, 100, 500, 1000, 2500 and 5000 μg per plate of cyproconazole with or without metabolic activation. The study of *E.coli* WP2 *uvrA* was carried out at dose level of 0, 31.3, 62.5, 125, 250, 500, 1000 and 2000 μg per plate of cyproconazole with or without metabolic activation.

Cyproconazole induced no appreciable increases in the number of revertant colonies of any strain at any dose with or without metabolic activation, compared with those of the corresponding control. Based on the result, cyproconazole was not considered to have capability of inducing reverse mutation.

(Hazleton Biotechnologies, 1986)
(The Institute of Environmental Toxicology, 1992)

2. In Vitro Chromosomal Aberration Assay in Chinese Hamster Ovary Cells

The ability of cyproconazole to induce chromosomal aberrations was investigated in Chinese Hamster Ovary cells with and without metabolic activation. The assay was conducted of cyproconazole with metabolic activation at a dose level of 0, 45.0, 59.9, 99.9, 150 and 200 μg/ml and without metabolic activation a dose level of 0, 60.1, 100, 150, 200 and 300 μg/ml.

Cyproconazole technical did not induce a significant level of chromosome aberrations and is considered to be negative in this assay system. (Hazleton Washington, 1990)

3. DNA Repair Test (Rec-assay)

The DNA-damaging potential was tested at a dose level of 0, 1, 2, 5, 10, 20, 50, 100, 200, 1000, 2000, 5000 and 10,000 μg/disk of cyproconazole technical using the recombination-wild (H-1 7) and -deficient (M-45) strains of *Bacillus subtils.*

In the absence or presence of metabolic activation system, the differences of growth inhibitory zone induced by cyproconazole technical between strain H-17 and M-45 were 3 mm or less.

It was considered that cyproconazole had no DNA damaging capability.

(The Institute of Environmental Toxicology, 1992)

SUMMARY

Cyproconazole technical was of low toxicity to rats, moderate toxicity to mice by oral administration. Its formulation was of low toxicity to rats and mice by oral administration. The technical and its formulation were of low acute dermal toxicity. The technical and its formulation were not skin irritant, although they were mildly irritating to eye. In a guinea pig skin sensitization study using the Maximization method no skin sensitization was induced by cyproconazole technical or its formulation.

In subacute toxicity studies in rats and dogs, clinical biochemistry parameters at middle or high dose levels were affected by treatment of cyproconazole technical. Decreased body weight gains and increased liver weights were found In rats and dogs receiving high dose levels of cyproconazole technical.

In a rat combined chronic toxicity/oncogenicity study, some parameters of haematology and clinical biochemistry mainly at high dose level were affected by treatment of cyproconazole technical. Decreased body weight gains and increased liver weights were found at high dose level of cyproconazole technical. Histopathological examination revealed hepatocelluar fatty changes in male and hepatocellular hypertrophy in female at high dose. The incidence of neoplastic lesions was not affected by the treatment at the terminal or interim sacrifice.

In mice oncogenicity study, reduced body weight gains and increased liver weight were seen at upper-middle and high dose levels of cyproconazole technical. An

incidence of hepatocytic neoplasia was increased in male at upper-middle or high and female at high dose level of cyproconazole technical. The mechanism leading to the observed tumours is tumour promotion as a result of hepatic enzyme induction, a non-genotoxic event.

In a dog chronic toxicity study, increased cytochrome P-450 activities were observed in both sexes at middle and high dose levels of cyproconazole technical. Reduced body weight gains in male and increased liver weight in both sexes were found at high dose level of cyproconazole technical. There were no treatment related findings in both sexes at low dose.

In a two-generation rat reproduction study, there were no treatment-related effects on the reproduction parameters. The only treatment-related finding was an increased hepatocellular fatty changes in F0 males at the high dose level of cyproconazole technical. In a rat teratology study, reduced body weight gains and increased postimplantation losses were observed at uppermiddle and high dose levels of cyproconazole technical. In a rabbit teratology study, reduced body weight gains and food consumption were observed at high dose level of cyproconazole technical. Postimplantation losses were increased at high dose level. There were no treatment-related external, skeletal or visceral abnormalities.

Cyproconazole technical did not induce mutations in bacterial or mammalian system.

Cyproconazole is one of the important fungicides for field crops since its registration in 1995.

要　　約

シプロコナゾールの毒性試験の概要

株式会社エス・ディー・エスバイオテック農薬対策室

シプロコナゾール原体は経口投与によりラットに対しては毒性は低く，マウスに対しては中程度の毒性を示した．その製剤の毒性は，経口投与でラットおよびマウスとも低かった．また原体・製剤とも経度毒性は低い値であった．原体・製剤とも眼に対して弱い刺激性が認められたが，皮膚に対しては刺激性は認められなかった．またモルモットを用いたMaximization法による皮膚感作性の試験では，原体・製剤とも感作性は認められなかった．

ラットあるいはイヌを用いた亜急性毒性試験において，シプロコナゾール原体投与により中用量および高用量群のいくつかの血液生化学検査項目が影響を受けた．また体重増加量の減少および肝臓重量の増加がラットおよびイヌの高用量群で認められた．

ラットを用いた慢性毒性/発癌性併合試験において，シプロコナゾール原体投与により一部の血液学的あるいは血液生化学検査項目が，おもに高用量群で影響を受けた．また体重増加量の減少および肝臓重量の増加が高用量群で認められた．組織病理学的検査の結果，高用量群において雄では肝細胞の脂肪化が，雌では肝細胞肥大が認められた．中間屠殺・最終屠殺時とも腫瘍性病変の発生率には，シプロコナゾール原体投与の影響は認められなかった．

マウスの発癌性試験において，シプロコナゾール原体の中高用量および高用量群で体重増加量の減少および肝臓重量の増加が認められた．また肝細胞腫の発生頻度が，雄の中高用量および高用量群および雌の高用量群で増加した．これらの観察された腫瘍を引き起こす機構は，肝酵素の誘導による腫瘍のプロモーション作用であり，非遺伝毒性的なものである．

イヌの慢性毒性試験において，シプロコナゾール原体を投与した中用量および高用量群の雌雄でチトクロームP-450活性の上昇が観察された．また高用量群の雄で体重増加量の減少，雌雄で肝臓重量の増加が認められた．雌雄とも低用量群ではシプロコナゾール原体投与の影響は何ら認められなかった．ラットを用いた2世代繁殖試験において，繁殖に関する検査項目に対して投与の影響は何ら認められなかった．唯一認められたシプロコナゾール原体投与の影響は，F0世代の雄の高用量群での肝細胞の脂肪化であった．ラットを用いた催奇形性試験では，シプロコナゾール原体の中高用量および高用量群で体重増加量の減少および着床痕の増加が認められた．またウサギを用いた催奇形性試験では，シプロコナゾール原体の高用量群で体重増加重および摂餌量の減少，着床痕の増加が認められた．シプロコナゾール原体投与に関連した外表，骨格あるいは内臓の異常は認められなかった．

シプロコナゾール原体は細菌あるいは哺乳類細胞を用いた試験系において，突然変異を引き起こさなかった．

シプロコナゾールは1995年に登録されて以来，畑地作物の重要な殺菌剤の一つである．

Contact
Regulatory Affairs Department, SDS Biotech K.K.
2-12-7, Higashi Shimbashi, Minato-ku, Tokyo 105, Japan

問合せ
株式会社エス・ディー・エスバイオテック　農薬対策室
〒105　東京都港区東新橋2-12-7