J. Pesticide Sci. **15**, 647–651 (1990)

Technical Information

Summaries of Toxicity Studies on Quinclorac

Registration Department, Agricultural Chemicals Division, BASF Japan Ltd.

(Received August 20, 1990)

DESCRIPTION OF THE TEST COMPOUND

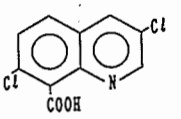
Quinclorac is a new chemical synthesized by BASF Aktiengesellschaft in the early 1980s, which belongs chemically to the class of quinoline carboxylic acids. Through a number of trials in which its biological activity was tested all over the world, it has been confirmed that Quinclorac is specifically effective against *Echinochloa crus-galli* with a wide range of application timing, and is safe on either direct seeded or transplanted rice plants. This article provides a toxicological feature of Quinclorac obtained from numerous toxicological studies with the technical grade (hereafter as QUINCLORAC TECH) and the 50% wettable powder formulation (hereafter as FACET WP).

The chemical structure and physicochemical properties of Quinclorac are given below:

Common name: Quinclorac

Chemical name: 3,7-Dichloroquinoline-8-carboxylic acid

Structural formula:



Molecular formula: $C_{10}H_5Cl_2NO_2$

Molecular weight: 242.1

Appearance: White crystals

Melting point: 274°C

Vapor pressure: $<1\times10^{-7}$ mbar (20°C)

Solubility (g/100 g solvent at 20°C): Water 0.0064, acetone 0.2, ethyl alcohol 0.2, ethyl ether 0.1, ethyl acetate 0.1, hardly soluble in toluene, acetonitril, *n*-octanol, dichloromethane, *n*-hexane

Partition coefficient (*n*-octanol/water): Log P_{ow}; −1.164 (pH 7 at 22°C)

Stability: No decomposition at 50°C for 2 years in an unopened original package. No decomposition in the respective buffer solutions of pH 5, 7 and 9 at 25°C for 30 days under dark condition. No decomposition after 7 days exposure to 20,000 lx when exposed in solid state.

ACUTE TOXICITY

Table 1 shows results of acute toxicity studies with QUINCLORAC TECH and FACET WP at different routes of administration.

In these tests dosing resulted only in non-specific signs of toxicity, which were reversible within an observation period of 14 days.

LOCAL TOLERANCE AND SENSITIZATION

Instillation of QUINCLORAC TECH (about 38 mg/eye) into the eyes of rabbits induced slight irritant effects on conjunctiva, being however reversible within 8 days. FACET WP (about 18 mg/eye) induced very slight irritant effects. Full recover was observed within 72 hr. (Department of Toxicology, BASF, 1983 and 1986)

The local tolerance was tested on the intact and abraded dorsal skin of rabbits by application for 24 hr under an occlusive dressing. Using about 0.5 g/patch, no signs of skin irritation were observed with QUINCLORAC TECH. FACET WP (about 0.25 g/patch) caused a very slight irritation, however, it disappeared within 48 hr. (Department of Toxicology, BASF, 1983 and 1986)

A (weak) sensitizing potential was indicated when QUINCLORAC TECH was tested in the maximization test for skin sensitizing effect, however, FACET WP induced no sensitizing effect when it was tested under practical condi-

Table 1

Test substance	Animal species, strain	Administration route	LD_{50} (mg/kg) Male	Female	Testing facility, reporting year
QUINCLORAC TECH	Rat, Wistar	Oral	3060	2190	Department of Toxicology, BASF, 1983
	Mouse, B6C3F1	Oral	5000	>5000	Department of Toxicology, BASF, 1986
	Rat, Wistar	Dermal	>2000		Department of Toxicology, BASF, 1983
	Rat, Wistar	Inhalation	>5.17 mg/l		Department of Toxicology, BASF, 1984
FACET WP	Rat, Wistar	Oral	3830	4070	Department of Toxicology, BASF, 1986
	Mouse, NMRI	Oral	>5000		Department of Toxicology, BASF, 1988
	Rat, Wistar	Dermal	>2000		Department of Toxicology, BASF, 1986
	Rat, Wistar	Inhalation	>5.15 mg/l		Department of Toxicology, BASF, 1986

tions in the open epicutaneous test. (Department of Toxicology, BASF, 1986 and 1987)

SUBACUTE TOXICITY STUDIES

Four-week range-finding studies were performed with rats, mice and dogs.

Wistar rats, 5 animals per sex and dose, were administered 0, 100, 400, 1600 and 6400 ppm *via* the diet. All doses were tolerated without clinical signs of toxicity, examination revealed no compound-related changes. The NOEL, therefore, is above 6400 ppm.

In a further four-week study Wistar rats were similarly administered 0, 15,000 and 30,000 ppm *via* the diet. Both dosages resulted in reduced food intake and body weight. In the 30,000 ppm group a variety of clinico-chemical and hematological changes were found, indicating impaired function of the target organs. The absolute weight of testes and liver were reduced, and involution of spleen and testes and a granular structure of the kidneys were observed. Corresponding histopathological changes were cloudy swelling of hepatocytes, tubular atrophy of the testes, vacuolization of the adrenal cortical cells and tubulopathy of the kidneys. The latter was the only substance-related finding in the 15,000 ppm group.

Combining the two studies the NOEL is 6400 ppm.

(Department of Toxicology, BASF, 1985)

Similarly, B6C3F1 mice, 5 animals per sex and dose level, were administered 0, 1000, 4000, 8000 and 16,000 ppm of QUINCLORAC TECH in the diet for four weeks.

16,000 ppm resulted in slightly reduced body weight gain, increased activities of alkaline phosphatase and glutamate puruvate transaminase, mainly in male mice, a decrease in the absolute kidney weight and an increase in the absolute liver weight. No histopathological changes were found in these or other organs. The NOEL in this study was 8000 ppm.

(Department of Toxicology, BASF, 1986)

Finally, two Beagle dogs per sex and dose level were administered 0, 1000, 3000, 9000 and 27,000 ppm of QUINCLORAC TECH in the diet for four weeks.

27,000 ppm resulted in reduced food consumption and a marked reduction in body weight. 27,000 and 9000 ppm produced a decreased alkaline phosphatase activity, decreased absolute testes weight and a chronic focal or multifocal interstitial nephritis. The NOEL is 3000 ppm.

(Department of Toxicology, BASF, 1985)

SUBCHRONIC STUDIES

In a three-month study with Wistar rats, 10 animals per sex and dose, QUINCLORAC TECH was administered in the diet at doses 0, 1000, 4000 and 12,000 ppm. Animals of the control and high dose groups were subjected in addition to the hematological and clinico-chemical examinations to an ophthalmological examination at the beginning and at the end of the administration period.

12,000 ppm resulted in a slight reduction of food consumption and of body weight gain, increased activity of glutamate oxalacetate and glutamate puruvate transaminase in male rats and a decrease of some red blood cell

parameters in females. The only pathological finding was a slight focal interstitial nephritis in male rats. The NOEL was 4000 ppm (=302.3 mg/kg body weight in males and 358.0 mg/kg body weight in females).

(Department of Toxicology, BASF, 1986)

B6C3F1 mice were equally administered QUINCLORAC TECH in the diet in doses of 0, 4000, 8000 and 16,000 ppm, 10 mice per sex and dose level for a period of three months.

16,000 ppm resulted in reduced body weight gain (8–10%) in both sexes, increased water consumption, and decreased eosinophilic granulocytes and monocytes in males, decreased kidney weight in both sexes and decreased liver weight in females only. Drinking water consumption was increased in both sexes.

8000 and 4000 ppm caused reduced body weight gain (6–8% and 5% respectively), decreased kidney weight in males and decreased liver weight in females, and at 8000 ppm a slight increase in drinking water consumption in both sexes.

Because of the lack of a NOEL a further study with a dose level of 500 ppm was initiated.

Combining the two studies the NOEL is 500 ppm (=85.4 mg/kg body weight in males and 129.8 mg/kg body weight in females).

(Department of Toxicology, BASF, 1988)

CHRONIC TOXICITY AND ONCOGENICITY

The long-term toxicity of Quinclorac was studied in Wistar rats given 0, 1000, 4000, 8000 or 12,000 ppm of QUINCLORAC TECH in the diet for 24 months. Twenty animals per sex and dose were used for the evaluation of chronic toxicity together with a satellite group of 10 rats per sex and dose for an interim kill after 12 months.

For the evaluation of carcinogenicity 50 animals per sex and dose were given doses of up to 8000 ppm for 24 months.

There was no compound-related influence on any of the usually examined parameters except a slight decrease in the body weight of female animals at 12,000 ppm. No dose-related neoplastic or non-neoplastic findings were observed.

The NOEL for chronic toxicity is >12,000 ppm (=>585.5 mg/kg body weight) for males and 8000 ppm (=490.8 mg/kg body weight) for females. There were no signs of a carcinogenic potential.

(The Institute of Environmental Toxicology/ Department of Toxicology, BASF,1988)

A combined chronic and carcinogenicity study was performed with B6C3F1 mice for a period of 78 weeks. The main study included 50 mice per sex and dose level of 0, 1000, 4000 or 8000 ppm of QUINCLORAC TECH in the feed with a satellite group of 10 mice per sex for an interim kill after six months.

Reduced body weight gain was found in both sexes at 8000 ppm (19%), 4000 ppm (16–17%) and 1000 ppm (11–17%). Reduced organ weights were not considered compound-related due to a lack of corresponding histopathological changes, and the decreased body weights.

In the satellite groups 8000 ppm reduced body weight gain in male and female mice were found, and doses of 4000 and 1000 ppm produced decreased body weight in males only.

As a NOEL was not reached, a further dose level of 250 ppm was initiated with 50 mice per sex in the main group and 10 mice in a satellite group. There were no signs of toxicity, and a NOEL was established at 250 ppm (=36.8 mg/kg body weight in males and 52.1 mg/kg body weight in females).

There were no signs of a carcinogenic potential. (Department of Toxicology, BASF, 1988)

In a twelve-month feeding study Beagle dogs, 6 animals per sex and dose, were administered 0, 1000, 4000 or 12,000 ppm of QUINCLORAC TECH in the diet.

12,000 ppm, and to a lesser degree 4000 ppm, resulted in reduced food consumption and body weight gain. In the 12,000 ppm group, additionally, there was a decrease in some red blood cell parameters and in increase in absolute and relative liver and kidney weights. There was also an increase of the latter in the 4000 ppm group. Histopathological changes consisted of mononuclear infiltrates in the liver and hydropic degeneration in the kidneys. The NOEL is 1000 ppm (=34.9 mg/kg body weight in males and 35.0 mg/kg in females).

(Department of Toxicology, BASF, 1988)

PRENATAL TOXICITY AND REPRODUCTION

The effect of QUINCLORAC TECH on the reproduction of Wistar rats was examined in a two-generation study with two litters in the first generation and one litter in the second. Twenty-four rats per sex and dose level were administered QUINCLORAC TECH in the feed at doses of 0, 1000, 4000 or 12,000 ppm. F_0 animals were mated to produce a first litter (F_{1a}) and subsequently remated to produce a second litter (F_{1b}), which were retained only until weaning. From the F_{1a} pups 24 rats per sex and dose level were selected to form the F_1 parental generation, and after weaning they were fed the same diet as their parents until mating and producing the F_{2a} litter. The study was terminated with the F_{2a} weanings.

12,000 ppm induced clear signs of maternal toxicity such as reduced food consumption and body weight gain. At the same dose level reduced pup weights, a retarded rate of growth and delayed development (*e.g.* eye and ear opening) were noted in both generations. Marginally increased mortality was noted in the F_{1a} and F_{2a} pups during their rearing period. There was no influence of fertility or reproduction parameters in any group.

The NOEL was >12,000 ppm for reproduction parameters, and 4000 ppm for systemic toxicity in parental animals and their offspring.

(Department of Toxicology, BASF, 1988)

To assess the prenatal toxicity of QUINCLORAC TECH, groups of 25 pregnant Wistar rats were orally (by stomach tube) administered doses of 0, 24.4, 146 or 438 mg/kg body weight in a 0.5% aqueous CMC suspension from day 6 to day 15 post coitum. Fetuses were removed by cesarean section on day 20 post coitum.

438 mg/kg resulted in severe signs of maternal toxicity, including mortalities, deteriorating general state of health, an increase in water intake, a decrease in food consumption and a corresponding slight decrease in body weight gain. At necropsy these animals showed severe ulcerations of the glandular stomach, but no adverse effects were found on the fetuses.

Thus the NOEL was 146 mg/kg body weight for the dams and >438 mg/kg body weight for the fetuses. There were no signs of a teratogenic effect.

(Department of Toxicology, BASF, 1987)

In a second test for prenatal toxicity, groups of 15 female Himalayan rabbits were dosed with 0, 70, 200 or 600 mg/kg body weight QUINCLORAC TECH in a 0.5% aqueous CMC suspension from day 7 to day 19 post insemination.. Fetuses were removed by cesarean section on day 29 post insemination.

The highest dose again produced severe signs of toxicity, including reduced food intake, decreased body weight gain and mortality. 200 mg/kg resulted in slightly reduced food consumption and body weight gain, indicating weak maternal toxicity.

In the 600 mg/kg group reduced numbers of live fetuses, increased post implantation loss, and slightly reduced fetal weights were found. Embryo/feto toxicity was observed only at dose levels inducing severe maternal toxicity. Teratogenic effects were not observed at any one dose level.

The NOEL was 70 mg/kg body weight for the dams and 200 mg/kg body weight for the fetuses.

(Department of Toxicology, BASF, 1988)

MUTAGENICITY STUDIES

Genetic damage resulting from gene mutation was investigated in the Ames test using *Salmonella typhimurium*, strains TA 98, TA 100, TA 1535 and TA 1537, and *Escherichia coli*, strain WP 2 uvr A, with and without metabolic activation (rat liver homogenate). QUINCLORAC TECH was used in doses between 20 and 5000 μg/plate (in DMSO). Under the test conditions chosen Quinclorac had no mutagenic effect.

(Department of Toxicology, BASF, 1988)

Genetic damage through chromosomal aberrations was investigated *in vitro* with human lymphocytes. QUINCLORAC TECH was used in concentrations of 250, 500 and 1000 μg/ml without metabolic activation and 500, 1000 and 2000 μg/ml with metabolic activation (rat liver homogenate). Chromosomal damage was found both with and without metabolic activation, but only at dose levels with clear cytotoxicity as indicated by the mitotic index.

(Department of Toxicology, BASF, 1986)

The same genetic endpoint was tested with QUINCLORAC TECH *in vivo* in NMRI-mice using the micronucleus test. The material, suspended in an aqueous 0.5% CMC solution, was administered once orally to male and female mice at doses of 500, 1000 or 2000 mg/kg body weight. The higher doses led to signs of toxicity such as irregular respiration, apathy or piloerection. There was a no increase in the number of micronuclei at any one dose level.

(Department of Toxicology, BASF, 1986)

A second *in vivo* chromosome aberration test was performed in male and female Chinese hamsters administered, by gavage, 2000, 4000 or 8000 mg/kg body weight QUINCLORAC TECH, suspended in 0.5% aqueous CMC solution. Systemic toxicity such as irregular respiration, apathy and a generally poor state of health was observed in the animals. Bone marrow preparation was performed 6, 24 and 48 hr after administration. There was no difference in types and frequency of chromosome aberrations between dose groups and controls.

(Department of Toxicology, BASF, 1988)

DNA damage and repair was investigated in the *in vitro* Rec-assay using *Bacillus subtilis*, strains H 17 (Rec^+) and M 45 (Rec^-). QUINCLORAC TECH, dissolved in DMSO, was used in concentrations of 1 to 10,000 μg/plate with and without metabolic activation (rat liver homogenate). 10,000 μg/plate without S-9 was toxic to both strains of *Bacillus subtilis*. At all dose levels both with and without metabolic activation, no indication for DNA damage was observed.

(Hazleton Biotechnologies, 1987)

SUMMARY

In order to investigate toxicological properties of Quinclorac, a number of toxicological studies were carried out with QUINCLORAC TECH and FACET WP. From these studies, it can be derived that the acute toxicity, subacute toxicity, and long-term toxicity are rather low. No critical irritant effects on eye and skin were noted, and under practical conditions a skin sensitizing effect and inhalation risk can be excluded. No adverse effect was observed on reproductivity, and no signs of teratogenic effects were noted. Mutagenicity was negative at non cytotoxic levels. There were no signs of an oncogenic response in any of the tested animals.

A withholding value has been set for the registration at 0.5 ppm on rice, and FACET WP, wettable powder formulation containing 50% Quinclorac, was registered to JMAFF on November 16, 1989.

A safety risk for Quinclorac, as far as it is used in accordance with the established safe use standard, is not to be expected.

Contact

Registration Department, Agricultural Chemicals Division, BASF Japan Ltd., 3–3, Kioicho, Chiyoda-ku, Tokyo 102

問合せ

ビーエーエスエフジャパン株式会社農薬部登録課

〒102 東京都千代田区紀尾井町三番三号