INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

Health and Safety Guide No. 99

DIFLUBENZURON HEALTH AND SAFETY GUIDE



UNITED NATIONS ENVIRONMENT PROGRAMME



INTERNATIONAL LABOUR ORGANISATION



WORLD HEALTH ORGANIZATION

WORLD HEALTH ORGANIZATION, GENEVA 1995

IPCS

Other HEALTH AND SAFETY GUIDES available: (continued on inside back cover)

Acetaldhyde (No. 90, 1995) Acrolein (No. 67, 1992) Acrylamide (No. 45, 1991) Acrylonitrile (No. 1, 1986) Aldicarb (No. 64, 1991) Aldrin and dieldrin (No. 21, 1988) Allethrins (No. 24, 1989) Amitrole (No. 85, 1994) Ammonia (No. 37, 1990) Arsenic compounds, inorganic, other than arsine (No. 70, 1992) Atrazine (No. 47, 1990) Barium (No. 46, 1991) Benomyl (No. 81, 1993) Bentazone (No. 48, 1990) Beryllium (No. 44, 1990) Brodifacoum (No. 93, 1995) Bromadiolone (No. 94, 1995) 1-Butanol (No. 3, 1987) 2-Butanol (No. 4, 1987) tert-Butanol (No. 7, 1987) Camphechlor (No. 40, 1990) Captafol (No. 49, 1990) Captan (No. 50, 1990) Carbaryl (No. 78, 1993) Carbendazim (No. 82, 1993) Chlordane (No. 13, 1988) Chlordecone (No. 41, 1990) Chloroform (No. 87, 1994) Chlorothalonil (No. 98, 1995) Cyhalothrin and lambda-cyhalothrin (No. 38, 1990) Cypermethrin (No. 22, 1988) Deltamethrin (No. 30, 1989) 1,2-Dichloroethane (No. 55, 1991) 1,3-Dichloropropene, 1,2-dichloropropane, and mixtures of 1,3-dichloropropene and 1,2-dichloropropane (No. 76, 1992) 2,4-Dichlorphenoxyacetic acid (2,4-D) (No. 5, 1987) Dichlorvos (No. 18, 1988) Difenacoum (No. 95, 1995) Dimethoate (No. 20, 1988) Dimethyl sulfate (No. 29, 1989)

Dimethylarsinic acid, methanearsonic acid, and salts (No. 69, 1992) Dimethylformamide (No. 43, 1990) Diquat (No. 52, 1991) Endosulfan (No. 17, 1988) Endrin (No. 60, 1991) Epichlorohydrin (No. 8, 1987) Ethylene oxide (No. 16, 1988) Fenitrothion (No. 65, 1991) Fenvalerate (No. 34, 1989) Folpet (No. 72, 1992) Formaldehyde (No. 57, 1991) Heptachlor (No. 14, 1988) Hexachlorobutadiene (No. 84, 1993) Hexachlorocyclohexanes, alpha- and beta- (No. 53, 1991) Hexachlorocyclopentadiene (No. 63, 1991) n-Hexane (No. 59, 1991) Hydrazine (No. 56, 1991) Isobenzan (No. 61, 1991) Isobutanol (No. 9, 1987) Isophorone (No. 91,1995) Kelevan (No. 2, 1987) Lindane (No. 54, 1991) Magnetic fields (No. 27, 1990) Methamidophos (No. 79, 1993) Methomyl (No. 97, 1995) Methyl bromide (Bromomethane) (No. 86, 1994) Methyl isobutyl ketone (No. 58, 1991) Methyl parathion (No. 75, 1992) Methylene chloride (No. 6, 1987) Mirex (No. 39, 1990) Monocrotophos (No. 80, 1993) Morpholine (No. 92, 1995) Nickel, nickel carbonyl, and some nickel compounds (No. 62, 1991) Paraquat (No. 51, 1991) Parathion (No. 74, 1992) Pentachlorophenol (No. 19, 1988) Permethrin (No. 33, 1989) Phenol (No. 88,1994) d-Phenothrin (No. 32, 1989) Phosphine (No. 28, 1989)

IPCS

Health and Safety Guide No. 99

DIFLUBENZURON HEALTH AND SAFETY GUIDE

This is a companion volume to Environmental Health Criteria 184: Diflubenzuron

Published by the World Health Organization for the International Programme on Chemical Safety (a collaborative programme of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization)

WORLD HEALTH ORGANIZATION, GENEVA 1995

n	his report contains the collective views of an international group of experts and does not ecessarily represent the decisions or the stated policy of the United Nations Environment rogramme, the International Labour Organisation, or the World Health Organization
۷	VHO Library Cataloguing in Publication Data
Ľ	Diflubenzuron: health and safety guide.
	(Health and safety guide ; no. 99)
	1. Diflubenzuron - toxicity 2. Insecticides 3. Environmental exposure 4. I. Series
	ISBN 92 4 151099 4 (NLM Classification: WA 240) ISSN 0259-7268
e F	is publications, in part or in full. Applications and enquiries should be addressed to the Office of Publications, World Health Organization, Geneva, Switzerland, which will be glad to provide the latest information on any changes made to the text, plans for new editions, and reprints and translations already available.
l t	Publications of the World Health Organization enjoy copyright protection in accordance with he provisions of Protocol 2 of the Universal Copyright Convention. All rights reserved.
1	The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the Secretariat of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.
1	The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.
	Computer typesetting by HEADS, Oxford OX8 8NY, England
	The Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (Federal Republic of Germany) provided financial support for, and undertook the printing of, this publication
	Printed by Wissenschaftliche Verlagsgesellschaft mbH · D-70009 Stuttgart 10

CONTENTS

I. PRO	DUCT	IDENTITY AND USES	-
1.1		y	-
1.2		al and chemical properties	5
1.3		tical methods	
1.4		ction and uses	1
2. SUM	IMARY	AND EVALUATION	10
2.1		ary	10
	2.1.1		-
		and analytical methods	10
	2.1.2	Sources of human and environmental	
		exposure	10
	2.1.3	Environmental transport, distribution,	1.
		and transformation	1(
	2.1.4	Environmental levels and human exposure .	1
		Kinetics and metabolism in laboratory animals	11
	2.1.6	Effects on experimental mammals and in vitro	1,
		test systems	12
	2.1.7	Effects on humans	13
	2.1.8	Effects on non-target organisms in the	1.
		laboratory and field	13
2.2	Evalua	tion	14
	2.2.1	Toxicological assessment	14
	2.2.2	Environmental assessment	15
	2.2.3	Toxicological criteria for setting guideline	
		values	17
		ONS AND RECOMMENDATIONS	19

CONTENTS

4.1	Main human health hazards, prevention and	
	protection, first aid	2
	4.1.1 Prevention and protection	2
	4.1.2 First aid	2
4.2	Advice to physicians	2
4.3	Explosion and fire hazards	2
4.4	Storage and transport	2
4.5	Spillage	2
4.6	Disposal	2
PRE	ARDS FOR THE ENVIRONMENT AND THEIR VENTION	4
PRE	RENT REGULATIONS, GUIDELINES, AND	-
PRE . CUF STA	VENTION	2
PRE . CUF STA 6.1	VENTION	2
PRE . CUF STA 6.1 6.2	VENTION	2
PRE . CUF STA 6.1	VENTION	
PRE . CUF STA 6.1 6.2 6.3 6.4	VENTION	
PRE . CUF STA 6.1 6.2 6.3 6.4	VENTION	

4

INTRODUCTION

The Environmental Health Criteria (EHC) monographs produced by the International Programme on Chemical Safety include an assessment of the effects on the environment and on human health of exposure to a chemical or combination of chemicals, or physical or biological agents. They also provide guidelines for setting exposure limits.

The purpose of a Health and Safety Guide is to facilitate the application of these guidelines in national chemical safety programmes. The first three sections of a Health and Safety Guide highlight the relevant technical information in the corresponding EHC. Section 4 includes advice on preventive and protective measures and emergency action; health workers should be thoroughly familiar with the medical information to ensure that they can act efficiently in an emergency. Within the Guide is a Summary of Chemical Safety Information which should be readily available, and should be clearly explained, to all who could come into contact with the chemical. The section on regulatory information has been extracted from the legal file of the International Register of Potentially Toxic Chemicals (IRPTC) and from other United Nations sources.

The target readership includes occupational health services, those in ministries, governmental agencies, industry, and trade unions who are involved in the safe use of chemicals and the avoidance of environmental health hazards, and those wanting more information on this topic. An attempt has been made to use only terms that will be familiar to the intended user. However, sections 1 and 2 inevitably contain some technical terms. A bibliography has been included for readers who require further background information.

Revision of the information in this Guide will take place in due course, and the eventual aim is to use standardized terminology. Comments on any difficulties encountered in using the Guide would be very helpful and should be addressed to:

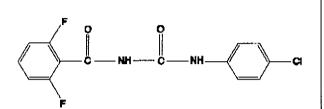
> The Director International Programme on Chemical Safety World Health Organization 1211 Geneva 27 Switzerland

THE INFORMATION IN THIS GUIDE SHOULD BE CONSIDERED AS A STARTING POINT TO A COMPREHENSIVE HEALTH AND SAFETY PROGRAMME

1. PRODUCT IDENTITY AND USES

1.1 Identity

Chemical structure:



Molecular formula:	C14H9ClF2N2O2
Common name:	diflubenzuron (accepted by ISO, BSI, ANSI, ESA)
Common trade names:	Dimilin; Micromite; Vigilante
Common abbreviation:	DFB
IUPAC name:	1-(4-chlorophenyl)-3- (2,6-difluorobenzoyl)-urea
CAS chemical name:	N-[[(4-chlorophenyl) amino] carbonyl]-2,6-difluorobenzamide
CAS registry number:	35367-38-5
RTECS registry number:	Y \$6200000

Technical diflubenzuron contains $\geq 95\%$ pure compound.

PRODUCT IDENTITY AND USES

1.2 Physical and Chemical Properties

Diflubenzuron is an odourless, white, crystalline solid. It is almost insoluble in water and poorly soluble in apolar organic solvents. In polar to very polar solvents, the solubility is moderate to good, e.g., in acetone 6.5 g/litre at 20 °C. Diflubenzuron is highly soluble in *N*-methylpyrolidone (200 g/litre), dimethylsulfoxide, and dimethylformamide (both 120 g/litre).

Some physical and chemical properties of diflubenzuron are given in Table 1.

Table 1. Physical and chemical properties of diflubenzuron

Relative molecular ma	355	310.7
Melting point technic	al ≥95%	210-230 °C
	≥99% pure	230-232 °C
Vapour pressure at 25	°C	0.00012 mPa
Volatility: solid mat	erial	< 4 %
from wate	erpH 5.6	<2% virtually non-volatile
Specific gravity		1.56
Partition coefficient n-	octanol/water (log K _{ow})	5000 _
Solubility in water (25	5 °C) (pH 5.6)	8×10^{-5} g/litre
Stability in water	after 3 weeks at pH 5	4% decomposition
(0.0001 g/litre)	after 3 weeks at pH 7	8% decomposition
in the dark	after 3 weeks at Ph 9	26% decomposition

Conversion factor: $1 \text{ ppm} = 12.7 \text{ mg/m}^3 \text{ at } 25 \text{ }^{\circ}\text{C}$

1.3 Analytical Methods

Two general types of assay procedures for residues of diflubenzuron in crops, soil, water, and biological samples are available, i.e., high-pressure liquid chromatography and gas chromatography with detection limits of approximately 0.01-0.05 mg/kg. The detection limit in water is $0.1 \mu g/litre$.

The Joint FAO/WHO Codex Alimentarius Commission has made recommendations for the methods of analysis to be used for the determination of diflubenzuron residues (FAO/WHO, 1989).

1.4 Production and Uses

The production figures are not available. Diffubenzuron is effective as a stomach and contact insecticide, acting by inhibition of chitin synthesis. It is usually applied directly on plants and in forest areas, and in water for mosquito control.

2.1 Summary

2.1.1 Identity, physical and chemical properties, and analytical methods

Diflubenzuron is a member of the benzoylphenylurea group of insecticides. Its insecticidal action is due to interaction with chitin synthesis and/or deposition. It forms odourless white crystals with a melting point of 230-232 °C. It is sparingly soluble in water (0.2 mg/litre at 20 °C) and is virtually non-volatile. It is relatively stable in acidic and neutral media but hydrolyses under alkaline conditions.

Diflubenzuron is produced by the reaction of 2,6-difluorobenzamide with 4-chlorophenylisocyanate.

Diflubenzuron residues may be measured in water, biological samples, and soils using HPLC with UV detection, or GC with ECD for analysis of the intact molecule or following derivatization of the liberated 4-chloroaniline with trifluoroacetic anhydride.

2.1.2 Sources of human and environmental exposure

Diflubenzuron is a synthetic compound used in agriculture, forestry, and public health programmes to control insect pests and vectors. Different formulations of diflubenzuron are available for these uses. There is no relevant information on human exposure to diflubenzuron.

2.1.3 Environmental transport, distribution, and transformation

Diflubenzuron is usually applied directly to plants and water. Uptake of diflubenzuron through plant leaves does not occur.

The adsorption of diflubenzuron on soil is rapid. It is immobilized in the top 10-cm layer of soil to which it is applied and is unlikely to leach. Diflubenzuron is degraded in soils of various types and origin under aerobic or anaerobic conditions with a half-life of a few days. The rate of degradation depends greatly on the diflubenzuron particle size. The main metabolic pathway (over 90%) is hydrolysis leading to 2,6-difluorobenzoic acid and 4-chlorophenylurea; these are degraded with half-lives of about

4 and 6 weeks, respectively. Free 4-chloroaniline has not been detected in soils.

Diflubenzuron degrades rapidly in neutral or alkaline waters. Studies on the application of diflubenzuron to water showed rapid partition to sediment; the parent compound and 4-chlorophenylurea may persist on sediment for more than 30 days.

Diflubenzuron does not bioaccumulate in fish.

2.1.4 Environmental levels and human exposure

Exposure of the general population to diflubenzuron via water or food, as a result of its use in agriculture, against forest insects, or in mosquito control, is negligible.

2.1.5 Kinetics and metabolism in laboratory animals

In experimental animals, diflubenzuron is absorbed from the digestive tract and to a lesser extent through the skin. There is a saturable absorption mechanism in the rat gastrointestinal tract. Consequently, a large proportion of orally administered diflubenzuron is found in the faeces. Diflubenzuron is widely distributed in the tissues, but it does not accumulate.

The metabolic fate of diflubenzuron has been studied in various species. The major route of metabolism in mammals is via hydroxylation. Hydrolysis of diflubenzuron may occur at any of the three carbon-nitrogen bonds. In pigs and chickens, the major route of hydrolysis is at the ureido bridge. In rats and cows, the major metabolic pathway is hydroxylation. The major metabolites in sheep, swine, and chickens are 2,6-difluorobenzoic acid and 4-chlorophenylurea; minor metabolites are 2,6-difluorobenzamide and 4-chloroaniline. In rats and cattle, 80% of the metabolites are 2,6-difluoro-3-hydroxydiflubenzuron, 4-chloro-2-hydroxydiflubenzuron and 4-chloro-3-hydroxydiflubenzuron. The metabolic studies indicate that little or no 4-chloroaniline is formed in rats or cattle.

The major route of elimination is via the faeces, ranging from 70 to 85% in cats, pigs, and cattle. In sheep, elimination is roughly equally distributed between the urine and faeces. Urinary excretion in rats and mice decreases

proportionally with increasing dosage level. Less than 1% of an oral dose is recovered in exhaled air. Only trace residues are found in milk.

No human studies on the kinetics and metabolism of diflubenzuron, including the extent of biotransformation to 4-chloroaniline, are available.

2.1.6 Effects on laboratory mammals and in vitro test systems

The acute toxicity of diflubenzuron is low, by any route of exposure. It has been classified by WHO as a "product unlikely to present an acute hazard in normal use", based on an acute oral LD_{50} of more than 4640 mg/kg body weight in rats. The acute dermal LD_{50} in rats is greater than 10 000 mg/kg body weight, while the acute inhalation LC_{50} for rats is greater than 2.49 mg/litre. No signs of intoxication have been observed during the 14-day period following a single administration of diflubenzuron, by various routes, to a variety of animal species.

Diflubenzuron is neither a skin irritant (in rabbits) nor a skin sensitizer (in guinea-pigs). It is marginally irritant to the eyes of rabbits.

Diflubenzuron causes methaemoglobinaemia and sulfhaemoglobinaemia. Dose-related methaemoglobinaemia has been demonstrated in various species after oral, dermal, or inhalation exposure to diflubenzuron. This effect is the most sensitive toxicological end-point in experimental animals. The no-observed-effect level (NOEL), based on methaemoglobin formation, is 2 mg/kg body weight per day in rats and dogs and 2.4 mg/kg body weight per day in mice. In long-term toxicity studies on mice and rats, treatment-related changes were principally associated with oxidation of haemoglobin or with hepatocyte changes.

In carcinogenicity studies on mice and rats given dietary levels of up to 10 000 mg/kg, there were no treatment-related effects on tumour incidence. Specifically, there were no mesenchymal neoplasms of the spleen or liver, as observed in carcinogenicity studies with 4-chloroaniline.

In several reproductive toxicity studies on rats, mice, rabbits, and three avian species, no effects were seen on reproduction and there was no embryotoxicity. Teratogenicity studies on rats and rabbits did not reveal teratogenic effects.

Diflubenzuron and its main metabolites have been examined in a variety of *in vitro* and *in vivo* mutagenicity tests. Neither diflubenzuron nor its major metabolites have produced any mutagenic effects.

The minor metabolite, 4-chloroaniline, was shown to be positive in several *in vitro* mutagenicity assays using various end-points. It is carcinogenic in rats and mice. The neoplastic lesions related to administration of 4-chloroaniline were benign and malignant mesenchymal tumours in the spleens of male rats and haemangiomas and haemangiosarcomas, primarily in the spleen and liver of male mice.

2.1.7 Effects on humans

The diflubenzuron metabolite, 4-chloroaniline, has been reported to cause methaemoglobinaemia in exposed workers and in neonates inadvertently exposed. Some individuals who are deficient in NADH-methaemoglobin reductase may be particularly sensitive to 4-chloroaniline and, hence, to diflubenzuron exposure.

2.1.8 Effects on non-target organisms in the laboratory and field

All chitin-synthesizing organisms showed susceptibility to diflubenzuron.

Bacteria were not affected by diflubenzuron at a concentration of 500 mg/kg soil; some stimulation of nitrogen fixation was seen. Diflubenzuron acetone solutions were degraded; the acetone was used as carbon source. Algal biomass increased at a diflubenzuron concentration of 1 μ g/litre. There were no adverse effects at concentrations above the limit of diflubenzuron solubility. Fungi were temporarily affected at 0.1 μ g/litre in laboratory streams.

Aquatic invertebrates showed variable responses to diflubenzuron. Molluscs were insensitive, the LC₅₀ being greater than 200 mg/litre. LC₅₀s for other invertebrates ranged from 1 to >1000 μ g/litre, reflecting the effects of the compound on juvenile, moulting stages. A Maximum Acceptable Toxicant Concentration (MATC) for *Daphnia* has been estimated at >40 and <93 ng/litre; as expected, larval mayflies and other aquatic insect juveniles were highly susceptible. Overspray of water bodies would be expected to kill some aquatic invertebrates.

In ecosystems and field experiments, where diflubenzuron was applied directly to the water, the effects on most taxa were less severe than predicted from acute laboratory tests. No effects on aquatic organisms have been found after aerial applications to forests.

The LC_{50s} for fish are > 150 mg/litre. Fish kills have never been recorded in field experiments.

The oral and contact LD_{50s} for honey-bees were greater than $30 \mu g$ /bee. Honey-bee colonies were not affected after aerial application of 350 g diflubenzuron/ha.

A 5-day dietary study on the mallard duck and bobwhite quail with levels of up to 4640 mg/kg did not reveal any observable signs of toxicity. Small songbirds in the forest ecosystem were not affected after aerial application of diflubenzuron at 350 g/ha.

Small mammal species in a forest did not show any reductions in numbers after application of diflubenzuron at 67 g/ha.

2.2 Evaluation

2.2.1 Toxicological assessment

The primary manifestation of diflubenzuron toxicity, i.e., methaemoglobin induction, occurred in a range of test animal species. It is attributable to the metabolite, 4-chloroaniline, which is known to induce methaemoglobin formation in several animal species and in humans.

Diflubenzuron did not cause any other toxic effects following long-term dietary administration. It was not mutagenic or carcinogenic in mice or rats. However, its metabolite, 4-chloroaniline, is mutagenic *in vitro* and is carcinogenic in mice and male rats. Although 4-chloroaniline is a minor urinary metabolite of diflubenzuron in rats, the extent to which it is formed *in vivo* in various animal species remains unknown. Similarly, the comparative extent of absorption of its parent compound in various species is not known.

The sensitivity of human haemoglobin to methaemoglobin formation by 4-chloroaniline *in vivo* is not known. However, since induction of methaemoglobinaemia has consistently been the most sensitive measure of

diflubenzuron toxicity in the various animal species tested, it may be used as a basis to estimate levels causing no toxicological effects.

2.2.2 Environmental assessment

Diflubenzuron adsorbs readily on soil particles with little subsequent desorption. Its mobility in soil is very low, practically all residues remaining within 15 cm of the surface, even in sandy loam soils; diflubenzuron does not leach. It is only partly removed from foliage by heavy rainfall. Nevertheless, some diflubenzuron may be present in surface water shortly after application, due to flooding of treatment areas or agricultural run-off.

Dissipation of diflubenzuron from water is rapid. Adsorption on sediment occurs within 4 days; both the parent compound and the metabolite, 4-chlorophenylurea, may persist on sediment for at least 30 days.

Uptake of diflubenzuron through the leaves of plants, after aerial application, does not occur. Some uptake of soil residues does occur in plants and this may be translocated. At the highest application rate (1 kg a.i./ha), following 1 month of aging of residues, up to 1 mg residue/kg was found in various crops.

Photolysis of diflubenzuron is slow with a calculated half-life of 40 days. Under environmental conditions, abiotic degradation in water and soil represents a minimum route of break-down. Aerobic degradation in water is a microbial process with a half-life of a few days, under both laboratory and field conditions. In the field, degradation of diflubenzuron, applied at practical rates, is influenced by pH, temperature, formulation, organic matter content, and depth of the water.

Degradation in soil through microbial hydrolysis is a rapid process, with a half-life of a few days, depending on diflubenzuron particle size. The major break-down products are 2,6-difluorobenzoic acid and 4-chlorophenylurea; a minor metabolite is parachloroaniline. All these are irreversibly bound to soil and/or further metabolized.

The half-life of diflubenzuron residues on citrus fruits was significantly decreased by high temperature and humidity.

Anaerobic degradation in water and sediment is slower than aerobic degradation.

Fish bioconcentrate diflubenzuron and some bioaccumulation takes place during extended exposure up to a plateau, depending on the water concentration, due to fast degradation of diflubenzuron and the excretion of metabolites; the depuration half-life is less than one day. The 4-chloroaniline metabolite has not been detected in fish.

Fish are not sensitive to diflubenzuron. The toxicity of metabolites of diflubenzuron for fish is also low. Long-term exposure to diflubenzuron at recommended application rates did not produce any effects on fish; the compound does not persist in water and no long-term exposure is expected.

Diflubenzuron, at the solubility limit concentration, was not phytotoxic for duckweed.

Honey-bees were not affected by topical applications of >30 μ g/bee or dietary concentrations of up to 1000 mg/kg. Broods in hives were reduced when bees were fed syrup at 59 mg diflubenzuron/kg. Broods were also reduced following exposure of flying colonies.

Earthworms were not affected at a concentration of 780 mg diflubenzuron/kg soil, which is at least three orders of magnitude above reported soil residues.

The acute toxicity of diflubenzuron for birds is low with oral and dietary $LD(LC)_{505}$ greater than 3000 mg/kg. At recommended application rates, diflubenzuron is not expected to pose a hazard for birds.

Extensive field studies have shown minimal or reversible effects on most aquatic invertebrates; daphnids were most seriously affected, with shortterm reductions in population of up to 75% following a single application of diflubenzuron. Fish were not affected by water overspraying. Neither bird nor mammal populations were adversely affected following forest spraying with diflubenzuron.

Risk quotients for avian and fish risk categories are summarized in Table 3.

Table 3. Toxicity-exposure ratios for birds and fish based on application rates of 2.5 kg diflubenzuron a.i./ha to soybeans (worst case)

Risk category	LC ₅₀ as mg/litre or mg/kg diet	0	Toxicity/exposure ratio (TER) ^c
Acute bird	3762	73.7-535.7	51.0-7.0
Acute fish (stream)	150	0.0007	214 300
Acute fish (pond) Acute aquatic	150	0.01	15 000
invertebrate (stream) Acute aquatic	0.005	0.0007	7.1
invertebrate (pond)	0.005	0.01	0.5

^aEstimated environmental concentration in the terrestrial environment (for bird exposure) is based on the stated application rate and the assumption of deposition on short grass, using the US EPA nomogram.

^bAquatic exposure concentrations were taken from the STEAM model, based on a single application and estimated runoff into water; no direct overspray is included.

^cTER is the toxicity (as LCs₀) divided by the exposure; values at, or below, 1.0 indicate the likely exposure to toxic concentrations of organisms in the different risk categories.

2.2.3 Toxicological criteria for setting guideline values

The toxicological studies on diflubenzuron of relevance for setting guideline values are shown in Table 4.

Table 4. Toxicological criteria for estimating guideline values for diflubenzuron

Exposure scenario (technical diflubenzuron)	Relevant route/effect/ species	Result/remarks
Short-term (1-7 days)	dermat, irritation, rabbit ocular, irritation, rabbit dermat, sensitization, guinea-pig	non-irritant marginal, high dose non-sensitizing
	inhalational, toxicity, rat	LC ₅₀ 2.49 mg/litre (single exposure)
Mid-term (1-26 weeks)		
3 weeks; 5 days/week	dermal, irritation, rabbit	NOEL = 70 mg/kg body weight per day
3 weeks; 5 days/week	inhalational, methaemo- globin formation, rat	NOAEL = < 0.12 mg/litre
Long-term	dietary, methaemo- globin formation, rat	NOEL = 2 mg/kg body weight per day
	dietary, methaemo- globin formation, mouse	NOEL = 2.4 mg/kg body weight per day
	dietary, methaemo- globin formation, dog	NOEL = 2 mg/kg body weight per day

3. CONCLUSIONS AND RECOMMENDATIONS

Considering the toxicological characteristics of diflubenzuron, both qualitatively and quantitatively, the CAG concluded, on the basis of the NOEL of 2 mg/kg body weight per day in long-term toxicity studies on mice, rats, and dogs, and applying a 100-fold uncertainty factor, that 0.02 mg/kg body weight per day will probably not cause adverse effects in humans, whatever the route of exposure.

Biomonitoring of 4-chloroaniline during occupational exposures should be carried out.

4. HUMAN HEALTH HAZARDS, PREVENTION AND PROTECTION, EMERGENCY ACTION

For general information see ILO (1993).

4.1 Human Health Hazards, Prevention and Protection, First Aid

The acute oral and dermal toxicities of diflubenzuron for humans appear to be low. Diflubenzuron is not a skin irritant or a sensitizer; it was marginally irritant when tested on rabbit eyes.

4.1.1 Prevention and protection

The following precautions should be observed during handling and use, in order to reduce the risk of accidental contamination.

- Avoid contact with skin and eyes.
- Do not smoke, drink, or eat in the workplace. Wash hands and any exposed skin before eating, drinking, or smoking, and after work.
- Avoid raising a dust cloud when handling wettable powder formulations.
- Avoid breathing the dust from powder products.
- When unloading and handling containers, wear protective PVC or neoprene gloves.
- When handling leaking containers or when dealing with leaks and spills, wear overalls and PVC or neoprene gloves and boots. If overalls become contaminated, change and wash them thoroughly before re-use.
- Store products in closed original containers, out of reach of children and away from food, drink, and animal feed.

4.1.2 First aid

Acute poisoning by diflubenzuron is unlikely because of its low acute toxicity.

When considering human health hazards and first aid, it is essential to determine which product the victim has been exposed to. It is essential to differentiate between dry products (diflubenzuron technical, the 90%

HUMAN HEALTH HAZARDS, PREVENTION AND PROTECTION, EMERGENCY ACTION

concentrate, the 25% wettable powder and other dry products, such as wettable powders with lower active ingredient and low percentage granular products, which may be available locally), water-based products (DIMILIN SC-48, DIMILIN SC-15, DIMILIN 4L), and oil-based products (DIMILIN ODC-45, DIMILIN OF 6 and DIMILIN 2F).

In cases of overexposure, apply routine first aid measures. If material has been spilled on the skin, immediately remove the victim from the source of contamination, remove all contaminated clothing, and wash affected areas with soap and running water. If the material is in the eyes, flush with clean water for at least 5-10 min. In case of ingestion of significant quantities, medical attention should be sought.

4.2 Advice to Physicians

The acute oral toxicity of diflubenzuron for humans is low. There is no specific antidote. Treat symptomatically, when required. If oil-based products have been ingested and the victim starts vomiting, it may be advisable to perform gastric lavage, in order to avoid aspiration into the lungs.

4.3 Explosion and Fire Hazards

Diflubenzuron is not flammable. If diflubenzuron is involved in a small fire, extinguish with carbon dioxide, dry powder, or alcohol-resistant foam.

4.4 Storage and Transport

All products should be stored under dry conditions under lock and key, out of reach of children and animals, and local regulations should be complied with. Containers should be sound and adequately labelled.

4.5 Spillage

Avoid contact with solid or dust. Keep spectators away from any leakage. The pesticide is highly toxic for aquatic invertebrates.

Absorb any spillage with sand or any other inert absorbent, collect the mixture into a clean, empty container, which should be adequately labelled and sent for incineration. Empty any product remaining in damaged or

HUMAN HEALTH HAZARDS, PREVENTION AND PROTECTION, EMERGENCY ACTION

leaking containers in a clean, empty container, which should be suitably labelled.

4.6 Disposal

Proper incineration is the method of choice for this compound.

5. HAZARDS FOR THE ENVIRONMENT AND THEIR PREVENTION

Diflubenzuron is not persistent and is readily degraded in soil and water. However, it is highly toxic for aquatic invertebrates. Water surfaces should not be oversprayed when diflubenzuron is applied for mosquito control.

6. CURRENT REGULATIONS, GUIDELINES, AND STANDARDS

6.1 Previous Evaluations by International Bodies

Diflubenzuron was classified by WHO (1992) as "a product unlikely to present an acute hazard in normal use", on the basis of an acute oral LD_{50} for rat greater than 4640 mg/kg body weight.

Diflubenzuron was evaluated by the FAO/WHO Joint Meeting on Pesticide Residues (JMPR) in 1981, 1984, and 1985. An acceptable daily intake (ADI) for man for diflubenzuron was estimated at 0-0.02 mg/kg body weight per day in 1985.

A guideline value of 22.5 μ g/litre for drinking-water was recommended, on the basis of allocation of the tolerable daily intake (TDI) of 0.0075 mg/kg body weight (WHO, 1991).

In the WHO Recommended Classification of Pesticides by Hazard, technical diflubenzuron has been classified as a product unlikely to present an acute hazard in normal use.

6.2 Exposure Limit Values

Some tolerances for food and animal feed products are given in Table 5.

For all agricultural uses, "pre-harvest intervals" have been defined in most countries.

6.3 Specific Restrictions

Diflubenzuron is approved as a pesticide in many countries. Specific uses, limitations, and precautions are listed in national regulatory documents.

6.4 Waste Disposal

Incineration at high temperature in a unit with effluent gas scrubbing is the method of choice.

Table 5. Tolerances and Maximum Residue Limits for food products Table 5. Tolerances and Maximum Residue Limits for food products Exposure limit description Value Country/ Food product Exposure limit description Value Brazil Specified plant products Acceptable limit 0.1-0.5 Brazil Specified plant products Acceptable limit 0.1-0.5 FAO/WHO Apples, blackcurants, brussels Maximum residue limit 0.1-0.5 FAO/WHO Apples, plackcurants, brussels Maximum residue limit 0.1-0.5 FAO/WHO Apples, plackcurants, brussels Maximum residue limit 0.1-0.5 Indication Numbrooms, soybeans 0.1-0.5 0.2 Cottonseed Maximum residue limit 0.1 0.5 Indication Wild strawberries, Maximum residue limit 0.1 Germany Wild strawberries, Maximum residue limit 0.1 0.5 ISA Raw agricultural products Acceptable residue limit 0.1 0.2 Soybean hulls and song stock Soybean hulls and song stock 0.1-0.5 0.2 Soybean hulls and sood stock 0.1-0.5			CURRENT REGULATIO	RRENT REGULATIONS, GUIDELINES, AND STANDARDS	STANDARDS	
Country/ OrganizationFood productExposure limit descriptionBrazilSpecified plant productsAcceptable limitBrazilSpecified plant productsAcceptable limitBrazilSpecified plant productsAcceptable limitFAO/WHOApples, blackcurrants, brusselsMaximum residue limitFAO/WHOApples, intersMaximum residue limitFAO/WHOApples, blackcurrants, brusselsMaximum residue limitFAO/WHOApples, blackcurrants, brusselsMaximum residue limitsprouts, cabbage, citrus fruits, mushroomsMaximum residue limitFinlandMushroomsMaximum residue limitGermanyWild strawberries, stone fruits, cabbage mushroomsMaximum residue limitUSARaw agricultural products (specified plant and animal products)Acceptable residue limitUSRSoybean hulls and soap stockMaximum residue limitUSRSpecified food productsMaximum residue limit		Table 5. Toler	ances and Maximum Residue Limits fi	or food products		
Specified plant productsAcceptable limitWHOApples, blackcurrants, brusselsMaximum residue limitsprouts, cabbage, citrus fruits, pears, plums, tomatoesMaximum residue limitisprouts, cabbage, citrus fruits, pears, plums, tomatoesMaximum residue limitdMushrooms, soybeansMaximum residue limitdMushrooms, soybeansMaximum residue limitdMushroomsMaximum residue limitdWild strawberries, stone fruits, cabbage mushroomsMaximum residue limitstone fruits, cabbage mushroomsAcceptable residue limitSoybean hulls and soap stock Specified food productsMaximum residue limit	<u> </u>	Country/ Organization	Food product	Exposure limit description	Value (mg/kg)	Effective date
 WHO Apples, blackcurrants, brussels Paers, plums, tomatoes contonseed mushrooms, soybeans cottonseed mushrooms, soybeans carcass meat, eggs, milk, meat by-products, poultry meat Mushrooms Mushrooms Mushrooms Maximum residue limit Wild strawberries, stone fruits, cabbage mushrooms Raw agricultural products Soybean hulls and soap stock Soybean hulls and soap stock Maximum residue limit 		Brazil	Specified plant products	Acceptable limit	0.1-0.2	1984
cottonseed mushrooms, soybeans carcass meat, eggs, milk, meat by-products, poultry meat a Mushrooms Mushrooms Maximum residue limit wild strawberries, stone fruits, cabbage mushrooms Raw agricultural products (specified plant and animal products) Soybean hulls and soop stock Specified food products Maximum residue limit		FA0/WHO	Apples, blackcurrants, brussels sprouts, cabbage, citrus fruits, pears, plums, tomatoes	Maximum residue limit	1.0	1988
mushrooms, soybeans carcass meat, eggs, milk, meat by-products, poultry meat meat by-products, poultry meat Maximum residue limit Wild strawberries, stone fruits, cabbage mushrooms Raw agricultural products (specified plant and animal products) Soybean hulls and soap stock Specified food products Maximum residue limit			cottonseed		0.2	
d Mushrooms eggs, milk, meat by-products, poultry meat meat by-products, poultry meat Mushrooms Maximum residue limit wy Wild strawberries, stone fruits, cabbage mushrooms Acceptable residue limit (specified plant and animal products) Acceptable residue limit Soybean hulls and soap stock Maximum residue limit			mushrooms, soybeans		0.1	
d Mushrooms Maximum residue limit uny Wild strawberries, stone fruits, cabbage mushrooms Acceptable residue limit (specified plant and animal products) Acceptable residue limit (specified plant and animal products) Maximum residue limit			carcass meat, eggs, milk, meat by-products, poultry meat		0.05	
 wild strawberries, stone fruits, cabbage mushrooms Raw agricultural products (specified plant and animal products) Soybean hulls and soap stock Specified food products Maximum residue limit 		Finland	Mushrooms	Maximum residue limit	0.1	1992
Raw agricultural products Acceptable residue limit (specified plant and animal products) Soybean hulls and soap stock Specified food products Maximum residue limit		Germany	Wild strawberries, stone fruits, cabbage mushrooms		2.0 1.0 0.2	1989
Soybean hulls and soap stock Specified food products Maximum residue limit		USA	Raw agricultural products (specified plant and animal products)	Acceptable residue limit	0.05-1.0	1984
Specified food products Maximum residue limit			Soybean hulls and soap stock		0.1-0.5	
		USSR	Specified food products	Maximum residue limit	0.1	1988

BIBLIOGRAPHY

CEC (1987) Legislation in dangerous substances - Classification and labelling in the European Communities - Vol. 1 & 2. Commission of the European Communities, London, Graham & Trotman, Ltd.

FAO (1985a) Guidelines for the packaging and storage of pesticides. Rome, Food and Agriculture Organization of the United Nations.

FAO (1985b) Guidelines for the disposal of waste pesticides and pesticide containers on the farm. Rome, Food and Agriculture Organization of the United Nations.

FAO (1985c) Guidelines on good labelling practice for pesticides. Rome, Food and Agriculture Organization of the United Nations.

FAO (1986) International code of conduct on the distribution and use of *pesticides*. Rome, Food and Agriculture Organization of the United Nations.

FAO/WHO (1964-present) *Evaluations of pesticide residues in food*. Rome, Food and Agriculture Organization of the United Nations.

FAO/WHO (1986) Codex Maximum Limits for pesticide residues. Codex Alimentarius Commission, CAC/Vol. XIII., Supplement 1 & 2, 3rd ed. Rome, Food and Agriculture Organization of the United Nations.

FAO/WHO (1989) Guide to Codex recommendations concerning pesticide residues. Part 8. Recommendations for methods of analysis of pesticide residues. 4th ed. Rome, Codex Commission on Pesticide Residues, Food and Agriculture Organization of the United Nations.

GIFAP (1982) Guidelines for the safe handling of pesticides during their formulation, packaging, storage and transport. Brussels, Groupement International des Associations Nationales des Fabricants de Produits Agrochimiques.

GIFAP (1983) Guidelines for the safe and effective use of pesticides. Brussels, Groupement International des Associations Nationales des Fabricants de Produits Agrochimiques.

GIFAP (1984) Guidelines for emergency measures in cases of pesticides poisoning. Brussels, Groupement International des Associations Nationales des Fabricants de Produits Agrochimiques.

BIBLIOGRAPHY

GIFAP (1987) Guidelines for the safe transport of pesticides. Brussels, Groupement International des Associations Nationales des Fabricants de Produits Agrochimiques.

HAYES, W.J., Jr & LAWS, E.R. Jr (1991) Handbook of pesticide toxicology (3 vol.). New York, Academic Press.

IARC (1972-present) *IARC Monographs on the evaluation of carcinogenic risk of chemicals to man.* Lyon, International Agency for Research on Cancer.

ILO (1991) Safety and health in the use of agro-chemicals - a guide. Geneva, International Labour Office.

ILO (1993) Safety and health in the use of chemicals at work - A training manual, prepared by Abu Bakar Che Man & David Gold. Geneva, International Labour Office.

IPCS (in preparation) Environmental Health Criteria No. 184 Diflubenzuron, Geneva, World Health Organization.

IRPTC (1985) *IRPTC file on treatment and disposal methods for waste chemicals*. Geneva, International Register of Potentially Toxic Chemicals, United Nations Environment Programme.

IRPTC (1987) *IRPTC legal file 1986*. Geneva, International Register of Potentially Toxic Chemicals, United Nations Environment Programme.

PLESTINA, R. (1984) Prevention, diagnosis, and treatment of insecticide poisoning. Geneva, World Health Organization (WHO unpublished document VBC/84.889).

SAX, N.I. (1984) Dangerous properties of industrial materials. New York, van Nostrand Reinhold Company, Inc.

UNEP/IEO (1990) Storage of hazardous materials: a technical guide for safe warehousing of hazardous materials. Paris, United Nations Environment Programme, Industry and Environment Office, 80 p.

UNITED NATIONS (1991) Consolidated list of products whose consumption and/or sale have been banned, withdrawn, severely restricted or not approved by Governments. 4th ed. New York, United Nations.

BIBLIOGRAPHY

UNITED NATIONS (1989) Recommendations on the transport of dangerous goods. 6th ed., New York, United Nations.

US NIOSH/OSHA (1981) Occupational health guidelines for chemical hazards. 3 Vol., Washington DC, US Department of Health and Human Services, US Department of Labor (Publication No. DHHS(NIOSH) 01-123).

WHO (1992) The WHO recommended classification of pesticides by hazard and guidelines to classification 1992-93, Geneva, World Health Organization (unpublished document WHO/PCS/92.14).

WORTHING, C.R. & HANCE, R.J. (1991) The pesticide manual. 9th ed., Farnham, United Kingdom, British Crop Protection Council.

IPCS

Other HEALTH AND SAFETY GUIDES available: (continued from inside front cover)

Phosphorus trichloride and phosphorus oxychloride (No. 35, 1989) Polybrominated biphenyls (PBBs) (No. 83, 1993) Polychlorinated biphenyls and polychlorinated terphenyls (PCBs and PCTs) (No. 68, 1992) Propachlor (No. 77, 1992) Propylene oxide (No. 15, 1988) Pyrrolizidine alkaloids (No. 26, 1988) Quintozene (No. 23, 1988) Resmethrins (No. 25, 1989) Rotenone (No.73, 1992) Tecnazene (No. 12, 1988) Tetrachloroethylene (No. 10, 1987) Tetradifon (No. 11, 1987) Tetramethrin (No. 31, 1989) Tri-allate (No. 89, 1994) Trichlorfon (No. 66, 1991) Trimellitic anhydride (No. 71, 1992) Vanadium (No. 42, 1990) Vinylidene chloride (No. 36, 1989) Warfarin (No. 96, 1995)

Price: Sw. fr. 5.-Price in developing countries: Sw. fr. 3.50

ISBN 92 4 151099 4