The NRA review of

ENDOSULFAN

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VOLUME 2

National Registration Authority for Agricultural and Veterinary Chemicals

Existing Chemicals Review Program

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FOREWORD

The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) is an independent statutory authority with responsibility for the regulation of agricultural and veterinary chemicals.

The NRA's Existing Chemicals Review Program (ECRP) systematically examines agricultural and veterinary chemicals registered in the past to determine whether they continue to meet current standards for registration. Chemicals for review are chosen according to pre-determined, publicly available selection criteria. Public participation is a key aspect of this program.

In undertaking reviews, the NRA works in close cooperation with advisory agencies including the Department of Health and Family Services (Chemicals and Non-Prescription Drug Branch), Environment Australia (Risk Assessment and Policy Section), National Occupational Health and Safety Commission (Chemical Assessment Division) and relevant State Departments.

The NRA has a policy of encouraging openness and transparency in its activities and community involvement in decision-making. The publication of evaluation documents for all ECRP reviews is a part of that process.

The NRA also makes these reports available to the regulatory agencies of other countries as part of bilateral agreements or as part of the OECD *ad hoc* exchange program. Under this program it is proposed that countries receiving these reports will not utilise them for registration purposes unless they are also provided with the raw data from the relevant applicant.

The summary provides a brief overview of the review of endosulfan that has been conducted by the NRA and its advisory agencies. The review's findings are based on information collected from a variety of sources, including data packages and information submitted by registrants, information submitted by members of the public, questionnaires sent to key user/industry groups and government organisations, and literature searches.

The information and technical data required by the NRA to review the safety of both new and existing chemical products must be derived according to accepted scientific principles, as must the methods of assessment undertaken. Details of required data are outlined in various NRA publications.

Other publications explaining the NRA's requirements for registration can also be purchased or obtained by contacting the NRA. Among these are: *Ag Manual: The Requirements Manual for Agricultural Chemicals; Vet Manual: The Requirements Manual for Veterinary Chemicals* and the *Agricultural Requirements Series*.

TABLE OF CONTENTS

VOLUME 1

VOLUME 2

BRIEF OVERVIEW

Endosulfan is an insecticide which has been widely used in Australia for over 30 years. The agricultural industry and State agricultural authorities advise that endosulfan is extremely important to agriculture and for some crop/pest situations there are no alternatives at all or none which work as well.

Endosulfan is an organochlorine chemical, but unlike most other members of this class, it largely disappears from soil in 3 to 6 months and does not remain in the bodies of animals or humans. Numerous scientific studies have not found any evidence of involvement in cancer, birth defects, damage to genetic material, disruption of the endocrine hormone system or other long term affects due to chronic, low level exposure. However, endosulfan has a high acute or immediate toxicity to humans which is a matter of concern for agricultural workers. In addition, endosulfan is quite toxic to fish and other aquatic organisms.

Although endosulfan concentrations in surface waters in areas of intensive use routinely exceed ANZECC criteria recommended to protect aquatic ecosystems, there is not yet clear evidence that endosulfan is causing long term harm to the general environment or biological communities. However, it is known that during parts of each year in the rivers and creeks of these regions, endosulfan reaches concentrations which are lethal to important species of native fish and native macroinvertabrates when tested under laboratory conditions. Regular attainment of such concentrations of endosulfan in regional surface waters is not acceptable on an ongoing basis. Concern over this problem is increased by predictions of some authorities that acreage of cotton, the main user of endosulfan, is likely to increase significantly in the next few years in some regions.

A simple ban of endosulfan could lead to other problems. This is because endosulfan has relatively low toxicity to many species of beneficial insects, mites and spiders (that is, ones which prey upon or parasitise damaging insect pests). Other chemicals, necessarily substituted for endosulfan, would kill beneficial insects leading to population explosions of damaging pests which in turn would require more frequent sprays of harsher chemicals than if endosulfan had been used in the first place. In addition, because endosulfan is from a different chemical class than almost all other available insecticides, its use is very important for slowing the development of insecticide resistance to the other chemicals. Loss of endosulfan would, therefore, also lead to more insecticide use due to increasing resistance among insect pests. The net result is greater overall danger to agricultural workers and to the environment.

To address the above concerns, the National Registration Authority has taken steps to manage the use of endosulfan on an interim basis while more data on worker safety and commodity residues are developed to determine specific requirements in those areas necessary for ongoing use. In addition, the NRA has taken steps designed to reduce the inappropriate use of endosulfan and to reduce the amount of endosulfan which is carried off farms into creeks and rivers. The results of environmental monitoring and an assessment of use patterns over the next three years will be examined to determine whether endosulfan can continue to be used.

ABBREVIATIONS AND ACRONYMS

ac	Active Constituent
ADI	Acceptable Daily Intake (for humans)
ai	Active Ingredient
ANZECC	Australia and New Zealand Environment and Conservation Council
Bt	*Bacillus thuringiensis*
ChE	Cholinesterase
d	Day
EC	Emulsifiable Concentrate
EC50	Concentration at which 50% of the test population are affected.
EEC	Estimated Environmental Concentration
GAP	Good Agricultural Practice
h	Hour
ha	Hectare
in vitro	Outside the living body and in an artificial environment
in vivo	Inside the living body of a plant or animal
IPM	Integrated Pest Management
kg	Kilogram
L	Litre
LC50	Concentration that kills 50% of the test population of organisms
LD50	Dosage of chemical that kills 50% of the test population of organisms
LOEL	Lowest Observable Effect Level
m	Metre
mg	Milligram
µg	Microgram
mL	Millilitre
MOE	Margin of Exposure
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
NHMRC	National Health and Medical Research Council
NOEL	No Observed Effect Level
NOHSC	National Occupational Health and Safety Commission
OP	Organophosphate
POEM	Predictive Operator Exposure Model
ppb	Parts per Billion
PPE	Personal Protective Equipment
ppm	Parts per Million
RBC	Erythrocyte
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGAC	Technical Grade Active Constituent
WHP	Withholding Period
WSA	Worksafe Australia

Section 3

CHEMISTRY ASSESSMENT

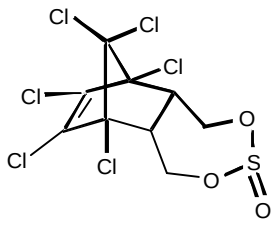
1. ACTIVE CONSTITUENT

1.1 Chemical Identity

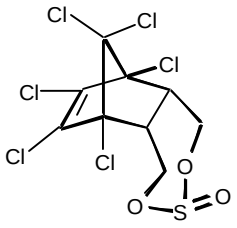
Endosulfan is an organochlorine insecticide. Technical endosulfan consists of a mixture of two stereoisomers, alpha-endosulfan stereochemistry 3α, 5aβ, 6α, 9α, 9aβ-, comprises 64 to 67% of the technical grade; beta-endosulfan stereochemistry 3α, 5aα, 6β, 9β, 9aα-, comprises 29-32% of the technical grade.

Common name :	Endosulfan (ISO, Standards Australia)
IUPAC name:	1,4,5,6,7,7-hexachloro-8,9,10-trinorborn-5-en-2,3-ylenebismethylene) sulfite
CAS name:	6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3-benzodioxathiepin-3-oxide
CAS Registry numbers:	115-29-7 (endosulfan); Technical endosulfan is a mixture of α (959-98-8) and β (33213-65-9) isomers in 2:1 ratio.
Development codes:	Hoe 02671, SHC-A-601, FMC 5462
Empirical formula:	$C_9H_6Cl_6O_3S$
Molecular weight:	406.9

Structural formula:



α-endosulfan



β-endosulfan

1.2 Physical and Chemical Properties

Physical and chemical properties of pure active constituent

Color:	colourless crystalline solid
Odour:	odourless
Physical state;	pure alpha-isomer - crystalline solid pure beta-isomer - crystalline solid
Melting Point:	80 ^{o}C (TGAC); α 109.2^{o}C, β 213.3^{o}C.
Density:	1.8 (TGAC).
Octanol/water partition coefficient:	α 4.74, β 4.79 in *n*-Octanol/Water at pH 5 (Sarafin and Aßhauer, 1987).
Henry's Law Constant:	α 1.48, β 0.07 Pa.m^{3}/mol at 22^{O}C estimated from vapour pressure and water solubility (Weller, 1990). Estimated water/air partition coefficients based on these data are 1660 and 34500.
Dissociation Constant:	Endosulfan does not contain any readily dissociable groups (ie those that can readily gain or lose a proton over the pH range of 5 to 9).
Vapour pressure:	1 x 10^{-5} mm Hg at 25^{0}C 9 x 10^{-3} mm Hg at 80^{0}C 1.7 mPa (TGAC). The vapour pressures of the individual isomers (α 1.9, β 0.09 mPa at 25^{O}C) differ by more than an order of magnitude (Sarafin, 1987a). At 20^{O}C, the vapour pressures are 0.96 and 0.04 mPa. Vapour pressures for endosulfan sulfate at the two temperatures are 0.023 and 0.01 mPa (unsubmitted Hoechst document A50940, cited by Raupach *et al*, 1996).
Specific gravity:	1.745 at 20^{0}C
Solubility in water:	α 0.33, β 0.32 mg/L (22^{O}C). Solubility was determined in double distilled water (pH < 7 due to dissolved CO_2). Solubility is considered to be independent of pH based on the structure (Görlitz, 1990). A column elution method was used for parent isomers (Sarafin, 1979), and for determining the solubility (0.5 mg/L) of the sulfate metabolite (Görlitz, 1986). Earlier measurements found solubilities of 0.15, 0.06 and 0.22 mg/L for α and β isomers and sulfate, respectively (NRCC, 1975).
Solvent solubility:	200 g/L (ethyl acetate, dichloromethane, toluene) 65 g/L (ethanol) 24 g/L (hexane)
Stability:	Stable at ambient temperatures

Hydrolysis:	Hydrolysed very slowly in acidic media, more rapidly in alkaline media. In aqueous solution, it is hydrolysed with a half life of: At 22^0C alpha-isomer: pH 5 T1/2 = >1 year pH 7 T1/2 = 22 days pH 9 T1/2 = 7 hr At 22^0C beta-isomer: pH 5 T1/2 = >1 year pH 7 T1/2 = 17 days pH 9 T1/2 = 5.1 hr

Physical and chemical properties of TGAC

Color:	brown	
Odour:	terpene odour	
Physical state;	crystalline flakes	
Density:	1.8	
Melting point:	70-100^{0}C	
Vapor pressure:	1x10^{-5} mm Hg at 25^{0}C1.7 mPa	
Specific gravity:	1.745 at 20^{0}C	
Solubility in water:	60-150 µg/litre	
Solubility in organic solvents:		
(per 100 g solvent at 20^{0}C)	chloroform	50 g
	xylene	45 g
	benzene	37 g
	acetone	33 g
	carbon tetrachloride	29 g
	kerosene	20 g
	methanol	11 g
	ethanol	5 g

1.3 Chemistry Aspects

The chemistry aspects (manufacturing process, quality control procedures, batch analysis results and analytical methods) of endosulfan TGACs were evaluated and found acceptable.

2. FORMULATION OF END-USE PRODUCT

Endosulfan is used in a formulated form as a broad spectrum contact and stomach insecticide in agriculture. It is available as emulsifiable concentrate and ultra-low-volume (ULV) formulations. The ULV formulation is almost exclusively used in cotton, and the EC formulation used predominantly in cotton but with significant use in tomatoes and vegetables and a broad range of minor uses.

3. DECLARATION OF COMPOSITION

The FAO monograph specifications for Technical endosulfan are listed below:

Endosulfan content:	not less than 940 g/kg
Isomer content:	alpha-isomer: 64 to 67%
	beta-isomer: 29-32%
Impurities:	endosulfan-ether: 10 g/kg maximum
	endosulfan-alcohol: 20 g/kg maximum
	endosulfan-sulfate: 2 g/kg maximum

The active content and impurities present in the technical material are determined by a gas chromatographic method with electron capture detection.

Endosulfan TGACs from 5 approved sources comply with the FAO specifications for endosulfan in respect of endosulfan content, endosulfan-ether and endosulfan-sulfate. However, in the majority of Declarations of Composition approved by the NRA, the limit for endosulfan-sulfate is not included. According to the literature, the toxicity of endosulfan-sulfate is similar to the parent compound.

3.1 Microcontaminants

Other compounds of toxicological significance (sulfotep, N-nitrosamines, halogenated dibenzo-p-dioxins or halogenated dibenzofurans and PCBs) are not expected in endosulfan TGAC due to the raw materials and synthetic chemistry route used.

4. CONCLUSION

The NRA will introduce a compositional standard for all endosulfan TGACs which is based on the latest FAO specifications for this chemical. All Declarations of Composition will be required to demonstrate compliance with the standard by 30 June 1999.

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ATTACHMENT 3: PRODUCTS AND TGACS AFFECTED BY THIS REVIEW

Registered products containing endosulfan

Product Name	**Applicant**
Campbell Endosulfan 350 EC Insecticide	Colin Campbell (Chemicals) Pty Ltd
Endosan ULV Insecticide	Crop Care Australasia Pty Ltd
Endosan Emulsifiable Concentrate Insecticide	Crop Care Australasia Pty Ltd
Davison Endosulfan 350 EC Insecticide	Davison Industries Pty Ltd
Davison Endosulfan 250 ULV Insecticide	Davison Industries Pty Ltd
Farm-oz Endosulfan 240 ULV Insecticide	Farmoz Chemicals Pty Ltd
Farm-oz Endosulfan 350 EC Insecticide	Farmoz Chemicals Pty Ltd
Thiodan ULV Insecticide	Hoechst Schering AgrEvo Pty Ltd
Thiodan Insecticide	Hoechst Schering AgrEvo Pty Ltd
Thiodan EC Insecticide	Hoechst Schering AgrEvo Pty Ltd
Thionex 350 EC Insecticide Spray	Makhteshim-Agan (Aust) Pty Ltd
Nufarm Endosulfan ULV 240 Insecticide	Nufarm Ltd (Laverton)
Nufarm Endosulfan 350 EC Insecticide	Nufarm Ltd (Laverton)
350 EC Bar Insecticide by Sanonda	Sanonda (Australia) Pty Ltd
240 ULV Bar Insecticide by Sanonda	Sanonda (Australia) Pty Ltd

***Approved sources of endosulfan* TGAC**

Endosulfan	Farmoz Pty Ltd	E.I.D. Parry (India) Limited Thane-Belapur Road Thane Maharashtra State INDIA	44288
Endosulfan	Hoechst Schering AgrEvo Pty Ltd	Hoechst Schering AgrEvo GmbH Werk Greisheim Stroofstrasse 27 D65933 Frankfurt am Main GERMANY	44305
Endosulfan	Makhteshim-Agan (Australia) Pty Ltd	Makhteshim Chemical Works Ltd New Industrial Estate Beer-Sheva 84100 ISRAEL	44093
Endosulfan	Pivot Limited	Excel Industries Ltd 6/2 Ruvapari Road Bhavnagar - 364001 Bombay 4000102 INDIA	44012

Products included in the review that are no longer registered

Product Name	**Applicant**
ICI Crop Care Endosan ULV Insecticide	Crop Care Australasia Pty Ltd
Crop King Endosulfan 240 ULV Insecticide	Crop Care Australasia Pty Ltd
Rhone-Poulenc Endosulfan Insecticide	Rhone-Poulenc Rural Aust Pty Ltd
Rhone-Poulenc Endosulfan ULV Insecticide	Rhone-Poulenc Rural Aust Pty Ltd
Velsicol Endosulfan 250 Emulsifiable Concentrate Insecticide	Velsicol Australia Ltd

