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Technical Information

Summary of Toxicity Studies on Fluazifop-butyl

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Fluazifop-butyl, the active ingredient of Onecide ®EC, is a new selective herbicide for the control of annual and perennial grasses in broadleaf crops.

The chemical structure and physiochemical properties of the herbicide are given below.

IDENTITY OF ACTIVE INGREDIENT

Trade name: Onecide ®EC

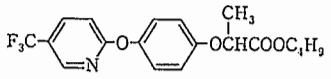
Common name: fluazifop-butyl

Chemical name: Butyl (*RS*)-2-[4-(5-trifluoromethyl-2-pyridyloxy)phenoxy]propionate.

Molecular weight: 383

Molecular formula: $C_{19}H_{20}F_3NO_4$

Structural formula:



PHYSICAL AND CHEMICAL PROPERTIES OF ACTIVE INGREDIENT

Color: clear to straw-colored

Odor: odorless

Physical state: oily liquid

Specific gravity: 1.21 at 20°C

Boiling point: 202°C at 3 mmHg

Vapor pressure: 5.5×10^{-5} Pa at 20°C

Solubility: miscible with acetone, toluene, methanol, xylene, hexane. Solubility in water approximately 2 ppm.

Stability: As undiluted material: No detectable decomposition at ambient temperatures or for at least 3 months at 50°C. In dilute aqueous solution hydrolyzes to parent acid as fluazifop at alkali condition.

Octanol/water partition coefficient:

log Pow fluazifop-butyl 4.17

log Pow fluazifop 2.11

ACUTE TOXICITY STUDIES

Species	Route	Sex	LD_{50} (mg/kg)	Laboratory (year)
Mouse	Oral	Male	1600	School of Medicine, Keio University Pharmaceutical Institute and Nippon Experimental Medical Research Institute Co., Ltd. (1981)
		Female	1900	
	Subcutaneous	Male	>2000	
		Female	>2000	
	Intraperitonial	Male	1255	
		Female	1240	
Rat	Oral	Male	3030	School of Medicine, Keio University Pharmaceutical Institute and Nippon Experimental Medical Research Institute Co., Ltd. (1982)
		Female	2910	
	Subcutaneous	Male	>5000	
		Female	>5000	
	Intraperitonial	Male	1700	
		Female	1620	
Rat	Dermal	Male	>6050	Life Science Research Ltd. (1978)
		Female	>6050	
Rat	Inhalation		LC_{50} (mg/*l*)	Life Science Research Ltd. (1980)
		Male	>5.24	
		Female	>5.24	

PRIMARY IRRITATION STUDIES

1. Eye Irritation: Rabbit

0.1 ml of fluazifop-butyl was instilled into the conjuctival sac of the right eye of each of nine male New Zealand White rabbits. After 20–30 sec the eyes of three of the rabbits were flushed with clean lukewarm water. Ocular lesions were scored using the Draize scale and classified according to a modified form of the system of Kay and Calandra.

Instillation caused practically no initial pain in 8 of the 9 animals and slight initial pain in one animal. Thereafter the only responses observed were minimal conjuctival redness in one of the six unrinsed rabbit eyes and in two of the three rinsed rabbit eyes. There was no corneal opacity or iritis.

On the basis of these results, fluazifop-butyl is described as "practically non-irritating" to the rabbit eye.

(Life Science Research, Ltd., 1979)

2. Skin Irritation: Rabbit

The primary skin irritation of fluazifop-butyl to the rabbit was assisted using the Draize method. Undiluted material (0.5 ml per test area) was applied for 24 hr under occlusive dressings to the intact and abraded skin of six male New Zealand White rabbits. Observations were made at 24, 72 hr and 7 days after application.

All animals displayed erythematous responses at either 24 or 72 hr. No animal displayed a response at both times and the only response observed on Day 7 was slight exfoliation affecting one animal.

Under the conditions of this study, fluazifop-butyl was placing in the "mildly irritating" classification.

(Life Science Research, Ltd., 1979)

SKIN SENSITIZATION STUDY: GUINEA PIG

The potential of fluazifop-butyl to cause delayed contact hypersensitivity was investigated in young male guinea-pigs of the Dunkin-Hartley strain using Draize method. The study incorporated positive and negative control groups.

Repeated intradermal injections of undiluted test material caused practically no irritation responses during the induction phase of the study.

There was no evidence of a delayed contact hypersensitivity reaction following the challenge injection of undiluted test material. All positive control group animals showed marked erythematous responses to challenge with 2% w/v DNCB in sesame oil.

Under the conditions of this study fluazifop-butyl did not show potential to cause delayed contact hypersensitivity reactions in guinea-pigs. (Life Science Research, Ltd., 1980)

SUBCHRONIC ORAL TOXICITY STUDIES

1. Rats

Groups of 20 male and 20 female Wistar rats were fed diets containing fluazifop-butyl at concentrations of 0, 10, 100 and 2000 ppm for 90 days.

There were no deaths and clinical signs were not affected by treatment. The top dose males showed reduced bodyweight gain, food consumption and water intake. Hematological and biochemical examination revealed some changes at 100 and 2000 ppm. Necropsy did not reveal any lesions attributable to treatment. The absolute liver weights were higher in males at 2000 ppm. Histopathological changes were seen in kidneys and liver only. There was a dose-related increase in the incidence and severity of renal tubular degeneration in males at 100 ppm and both sexes at 2000 ppm. Hepatocytic hypertrophy was recorded in males at 2000 ppm.

On this basis the toxicological no-effect level for fluazifop-butyl when administered to rats in the diet for 90 days is considered to be between 10–100 ppm for male and 100–2000 ppm for females.

(Institute for Animal Reproduction, 1983)

2. Mouse

The toxic effects of fluazifop-ethyl were investigated by dietary administration to five groups of each ten ICR female mice for 11 weeks at the dietary levels of 0, 10, 30, 100 and 300 ppm.

There were no abnormal clinical signs, death and depression in bodyweight gain. No hematological and biochemical changes at-

tributable to treatment were observed. Gross pathological examination revealed changes attributable to the treatment being only in the liver. The changes in the liver were dark discoloration in 30, 100 and 300 ppm groups and enlargement in 100 and 300 ppm groups. Organ weight analysis revealed dosage-related increase in absolute and bodyweight-relative liver weights. The increase was statistically significant in 300 ppm group.

From the above results, it was concluded that in this dietary administration of test substance in female mice the target organ was the liver, and the toxic effects were observed at the dietary level of 30 ppm or higher. Consequently no-effect level is considered to be 10 ppm. (Central Research Laboratory Ishihara Sangyo Kaisha, Ltd., 1978)

SUBACUTE DERMAL TOXICITY STUDY: RABBIT

Fluazifop-butyl in corn oil was applied, under occlusion, to the shaven and either intact or abraded skin of groups of 10 male and 10 female New Zealand White rabbits, for 6 hr per day, five days per week for three successive weeks, at doses of 0, 100, 500 and 2000 mg/kg/day. The animals were observed for reaction to treatment, food intake and bodyweight changes. Blood samples were taken, all animals were subjected to necropsy and histopathological evaluation of the major organs.

Four males and five females in the top dose group died or were killed *in extremis* and a single male at 500 mg/kg/day died. Animals which survived, showed no treatment-related clinical signs. The animals which died had previously shown severe inappetence and weight loss, together with disturbances in the morphology and composition of the blood, which were considered to be treatment-related. There were no reactions at the treatment site, other than those attributable to the vehicle. Findings at necropsy included gastric ulceration and abnormally colored gastrointestinal contents. The only histopathological change consistently attributable to treatment was centriacinar hepatocytic hypertrophy, which was seen in most of the decedents and one male survivor in the top dose group.

Under the conditions of this study, the no-effect level was 100 mg/kg/day for male and 500 mg/kg/day for female.

(Life Science Research, Ltd., 1981)

CHRONIC TOXICITY STUDY: DOG

Groups of six male and six female beagle dogs received fluazifop-butyl at dosages of 0, 5, 25 or 125 mg/kg/day orally in gelatin capsules for 55 weeks.

Five males and two females receiving 125 mg/kg/day were killed *in extremis*. Reaction and bodyweight gain in surviving dogs were not clearly affected by treatment with test material. Necropsy of dogs killed at termination and organ weight analysis did not reveal any clear effects of fluazifop-butyl. Histopathology revealed thymic involution and lenticular changes in the eyes of the high dose level group and cortical fatty vacuolation in the adrenals of several high dosage dogs and one female in the intermediate dosage group. Erythrocytosis and erythrophagocytosis in the lymph nodes occurred more frequently in treated dogs than in controls; the difference between the low dosage and controls was small and considered to be of no toxicological significance.

It is concluded that treatment with fluazifop-butyl at 5 mg/kg/day resulted in no significant toxic change.

(Life Science Research, Ltd., 1982)

CHRONIC-TOXICITY AND ONCOGENICITY STUDIES

1. Rat

Fluazifop was administered continuously to groups of 70 male and 70 female CD rats, *via* the diet, at levels of 0, 0.1, 0.3, 1.0 or 3.0 mg/kg/day for a minimum of 105 weeks of treatment. A maximum of 10 males and 10 females from each group were sacrificed after 51 weeks to provide interim histopathological data.

Soft hair was recorded in male rats after 65 weeks of treatment, but the toxicological significance of this finding is equivocal. There were no depression in bodyweight gain and hematological, biochemical or macropathological changes attributable to treatment. There

were no microscopic treatment-related changes, with the sole exception of a slight decrease in the number of male rats at the top dose with periacinar hepatocyte vacuolation after 51 weeks. There was no disturbance in the type or incidence of any tumors.

It is concluded that fluazifop has no oncogenic potential in rats, the toxicological no-effect level in this study was 1.0 mg/kg/day for male and 3.0 mg/kg/day for female.

(Life Science Research, Ltd., 1981)

2. Mouse

Fluazifop was administered continuously, *via* the diet, to groups of 72 male and 72 female ICI Alderley Park mice at doses of 0, 0.1, 0.3, 1.0 or 3.0 mg/kg/day for a period of 81 weeks. A Maximum of 12 males and 12 females from each group were sacrificed during Week 52 to provide interim histopathological data.

There were no clinical signs of treatment-related effects, the incidence of mortality during the course of the study was unaffected by treatment. Bodyweight gain, food consumption and water intake were not affected by treatment. There were no hematological, biochemical or macropathological changes attributable to treatment. The only treatment-related micropathological effects were limited to the livers of the top dose males at the interim sacrifice. There was an increased incidence of periacinar hepatocytic enlargement, accompanied by loss of basophilia. Hepatocellular masses (type A nodules) were found more frequently in males in the 0.1 or 1.0 dose groups than in controls, but this was attributable to a low control incidence in this study relative to the historical control. The lack of dose response and low control incidence show that this finding was unrelated to treatment.

It is concluded that fluazifop has no oncogenic effect in mice at all dose levels tested in this study. In term of chronic toxicity effects, the no-effect level is 1.0 mg/kg/day for male and 3.0 mg/kg/day for female.

(Life Science Research, Ltd., 1981)

REPRODUCTION STUDY: RAT

Fluazifop-butyl was administered continuously at 0, 10, 80 and 250 ppm in the diet to groups of 30 male and 30 female Wistar rats throughout three successive generations. F_0 animals received these diets for 91 days before pairing.

Litter generated by the first mating(F_1A) were reared to weaning and discarded. After the second pairing (F_1B), half the mated females were killed on Day 20 for examination of their uterine contents. The remaining animals were allowed to litter and to rear their offspring to weaning. After wearing, F_1B offspring were randomly selected from each group to form the F_1 generation for continuation of the study. These procedures were repeated.

The general condition of animals in the study remained good at all dietary levels. The number of parental deaths was small, was distributed across all groups and was not related to the administration of fluazifop-butyl. There was no evidence of an effect on any of the reproductive parameters at 10 ppm. At higher levels of 80 and 250 ppm, a number of findings were associated with treatment, including slight reductions in bodyweight gains, reduced foetal weight and ossification, slightly extended gestation length, reduced testicular weight and increased prostate weights. Additionally, at the highest level, reduced spleen weight and a low incidence of foetal abnormalities were observed. Mating performance, fertility and offspring survival were, however, unaffected.

In conclusion 250 ppm is the no-effect level for reproductive performance in this study and 10 ppm is the no-effect level for all reproductive parameters recorded.

(Life Science Research, Ltd. and Institute of Environmental Toxicology, 1982)

TERATOLOGY STUDIES

1. Rat

Groups of 22 Sprague Dawley rats received fluazifop-butyl in corn oil by gavage at dose levels of 0, 10, 50 and 200 mg/kg/day over days 6–20 of pregnancy. On Day 21 of gestation, the rats were killed for examination of their uterine contents.

Maternal health and food consumption were unaffected by treatment but bodyweight gain

during gestation was reduced at 200 mg/kg/day. There was a dose-related reduction of fetal ossification in all treated groups, which correlated with reductions in fetal weight. The effects at 10 and 50 mg/kg/day were, however, slight and within the background control range. One fetus in the low dose group (10 mg/kg/day) and three fetuses in the high dose group (200 mg/kg/day) exhibited diaphragmatic hernia. To ensure the detection of a very low incidence phenomenon such as diaphragmatic hernia, groups of 160 rats were used to a second study. Dose levels were 0, 1, 5, 10 and 200 mg/kg/day. The study confirmed the occurrence of compound-induced diaphragmatic hernia at the top dose level. The occurrence in the other three treatment groups were similar, indicating a no-effect level of at least 10 mg/kg/day and from the first study possibly higher than 50 mg/kg/day. The no-effect level for foetotoxic responses is 1 mg/kg/day.

(Life Science Research, Ltd., 1980 & 1981)

2. Rabbit

Groups of 20–24 New Zealand White rabbits received fluazifop-butyl in corn oil by gavage at dose levels of 0, 10, 30 and 90 mg/kg/day over days 6–28 of pregnancy. On Day 29 of gestation the rabbits were killed for examination of their uterine contents.

Maternal health, bodyweight and food consumption were unaffected by treatment. The top dose produced an increase in the frequency of minor gall bladder variants, some eye opacities and some evidence of skeletal retardation in the fetus. It was concluded that 30 mg/kg/day was a clear no-effect level.

(Life Science Research, Ltd., 1980)

MUTAGENICITY STUDIES

1. Reverse Mutation

Fluazifop-butyl was tested by the reverse mutation assay, described by Ames *et al.* The assay was conducted on *Salmonella typhimurium* (five strains of TA1535, TA1537, TA1538, TA100 and TA98) and *Escherichia coli* (WP2 *hcr*), both with and without metabolic activation. The test system was validated with concurrent positive controls using AF-2, ENNG, 9-AA and 2-AA.

The positive control substances all gave a positive mutagenic response. Fluazifop-butyl did not give a positive response.

(Institute of Environmental Toxicology, 1982)

2. Cytogenetic Study

The clastogenic potential of fluazifop-butyl to male CD rats was assessed by administering the compound by gavage as a solution in corn oil at 21, 67.2 and 210 mg/kg. These doses were administered either singly or daily for 5 consecutive days. A positive control substance, ethyl methanesulfonate, was used. The bone marrow cells from one femur of each animal were then isolated and prepared for microscopic analysis.

In the acute dosing study, there was no indication that fluazifop-butyl caused any increase in the frequency of chromatid or chromosomal aberrations. The positive control substance did cause a highly significant increase.

In the subacute study there was some indication of an increase in the frequency of cells bearing any aberration in the top dose group. The aberration frequency, however, was not significantly different from the controls when cells containing gaps only were excluded. The positive control substance caused a large increase in aberration frequency.

It is concluded that the observed increase in chromatid gap frequency following subacute administration of fluazifop-butyl at the top dose, since this has the least biological significance of the range of potential responses, does not indicate a mutagenic risk to man.

(Inveresk Research International, 1980)

3. Dominant Lethal Study

Fluazifop-butyl was administered by gavage to male CD-1 mice, as a solution in corn oil, daily for 5 consecutive days at 28.7, 91.8 and 287.0 mg/kg/day. A positive control group was given ethyl methanesulfonate at 100 mg/kg/day. After dosing, each male was caged with 2 virgin females for 6 days, followed by a further 2 virgin females each week for 7 consecutive weeks. The females were killed 15 days after caging with the treated males, and their uteri examined for live implantations, early fetal deaths and late fetal deaths.

The fluazifop-butyl treatment had no effects

on pregnancy frequency, the total number of implantations, the number of early deaths per pregnancy or late deaths per pregnancy. The positive control gave a response in mating weeks 1 and 2.

It is concluded that fluazifop-butyl has no potential for inducing dominant lethal mutations in male mice under the conditions of this study. (Inveresk Research International, 1980)

4. DNA Repair Test

A DNA repair test was carried out to investigate whether fluazifop-butyl damages DNA by using *Bacillus subtilis* H17 and H45 with and without metabolic activation preparation added.

The results showed that any difference of growth inhibition was not observed on fluazifop-butyl in all concentration ranges, but positive control Mytomycin C inhibited the growth of both strains in a clearly different manner.

Fluazifop-butyl is thus assumed to have no DNA damage potential under the conditions of the present test.
(Institute of Environmental Toxicology, 1982)

SUMMARY

A wide variety of toxicological studies on fluazifop-butyl have been conducted to assess its safety. The results of these studies support the view that this herbicide will be safe it used following the recommended use instruction.

Onecide ®EC herbicide containing fluazifop-butyl as its a.i., was registered to JMAFF at October 1986, the "Standard for withholding registration" were established with 0.1 ppm for peas, potatoes, sugar beet and fruits, 0.2 ppm for vegetables.

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