United States
Environmental Protection
Agency

Office of Pesticides and Toxic Substances
Office of Pesticide Programs (TS-766C)
Washington, DC 20460

EPA

Pesticide Fact Sheet

Name of Chemical: NORFLURAZON
Reason for Issuance:
Date Issued: December 1, 1984
Fact Sheet Number: 60

1. Description of the chemical

Generic name: 4-chloro-5-(methylamino)-2-(alpha, alpha, alpha-trifluoro-m-tolyl)-3(2H)-pyridazinone
Common name: Norflurazon
Trade name: Zorial®, Solicam® and 'Evital®
'EPA Shaugnessy Number: 105801
Chemical Abstract Service Registry Number (CAS): 27314-13-2
Year of initial registration: 1974
Pesticide Type: Herbicide
Chemical Family: Fluorinated pyridazinone
U.S. & foreign producer: Sandoz Inc.

2. Use patterns and formulations

Application sites: Norflurazon is registered for use as a selective preemergent herbicide to control germinating annual grasses and broadleaf weeds in cranberries, cotton, soybeans, almonds, apples, apricots, cherries, citrus (all), filberts, hops, nectarines, peaches, pears, pecans, plums, prunes, walnuts, and noncrop areas such as storage areas, airports and rights-of-way.
Types of formulations: Norflurazon is the sole active ingredient in the following: 97% active ingredient (a.i.) technical manufacturing-use-product, 80% a.i. wettable powder, 50% a.i flowable, and 5% a.i. granular.
Types and methods of applications: Band or broadcast ground application to soil surface. Aerial application is registered for cotton, cranberry and soybean use.
Application rates: 0.5 to 8 lb. a.i. per acre (A): cranberries 4-8 lb. a.i./A; cotton and soybeans 1-2 lb. a.i./A (split application 0.5-1.0 lb. a.i./A); tree fruit, nut tree, citrus and hops 2-4 lb. a.i./A; and noncrop sites 4-8 lb. a.i./A.
Usual carrier: Water

3. Science Findings

Summary science statement:

Norflurazon has a low acute toxicity and is not an eye or skin irritant or a skin sensitizer. The subchronic, chronic feeding, and reproduction studies did not produce results of toxicological concern. Norflurazon is not considered to be an oncogen or a teratogen. The mutagenicity studies reviewed thus far are negative. Norflurazon appears to be mobile in mineral soils and immobile in soils with high organic material and is persistent in soil. Norflurazon is relatively non-toxic to avian test species and is moderately to slightly toxic to aquatic (fresh water and marine) organisms. Data are available to determine and establish tolerances for residues of norflurazon and its desmethyl metabolite in over half of the commodities with established tolerances. Based on the established tolerances and the 6-month dog feeding study the percent of the accepatable daily intake utilized is 39%.

Chemical characteristics:

Norflurazon is a buff-white odorless crystalline solid. The melting point is 177 ± 3° C. The solubility of norflurazon at 25° C is 5 grams (g)/ 100 milliliters (ml) in acetone, insoluble in carbon disulfide, 14.2 g/100 ml in ethyl alcohol, 0.25 g/100 ml in xylol, and 28 parts per million (ppm) (w:w) in water. The vapor pressure is $< 1 \times 10^{-5}$ Torr (25°C). Norflurazon is quite stable in dilute acidic or basic aqueous solution and storage stability is greater than 2 years. No unusual handling characteristics were noted.

Toxicological characteristics:

Acute studies indicate the following:

- Rat acute oral was 9,000 milligrams (mg)/kilogram (kg), Toxicity Category IV.
- Rabbit acute dermal was > 20,000 mg/kg, Toxicity Category IV.
- Male rat acute inhalation of 80% WP was > 200 mg/Liter (L)/ 1 hour, Toxicity Category IV.
- Not an eye or skin irritant, Toxicity Category IV.
- Not a skin sensitizer.

Subchronic studies indicated the following:

- In a 6-month dog feeding study, the primary effects seen were congestion of the liver, hepatocyte swelling, increased liver weight, and an increase in colloidal vacuole in thyroid at 450 ppm. The No Observed Effect Level (NOEL) was 150 ppm. Levels tested were 0, 50, 150 and 450 ppm.
- In a 90-day rat feeding study, the primary effects were hypertrophic change in the thyroid glands at 2,500 ppm. The NOEL was 500 ppm. Levels tested were 0, 250, 500 and 2,500 ppm.
- In a 28-day mouse feeding study, diffuse and smooth granular livers and increased liver/body weight ratios were observed at 2,520 ppm. The NOEL was 420 ppm. Levels tested: 0, 70, 210, 420 and 2,520 ppm.
- A 14-day inhalation study in the rat was submitted. Levels tested were 0.1, 1.0, and 10.0 mg/L. The NOEL was 10 mg/L.
- A 21-day dermal toxicity study in the rabbit was performed on 80% WP (Wettable Powder) norflurazon. Levels tested were 750 mg/kg/day and 2000 mg/kg/day. The NOEL was > 2000 mg/kg/day.

The chronic studies indicated the following:

Chronic-feeding studies:

A 2-year rat feeding study was conducted using technical norflurazon. Rats were fed dietary levels of 2, 15, 125, 375 and 1025 ppm. In the high dose group histopathological alterations included an increase in the number of chromophobe adenomas of the pituitary, nodular or cortical hypertrophy in adrenals and nephritis and/or casts in kidneys of the male rats; and fatty changes in adrenals, edometritis and squamous metaplasia of the uterus, cystic ovaries and hyaline casts and/or nephritis in kidneys of the females. A NOEL was demonstrated at 375 ppm. Norflurazon domonstrated no tumorigenic effect in the test animals in any of the dose levels tested.

In a 2-year feeding study, mice were fed 0, 0 (double control), 85, 340 and 1360 ppm of technical norflurazon. Histopathological alterations included hepatoma/hyperplasia - hypertrophy in the liver at 1360 ppm. The NOEL level observed was 340 ppm. There was no significant increase in these lesions in the lower levels over that of the control. The failure to induce such lesions in the other long term studies permits the conclusion that this is not a potential carcinogenic response, but a toxic response to rather high level of chemical insult.

Reproduction studies:

A 3-generation reproduction study was conducted in the rat. Norflurazon was fed at dietary levels of 0, 125, 375 and 1025 ppm for three generations. At 1025 ppm norflurazon caused reduced fertility, gestation and viability indices. No teratogenic effects were seen at any dose tested. The NOEL was established at 375 ppm.

In a 1-generation reproduction study in the mouse, norflurazon was fed at dietary levels of 0, 0, 85, 170 and 340 ppm. No adverse findings were observed in any of the doses tested. The NOEL was established at 340 ppm.

Teratogenicity studies:

Pregnant rabbits were fed a diet containing 0, 10, 30, and 60 mg/kg norflurazon on gestation days 6 through 15. Norflurazon was not teratogenic at 60 mg/kg/day. Maternal body weight was decreased at 60 mg/kg. Fetotoxic effects seen at 30 and 60 mg/kg/day were decreased weight and incomplete ossified variations. Maternal toxic NOEL was observed at 30 mg/kg/day. Fetotoxic NOEL was observed at 10 mg/kg/day.

In the second teratology study, pregnant rats were fed 0, 100, 200 and 400 mg/kg/day of norflurazon on gestation days 6 through 15. Norflurazon was not embryotoxic or teratogenic. The NOEL was 400 mg/kg/day.

Mutagenicity studies:

In two Ames mutagenic assays, norflurazon was tested in Samonella typhimurium strains, TA-1535, TA-1537, TA-1538, TA-98, TA-100 and D-4 Saccharomyces cerevisiae strain. The doses employed ranged from 0.1 micrograms (ug) to 500 ug per plate. The compound was tested directly in the presence of liver microsomal enzyme preparation from Aroclor induced rats. Norflurazon did not demonstrate mutagenic activity.

A reverse mutagenicity assay using Salmonella typhimurium strains TA-1535, TA-1537, TAS-1538, TA-98 and T-100, also E. coli, WP2 hcr strain (tryptophanrequiring strain) was conducted. The doses employed were 5, 10, 50, 100, 1,000 and 5000 ug per plate. Norflurazon was negative in this test.

Metabolism studies:

(^{3}H, ^{14}C)- norflurazon was administed by gavage to 10 male Wistar strain rats at a dose of 10 mg per day for 15 days. Approximately 17 percent of the administed dose was excreted in the urine and about 57 percent in the feces. Small amounts of the parent compound were isolated from the urine (0.1%) and and larger amounts from the feces (5.4%). Only traces of radioactivity were present in the tissues examined. Three major pathways seem to be operative in detoxification of norflurazon in the rat: Desmethylation, yielding desmethyl metabolite of norflurazon; a hydroxylation process involving the replacement of chlorine on carbon-4 of the pyridazinon ring; and conjugation through sulfur introduced at carbon-4 of the pyridazinon ring.

Physiological and biochemical behavioral characteristics:

Norflurazon is absorbed by the roots of weeds as they germinate and is translocated to the growing parts where it inhibits carotenoid biosysnthesis resulting in chlorophyll photodegradation in susceptible species. On emergence from the soil, the weed seedlings turn white or pinkish, become necrotic and die.

Environmental characteristics:

Norflurazon residues appear to be relatively mobile in most mineral soils and immobile in soils with high organic matter. The half-life in soils ranges from 38 days to 731 days.

Ecological characteristics:

Avian studies:

Acute oral (Mallard duck) > 2510 mg/kg.
Acute dietary (Bobwhite quail) > 10,000 mg/kg.
Acute dietary (Mallard duck) > 10,000 mg/kg.
Reproduction (Mallard duck and bobwhite quail) was not affected up to 40 ppm dietary exposure (highest dose tested).

Aquatic species studies:

Daphnia magna acute 48 hour no effect level was 15 ppm (the highest level tested due to solubility of norflurazon technical).
Daphnia magna chronic life cycle minimum treshold concentration was > 1.0 < 2.6 ppm due to effect on offspring production.
Bluegill sunfish 96-hour acute was 16.3 ppm.
Rainbow trout 96-hour acute was 8.1 ppm.
Fathead minnow partial chronic maximum toxicant concentration (MATC) was > 1.1 < 2.1 ppm based on growth.

Rainbow trout partial chronic MATC was > 0.77 < 1.5 ppm based upon survival and growth.
Atlantic oyster larvae acute NOEL was 10 ppm.

Tolerance assessments:

U.S. tolerances for residues of norflurazon and its desmethyl metabolite in or on raw agricultural commodities are as follows [40 CFR §180.356(a)]:

Commodities	Maximum Residue Limit (ppm)
Almond, hulls	1.0
Almonds, meat	0.1
Apricots	0.1
Apples	0.1
Cattle, fat	0.1
Cattle, meat	0.1
Cattle, meat-by-products (mbyp)	0.1
Cherries	0.1
Citrus fruit	0.2
Cottonseed	0.1
Cranberries	0.1
Filberts	0.1
Goats, fat	0.1
Goats, meat	0.1
Goats, mbyp	0.1
Hogs, fat	0.1
Hogs, meat	0.1
Hogs, mbyp	0.1
Hops, green	1.0
Horses, fat	0.1
Horses, meat	0.1
Horses, mbyp	0.1
Milk	0.1
Nectarines	0.1
Pecans	0.1
Peaches	0.1
Pears	0.1
Plums (fresh prunes)	0.1
Poultry, fat	0.1
Poultry, meat	0.1
Poultry, mbyp	0.1
Sheep, fat	0.1
Sheep, meat	0.1
Sheep, mbyp	0.1
Soybeans	0.1
Soybean forage	1.0
Soybean hay	1.0
Walnuts	0.1

U.S. tolerances for indirect residues of norflurazon and its desmethyl metabolite in raw agricultural commodities when present as a result of application to cotton when peanuts are a replacement or follow-up crop are as follows [40 CFR §180.356(b)]:

Commodities	Maximum Residue Limit (ppm)
Peanuts	0.2
Peanut, hay	0.5

Peanut, hulls	0.5
Peanut, vines	0.5

A food additive tolerance has been established for residues of norflurazon and its desmethyl metabolite in dried hops at 3.0 ppm [21 CFR §193.324].

Feed additive tolerances have been established for residues of norflurazon and its desmethyl metabolite in citrus molasses at 1.0 ppm and dried citrus pulp at 0.4 ppm [21 CFR §561.283].

No Codex Alimentarius or Mexican or Canadian tolerances have been established for residues of norflurazon on the above commodities.

The acceptable daily intake (ADI) was established using the 6-month dog feeding study with a no observed effect level of 150 ppm (3.750 mg/kg/day). Using a 1,000 fold safety factor the ADI is calculated to be 0.0038 mg/kg/day. The maximum permitted intake (MPI) for a 60 kg human is calculated to be 0.2250 mg/day. The current theoretical maximum residue contribution (TMRC) for norflurazon, based on the established tolerances, is 0.0877 mg/day for a 1.5 kg diet and the percent ADI utilized is 38.98%.

Residue studies are adequate to support tolerances established for almonds, apricots, cherries, cranberries, cottonseed, filberts, grapes, nectarines, peaches, peanut hulls, pears, pecans, walnuts, milk, and the fat, meat, and meat-by-products of cattle, goats, hogs, horses, poultry, and sheep.

4. Summary of Regulatory Position and Rationale

Use, formulation, manufacturing process or geographical restrictions: None are required.

Unique precautionary statements, protective clothing requirements or reentry intervals: None required.

Risk/benefit review: None of the risk criteria set forth in Title 40 Code of Federal Regulations §162.11 have been exceeded by norflurazon.

Ground Water Potential: Because of the mobility and long half-life, norflurazon presents a potential for ground water contamination. The Ground Water Studies will be requested in an accelerated time frame. Due to the inadequate data base and since norflurazon to date has not been found in ground water, no interim restrictions were imposed. Any future decisions depend on the results of the required studies.

5. Summary of major data gaps and when these are due to be filled

Ground Water Studies:

- Hydrolysis, photodegradation and mobility are required within 6 months after receipt of the Guidance Package.
- Metabolism, soil and aquatic (sediment) dissipation are required within 2 years after receipt of the Guidance Package.
- Soil, long term dissipation is required within 4 years after receipt of the Guidance Package.

Short term studies required to be filled within 6 months after receipt of the Guidance Package:

- Product Chemistry: Description of manufacturing process, discussion of formation of impurities, analysis of product, density, dissociation constant, octanol/water partition coefficient, oxdizing or reducing action, explodability, pH and stability.

Honeybee acute contact.
Female rat metabolism.

Mutagagenicity studies for chromosomal aberation and other mechanisms of mutagenicity are required to be filled within 1 year after the receipt of the Guidance Package.

Long term studies required to be filled within 2 years after the receipt of the Guidance Package:

Rotational crops.
Plant and animal metabolism.
Analytical methods and stability of residues under storage.
Crop residues studies for soybeans, citrus, apples, plums, hops and peanuts.

6. Contact person at EPA

Richard F. Mountfort
Product Manager (23)
Environmental Protection Agency (TS-767C)
401 M Street S.W.
Washington, D.C. 20460
(703) 557-1830