Diflubenzuron
Decision Document

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I. Background

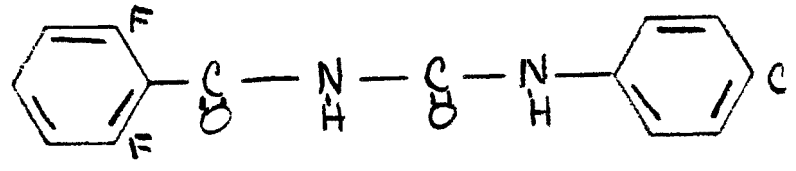
A. Chemical and Physical Characteristics

Diflubenzuron (N-[[(4-chlorophenyl)amino]carbonyl]-2 6-difluorobenzamide) is the common name for Dimilin^{R}, PH-6040^{R}, and TH-6040^{R}. It belongs to a new class of chemicals known as insect growth regulators. Diflubenzuron prevents insect growth by inhibiting the deposition of a chitin exoskeleton in insect larvae.

Some of diflubenzuron's physical characteristics are:

Melting point	210-230°C
Molecular Weight	210.7
Appearance	White crystals
Solubility	0.2 mg/liter in water
Partition Coefficient	> 50 (dichloromethane/H_2O)

The structure of diflubenzuron is:



B. Registered Uses, Production, and Tolerances

1. Registered Uses

The only registration for diflubenzuron in the United States is to control gypsy moths in hardwood forests. EPA issued this registration in 1976.

2. Production

Diflubenzuron is manufactured by Phillips-Duphar, B. V., in the Netherlands. It is imported into the United States and formulated as a 25% wettable powder by Thompson-Hayward Chemical Company. The amount of diflubenzuron produced and imported is a trade secret protected by Section 10 of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended.

3. Tolerances

The Agency has received three applications for the registration of diflubenzuron. The proposed uses are for controlling boll weevils on cotton; green cloverworms, velvetbean caterpillars, and Mexican bean beetles on soybeans; and mosquito larvae in temporary flood waters. Under the Federal Food, Drug, and Cosmetic Act (FFDCA), the Agency grants tolerances for the amount of the pesticide that may persist as residues on raw agricultural commodities, feed, and food. Accordingly, Thompson-Hayward has requested tolerances for two of the three registrations for which they have applied:

0.2 ppm in/on cottonseed

0.05 ppm in/on soybeans

0.05 ppm in/on meat, milk, eggs, and meat byproducts of cattle, goats, hogs, sheep, and fowl.

C. Fate in the Physical Environment

1. Soil

Diflubenzuron degrades in soil with a half-life in the range of 0.5 to 1 week for technical material pulverized to 2 micron (u) particles and applied at 1 ppm (Nimmo and de Wilde, 1975). Particle size and formulation appear to be critical factors in the rate of degradation in soil. The work of Nimmo and de Wilde (1973, 1974, 1975) indicates a ten-fold difference in degradation rates and persistence in the particle size, which ranges from 2 to 10 u, with the larger particles degrading at a slower rate. The initial products of soil degradation are 2,6-diflurobenzoic acid and 4-chlorophenyl urea, which degrade respectively to 2,6-diflurobenzamide and 4-chloroaniline.

Binding of diflubenzuron degradation products to soil increases with time. The half-life for the conversion of 4-chlorophenyl urea and 2,6-diflurobenzoic acid to the respective chloroaniline and benzamide was 2 to 3 weeks and 4 weeks, respectively (Nimmo and de Wilde, 1973, 1974, 1975). Information on the degradation rate of 4-chloroaniline in soil is not available, but it is presumed to degrade slowly.

Soil temperature affects the breakdown of diflubenzuron. In a report by Bull and Ivie (1978) there was a more rapid breakdown of diflubenzuron in the summer than in the cooler spring and fall. Winter residues of diflubenzuron were the most persistent. The data presented by Bull and Ivie indicate that approximately 16% of the previous year's diflubenzuron application would remain in the soil as carryover for the next growing season, presupposing the normal agricultural practice of plowing under crop stubble.

Diflubenzuron is a nonionic pesticide with low water solubility. It shows little mobility in organic soils (Carringer et al., 1975) and consequently has little potential to leach from the soils. Very little leaching of diflubenzuron can be expected to occur under normal field conditions. Helling (1975) observed that downward movement decreased as soil organic matter increased. Rieck (undated) found that the soil metabolite 4-chlorophenyl urea leached more rapidly than the parent compound.

Booth (undated) reported in Pesticide Petition 7F1898 that field application of diflubenzuron in a variety of aquatic environments resulted in residues in sediment ranging from less than 50 to 200 ppb. Single and multiple applications were made to both fresh and salt water ecosystems. About two-thirds of sediment samples showed no detectable residues (< 0.05 ppm).

Runoff of diflubenzuron and its metabolites is in part dependent on the organic matter content of the soil since diflubenzuron will bind into organic soil matter. Suspended sediment containing diflubenzuron and 4-chloroaniline could be expected to be found in the runoff. Carringer et al. (1975) reported a partition coefficient of 4000 between organic matter and water. Thus, for a soil containing 1% organic matter the overall coefficient will be 4000/100 or 40:1. This suggests that in typical river water where the suspended sediment represents only a small percentage of the total mass, the preponderance of the diflubenzuron will be in the water phase.

2. Water

Hydrolysis of diflubenzuron yields 4-chlorophenyl urea and 2,6-diflurobenzoic acid. Diflubenzuron is stable at neutral or mildly acidic pH levels with half-lives expected to exceed 2 weeks (Nimmo and DeWilde, 1975). Under alkaline conditions, tested up to pH 12, the half-life is reported as being under 2 weeks (Phillips-Duphar, December 8, 1975). Under field conditions diflubenzuron exhibited a half-life of 1 day in alkaline pastures whereas in neutral lake water (pH 7) the half-life was 10 to 15 days (Nimmo and deWilde, 1975).

1978). Residues were analyzed in rotational crops grown in soils receiving multiple applications of diflubenzuron. However, only very low levels (< 0.01 ppm wet weight) were found in various rotational crops following six to ten applications of diflubenzuron to cotton at a rate of 1 oz. per acre (Bull and Ivie, 1978).

Cottonseed was analyzed in two different studies after the plants had been sprayed with diflubenzuron. In a greenhouse study, leaves of cotton plants were sprayed three times with labeled diflubenzuron. After 45 days, radioactivity equal to 53 to 94 ppb diflubenzuron was found in the cottonseed. The authors, Mansager and Still (unpublished), attempted to extract and identify the radioactivity but were unsuccessful. However, they concluded that, since no extractable residue was released, the radioactivity was not due to diflubenzuron but to a contaminant (USDA/State, 1978). This study was not repeated.

A field study by Bull and Ivie (1978) also demonstrated low radioactive residues (< 0.01 ppm) in cottonseed. This study employed six to ten applications of labeled diflubenzuron. The authors made no attempt to identify the radioactive materials (USDA/State, 1978).

3. Photochemistry

Diflubenzuron was photochemically stable on leaf surfaces under natural sunlight (Bull and Ivie, 1978). In studies with soil and water mixtures, negligible degradation was measured under natural light (Phillips-Duphar, December 19, 1973; October 7, 1974).

D. Fate in the Biological Environment

1. Plants

Diflubenzuron applied to various types of plant leaves was neither absorbed into the plant nor degraded on the leaf surface (USDA/State, 1978). However, it appeared that diflubenzuron adsorbed onto the plant leaf surface within the initial 24 to 48 hours after application. Once the material was adhered to the leaf surface, only wind-abrasion, rain-washing, or the fall of senescent leaves moved the material into the soil. Only negligible amounts of diflubenzuron were measured, as total radioactivity, in leaves, stems, bolls, and other fruiting structures of the plant (USDA/State, 1978).

Uptake of diflubenzuron from soils has been measured in several plant species. Most of the material found, measured by total radioactivity, was in the aerial portions of the growing plants. Lesser amounts of diflubenzuron or its metabolites were found in the root structures (USDA/State,

EPA scientists have analyzed the residue data presented by Thompson-Hayward (Pesticide Petition 7F1898) and concluded that the use of diflubenzuron at 1 oz. per acre before cotton bolls open may lead to occasional trace residues of diflubenzuron on the undelinted cottonseed. However, the possible contaminative residues in delinted cottonseed and processed commodities derived from cottonseed would be below detectable levels of 0.05 ppm. They anticipated no detectable residues of diflubenzuron metabolites in either cottonseed or processed commodities from cottonseed (Hummel, 1976a).

2. Animals

This section is based on a review of the literature submitted by a USDA/State team in the report "Effects of Diflubenzuron (Dimilin^{R}) on Non-Target Avian and Aquatic Organisms and Its Fate in the Environment" (USDA/EPA/State, 1978), the USDA/EPA/State Assessment Team report "Potential Exposure of Diflubenzuron to Birds, Non-Target Aquatic Organisms and Humans" (USDA/EPA/State, 1978), and reports compiled by the Residue Chemistry Branch of the Office of Pesticide Programs on the data submitted by Thompson-Hayward (Pesticide Petition 7F1898).

a. Mammals

Metabolism studies with diflubenzuron have been performed in rats, cows, and sheep. Rats administered ^{14}C-labeled diflubenzuron excreted 70 to 95% of the dose in the urine and feces within 6 days of administration. Radioactivity remaining in the carcasses was quantified as 5% of the dose. No unmetabolized diflubenzuron was found in the urine. Metabolites identified were 2,6-diflurobenzoic acid and 4-chlorophenyl urea. Other compounds were present but were not characterized (USDA/State, 1978).

Diflubenzuron was metabolized and almost totally excreted by cows and sheep. About 0.2% of the dose fed to cows was found in their milk. Metabolites excreted by both species include 4-chlorophenyl urea; 2,6-difluorobenzamide; and 2,6-difluro-3-hydroxyl-diflubenzuron; 2,6-diflurobenzoic acid; and the glycerine conjugate of 2,6-difluorobenzoic acid (USDA/State, 1978).

Further studies on the metabolism of diflubenzuron indicated that microsomal activity may be responsible for the metabolism of the molecule. Labeled diflubenzuron

was metabolized by sheep liver microsomes into 2,6-difluro-benzoic acid, 2,6-diflurobenzamide, 4-chlorophenyl urea, 4-chloroacetanilide, 4-chloroaniline and the N,N-dimethyl derivative of 4-chloroaniline (USDA/State, 1978).

The Agency reviewed a 28-day feeding study in which 250, 5, 0.5 and 0.05 ppm diflubenzuron was fed to lactating dairy cattle. This study indicated that milk did not contain detectable residues of diflubenzuron except at the two highest feeding levels of 5 and 250 ppm. Diflubenzuron residues were measured as 0.013 and 0.22 ppm, respectively. At the lower feeding levels, 0.05 and 0.5 ppm, any diflubenzuron residues were below 0.3 and 1.4 ppb, respectively. In the only segment of the study designed to show decline levels, the 5 ppm dose, a withdrawal period of 4 days reduced any diflubenzuron levels below the detection limit, 1.6 ppb (Hummel, 1977b). Chromatographic analyses of the detectable residues in milk indicated that the residues found were not diflubenzuron. However, there was no indication of what metabolites were present (USDA/State, 1978).

Analyses of tissue extracts indicated that in the liver, the metabolite 2,6-diflurobenzoic acid was predominantly found, but diflubenzuron, 4-chlorophenyl urea, and 4-chloroaniline were also found. Residue levels,

expressed as the parent compound diflubenzuron, were measured at all feeding levels (Table I-1). A 7-day withdrawal period did not reduce the residues (Hummel, 1977b).

b. Poultry

White Leghorn and Plymouth Rock-Rhode Island Red Cross hens excreted 80-90% of the diflubenzuron administered to them within 3 days (Opdycke et al., 1976). From 0.3 to 0.8% of the dose was found in the eggs 12 days after treatment. Most of the labeled compound in these eggs was unmetabolized diflubenzuron. Tables I-2 and I-3 list the residues found in the hens and their eggs. Major diflubenzuron metabolites were 2,6-diflurobenzoic acid, 4-chlorophenyl urea, and 4-chloroaniline.

Additional studies cited in the USDA/EPA State report (USDA/EPA/State, 1978) also indicated that, in poultry, labeled diflubenzuron was secreted into the eggs and retained in muscle, liver, fat, and kidney tissue. In addition, the metabolite 4-chlorophenyl urea was identified in the eggs and kidney. Additional work with unlabeled diflubenzuron gave essentially similar findings and provided an indication that different strains of chickens differed somewhat in their ability to accumulate residues of diflubenzuron. Leghorn chickens accumulated diflubenzuron residues in eggs at twice the levels found in New Hampshire strain chickens.

Table I-1. Liver Residues of Diflubenzuron

Feeding Level (ppm)	Residues Found (ppm)
0.05	0.01
0.5	0.08
5.0	0.54
250.0	6.00

Table I-2. Total Activity Expressed as Diflubenzuron Found in Chickens.

Commodity	Feeding Level, ppm		
	0.05	0.5	5
Fat	0.0175	0.033	1.160
Kidney	0.0026	0.013	0.338
Liver	0.0026	0.044	0.453
Breast Muscle	0.0017	<0.005	0.054
Leg Muscle	0.0016	<0.005	0.099
Whole Egg	0.0029	0.100	0.833

Table I.3. Components of Diflubenzuron Expressed as 1% of Total Activity Ethyl Acetate Extractable

Commodity	Diflubenzuron	4-CPU	2,6-DFBA	Non-Extrable / Extractable (Not identified)
Fat	100	0	0	0 / 0
Leg Muscle	66.3	13	6.8	12.3 / 1.6
Breast Muscle	63.4	22.1	9.2	0 / 5.3
Liver	18.6	49.8	7.4	19.0 / 5.2
Kidney	23.8	40.0	0	36.2 / 0
Egg	68.8	11.2	3.7	16.3 / 0

c. Fish

Booth et al. (1976) studied the accumulation and fate of diflubenzuron in rainbow trout and bluegill sunfish in water treated with 1.0 ppm ^{14}C-labeled material. After 20 days, about 60% of the total radioactive residues in fish meat was 4-chloroaniline, 12 to 15% was difluobenzoic acid, and 1 to 5% was 4-chlorophenyl urea. Intact diflubenzuron comprised 1 to 2% of total meat residues. A rapid depletion of these residues was reported. Apperson et al. (1978) also reported accumulations of diflubenzuron with maximum residues of 355 ppb in white crappie from a lake treated with 5 ppb diflubenzuron.

The analysis of the residues found in the Booth study is reported in Table I-4. The data shows that fish (trout and bluegill) metabolize diflubenzuron to 4-chloroaniline. The unidentified component was material which did not migrate in the chromatography and was not further characterized (Hummel, 1976).

TABLE I-4. Residues of Diflubenzuron and Metabolites in Rainbow Trout and Bluegill Sunfish

Component	Percent of Extractable Residue					
	Rainbow Trout			Bluegill Sunfish		
	Water		Fish	Water		Fish
	Day 9	Day 20	Day 20	Day 9	Day 20	Day 20
Diflubenzuron	83	74	19	41	19	14
2,6-Difluorobenzoic acid	1	3	19	20	37	30
4-Chlorophenyl urea	1	4	16	10	23	7
4-Chloroaniline	15	17	29	29	16	21
Unidentified	0	2	17	0	5	28

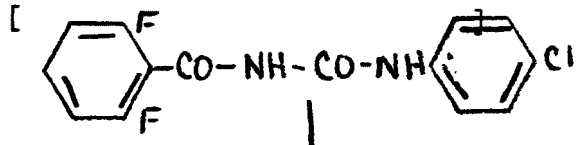
Table I-5 shows the general metabolic pathway for diflubenzuron in soil, water, plants, and animals. The pathway is common for the production of 4-chloroaniline and 2,6-diflurobenzoic acid in all situations (Opdyck et al., 1976; Philips-Duphar, December 1, 1975, and December 22, 1975; Booth et al., 1976; Bull and Ivie, 1978; and Nimmo and de Wilde, 1975). The metabolism beyond 4-chloroaniline was reported by Metcalf et al. (1975) in a model ecosystem, to include 4-chloroacetanilide and the 4-chloro-N,N-dimethyl-aniline. The production of 4-chlorophenyl hydroxylamine and 4-chloronitrobenzene in animals was theorized by O.R. Offringa of Phillips-Duphar in a statement filed by Thompson-Hayward Chemical Company (1977).

E. Residues

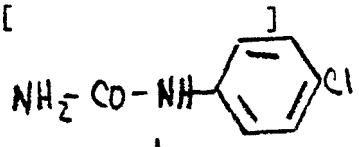
In order to estimate the potential levels of diflubenzuron which may be found in local rivers in treated areas, EPA researchers constructed a computer-simulated model of cotton and soybean fields to estimate the agricultural runoff from four applications of 4 or 3 or 2 or 1.5 oz. diflubenzuron/acre on cotton (Falco et al., 1979). Key assumptions in the simulation included: 1) all diflubenzuron was applied to cotton in late June and early July, and was degraded by October, 2) cotton grown in irrigated areas was not considered, even though the affected acreage is extensive,

Table I-5. Metabolic Pathway of Diflubenzuron

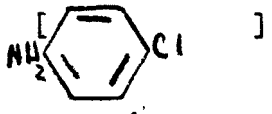
Diflubenzuron



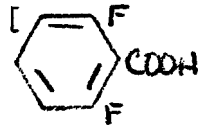
4-chlorphenyl urea



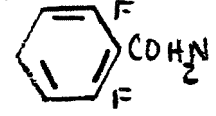
4-chloroaniline



2,6-diflurobenzoic acid

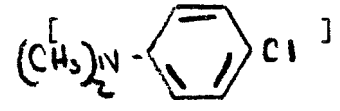


2,6-diflurobenzamide

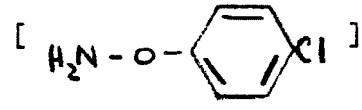


4-chloroacetanilide

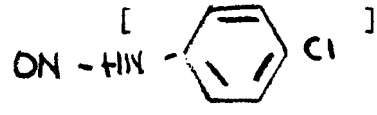
4-chloro-NN-dimethylaniline



4-chlorophenyl hydroxylamine (proposed)



4-chloronitroso benzene (proposed)



because the possibility of runoff from these areas is low, 3) rainfall was based on data for Beeville, Texas, 4) rainfall in Beeville, Texas, was representative of rainfall occurring throughout the cotton areas analyzed, 5) diflubenzuron is sprayed throughout a river basin on a simultaneous and uniform treatment schedule.

As a result of the assumptions used to make the model, it is likely that the predicted concentrations of diflubenzuron are too high and that the duration of the predicted concentrations is too short. However, the researchers estimated that the error would not exceed one order of magnitude.

Table I-6 shows the maximum diflubenzuron and 4-chloroaniline levels predicted at the mouths of the modeled rivers. Table I-7 shows the predicted average concentrations of diflubenzuron and 4-chloroaniline at the mouths of the modeled rivers during the summer months. Table I-8 shows the average summer concentration of diflubenzuron in sediment at the mouth of the modeled rivers.

EPA chemists reviewed the model and pointed out that the 4-chloroaniline levels predicted by the model probably were much less than actual levels to be expected because the model did not account for 4-chloroaniline formation in soil

TABLE I-6. Maximum Daily Diflubenzuron and 4-Chloroaniline Concentrations at the Mouth of Each River from Use on Cotton

Basin	Year	Diflubenzuron Concentration from Cotton Application ug/l	4-Chloroaniline Concentration from Cotton Application ug/l
Mississippi	1971	1.9	7.8
Atchafalaya	1971	2.2	18.5
Tombigbee	1972	0.22	0.85
Brazos	1974	3.7	11.9
Colorado	1971	13.8	22.0
Nueces	1975	25.0	3.3*
Rio Grande	1971	109.3	66.6

Note: These are the projected residues from four 1.5-oz. applications.

*Occurred in 1973.

Table I-7. Average Summer Concentrations of Diflubenzuron and 4-Chloroaniline at the Mouth of Each River from Use on Cotton

Basin	Year	Diflubenzuron Concentration ug/l	4-Chloroaniline Concentration ug/l
Mississippi	1971	0.20	0.94
	1972	0.09	0.41
	1973	0.11	0.49
	1974	0.06	0.26
	1975	0.05	0.20
Atchafalaya	1971	0.28	1.7
	1972	0.13	0.75
	1973	0.11	0.52
Tombigbee	1971	0.03	0.06
	1972	0.05	0.07
	1973	0.05	0.07
	1974	0.01	0.02
	1975	0.01	0.02
Brazos	1973	0.49	0.90
	1974	0.71	1.3
	1975	0.29	0.45
Colorado	1971	1.5	1.3
	1972	1.3	1.2
	1973	0.41	0.35
	1974	0.20	0.18
	1975	0.08	0.07
Nueces	1973	1.3	0.08
	1974	0.08	0.05
	1975	1.2	0.08
Rio Grande	1971	6.4	1.5
	1972	0.49	0.12
	1973	0.23	0.05
	1974	0.41	0.10
	1975	0.01	0.004

NOTE: These are the projected residues from four 1.5-oz. applications.

Table I-8. Average Summer Concentrations of Diflubenzuron in Sediment at the Mouth of Each River from Use on Cotton.

Basin	Year	Diflubenzuron Concentrations ug/gm
Mississippi	1971	0.39
	1972	0.17
	1973	0.21
	1974	0.12
	1975	0.09
Atchafalaya	1971	0.56
	1972	0.26
	1973	0.22
Tombigbee	1971	0.07
	1972	0.09
	1973	0.09
	1974	0.03
	1975	0.03
Brazos	1973	0.96
	1974	1.40
	1975	0.56
Colorado	1971	2.88
	1972	2.59
	1973	0.81
	1974	0.39
	1975	0.16
Nueces	1973	2.51
	1974	1.63
	1975	2.37
Rio Grande	1971	12.6
	1972	0.96
	1973	0.46
	1974	0.81
	1975	0.03

NOTE: These are the projected residues from four 1.5-oz. applications

before runoff (Collier and Severn, 1978). This 4-chloroaniline formed in the soil would be additive to the 4-chloroaniline formed in the water. The 4-chloroaniline values calculated are reported in Table I-9.

F. Regulatory History

1. Experimental Use Permits

The Agency issued an Experimental Use Permit (EUP) in 1976 to allow for efficacy testing of diflubenzuron on large plots of cotton. A temporary tolerance of 0.2 ppm on cottonseed was issued in conjunction with the EUP to permit the sale of the seed.

After the 1976 season was completed, the EUP lapsed and Thompson-Hayward requested an extension for the 1977 season. The Agency approved Thompson-Hayward's application for the 1977 season but stipulated that the seed could not be used for food because of adverse toxicological findings. In 1978, Thompson-Hayward once again applied for an extension of the EUP with a temporary tolerance. The Agency granted both the EUP and the tolerance after it performed a risk estimate which indicated that the use for which the permit was requested would not have a significant adverse effect on human health.

Table I-9. Predicted Levels of 4-Chloroaniline in Five Representative Rivers

River	Diflubenzuron* Conc, ug/l	4-Chloroaniline Conc. ug/l (calc)	4-Chloroaniline Range ug/l	Potential Ingestion ** exposure ug/yr
Mississippi	0.55	0.28	0.1-1	18-180
Atchafalaya	0.80	0.40	0.2-2	36-360
Tombigbee	0.28	0.14	0.05-0.5	9-90
Brazos	0.95	0.48	0.2-2	36-36
Colorado	3.2	1.6	0.5-5	90-900

*Highest average summer concentration of diflubenzuron predicted from four applications at 2 oz/acre for cotton and four applications at 1 oz/acre for soybeans.

**The potential ingestion exposure may then be calculated as follows (assuming that water treatment works have no effect on the 4-chloroaniline concentration):

0.1-1.0 ug/l 4-Chloroaniline x 21/day x 90 days per season = 18-180 ug/yr ingestion of 4-Chloroaniline. These data are included in the table.

c. Mosquito Control

The original registration filed by Thompson-Hayward indicated the possible accumulation of residues in fish and potable water (Pesticide Petitions 6H5130, 6F17731). Therefore, a tolerance was necessary for potable water and fish to allow residues in these items. EPA scientists concluded that the data did not provide a basis for the establishment of permanent tolerances for these major reasons: the tolerance must be addressed in terms of diflubenzuron and its metabolites for fish and potable water, the analytical methodology for enforcement of the tolerance is inadequate, further characterization of residues may be needed once levels of residue in fish meal are established, studies reflecting residues of diflubenzuron in additional fish and shellfish are needed, and data from processed food products derived from fish are needed (Hummel, 1976).

Thompson-Hayward subsequently submitted a version of the proposed revised label for diflubenzuron that eliminated the need for tolerances. The proposed label limits application to temporary rain pools; drainage ditches and lagoons from dairy, poultry, and swine-holding areas; overflow; and intermittently flooded sites associated with urban and residential areas. Aerial application of diflubenzuron

2. Registration and Tolerances

a. Cotton

Use of diflubenzuron on cotton requires a tolerance for residues on cotton seed. EPA scientists, in reviewing the data presented by Thompson-Hayward in Pesticide Petition 7F1898, concluded that diflubenzuron residues would not exceed the requested tolerance provided appropriate rotational crop restrictions and restrictions on grazing and feeding of treated foliage were placed on the product label. However, unresolved toxicological issues precluded granting the requested tolerance at the time of EPA's review of Thompson-Hayward's petition.

b. Soybeans

Diflubenzuron use on soybeans requires a tolerance for diflubenzuron residues in soybeans. The data submitted to EPA does not yet provide a basis for establishment of a tolerance because the issue of whether the diflubenzuron residues concentrate in soybean hulls and soapstock is unresolved. EPA has determined that the concentration of diflubenzuron in the hulls and soapstock requires a Feed Additive Tolerance. The registrant is questioning this conclusion. Consequently, until this issue is resolved, no further review will be conducted on this application.

is proposed. The EPA has notified Thompson-Hayward that deficiencies exist in the application which preclude issuance of a registration for this use (Gee, 1979). Data requirements include environmental fate of the diflubenzuron in water and sediment and efficacy data for the granular formulation. Labeling changes required by the Registration Division include removal of aerial application instructions. Consequently, as with soybeans, this use will not receive further review at this time.

d. Gypsy Moth

Diflubenzuron was registered to control gypsy moths in forests in 1976. This use is limited to application by State and Federal personnel. Currently, there are two separate programs designed to control the spread of the gypsy moth: an eradication program and a USDA control program. The Animal Plant Health Inspection Service (APHIS) uses diflubenzuron in an eradication program to control outbreaks of gypsy moth in geographical locales distinct from the original infestation. The Forest Service of USDA and state governments use diflubenzuron to control active infestations within the area of the original outbreak. This use, registered for forests only, will not be dealt with further until a Generic Standard is proposed for this chemical.

e. Douglas Fir Tussock Moth

The Forest Service of USDA had an experimental use permit (EUP) for diflubenzuron to control the Douglas Fir Tussock Moth, a pest of the Pacific Northwest forests. At present no application is on file with the Agency for this proposed use. Consequently, although diflubenzuron has a potential use for control of the Douglas Fir Tussock Moth, no decisions with respect to the registration of the compound for this use can be made in this document.

3. Referral for Rebuttable Presumption Against Registration

Diflubenzuron was referred to the Special Pesticide Review Divison for rebuttable presumption against registration review in October 1977 because the compound was suspected to cause tumors and chronic blood effects in humans (methemoglobinemia and sulfhemoglobinemia), testosterone depression in domestic animals, reproductive effects in birds (diminished egg production and reduced hatching), and effects to nontarget organisms (acute toxicity to crustaceans from direct application to water, and acute and chronic toxicity to crustaceans from runoff from treated fields (Campt, 1977)).

II. Risk Analysis

A. Chronic Effects

1. Oncogenicity

Thompson-Hayward Chemical Company presented two chronic feeding studies conducted by Huntingdon Laboratory in support of its application for the registration of diflubenzuron: "Effects of DU 112307 in Dietary Administration to Rats for 104 Weeks" (Huntingdon, 1976) and "Tumorigenicity of DU 112307 to Mice" (Huntingdon, 1977). These studies were reviewed by EPA's Carcinogen Assessment Group (CAG). CAG also considered in its cancer assessment a National Cancer Institute (NCI) chronic feeding study in which 4-chloroaniline, a metabolite of diflubenzuron found in mammalian systems, was administered to rats and mice.

CAG concluded that the Thompson-Hayward studies suffered from several severe deficiencies in design which greatly reduced their sensitivity with respect to the detection of a carcinogenic response. These deficiencies preclude any interpretation of the results of these studies as evidence of a negative response. In addition, CAG concluded, based on the diagnoses of several pathologists, that the Thompson-Hayward mouse study provides suggestive evidence of a carcinogenic response in lymphoreticular tissues.

Additional evidence that diflubenzuron may pose a carcinogenic risk to humans is provided by the NCI study on 4-chloroaniline in which an increase in mesenychymal tumors in the spleen of male rats and hemangiomatous tumors in mice appeared to be associated with the administration of the test compound. A more detailed discussion of these studies, their results, and their deficiencies is provided below. The source of this discussion is the CAG report on diflubenzuron (hereafter "CAG Report") (Albert, 1979).

a. Mouse Study - Oral (Thompson-Hayward)

Mice (CFLP) of known litter origin were randomly distributed according to body weight in five test groups of 52 males and 52 females in each group. Four mice were housed in each cage. The diet was powdered laboratory food mixed with the required amounts of diflubenzuron (DU 112307 batch P 7227). Dietary levels of 0, 4, 8, 16, and 50 ppm diflubenzuron were fed for 80 weeks to groups 1-5, respectively. All animals were examined daily for signs of ill health, toxicity, and behavioral changes. Food and water consumption were recorded. On completion of the treatment period, all the surviving mice were killed with CO_2. Gross pathology was done on all animals. All abnormalties were recorded including appearance and size. Microscopic examination was routinely performed on lymph

nodes (cervical and mesenteric), liver, spleen, ovaries, thyroid, adrenals, pituitary glands, and all macroscopically observed lesions suggestive of neoplasia. Blood and bone marrow smears were made.

(i) Results

A significant increase in lymphoreticular tumors (lymphosarcoma, reticulum cell sarcoma, myeloid leukemia) according to Fisher's exact test ($p=0.014$) was diagnosed originally by Huntingdon Laboratory in the group of female mice treated with 16 ppm diflubenzuron compared to controls. No significant increase of lymphoreticular tumors was found in any other treatment group of female mice or in any treatment group of male mice.

In addition, according to the Huntingdon Laboratory's original diagnosis, lymphosarcomas in female mice were found as early as 14 weeks in the 16 ppm treatment group, 6 and 37 weeks in the 50 ppm treatment groups, and 44 weeks in the control group. This suggests a carcinogenic response with a decrease in latency period as doses increase.

Huntingdon Laboratory reassessed the histopathology results for lymphoreticular tumors (Huntingdon, 1975) and presented results slightly different from those in its original submission. A comparison of the original diagnosis with the reassessment is summarized in Table II-1.

Dr. D. Goodman of Clement Associates performed an histopathologic evaluation of all slides from all female mice. Her conclusion was that diflubenzuron was noncarcinogenic in this study. However, according to her diagnoses, there was a significant increase of lymphoreticular tissues tumors in the 16 ppm group of female mice as compared to controls by Fisher's exact test ($p=0.035$).

Thompson-Hayward Chemical Company requested Clement Associates to convene an independent panel of pathologists to review the diagnosis of lymphoreticular tumors in the female mice from the Huntingdon study. The panel consisted of Drs. D. Goodman, R. Squire, S. Vesselinovitch, and A. Rogers.

The panel reviewed animal tissue from all female mice in all dose groups previously diagnosed by Huntingdon Laboratory as having hematopoietic tumors, plus all additional female mice from the 0, 16, and 50 ppm dose groups that were found to have hematopoietic tumors by either Dr. Goodman or Dr. Vesselinovitch. This panel concluded that there was no evidence of a carcinogenic effect in the lymphoreticular tissues from female mice in this study. However, according to their diagnoses, there was a significant increase of lymphoreticular tissue tumors in female mice dosed at the 16 ppm level as compared to controls by Fisher's exact test ($p=0.035$).

The first report indicated that the tissue in some cases had autolyzed and that a histopathological evaluation was not performed. Inexplicably, the second report included the histopathology for these tissues.

Table II-1

Total Number of Lymphoreticular Tissue Tumors in Male and Female Mice (Huntingdon Laboratory)

Groups	0 ppm	4 ppm	8 ppm	16 ppm	50 ppm
Original Diagnosis					
Males	8	3	6	9	5
Females	7	11	10	15 (p=0.019)	13
Revised Diagnosis					
Males	9	5	7	9	6
Females	9	10	12	15 (p=0.0577)	13

As can be seen, Huntingdon, in its reevaluation, changed its original finding of a significant increase by Fisher's exact test of lymphoreticular tumors in the 16 ppm treatment group, into an insignificant increase. Because of this revision, further review of microscopic slides from the study was done by several pathologists at the request of either the registrant or EPA.

Dr. N. Dubin, consultant to CAG, reviewed all available tissues from female mice in the 0, 16, and 50 ppm dose groups. He stated that there was no evidence for the carcinogenicity of diflubenzuron. However, according to his diagnoses there was a borderline response at 16 ppm (Fisher's exact test P=0.059).

A panel consisting of Drs. Werner Kirsten, James Varinman, and Diana Variakojis of the Department of Pathology at the University of Chicgo Medical School reviewed 31 related cases (approximately 300 slides) from the study. These cases were selected for either background baseline lesions (which had uniform positive or negative findings) or for confirmation of the presence (or absence) of lymphoreticular tumors where pathologists had not previously been able to completely agree. The diagnoses of Dr. Kirsten's panel, when combined with the unanimous findings of the other pathologists, demonstrated a significant response by Fisher's exact test in both the 16 and 50 ppm treatment groups. (P=0.0050 and P=0.04, respectively).

The data from all the pathological diagnoses other than those of the Kirsten panel are summarized in Table II-2. The Data from the Kirsten panel are summarized in Table II-3.

Table II-2. This table shows the incidence of lymphoreticular tumors in female mice and the statistical significance values by Fisher's exact test between control and respective treatment groups.

Diflubenzuron Dosage Group	Dr. I.N. Dubin	Clement Associates (Dr. Squire & Panel	Huntingdon Laboratory (original)	Huntingdon Laboratory (revised)	Dr. D. Goodman
0 ppm	12/49	8/49	7/49	9/49	8/49
16 ppm	18/43 p=0.0586	15/43 p=0.0345	15/143 p=0.0190	15/43 p=0.0578	15/43 p=0.0345
50 ppm	17/49 p=0.1751	10/49 p=0.3645	13/50 p=0.1117	13/50 p=0.2352	10/49 p=0.3645

Table II-3

Diflubenzuron Dosage Group	Dr. Kirsten's Group Positive for Lymphoreticular Tumors (a)	Previous Pathologists Unamimous for Lymphoreticular Tumors (b)	Total Positive Diagnoses Attributed Dr. Kirsten's Panel (c)
0 ppm	3/12	3/27	6/49
16 ppm	2/7	14/36	16/43 p=0.0050[d]
50 ppm (Dr. Kirsten only reviewed positive cases)	4/9	10/40 (Clement Assoc. Drs. Squire, Goodman, etc.) or	14/49 p=0.035[d] or
		10/41 (Dr. Dubin & Huntingdon)	14/50 p=0.0430[d]

a/ Slides were selected for review on the basis of conflicting diagnoses.
b/ Slide to which all pathologists agreed on positive diagnosis.
c/ Assuming that the Kirsten's panel would have agreed to the unanimous diagnosis of positive findings by pathologists listed in Table II-2.
d/ Statistically significant values were calculated according to Fisher's exact test.

(ii) Quality of the Study

The mouse study suffered from several severe deficiencies which greatly reduced its sensitivity for detecting a carcinogenic response. These deficiencies are discussed in detail in the CAG Report. Briefly summarized, these deficiencies are as follows:

1. There is no indication that the maximum tolerated dose (MTD) was used in this experiment. According to the National Cancer Institute Guidelines for Carcinogenic Bioassay in Small Rodents (Sontag et al., 1976), the MTD is defined as "the highest dose of the test agent given during the chronic study that can be predicted not to alter the animal's normal longevity from effects other than carcinogenicity." It is important that the MTD be used to maximize the ability to detect a carcinogenic response.

Several steps need to be taken in determining the MTD. One important step is to conduct a subchronic test on both sexes of the test animal to be used in the chronic study. The highest dose of the test agent to be used in the subchronic study should be the maximum dose which has not been demonstrated to cause toxic effects in properly conducted acute studies. According to these procedures Huntingdon Laboratory should have used doses possibly as high as 50,000 ppm in the diet on both sexes of mice in its

subchronic study. Instead, it used only male mice in the subchronic study and used a highest dose of only 50 ppm in the test. On this basis, it chose 50 ppm as the MTD to be used in the chronic study. If the subchronic study had been properly conducted, the MTD might have been demonstrated to be several orders of magnitude higher.

It appears that the Huntingdon Laboratory selected 50 ppm as the MTD for the chronic test because it observed foci of liver cell necrosis in three of eight male mice that received 50 ppm diflubenzuron for 6 weeks in the subchronic study. However, the fact that no liver necrosis was found in the mice administered 50 ppm over 80 weeks in the chronic study suggests that the liver lesions found in the subchronic study were not caused by the diflubenzuron, but rather had some other etiology. In addition, if several doses higher than 50 ppm had been administered in the subchronic study, an absence of liver necrosis at the higher dose levels would have demonstrated that the liver necrosis found at the 50 ppm level was not caused by the test agent.

It should be noted that two Thompson-Hayward consultants, Dr. Robert A. Squire and Dr. Jack L. Radomski, have questioned (Appendices II-1 and II-2) whether the MTD was used in this study. In fact, Dr. Radomski was of the

opinion that the highest dose used in the chronic study was substantially lower than the MTD.

2. Another deficiency of the mouse study is that only seven tissues (lymph nodes, spleen, liver, thyroid, ovaries, adrenal gland, and pituitary gland) were routinely examined microscopically. The NCI guidelines specify over 30 tissues and organs that should be routinely examined microscopically. Many of the organs not examined microsopically were examined macroscopically. However, this procedure alone is inadequate since many small tumors could have been missed. It should be noted that the lungs were excluded from routine microscopic examination even though this is frequently found to be a target tissue.

3. There is no indication in the report of the chronic mouse study that the doses of diflubenzuron administered to the mice were verified by chemical analysis of the diet of the treated mice during the course of the experiment. Thus, there is some question as to whether the mice were in fact administered the doses indicated in the report.

4. The experiment was of suboptimal length (80 weeks). The mice should have been administered diflubenzuron at least 104 weeks before sacrifice. If the study had been conducted longer, a greater number of tumors may have been observed.

b. Rat Study - Oral (Thompson-Hayward)

Sprague-Dawley rats of the CD strain (five groups) each composed of 45 female and 45 male rats constituted the main group for the carcinogenic study. The 15 male and 15 female rats which constituted the satellite group to the toxicity study were randomly distributed according to body weight into five test groups. Rats were housed five to a cage. Animal room temperature and humidity were controlled at $21^{\circ} \pm 2^{\circ}C$ and $50\% \pm .0\%$, respectively. Lighting was controlled to give 12 hours light and 12 hours dark per 24 hours. The diet was powdered laboratory food mixed with the designated amount of diflubenzuron (DU 112307). Dietary levels of 0, 10, 20, 40, and 160 ppm diflubenzuron were fed for 104 weeks. All rats were examined daily for signs of ill health, toxicity, and behavioral changes. Food and water consumption were recorded including utilization of the food.

All rats were examined macroscopically to determine the cause of death. Urine and blood were examined frequently. At termination, all surviving rats were killed by CO_2 asphyxiation. The microscopic examination was routinely performed on seven tissues (adrenals, thyroid, ovaries, liver, spleen, lymph nodes, and pituitary gland) and all macroscopically observed lesions suggestive of neoplasia. Blood smears were

(iii) Conclusions on the Mouse Study

Because the mouse study suffers from several severe deficiencies which make it insensitive for purposes of detecting an oncogenic response, it cannot, according to any interpretation of its results be considered valid evidence of a negative oncogenic response.

The study did provide suggestive evidence of a carcinogenic response. Most of the pathologists who reviewed the lymphoreticular slides from the female mice found a statistically significant increase in lymphoreticular tumors in the 16 ppm treatment group compared to controls by Fisher's exact test. If CAG had used the practice now common at NCI in multiple-dose experiments, of using the Bonferroni upper bound as a significant level for a single dose comparison, only the Kirsten panel diagnoses would have provided statistically significant results. The Bonferroni upper bound is the normal significance level divided by the number of dosage levels. However, CAG has not followed the approach of using the Bonferroni procedure with Fisher's exact test since this procedure tends to mask weak carcinogenic responses. Furthermore, the Agency concludes that the more conservative approach of not using the Bonferroni correction in evaluating an insensitive and poorly conducted study such as this one is especially justified.

also routinely made. Abnormalities detected on the blood smear were confirmed by examination of bone marrow sections.

(i) Results

No significant difference was found in the control versus experimental groups for any type of tumor.

(ii) Quality of the Study

As was the case with the mouse study, the rat study suffered from several severe deficiencies which made it incapable of detecting a carcinogenic response. The discussion of these deficiencies, from the CAG Report, is summarized as follows:

1. There is no indication that the maximum tolerated dose (MTD) was used in this study. The definition of the MTD, the importance of using the MTD to maximize the ability to detect a carcinogenic response, and the appropriate method of determinining the MTD have already been discussed. In the subchronic study to determine the MTD, the highest dose of diflubenzuron in the diet was only 200 ppm. Based on the results of preliminary acute toxicity studies, doses possibly as high as 50,000 ppm diflubenzuron in the diet should have been used. If much higher doses had been used in the subchronic study, it is possible that the MTD would have been determined to be much higher than 160 ppm, the highest dose used in the chronic study.

It appears that Huntingdon Laboratory selected 160 ppm as the MTD for the chronic test because it observed "piecemeal" necrosis of the hepatocytes in rats of both sexes administered 50 and 200 ppm diflubenzuron in the subchronic study (Phillips-Duphar, B.V., 1973b). However, independent evaluations of liver slides from this study by Drs. A.J. Newman and C.A. van der Heyden (Phillips-Duphar) did not confirm these findings. Moreover, no liver necrosis was reported among any of the experimental groups in the 104-week chronic study.

The registrant has suggested that the presence of methemoglobinemia in rats treated with 160 ppm diflubenzuron in the chronic study is evidence that the MTD was used in that study. However, the level of methemoglobinemia found in the 160 ppm group was not significantly different from the level found in the controls. Furthermore, even if it had been significantly different, this fact could not have been used as a basis for determining the MTD since a life-shortening toxic effect must be found in the subchronic study. The methemoglobinemia was found only in the chronic study and was not established to shorter life.

Two Thompson-Hayward consultants, Robert A. Squire and Jack I. Radomski, have questioned whether the MTD was used in this study (Appendices II-1 and II-2).

(iii) Conclusions on the Rat Study

This study is not valid in view of the defects discussed above. Thus, the Agency is precluded from using the results of this study as evidence of the oncogenic potential of diflubenzuron.

c. 4-Chloroaniline - (Oral study in rats and mice) (NCI)

A bioassay testing for the possible carcinogenicity of 4-chloroaniline was conducted by the NCI bioassay program using Fischer 344 rats and B6C3F1 mice. The NCI camera-ready report of this bioassay was reviewed by CAG and the summary of the report was accepted by CAG as an accurate interpretation of the results (NCI, unpublished). The NCI summary is presented in its entirety below:

> P-Chloroaniline was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. Twenty animals of each sex and species were placed on test as controls. The high and low dietary concentrations of p-chloroaniline were, respectively, 500 and 250 ppm for rats and 5000 and 2500 ppm for mice. The compound was administered in the diet for 78 weeks, followed by an observation period of 24 weeks for rats and 13 weeks for mice.
>
> There were no significant positive associations between the dietary concentrations of p-chloroaniline administered and mortality in female rats or in mice of either sex; however, there was a significant positive association between concentration and mortality in male rats. Adequate numbers of animals in all groups survived sufficiently long to be at risk from

2. Another severe deficiency in this study is that only seven tissues were routinely examined microscopically in spite of the fact that the NCI guidelines specify over 30 tissues and organs which should be so examined. As a consequence, many small tumors could have been missed in the other tissues and organs, which were examined only macroscopically.

3. The strain of rats used was not suitable for this experiment for two reasons. First, the female control rats had an unusually high incidence of tumors (91-98%). Second, the survival rate for all groups of rats, including the controls, was very low. Terminal percent survival (e.g. percentage of animals living through the term of the experiment) for male and female rats ranged from only 14% to 36% and was only 21% and 36% in male and female controls, respectively.

Both of these factors (high spontaneous tumor rate and lower terminal survival) make it very difficult to detect an oncogenic response.

4. The report of the results of the chronic rat studies did not indicate that the doses of diflubenzuron were verified by chemical analysis of the diet of the treated rats during the course of the experiment.

late-developing tumors. Mean body weight depression, in relation to controls, was observed in high dose female rats and dosed mice of both sexes, indicating that the concentrations of p-chloroaniline administered to these animals may have approximated the maximum tolerated concentrations. Although splenic lesions were observed in male rats, no mean body weight depression relative to controls was associated with administration of p-chloroaniline to the animals. Therefore, it is possible that these animals may have been able to tolerate a higher dietary concentration of the compound.

The only neoplastic lesions found that might be related to administration of the compound were mesenchymal tumors in the spleens of male rats and hemangiomatous tumors in mice. In male rats, there was significant positive association between compound administration and the incidences of fibroma or fibrosarcoma of the spleen. The incidences of these tumors were not significantly elevated when compared to those in control rats, but the rarity of these tumors in male Fischer 344 rats (0/360 in historical male control rats in this laboratory) strongly suggests a chemically related effect. In adddition, three sarcomas of other types were found in high dose male rats. In mice of both sexes, hemangiomas and hemangiosarcomas were found at elevated incidences, when compared to control mice, in the spleen, liver, kidney, and multiple body sites. The increased incidences in dosed mice were statiscally related to dose but were not statistically significant when compared directly to matched control animals. In comparison to historical control data, the incidences of hemangiomatous tumors in the dosed mice were elevated, but not greatly. The evidence was considered insufficient to conclusively relate the hemangiomatous tumors in mice to compound administration. Nonneoplastic proliferative and chronic inflammatory lesions were also found in the spleens of dosed rats and mice.

and sarcomas in the spleens of male rats was considered strongly suggestive of carcinogenicity because of the rarity of these tumors in the spleens of control rats. Hemangiomatous tumors in dosed mice may also have been associated with administration of p-chloroaniline. However, it is concluded that, under the conditions of this bioassay, sufficient evidence was not found to establish the carcinogenicity of p-chloroaniline for Fischer 344 rats or B6C3F1 mice.

d. Overall Conclusion on the Carcinogenic Risk of Diflubenzuron

The rat study suffered such severe deficiencies that the data cannot be used to determine whether or not diflubenzuron is an oncogen. Because of the invalidity of this study and the deficiencies of the mouse study, the Agency is not able to fully assess the oncogenic potential of diflubenzuron. However, the Agency has determined that the increase of lymphoreticular tumors in female mice in the 16 ppm dosage group was suggestive of a positive effect. These results were used to estimate the risk resulting from diflubenzuron use on cotton that is developed in the following section.

In addition, the NCI study provides strongly suggestive evidence of the oncogenicity of 4-chloroaniline, a metabolite of diflubenzuron, that has been identified in mammalian systems, plants, soil, and water.

2. Methemoglobinemia and Sulfhemoglobinemia

Methemoglobinemia and sulfhemoglobinemia are impairments of the oxygen transport capability of the blood. The formation of methemoglobin is reversible in adults, but is not known to be reversible in children. The formation of sulfhemoglobin is not known to be reversible in either adults or children. Therefore, methemoglobinemia in children and sulfhemoglobinemia will persist until the affected red blood cells are replaced by red blood cells subsequently manufactured by the body.

Methemoglobinemia has been demonstrated after inhalation, oral, and dermal exposure to diflubenzuron in rats, mice, rabbits, and sheep. Sulfhemoglobinemia was demonstrated only after oral exposure of diflubenzuron to rabbits and rats. A study using beagle dogs was negative for both methemoglobinemia and sulfhemoglobinemia.

Table II-4 summarizes the results of these studies. Methemoglobinemia and sulfhemoglobinemia were detected in rabbits orally administratered 19.2 mg/kg diflubenzuron. A no-observed-effect level (NOEL) was not demonstrated in the rabbit. In rats, methemoglobinemia was detected at a dietary dosage level of 40

Table II-4. Methemoglobinemia Formation

Test Aminal	Sex	Report No.	Dosage	Result
			Oral Exposure	
Mice	M	56645	10,000 mg/kg (Gastric Intubation)	Me Hb detected
Rabbit	M	56645/2/77	19.2 mg/kg (Dietary)	Su Hb detected Me Hb
Rabbit	M	56645/13/77	4640 mg/kg (Gastric)	Me Hb detected
Sheep	M/F	229/77226	20 mg/kg 100 mg/kg 400 mg/kg (Dietary)	Me Hb detected 100 mg/kg
Rats	M	56645/15/77	5000 mg/kg (Gastric Intubation)	Me Hb and Su Hb
Rats	M/F	243/77208	40 mg/kg 200 mg/kg 1000 mg/kg 5000 mg/kg (Dietary)	Me Hb detected in Male all levels Me Hb detected in female at 200 mg/kg level or higher
Beagle Dog	M/F	169/74157	0.41 mg/kg 0.84 mg/kg 1.64 mg/kg 6.24 mg/kg (Dietary)	No Me Hb detected
			Inhalation Exposure	
Rat	M/F	197/741013	0.1 mg/L 0.8 mg/L 1.85 mg/L	Me Hb all levels
			Dermal Exposure	
Rabbit	M/F	200/7485	69 mg/Kg 150 mg/kg 320 mg/kg	Me Hb detected all levels both sexes
Rabbit	M/F	146/73845	170 mg/kg 425 mg/kg	Me Hb detected all levels both sexes
Rabbit	M	56645/2/77	1050 mg/kg	Me Hb detected

mg/kg, the lowest level tested. A response was not demonstrated at dietary dose levels from 0.41 to 6.24 mg/kg in the beagle dog. Thus, an NOEL was not shown in either the dermal or inhalation tests in rats and rabbits. As a matter of policy, the Agency bases its risk assessments on the most sensitive species tested, which in this case appears to be the rabbit.

The causative agent for methemoglobinemia and sulfhemoglobinemia is believed to be 4-chlorophenylhydroxylamine, a metabolite of diflubenzuron. Identification of 4-chlorophenylhydroxylamine was made in Phillips-Duphar study 56654/8/77 (Phillips-Duphur BV, 1977). In this study rats developed methemoglobinemia after dietary exposure to diflubenzuron. Analysis of the urine revealed 4-chloroaniline and its N-oxidation product 4-chlorophenylhydroxylamine. N-Hydroxylamines are known to be potent agents for induction of methemoglobinemia.

A similar mechanism is believed to be responsible for the induction of sulfhemoglobinemia. The major difference between methemoglobinemia and sulfhemoglobinemia is that in sulfhemoglobinemia a permanent change in the chemical structure results.

In summary, while studies are available to demonstrate that diflubenzuron induces methemoglobinemia

and sulfhemoglobinemia in test animals, the studies did not demonstrate NOEL's. The Agency must have studies conducted in the most sensitive species and with a demonstrated NOEL in order to fully evaluate the effect of methemoglobinemia and sulfhemoglobinemia.

3. Mutagenicity

a. Ames Test

This test is the best validated test for the correlation between mutagenicity and carcinogenicity. Diflubenzuron and its metabolites have been tested in a full or partial Ames battery of Salmonella typhimurium strains by a number of different laboratories with varying protocols and results. Seuferer (December 1977 thesis) reported 2,6-diflurobenzoic acid as a base-pair and frame-shift mutagen in all strains. This is in conflict with the results of Litton and Dorough (1977). Several other diflubenzuron metabolites including 4-chloroaniline were considered slightly mutagenic.

Litton Bionetics [proprietary data, Thompson Hayward] performed an Ames test with negative results on diflubenzuron. However, 4-chloroaniline was found to be mutagenic.

Dorough (1977) [proprietary data, Thompson-Hayward], used the TA-1537 and TA-98 strains of bacteria.

He did not find activity with diflubenzuron but did obtain positive dose-response results for 4-chloroaniline in Strain TA-98 with metabolic activation. Subsequently, he tested diflubenzuron more extensively in the entire Ames tester set using the spot test. It also included a Salmonella typhimurium bacteria repair test with strain TA-1978. These were also negative. Other metabolites tested were negative (MacGregor et al., 1979).

b. Other Studies

Negative results in mutagenicity studies on diflubenzuron were obtained in the following: yeast (Saccharomyces), a mouse micronucleous test, unscheduled DNA synthesis in mammalian cells, and the dominant-lethal test [proprietary data, Thompson-Hayward].

In summary, diflubenzuron is not mutagenic in the Ames test. This result was confirmed in a number of laboratories. Other mutagenicity tests performed do not meet the multi-test criteria. Diflubenzuron is a halogenated compound. This class of compound correlates poorly in terms of mutagenicity/carcinogenicity test results. A metabolite, 4-chloroaniline, is mutagenic in the Ames test. However, this one positive finding is not sufficient to declare that the metabolite poses a mutagenic potential.

4. Hormonal Effects

The Agency has reviewed several papers and summary reports dealing with the effect of diflubenzuron on testosterone levels in avians and animals. Most of this work (two reported studies) was done at the USDA's Veterinary and Toxicological Entomology Research Laboratory in College Station, Texas. One additional study was conducted by the USDA at the Poultry Research Laboratory, Beltsville, Maryland.

The Texas studies were judged invalid by the USDA investigator for technical reasons. An EPA team of scientists reviewing these studies agreed with the assessment of the USDA investigator (Chitlik and Biscardi, 1979). The Beltsville study shows a trend of decreasing testosterone levels with diflubenzuron treatment. This result was not statistically significant.

EPA has recently completed a study to determine the effect of diflubenzuron on testosterone levels in the rat. Preliminary results have been received, but until a validation of the entire study can be completed, no conclusions can be made.

B. Nontarget Effects

1. Aquatic Invertebrates

Effects to nontarget organisms constitute a major concern of the Agency. The projected use patterns and registered use patterns of diflubenzuron could impact significantly on the life-cycles of nontarget organisms which come in contact with diflubenzuron through the use of habitats common to areas of diflubenzuron use or diflubenzuron runoff. The Agency reviewed the area of potential significant adverse effects for nontarget exposure to aquatic invertebrates including estuarine crustaceans.

Data available to EPA indicated that diflubenzuron has acute and chronic effects on several aquatic invertebrates. The effects on specific organisms are listed in Table II-5. These data clearly indicate that diflubenzuron, in laboratory situations, is toxic at extremely low levels to aquatic invertebrates. The aquatic species at risk are located primarily in estuaries and other areas in the coastal zone.

Tables II-6 and II-7 compare the levels of diflubenzuron exposure resulting in toxic effects in various aquatic species with the levels of diflubenzuron predicted by the Athens Environmental Research Laboratory model to occur at the mouths of certain rivers. These tables

Table II-5

Effects of Diflubenzuron Upon Aquatic Invertebrates

Acute Effects

Organism	Effect Level
Daphnia (water flea)	1.5 ppb LC_{50}
Gammarus (sand flea)	30-45 ppb LC_{50}
Eulimnadia (clam shrimp)	0.15 ppb LC_{50}
Triops (tadpole shrimp)	>0.75 ppb LC_{50}
Mysidopsis (mysid shrimp)	2.0 ppb LC_{50}
Artemia (brine shrimp)	10 ppb LC_{50}

SubAcute or Chronic Reproductive Effects

	Test Duration	Effect Level
Mysid shrimp	27 days	0.2 - 0.6 ppb
Grass shrimp	35 days	0.45 ppb
Blue Crab	6-18 days	0.50 ppb
Daphnia	42 days	0.61 ppb
March Crab	20-30 days	1.0 ppb
Brine Shrimp	80 days	2.0 ppb

Table II-6. Mean Summer Concentrations of Diflubenzuron at the Mouth of Selected Rivers From Applications To Cotton* And the Nontarget Aquatic Invertebrates Likely to Be Exposed

Basin	Year	Mean Diflubenzuron Conc. For Cotton Application (ppb)	Nontarget Aquatice Effects (Lowest Effect Level) Mysid Shrimp >0.2 ppb	Grass Shrimp >0.45 ppb	Blue Crab >0.5 ppb	Marsh Crab >1.0 ppb	Brine Shrimp >2.0 ppb
Mississippi	1971	0.40	X				
	1972	0.17					
	1973	0.22	X				
	1974	0.12					
	1975	0.09					
Atachafalaya	1971	0.57	X	X	X		
	1972	0.26	X				
	1973	0.23	X				
Tombigbee	1971	0.07					
	1972	0.09					
	1973	0.09					
	1974	0.03					
	1975	0.02					
Brazos	1973	0.98	X	X	X		
	1974	1.43	X	X	X	X	
	1975	0.57	X	X	X		
Colorado	1971	2.93	X	X	X	X	X
	1972	2.63	X	X	X	X	X
	1973	0.83	X	X	X		
	1974	0.40	X				
	1975	0.17					
Nueces	1973	2.55	X	X	X	X	X
	1974	1.65	X	X	X	X	
	1975	2.40	X	X	X	X	X

* Total amount applied to cotton is 12 oz. AI/A/season (Note that operational use would call for 6 applications at 2 oz./application but the EPA model used 4 applications at 3 oz./application for predicting concentrations in water).

Table II-7. Mean Summer Concentrations of Diflubenzuron at the Mouth of Selected Rivers From Applications To Cotton* And the Nontarget Aquatic Invertebrates Likely to Be Exposed

Basin	Year	Mean Diflubenzuron Conc. For Cotton & Soybean Application (ppb)	Nontarget Aquatice Effects (Lowest Effect Level) Mysid Shrimp >0.2 ppb	Grass Shrimp >0.45 ppb	Blue Crab >0.5 ppb	Marsh Crab >1.0 ppb	Brine Shrimp >2.0 ppb
Mississippi	1971	0.20	X				
	1972	0.09					
	1973	0.11					
	1974	0.06					
	1975	0.045					
Atachafalaya	1971	0.28	X				
	1972	0.13					
	1973	0.11					
Tombigbee	1971	0.035					
	1972	0.045					
	1973	0.045					
	1974	0.015					
	1975	0.01					
Brazos	1973	0.49	X	X			
	1974	0.71	X	X	X		
	1975	0.29	X				
Colorado	1971	1.46	X	X	X	X	
	1972	1.31	X	X	X	X	
	1973	0.41	X				
	1974	0.20	X				
	1975	0.08					
Nueces	1973	1.28	X	X	X	X	
	1974	0.82	X	X	X		
	1975	1.20	X	X	X	X	

*Total amount applied to cotton is 6 oz. ai/A/season (Note that the operational use of Dimilin would call for 6 applications at 1 oz. ai/A but the EPA model used 4 applications at 1.5 oz./application for predicting concentrations in water).

indicate that diflubenzuron runoff may affect several important species at the maximum use rates on the proposed label for cotton (e.g., a maximum of 12 oz. per season for cotton).

At a lower use rate of 6 oz. per season for cotton, the potential for reproductive and acute effects is reduced. The data indicate that the effluent in the southeastern rivers has a lower hazard potential to aquatic invertebrates than the effluent in the southwestern rivers. The data also indicate that among the threatened species are economically important crustaceans and aquatic invertebrates which are environmentally important as indicator organisms. However, there is little field data available to confirm or deny the results predicted in the model.

2. Avian Reproductive Effects

A study performed on bobwhite quail by Cannon Laboratories was submitted by Thompson-Hayward. An initial review by the Agency indicated that at dietary levels of 10 ppm and 40 ppm lowered fertility and decreased egg production and hatchability resulted.

This study was again reviewed by the Agency after referral to SPRD. The Agency scientists who conducted this review concluded that the adverse effects observed were artifacts of the improper methodology of the study.

Flaws included improper male:female ratios and lighting which invalidated the data generated. The registrant has subsequently submitted other studies on bobwhite quail which did not demonstrate adverse reproductive effects at feeding levels up to 250 ppm. They also submitted reports of field studies of diflubenzuron treatments which did not show any adverse effects on wild avians (Tucker and Rabert, 1978).

C. Exposure

1. Dietary Exposure

In developing the exposure profiles, a "worst case" situation was assumed in which residues on cottonseed, meat, milk, poultry, and eggs were projected to approach levels as high as the minimum sensitivity of the analytical enforcement method (0.05 ppm), or the tolerance level. It was also assumed that all cottonseed products were derived from diflubenzuron-treated crops. The typical human diet contains about 0.15% cottonseed products according to the Lehman food factor (Table II-8). On the basis of these assumptions, it was estimated that the direct consumption of cottonseed products will result in a worst case dietary intake of diflubenzurón of 0.00000188 mg/kg/day.

Under worst case exposure of cattle to cottonseed from treated crops, the levels of diflubenzuron expected in milk and edible tissues are predicted to be in the

Table II-8. Human Dietary Intake of Diflubenzuron Residues[a/]

Human Food Source	Proposed Tolerance (ppm)	Percentage of a Diet	Projected maximum residue present (mg/kg)	Specific commodity intake (kg food/ (60 kg person[c/])	Maximum difl. intake (mg dif/ 60 kg person/day	Maximum difl intake (mg/dif/kg body weight/day)
Cottonseed	0.2	0.15	0.05	0.00225	0.00011250	0.00000188
Meats, red [b/]	0.05	10.81	0.00001	0.16215	0.00000162	0.00000003
Milk and dairy products	0.05	28.62	0.000008	0.4293	0.00000340	0.00000006
Poultry	0.05	2.94	0.001	0.0441	0.00004410	0.00000074
Eggs	0.05	2.77	0.001	0.04155	0.00004155	0.00000069
				Total	0.00020317	0.00000340

[a]Estimates from Lehman, (1962).

[b]Average "residue for edible tissues of red meat producing animals

[c]Based on 1.5 kg food intake/day/60 kg person.

subparts per billion range. Data generated in studies performed by Smith and Merricks using radio-labeled diflubenzuron projected that residues of diflubenzuron and its metabolites were in the 8×10^{-7} ppm range for milk and 8.6×10^{-4} ppm range for liver. A study by Miller using unlabeled diflubenzuron gave values of 2×10^{-7} ppm for milk and 7.5×10^{-7} ppm for the liver.

The maximum calculated residue in the eggs and edible tissue of poultry fed cottonseed from treated crops falls within the 4.5×10^{-5} ppm range for eggs and 3×10^{-5} to 6×10^{-4} ppm range for the edible tissues.

The likelihood of fish accumulating significant residues of diflubenzuron is thought to be quite low. It is possible that, through runoff, drift, or a combination thereof, water concentrations of diflubenzuron as high as 0.001 ppm might, on occasion, be sustained over a period of at least a few days. If such were the case, residues in fish meat might reach levels approaching 0.05 ppm, assuming a biomagnification of 50 times (Aperson et al., 1978; Booth et al., 1976; Schaefer et al., 1978). Although fish are capable of limited biomagnification of diflubenzuron from water, appreciable water contamination from the cotton use should be infrequent, since diflubenzuron is not highly persistent in water (Schaefer and Dupras, 1976). Fish are

also capable of rapidly depleting residues of diflubenzuron from the body once exposure to the compound is terminated (Booth et al., 1976; Schaefer et al., 1978). Thus, the potential for significant human dietary exposure to diflubenzuron via residues in fish would appear to be slight.

Using the proposed tolerance values for cotton, the "worst case" of the total dietary exposure to diflubenzuron is estimated to be 3.40×10^{-6} mg/kg body weight for a 60-kg person. The contributions of the individual food items are listed in Table II-8.

These dietary exposure levels reflect the normal human adult average daily diet.

2. Mixer-Loader, Applicator, and Bystander Exposure

The exposure levels projected for mixer-loaders for ground spray applications, mixer-loaders for aerial applications, pilots, boom-spray drivers and bystanders are reported in Table II-9 for the cotton use. The key assumptions utilized in calculating exposure are listed below.

1) Mixer-loaders will receive their primary exposure by contact with dust.
2) No flagman will be utilized in the spray operations.

Table II-9. Lifetime Exposure and Cancer Risk to Various Groups Exposed to Diflubenzuron from Use on Cotton

Worker Group	Number Exposed	Days/year Exposed	Dose mg/day	Dose mg/kg/year	Lifetime Avg. Dose (ppm) in Diet	Lifetime Probability of Tumors Due to Diflubenzuron	Expected Tumor per Year Due to Diflubenzuron
1) Mixer Loader (Aerial)	440	42					
Dermal			26.5	18.55	1.16	1.99×10^{-2}	.125
Inhalation			.31	.217	1.4×10^{-2}	2.41×10^{-4}	.002
Total			26.81	18.77	1.17	2.01×10^{-2}	.127
2) Mixer Loader (Tractor Boom Spray)	1540	10					
Dermal			26.5	4.42	.277	4.76×10^{-3}	.105
Inhalation			.31	5.17×10^{-2}	3.24×10^{-3}	5.57×10^{-5}	1.23×10^{-3}
Total			26.81	4.47	.280	4.82×10^{-3}	106
3) Pilots	440	42					
Dermal			.08	.056	3.5×10^{-3}	6.01×10^{-5}	3.8×10^{-4}
Inhalation			.005	.004	2.5×10^{-4}	3.44×10^{-6}	2.16×10^{-5}
Total			.085	.060	3.75×1^{-3}	6.35×10^{-5}	4.02×10^{-4}
4) Tractor Drawn Boom Applicators	1540	10					
Dermal			5.6	.933	.058	9.96×10^{-4}	.022
Inhalation			.03	.005	.0003	5.15×10^{-6}	1.13×10^{-4}
Total			5.63	.938	.0583	1.00×10^{-3}	2.21×10^{-2}
5) Area Residents (Distance from Sprayed Area)							
0-25 meters.	6875	9	.64	.096	1.05×10^{-2}	1.80×10^{-4}	1.77×10^{-2}
26-45 meters	6875	9	.33	.050	5.48×10^{-3}	9.41×10^{-5}	9.21×10^{-3}
46-96 meters	6875	9	.15	.023	2.52×10^{-3}	4.33×10^{-5}	4.26×10^{-3}

Levels	
Total Risk from Application Aerial Applicators	2.01×10^{-2}
	6.35×10^{-5}
	2.01×10^{-5}

Levels	
Total Risk from Application Ground Applicators	4.82×10^{-3}
	1.00×10^{-3}
	5.82×10^{-3}

	Ground	Aerial	By-standers
Total Risk including	5.82×10^{-3}	2.01×10^{-2}	1.80×10^{-4}
	2.6×10^{-6}	2.6×10^{-6}	2.6×10^{-6}
	5.82×10^{-3}	2.01×10^{-2}	1.82×10^{-4}

3) All spray areas will be posted to minimize exposure to bystanders.

4) Exposure via ground application will be similar to that described by Wolfe (1961) for dinoseb.

D. Risk Calculations

1. Oncogenicity

The Interim Cancer Guidelines state that when a chemical is judged to be a potential human carcinogen, the Agency will estimate its possible impact on public health at anticipated levels of exposure. These guidelines also recognize that the available techniques for assessing the magnitude of cancer risk to human populations based on animal data are at best very crude. This is due, among other causes, to uncertainties in the extrapolation of dose-response data to very low dose levels and to differences in levels of susceptibility of animals and humans. Accordingly, the risk estimates are neither scientific certainties nor absolute upper limits, but are used by the Agency only as rough approximations of potential health risks.

a. Dietary

The risk levels were predicted from the one-hit model using the proportion of tumors in the controls

and that in the 16 ppm dose group. This equation is expressed below.

$$B = \log n [(1-PX) - (1-P0)]D^{1/}$$

$$B = \log n [(1-15/43)/(1-7/49)]/16$$

$$= 1.718 \times 10^{-2}$$

The slope of the one-hit model, (B, or 1.718×10^{-2}), is used to calculate lifetime probability (P) of a tumor caused by diflubenzuron. This is shown below:

$$P = Bx$$

$$(1.718 \times 10^{-2})x$$

where x is the average equivalent exposure of diflubenzuron in the diet.[2/]

1/ B = slope
logn = natural logaritham
Po = mice with tumors in the control group
Px = mice with tumors in the treated group
D = dose

2/ Another method of conducting a conservative extrapolation is to follow the approach suggested by Ian Nesbit in the Clement Associates submission. He fitted a linear model to all the data points and obtained a slope of .11 with an estimated 99% confidence bound on the slope equal to .6. However, it appears that a numerical error was made in the estimation of the confidence limit. The correct estimate for the confidence interval of the slope would be .85. Using this value, the risk would be about one-half that found by the CAG for all exposure situations.

The dietary risks were determined from the dietary exposure after adjusting mg/kg to ppm in the diet. The calculated values are shown in Table 11-10. Lifetime dietary exposure was assumed in making these calculations. The risk resulting from consumption of diflubenzuron-treated cottonseed, meat, milk, poultry, and eggs exceeds 2.6×10^{-6}. This represents roughly 2.6 tumors per million people exposed to diflubenzuron for a lifetime.

b. Applicators and Bystanders

The oncogenic risk for these groups was calculated from the exposure levels projected in Table II-9. The risk estimates are also provided in Table II-9. Conversion from mg/kg/year to equivalent ppm in the diet is expressed in the equation below:

$$x = \frac{(60\ \text{kg})}{(365\ \text{days})} \frac{u3/}{(70\ \text{years})} \frac{(40\ \text{years})}{(1.5\ \text{kg})}$$

$$= 6.26 \times 10^{-6}\ u$$

$$= \frac{\text{per lifetime diflubenzuron}}{\text{mg kg food eaten per lifetime}}$$

where x is the ppm in the diet and u is the mg/kg/year. The 40 years refers to work history and 70 years is the lifespan. This equation assumes a 40-year exposure for workers. For bystanders, a 70-year exposure is assumed.

3/ U = mg/kg/year

The oncogenic risk to applicators from the mixing and loading of diflubenzuron and the oncogenic risk to bystanders for cotton programs are shown in Table II-9. For the use on cotton the oncogenic risk to the mixer-loader in aerial applications and ground applications is 2.01 x 10^{-2} and 4.82 x 10^{-3}, respectively. This means that, assuming a 40-year occupational exposure, the number of tumors produced from exposure to diflubenzuron in the respective groups is two per 100 for aerial application personnel and five per 1,000 for ground application personnel. The pilots and tractor drivers would have risk levels of 6.35 x 10^{-5} and 9.96 x 10^{-4} or roughly six tumors per 100,000 pilots and one per 1,000 tractor drivers for a 40-year exposure. If any of these personnel perform both functions (e.g., mixing-loading and applying the pesticide), the risks produced from each increment would be additive. In all cases the applicator risk is additive to the dietary risk.

The highest projected risk is to mixer-loaders, with the majority of the risk coming from dermal exposure. The risk from inhalation is approximately one or two orders of magnitude below the risk from dermal exposure.

Bystanders in the cotton areas are assumed to include workers in other fields as well as people living

nearby. It was assumed that they would not be protected in any special manner other than by wearing standard clothing common to field workers and farm families. It was also assumed that they would be exposed for a lifetime of 70 years.

2. Methemoglobinemia and Sulfhemoglobinemia

No-observed-effect levels (NOEL's) for methemoglobenemia and sulfhemoglobinemia have not been established for certain species of animals including the rabbit. However, the lowest daily doses causing observed effects in all of these species were considerably greater than the anticipated exposure to humans from the diet or pesticide application. In studies on other animals, such as beagle dogs, where NOEL's were demonstrated, these levels were also greater than the theoretical exposure to humans.

The Agency has concluded that these studies do not raise significant concern about the potential for adverse effects on humans exposed to diflubenzuron. However, further study of the relationship between diflubenzuron exposure and methemoglobinemia and sulfhemoglobinemia is necessary before the risk to humans can be fully evaluated.

3. Hormonal Effect

The studies performed with avians at VTERL were not valid. The Beltsville study data showed a trend of

decreased testosterone levels, but this trend was not statistically significant. The study in rats done by EPA cannot be used as a measure of effects until the entire report is reviewed and validated. Thus, the data on hormonal effects which have been reviewed do not raise significant concerns about the potential for adverse effects on humans exposed to diflubenzuron.

4. Non-Target Effects

The risks to nontarget organisms posed through use of diflubenzuron on cotton are qualitatively addressed in Tables II-6 and II-7. These risks impact several species of aquatic invertebrates. However, since the exposure levels used in determining risks are based on a model which has not been validated by field studies, there is no certainty as to the actual levels of diflubenzuron to which nontarget organisms may be exposed. In the model, there was a significant trend towards reduction of hazard with reduction of diflubenzuron usage. The data indicate that the use of 12 oz. of diflubenzuron (A.I.) per season per acre results in a linear increase over the use of 6 oz. in the number of species subjected to hazardous levels of the compound and in the frequency of adverse effects occurring over a 5-year span. The use of diflubenzuron, if limited to 6 oz. per acre per season, may well represent a tolerable

risk. A small number of aquatic species may be significantly affected even at this application rate. However, the Agency does not have sufficient data on the extent to which diflubenzuron runoff into bodies of water occurs to make any definite risk assessments.

III. Benefits

This section discusses the benefits of the proposed use of diflubenzuron to control bollweevils on cotton. This analysis is based on the "Preliminary Biological and Economic Assessment of Diflubenzuron" which was prepared by an Assessment Team composed of scientists and economists from EPA, the U.S. Department of Agriculture, and cooperating State agencies and land-grant universities. In order to assess the benefits of the proposed use of diflubenzuron on cotton, the Assessment Team had to estimate the range of diflubenzuron use, the frequencies and rates of application, the restrictions that might be placed on its use, and the cost. Most assumptions are based on expert opinion and reflect the best information available.

A. Biological Assessment

The boll weevil (Anthonomus grandis) infests two-thirds of the cotton belt, i.e., the eastern two-thirds of the Southwest region, the Delta region, and the Southeast

region. The Southwest region includes Texas and Oklahoma; the Delta region consists of Missouri, Arkansas, Tennessee, Mississippi, Louisiana, and Kentucky; and the Southeast region is comprised of Virginia, North Carolina, South Carolina, Georgia, Florida, and Alabama.

The boll weevil is an insect causing extensive damage to cotton in the areas listed above. A total of 7.3 million acres of cotton are infested with boll weevils. These insects lay their eggs in cotton squares, which become food sources for the immature weevil. Under favorable weather conditions, weevil populations can increase 2.5 times a week. Dry weather may drastically reduce this rate of increase.

The bollworm-budworm complex (Heliothis zea and H. virescens) also causes very extensive damage to cotton in the area defined. Other pests include thrips, aphids, cutworms, plant bugs, fleahoppers, and spider mites.

Cotton is currently treated at frequent intervals from early spring to late summer to control both boll weevils and the bollworm-budworm complex. The insecticides used for control are predominantly organophosphorous compounds.

Diflubenzuron does not kill adult boll weevils but inhibits egg hatching and interferes with the growth of the weevil larvae by inhibiting enzymes necessary

for the synthesis of chitin. Unlike currently used insecticides, diflubenzuron controls boll weevils without significantly reducing the populations of most of the natural parasites and predators of cotton pests. The boll weevil appears early in the season at the pinhead-square stage of development of the cotton. Therefore, in order to control the boll weevil, pesticide application must begin early in the season. On the other hand, use of pesticides to control the bollworm-budworm complex does not begin until mid-season, when these pests first become a problem. Diflubenzuron which does not kill the bollworm-budworm complex, assists in its control because it does not kill its natural predators and parasites. In contrast, the organophosphate pesticide regime currently used for cotton insect control destroys the predators and parasites which attack the bollworm-budworm complex. Therefore, greater quantities of pesticides are required to control the bollworm-budworm complex when alternative pesticides are used to control the boll weevil than when diflubenzuron is used.

Predators and parasites of cotton pests include big-eyed bugs (Geocoris spp.), lady beetles (Hippodamia spp.), damsel bugs (Nubis spp.), and green lacewings (Chrysopa spp.). Under natural conditions, these insects frequently hold bollworm-budworm populations below

economic loss thresholds early in the season. Thus, if populations of these beneficial species can be preserved, initial treatments of conventional insecticides for control of the bollworm-budworm complex can be delayed. However, the data available from field trials with diflubenzuron do not conclusively show that predators and parasites will keep bollworm-budworm populations below economic thresholds.

B. Economic Assessment

This economic analysis compares two insecticide regimes: that which is currently used, and a combination of diflubenzuron and currently-used insecticides. This analysis is separated into a discussion of the benefits of the use of diflubenzuron by individual farmers in boll weevil control, and the impact of its use in the APHIS program to eradicate boll weevils. The savings in control costs realized when diflubenzuron is used represents the measure of the benefit of the compound.

1. Boll Weevil Control

Because diflubenzuron is not currently registered for use on cotton, several assumptions had to be made to perform this analysis. These assumptions follow:

- Six 1-oz. applications of diflubenzuron would be applied at 5- to 7-day intervals beginnning when pinhead squares appear

on the plant and terminating no later than when the bolls opened.

- Diflubenzuron will cost $3.00 per ounce.
- The Farm Enterprise Data Systems (FEDS)[1/] budgets represent the cost of controlling all cotton pests with currently-used insecticides.

Because alternative pesticides are less expensive and approximately as efficacious as diflubenzuron, economists estimated that diflubenzuron could probably be used only where fields are infested by both boll weevils and the bollworm-budworm complex and where current control costs are high, i.e., $45 or more per acre according to the FEDS data. The extent of the acreage where these conditions exist is given in Table III-1, Column 3. The average cost for control of all insects is listed in Column 4 by FEDS area. These figures were obtained by increasing the 1975 costs, the most recent available, by a composite inflation factor derived from fourteen leading economic indicators. This average cost includes the price of controlling spider mites, thrips, leafhoppers, and other cotton pests, as well as boll weevils and the bollworm-budworm complex.

1/ FEDS is a system of budgets and cost-estimating procedures operated by the Economic Research Service of USDA in cooperation with Oklahoma State University. It provides production cost estimates and projections.

Table III-1. Representative Boll Weevil and Heliothis Control Costs for the Currently-Used Insecticide Regime and the Diflubenzuron Regime

Region and State	FEDS Area	Acreage in Area (1,000 Acres)	Control Costs With Currently Used Insecticides: All Insects[b]	Boll Weevil and Heliothis[c]	Weevils[d]	Heliothis[e]	Value of Natural Predators[f]	Cost of Heliothis Control in the Diflubenzuron Regime[g]	Cost of Weevil and Heliothis Control in Diflubenzuron Regime[h]	Savings from Use of Diflubenzuron Regime: Per acre[i]	Feasible Acreage (1,000 acres)	Aggregate ($1,000)
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)
			(Dollars/Acres)									
Southeast												
Alabama	100-200	81.1	50.84	41.94	18	23.94	7.66	16.28	42.68	0	—	0
	500	67.0	48.24	39.80	18	21.80	6.98	14.82	41.22	0	—	0
Georgia	400	75.7	92.24	90.12	30	60.12	18.04	42.08	71.48	18.64	75.7	1,411.0
	500	57.3	80.89	79.03	30	49.03	14.71	34.32	63.72	15.31	57.3	877.3
North Carolina	All	56.0	85.74	61.74	21	40.00	8.00	32.00	61.40	0.32	56.0	17.9
South Carolina	100	47.4	54.73	49.80	18	28.80	1.15	27.65	54.65	0	—	0
	200	45.7	101.97	92.79	21	71.79.	2.87	68.92	95.95	0	—	0
Total		430.2									189.0	2,306.2
Delta												
Lousiana	100	289.0	65.00	58.18	15	43.18	16.41	26.77	54.67	3.51	289.0	1,014.4
Mississippi	100	712.5	68.29	62.14	15	47.14	22.16	24.98	54.38	7.76	712.5	5,529.0
Total		1,001.5									1,001.5	6,543.4
Southwest												
Texas	600	55.5	46.62	41.96	24	17.96	10.78	7.18	38.08	3.88	55.5	215.3
	600	55.9	53.46	53.46	24	29.46	17.68	11.78	38.78	14.68	55.9	820.6
Total		111.4									111.	
TOTAL		1,543.1									1,301.9	9,885.5

a/ USDA, ERS, Firm Enterprise Data System, prepared in cooperation with Oklahoma State University, Stillwater, Oklahoma, 1975. All costs have been inflated to 1977 price levels.
b/ Includes spidermites, thrips, leaf hoppers, etc. in addition to boll weevils and the bollworm-budworm complex.
c/ Cost of currently used insecticides regime. Calculated by subtracting control costs for all insects except boll weevils and the bollworm-budworm complex from Column 4. The cost of controlling the other insects was obtained from the Assessment Team survey.
d/ Costs of insecticide, oil carrier, and application.
e/ Column 5 minus boll weevil control costs.
f/ Data from the Assessment Team Survey.
g/ Column 7 minus Column 8
h/ Column 9 plus the cost of diflubenzuron to control boll weevils.
i/ Column 5 minus Column 10.

Source: USDA/EPA/State Assessment Report

The occurrence of insects other than the boll weevil and the bollworm-budworm complex would make the use of diflubenzuron impractical since organophosphates would be needed to control these insects.

The Assessment Team conducted a survey to determine the number of acres in which the simultaneous infestation of boll weevils and insects other than the bollworm-budworm complex would occur. Column 5 shows the current cost of controlling cotton pests when these acres are eliminated from consideration.

Applying organophosphates to control the boll weevil costs $3.00 per treatment. This cost was multiplied by the number of applications the survey showed was needed in each region to generate the cost of controlling boll weevils (Column 6). This figure was subtracted from the cost of controlling boll weevils and the bollworm-budworm complex (Column 5) to give the cost of controlling the bollworm-budworm complex with the current insecticide regime (Column 7).

The Assessment Team used this survey to estimate where natural predators surviving diflubenzuron treatments would be able to control bollworm-budworm populations. The "Value of Natural Predators" (Column 8) shows the savings in the cost of organophosphate insecticides used to

control the bollworm-budworm complex that would accrue when diflubenzuron is used for boll weevil control. Values in Column 8 were subtracted from the cost of bollworm-budworm complex control using conventional insecticides (Column 7) to give the cost of bollworm-budworm complex control in the diflubenzuron regime (Column 9).

The cost of six diflubenzuron applications was added to the cost of controlling the bollworm-budworm complex, found in Column 9, to give the total cost of treating cotton with insecticides when diflubenzuron is used (Column 10). When the diflubenzuron regime was more expensive than currently used insecticides, a zero was entered in the column.

"Feasible Acreage" (Column 12) represents those areas where diflubenzuron is less expensive than its alternatives. The feasible acreage was multiplied by the savings per acre to give the aggregate savings (Column 13). Analysts identified 1.3 million acres where the diflubenzuron regime for suppression of boll weevil populations and control of the bollworm-budworm complex would be used because it is more cost-efficient than the current insecticide regime (Column 12). These 1.3 million acres are approximately 18% of the cotton fields that are infested with boll weevils, or 18% of the Southeast, 27% of the Delta, and 2% of the Southwest.

The total decrease in insect control costs for all regions is roughly estimated at $9.9 million. Most of this savings ($6.5 milion) would go to growers in the Delta, with smaller portions realized by growers in the Southeast ($2.3 million) and in the Southwest ($1.0 million). The weighted average of the savings per acre was $7.80. In areas where diflubenzuron is likely to be used, the average savings per acre ranged from $0.32 in North Carolina to $18.64 in Georgia.

The Assessment Team did not associate use of diflubenzuron with changes in crop yield. A number of entomologists from cooperating State agencies and land grant universities, however, believe that cotton yields would increase because a reduction in the amount of organophosphate insecticide used would allow the crop to mature earlier, and beneficial insects would provide greater control of the resistant strain of tobacco budworm.

2. Boll Weevil Eradication (APHIS)

USDA's Animal and Plant Health Inspection Service (APHIS) is investigating the technical and economic feasibility of instituting a national boll weevil eradication program (USDA/EPA/State, 1978). They are now conducting a trial eradication program in North Carolina. If a complete beltwide eradication program is initiated, it will begin in

this eastern area and gradually extend to contiguous affected areas.

The currently proposed eradication technology integrates chemical, biological, and agricultural control measures. Specifically, it contains the following elements: destruction of the source of food supply for boll weevils by defoliation and stalk destruction, use of pheromone traps, release of sterile boll weevils, and use of determinant strains of cotton.

USDA has proposed the use of diflubenzuron to augment the present eradication strategy. Diflubenzuron, through its specific mode of action, augments the effects from the release of sterile insects in the eradication program; that is, it does not kill mature adults, but rather, inhibits the synthesis of chitin, which disrupts body wall formation and causes larval death. At the same time, it helps minimize flair-up in the bollworm-budworm problem because the natural enemies of the bollworm-budworm complex are not eliminated as they are with the use of conventional insecticides. It is predicted that there could be substantial cost savings in the eradication program if diflubenzuron is utilized as the primary element of control.

IV. Risk/Benefit Analysis of Alternative Courses of Action

A. Introduction

The foregoing review analyzes and summarizes information on the risks and benefits of the use of diflubenzuron on cotton. This section presents the basis for the Agency's development of regulatory options, identifies the options selected for consideration, and discusses the risks and benefits of each of these options.

B. Basis for the Development of Regulatory Options

The Administrator may register a pesticide only if he has first determined that its use will not pose an unreasonable risk to man or the environment. This determination must be made for each proposed use of a pesticide and must take into account the risks and benefits associated with each use. Even if the Administrator determines that a pesticide will pose an unreasonable risk if used as proposed, before denying registration he must consider whether prescribing any restrictions on the pesticide's use will sufficiently reduce the risks to warrant registration.

It is therefore apparent that the Administrator must consider a spectrum of regulatory options for each use of a pesticide. Approval of registration with no added restriction and denial of registration are the regulatory options at opposite ends of this spectrum. Between these end points are options the Administrator may consider which

approve registration but with prescribed restrictions and conditions designed to reduce risks. For example, the Administrator may specify the permissible sites for use, the directions for use, the labeling language, and may require that the pesticide be used by certified applicators only.

Under special circumstances, the Administrator may conditionally register a pesticide when the full complement of data required for full registration under Section 3(c)(5) has not been submitted. The conditional registration provision of FIFRA which is applicable to diflubenzuron is Section 3(c)(7)(B) of FIFRA as amended in 1978. Diflubenzuron falls within the purview of Section 3(c)(7)(B) because it is currently registered for use as a pesticide to control gypsy moths. This Section provides that the Administrator may conditionally register additional uses of a currently registered pesticide if he determines: first, that the applicant has submitted satisfactory data pertaining to the proposed additional use, and second, that the conditional registration of the additional use will not significantly increase the risk of any unreasonable adverse effect on the environment. The conditional registration of the new use is not permitted if the Administrator has issued a notice stating that the pesticide or any of its ingredients meets or exceeds the risk criteria enumerated in 40 CFR 162.11 for human dietary exposure or if the additional use of the

pesticide involves a major food or feed crop or a minor food or feed crop where an effective alternative pesticide which does not meet or exceed the risk criteria is available.

If the Administrator makes these determinations and grants conditional registration, the registrant is required to generate and submit data required for full registration within the time required by Section 3(c)(7)(B), or if such time requirements are inapplicable, in the time specified by the Administrator. Furthermore, the Administrator may impose other terms and conditions that he deems appropriate. For example, the Administrator may provide for the automatic termination of the conditional registration after passage of a specific interval of time or if data generated after conditional registration has been granted indicate that the risks caused by the registration are significantly greater than initially anticipated. In addition, restrictions on the use and method of application of the pesticide may be imposed.

If the Administrator determines that the registrant has failed to take appropriate steps toward fulfilling any condition imposed, or that a condition has not been met within the period prescribed for satisfying such a condition, the Administrator shall issue a notice of intent to cancel the conditional registration.

C. Alternative Pesticides

The weighing of regulatory options includes a consideration of the risks and benefits of the alternative pesticides that are available for use. Alternative pesticides currently used on cotton are, in descending order of predominance of use, methyl parathion, a combination of toxaphene and methyl parathion, azinphosmethyl (Guthion), monocrotophos (Azodrin), and EPN. Table IV-1 summarizes the toxicological hazards and the environmental effects of these compounds. Methyl parathion and the combination of toxaphene and methyl parathion, the most prevalently used pesticides for the control of cotton pests, have a very high acute toxicity for humans and are very toxic to fish, birds, and bees. The other pesticides currently in use also have a high acute toxicity for humans and also pose extremely high hazards to various nontarget species.

Toxaphene is currently under RPAR review for oncogenicity. The administration of toxaphene to two mouse strains resulted in a statistically significant increase in the incidence of hepatocarcinomas in both male and female animals. A study with rats provided suggestive evidence for the increased incidence of thyroid tumors with toxaphene treatment. In addition, toxaphene has been shown to be far more toxic to aquatic species than diflubenzuron and is

Table IV-1. Alternate Chemicals for Cotton

Pesticide	RPAR Candidate	ADI mg/kg/day	Acute Toxicity Category	Environmental Effects	Chemical Class	Use Rate Frequency
Methyl Parathion	No	0.001	Highly Toxic	Very Toxic to Fish, Birds, and Bees	Organo-phosphate	1-2 lbs. AI/A 4-5 days
Toxaphene (with Methyl Parathion)	Yes	0.001	Highly Toxic	Very Toxic to Fish, Birds, and Aquatic Inverte-brates	Organo-chlorine	3 lbs. AI/A Weekly intervals
Azinphosmethyl	No	0.0025	Highly Toxic	Very Toxic to Fish and Aquatic Invertebrates	Organo-phosphate	0.25 lb. AI/A as needed
Monocrotophos	No	0.0003	Highly Toxic	Very Toxic to Birds, Aquatic Invertebrates, and Bees	Organo-phosphate	0.75 lb. AI/A as needed
EPN	Yes	None	Highly Toxic	Very Toxic to Fish and Aquatic Invertebrates	Organo-phosphate	1 lb. AI/A 5 days
Malathion	No	0.02	Moderately Toxic	Very Toxic to Fish, Aquatic Invertebrates, and Bees	Organo-phosphate	1 lb. AI/A as needed
Diflubenzuron	Yes	None	Slightly Toxic	Very Toxic to Aquatic Inver-tebrates	Organo-chlorine	0.06 lb. AI/A 5-7 days

apparently far more persistent than diflubenzuron. The only other alternative chemical currently under review in the RPAR process is EPN, which has been shown to cause delayed neurotoxic effects.

As shown in Table IV-1, the application rates for the most predominantly used chemicals, i.e., methyl parathion and the combination of toxaphene and methyl parathion, are much higher than those for diflubenzuron. The remaining alternative chemicals have application rates ranging from 1/4 pound/acre for azinphosmethyl to 1 pound/acre for EPN. There is no restriction on the number of applications per season for these six alternatives; a minimum of six applications per season is generally required to obtain control.

The proposed application rate for diflubenzuron is 1 oz./acre with a maximum of six applications per season to control boll weevils on cotton. Thus, the use of diflubenzuron to replace methyl parathion, the combination of methyl parathion and toxaphene, and the other alternatives which have higher application rates, will achieve a significant reduction in the total poundage of pesticides used in cotton pest control. Most significantly, the use of diflubenzuron to replace toxaphene will substantially diminish the oncogenic hazard attributed to toxaphene for the human population at risk.

D. Regulatory Options Selected

From the range of possible conditions of registration, the Agency has formulated three regulatory options for consideration in making the decision regarding registration. In order of increasing restrictiveness, the options selected are:

1) Conditionally register diflubenzuron until January 1, 1984, under the condition that required studies are submitted by January 1, 1983.

2) Conditionally register diflubenzuron until January 1, 1984, with the data requirements set forth in Option 1 and restrictions on use.

3) Deny the application for the registration of diflubenzuron on cotton.

Granting full ("unconditional") registration of diflubenzuron on cotton was not selected as an option because some of the data supporting the petition for registration are not sufficient to meet the Agency's requirements for full registration under Section 3(c)(5) and therefore do not warrant a balancing of the risks and benefits resulting from long-term use. Specifically, the chronic feeding studies submitted by the registrant suffer from severe deficiencies in design which preclude a long-term risk assessment. The Agency has also concluded that insufficient data exist for

determining the long-term hazard to humans from methemoglobinemia and sulfhemoglobinemia and the long-term hazard to aquatic species that might result from runoff of diflubenzuron into streams, rivers, estuaries, and other water bodies. Finally, the Agency has determined that field studies substantiating the efficacy and benefits of diflubenzuron are necessary before a long-term risk/benefit analysis can be performed.

Under both options of conditional registration, the Agency would require that more studies be submitted by January 1, 1983. These include additional chronic feeding studies in rats and mice, studies establishing NOEL's for methemoglobinemia and sulfhemoglobinemia in an appropriate species, monitoring data on the runoff of diflubenzuron and its breakdown products, and field studies on the benefits of diflubenzuron. Such field studies should confirm the measurable benefit of diflubenzuron from an increase in crop yield or a decrease in the costs of controlling Heliothis spp. In addition, the registrant would be required to develop a method for formulating the pesticide that would reduce exposure to applicators. Finally, the Agency may require the generation and submission of any other data it determines are necessary to meet the requirements for full registration.

Under Option 2 the following restrictions would be imposed.

1) Diflubenzuron would be classified for restricted use by certified applicators only.

2) Applicators would be required to wear protective clothing and respirators while mixing, loading, and applying diflubenzuron.

3) Application of diflubenzuron would be prohibited in the coastal zone of the Gulf States.

4) Application of diflubenzuron near any person or dwelling would be prohibited. Use of flagmen in the field would be prohibited.

5) Workers would be prohibited from entering treated fields until the day following application and the spray deposit has dried.

6) Use of diflubenzuron would be limited to six 1-oz. applications/acre per season.

Under Option 2, the Agency could impose any other restrictions on use which it determines are necessary to prevent a significant increase in the risk of any unreasonable adverse effects during the period of conditional registration.

E. Impact of Regulatory Options

1. Option 1. Conditionally register diflubenzuron for use on cotton until January 1, 1984, under the condition that required studies are submitted.

Choosing Option 1 would indicate that the Agency had reached the following conclusions: first, the data

pertaining to the use of diflubenzuron on cotton is satisfactory for purposes of assessing the risks and benefits resulting from this use over a period of four growing seasons; second, conditional registration for this period would not significantly increase the risk of unreasonable adverse effects on humans or the environment; and third, granting conditional registration of diflubenzuron would be in the public interest.

There is considerable uncertainty as to whether diflubenzuron is an oncogen. Section II of this document contains a "worst case" risk assessment of the oncogenicity of diflubenzuron that is based on the available data. This assessment shows that the risks to the general population from a lifetime exposure (70 years) to the compound would be slight. The risk from using diflubenzuron for four growing seasons would be decreased proportionately.

There is also uncertainty concerning the risks of methemoglobinemia and sulfhemoglobinemia. Although an NOEL for this effect has not been established for some of the species of laboratory animals tested, the NOEL's available and the lowest daily doses causing observed effects in all species studied were considerably greater than the anticipated exposure to humans. Thus, the Agency has concluded that the available studies on methemoglobinemia and sulfhemoglobinemia do not raise significant concern about the potential for

adverse effects to humans exposed to diflubenzuron. However, further study of these effects is necessary before the risks to humans can be fully evaluated.

Conditionally registering diflubenzuron for use on cotton will result in some hazard to certain aquatic invertebrates from diflubenzuron runoff. Monitoring studies on the runoff of diflubenzuron and its metabolites, particularly in areas of high usage and the Gulf States, are necessary before the Agency can complete its assessment of risk.

Although use of diflubenzuron on cotton would pose some risks, conditionally registering it would reduce the overall risks posed by pesticides used on cotton. Specifically, diflubenzuron would replace other pesticides used to control boll weevils such as the organophosphates and toxaphene, which appear to pose substantially greater risks to man and the environment. Organophosphates are much more acutely toxic to man and substantially more toxic to aquatic species than diflubenzuron. NCI and CAG have determined that toxpahene is a carcinogen. It is much more toxic to aquatic species and more persistent in the environment. Furthermore, the risks, as stated above, are compounded by the fact that the application rates of the alternates are much higher than the diflubenzuron application rate. It is anticipated that the overall risks would be reduced by the fact that diflubenzuron's use for boll

weevil control will leave the populations of the beneficial insects intact, thereby reducing the amount of organophosphate pesticides required to control the bollworm-budworm complex.

Choosing Option 1 may also result in substantial economic benefits. As noted previously, diflubenzuron does not kill the natural predators of the bollworm-budworm complex. Therefore, use of diflubenzuron for boll weevil control instead of other pesticides that do kill natural predators would reduce the amount of pesticides used to control the bollworm-budworm complex. This reduction in pesticide use could result in an overall saving of up to $10 million a year for cotton growers.

Additional significant economic benefits may be realized if diflubenzuron is used in the boll weevil eradication program.

2. Option 2. Conditionally register diflubenzuron until January 1, 1984, with the same data requirements set forth in Option 1 and restrictions on use.

Choosing this option would indicate that the Agency had reached the conclusions described under Option 1 regarding the adequacy of the data, the level of risk, and the serving of the public interest, providing that the specified restrictions were imposed.

The risks and benefits of this option are the same as those for Option 1 except as modified by restrictions. These restrictions and their impacts are described below.

a) Classify diflubenzuron as a restricted use pesticide requiring certified applicators.

Under FIFRA, hazardous pesticides may be classified for restricted use and may be limited to use only by or under the direct supervision of certified applicators. Certification programs are administered primarily by the States. These programs use various methods to certify applicators, after a determination that these applicators are competent to use restricted pesticides.

The Agency believes that the classification of diflubenzuron for restricted use would ensure that the material would be available only to competent persons. Preventing untrained persons from using the pesticide would significantly reduce the risk of human exposure due to misuse or carelessness. Any marginal costs that might result from restriction to certified applicators would be minimal since programs to certify applicators are operational in all States, there are many certified applicators, and cotton pesticides are usually applied by certified applicators.

b) Require the use of protective clothing during the mixing, loading, and application of diflubenzuron. Require respirators during mixing, loading, and ground application of diflubenzuron.

Dermal exposure to diflubenzuron is of considerable concern to the Agency. This exposure may arise from mixing and loading, spills, maintenance of application equipment, ground spray application, and aerial spray application (including wind drift).

The estimates of dermal and inhalation exposure to mixers, loaders, and applicators set forth in Section II were made with the assumption that 85% of the body would be clothed and that respirators would not be worn. Accordingly, it was assumed that the hands, forearms, neck, face, upper chest, and hair would be exposed. Requiring protective finely-woven overgarments, gloves, and a hat would leave only 3.5% of the body exposed. Thus, these protective measures would reduce the risk from dermal exposure by more than 75%. Requiring a respirator designed to filter dust particles and spray mists would reduce inhalation exposure to very low levels. The Agency estimates that the economic impact of these protective measures would be very small, especially in light of the fact that certified applicators ordinarily have protective clothing and respirators available.

c) Prohibit application of diflubenzuron within the coastal zone of the Gulf States.

The estuaries and waters of the Gulf Coast contain most of the aquatic species to which diflubenzuron is very acutely toxic, including those aquatic species that are most economically important. Therefore, the Agency considers the risk to aquatic species from use of diflubenzuron greatest in these waters. This zone includes: 1) the area between the coastline and a parallel 3-mile line from the coastline including any bays or estuaries that are contiguous to the sea and 2) the area with 3 miles of tidally-influenced waters including coastal salt marshes and rivers. Prohibition of the application of diflubenzuron in these areas is anticipated to reduce the amount of runoff into waterways where aquatic species would be most at risk.

d) Prohibit application of diflubenzuron near persons and dwellings. Prohibit the use of flagmen in the field.

Bystanders in the vicinity of the cotton fields at the time of diflubenzuron application may be exposed to levels of the chemical that could present a hazard to these individuals. This option would require that the label instructions state that the application of diflubenzuron

near any person or dwellng is prohibited. The instructions would also recommend that the product be applied at least 300 feet from dwellings when they are downwind. The use of flagmen to mark the spray swath or pattern would be prohibited.

e) Prohibit workers from entering treated fields until the day following application and the spray deposit has dried.

Fieldworkers entering fields after application may be dermally exposed to residues of diflubenzuron on the surface of cotton leaves. Therefore, this option would require that workers be prohibited from entering the fields until the day following application and the spray deposit has dried.

f) Limit use of diflubenzuron to six 1-oz. AI/acre applications per season with 5- to 7-day intervals between applications.

This option would require that the label limit the use of diflubenzuron to a maximum of six 1-oz. AI/acre applications per season with 5- to 7-day intervals between applications. The label would also specify that diflubenzuron may not be applied after the bolls have opened.

Data available to the Agency indicate that this regime will adequately control boll weevils. Diflu-

benzuron applied to open bolls could contaminate the fiber, seed, oil, and meal, rendering the crop unfit for use.

3. Option 3. Deny the application for the registration of diflubenzuron for use on cotton.

Choosing this option would mean that the Agency has reached one or more of the following conclusions: 1) data satisfactory for making a short-term risk/benefit assessment have not been submitted, 2) conditional registration of diflubenzuron on cotton for four growing seasons would significantly increase the risk of unreasonable adverse effects on humans or the environment even if the restrictions in Option 2 were adopted, or 3) conditional registration is not in the public interest.

Adopting this option would maintain the status quo regarding pesticide use on this crop. Therefore the option would eliminate the possibility of reducing the overall risk from pesticide use on cotton. In addition, this option would eliminate a potential benefit of $10 million per year for cotton growers and other possible economic benefits resulting from the use of diflubenzuron in a government-sponsored boll weevil eradication program.

V. Recommended Option

The Agency has determined that Option 2 is the most desirable course of action. It would allow conditional registration of diflubenzuron's use on cotton for four growing seasons. Diflubenzuron would be classified for restricted use and would be applied only by certified applicators. These applicators would be required to wear protective clothing and respirators. Reentry intervals and protective measures for bystanders would be established. A new method for formulating the pesticide, which would reduce exposure to humans, would be required. The rate of application would be limited to six 1-oz./acre applications per season. Application would be prohibited in the coastal zone of the Gulf States.

This option also requires more studies including additional chronic feeding studies in rats and mice, monitoring studies of diflubenzuron runoff, studies establishing the NOEL's for methemoglobinemia and sulfhemoglobinemia in an appropriate species, and field studies demonstrating the benefits of diflubenzuron's use on cotton. The registrant would also be required to develop a method for formulating the pesticide that would reduce exposure to applicators. These studies must be submitted by January 1, 1983, with annual reports of progress. Additional restrictions and

studies may be required before or during the period of conditional registration if the Agency determines that they are necessary.

Option 2 has been selected for several reasons. The data submitted by the registrant are satisfactory for balancing the risks and benefits resulting from the use of diflubenzuron for four growing seasons. Although the chronic feeding studies on mice and rats submitted by the registrant suffer from severe deficiencies, the Agency believes that they are sufficient for concluding that the use of diflubenzuron for the term of the conditional registration will pose very small risks to humans, particularly when the specified restrictions on use are considered.

The Agency has determined that the conditional registration of diflubenzuron on cotton would not significantly increase the risk of unreasonable adverse effects on man or the environment. Diflubenzuron would replace pesticides currently used for boll weevil control that appear to be more toxic to humans and more harmful to the environment. In addition, it would reduce the amount of pesticides required to control both boll weevils and the bollworm-budworm complex. As a consequence, conditional registration of diflubenzuron for use on cotton would result in a reduction of the overall risks posed by pesticides used on cotton.

Moreover, use of diflubenzuron may result in economic benefits to growers and potentially significant, although unquantifiable, benefits in the proposed USDA eradication program.

Finally, conditional registration of diflubenzuron for four growing seasons is in the public interest because its use is anticipated to result in an overall reduction in the risks to humans and the environment from pesticide use on cotton.

Option 1 was not chosen because the Agency anticipates that the restrictions on use delineated in Option 2 will significantly reduce the risks to humans and the environment with only a minimal impact on the economic benefits. These precautions are particularly appropriate in light of the weaknesses of the risk data.

APPENDIX-II-1

Thompson-Hayward's Consultant (Submission October 19, 1977)
Robert A. Squire, D.V.M., Statements

"Although the proportions of diflubenzuron absorbed apparently do not increase proportionally with dosage, greater amounts are nonetheless absorbed as dosage increases.

The case may be made that bioavailability and potential toxicity will not increase proportionally with dose, and since the compound is relatively non-toxic at all levels tested, one may conclude that little toxicity could be predicted at higher doses. However, it must be recognized that the only way to confirm this assumption is to actually test the compound at a maximum tolerated dose (MTD)."

Dr. Squire therefore, by this statement establishes that the experiment was not done at the MTD.

APPENDIX-II-2

STATEMENT OF Jack L. Radomski
(Thompson-Hayward's Consultant)
(Submission of October 19, 1977)

Review of Chronic Toxicity Studies of
DU112307 (Diflubenzuron) and p-chloroniline

"I have the following comments in response to the questions (1-7) asked:

1) It seems to me that both the rat and mouse study were carried out at a dose well below the MTD. This probably happened because of the erroneous judgement that 200 ppm had a toxic effect in the sub-acute feeding study.

2) I see no evidence that there was any significant increase in tumor incidence due to the feeding of DU112307 to rats at dietary concentrations up to 160 ppm for 104 weeks.

3) Perhaps the focal liver necrosis observed was fortuitous, since it did not show up in the chronic experiment.

4) I see no evidences of a dose-dependent response or an increased tumor incidence due to the feeding of DU112307 to mice in concentrations up to 50 ppm in the diet for 80 weeks. Statistical analyses were not performed.

5) In my opinion the absorption studies carried out with DU112307 do not support the notion that there would be no point to testing this substance at concentrations higher than 50 to 200 ppm in the diet for the following reasons:

1) The studies were carried out in aqueous suspension in gum tragacanth. I have been unable to find out what the solubilities of this compound are in organic solvents, but my experience has been that gum tragacanth will tend to retard absorption (being un-absorbed itself) particularly at the larger doses. If the material is soluble in corn oil, studies in corn oil solution may have given quite different results. In addition, these aqueous solutions are not analagous to the way the material is fed in a diet. Usually the oil present in an experimental diet tends to promote absorption of oil soluble compounds.

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