Public Release Summary
on

Evaluation of the new active

FLUBENDIAMIDE

IN THE PRODUCT/S

BELT 480 SC INSECTICIDE
&
BELT 240 WG INSECTICIDE

Australian Pesticides and Veterinary Medicines Authority

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FOREWORD

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is an independent statutory authority with responsibility for assessing and approving agricultural and veterinary chemical products prior to their sale and use in Australia.

In undertaking this task, the APVMA works in close cooperation with advisory agencies, including the Department of Health and Aging, Office of Chemical Safety (OCS), Department of the Environment, Water, Heritage and the Arts (DEWHA), and State Departments of Primary Industry.

The APVMA has a policy of encouraging openness and transparency in its activities and of seeking community involvement in decision making. Part of that process is the publication of public release summaries for all products containing new active ingredients and for all proposed extensions of use for existing products.

The information and technical data required by the APVMA to assess the safety of new chemical products and the methods of assessment must be undertaken according to accepted scientific principles. Details are outlined in the APVMA's Manual of Requirements and Guidelines - *The Manual of Requirements and Guidelines - MORAG for Agricultural and Veterinary Chemicals [Ag MORAG & Vet MORAG]*.

This Public Release Summary is intended as a brief overview of the assessment that has been completed by the APVMA and its advisory agencies. It has been deliberately presented in a manner that is likely to be informative to the widest possible audience thereby encouraging public comment.

More detailed technical assessment reports on all aspects of the evaluation of this chemical can be obtained by completing the order form in the back of this publication and submitting with payment to the APVMA. Alternatively, the reports can be viewed at the APVMA Library, 18 Wormald Street, Symonston, ACT.

The APVMA welcomes comment on the usefulness of this publication and suggestions for further improvement. Comments should be submitted to the Pesticides Program Manager, Australian Pesticides and Veterinary Medicines Authority, PO Box 6182, Kingston ACT 2604.

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LIST OF ABBREVIATIONS AND ACRONYMS

ABBREVIATIONS

Time

d	Day
h	Hour
Min	Minute
Mo	Month
Wk	Week
S	Second
Yr	Year

Length

cm	Centimetre
M	Metre
µm	Micrometre
mm	Millimetre
Nm	Nanometre

Volume/Area

ha	hectare
vmd	volume median diameter
µL	Microlitre
L	Litre
mL	Millilitre

Weight

bw	Body weight
g	Gram
kg	Kilogram
µg	Microgram
mg	Milligram
ng	Nanogram
wt	Weight

Dosing

id	Intradermal
im	Intramuscular
inh	Inhalation
ip	Intraperitoneal
iv	Intravenous
po	Oral
sc	Subcutaneous
mg/kg bw/d	mg/kg bodyweight/day

Concentration

m	Molar
ppb	Parts per billion
ppm	Parts per million

Clinical chemistry, haematology, toxicology

A/G	Albumin/globulin ratio
ALT	Alanine aminotransferase (SGPT)
AP	Alkaline phosphatase
AST	Aspartate aminotransferase (SGOT)
AUC	Area under curve
BUN	Blood urea nitrogen
ChE	Cholinesterase
CHO/HGPRT	Chinese hamster ovary/hypoxanthin-guanine-phosphoribosyl transferase (assay)
CPK	Creatine phosphatase (phosphokinase)
GGT	Gamma-glutamyl transferase
Hb	Haemoglobin
Hct	Haematocrit
LDH	Lactate dehydrogenase
LH	Luteinising hormone
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
NTE	Neurotoxic target esterase
PCV	Packed cell volume (Haematocrit)
PT	Prothrombin time
RBC	Red blood cell/erythrocyte
T_3	Triiodothyroxine
T_4	Thyroxine
TSH	Thyroid stimulating hormone (thyrotropin)
WBC	White blood cell/leucocyte
WBC-DC	White blood cells – differential count

Anatomy

CNS	Central nervous system
GIT	Gastro-intestinal tract
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal

Chemistry

GC	Gas chromatography
GLC	Gas liquid chromatography
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
LC-MS/MS	Liquid chromatography, mass spectroscopy
MS	Mass spectrometry
RIA	Radioimmunoassay
TGAC	Technical grade active constituent
TLC	Thin layer chromatography

Terminology

ac	active constituent
ADI	Acceptable Daily Intake
ai	active ingredient
AOEL	Acceptable Operator Exposure Level
ARfD	Acute Reference Dose
bw	bodyweight
DAT	Days After Treatment
DT_{50}	Time taken for 50% of the concentration to dissipate
DT_{90}	Time taken for 90% of the concentration to dissipate
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EC_{50}	concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
Fo	original parent generation
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
IPM	Integrated Pest Management
K_{oc}	Organic carbon partitioning coefficient
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOEL	Lowest Observed Effect Level
LOD	Limit of Detection – level at which residues can be detected
LOQ	Limit of Quantitation – level at which residues can be quantified
MRL	Maximum Residue Limit or Level
MSDS	Material Safety Data Sheet
NOEL	No Observed Effect Level
NOAEL	No Observed Adverse Effect Level
NOEC/NOEL	No Observable Effect Concentration/Level
OP	Organophosphorus pesticide
OC	Organic Carbon
OM	Organic Matter
PPE	Personal Protective Equipment
Q-value	Quotient-value
SC	Suspension Concentrate
TRR	Total Radioactive Residues
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
WG	Water Dispersible Granule
WHP	Withholding Period

Organisations & publications

AGCS	Advisory Group on Chemical Safety
AHMAC	Australian Health Ministers Advisory Council

APVMA	Australian Pesticides and Veterinary Medicines Authority
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
CAC	Codex Alimentarius Commission
DEW	Department of the Environment and Water Resources
ECETOC	European Chemical Industry Ecology and Toxicology Centre
FAO	Food and Agriculture Organisation of the UN
FAISD	First Aid Instructions & Safety Directions
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety
JECFA	FAO/WHO Joint Expert Committee on Food Additives
JMPR	Joint Meeting on Pesticide Residues
NCI	National Cancer Institute
NDPSC	National Drugs and Poisons Scheduling Committee
NHMRC	National Health and Medical Research Council
NOHSC	National Occupational Health & Safety Commission
NTP	National Toxicology Program
OCS	Office of Chemical Safety
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
US EPA	United States Environmental Protection Agency
WHO	World Health Organisation

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INTRODUCTION

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of *BELT 480 SC INSECTICIDE* and *BELT 240 WG INSECTICIDE,* which contain the new active constituent flubendiamide. Both products are proposed for use as foliar insecticides for the control of diamondback moth, cabbage white butterfly, cluster caterpillar, soybean looper and heliothis in brassica vegetables.

The purpose of this summary is to inform the public of the proposed registrations and invite comment on this proposal.

Responses to this Public Release Summary will be considered prior to registration of the products. They will be taken into account by the APVMA in deciding whether the products should be registered and in determining appropriate conditions of registration and product labelling.

Copies of full technical evaluation reports on flubendiamide, covering toxicology, occupational health and safety aspects, residues in food and environmental aspects are available from the APVMA on request (see order form on last page of this document). They can also be viewed at the APVMA library located at the APVMA offices, 18 Wormald St, Symonston, ACT 2609.

Written comments should be received by the APVMA by 3 March 2009. They should be addressed to:

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Applicant

Bayer CropScience Pty Ltd

Details of Products

It is proposed to register *BELT 480 SC INSECTICIDE (BELT 480*), containing flubendiamide at 480g/L as a suspension concentrate formulation, and *BELT 240 WG INSECTICIDE* (*BELT 240*) containing flubendiamide at 240 g/kg as a water dispersible granule formulation.

Flubendiamide is the first member of a new chemical class, the phthalic acid diamides, with a novel chemical structure. The structure consists of three parts; a heptafluoroisopropyl group in the anilide moiety, a sulfonylalkyl group in the aliphatic amide moiety, and an iodine atom at the 3-position of the phthalic acid moiety. The mode of action of flubendiamide exhibits larvicidal activity as an orally ingested toxicant by targeting and disrupting the $Ca2^{+}$ balance. This results in rapid cessation of feeding and extended residual control.

The compound shows strong insecticidal activity especially against lepidopterous pests including resistant strains. Acceptable safety to in-crop non-target organisms has been demonstrated. Flubendiamide exhibits no cross-resistance to conventional chemistries and is

expected to be a suitable agent for controlling lepidopterous insects as part of insect resistance management and integrated pest management programs. Flubendiamide is in a new Group 28 for Insecticides Resistance Management.

BELT 480 and *BELT 240* are proposed for use in Australia as foliar insecticides for the control of diamondback moth, cabbage white butterfly, cluster caterpillar, soybean looper and Heliothis in Brassica vegetables.

Flubendiamide formulations are new to the insecticide market and are not registered anywhere in the world. Registrations are being sought currently in Europe and the US as well as Australia.

CHEMISTRY AND MANUFACTURE

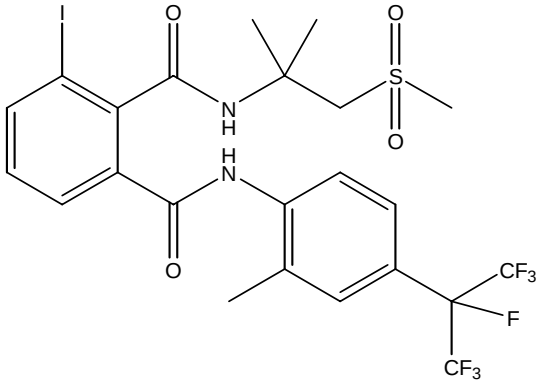
ACTIVE CONSTITUENT

Flubendiamide is a new insecticide with a novel mode of action (ryanodine receptor agonist) that confers good specificity for the target pests.

Manufacturing Site

The active constituent flubendiamide is manufactured by Bayer CropScience AG, Industrial Operations, Alte Heerstrasse D-41538 Dormagen, Germany

Chemical Characteristics of the Active Constituent

Common Name:	Flubendiamide
IUPAC Name:	3-iodo-*N*'-(2-mesyl-1,1-dimethylethyl)-*N*-{4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-*o*-tolyl}phthalamide
CAS Name:	N^2-[1,1-dimethyl-2-(methylsulfonyl)ethyl]-3-iodo-N^1-[2-methyl-4-[1,2,2,2-tetrafluoro-1-(triflouromethyl)ethyl]phenyl]-1,2-benzenedicarboxamide
CAS Number:	272451-65-7
Molecular Formula:	$C_{23}H_{22}F_7IN_2O_4S$
Molecular Weight:	682.4 g/mol
Manufacturer's Codes:	NNI-0001
Structure:	

APVMA Active Constituent Standard for Flubendiamide Active Constituent

Constituent	Specification	Level
Flubendiamide	Flubendiamide	Not less than 960 g/kg

Physical and Chemical Properties of Pure Active Constituent and Technical Material

Colour	White crystalline powder (99.1% pure)
Physical state	Solid
Odour	No characteristic odour
Melting point	217.5 – 220.7°C (99.6% pure)
Boiling point	Not feasible due to thermal degradation
Relative Density @ 20 ^{o}C	1.659
Water Solubility (pH 4 – 10)	29.9 ± 2.87 µg/L at pH 5.98 Solubility is not pH dependent in the range pH 4 – 10.

Solubility in Organic Solvents @ 20 ºC	Methanol: 26.0 g/L Acetone: 102 g/L *n*-heptane: 0.0008 g/L Ethyl acetate: 29.4 g/L 1,2-Dichloroethane: 8.12 g/L
Vapour Pressure @ 20 ºC	$< 10^{-4}$ Pa (at 200 ºC)
Partition Co-efficient (1-octanol/water) @ 19 ºC	log P_{ow} = 4.13 ± 0.02 at pH 4 log P_{ow} = 4.2 ± 0.02 at pH 6 log P_{ow} = 4.14 ± 0.02 at pH 7 log P_{ow} = 4.11 ± 0.04 at pH 9

PRODUCT

Distinguishing name: **Belt 240 WG Insecticide**
Formulation type: Water dispersible granule
Active constituent concentration: Flubendiamide 240 g/kg

Physical and Chemical Properties of the Product

Appearance	Brown granules
Odour	Weak mouldy
Acidity/Alkalinity	Not applicable (pH not ≤4 or ≥10)
Density	Pour: 0.87 g/mL Tap: 0.91 g/mL
Flash point	Not applicable
Flammability	Not flammable
Contact with water emit flammable gases	Does not liberate gases in hazardous amounts
Explosive properties	Not explosive
Spontaneous combustion	Relative spontaneous ignition temperature: 287 °C
Oxidising properties	No oxidising properties
Self-heating substance	Does not undergo spontaneous combustion at 140 °C using a 1 L cube
Dielectric breakdown voltage	Not applicable, formulation is not intended for use around electrical equipment
Dangerous goods classification	Not dangerous good according to the Australian Code of Transport of Dangerous Goods by Road and Rail

Distinguishing name: **Belt 480 SC Insecticide**
Formulation type: Suspension Concentrate
Active constituent concentration: Flubendiamide 480 g/kg

Physical and Chemical Properties of the Product

Appearance	White suspension
Odour	Weak aromatic
Acidity/Alkalinity	Not applicable (pH not ≤4 or ≥10)
pH	6.7 (undiluted)
Density	D_4^{20} = 1.23

Active content	480 g/L
Wet sieve test	Residue on 75 µm sieve; 0.03%
Suspensibility	Chemical assay: 99.2% (0.01% preparation) 99.6% (0.225% preparation)
Viscosity	Dynamic; 0.053 Pa.S Kinematic: 4.3×10^{-5} m^2/s
Surface tension	49.5 mN/m
Flash point	No flash point up to boiling point
Flammability	Not flammable
Explosive properties	Not explosive
Oxidising properties	No oxidising properties
Corrosive hazard	Slightly corrosive to mild steel, copper, tin plate, aluminium and brass
Dielectric breakdown voltage	Not applicable, formulation is not intended for use around electrical equipment
Dangerous goods classification	Not dangerous good according to the Australian Code of Transport of Dangerous Goods by Road and Rail

Recommendation

Based on a review of the chemistry and manufacturing details provided by the applicant, registration of Belt 240 WG Insecticide and Belt 480 SC Insecticide are supported.

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TOXICOLOGICAL ASSESSMENT

Summary

Bayer CropScience is seeking registration for two products, *BELT 480* Insecticide and *BELT 240* Insecticide, containing the new insecticidal active constituent, flubendiamide.

Flubendiamide belongs to the phthalic acid diamide chemical class, a ryanodine receptor agonist, which activates ryanodine-sensitive intracellular calcium release channels in insect neurons. Flubendiamide shares its mode of action with chlorantraniliprole, another diamide insecticide. The release of calcium causes muscle contraction, resulting in the death of the insect. This mode of action has been shown to be highly specific to insect ryanodine receptors and not to affect mammalian ryanodine receptors.

The data submitted were complete and comprehensive, and included the full battery of studies currently required for registration purposes. They included toxicokinetics and acute, short-term, sub-chronic, and chronic studies, as well as some mechanistic and neurotoxicity studies. Studies were well conducted and conformed with current test guidelines and protocols. Additionally, a series of acute and genotoxicity studies were provided for the two products and the main metabolites. The scientific and regulatory quality of the toxicology database is high and is considered sufficient to clearly define the toxicity of flubendiamide.

Flubendiamide was moderately well absorbed by the oral route, but due to biliary excretion it was mostly excreted in the faeces. The log K_{ow} value suggests that flubendiamide is lipophilic; repeat dose toxicokinetic studies indicate some potential for accumulation in fat tissue. Flubendiamide showed little acute toxicity. One of the most sensitive endpoints was liver effects, which were observed in all species tested via both the oral and dermal routes and in short term, subchronic and chronic dosing regimes. Effects on the thyroid in rats were considered to be secondary to liver effects. Blood was also a target organ of toxicity, with altered haematological parameters (microcytic anaemia) observed in rat studies. Reproduction studies disclosed delay in preputial separation and enlarged eyeballs in offspring; however, the NOEL for these effects was higher that that established in a one year dietary rat study. Developmental studies were negative. Flubendiamide and its derivatives were not found to be genotoxic.

An ADI of 0.01 mg/kg bw/d was established for flubendiamide based on effects on liver and blood in a 1 year dietary study in rats with a NOEL of 1 mg/kg bw/d, and using a 100-fold safety factor. An ARfD was not established because significant toxicity was not observed in any single dose study.

Public exposure during use of the products is considered unlikely. Also, worker exposure levels will be low compared with the relevant NOEL and workers are not expected to be at risk from using the products under consideration.

At its 51st meeting, on 16-17 October 2007, the NDPSC agreed that, based on the acute toxicity, flubendiamide be included in Schedule 5 of the SUSDP.

The toxicology data and other information on the product provided and considered in this assessment justify the Safety Directions established in this evaluation.

The proposed use of "*BELT 480*" and "*BELT 240*" is not considered to pose an undue health hazard to humans according to the criteria stipulated in Section 14 (5)(e) of the Ag/Vet Code Act of 1994.

Absorption, distribution, metabolism and excretion in mammals

Rate and extent of oral absorption	Greater than 20%
Dermal absorption	2% or less in monkeys
Distribution	Highest tissue concentrations were found in the liver followed by intestines, kidneys and lungs.
Potential for accumulation	High bioaccumulation in fat; plasma:fat ratio 4-fold higher in females (1:19) compared to males (1:5), following a single oral administration.
Rate and extent of excretion	93-99% excreted via faeces; ~75% after 24h, > 90% after 48h.
Metabolism	Poorly metabolised, excreted predominately as unchanged parent compound.
Toxicologically significant compounds (animals, plants and environment)	Iodophthalimide metabolite
Toxicologically relevant compounds For Residue Definition	Iodophthalimide metabolite

Acute toxicity

Rat oral LD_{50} (mg/kg bw)	>2000 (no deaths)
Worst oral LD_{50} in other species	No data
Rat dermal LD_{50} (mg/kg bw)	>2000 (no deaths)
Worst dermal LD_{50} in other species	No data
Rat inhalation LC_{50} (mg/m^3)	>68.5 (no deaths)
Worst inhalation LC_{50} in other species	No data
Skin irritation	Non-Irritant
Eye irritation	Slight Irritant
Skin sensitization	Non-sensitiser (maximisation)

Short-term toxicity

Target/critical effect	Hepatotoxicity, thyroid toxicity, haematological perturbations
Lowest relevant oral NOEL (mg/kg bw/d)	4; (28-d dietary exposure in rats)
Lowest relevant dermal NOEL (mg/kg bw/d)	100; (30-d dermal study in rats)
Lowest relevant inhalation NOEC (mg/m^3)	NA
Genotoxicity	Non-genotoxic

Long-term toxicity and carcinogenicity

Target/critical effect	Increased liver weights, microcytic anaemia
Lowest relevant NOEL (mg/kg bw/d)	1.0; (1 year dietary study in rats)

Carcinogenicity	None.

Reproductive toxicity	
Reproduction target/critical effect	Delayed preputial separation.
Lowest relevant reproductive NOEL (mg/kg bw/d)	16; (1-generation reproduction study in rats)

Developmental target/critical effect	No developmental effects noted up to 1000 mg/kg bw/d in rat and rabbit
Lowest relevant developmental NOEL (mg/kg bw/d)	1000

Neurotoxicity	No effects noted in an acute oral neurotoxicity screening study with doses up to 2000 mg/kg bw

Summary	NOEL (mg/kg bw/d)	Study	Safety factor
ADI (0.01 mg/kg bw/d) [hepatotoxicity, microcytic anaemia]	1.0	1 year dietary in the rat	100
ARfD (mg/kg bw)	Not established since no significant toxicity could be related to a single dose in any study.		
NOEL for OHS Risk Assessment [hepatotoxicity]	100	30-d dermal in rats	

Summary of Toxicological Studies

Toxicokinetics and Metabolism Studies

Toxicokinetics of flubendiamide was investigated in rats following administration of a single oral dose at 2 mg/kg bw [phthalic ring-(U)-^{14}C-flubendiamide] or 200 mg/kg bw [aniline-(U)-^{14}C-flubendiamide]. The absorption via the GI tract based on urinary excretion data was relatively low (~5%). The T_{max} was 12 and 6 h in males and females, respectively, suggesting faster absorption in females than males. However, the $T_{1/2}$ was about 3-fold longer in females (38 h) compared to males (13 h). Distribution into tissues was extensive with the highest amounts of radioactivity being detected in the liver followed by intestines, kidneys and lungs. Tissue levels declined rapidly, except for that in the liver and fat tissue, where it was slow. At 168 h post dose, approximately 1% and 5% of the administered dose was retained in the residual carcass of males and females, respectively. Metabolism was fairly extensive in males compared to females. A maximum of about 2% of the administered radioactivity was eliminated in urine of males, but this was about 0.4% in females suggesting slow elimination. Elimination in faeces was about 93-99% of the administered dose. Females eliminated greater amounts of the parent compound in faeces than males. The data showed clear gender differences in toxicokinetics of flubendiamide in rats (Motoba, 2005a).

Following repeat dosing of flubendiamide to rats at 2 mg/kg bw/d for 14 d, maximum plasma levels were seen at 9 h after the last dose. Based on the radioactivity eliminated in urine and that remained in the residual carcass, the absorption via the GI tract was relatively low, being about 1.0% of the administered dose. At 9 h after the last dose, the highest levels in males were found in the liver followed by large intestines, fat, adrenals and kidney, whilst that in females were seen in fat and the liver followed by large intestines, adrenals, bone marrow, small intestines and salivary glands. In males, the tissue levels declined with time to low or non-detectable levels 168 h after the last dose, but some tissues retained about 5-15% of the 9 h levels. In females, the tissue concentrations at 9 h were generally 2 – 3-fold greater than the levels in males. Decline of tissue levels in females was slow and a greater range of tissues retained flubendiamide (at about 25% of the 9 h levels) than males at 168 h after the last dose. A tendency for retention was seen in tissues such as fat, plasma and the liver, ovary, bone marrow, kidney and thyroid of females. Slow elimination from organs/tissues probably due to slow metabolism and excretion may lead to tissue accumulation of flubendiamide and its metabolites in females as suggested by increasing plasma to fat tissue concentration ratio. The majority of radioactivity in the fat of both sexes represented the parent compound. In females, about 95% of radioactivity in fat was accounted for by the parent compound, with only trace quantities of one metabolite. Three metabolites were detected in fat tissue of males. In both sexes, urinary metabolites and the parent compound accounted for <1% of its total radioactivity. About 82% and 91% of the faecal radioactivity in males and females, respectively, was for unchanged flubendiamide. The data show that more extensive metabolism occurred in males than in females. Excretion of the dosed radioactivity mainly occurred via faeces, which became steady after administration of about 2 doses to males and 7 doses to females, probably suggesting some tissue accumulation. The amount of radioactivity detected in the residual carcass was about 0.02% and 0.42% of the total dose for males and females, respectively. The data show clear gender differences in metabolism and toxicokinetics in rats. These included faster absorption, low metabolism, wider tissue distribution and retention, and slower excretion in females than males. Based on a low plasma:fat concentration ratio that decreased with time, of particular concern was the increased tissue retention of the test material in fat and a range of other tissues of females (Motoba, 2005b).

Distribution of flubendiamide in plasma, the liver and fat tissue was examined in mice and rats following administration of repeated doses at 200 mg/kg bw/d for 14 days. Except for female rats, the plasma of both species generally contained comparable levels of

flubendiamide at all sampling times. In female rats, the plasma concentrations were about 10-fold greater than in mice and male rats. In mice, there were no remarkable gender differences in concentrations in the liver. However, the levels in fat tissue was about 2- to 4-fold greater in males than females. There were significant sex differences in the liver and fat tissue concentrations in rats. The levels in the liver and fat tissue of females were approximately 20-fold and 8-fold greater in females than males, respectively. Generally, the liver and fat tissue levels in mice were about 2- to 4-fold lower than that in rats. The data showed that there is a possible tendency for accumulation in the liver and fat tissues of female mice and rats. The metabolite, flubendiamide-iodophthalimide was detected only in the fat tissue of rats, showing a tendency to accumulate in this tissue in female rats (Motoba, 2005c).

In this study, *in vitro* metabolism of radiolabelled flubendiamide was investigated using microsomes obtained from mice, rats, dogs and humans. To identify the specific microsomal P450 isoforms responsible for the metabolism of the test material, those microsomes expressing specific P450 isoform genes and specific antisera and antibodies for selected P450 isoforms were used. Sex-related differences in metabolism was seen with both mouse and rat liver microsomes, where increased metabolism (by over 30%) was seen with microsomes of male mice. In rats, only male liver microsomes metabolised the test material. There were no apparent sex differences in metabolism with dog microsomes. Female human liver microsomes showed increased metabolism (about 37%) compared to males, showing a contrasting sex difference relative to mouse and rat liver microsomes. The metabolism in rats may be mediated by certain P450 isoform(s) immunologically indistinguishable from CYP2C11. On the other hand recombinant rat-CYP2C11 could not metabolise flubendiamide to its benzyl alcohol derivative, although rat CYP3A2 exhibited some capacity for oxidation, albeit at a low level. These data suggest that the oxidation reaction is probably mediated by certain specific microsomal P450 isoforms that are indistinguishable from rat CYP2C11. Under *in* vitro conditions human CYP3A4 isoform was principally involved in the oxidation of flubendiamide to form its benzyl alcohol derivative. There was no apparent quantitative sex difference in metabolism (Motoba, 2005d).

Percutaneous Absorption

Following intravenous administration of ^{14}C-flubendimaide (30 µg/kg bw) to a male rhesus monkey, 8% of the administered dose was eliminated via urine over 316 h, with 81% being eliminated in faeces. The overall total recovery of radioactivity for the i.v. dosed animal was 92.8%. Dermal administration of ^{14}C-flubendimaide SC 480 (46.5 µg/kg bw) resulted in excretion of approximately 0.01% and 0.4% of the administered dose in urine and faeces, respectively, suggesting very low absorption through the skin. The overall total recovery of radioactivity for dermally treated animal was 97.7%, with the majority of the topically applied dose (95.7%) recovered from the application site. The dermal absorption was determined to be approximately 2% of the administered dose in this monkey, treated for 8 h (Sebesta, 2005a).

Dermal administration of ^{14}C-flubendimaide SC 480 (dose range 11.5 – 22.7 µg/kg bw; 24 cm^2 skin area) to the back of four male rhesus monkeys for 8 h resulted in excretion (during a 120 h period) of ~0.01% and <0.01% of the administered dose in urine and faeces, respectively, suggesting very low absorption through the skin. The majority (~99%) of the applied dose was associated with patch (~4.68%), and soapy water swabs (81.02%). Total recoveries of the dose were greater than 100% for all monkeys. The mean dermal absorption was determined to be approximately 0.02% of the administered dose in the monkeys, 100-fold less than that observed in the preliminary study.

Acute Studies

Active

Flubendiamide has low acute oral (LD_{50} >2000 mg/kg bw) and dermal (LD_{50} >2000 mg/kg bw) toxicity in rats. Due to the property of the chemical and technical difficulties, acute inhalational toxicity could not be adequately tested. At the maximum attainable concentration of 68.5 mg/m^3, no clinical signs or mortality were observed in the animals. Flubendiamide was a slight eye irritant in rabbits but was not a skin irritant in the same species, nor a skin sensitiser in guinea pigs.

Additionally, acute oral toxicity studies were conducted for 9 flubendiamide derivatives and they all have low acute oral toxicity (LD_{50} >2000 mg/kg bw) in rats.

Products

Belt® 480 SC Insecticide, containing 480 g/L flubendiamide, is of low acute oral (LD_{50} >2000 mg/kg bw), dermal (LD_{50} >4000 mg/kg bw) and inhalational (LC_{50} >2564 mg/m^3) toxicity in rats. It was a slight eye irritant, but was not a skin irritant in rabbits, nor a skin sensitiser in guinea pigs when tested using the Buehler method.

Belt® 240 WG Insecticide, containing 240 g/L flubendiamide, is of low acute oral (LD_{50} >2000 mg/kg bw) and dermal (LD_{50} >2000 mg/kg bw) toxicity in rats. It was a slight eye irritant, but not a skin irritant in rabbits, nor a skin sensitiser in guinea pigs when tested using the Buehler method.

Based on low acute oral and dermal toxicities of flubendiamide, and low inhalational toxicity of the product Belt® 480 SC Insecticide (containing approximately ~50% of flubendiamide), it is expected the acute inhalational toxicity of flubendiamide will be low.

Short-term Studies

Flubendiamide was incorporated into the diet to provide concentrations of 0, 20, 200, 2000 or 20000 ppm and administered *ad libitum* to groups of mice for four weeks. There were no treatment-related mortalities or clinical signs. The short term toxicity of flubendiamide in the mouse was limited to liver effects, which were more pronounced in males. There were treatment-related increases in AP activity observed in females at 20000 ppm. In the highest dose (20000 ppm) males, two animals had dark coloured livers, one had accentuated lobular liver pattern and another had enlargement of the liver. These abnormalities were also observed in one male at 2000 ppm. A statistically significant increase in relative liver weight was seen in males at 20000 ppm. Although statistical significance was not achieved, there were increases (about 7-9%) in both absolute and relative liver weights in both sexes ≥2000 ppm relative to controls. Except for females at 2000 ppm, the incidence of centrilobular hepatocyte hypertrophy was significantly elevated in both sexes ≥2000 ppm. Fatty change in centrilobular hepatocytes was seen in males ≥2000 ppm and in females at 20000 ppm. Based on treatment-related increased incidence of histopathological liver abnormalities ≥2000 ppm, the NOEL was considered to be 200 ppm (30 mg/kg bw/d).

Rats received flubendiamide incorporated in the diet at 0, 20, 50, 200, 2000 or 20000 ppm for four weeks. There were no mortalities or any clinical signs. The short term toxicity of the chemical in rats involved liver, thyroid and changes in haematological parameters. Enlargement of the liver was noted in females ≥ 2000 ppm. Significant increases in liver weights were seen in males at ≥ 2000 ppm and females at ≥ 200 ppm with associated abnormal histopathology. Clinical chemistry showed statistically significant decrease in AP activity in males at 20000 ppm, and in females at doses ≥ 2000 ppm, decreased SGOT in both sexes at 20000 ppm and SGPT in males at 20000 ppm, increased GGTP activity in females ≥ 200 ppm, and dose-related decreases in plasma ChE activity in females ≥ 2000 ppm. Statistically significant decreases in MCV were noted in males at 20000 ppm and females at

doses ≥ 2000 ppm. Thyroid weights were also increased in both sexes at 2000 ppm and above with associated abnormal histopathology noted in males at 20000 ppm and females at doses ≥ 2000 ppm. Based on the toxic effects on the liver of females at doses ≥ 200 ppm, a NOEL of 50 ppm (4 mg/kg bw/d) was established.

Flubendiamide was incorporated into the diet to provide concentrations of 0, 40, 400, 4000 or 40000 ppm for four weeks in a dose-range finding study in dogs. There were no treatment-related mortalities during the study, but the incidence of loose stools was elevated in both sexes at 40000 ppm. Clinical chemistry showed time and dose-related increases in AP activity ≥400 ppm, suggestive of liver disease. A tendency toward an increase in liver weights was noted in animals at 40000 ppm. A NOEL was not established as this was a dose-range finding study.

Groups of rats received repeated dermal applications (under semi-occlusive conditions for 6 h) of flubendiamide at 0, 10, 100 or 1000 mg/kg bw/d for 30 days. There were no treatment-related clinical signs, local skin reactions or effects on skin-fold thickness. Liver weights (absolute and relative) were significantly increased at the high dose of 1000 mg/kg bw/d in both sexes and were associated with abnormal histopathology (fatty deposits) in the periportal zone of the liver. This abnormality was also noted in males but in a dose-independent manner. A statistically significant decrease in SGOT (AST) was observed in females at the high-dose. Females of the 1000 mg/kg bw/d showed a slightly higher incidence of follicular cell hypertrophy of the thyroid gland compared to control and lower dose groups, but the thyroid weight was not recorded. Statistically significant perturbations were seen in several haematological parameters in all treated animals. Owing to the lack of clear dose-response relationships and the fact that the changes were generally small (<5%), only those effects seen at the high-dose were considered to be treatment-related. Based on the effects on liver, thyroid, SGOT activity and some haematological parameters at 1000 mg/kg bw/d, the NOEL was considered to be 100 mg/kg bw/d.

Subchronic Studies

Flubendiamide was incorporated into the diet of mice to provide concentrations of 0, 50, 100, 1000 or 10000 ppm for 90 days. There were no treatment-related mortalities or any clinical signs. As with the short-term studies, the target organ was the liver. A statistically significant increase in total plasma bilirubin level was seen in females at 10000 ppm. Necropsy showed a significantly increased incidence of dark coloured livers in males at 10000 ppm. Significantly increased relative liver weights were observed in males at 10000 ppm, and both absolute and relative liver weights were increased in females at doses ≥1000 ppm. A dose-related increase in the incidence of centrilobular hepatocyte hypertrophy and fatty change in centrilobular hepatocytes was seen in both sexes ≥1000 ppm. In addition, the relative weights of the ovaries in females were elevated at 10000 ppm. Based on the findings, the NOEL was considered to be 100 ppm (12 mg/kg bw/d).

Rats received flubendiamide in the diet at 0, 20, 50, 200, 2000 or 20000 ppm for 90 days. There were no treatment-related mortalities or any clinical signs. Increases in food consumption and body weights were seen in males at doses ≥2000 ppm. In males, platelet counts were elevated at doses ≥2000 ppm and MCV was increased at 20000 ppm. In females, the effects were more pronounced with several parameters showing significant perturbations at doses ≥2000 ppm, with MCV values displaying dose-related decreases at doses ≥200 ppm. Statistically significant and treatment-related clinical chemistry alterations occurred in males at 20000 ppm and in females at doses ≥2000 ppm. At necropsy, increased incidences of dark coloured livers were seen in both sexes at 20000 ppm, and enlargement of the liver in males at the top-doses and in females at doses ≥2000 ppm. Treatment caused significant increases in liver weights in males at doses ≥2000 ppm, and in females at doses ≥200 ppm. Only in

females, increases in kidney weights at dose ≥2000 ppm and adrenal weights at 20000 ppm were also observed. Both the absolute and relative weights of the ovary and relative heart weight were elevated in females at 20000 ppm. Although no statistical significance was achieved, about 12-13% increases in thyroid weights were noted in females at doses ≥2000 ppm. Histopathology revealed significantly increased incidences of fatty changes in periportal hepatocytes at doses ≥200 ppm, and hypertrophy of hepatocytes and follicular cells of the thyroid at dose ≥2000 ppm were seen in females. The effects of flubendiamide were more pronounced in females than males, and the data showed that some abnormalities seen at doses ≥2000 ppm were not reversible even after a 4-week recovery period. Based on the findings, the NOEL for the study was considered to be 50 ppm (1.2 mg/kg bw/d).

Flubendiamide was incorporated into the diet to provide concentrations of 0, 100, 2000 or 40000 ppm for 90 days in a study in dogs. There were no treatment-related mortalities. The incidence of loose stools was elevated in males at 40000 ppm, and in females at doses ≥2000 ppm. Body weight gain in males was significantly reduced at doses ≥2000 ppm. Treatment-related decreases in APTT and increases in AP activity were observed in both sexes at doses ≥2000 ppm in time-related manner. In females, triglyceride levels were elevated at doses ≥2000 ppm in a time dependent manner. Although no statistical significance was achieved, absolute and relative weights of the liver and adrenal glands tended to increase in both sexes at doses ≥2000 ppm. A similar trend was seen with thyroid weights of males at 40000 ppm and in females at doses ≥2000 ppm. Histopathology revealed cortical hypertrophy of the adrenals in 2/4 males and 1/4 females at 40000 ppm, and in 2/4 females at 2000 ppm. Slight microgranuloma in the liver was seen in 2/4 males and 1/4 females at 40000 ppm. Based on clinical signs in females, perturbations in some clinical chemistry parameters in males and/or females, and histopathological abnormalities in the adrenal glands of females at doses ≥ 2000 ppm, the NOEL was considered to be 100 ppm (2.6 mg/kg bw/d).

Chronic Studies

Groups of rats received flubendiamide at 20, 50, 2000 and 20000 ppm in the basal diet for one year. There were no treatment-related mortalities. Detailed clinical observations revealed an increase in rearing behaviour in 20000 ppm females. Food intake was increased in both sexes at 20000 ppm; however, there was no change in bodyweight gain or food efficiency. Slight microcytic anaemia was observed in females at 50 and 2000 ppm, and in both sexes at 20000 ppm, including reduced hematocrit, haemoglobin concentration, mean corpuscular volume and mean corpuscular haemoglobin. In bone marrow cytology, females at 20000 ppm had decreased erythroblasts. Platelet count was increased at doses ≥2000 ppm in both sexes. Males treated with 2000 and 20000 ppm showed dose-related increases in prothrombin and activated partial thromboplastin times. Plasma cholinesterase was decreased in females dosed at doses ≥2000 ppm, but there were no toxicologically relevant changes to erythrocyte cholinesterase or brain cholinesterase activities at any dose level. Males at 2000 ppm and above had increased liver weights, but no macroscopic lesions. Also, males at 20000 ppm had increased thyroid weight. In females, significantly increased liver weights were seen at 50 ppm and above. At 20000 ppm, the livers were dark in colour and observably enlarged. Females at 2000 ppm and above also had increased kidney and adrenal weights and decreased spleen weight. Ovary weight was increased in 20000 ppm females. Males and females at and above 2000 ppm had an increase in follicular cell hypertrophy of the thyroid. Females at 2000 ppm and above showed statistically significant increases in the incidence of periportal fatty change and diffuse hypertrophy of hepatocytes in the liver. There were no differences in the incidence of neoplastic lesions between control and treated groups. Administration of flubendiamide to rats for one year revealed significant toxicological differences between the sexes. The NOEL in this study was 20 ppm (1.0 mg/kg bw/d), based on microcytic anaemia and increased liver weights at the next highest dose.

Groups of beagle dogs (4/sex/dose) received flubendiamide at 0, 100, 1500 or 20000 ppm in the basal diet for one year. There were no treatment-related deaths. At 20000 ppm there was an increased incidence of loose stools and decreased bodyweight in both sexes. Red discharges from the vagina were observed in all females in all treated groups versus 1/4 in the control group. Platelet count was increased in 20000 ppm females. At 1500 ppm and above in both sexes, activated partial thromboplastin time was shortened, and plasma alkaline phosphatase activity was increased. Glutamic pyruvic transaminase was increased in both sexes at 20000 ppm and in males at 1500 ppm. In males and relative to the controls, albumin and the albumin/globulin ratio was decreased at and above 1500 ppm. Triglycerides and plasma cholinesterase activity were increased in males at 1500 ppm and in both sexes at 20000 ppm. Liver weights were increased in both sexes at 1500 ppm and above, and in 20000 ppm females there was an increased incidence of enlarged livers which were dark in colour. There was an increased incidence of brown pigment deposition in the Kupffer cells in the liver in both sexes at 20000 ppm. Relative thyroid weight was increased in 20000 ppm females. There was an increase in the incidence of skin granulomas in both sexes at 20000 ppm. The NOEL in this study was 100 ppm (2.2 mg/kg bw/d), based on hepatotoxicity at the next highest dose of 1500 ppm.

Groups of rats (50/sex/dose) received flubendiamide at 0, 50, 1000 or 20000 ppm admixed to the basal diet for two years. There was no treatment-related mortality or significant clinical observations. Body weight gains were reduced in 20000 ppm females. Females treated at 1000 ppm and above showed increased hair loss, associated with increase incidence of folliculitis. Eosinophils were decreased in males at 1000 ppm and above. In males, liver weight was increased 1000 ppm and above, associated with abnormal histopathology and masses. In males at 20000 ppm, increases were seen in thyroid and testis weight, and there was an increased incidence of dark in colour spleen. In females, liver weights were increased at 1000 ppm and above, and this was associated abnormal gross pathology and histopathology. In females, increases were seen in kidney weight at 1000 ppm and above, and in thyroid, heart, adrenals and ovary weight at 20000 ppm. In males, there was increased incidence of dark in colour thyroid at 1000 ppm and above, associated with abnormal histopathology at 20000 ppm. Females at and above 1000 ppm had increased follicular cell hypertrophy of the thyroid. There was a trend of increased chronic nephropathy in females. There were no toxicologically relevant differences in the incidence of neoplastic lesions between control and treated groups. The NOEL in this study was 50 ppm (1.7 mg/kg bw/d).
Groups of mice (52/sex/dose) received flubendiamide at 0, 50, 1000 or 10000 ppm in the basal diet for 18 months. There was no statistically significant differences in mortality, food consumption, body weight or clinical signs between treated and control animals. Eosinophils were decreased in males at 10000 ppm. This study did not include detailed haematology or clinical chemistry. In both sexes, liver weights were increased at 1000 ppm and above, which was associated with abnormal gross pathology and/or histopathology of the liver. In both sexes, enlarged thyroid was seen at 1000 ppm and above, with thyroid weights significantly increased at 10000 ppm relative to controls. In the thyroid, males at 1000 ppm and above had increased incidences of: follicular cell hypertrophy with hydropic change, increased large-size follicles, and altered colloid. In females at 10000 ppm, there were increases in altered colloid and follicular cell hyperplasia. The NOEL in this study was 50 ppm (4.4 mg/kg bw/d), based on the increased organ weights at the next dose level.

Reproduction Study

In a preliminary reproduction toxicity study, rats were fed flubendiamide in the diet at 0, 20, 200, 2000 or 20000 ppm for approximately 11 weeks (equivalent to 1.17/2.23, 11.68/22.2, 118.3/224 and 1196/2214 mg/kg bw/d in male/females, respectively). In parental animals, no treatment-related clinical signs or mortality were noted. No treatment-related effects were noted on body weight, body weight gain, food consumption or reproductive performance throughout the study. In the 2000 ppm and 20000 ppm group, 5/8 and 6/8 females showed

enlargement and/or dark coloration of the liver. In the 2000 and 20000 ppm treatment groups of either sex, significantly (either biologically or statistically) higher absolute and relative liver weights were noted compared to controls. In the offspring, there were no clinical signs attributable to the test substance. No treatment-related differences were noted in the number of pups delivered, sex ratio or the viability index. Mean pup body weights in the 20, 200 and 2000 ppm groups were comparable to those in the control group throughout the lactation period. In the 20000 ppm group, the mean body weights of male and female pups on LD 21 were lower than controls (-9%, $p<0.05$). No treatment-related gross pathological findings were noted in pups in any treatment group (Hojo, 2001).

In a two-generation reproduction study, parental (F0/F1) rats received flubendiamide in the diet at 0, 20, 50, 2000 or 20000 ppm for ~16 weeks (males) or 18-19 weeks (females) (doses were equivalent to 0, 1.21-2.03, 3.04-5.07, 121.2-196 and 1215-2029 mg/kg bw/d, respectively). There were 4 treatment-related maternal deaths (1/4 at 2000 ppm; 3/4 at 20000 ppm) that occurred during delivery on GD 21-3 without clinical signs. No treatment-related effects were noted on food consumption, body weight or body weight gain in either sex of the F0 or F1 generations. In F1 parental males, there was a delay in sexual developmental as measured by the degree of preputial separation that was considered to be related to treatment in the 2000 and 20000 ppm groups. During gross pathological examinations, the incidence of dark coloured livers was significantly elevated in F0 and F1 parental females compared to controls at 2000 and 20000 ppm. With the exception of F0 males in the 2000 ppm group, brown colour of the thyroids was also observed in F0 and F1 parental males and females in the 2000 and 20000 ppm groups. In 2000 ppm F0 males only, significant ($p<0.01$) increases were noted in the relative liver weight and absolute thyroid weight. In the 20000 ppm group, both F0 and F1 males had significantly increased absolute/relative liver and thyroid weights compared to controls. Also in the 20000 ppm group, there was a significant ($p<0.01$) increase in absolute adrenal weight in F0 males, and a decrease in the relative pituitary weight in F1 males compared to controls. In F0 females from the 2000 and 20000 ppm groups, significant increases were noted in the absolute and relative liver weights, absolute adrenal weights, absolute and relative kidney, uterus and thyroid weights and absolute ovary weights, as well as decreases in relative spleen weights. In F1 females treated with 2000 or 20000 ppm, significant increases were also noted in the relative pituitary weights, absolute and relative weights of the liver, kidneys and spleen and absolute thyroid weights. The significant increase in liver and thyroid weights in both parental (F0/F1) sexes treated with 2000 and 20000 ppm was associated with a significant increase incidence of abnormal histopathology (diffuse and follicular cell hypertrophy) in those organs and was considered to be related to treatment. Female livers were more severely affected than males. Although it was only noted in females, the decreased spleen weights and increased kidney weights in both generations was considered treatment-related due to the increased severity with increasing dose. The increased relative ovary and uterus weights observed only in the parental F0 females could not be discounted as being unrelated to treatment, as a similar effect was noted in long term feeding studies in Fischer rats at the same doses (Enomoto, 2004). The decrease in relative pituitary weights of F1 animals was coupled with abnormal histopathology in that organ, thus was considered be related to treatment.

In the offspring (F1/F2 pups), there were no treatment-related, clinical signs or differences in the number of pups delivered, sex ratio or the viability index noted. Relative to the control group, there was a greater incidence of enlarged eyeballs in pups noted in the 2000 and 20000 ppm groups, which could not be discounted as being unrelated to treatment. In the 2000 and 20000 ppm groups, statistically significant decreases were noted in absolute and relative weights of the spleen and liver from both pup F1/F2 sexes and was considered to be treatment-related. Histopathological examinations of F1/F2 male and female pups in the 2000 and 20000 ppm groups revealed hypertrophy of follicular cells in the thyroid, diffuse fatty change of the liver and hypertrophy of hepatocytes, brown pigmentation and proliferation of bile ducts of the liver. The NOEL for reproductive performance is 50 ppm (3.61 mg/kg bw/d)

on the basis that in F1 parental males a treatment-related delay in preputial separation was noted in males treated with 2000 and 20000 ppm. This NOEL is supported by the decreased liver weights of parental animals and pups in the 2000 and 20000 ppm groups, which was associated with abnormal histopathology, as well as decreased spleen and thyroid weights in parental animals at these doses (Hojo, 2004a).

In a one-generation reproduction study, parental (F0/F1) rats received flubendiamide in the diet at 0, 50, 200, 2000 or 20000 ppm (equivalent to 0, 2.97-5.28, 11.90-21.00, 117.2-205.5 and 1187-2088 mg/kg bw/d, respectively). Two F0 female of the 20000 ppm group died during delivery without any clinical signs. In clinical observations of parental animals, enlargement of eyeballs was found in one F1 control male, one F1 female of the 2000 ppm group, and one F1 male and female of the 20000 ppm group, which could not be excluded as being unrelated to treatment. No treatment-related effects were noted on food consumption, body weight or body weight gain in either sex of the F0 or F1 generations. In F1 males there was a significant treatment-related delay in sexual developmental as measured by the degree of preputial separation in the 2000 and 20000 ppm groups. In F1 females, a significant delay ($p<0.05$) in sexual development was noted in the 20000 ppm group, as represented by the increased mean number of days of age until the completion of vaginal opening.

In gross pathological examinations, there was an increased incidence of dark coloured livers in F0 and F1 females compared to controls at 200 ppm and above. Enlargement of the liver and brown coloration of the thyroid was also noted in F0 females treated with 2000 ppm and above. In males, significant increased incidence of the dark coloration of the liver (F1 animals only) and thyroid (F0 and F1 animals) were noted in rats treated with 20000 ppm compared to controls. In F0/F1 males treated with 20000 ppm, significant increases ($p<0.001$) in absolute and relative liver weights were noted. At doses of 2000 ppm and above, absolute and relative pituitary weights of F1 males were significantly decreased compared to controls. In F0/F1 females of the 2000 and 20000 ppm treatment groups, significant increases in absolute and relative liver and kidney weights were noted compared to control animals. Additionally, F1 females in the 200 ppm treatment group had significantly increased absolute and relative kidney weights relative to the controls. These increases in liver and kidney weights in both sexes were considered to be treatment-related. Relative to control values, F1 females had significantly decreased absolute and relative pituitary weights. A treatment-related significant increase of both absolute and relative ovarian weights was noted in F1 females at 2000 ppm and above.

In F1 offspring, enlargement of eyeballs were observed at doses of 2000 and 20000 ppm. In the 20000 ppm treatment group only, mean body weights of male and female F1 pups on LD 21 were significantly lower. No treatment-related differences were noted in the number of pups delivered, sex ratio or the viability index. There was a significant treatment-related increased incidence of dark-coloured liver that was observed in the 2000 and 20000 ppm groups. In F1 males, significantly increased absolute and relative, liver and spleen weights at 2000 and 20000 ppm were noted compared to control animals. Relative to controls, significant decreased absolute thymus weights were also noted in F1 males treated with 20000 ppm. In F1 females, significantly decreased absolute and relative thymus and spleen weights, as well as a significant increase in absolute and relative liver weights were noted at doses of 2000 ppm and above compared to control animals. The NOEL for reproductive toxicity is 200 ppm (15.94 mg/kg bw/d) on the basis that in F1 parental males a treatment-related delay in preputial separation was noted in males treated with 2000 and 20000 ppm. A parental NOEL of 50 ppm (21.0 mg/kg bw/d) was derived on the basis of increased absolute and relative kidney weights in F1 parental females at 200 ppm that could not be discounted as being unrelated to treatment (Hojo, 2004b).

In the above one-generation reproductive toxicity study in rats conducted at dose levels of 0, 50, 200, 2000 and 20000 ppm (IET 03-0013), treatment-related ocular lesions were observed

at necropsy in the weanlings of both sexes at the two highest doses. Histopathological examinations were performed on a subset of weanlings of the 0, 200, 2000 and 20000 ppm groups. Histopathological examinations revealed that the eyes with gross abnormalities had various histological lesions including anterior synechia, hemorrhage into the anterior/posterior chamber, keratitis, iritis, cataract, hydropic degeneration of basal layer of the corneal epithelium, and/or corneal epithelial vacuolation. Conversely, the eyes without abnormalities revealed that ~ 10-30% of the weanlings of either sex in the control, 200, 2000 and 20000 ppm groups had various histological lesions including anterior synechia, hemorrhage into the anterior/posterior chamber, keratitis, and/or hydropic degeneration of basal layer of the corneal epithelium. Although there were no statistical significant differences in the incidence of these ocular lesions between control and treated groups, the severity of the observed lesions was milder than that observed in the eyes with gross abnormalities (Takeuchi, 2005).

Developmental Studies

In a perinatal ocular toxicity study in mice, two groups of inseminated CD-1 were exposed to doses of flubendiamide from 0 to 1000 mg/kg bw/d from day 6 post-coitum to day 21 postpartum. Clinical signs, food and water intake, body weight and feed consumption were monitored in the dams. Reproductive parameters were also monitored. Mortality and clinical signs were checked at least twice daily in the pups. Pups were weighed regularly and any gross pathological findings in dams and pups were recorded. There were no noteworthy findings. In particular, there was no evidence of eye lesions in the pups despite exposure of the dams to 1000 mg/kg bw/d of flubendiamide.

In the dose range-finding study in rats, flubendiamide in 1% aqueous solution of carboxymethylcellulose was administered once daily to pregnant female rats at 0, 20, 100 or 1000 mg/kg bw/d by po gavage from gestation day 6 through 19 inclusive. Control animals received the vehicle alone in the same manner. There were no treatment-related clinical signs or changes in mean maternal body weights, mean maternal body weight gains or food consumption noted. No gross pathological changes were observed in any maternal rat in all groups including the control group. No statistically significant differences were noted in the gravid uterine weights, mean numbers of corpora lutea and implants or % pre-implantation losses compared to the control. There were no treatment-related differences in the number of live foetuses, the incidence of resorption, foetal death, sex ratio, foetal body weight and placental weight. Visceral examination revealed no foetal malformations or variations attributed to treatment. In skeletal examinations conducted for the control and 1000 mg/kg bw/d group foetuses, no malformations were noted, but skeletal variations were noted and included, cervical rib, supernumerary rib and lumbosacral transitional vertebra. The greater incidence of supernumerary ribs in 1000 mg/kg bw/d fetuses compared to the *in-situ* controls and historical control data suggests that this skeletal variation may be treatment-related (Aoyama, 2002a).

Flubendiamide in 1% CMC was administered once daily to pregnant female rats at 0, 10, 100, or 1000 mg/kg bw/d by po gavage from gestation day 6 through 19 inclusive. No maternal deaths occurred in any groups during the study period. There were no treatment-related clinical signs or changes in mean maternal body weights, mean maternal body weight gains or food consumption noted. No statistically significant differences were noted in the gravid uterine weights, mean numbers of corpora lutea and implants or % pre-implantation losses compared to the control. At necropsy, there was a significant dose-related increase in the liver weights of maternal rats in the 100 and 1000 mg/kg bw/d groups. There were no treatment-related differences in the number of liver foetuses, the incidence of resorption, foetal death, sex ratio, foetal body weight and placental weight. No treatment-related external malformations were noted. No treatment-related increases in the incidences of visceral malformations or variations between control or treatment groups. In skeletal examinations, no treatment-related skeletal malformations were noted in any group. Skeletal variations

included cervical rib, misaligned sternebra, and supernumerary rib, but none of the variations showed a dose-response relationship, thus skeletal variations were considered incidental and unlikely to be related to treatment. On the basis that flubendiamide did not induce any treatment-related developmental effects in rats at dose levels up to 1000 mg/kg bw/d, a developmental NOEL of 1000 mg/kg bw/d was established. On the basis of increased absolute and relative liver weights in maternal animals at 100 mg/kg bw/d and above, the maternal NOEL in rats is 10 mg/kg bw/d (Aoyama, 2002b).

In a preliminary developmental study, flubendiamide in 1% CMC was administered once daily to artificially inseminated female rabbits at 0, 30, 100, 300 or 1000 mg/kg bw/d by po gavage from gestation day 6 through 27 inclusive. There were no treatment-related maternal deaths, clinical signs or changes in mean maternal body weights, mean maternal body weight gains or food consumption noted. There were no statistically significant differences noted in the incidences of the gross pathological findings between the control group and any of the treated groups. There were no treatment-related differences in the number of liver foetuses, the incidence of resorption, foetal death, sex ratio, foetal body weight and placental weight. There were no external, soft tissue or skeletal alterations that could be attributed to treatment. The developmental NOEL was 1000 mg/kg bw/d, the highest dose tested (Takahashi, 2001). Flubendiamide in 1% CMC was administered once daily to artificially inseminated female rabbits at 0, 20, 100, or 1000 mg/kg bw/d by po gavage from gestation day 6 through 27 inclusive. No maternal deaths occurred in any groups during the study period. Apart from loose stools (7/25 maternal rabbits in the 1000 g/kg bw/d group), no other treatment-related clinical signs were noted. There were no treatment-related changes in mean maternal body weights, mean maternal body weight gains or food consumption noted. During gross pathological examination, one female from the 1000 mg/kg bw/d group was found to have a yellow coloured liver. On examination of the ovary and uterus, no statistically significant differences from the control group were noted in the gravid uterine weights, mean numbers of corpora lutea, implants and % pre-implantation losses in any treated group. In the offspring, there were no treatment-related differences in the number of liver foetuses, the incidence of resorption, foetal death, sex ratio, foetal body weight and placental weight. No treatment-related visceral malformations or variations were noted. There were skeletal malformations and variations noted, which included fused sternebrae, thoracic centrum or ribs, small thoracic arch, misaligned sternebra, cervical rib, but the incidences were not statistically different to the control and/or fell within the historical control range. Thus it was concluded that flubendiamide did not induce any treatment-related effects on any of the parameters tested in rabbits at dose levels up to 1000 mg/kg bw/d (Takahashi, 2002), which was therefore the developmental NOEL.

Genotoxicity Studies

Flubendiamide was negative in genotoxicity tests, including a bacterial reverse mutation test, an *in vitro* chromosome aberration test, an *in vitro* HPRT test for forward mutations, and a mouse micronucleus test. Nine flubendiamide derivatives tested negative in bacterial reverse mutation tests, with diiodo-flubendiamide also testing negative in *in vitro* tests for chromosome aberrations and mutations involving mammalian cells.

Neurotoxicity Studies

In an acute study, flubendiamide was administered in a single oral gavage dose to rats at 0, 200, 700 and 2000 mg/kg bw/d. Mortality, clinical signs and weight were monitored. Functional observation battery (FOB) tests and motor activity assessments were conducted one week prior to dosing, approximately 8 h after dosing on day 0 and on days 7 and 14 thereafter. On days 14 or 15 after dosing, all animals were sacrificed and a gross necropsy and histopathology were conducted with emphasis on the nervous system. There was no evidence of neurotoxicity at any dose.

Immunotoxicity Study

Groups of rats received flubendiamide technical in diet at 0, 40, 400 or 4000 ppm for 28-29 days (equivalent to M/F 0, 3.3/4.0, 34/38 and 336/359 mg/kg bw/d). There were no treatment-related mortalities or clinical signs. Dose-related decreases in food consumption were noted in females at and above 400 ppm. RBC counts, Hb concentration and Hct values in females showed statistically significant treatment-related decreases at and/or above 400 ppm. SGOT activity in males and SGPT activity in both sexes were significantly depressed at 4000 ppm. The incidence of pale kidneys was increased in males at 4000 ppm. Organ weights showed significant increases in both absolute and relative liver weights in females at and above 400 ppm, relative liver weight in males at 4000 ppm, thyroid weights in females at 4000 ppm. Flow cytometry revealed a decrease in CD45 (total) and CD45 (high) positive lymphocytes and consequently an increase in CD (low) positive lymphocytes in both sexes at 4000 ppm. A significant decrease in IgA antibody titre was seen in females at 4000 ppm. Based on these findings, the NOEL for systemic toxicity was 40 ppm (4.0 mg/kg bw/d) and immunotoxicity was 400 ppm (38 mg/kg bw/d) (Krotlinger and Vohr, 2005).

Mechanistic Studies

Groups of rats received flubendiamide technical in diet at 0, 1000 or 10000 ppm (equivalent to 0, 83 and 812 mg/kg bw/d flubendiamide) for 7 or 28 days. There were no treatment-related mortalities or clinical signs. Body weights were slightly (5%) elevated at 10000 ppm. The microsomal P450 content was significantly increased in both dose groups at both observation times, indicating that flubendiamide induces cytochrome P450 group of enzymes (specifically ethoxyresorufin-dealkylase and uridine diphosphate-glucuronyltransferase activity). It is suggested that flubendiamide probably induces the CYP-1A group of microsomal enzymes but not the CYP-2B group. T3 values showed significant increases after 7, 14 and 28 days of treatment at both dose levels. Statistically significant increases in TSH levels were seen after 14 and 28 days of treatment at both dose levels. Histopathology showed treatment-related abnormalities in the liver and thyroid at both treatment levels after 7 and 28 days (Amanuma, 2005).

Although it is an iodobenzene derivative, flubendiamide (1, 10, 100 μM) did not inhibit iodothyronine deiodinase type 1 (ID-I), the enzyme that deiodinates L-thyroxine (T4) to 3,3'5'-L-triiodothyronine (T3) in the periphery ID-I in the periphery in rats *in vitro*. These results suggest that flubendiamide does not affect thyroid homeostasis at the level of ID-I (Freybergher, 2005).

Discussion of Toxicity Data

Flubendiamide is moderately well absorbed across the gut (between 20% and 35% of the dose). However very little is excreted in the urine, with most of the absorbed compound undergoing biliary excretion. Over 90% of an oral dose is eliminated in the faeces. There was some evidence for accumulation of absorbed material in the liver and fat. Flubendiamide is lipophilic. In the case of rats, females tended to retain more material in the tissues and metabolise and excrete it more slowly than males. There were differences in the metabolism of flubendiamide between the sexes in the rat. These sex differences in toxicokinetics and metabolism may help explain the generally greater sensitivity of females to the effects of flubendiamide. Female rats are less able to oxidise flubendiamide in the liver than male rats and both sexes of other species tested, and it is possible that their relative inability to produce polar metabolites may slow down their excretion of flubendiamide.

The tendency for flubendiamide to accumulate in fat was reflected in low plasma:fat ratios particularly in female rats after repeated doses. The long-term dietary studies will have permitted accumulation of flubendiamide and their results should help address any toxicological implications of this accumulative tendency, although loss of body weight and therefore fat mobilisation were not observed in the long-term rodent studies. Mobilisation of fat reserves during and after pregnancy may also release flubendiamide, and the results of the developmental and reproductive studies will have helped identify any consequent effects.

The liver was a significant target organ in repeat dose studies in all species. Typical effects included increased liver weight and associated histopathological abnormalities. Liver effects, together with microcytic anaemia, were the basis of the lowest NOEL in the database, namely 1.0 mg/kg bw/d in a rat one-year dietary study. Another effect that occurred at relatively low doses in both males and females was follicular cell hypertrophy of the thyroid. Evidence was adduced that this effect on the thyroid was secondary to the induction of UDT-GT in the liver and a subsequent decrease in circulating T4, resulting in stimulation of the thyroid.

Female rats were generally more susceptible to the microcytic anaemia observed in a number of studies. Examination of the spleen and bone marrow did not disclose a clear basis for this effect, although there was some reduction in erythroblasts in the bone marrow at a high dose in a one-year dietary rat study.

There were no developmental effects associated with the treatment. The only noteworthy reproductive effect was delayed balanopreputial separation, which was not accompanied by a decrease in anogenital distance as would be expected if this were an anti-androgenic effect. At the same doses in the reproduction studies, an incidence of enlarged eyeballs (buphthalmia) was observed in pups of both sexes. It is possible that the slower metabolism of flubendiamide in female rats compared with other species might explain why this effect was seen in rat studies but not in a mouse study. A clear NOEL for the effect (buphthalmia) in rat neonates of 16 mg/kg bw/d was demonstrated (in the 1-generation reproduction study in rats) and the overall NOEL established for flubendiamide (1.0 mg/kg bw/d) is expected to be protective of the ocular effects observed.

Public Health Standards

Poisons Schedule Considerations

- The current application is for the approval of flubendiamide, the active constituent in the products proposed for registration: Belt® 480 SC and Belt® 240 WG contain flubendiamide at 480 and 240 g/L respectively. These products are proposed for use as a foliar insecticide for the control of diamondback moth, cabbage white butterfly, cluster caterpillar, soybean looper and heliothis in brassicas.
- Flubendiamide has low acute oral (LD_{50} >2000 mg/kg bw) and dermal (LD_{50} >2000 mg/kg bw) toxicity in rats. It is not a skin irritant in rabbits or a skin sensitiser in guinea pigs at the doses tested. However, it is a slight eye irritant in rabbits.
- The products have similar acute toxicity profiles to flubendiamide. They both possess low acute oral toxicity in female rats with an LD_{50} >2000 mg/kg bw. Belt® 480 SC has low dermal toxicity (LD_{50} >4000 mg/kg bw) and low inhalational toxicity (LC_{50} > 2564 mg/m^3) in male and female rats. Belt® 240 WG also has low dermal toxicity (LD_{50} >2000 mg/kg bw), with no inhalational studies provided. Both products are not skin irritants in rabbits or skin sensitisers in guinea pigs. They were, however, shown to be slight eye irritants in rabbits, presumably due to the presence of the active, flubendiamide.
- Based on the low acute oral and dermal toxicities of flubendiamide, and low inhalational toxicity of the product Belt® 480 SC Insecticide (containing approximately ~50% of flubendiamide), it is expected the acute inhalational toxicity of flubendiamide will be low.

- Flubendiamide was found to have similar effects in short-term and long-term repeat dose studies, often at relatively low doses. The primary target organ in all animal species (mice, rats and dogs) was the liver, with the thyroid gland affected in some studies. In rats, effects on red blood cells manifested by microcytic anemia were observed.

- Pups in reproductive studies showed treatment-related delay in preputial separation, as well as an incidence of enlarged eyeballs. Developmental studies revealed no teratogenicity in rats and rabbits at dose levels up to 1000 mg/kg bw/d.

- Flubendiamide was not genotoxic in a range of *in vitro* and *in vivo* tests.

- Flubendiamide was not carcinogenic.

- At its 51st meeting, on 16-17 October 2007, the NDPSC agreed that, based on the acute toxicity, flubendiamide be included in Schedule 5 of the SUSDP

Dose Levels Relevant For Dietary Risk Assessment

To determine the appropriate NOEL for the establishment of an ADI, a summary of the NOELs determined in those studies deemed adequate for regulatory purposes is shown in the Table 1 below.

Table 1. Summary of relevant NOELs from repeat dose studies with flubendiamide

Study duration	**Species & route**	**Doses (mg/kg bw/d or ppm)**	**NOEL (mg/kg bw/d or ppm)**	**LOEL (mg/kg bw/d) & endpoints**
Short-/medium-term studies				
28-d	Mice Dietary	0, 20, 200, 2000, 20000 ppm	30 mg/kg bw/d	2000 ppm (~300 mg/kg bw/d) increased incidences of histopathological changes in the liver (Takeuchi, 2001)
28-d	Rats Dietary	0, 20, 50, 200, 2000 & 2000 ppm	50 ppm (4 mg/kg bw/d)	200 ppm (15 mg/kg bw/d) increased incidences of histopathological changes in the liver of females (Enomoto, 2001)
28-d	Dogs, oral	0, 40, 400, 4000, 40000 ppm	NA – dose-range finding study	400 ppm (1 mg/kg bw/d): increases in AP activity with elevation in liver weights at 40000 ppm (1180 mg/kg bw/d) (Kuwahara, 2001)
30-d	Rats Dermal	0, 10, 100, 1000 mg/kg bw/d	100 mg/kg bw/d	1000 mg/kg bw/d: Perturbations of some haematological parameters, decreased AST and increased liver weights with associated abnormal histopathology at 1000 mg/kg bw/d.
90-d	Mice, dietary	0, 50, 100, 1000, 10000 ppm	100 ppm (12 mg/kg bw/d)	1000 ppm (120-140 mg/kg bw/d): liver effects with histopathological abnormalities
90-d	Rats, dietary	0, 20, 50, 200, 2000, 20000 ppm	20 ppm (1.2 mg/kg bw/d)	50 ppm (2.8-3.3 mg/kg bw/d): perturbations in a variety of haematological parameters and clinical chemistry, organ weights changes and histopathological abnormalities in the liver in females (Enomoto, 2003)
90-d	Dogs, dietary	0, 100, 2000, 40000 ppm	100 ppm (2.6 mg/kg bw/d)	2000 ppm (53-60 mg/kg bw/d); loose stools, decreases in body weights (males), and perturbations in clinical chemistry parameters in males and/or females. Increased liver and adrenal weights associated with histopathological abnormalities in the adrenal glands of females at and above 2000 ppm (Kuwahara, 2003).
Chronic studies				
1-year	Rats, Dietary	0, 20, 50, 200, 2000, 20000 ppm	20 ppm (1.0 mg/kg bw/d)	50 ppm (2.4 mg/kg bw/d); based on slight microcytic anaemia and increased liver weights in females. Administration of flubendiamide to rats for one year revealed significant toxicological differences between the sexes (Enomoto, 2004).
1-year	Dogs, Dietary	0, 100, 1500, 10000 ppm	100 ppm (2.2 mg/kg bw/d)	1500 ppm (35-38 mg/kg bw/d); hepatotoxicity (increased liver weights and enzymes) (Kuwahara, 2004).
2-year	Rats, Dietary	0, 50, 1000, 20000 ppm	50 ppm (1.7 mg/kg bw/d)	1000 ppm (34-44 mg/kg bw/d); In females, reduced food consumption; increased hair loss; hepatotoxicity; thyroid toxicity; and nephrotoxicity. In males at 1000 ppm,

Study duration	Species & route	Doses (mg/kg bw/d or ppm)	NOEL (mg/kg bw/d or ppm)	LOEL (mg/kg bw/d) & endpoints
				effects included: decreased eosinophils, hepatotoxicity and nephrotoxicity (Enomoto, 2004).
2-year	Mice, Dietary	0, 50, 1000, 10000 ppm	50 ppm (4.4 mg/kg bw/d)	1000 ppm (93-94 mg/kg bw/d); hepatotoxicity and thyroid toxicity Takeuchi Y (2004).
Reproduction studies				
1-generation	Rats, gavage	0, 50, 200, 2000, 20000 ppm	200 ppm (reproduction) (15.94 mg/kg bw/d)	2000 ppm (117.2-205.5 mg/kg bw/d); In F1 parental males a treatment-related delay in preputial separation was noted. Increased incidence of enlarged eyeballs (Hojo, 2001b; Takeuchi, 2005).
			50 ppm (parental) (5.28 mg/kg bw/d)	200 ppm (~16 mg/kg bw/d); increased absolute and relative kidney weights in F1 parental females. Hepatotoxicity and increased pituitary weights (Hojo, 2001b).
2-generation	Rats, gavage	0, 20, 50, 2000, 20000 ppm	50 ppm (reproduction/ foetal) (3.61 mg/kg bw/d)	2000ppm (121-196 mg/kg bw/d); In F1 parental males a treatment-related delay in preputial separation, and increased liver weights associated with abnormal histopathology in F0/F1 pups. Also increased incidence of enlarged eyeballs in F1/F2 pups.
			50 ppm (parental) (3.04 mg/kg bw/d)	2000ppm (121-196 mg/kg bw/d); increased liver weights associated with abnormal histopathology (Hojo, 2001a).
Developmental studies				
Day 6-19 inclusive	Rats, Oral gavage	0, 10, 100, 1000 mg/kg bw/d	1000 (foetal)	Flubendiamide did not induce any treatment-related developmental effects in rats at dose levels up to 1000 mg/kg bw/d (Aoyama, 2002b).
			10 (maternal)	100 mg/kg bw/d: Increased absolute and relative liver weights in maternal animals (Aoyama, 2002b).
Day 6-27 inclusive	Rabbits, Oral gavage	0, 20, 100, 1000 mg/kg bw/d	1000 (foetal)	Flubendiamide did not induce any treatment-related developmental effects in rabbits at dose levels up to 1000 mg/kg bw/d.
			100 (maternal)	1000 mg/kg bw/d; increased incidence of loose stools in maternal animals (Takahashi, 2002).

Acceptable daily intake (ADI) and Acute Reference Dose (ARfD) considerations

The table above summarises the NOELs observed and shows that rats were the most sensitive species for flubendiamide toxicity in repeat-dose studies. The most sensitive toxicological end points were hepatotoxicity and microcytic anaemia and the NOEL for these effects is the basis for the establishment of the ADI. The lowest NOEL amongst the studies submitted was 1 mg/kg bw/d after 12 months dosing in rats. Since the database for flubendiamide is extensive and adequate for characterising its toxicological profile, a 100-fold safety factor is appropriate. On this basis, the ADI is established at 0.01 mg/kg bw/d.

Establishment of an ARfD is not justified for flubendiamide based on the lack of identified toxic effects in the acute oral toxicity study, which reported an LD_{50} value of >2,000 mg/kg in female rats. All test animals survived and gained weight throughout the study period. No clinical signs of toxicity were observed. No gross lesions were observed at necropsy. In addition to the lack of acute oral toxicity, flubendiamide was not a developmental toxicant in rats and rabbits at doses up to 1000 mg/kg/day and no clinical signs were observed in a micronucleus test in mice (at up to 2000 mg/kg bw). There was no toxic effect identified that was attributable to a single dose/exposure and therefore the establishment of an ARfD is not possible.

Selection of a NOEL for OHS Risk Assessment

Based on the use pattern of the product, the NOEL of 100 mg/kg/ bw/d from the 30-day dermal study was determined as most representative for use in the occupational risk assessment.
The NOEL of 100 mg/kg bw/d was based on effects on the liver, thyroid, haematology changes and decreased activity of AST at 1000 mg/kg bw/d.

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Metabolism

Plants

The metabolism of flubendiamide was investigated in 4 different crops (cabbage, tomato, apple and corn), using flubendiamide labelled with ^{14}C in either the phthalic or aniline ring (figure 1).

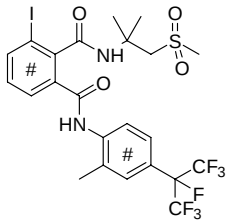

Figure 1: Position of ^{14}C labels (#) in flubendiamide

Cabbage

In cabbage leaves, parent compound accounted for ~90% of the total radioactive residue (TRR) 3 weeks after treatment with radiolabelled flubendiamide. Similar levels of parent compound were observed at 6 weeks. Small amounts (<0.01 mg equivalents/kg) of a des-iodo metabolite, a phenol metabolite, a benzyl alcohol and a benzoic acid metabolite were also detected. Residues in the edible parts (cabbage head) and in roots were low, ≤0.07% of applied radioactivity, suggesting that the majority of flubendiamide residues remained on the surface of the treated leaves with no significant translocation to other plant tissues.

Tomato

Unchanged parent compound was the main component detected in tomato fruit after treatment radiolabelled flubendiamide. Unchanged parent accounted for 99% of the TRR in fruit at day 0, falling to 96% four weeks later. Small amounts (<0.01 mg equivalents/kg) of a des-iodo metabolite, a phenol metabolite, a benzyl alcohol, a benzoic acid and a des-anilino metabolite were also detected.

Unchanged parent was also the main component found in leaves, accounting for 95 – 99% of the TRR at 0 and 4 weeks after treatment. Small amounts (<0.1 mg equiv./kg) of the same metabolites found in fruit were also found in leaves. Four weeks after the application only 1.1% of the applied radioactivity was detected in untreated plant parts again suggesting very little translocation of the test substance from the application site.

Apple

Unchanged parent compound was the major residue detected in apple fruit after treatment with radiolabelled flubendiamide. Unchanged parent in fruit decreased from a maximum of 81 – 94% of the TRR at 7 days after treatment to 50 – 54.5% of the TRR at 56 days after treatment. The only other residue identified in apple fruit was the des-iodo metabolite, which was present at <0.002 mg equivalents/kg. Residues remaining unextracted in the solids increased from 2 – 6% of the TRR at 0 DAT to 18 – 20% at 56 DAT.

Unchanged flubendiamide was also the major residue found in leaves at 0 DAT, accounting for 104 – 106% of the TRR. By 56 DAT residues of parent had declined to 53 – 62% of the TRR. Residues remaining unextracted in the solids increased from 1 – 2% of the TRR at 0 DAT to 10 – 11% at 56 DAT. Several metabolites were observed in apple leaves including the des-iodo, 3-phenol metabolite, iodophthalimide, benzyl alcohol, benzoic acid and iodophthalic acid. All metabolites were present at <10% of the TRR.

Corn
Corn was treated with 4 applications of radiolabelled flubendiamide. Corn forage and sweet corn samples were collected on the day after the final treatment. Corn grain and fodder were collected 22 days later.

Unmetabolised parent was the major component in forage and fodder from both labels, accounting for 77 – 90% of the TRR for forage and 78 – 84% of the TRR for fodder. The only metabolite detected in forage and fodder was the des-iodo, which accounted for 5 – 18% of the TRR in forage, and 9 – 10% of the TRR in fodder. Non-extractable residues accounted for <1 – 5% of the TRR in forage and for <1 – 2% of the TRR in fodder.

Residue levels in sweet corn and grain were too low for analysis.

Plant Metabolism Summary

The proposed metabolic pathway of flubendiamide in plants is shown in figure 2. The main routes for degradation of the parent compound were:

1. Des-iodination of the parent followed by hydroxylation to give the phenol derivative NNI-0001-3-OH
2. Stepwise oxidation of the methyl group at the aniline ring to form a benzyl alcohol followed by a benzoic acid.
3. Elimination of the amino-ethyl-sulfonyl substituent to form an iodophthalimide (apple only).
4. Cleavage of the parent to form an iodo-phthalic acid (apple only).
5. Cleavage of the parent to form NNI-0001-des-anilino (tomato only).

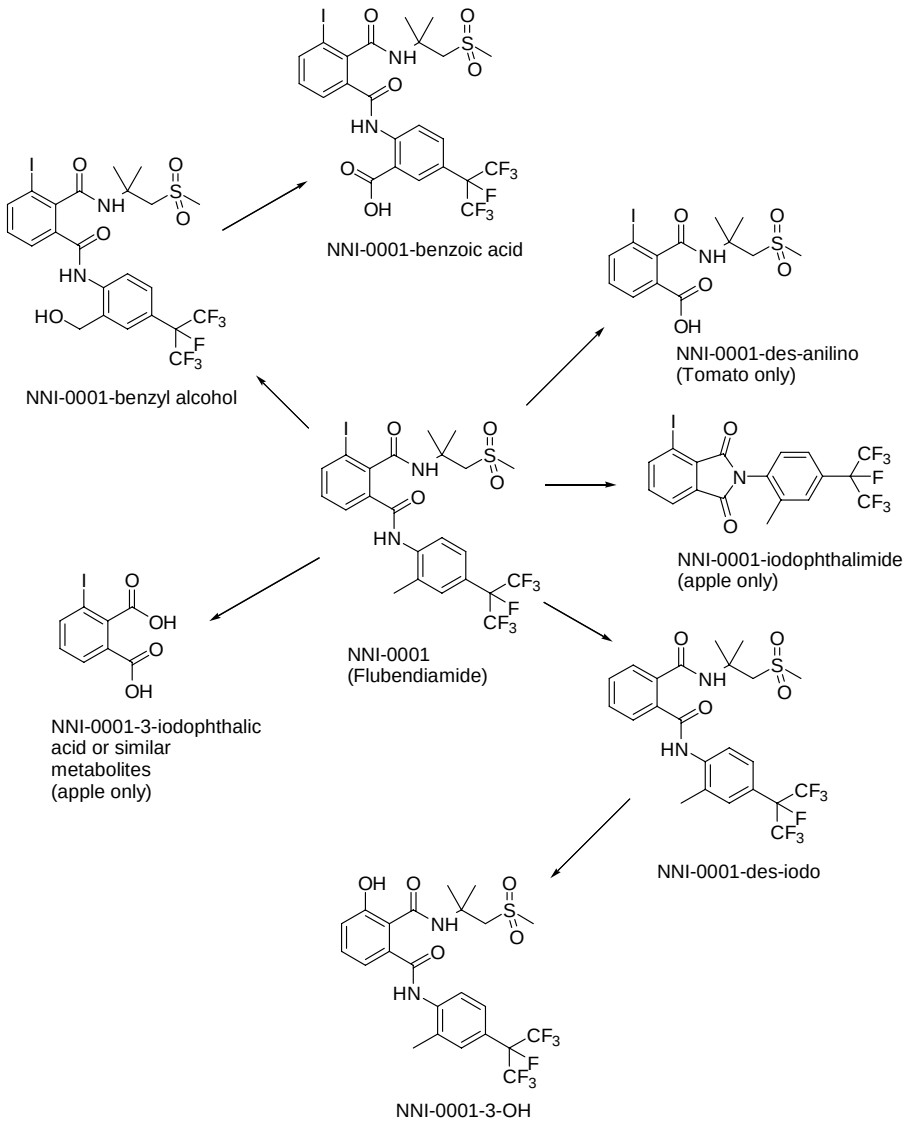

Figure 2 : Proposed metabolic pathway of flubendiamide in plants

Confined Rotational Crops

The metabolism of flubendiamide was investigated in the rotational crops, spring wheat, Swiss chard and turnips for 3 consecutive rotations using phthalic or aniline labelled compound.

Radiolabelled flubendiamide was applied uniformly by spray application to the soil of a planting container at approximately 10× the maximum label rate. Crops of the 1st, 2nd and 3rd rotation were sown at 29, 135 and 274 days after application. Samples were harvested at maturity, except for wheat forage and hay (soft dough stage).

The total radioactive residues (TRRs) were relatively low for all crops and all rotations as summarised below in table 1.

Table 1: Total radioactive residues in confined rotational crops after treatment with phthalic or aniline labelled flubendiamide.

TRR	**Wheat**				**Swiss**	**Turnips**	
(mg equiv./kg)	**forage**	**hay**	**straw**	**grain**	**Chard**	**Leaves**	**Roots**
Phthalic label							
1st rotation	0.013	0.045	0.070	0.003	0.022	0.011	0.006
2nd rotation	0.008	0.032	0.063	0.002	0.019	0.005	0.002
3rd rotation	0.016	0.022	0.050	0.003	0.015	0.006	0.002
Aniline label							
1st rotation	0.011	0.045	0.137	0.002	0.013	0.003	0.002
2nd rotation	0.010	0.034	0.068	0.002	0.009	0.002	0.001
3rd rotation	0.013	0.021	0.039	0.005	0.019	0.006	0.003

The maximum TRR (0.07 – 0.14 mg equiv./kg) was observed in wheat straw of the first rotation. This decreased to 0.063 – 0.68 mg equiv./kg for the 2nd rotation and to 0.039 – 0.050 mg equiv./kg for the 3rd rotation respectively. A similar decline was observed in the TRR for wheat hay which decreased from 0.045 to 0.032 – 0.34 mg equiv./kg in the 2nd rotation and then to 0.021 – 0.022 mg equiv./kg in the 3rd rotation.

The main component of the residue in most plant samples was unmetabolised parent accounting for 22 – 88% of the TRR (0.001 – 0.099 mg equiv./kg). The exception was wheat grain, where parent accounted for only 4 – 8% of the TRR in the first rotation, declining to 2.2 – 2.8% in the 2nd rotation and ≤0.5% in the 3rd rotation.

The major metabolite detected in both studies was the des-iodo derivative which accounted for 8 – 10.8% of the TRR in Swiss chard of the 2nd rotation. The des-iodoalkylphthalimide was significant for the phthalic label study, accounting for 16% of the TRR for straw of the 2nd rotation. Further identified metabolites were the benzyl alcohol, the benzoic acid, the iodo-alkylphthalimide (phthalic label only) and the des-anilino (phthalic label only). Each of these metabolites accounted for <0.01 mg equiv./kg.

The proposed metabolic pathway for flubendiamide in confined rotational crops is shown below in figure 3. The main reactions observed were:

1. Reduction of the parent compound by elimination of the iodine substituent.
2. Elimination of the N-aryl moiety leading to the iodo-alkylphthalimide, the des-anilino derivative and the des-iodo-alkylphthalimide.
3. Hydroxylation of the parent compound to give the benzyl alcohol, which was further oxidised to the benzoic acid derivative.

The studies suggest it is unlikely that residues will be observed on rotational crops in practice, given that flubendiamide was applied at an exaggerated rate (~10×) and the total radioactive residues were relatively low for all crops and all rotations. Also in practice the chemical

would not be applied directly to the soil with the majority intercepted by the crop undergoing treatment.

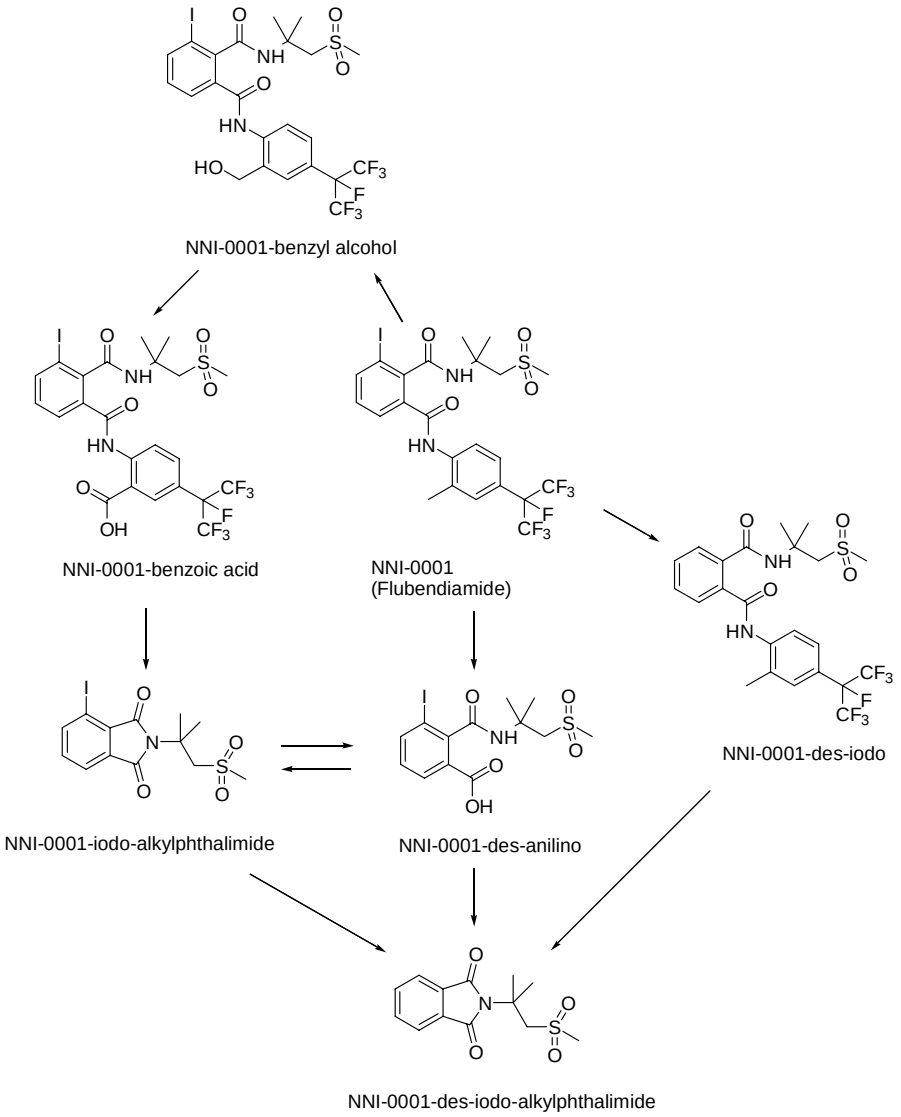

Figure 3: Proposed metabolism of flubendiamide in rotational crops

Animals

Studies were conducted on the metabolism of flubendiamide in lactating goats and laying hens.

Lactating goats

Two studies were provided in which lactating goats were administered flubendiamide labelled with ^{14}C in either the phthalic acid or aniline ring at 5 mg/kg bw/day for 4 consecutive days.

Until sacrifice 77 hours after the first administration (5 h after the last) 24 – 44% of the total dose was excreted with the faeces, while only 0.25 – 0.53% was excreted with urine. A low amount of radioactivity (0.4 – 0.53% of the total dose) was secreted in the milk. For the phthalic label, the percentage of the dose eliminated with the milk was 0.116% on day 1, 0.141% on day 2 and 0.175% on day 3. For the aniline label, the percentage of the dose eliminated with the milk was 0.067% on day 1, 0.153% on day 2 and 0.191% on day 3. These results demonstrate that a plateau level in milk was not reached during the observation period in either study. The peak concentration in milk at sacrifice (77 h after the first dose) was 1.7 mg equiv./L for the phthalic label and 3.3 mg equiv./L for the aniline label.

At sacrifice the highest residues in tissues were observed in the fat (10.1 – 22 mg equiv./kg). High residues were also observed in liver (10.1 – 13.2 mg equiv./kg). Other organs and tissues contained significantly lower residue levels: kidney 2.4 – 4.4 mg equiv./kg, muscle 0.76 – 2.2 mg equiv./kg.

Unchanged parent was the major residue in faeces (up to 82% TRR). A carboxy derivative was a major metabolite in urine, bile and faeces (16 – 51% TRR). Carboxy glucuronide and benzyl alcohol glucuronide derivatives were also significant metabolites accounting for 32 – 38% of the TRR in bile and 28 – 51% of TRR in urine respectively.

In both studies, unchanged parent compound was the main residue found in milk, accounting for 72 – 78% of the TRR. The iodophthalimide metabolite was also detected in significant amounts in milk (11 – 17% of TRR). Other metabolites were only detected at low levels in milk (≤3% of TRR).

In both studies, the parent compound was the main residue found in edible tissues (muscle, fat, liver, kidney), accounting for 75 – 93% of the TRR in the corresponding samples. The iodophthalimide metabolite was also detected in significant amounts in fat (11 – 24 % of TRR). This metabolite was also found in muscle, accounting for 7 – 8% of the TRR. Other metabolites were only detected at low levels (≤5% of TRR) in edible tissues.

The proposed metabolic pathway of flubendiamide in goats involves oxidation of the methyl groups to a primary alcohol, followed by further oxidation to carboxylic acid and conjugation with glucuronic acid (figure 4).

Laying Hens

Two studies were provided in which laying hens were administered flubendiamide labelled with ^{14}C in either the phthalic acid or aniline ring at 1 mg/kg bw/day for 14 days.

The majority of the dose was detected in the excreta (62 – 66% until sacrifice). A continuous increase in the TRR for eggs was detected over the dosing period. The highest residues in eggs were 2.8 – 3.4 mg equivalents/kg at the end of the experiment (24 h after the last dose), indicating that residues had not reached a plateau. Within the organs and tissues the highest residue was found in the sub-cutaneous fat (12.4 – 18 mg equiv./kg). This was followed in decreasing order by the residue in the skin without subcutaneous fat (3.6 – 6.5 mg equiv./kg), liver (3.0 – 4.0 mg equiv./kg), kidney (1.8 – 2.4 mg equiv./kg) and leg and breast muscle (1.0 to 1.5 mg equiv./kg and 0.38 – 0.5 mg equiv./kg respectively).

Unchanged parent was the main residue found in eggs, accounting for 92% of the TRR for eggs collected on days 10 to 14 in both studies. A benzyl alcohol derivative was also detected as a minor metabolite at 2.8 to 4.5% of the TRR in eggs collected on days 10 to 14. The iodophthalimide and iodoalkylphthalimide were detected as trace metabolites in eggs in the study using phthalic labelled flubendiamide.

In edible tissues, unchanged parent was the main residue component accounting for 82 – 98% of the TRR. A benzyl alcohol derivative was also detected as a minor metabolite in liver, muscle and fat at 1 – 9% of the TRR. The iodophthalimide and iodo-alkylphthalimide metabolites formed by cleavage of the amide bonds followed by cyclisation were found as trace products in fat (up to 1.6% of the TRR).

The proposed metabolic pathway for flubendiamide in the laying hen involves oxidation of the methyl groups to a primary alcohol, followed by further oxidation of the aliphatic alcohol group to a carboxylic acid. The carboxylic acid is conjugated to glucuronic acid as the major pathway. The carboxylic acid and the final glucuronic acid conjugate were found exclusively in bile and excreta accounting for 6 to 18% and 4 to 14% of the TRR respectively.

Animal metabolism summary

The proposed metabolic pathway for flubendiamide in animals is shown in figure 4. The main routes for degradation of the parent compound were:

1. Stepwise oxidation of the aliphatic methyl group to form an alcohol followed by a carboxylic acid.
2. Oxidation of the aniline methyl group to form a benzyl alcohol.
3. Conjugation of carboxylic acid and benzyl alcohol (goat only) derivatives to glucuronic acid (exclusively in bile and excreta).
4. Cleavage of parent to form an iodo-phthalimide derivative followed by des-iodination (goat only).
5. Cleavage of parent to form an iodo-alkylphthalimide derivative.

Conclusion

The metabolism studies provided by the applicant demonstrate that unchanged parent compound is the major residue of concern in both plants and animals. For plants, the des-iodo metabolite is a significant product, especially in corn forage and fodder, where it accounted for 5 to 18% of the TRR. For animals, the iodophthalimide metabolite is a significant product accounting for 11.4 to 17% of TRR in milk and 10.6 to 24 % of TRR in fat in the goat metabolism study.

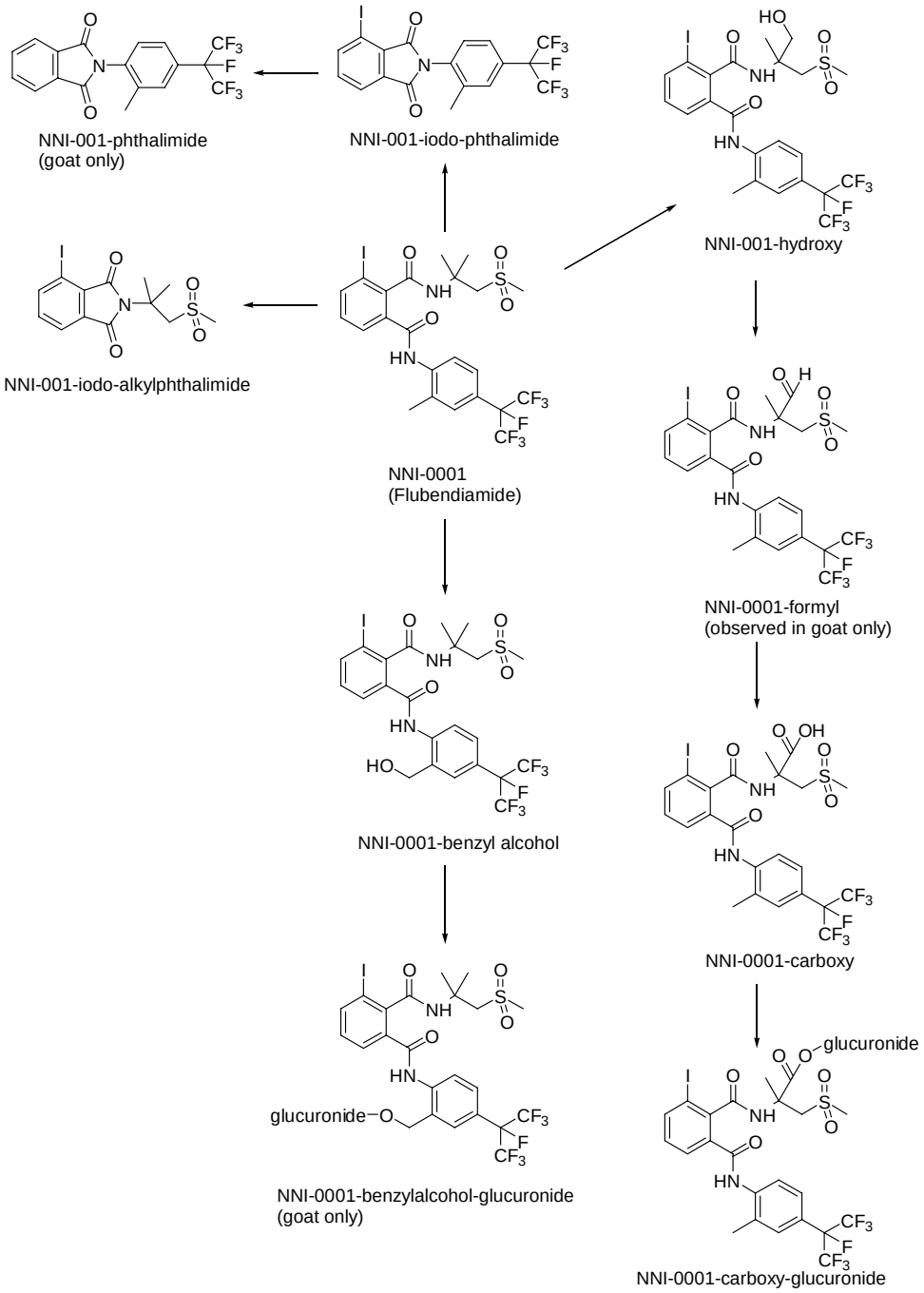

Figure 4 : Proposed metabolic pathway of flubendiamide in animals (goat and hen)

Analytical Methods

Commodities of plant origin
Residues in crop samples were extracted with acidified acetonitrile. The extract was filtered and diluted with formic acid. Residues of flubendiamide and the des-iodo metabolite were quantified by HPLC MS/MS with internal standardisation. The LOQ for the method was 0.02 mg/kg for each component, and 0.045 overall, expressed as total flubendiamide equivalents.

Commodities of animal origin
Flubendiamide and its iodophthalimide metabolite were extracted from animal tissues and milk using an acetonitrile/water mixture (4:1). After evaporation, the iodophthalimide derivative was hydrolysed under mild alkaline conditions to give des-alkylamino flubendiamide isomers. Residues of flubendiamide and the 2 des-alkylamino isomers were cleaned up using disposable columns filled with diatomaceous earth, eluting with ethyl acetate. The organic solution was evaporated to dryness and the residues dissolved in acetonitrile/water and analysed by HPLC-MS/MS.

The LOQ for flubendiamide and the iodophthalimide metabolite was 0.01 mg/kg for all animal commodities. When expressed as parent equivalents the LOQ for the iodophthalimide metabolite was 0.013 mg/kg for all matrices.

Stability of pesticide residues in stored analytical samples
The applicant has provided storage stability studies which demonstrate that no degradation of flubendiamide or its des-iodo metabolite occurred in samples of tomato (fruit), vegetable (oil), wheat (grain), head cabbage (head), bean (bean with pod) and citrus (fruit) on storage for 18 months at –18 °C. In the residue trials submitted, all samples were maintained under freezer conditions, (i.e.–5 to –20 °C) prior to analysis and tested within 12 months of collection.

Residue Definition

The applicant has provided analytical methods capable of determining the residue of parent and des-iodo metabolite in commodities of plant origin. The des-iodo metabolite was only significant in corn forage and fodder, where it accounted for 5 to 18% of the TRR in the radiolabelled study. The des-iodometabolite was not a significant residue in the cabbage, tomato or apple metabolism studies. Also results from the residue trials provided by the applicant show that residues of the des-iodo metabolite were below the LOQ. The metabolism and crop data support a residue definition of parent compound for commodities of plant origin.

For commodities of animal origin, analytical methods to determine residues of parent and the iodophthalimide metabolite were provided. The iodophthalimide metabolite was a significant product in the goat metabolism study where it accounted for 11.4 to 17% of TRR in milk and 10.6 to 24 % of TRR in fat. In poultry and cattle feeding studies, the iodophthalimide metabolite was not quantifiable in most of the investigated animal matrices, except in fat where it represented 6 to 23% of the total residue when expressed as flubendiamide equivalents.

The Office of Chemical Safety report on flubendiamide identified the iodophthalimide metabolite as a toxicologically relevant compound for the residue definition. Therefore, the residue definition for commodities of animal origin should therefore include parent compound and the iodophthalimide metabolite.

The following residue definition for flubendiamide is appropriate:

Compound	Residue
Flubendiamide	Commodities of plant origin: Flubendiamide Commodities of animal origin: sum of flubendiamide and 3-iodo-N-(2-methyl-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]phenyl)phthalimide, expressed as flubendiamide.

Residue Trials

Residue data were provided for broccoli, Brussels sprouts and cabbage.

Broccoli
Three Australian trials were provided for broccoli. Three foliar applications of a 240 WG or 480 SC formulation of flubendiamide were made at weekly intervals at rates of 48 – 108 g ai/ha (1× to 2.2×). Applications were made just prior to crop maturity. Residues of flubendiamide in broccoli at the proposed 3 day withholding period were 0.128, 0.218 and 0.25 mg/kg after 3 applications of product at the maximum proposed rate (48 g ai/ha).

Brussels sprouts
Two Australian trials were provided for Brussels sprouts. Three foliar applications of a 240 WG formulation of flubendiamide were made at weekly intervals at rates of 48 – 108 g ai/ha (1× to 2.2×). Applications were also made at the alternative rates of 4.8 – 10.8 g ai/100 L (1× to 2.2×). Applications were made just prior to crop maturity. Residues of flubendiamide in Brussels sprouts after treatment with 3 applications of product at 48 g ai/ha (1× proposed) were 0.048 and 0.176 mg/kg at the proposed 3 day WHP. After 3 treatments at the alternative rate of 4.8 g/100 L (1× proposed) residues were significantly higher at 0.50 and 1.120 mg/kg three days after the last application. The spray volumes used for the alternative application rates corresponded to ~2800 L/ha in the first trial and 1900 – 2700 L/ha in the second trial.

Cabbage
Six Australian trials were provided for cabbage. Three foliar applications of a 240 WG or 480 SC formulation of flubendiamide were made at weekly intervals at rates of 48 – 108 g ai/ha (1× to 2.2×). Applications were made just prior to crop maturity. Residues of flubendiamide in cabbage heads after treatment with 3 applications of product at 48 g ai/ha (1× proposed) were <0.045, 0.190, 0.27, 0.303, 0.76 and 2.72 mg/kg at the proposed 3 day WHP.

MRL recommendation
If the results for broccoli, Brussels sprouts and cabbage are grouped together the STMR is 0.25 mg/kg and the highest residue is 2.72 mg/kg. This supports the establishment of a group MRL of 3 mg/kg for Brassica (cole or cabbage) vegetables, Head cabbages, Flowerhead brassicas.

Animal Commodity MRLs
Brassicas are not a major animal feed. Use of the products on brassicas grown for forage or fodder is prohibited. Although grazing of brassica vegetables is not common practice, a do not graze statement is also included on the labels. No animal commodity MRLs will therefore be established at this time.

Estimated Dietary Intake

The chronic dietary exposure to flubendiamide is estimated by the National Estimated Daily Intake (NEDI) calculation encompassing all registered/temporary uses of the chemical and the mean daily dietary consumption data derived from the 1995 National Nutrition Survey of Australia. The NEDI calculation is made in accordance with WHO Guidelines[1] and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for flubendiamide is equivalent to 9.7% of the ADI.

It is concluded that the chronic dietary exposure of flubendiamide is acceptable and residues in food will not pose an undue hazard to the safety of people.

The acute dietary exposure is estimated by the National Estimated Short Term Intake (NESTI) calculation. The NESTI calculations are made in accordance with the deterministic method used by the JMPR with 97.5th percentile food consumption data derived from the 1995 National Nutrition Survey of Australia. NESTI calculations are conservative estimates of acute exposure (24 hour period) to chemical residues in food.

An acute reference dose was considered unnecessary by the OCS. A NESTI calculation has not been undertaken.

Bioaccumulation Potential

Flubendiamide has a K_{ow} log P of 4.20 (pH 5.9, T 25 °C) indicating the potential for preferential partitioning into fat. The goat and hen metabolism studies provided with the application demonstrate that flubendiamide partitions into fat. In both sets of studies the highest residues in organs and tissues were found in fat. The cattle animal transfer study showed that residues of flubendiamide in fat declined by 54-69% during the first week of depuration. Thereafter residues continued to decline, however much more slowly.

Recommendations

The following MRLs will be established:

Table 1

Compound	Food		MRL (mg/kg)
Flubendiamide	VB 0040	Brassica (cole or cabbage) vegetables, Head cabbages, Flowerhead brassicas	3

Table 3

Compound	Residue
Flubendiamide	Commodities of plant origin: Flubendiamide Commodities of animal origin: sum of flubendiamide and 3-iodo-N-(2-methyl-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]phenyl)phthalimide, expressed as flubendiamide.

The following withholding periods are required in relation to the above MRLs:
Harvest (H)
Brassica vegetables: DO NOT harvest for 3 days after application

1.Guidelines for predicting dietary intake of pesticide residues, WHO, 1997.

Grazing (G)
Brassica vegetables: DO NOT graze treated brassica crops.
DO NOT use on brassicas grown for forage or fodder.

Commodities Exported

Brassica vegetables are not considered major export commodities[2] and the overall risk to export trade is considered to be small. Details of export volumes, values and markets are summarised below. [3]

Destination and Value of Exports

Broccoli
In 2002/03 Australia exported 6,428 tonnes of broccoli valued at $13,310,000. The major export markets were Singapore (2,764 tonnes), Malaysia (1,399 tonnes) and Japan (770 tonnes).

Brussels sprouts
In 2002/03 Australia exported 653 tonnes of Brussels sprouts valued at $829,000. The major export markets were the Netherlands (451 tonnes), New Zealand (108 tonnes) and the United Kingdom (40 tonnes).

Cabbage
In 2002/03 Australia exported 1,913 tonnes of cabbage valued at $1,918,000. The major export markets were Japan (508 tonnes), Taiwan (419 tonnes) and Singapore (322 tonnes).

Cauliflower
In 2002/03 Australia exported 16,567 tonnes of cauliflower valued at $23,409,000. The major export markets were Malaysia (10,200 tonnes), Singapore (5,360 tonnes) and Hong Kong (369 tonnes).

Codex Alimentarius Commission and Overseas MRLs

The Codex Alimentarius Commission (Codex) is responsible for establishing Codex Maximum Residue Limits (CXLs) for pesticides. Codex CXLs are primarily intended to facilitate international trade, and accommodate differences in Good Agricultural Practice (GAP) employed by various countries. Some countries may accept Codex CXLs when importing foods. Flubendiamide has not been considered by Codex.

No flubendiamide products are currently registered overseas and there are no overseas MRLs established.

Potential Risk to Trade

Export of treated produce containing finite (measurable) residues of flubendiamide may pose a risk to Australian trade in situations where (i) no residue tolerance (import tolerance) is established in the importing country or (ii) where residues in Australian produce are likely to exceed a residue tolerance (import tolerance) established in the importing country.

Residues are expected to occur in Brassicas and export markets have not established MRLs or import tolerances, creating a potential risk to trade. The following export advice is included on the draft labels to mitigate this risk:

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[2] Part 5B of the Vet Requirements Series and Ag Requirements Series, Overseas Trade Aspects of Residues in Food Commodities, August 2004.

[3] The Australian Horticulture Statistics handbook 2004.

Growers should note that MRLs or import tolerances do not exist in all markets for edible produce treated with *BELT 240* (or 480 SC). If you are growing edible produce for export, please check with Bayer CropScience Pty Ltd for the latest information on MRLs and import tolerances before using *BELT 240* (or 480 SC).

Conclusions

Quantifiable residues of flubendiamide are likely to occur in Brassicas when *BELT 480* and *BELT 240* Insecticides are used as directed. This creates a potential risk to trade as there are currently no established overseas MRLs for flubendiamide. In this situation, use of the products is not recommended in the production of crops destined for export.

Comments are sought on the potential for *BELT 240* and 480 SC Insecticides to unduly prejudice Australian export trade when they are used on brassica crops to control diamondback moth, cabbage white butterfly, cluster caterpillar, heliothis and soybean looper.

Product Use Pattern

BELT 480 and *BELT 240* will arrive in Australia fully packaged. The products are to be used on Brassica vegetables (e.g. brussels sprouts, cabbage, broccoli, cauliflower) to control diamondback moth (*Plutella xylostella*), cabbage white butterfly (*Pieris rapae*), cluster caterpillar (*Spodoptera litura*), heliothis (*Helicoverpa spp.*) and soybean looper (*Thysanoplusia orichalcea*). In the southern parts of Australia, the products will be used on brassicas between September-April. In the northern parts of Australia, the products will be used on brassicas between February-May.

The draft label does not propose any specific re-entry/re-handing intervals. A withholding period of 3 days is proposed on the draft label for brassicas.

BELT 480

BELT 480 will be supplied in 1L and 5L high density polyethylene (HDPE) bottles with 36 mm, 50 mm, or 63 mm neck size.

The product will be applied to brassicas at up to 100 mL/ha (48 g ai/ha), in 500-1000 L water/ha, with three applications per season at intervals of 7-14 days. Prior to use, the product will be diluted in water with the addition of a non-ionic surfactant.

The product will be applied by open- or closed-cab tractor mounted or drawn sprayers fitted with hydraulic nozzles (e.g. boom sprayers) or knapsack sprayers with hydraulic nozzles. The draft label includes the restraint: “do not apply by air”. The applicant has stated that the area treated per day would be up to 10 ha/day for vehicle mounted or drawn sprayers, and up to 0.5 ha/day when using a knapsack. The applicant calculated these values based on 3 hours of application per day. Based on this information, the maximum amount of product which would be handled is 1.5 L/day (720 g ai/day) for boom spraying, and 75 mL/day (36 g ai/day) for knapsack application.

BELT 240

BELT 240 will be supplied in 2 kg and 10 kg multi-layer paper bags with LDPE-Aluminium foil-LDPE linings. The majority of the granular product (>99%) has particle size 250-500µm, and <0.05% of particles are under 125µm. The product is nearly dust-free.

The products will be applied to brassicas at up to 200 g/ha (48 g ai/ha), in 500-1300 L water/ha, with three applications per season at intervals of 7-14 days. Prior to use, the product will be diluted in water with the addition of a non-ionic surfactant.

The product will be applied by open- or closed-cab tractor mounted or drawn sprayers fitted with hydraulic nozzles (e.g. boom sprayers) or knapsack sprayers with hydraulic nozzles. The draft label includes the restraint: “do not apply by air”. The applicant has stated that the area treated per day would be up to 10 ha/day for vehicle mounted or drawn sprayers, and up to 0.5 ha/day when using a knapsack. The applicant calculated these values based on 3 hours of application per day. Based on this information, the maximum amount of product which would be handled is 3 kg/day (720 g ai/day) for boom spraying, and 150 g/day (36 g ai/day) for knapsack application.

Exposure Estimation

Public

The products will not be used in the home garden. Bystander exposure during application is unlikely, as the products will not be applied from aircraft or using airblast equipment. Post-application exposure is unlikely as the product is for use on crops, and the public is not expected to come into contact with treated crops before they are harvested.

Occupational Exposure Characterisation

The formulated products will arrive in Australia fully packaged.
Farmers and their employees will be the main users of the product. Workers may be exposed to the product when opening containers, mixing/loading, application, and cleaning up spills and equipment. The main route of exposure will be dermal, inhalation and ocular.

Exposure During Use

Worker Exposure Studies / Information

No worker exposure studies were submitted.

Worker Exposure Estimates - POEM

The applicant supplied estimates of occupational exposure based on the UK Predictive Operator Exposure Model (POEM). These estimates were used as predictors of occupational exposure with some modifications.

Worker Exposure Estimates - PHED

In addition to the applicant's estimate of exposure using POEM, the OCS also estimated exposure using the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (1998).

For the purposes of the occupational health and safety assessment a NOEL from the dermal study in rats (100 mg/kg bw/d) was selected. The applicant has stated that for both formulations a worker will handle approximately 0.72 kg flubendiamide/day for boom spraying and 0.036 kg flubendiamide/day for knapsack application.

Risk Assessment and Management

Public

Exposure of the public to flubendiamide from use is unlikely to occur either during application or post-application.

Occupational application

PPE based on Acute Hazards

The primary acute hazard arising from the acute toxicity studies conducted on both products was slight eye irritation. Exposure to the product is possible during mixing/loading and when preparing spray. However no PPE is indicated for this level of hazard.

Based on a dermal NOEL of 100 mg/kg bw/day derived from animal toxicity testing a margin of exposure (MOE) of 100 or above is considered to be acceptable. The MOE takes into account both interspecies extrapolation and intraspecies variability. Based on both POEM and PHED exposure estimates, and for repeat dose risk assessments, all MOEs are >100 for both products. Therefore no personal protective equipment is required.

Re-entry or Re-handling Risk

Based on the US Occupational Post-Application Risk Assessment Calculator (US EPA, 2000), the maximum post application dermal exposure to workers following application to brassicas is 0.0309 mg/kg bw/d. The MOE is greater than 100. The default re-entry statement for crop application is appropriate when the risk to workers is considered very low.

No additional re-entry or rehandling statements are required. The following re-entry statement is appropriate:
Do not allow entry into treated areas until the spray has dried, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.

Recommended Hazard Classification Statements

With the available toxicology information, OCS has not classified flubendiamide or the formulated products *BELT 480* or *BELT 240* as a hazardous substance according to NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

Conclusion
The registration of flubendiamide at 480 g/L as a suspension concentrate formulation in *BELT 480* and 240 g/kg as a water dispersible granule in *BELT 240* for use as directed in brassica vegetable crops, is supported.

BELT 480 and *BELT 240* can be used safely if handled in accordance with the instructions on the product label and any other control measures described above. Additional information is available on the product MSDS.

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Environmental Chemistry and Fate

The data package presented in support of the application for the registration of the two Belt products addresses the environmental fate and toxicity of flubendiamide and its relevant metabolites. Various tests were conducted using ^{14}C-labelled flubendiamide, with the label in either the aniline ring or the phthalic ring as well as with unlabelled flubendiamide. Tests were affected on occasion by the very low water solubility of flubendiamide (29.9 µg/L), necessitating the use of cosolvents to obtain water solutions.

Hydrolysis

Flubendiamide only hydrolyses slightly at pH 4-9 with radiolabelled studies indicating that, in pH 4, 5, 7 and 9 buffers for up to 31 days, flubendiamide made up >93% of the remaining applied radioactivity. Metabolites were identified as present in only small amounts, each generally at <1% of the applied radioactivity.

Aqueous photolysis

Aqueous photolysis of radiolabelled flubendiamide with artificial sunlight showed that, in distilled water, flubendiamide decomposed with an average half-life of 5.5 days continuous artificial sunlight, with photolysis slightly accelerated in natural water, where the half life was 4.3 days continuous artificial sunlight. Major degradates identified were the des-iodoflubendiamide (maximum of 10.1 to 31.9% of the applied radioactivity after 168 hours), 3-hydroxyflubendiamide (0.2 to 13% of the applied radioactivity at 24 to 168 hours) and 3-hydroxy-hydroxyperfluoroalkylflubendiamide, formed from the 3-hydroxymetabolite (0.2 to 13% of the applied radioactivity at 48 to 168 hours).

The environmental half-life of flubendiamide as a result of direct photodegradation by sunlight was estimated to have a minimum, mean and maximum half-life in central Europe in mid-summer of 9.7, 15 and 58 days, respectively. The des-iodoflubendiamide was identified as stable to phototransformation with estimated half-lives in full sunlight >1 year at all latitudes and seasons. The 3-hydroxy-hydroxyperfluoroalkyl metabolite, at neutral to acid pH values, exhibited a medium rate of direct photo-transformation in water with half-lives of the order of 1.5 months or longer at all latitudes and in all seasons. However, phototransformation of the substance at pH 9 was much more rapid, with half-lives of <1 day at all latitudes and in all seasons.

Soil photolysis

Photolytic breakdown of radiolabelled flubendiamide on a soil surface gave calculated half-lives 11.4 and 11 experimental days of continuous exposure of the phthalic acid and aniline radiolabelled flubendiamides, which correspond to, respectively, 34.9 and 33.6 solar days based on average global light intensity. Such results are indicative of photodegradation on soil surfaces being a route of dissipation of flubendiamide in the environment. The photodegradative pathway on soil has the des-iodoflubendiamide metabolite initially forming and then either breaking down to flubendiamide oxalinic acid or mineralising to carbon dioxide and soil bound residues.

Atmospheric photolysis

The rate of photooxidation of flubendiamide in the troposphere was calculated and showed the day time half life of flubendiamide in air was estimated to be 8.78 h, corresponding to a chemical lifetime in air of 12.7 h. If flubendiamide were to be present in air in the gaseous phase, it would not be expected to be transported over large distances.

Soil metabolism – aerobic degradation

The degradation of radiolabelled flubendiamide was studied under dark laboratory conditions at 20°C for 120 days in three European soils, and for 360 days in one US soil, after dosing at a rate equivalent to 216 g flubendiamide/ha (compared to the proposed maximum Australian rate of 72 g flubendiamide/ha). The European soils were a pH neutral sandy loam, silt loam and silt, and the US soil a slightly acidic loamy sand. It was not possible to determine the reaction kinetics with any precision as limited degradation occurred and the projected half life on the soils was well above a year. Identification of small amounts of four degradation products revealed three degradation pathways, being substitution of the iodide substituent by an hydroxyl group, desiodination followed by cyclisation to the substituted phthalimide (with removal of the anilide group) and oxidation of the methyl substituent on the anilide ring to the benzoic acid. At the termination of the studies, flubendiamide made up 83.3 to 87.5% of the applied radioactivity. Unidentified radioactivity comprised 0.7 to 2.9% of the applied radioactivity at the termination times. Small amounts of radiolabelled carbon dioxide were released towards study termination (≤0.4% of the applied radioactivity).

The degradation of radiolabelled flubendiamide was studied for 365 days under outdoor conditions in Germany in sandy loam soil. Flubendiamide was applied at 225 g/ha and was found to dissipate by around half during the first 100 days after treatment, but remaining concentrations remained relatively stable through the rest of the study. The visually estimated mean half-life for loss of extractable flubendiamide was 114 days. Losses to leaching and translocation into grass were minimal.

Soil metabolism – anaerobic degradation

The anaerobic degradation of radiolabelled flubendiamide was studied under dark laboratory conditions at 20°C for 120 days in the same US loamy sand used for the aerobic study. No transformation/degradation products were identified in the course of the study. The study revealed that flubendiamide is stable in soil under the conditions tested, with a half-life in the order of greater than one year. However, this result should be treated with caution as the water column is considered not to have reached a fully anaerobic state in this study.

Aerobic aquatic metabolism

An aerobic aquatic metabolism study with two natural water/sediment systems showed that flubendiamide moved mainly from the water column to the sediment. At time 0, 64 to 68% of the applied flubendiamide was in the water column and 24 to 29% in the sediment. After 125 days, 3 to 4% of the flubendiamide remained in the water column with 73 to 75% in the sediment. The maximum amount of volatile carbon dioxide was 1.36% of the applied radioactivity. In the water column, the DT50 values determined were 15 and 39 days with DT90 values of 108 and 949 days. For the entire system, the DT50 values were >1 year and 539 days with the DT90 values being both much greater than one year. Flubendiamide only extremely slowly degrades in water/sediment systems with the majority of the material moving to the sediment where it persists over time. Dissipation, rather than degradation, is the major route of removal from the water column.

Anaerobic aquatic metabolism

An anaerobic aquatic metabolism study was conducted with a pond water/sediment system over 365 days in the dark. Radiolabelled flubendiamide was applied to the water surface at a rate of 262 g/ha and, under the anaerobic conditions, flubendiamide degraded mainly to the des-iodoflubendiamide with non-extractable residues in the sediment identified as a minor dissipation pathway. In water, the DT50 for flubendiamide was 11 days with a DT90 of 37 days while in the entire system, the DT50 was 284 days and the DT90, 942 days. The des-

iodoflubendiamide underwent no further degradation and was still increasing at study's end (when it constituted 22% of the applied radioactivity in the water column and 37% of the applied radioactivity in the sediment – corresponding amounts of flubendiamide at that time were 56 and 64% respectively). While there was appreciable degradation of flubendiamide under the anaerobic test conditions, this was to the des-iodoflubendiamide which persisted under the anaerobic test conditions. Note that the water column and sediment did not maintain fully anaerobic conditions in the later stages of the exposure period.

Mobility - field volatility

The vapour pressure of flubendiamide is reported as $<10^{-4}$ Pa at 200°C while the Henry's law constant is approximately 2 X 10^{-9} Pa.m^3/mol at 20°C, consequently, flubendiamide is not expected to show any significant volatility in the field.

Mobility - soil adsorption/desorption

The adsorption/desorption of flubendiamide was studied in two German (a silt and sandy loam) and three North American (a silty clay, a loamy sand and a loam soil) using radiolabelled flubendiamide. The adsorption constants ($K_{d(ads)}$) in the five test soils ranged from 17.3 to 30.0 mL/g ($K_{oc(ads)}$ values were 1076 to 3318 mL/g). The desorption constants ($K_{d(des)}$) were approximately 1.7 to 4 times higher than the respective adsorption constants, indicating a strong binding of the flubendiamide once bound to the soil. Based on the McCall's Mobility Classifications (McCall et al., 1980), low to medium mobility would be assigned to the German soils and one of the North American soils and low to slight mobility to the remaining North American soils.

Field dissipation

Field dissipation studies were presented for soils in five European countries and in the US states of California, Mississippi and Washington.

In the European studies, flubendiamide was applied to soils as a 480 SC formulation at the rate of 180 g flubendiamide/ha. Soils were sampled for periods of up to 728 days after application and residues of flubendiamide and its metabolites determined. Initial concentrations of flubendiamide in the top 10 cm of soil ranged from 123 to 142 µg/kg dry soil while at the end of the studies, the flubendiamide concentrations in that soil layer ranged from 15.9 to 65.4 µg/kg dry soil (equivalent to ~11 to 53% of the respective starting concentrations), clearly showing the slow dissipation of flubendiamide and its presence in measurable quantities well after the application period. The des-iodoflubendiamide and flubendiamide-benzoic acid were the only metabolites of significance. The des-iodo metabolite was present in the top 10 cm soil layers at 1.60 to 1.88 µg/kg dry soil at day 0 and, at studies' ends, 0.664 to 2.63 µg/kg dry soil. The benzoic acid metabolite was generally present from shortly after application to the end of the studies, maximum concentration was 2.67 µg/kg dry soil with maxima occurring between 176 and 365 days followed by slow declines. Kinetic analysis of the data gave DT50 values of 5.8 to 971 days (from various models, based on best fit) and DT90s of 855 to >1000 days (again, based on best fit of the models used).

The study results show that flubendiamide degraded only slowly under the northern and southern European conditions tested with the dissipation slowing markedly over time. As indicated by the very long DT90 values, flubendiamide is persistent in soils.

A further consideration of these European data confirmed that the bulk of the applied flubendiamide was identified as staying close to the soil surface throughout the study with a rapid decline seen over the first few days followed by a much slower decline until the end of the study. Kinetic modelling using a hockey stick model, which is a combination of two first order kinetic curves, one a fast degradation and the other, slow. With this approach, the mean

DT50 for the fast degradation phase was 12.8 days and the mean DT50 for the slow phase was 587 days with the mean changeover time between the two phases being 13.8 days.

In the three soil dissipation studies conducted in the USA, a single application of flubendiamide, as a 480 SC formulation, was made at a rate of ~767-790 g flubendiamide/ha to bare soil or fallow plots. Soils were sampled for periods of 538 to 552 days with analyses for flubendiamide and its metabolites. In the Californian study, initial and final flubendiamide concentrations in the top 15 cm soil layer were 248 and 151 μg/kg dry soil with the Mississippi study reporting equivalent results of 341 and 149 μg/kg dry soil and the Washington study, 248 and 44.6 μg/kg dry soil with these results indicating 18 to 61% of the flubendiamide after approximately 18 months. The des-iodoflubendiamide and the flubendiamide benzoic acid metabolite were again identified as the only degradation products present in significant amounts and were present throughout the studies at concentrations not exceeding 9.30 μg des-iodoflubendiamide/kg dry soil and 8.03 μg flubendiamide benzoic acid/kg dry soil (respectively equivalent to ~3.8 and 3.3% of the concentration of flubendiamide initially in the soil). The DT50 values reported were 61 days in the first rapid phase and greater than 18 months in the second slower phase (California), 17.2 days in the first phase and greater than 18 months in the second slower phase (Mississippi) and 250 days (Washington, using a different kinetic model based on simple first order decay, rather than the biphasic models used for other two US states).

In all the soil dissipation studies, there was movement of some flubendiamide to below the 30 cm soil profile, up to the 50 cm depth on occasion. In contrast, the des-iodoflubendiamide tended to remain in the upper soil profiles while the benzoic acid metabolite was found at depths associated with the presence of the flubendiamide.

The dissipation of flubendiamide after its application as a 480 SC formulation to grass plots between rows of apple trees was studied in Germany where two grass plots were sprayed with the 480 SC formulation under field conditions at a rate of 180 g flubendiamide/ha. There were two applications with a 19 day interval between. Grasses were sampled for up to 28 days after treatment and analysed for flubendiamide residues. Initial residue concentrations ranged from 12.2 to 13.6 mg flubendiamide/kg of grass after spraying to 2.77 mg flubendiamide/kg of grass after 14 days and 0.79 mg flubendiamide/kg grass after 28 days. No degradation products were reported identified. Half-lives of flubendiamide in the grass ranged from 3.9 days (after the second application) to 14.6 days (after the first application). The study indicates that flubendiamide on sprayed plant material is expected to dissipate fairly readily but with measurable residues still expected to be present at 28 days after treatment.

Flubendiamide residues in potential arthropod prey of birds and mammals

In a study to determine the level and time course of flubendiamide residues on potential arthropod prey of birds and mammals, to quantify the supply of arthropod food and to determine its taxonomic composition, differentiated for the strata ground and foliage, a vineyard was sprayed with flubendiamide SC 480 on four occasions at a nominal application rate of 154 g flubendiamide/ha. The applications were on days 0, 15, 29 and 43 of the study.

The application of the test substance had no apparent effect on abundance of the arthropods sampled, consistent with its specificity as a *Lepidoptera* larvicide. The results of residue analysis showed a general pattern of reduction within ground and foliage dwelling arthropods throughout the study period. The maximum initial residual values of the test substance after the first and second applications were followed by rapid declines, less rapid declines after the third application, and actually increased during the following days after the last application. After the last application, the concentration declined slowly and then a second maximum was observed 11 days after the final application. The highest peak and average residue levels were found in foliage dwelling organisms, likely due to higher interception factors for spray reaching the soil surface. The study's result indicate that an abundant arthropod food source may remain after a spray program with flubendiamide.

Modelling studies

A modelling study to predict environmental concentrations in soil in greenhouse applications with a worst case late use scenario was considered, involving 2 applications at 120 g flubendiamide/ha at a 7 day interval, with 80% crop interception. The predicted environmental concentration in the soil from one annual application sequence was 0.064 mg/kg in the top 5 cm of soil, with a long term plateau concentration after several years of application of 0.075 mg/kg in the surface 20 cm, and maximum predicted concentration in the top 5 cm and top 10 cm of soil, respectively, of 0.139 mg/kg and 0.107 mg/kg. While an accumulation is expected to occur under the proposed Australian use conditions, the modelling indicates the extent to which soil accumulation could occur in a worst case situation, e.g. where photolytic reactions on the soil surface are inhibited, e.g. as could also occur by soil coverage due to cultivation.

The long life of flubendiamide in the soil (as shown in the European and US field dissipation studies) has the potential for soil accumulation to occur and modelling of the likely soil residue levels of flubendiamide as a result of the proposed Australian use patterns showed that on bare soil residues of flubendiamide do reach a plateau level by approximately 10 years with an estimated maximum soil concentration of 0.59 mg flubendiamide/kg of soil. Interception by the crop would lower this figure.

A further modelling study to determine upper bound concentrations of flubendiamide in aquatic systems from the use of flubendiamide on cotton, tree fruit, nut and vine crops and vegetable crops in the USA was presented. The modelling, using a 2 metre deep static water body and assuming various agricultural application scenarios, indicated that maximum water concentrations would range from 0.17 to 5.6 µg flubendiamide/L. Another modelling study conducted with the objective of determining upper bound concentrations of flubendiamide in drinking water for dietary risk assessment from use on cotton, tree fruit, nut and vine crops and vegetable crops in the USA estimated environmental concentrations in surface and groundwater. Predicted upper 90th percentile peak annual concentrations in surface water of 0.7 to 7.7 µg flubendiamide/L and corresponding average concentrations of 0.3 µg flubendiamide/L and 4.3 µg flubendiamide/L, considered very conservative estimates.

Predicted concentrations in groundwater ranged between 0.06 µg flubendiamide/L (cole crops, 3 applications at 50 g flubendiamide/ha - ~70% of the proposed Australian rate for sweet corn) and 0.22 µg ac/L. While the use scenarios differ from proposed use in Australia and local soil/topography/climate situations also differ, the modelling indicates that even with many years of repeated use, little movement of flubendiamide to groundwater is to be expected.

Bioaccumulation

Two studies were presented on the bioaccumulation of flubendiamide in fish, one with the parent substance and one with the des-iodo metabolite.

A study of the bioconcentration and biotransformation of flubendiamide in bluegill sunfish (*Lepomis macrochirus*), using radioabelled flubendiamide, was presented. The study was conducted in two parts: a 42 day phase to examine bioconcentration and depuration and a 10-13 day exposure study to investigate biotransformation. The bioconcentration factor (BCF) for the parent compound (based on whole fish, wet weight) at the steady state was about 73. such a value rates flubendiamide as slightly concentrating (BCF < 100). Flubendiamide depurated over time from fish after exposure such that after 14 days in uncontaminated water, 83 to 86% (of the mean plateau radioactivity) were depurated from whole fish. The major compound detected in all fish samples was flubendiamide. It made up about 72-76% of the total radioactive residues (TRR) in the edible portions and 71-81% of the TRR in the viscera. The metabolites identified in the edible and visceral portions were the flubendiamide benzyl alcohol and flubendiamide-benzylalcohol-glucuronide, each accounting for 1-4% of the TRR.

The bioconcentration, depuration and biotransformation of radiolabelled des-iodoflubendiamide was examined over 42 days. The radiolabelled des-iodoflubendiamide accounted for 100% of the radioactivity in all water samples, i.e. no metabolism of the des-iodoflubendiamide occurred. The BCF for the parent compound (whole fish, wet weight) at the steady state was 12.6. Consequently, des-iodoflubendiamide is considered as slightly concentrating (BCF < 100) and is depurated over time from fish after exposure.

Soil accumulation

Soil accumulation is an issue of concern as the long life of flubendiamide in the soil (as shown in the European and US field dissipation studies) has the potential for soil accumulation to occur. Examination of the field dissipation data indicates that, while there is a rapid degradation phase in the soil, there is a long secondary phase in which concentrations of flubendiamide only very slowly disappear. An ongoing long term soil accumulation study conducted at sites in Germany and Italy with three applications per year applied at 90 g flubendiamide/ha/application with a nominal 14 days between applications, has shown that over a three year period, 52% of the applied flubendiamide at one site and 36% at a second site still remained in the soil. Because plateau levels had not been achieved after three years, the study is still being continued.

Environmental Effects

Avian

Six avian studies were presented for assessment – two acute oral toxicity studies with bobwhite quail and either flubendiamide or a 480 SC formulation, two subacute 5 day dietary studies using flubendiamide, one with bobwhite quail and one with mallard ducks. Additionally, bobwhite quail and mallard duck reproduction studies were presented.

Bobwhite quail were not acutely sensitive to single oral applications of flubendiamide and the 480 SC formulation of flubendiamide, up to the highest tested concentrations of 2000 and 800 mg ac/kg body weight for the active constituent and formulation, respectively.

Subacute toxicity effects were not observed in bobwhite quail after a 5 day feed exposure to flubendiamide. No mortalities occurred, and bird weights and feed intake were not significantly affected, resulting in an LC50 value >5000 mg ac/kg feed. Chronic exposure of male and female bobwhite quail to flubendiamide at mean measured concentrations up to 1059 mg ac/kg feed identified no compound related symptoms of toxicity in the adults and offspring. Similarly, there was no statistically significant adverse effects on any of the reproductive parameters measured, resulting in a NOEL of 1059 mg ac/kg feed.

There were no compound or dose related effects with respect to gross pathology of the birds and the NOEL was again set at 1059 ppm.

Subacute toxicity effects were not observed in mallard ducks after a 5 day feed exposure to flubendiamide. No mortalities occurred, and there were no other treatment related adverse effects to the birds, resulting in an LC50 value >4535 mg ac/kg feed.

No compound related symptoms of chronic toxicity in adults and their offspring were identified in mallard ducks exposed over 22 weeks to dietary concentrations up to 960 mg ac/kg feed. In addition, there were no dose related gross pathology effects, allowing establishment of a NOEC of 960 ppm for these parameters. Statistically significant differences were observed in some instances, but based on the magnitude of the measured results and the absence of clear dose relationships, such results were considered not to be biologically significant. However, statistically significant differences in eggshell thickness and percentage survival of 14 day old hatchlings was observed at the 960 mg ac/kg feed level were considered to be biologically significant. Consequently, the NOECs based on the percent

of 14 day old hatchlings and on eggshell quality (strength and thickness) were both set at 289 ppm flubendiamide.

From the avian tests, it may be concluded that flubendiamide did not cause toxic effects in bobwhite quails at all levels tested. Chronic toxicity was only seen in the eggs and offspring in mallard ducks exposed to the highest test concentration of 960 mg ac/kg feed. The lowest chronic toxicity endpoint observed was 289 mg ac/kg feed.

Fish

Seven acute fish studies were presented for assessment – five with flubendiamide and two with the 480 SC formulation together with an early life stage toxicity study of flubendiamide to the fathead minnow and a full life-cycle toxicity test with flubendiamide, also to the fathead minnow. Testing of flubendiamide was generally up to the solubility limit allowed with solvent addition.

Rainbow trout were not acutely sensitive to applications of pure (97%) flubendiamide or to the 480 SC formulation, with no recorded mortalities at test concentrations up to 61.9 µg ac/L and 88.4 mg ac/L respectively. However, the presence of excessive turbidity in the test solutions in the formulation study means the dissolved concentrations remain unknown, resulting in lowered confidence in the reported ecotoxicological endpoint.

Similarly, no bluegill sunfish mortalities were recorded from acute exposure to flubendiamide and the 480 SC formulation, resulting in LC50 values of >67.7 µg ac/L and >80.2 mg ac/L. However, excessive turbidity in the test solutions again means the latter endpoint should be treated with caution.

The fathead minnow, sheepshead minnow and carp were not acutely sensitive to flubendiamide, with no recorded mortalities, with LC50 values of >66.5, 29.8 and 84.7 µg ac/L.

No treatment related effects occurred in the early life stage exposure of fathead minnow to flubendiamide. Therefore, the NOEC was determined to be 60.2 µg flubendiamide/L, for fish hatchability, survival and growth.

A total of 23 biological endpoints were statistically evaluated during the full-life cycle exposure of fathead minnow to flubendiamide (hatching success, survival, growth and reproductive success of the parent and first generation fish and reproductive success for the first generation fish). There were no significant effects, and therefore the NOECs were determined to be 49 µg flubendiamide/L for all F0 and F1 endpoints tested.

The lowest acute endpoint reported was an LC50 >29.8 µg ac/L, however, no effects were observed. No treatment related effects were observed for any of the fish toxicity tests.

Aquatic Invertebrates

There were 14 aquatic invertebrate studies presented for assessment – six with flubendiamide, four with the 480 SC formulation, two with the 240 WG formulation and two with the metabolite.

Daphnids were not acutely sensitive to applications of pure (97%) flubendiamide up to the limit of its solubility (EC50 >60 µg ac/L). However, acute toxic effects were observed when the daphnids were exposed to the two formulation products of flubendiamide. LC50 values of 2.24 µg ac/L and 1.5 µg ac/L were calculated for daphnids exposed to the 480 SC and 240 WG formulations respectively, indicating possible solvent toxicity or other formulation effects. Toxicity to daphnids with access to up to 10^4 cells/mL algae was reduced (EC50 = 4.2 µg ac/L), and toxic effects were completely eliminated at an algal cell density of 10^6 cells/mL. The metabolite des-iodoflubendiamide was not toxic to daphnids up to the limit of its solubility, with an EC50 >880 µg metabolite/L.

Daphnid survival (EC50 > 60 µg ac/L) was not affected from chronic exposure to pure (97%) flubendiamide, however, significant effects on reproduction resulted in a 21 day NOEC of 33 µg ac/L. In a pattern similar to that observed in the acute toxicity tests, daphnids, with a 21 day EC50 of 2.28 µg ac/L and NOEC value of 1.19 µg ac/L, were far more susceptible to the 480 SC formulation of flubendiamide. These results again imply the existence of toxic effects not necessarily attributable to the active constituent.

Acute toxicity effects were not observed in mysids or the eastern oyster, when exposed to pure (97%) flubendiamide. No mortality occurred in mysids, and shell deposition in treated oysters was in the range of the control, resulting in EC50 values of >28 µg ac/L and >49 µg ac/L, respectively.

Mysids were not reported to be affected by chronic exposure to pure (98.1%) flubendiamide, with a NOEC of 19 µg ac/L (highest tested concentration) based on a final definitive test. This value should, however, be treated with caution as NOEC values <0.25 µg ac/L were calculated for preliminary tests and the first definitive test. It is likely that some of the toxicity may be explained by higher concentrations of the solvent dimethylformamide.

Chironomids were far more sensitive to acute exposure of the 240 WG than the 480 SC formulation of flubendiamide (although dose responsiveness was observed in both), with EC50 values of 0.20 mg ac/L and 2.32 mg ac/L respectively. The endpoints provided in the test reports were calculated based on nominal concentrations, using Probit analysis. Given the low test substance recoveries (39-80%) on Day 2 for both tests, the chironomids may be even more sensitive than reported.

Chronic exposure of chironomids to pure (97.4%) flubendiamide resulted in significant effects to emergence and development at 80 µg ac/L with a 28 day LOEC of 39 µg ac/L. In an effect opposite to that in daphnids, chironomids were more sensitive to the metabolite des-iodoflubendiamide, with an emergence NOEC of 2.14 µg ac/L.

Of the aquatic invertebrates, daphnids were most sensitive to acute exposure, in particular from exposure to the two formulations, with the lowest acute endpoint being a 48 hour EC value of 1.5 µg ac/L (240 WG formulation). Daphnids were also most sensitive to chronic toxicity, with a 21 day NOEC of 1.19 µg ac/L. Chironomids were also very sensitive to chronic exposure with the des-iodoflubendiamide (NOEC = 2.14 µg ac/L).

Algae

There were 3 aquatic invertebrate studies presented for assessment – two with flubendiamide and one with the 480 SC formulation.

No toxic effects were observed in green algae exposed to pure (96.7%) flubendiamide or to the 480 SC formulation, with ErC50 values greater the highest tested concentrations attainable of 69.3 µg ac/L and 50 mg ac/L respectively. In addition, duckweed was not sensitive from exposure to pure (96.9%) flubendiamide, resulting in a 7 day EC50 >54.6 µg ac/L.

Mesocosm

Studies on the toxicity of the 480 SC formulation to a variety of zooplankton, phytoplankton and macroinvertebrates was assessed in a 16 week simulated contamination mesocosm study.

All species were placed in replicate tanks, under identical, simulated outdoor conditions. The mesocosms were exposed to test concentrations of 0.4, 1.0, 2.3, 5.3 and 12 µg ac/L, after which population numbers and effects were measured over the course of and at the end of the study period.

The most sensitive species was *Daphnia longispina*, which showed toxic effects at concentrations ≥2.3 µg ac/L over the first week of the study and then at ≥5.3 µg ac/L up for a further 3 weeks, at which point the daphnids at the affected concentrations recovered to the range of the control and unaffected concentrations. On the basis of these effects, the NOEC

for *D. longispina* was reported as 1 µg ac/L. Another zooplanktonic species, *Simocephalus vetulus*, was also affected at the highest test concentration, however, this was only observed at one sampling day. Numbers of *Chydorus spaericus* were seen to decline at all test concentrations at the beginning of the study, and quickest at 12 µg ac/L, however, this was not reported as significant.

One of the species living in the Artificial Substrate Samplers (ASS), the Tubificidae, were sensitive to the highest test concentration between Days 14 and 42, after which recovery to control levels was observed. Toxic effects of the test substance were also observed in Cryptophyceae during the first two weeks of the study, however, full recovery occurred after this point.

Significant differences to the control for other species were either absent or occurred on one sampling day only. No long term effects were seen over the course of the study, with affected species recovering to control levels at some point during the study, however, because only one replicate was used at the highest test concentration, the NOEAEC (no observed ecological adverse effect concentration) was reported at 5.3 µg ac/L. Although only short-term effects on *D. longispina* were observed, there were no repeated exposures as would be expected from practical use of the formulation. The ecotoxicological endpoint for *D longispina* (NOEC = 1 µg ac/L) should remain significant.

Terrestrial Invertebrates

There were 18 terrestrial invertebrate studies presented for assessment – 3 with flubendiamide, 11 with the 480 SC formulation, 4 with the 240 WG formulation, and 1 with the metabolite des-iodoflubendiamide.

Honey bees were not acutely sensitive to applications of flubendiamide, or to the 480 SC formulation, with LD50 values greater than the highest test concentration of 200 µg ac/bee. Chronic exposure to the 480 SC formulation had no effect on mortality and flight intensity, but highly variable results, which could not be separated from variability in the control, were observed in reproduction endpoints. The 21 day NOEC for honey bees was equal to the highest test concentration of 180 g ac/ha. Chronic exposure (99, 114.8 and 118.8 g ac/ha over 7 consecutive days) to the 240 WG formulation resulted in no sensitivity compared to the control in bumblebees. The NOEC was equal to the highest application of 118.8 g ac/ha.

Earthworms were not found to be acutely sensitive to flubendiamide, the 480 SC formulation, or to the metabolite, des-iodoflubendiamide, with EC50 values exceeding the highest test concentrations of each (14 day EC50 >1000, 400 and 1000 mg ac/kg dry weight soil, respectively). In addition, the SC formulation did not result in chronic effects with a NOEC equal to the highest tested concentration (56 day NOEC = 1000 mg ac/kg dry weight soil). However, with the 240 WG formulation earthworm reproduction was significantly affected at the highest test concentration (1000 mg ac/kg dry weight soil), resulting in a 56 day NOEC of 562 mg ac/dry weight soil.

Exposure of the 480 SC and 240 WG formulations of flubendiamide to predatory mites resulted in low mortality rates, and reproduction in the range of the controls, at all concentrations tested (14 day LD50 > 675 g ac/ha and > 616 g ac/ha respectively). An effect was noticeable at the highest test concentration of the 240 WG formulation, with 14% mortality and 23.6% lower reproduction compared to the control, however, this was not considered significant.

Acute toxicity effects and chronic reproduction effects were not observed in parasitic wasps after application of the 480 SC and 240 WG formulations of flubendiamide, with low mortality rates, and reproduction in the range of the controls, at all concentrations tested (14 day EC50 > 675 g ac/ha and > 616 g ac/ha respectively). It is worth noting, however, that significant and dose responsive mortality effects were seen in the first bioassay, indicating an endpoint value of 275 g ac/ha > LR50 > 675 g ac/ha.

No toxic effects were observed after exposure of the 480 SC formulation to the green lacewing. Mortality was low and not dose-dependent, and reproduction was in the range of the control. Exposure of the 480 SC formulation to Collembola resulted in lower reproduction and higher adult mortality at concentrations of 100 mg ac/kg dry weight soil and above, however, only the reproductive effects were considered significant. Dose responsiveness was not observed in either parameter. A NOEC of 31.6 mg ac/kg dry weight soil was reported.

Reproduction in ladybird beetles remained unaffected from exposure to leaves with the 480 SC formulation of flubendiamide, with NOEC values equal to the highest concentrations tested. However, preimaginal mortality was shown to exceed 50%, with LC50 values of 407 g ac/ha (leaf exposure only) and 106.1 g ac/ha (leaf exposure and aphid food exposure).

Microorganisms

There were 5 microorganism studies presented for assessment – one with flubendiamide and four with the 480 SC formulation.

Exposure of the 480 SC formulation of flubendiamide to microorganisms resulted in no significant toxic effects on glucose simulated respiration or microbial mineralisation up to the highest concentrations tested (3 mg ac/kg dry weight soil). In addition, no significant effect on soil litter degradation was observed after incorporation into the soil, and subsequent application of the formulation on the soil at up to 508 g ac/ha. Pure (97%) flubendiamide was also found to be non-toxic to sewage microorganisms up the highest concentration tested (10,000 mg ac/L).

It can be concluded that flubendiamide is not inhibitory to microbial activity, nor toxic to sewage microorganisms up to the highest levels tested.

Terrestrial Plants

There were 5 terrestrial plant studies presented for assessment – 2 with the 480 SC formulation and 3 with the 480 SC formulation of flubendiamide.

The 480 SC formulation, when applied at the highest proposed seasonal application rate of 526 g ac/ha, caused no significant toxic effects to the emergence, survival, phytotoxicity or plant height and weight in a range of representative target monocot and dicot crops.

The 240 WG formulation was not found to affect any of the above-mentioned parameters, when applied at 180 g ac/ha, to a similar range of species, except to sunflowers, which experienced 33% inhibition of germination at 180 g/ha. Emergence, survival, phytotoxicity and growth in the treated plants were in the same range as the control.

Environmental risk summary

Birds

Exposure at the time of application could occur by birds and mammals eating contaminated insects or by direct contact with the spray or indirect contact with treated vegetation. Estimated concentrations resulting in a diet exclusively based on such exposure ranged between 1.86 and 17.4 mg flubendiamide/kg feed for one to three applications (equivalent to 48 and 144 g flubendiamide/ha). These worst case concentrations are well below the 5-day dietary LC50 values for two bird species. Consequently, the proposed use is not likely to present an acute or dietary risk to birds.

Aquatic organisms

Contamination of a shallow (15 cm deep), static waterbody with direct overspray at the maximum application rate of 48 g flubendiamide/ha is calculated to give a notional concentration in the water of 32 µg flubendiamide/L. Based on the relevant ecotoxicity endpoints, acute risk to fish, the water flea, the algae species tested and duckweed from the proposed use patterns is unacceptable. Acute risk to chironomids is mitigable under this overspray scenario. With a 10% overspray, the risk to chironomids, algae and duckweed is

indicated as acceptable with risk to fish and daphnia requiring further mitigation. A further refinement of risk to fish and daphnia from spray drift of flubendiamide is possible from use of the AgDrift spray drift model for ground application. This shows that, for a single application as a medium quality spray, the required downwind no spray zones are 30 metres for Belt 480 SC and 60 metres for Belt 240 WG. With coarse quality spray, the 480 SC formulation requires a 15 metre downwind no-spray zone while the 240 SC formulation requires a 30 metre distance.

For two applications, Belt 480 SC would require downwind no-spray zones of 60 and 30 metres respectively for medium and coarse spray applications. The 240 WG formulation would require respective distances of 100 and 60 metres.

For three applications, Belt 480 SC would require downwind no-spray zones of 80 and 60 metres respectively for medium and coarse spray applications. The 240 WG formulation would require respective distances of 140 and 80 metres.

Flubendiamide can be expected to be stable in aquatic systems and chronic aquatic exposure is a possibility. Based on the chronic aquatic toxicity endpoints available for flubendiamide and a worst case scenario involving drift from three applications of flubendiamide into a 15 cm deep water and no degradation or loss from the water column, chronic risk is shown to be acceptable provided the above acute no-spray zones are adhered to.

Because flubendiamide is expected to show low to medium mobility and be persistent in the environment, there is a potential for both active constituents to enter aquatic habitats in runoff water as a result of their presence in the runoff from treated land. A simple modelling of such runoff indicates unacceptable risk to fish and daphnia. Mitigation of this risk based on a more realistic runoff scenario, one cycle of adsorption of flubendiamide to the soil and crop interception shows that aquatic risk from runoff from the proposed use patterns are expected to be acceptable. Risk to groundwater is not anticipated from the proposed use patterns

Non-target invertebrates and micro-organisms

The proposed registration of Belt Insecticides at a maximum use rate of 72 g flubendiamide/ha use is not expected to present unacceptable risks to bees, insect predators and parasites, collembola and earthworms, or to have lasting effects on soil respiration and nitrification processes. This is based on studies showing that relevant toxicity endpoints were well below the concentrations tested which showed no adverse effects. In the cases of green lacewing larvae and adult ladybirds, the maximum rates tested were less than the possible maximum levels of flubendiamide which could be applied via the three proposed applications. However, the results provided were all laboratory studies and toxicity in field situations is expected to be reduced. This is shown by the study which showed that when a vineyard was sprayed on four occasions at nominal rates of 154 g flubendiamide/ha (cf. the maximum proposed Australian rate of 72 g flubendiamide/ha), the application had no apparent effect on abundance of the ground and foliage dwelling arthropods sampled, consistent with its specificity as a Lepidoptera larvicide. Consequently, risk to green lacewings and adult ladybirds is expected to be acceptable.

Native Vegetation

Flubendiamide is unlikely to present a risk to plants when used as proposed, consistent with its insecticidal properties. The NOEC vales from seedling emergence and vegetative vigour tests in ten crop species remained above 534 g/ha, which is more than twice the maximum proposed seasonal application rate.

Conclusion

The proposed use of the Belt 480 SC and Belt 240 WG formulations is not likely to present either an acute or dietary risk to birds ingesting residues on plants or insects. Risk to aquatic invertebrates is expected to be acceptable provided the following mandatory downwind n-spray zones are observed.

Belt 480 SC Insecticide

DO NOT apply when there are aquatic and wetland areas including aquacultural ponds or surface streams and rivers downwind from the application area and within the mandatory no-spray zone shown in the table below.

DOWNWIND NO-ZONES for GROUND APPLICATION	
Medium quality spray applications (high boom)	
A single application	30
Two applications	60
Three applications	80
Coarse quality spray applications (high boom)	
A single application	15
Two applications	30
Three applications	60

* According to ASAE S572's definitions for standard nozzles.

Belt 240 WG Insecticide

DO NOT apply when there are aquatic and wetland areas including aquacultural ponds or surface streams and rivers downwind from the application area and within the mandatory no-spray zone shown in the table below.

DOWNWIND NO-ZONES for GROUND APPLICATION	
Medium quality spray applications (high boom)	
A single application	60
Two applications	100
Three applications	140
Coarse quality spray applications (high boom)	
A single application	30
Two applications	60
Three applications	80

* According to ASAE S572's definitions for standard nozzles.

To take into account changes resulting from State legislation that prohibits on-farm burial or burning of empty pesticide containers, the label statements for disposal (under "Storage and Disposal") for both the Belt® 480 SC Insecticide and the Belt® 240 WG Insecticide require inclusion of the following statement:

"Triple rinse containers before disposal. Add rinsings to spray tank. DO NOT dispose of undiluted chemicals on site. If not recycling, break, crush or puncture and deliver empty packaging to an approved waste management facility. DO NOT burn empty containers or product."

Acceptance of these recommendations allows DEWHA to recommend that the APVMA be satisfied that the proposed use of Belt 480 SC or Belt 240 WG would not be likely to have an unintended effect on animals, plants, things or on the environment.

Justification for use and Mode of Action

This application seeks the registration of *BELT 480* and *BELT 240* which both contain flubendiamide as their only active constituent. They are for application as a foliar spray for the control of various lepidopteran pests including diamondback moth (*Plutella xylostella*), Heliothis (*Helicoverpa* spp.), cabbage white butterfly (*Pieris rapae*), soybean looper (*Thysanoplusia orichalcea*) and cluster caterpillar (*Spodoptera litura*) in brassica vegetable crops.

Flubendiamide is the first member of a new chemical class, the phthalic acid diamides, with a novel chemical structure. The compound shows strong insecticidal activity especially against lepidopterous pests including resistant strains. Acceptable safety to in-crop non-target organisms has been demonstrated. Flubendiamide exhibits no cross-resistance to conventional chemistries and is expected to be a suitable agent for controlling lepidopterous insects as part of insect resistance management and integrated pest management programs.

Proposed use pattern

BELT 480 and *BELT 240* will be applied to various brassica vegetable crops (broccoli, Brussels sprouts, cabbage, cauliflower, kohlrabi) as a foliar spray with up to three sequential applications of either product at 7 to 14 day intervals. Application windows for control of diamondback moth are also subject to a CropLife Australia insecticide resistance management strategy for this pest. The product application rate for *BELT 480* is 75 or 100 mL/ha or 10 mL/100L for diamondback moth, cabbage white butterfly, cluster caterpillar and Heliothis, and 50 or 75 mL/ha or 7.5 mL/100L for soybean looper. The application rate for *BELT 240* is 150-200g/ha or 20 g/100L for diamondback moth, cabbage white butterfly, cluster caterpillar and Heliothis, and 100-150g/ha or 15g/100L for soybean looper. The higher application rates and/or shorter application periods (7 to 10 days) are used during periods of high pest pressure or rapid crop growth.

Use is proposed for all States and territories.

It is proposed that *BELT 480* will be available in 1L and 5L high-density polyethylene containers and *BELT 240* in 2kg and 10kg multi-layer paper bags with LDPE-Al foil-LDPE lining.

The following Withholding Period statements are recommended for the product:

Harvest (H)
Brassica vegetables: DO NOT harvest for 3 days after application.

Grazing (G)
Brassica vegetables: DO NOT graze treated brassica crops.
DO NOT use on brassicas grown for forage or fodder.

Evaluation of efficacy and crop safety

BELT 480

Nine field trials from Brassica crops (6 x Brussels sprouts, 1 x broccoli, 1 x cabbage, 1 x Chinese cabbage) were presented to demonstrate the efficacy/crop safety of *BELT 480* for the control of diamondback moth, Heliothis and other lepidopteran pests.

All trials were designed as randomized complete blocks with 4-5 replicates and included an untreated control.

BELT 480 was evaluated at the active rates of 12-72 g ai/ha for broadcast overhead applications or 2.4-9.6 g ai/100 L for high volume full canopy applications using a hand-held wand. Two to five applications of the chemical were made per trial at 6-18 day intervals. Data from eight trials of *BELT 240*, a water dispersible granule formulation containing the same active constituent, were used to support the label claim of *BELT 480*. This is acceptable as the data demonstrated both formulations were comparable for the control of lepidopteran pests.

Efficacy of *BELT 480* against diamondback moth was assessed in seven trials and that against cabbage white butterfly in five trials. Two trials of *BELT 240* were used to support the efficacy claim of *BELT 480* against the two pests in Brassica crops. Significant control of the two pests was achieved in all trials at the active rates of 24-72 g ai/ha or 2.4-9.6 g ai/100L. One trial of *BELT 480* showed that the insecticide was effective against soybean looper, and cluster caterpillar and Heliothis in Chinese cabbage at the rate of 24-60 g ai/ha. A similar range of effective active rates was obtained from another trial of *BELT 480* against Heliothis in cabbage and a trial of *BELT 240* against various lepidopteran pests in cabbage. The control level was similar to or better than industry standards Avatar® or Success®.

No symptoms of phytotoxicity were observed in any trials. Three trials conducted in cotton assessed the impact of *BELT 480* on beneficials of cotton pests. At the high rate of 96-100 g ai/ha, the chemical did not show any significant negative impact on a range of beneficial arthropods including spiders, various predatory beetles, predatory bugs, lacewings, wasps and ants. It was significantly less disruptive than endosulfan or Talstar®. Although the trials were conducted in cotton, the results were relevant in terms of the general impact of the chemical on potential predators and parasitoids. Due to low abundance during the trials, the impact of the chemical on some beneficial arthropods such as lacewings and pirate bugs could not be determined conclusively. However, it is accepted the chemical is relative soft on beneficials, based on the general pattern of impact in the data.

Data from 9 trials of *BELT 480* demonstrate the efficacy against the target pests and crop safety of the product in Brassica crops in major commercial growing regions in Australia over three seasons. An additional three trials in cotton provided data on the impact of *BELT 480* on beneficial organisms. The data support the label claim that the chemical at label rates is safe to host crops and relatively soft on beneficial arthropods.

BELT 240

Six field trials from Brassica crops (4 x Brussels sprouts, 1 x broccoli, 1 x cabbage) were presented to demonstrate the efficacy/crop safety of *BELT 240* for the control of Diamondback moth, Heliothis and other Lepidopteran pests.

All trials were designed as randomized complete blocks with 4-5 replicates and included an untreated control.

BELT 240 was evaluated at the active rates of 24-96 g ai/ha for broadcast overhead applications or 2.4-7.2 g ai/100 L for high volume full canopy applications. Two to four applications of the chemical were made per trial at 7-14 day intervals. Data from 15 trials of *BELT 480*, a suspension concentrate formulation containing the same active constituent, were used to support the efficacy claim of *BELT 240*. This is acceptable as the data demonstrated both formulations were comparable for the control of lepidopteran pests.

Efficacy of *BELT 240* against diamondback moth and cabbage white butterfly was assessed in four trials. Seven and five trials of *BELT 480* were used to support the efficacy claim of *BELT*

240 against diamondback moth and cabbage white butterfly respectively. Significant control of the two pests was achieved in all trials at the active rates of 24-72 g ai/ha or 2.4-7.2 g ai/100 L. One trial each of *BELT 240* and *BELT 480* demonstrated the efficacy of the two flubendiamide formulations in controlling soybean looper and cluster caterpillar in Brassica crops at the active rates of 24-72 g ai/ha. One trial of *BELT 240* and two trials of *BELT 480* were presented to support the efficacy claim of *BELT 240* against Heliothis in Brassica crops. In all three trials the two formulations showed significant and similar levels of control of the pest at all tested active rates from 24 to 72 g ai/ha. Control levels of *BELT 240* and *BELT 480* were similar to or better than industry standards Avatar® or Success®.

No symptoms of phytotoxicity were observed in any trials. Three trials conducted in cotton assessed the impact of *BELT 480* on beneficials of cotton pests. At the high rate of 96-100 g ai/ha, the chemical did not show any significant negative impact on a range of beneficial arthropods. Although *BELT 480* instead of *BELT 240* was tested and the trials were conducted in cotton instead of Brassica crops, the results were relevant in terms of potential impact of the common active constituent flubendiamide on potential predators and parasitoids. While further studies are needed to confirm the short and long-term impact of the *BELT 240* on specific beneficial arthropods, it is accepted the chemical is relatively soft on beneficials based on the data presented.

Data from eight trials of *BELT 240* demonstrate efficacy against the target pests and crop safety of the chemical in Brassica crops in major commercial growing regions of Australia over three seasons. Data from 9 trials of *BELT 480* also support the claims. An additional three trials of *BELT 480* in cotton were used to argue for the IPM compatibility of *BELT 240* for the control of the target pests in the two crops. The data support the label claim that the chemical at label rates is safe to host crops and relatively soft on beneficial arthropods.

Resistance management

Flubendiamide exhibits no cross-resistance to conventional chemistries and is expected to be a suitable agent for controlling lepidopterous insects as part of insecticide resistance management and integrated pest management programs. Flubendiamide is in a new Group 28 for Insecticides Resistance Management.

Conclusion

Sufficient statistically analysed data from suitably designed and scientifically conducted trials has been presented to substantiate the claims for use shown on the proposed labels. The data demonstrate that the products *BELT 480* and *BELT 240* should be suitable for control of diamondback moth (*Plutella xylostella*), Heliothis (*Helicoverpa* spp.), cabbage white butterfly (*Pieris rapae*), soybean looper (*Thysanoplusia orichalcea*) and cluster caterpillar (*Spodoptera litura*) in brassica vegetable crops, when used in accordance with the proposed label instructions and Good Agricultural Practice (GAP).

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MAIN PANEL

CAUTION

KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS BEFORE OPENING OR USING

Belt® 480 SC

INSECTICIDE

ACTIVE CONSTITUENT: 480 g/L FLUBENDIAMIDE

GROUP 28 INSECTICIDE

For the control of various pests of brassica vegetables as specified in the DIRECTIONS FOR USE table.

*** L**

IMPORTANT: READ THE ATTACHED BOOKLET BEFORE USE

(Label code)

* 1, 5 L

BELT 480 SC INSECTICIDE

STORAGE AND DISPOSAL

Keep out of reach of children. Store in the closed, original container in a cool, well-ventilated area. Do not store for prolonged periods in direct sunlight.

1 litre packs

Triple rinse containers before disposal. Add rinsings to spray tank. DO NOT dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush, or puncture and deliver empty packaging to an approved waste management facility. DO NOT burn empty containers or product. DO NOT re-use empty containers for any other purpose.

5 litre packs

Triple rinse or preferably pressure rinse containers before disposal. Add rinsings to spray tank. DO NOT dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush, or puncture and deliver empty packaging to an approved waste management facility. DO NOT burn empty containers or product. DO NOT re-use empty containers for any other purpose.

SAFETY DIRECTIONS

May irritate the eyes. Avoid contact with eyes. When opening the container and preparing spray wear elbow-length PVC gloves. Wash hands after use.

FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre (telephone 13 11 26).

MATERIAL SAFETY DATA SHEET

Additional information is listed in the Material Safety Data Sheet, which can be obtained from www.bayercropscience.com.au.

EXCLUSION OF LIABILITY

This product must be used strictly as directed, and in accordance with all instructions appearing on the label and in other reference material. So far as it is lawfully able to do so, Bayer CropScience Pty Ltd accepts no liability or responsibility for loss or damage arising from failure to follow such directions and instructions.

APVMA Approval No.: 61223/xxxx

IMPORTANT: READ THE ATTACHED BOOKLET BEFORE USE

FOR 24 HOUR SPECIALIST ADVICE IN EMERGENCY ONLY PHONE **1800 033 111**	BARCODE

Bayer CropScience Pty Ltd
ABN 87 000 226 022
391-393 Tooronga Rd
East Hawthorn Vic. 3123

Phone: (03) 9248 6888
Fax: (03) 9248 6800
Website: www.bayercropscience.com.au
Technical Enquiries: 1800 804 479

(Label code)

Batch Number:
Date of Manufacture:

READ SAFETY DIRECTIONS BEFORE OPENING OR USING

BELT 480 SC INSECTICIDE

ACTIVE CONSTITUENT: 480 g/L FLUBENDIAMIDE

For the control of various pests of brassica vegetables as specified in the DIRECTIONS FOR USE table.

STORAGE AND DISPOSAL

Keep out of reach of children. Store in the closed, original container in a cool, well-ventilated area. Do not store for prolonged periods in direct sunlight.

1 litre packs

Triple rinse containers before disposal. Add rinsings to spray tank. DO NOT dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush, or puncture and deliver empty packaging to an approved waste management facility. DO NOT burn empty containers or product. DO NOT re-use empty containers for any other purpose.

5 litre packs

Triple rinse or preferably pressure rinse containers before disposal. Add rinsings to spray tank. DO NOT dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush, or puncture and deliver empty packaging to an approved waste management facility. DO NOT burn empty containers or product. DO NOT re-use empty containers for any other purpose.

SAFETY DIRECTIONS

May irritate the eyes. Avoid contact with eyes. When opening the container and preparing spray wear elbow-length PVC gloves. Wash hands after use.

FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre (telephone 13 11 26).

MATERIAL SAFETY DATA SHEET

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EXCLUSION OF LIABILITY

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APVMA Approval No.:61223/xxxx

IMPORTANT: READ THIS BOOKLET BEFORE USE

Bayer CropScience

DIRECTIONS FOR USE

Restraints

DO NOT apply by air.

DO NOT apply when wind speed is less than 3 or more than 20 kilometres per hour at the application site.

DO NOT apply with smaller than MEDIUM spray droplets according to ASAE S572 definition for standard nozzles.

DO NOT apply if there are aquatic and wetland areas including aquacultural ponds or surface streams and rivers within 80 metres downwind from the application area.

CROP	PEST	RATE	WHP	CRITICAL COMMENTS
Brassica vegetables (broccoli, Brussels sprouts, cabbage, cauliflower, kohlrabi)	Diamondback moth (*Plutella xylostella*), cabbage white butterfly (*Pieris rapae*), cluster caterpillar (*Spodoptera litura*), heliothis (*Helicoverpa* spp.)	75 or 100 mL/ha or 10 mL/100 L	3 days (H)	Monitor crops and commence insecticide applications once local economic spray thresholds are reached. Apply up to 3 sequential applications of Belt 480 SC at 7 to 14 day intervals (for diamondback moth, refer to additional comment below regarding application windows). Use the higher application rate and/or shorter application interval (7 to 10 days) during periods of high pest pressure or rapid crop growth. **Always add a non-ionic surfactant at appropriate label rates.** Further treatments should be made with alternate mode of action insecticides, as necessary, and in accordance with resistance management strategies. Belt 480 SC is compatible with integrated pest management (IPM) production systems. **Diamondback moth:** Refer to the current CropLife Australia insecticide resistance management strategy for application windows for this product in your region.
	Soybean looper (*Thysanoplusia orichalcea*)	50 or 75 mL/ha or 7.5 mL/100 L		

NOT TO BE USED FOR ANY PURPOSE OR IN ANY MANNER CONTRARY TO THIS LABEL UNLESS AUTHORISED UNDER APPROPRIATE LEGISLATION

WITHHOLDING PERIODS

Harvest (H)

Brassica vegetables: **DO NOT HARVEST FOR 3 DAYS AFTER APPLICATION**

Grazing (G)

Brassica vegetables: **DO NOT USE ON BRASSICAS GROWN FOR FORAGE OR FODDER. DO NOT GRAZE TREATED BRASSICA CROPS.**

Export of treated produce

Growers should note that MRLs or import tolerances may not exist in all markets for edible produce treated with Belt 480 SC. If you are growing edible produce for export, please check with Bayer CropScience Pty Ltd for the latest information on MRLs and import tolerances before using Belt 480 SC.

GENERAL INSTRUCTIONS

Insecticide Resistance Warning

GROUP	28	INSECTICIDE

For insecticide resistance management Belt 480 SC Insecticide is a Group 28 insecticide.

Some naturally occurring insect biotypes resistant to Belt 480 SC and other Group 28 insecticides may exist through normal genetic variability in any insect population. The resistant individuals can eventually dominate the insect population if Belt 480 SC or other Group 28 insecticides are used repeatedly. The effectiveness of Belt 480 SC on resistant individuals could be significantly reduced. Since occurrence of resistant individuals is difficult to detect prior to use, Bayer CropScience Pty Ltd accepts no liability for any losses that may result form the failure of Belt 480 SC to control resistant insects.

Belt 480 SC may be subject to specific resistance management strategies. For further information contact your local supplier, Bayer CropScience representative or local agricultural department agronomist.

Mixing
Shake the container well before using. Partially fill the spray tank with clean water and add the required volume of product to the water whilst agitating. Add non-ionic surfactant then, top up the tank with clean water to the required volume. Belt 480 SC should be applied as soon after mixing as possible.

Application
Ground application
Thorough coverage of the crop is essential. Do not apply when conditions are unsuitable for water-based spray applications. Avoid high temperatures, strong winds, inversion conditions, imminent rain or any conditions that may reduce the quality of spray coverage or result in drift from the target area.

A non-ionic surfactant / wetting agent (e.g. Agral 600) MUST be used when applying Belt 480 SC to brassica crops. Apply at a rate of 0.01% v/v.

Apply in sufficient water,with correct nozzles and pressure to achieve medium spray droplets as defined in ASAE S572, and using suitable application parameters (boom height, speed etc) to ensure thorough coverage of the target area. If using rates per 100 L, aim to spray plants to "point of run-off" stage, thoroughly covering all plant surfaces.

Aerial application
DO NOT apply by air.

Compatibility
Belt 480 SC may be mixed with the following crop protection products: Blue Shield® DF, Bayfidan® 250 EC, Confidor® 200 SC and Kocide® 350 DF. For the latest information on the compatibility of Belt 480 SC with other products, contact your local Bayer CropScience Area Manager or your local reseller.

PRECAUTIONS
Re-entry
Do not allow entry into treated areas until the spray has dried, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT
Very toxic to aquatic invertebrates.
Overspray or drift to aquatic habitats should be avoided.
Do not apply under weather conditions or from spraying equipment which could be expected to cause spray to drift onto adjacent areas, particularly wetlands, water bodies or watercourses.
Do not contaminate dams, waterways or drains with the product or its container.

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Technical Enquiries: 1800 804 479

(Label code)

MAIN PANEL

CAUTION

KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS BEFORE OPENING OR USING

Belt® 240 WG

INSECTICIDE

ACTIVE CONSTITUENT: 240 g/kg FLUBENDIAMIDE

GROUP 28 INSECTICIDE

For the control of various pests of brassica vegetables as specified in the DIRECTIONS FOR USE table.

*** kg Net**

IMPORTANT: READ THE ATTACHED BOOKLET BEFORE USE

(Label code)

* 2, 10 kg

BELT 240 WG INSECTICIDE

STORAGE AND DISPOSAL

Keep out of reach of children. Store in the closed, original container in a dry, cool, well-ventilated area out of direct sunlight. Single rinse before disposal. Add rinsings to spray tank. DO NOT dispose of undiluted chemicals on site. Break, crush, or puncture and deliver empty packaging to an approved waste management facility. DO NOT burn empty bags or product. DO NOT re-use empty containers for any other purpose.

SAFETY DIRECTIONS

May irritate the eyes. Avoid contact with eyes. When opening the container and preparing spray wear elbow-length PVC gloves. Wash hands after use.

FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre (telephone 131126).

MATERIAL SAFETY DATA SHEET

Additional information is listed in the Material Safety Data Sheet, which can be obtained from www.bayercropscience.com.au.

EXCLUSION OF LIABILITY

This product must be used strictly as directed, and in accordance with all instructions appearing on the label and in other reference material. So far as it is lawfully able to do so, Bayer CropScience Pty Ltd accepts no liability or responsibility for loss or damage arising from failure to follow such directions and instructions.

APVMA Approval No.: 61224/xxxx

IMPORTANT: READ THE ATTACHED BOOKLET BEFORE USE

FOR 24 HOUR SPECIALIST ADVICE IN EMERGENCY ONLY PHONE **1800 033 111**	BARCODE

Bayer CropScience Pty Ltd
ABN 87 000 226 022
391-393 Tooronga Rd
East Hawthorn Vic. 3123

Phone: (03) 9248 6888
Fax: (03) 9248 6800
Website: www.bayercropscience.com.au
Technical Enquiries: 1800 804 479

(Label code)

Batch Number:
Date of Manufacture:

READ SAFETY DIRECTIONS BEFORE OPENING OR USING

BELT 240 WG INSECTICIDE

ACTIVE CONSTITUENT: 240 g/kg FLUBENDIAMIDE

For the control of various pests of brassica vegetables as specified in the DIRECTIONS FOR USE table.

STORAGE AND DISPOSAL

Keep out of reach of children. Store in the closed, original container in a dry, cool, well-ventilated area out of direct sunlight. Single rinse before disposal. Add rinsings to spray tank. DO NOT dispose of undiluted chemicals on site. Break, crush, or puncture and deliver empty packaging to an approved waste management facility. DO NOT burn empty bags or product. DO NOT re-use empty containers for any other purpose.

SAFETY DIRECTIONS

May irritate the eyes. Avoid contact with eyes. When opening the container and preparing spray wear elbow-length PVC gloves. Wash hands after use.

FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre (telephone 131126).

MATERIAL SAFETY DATA SHEET

Additional information is listed in the Material Safety Data Sheet, which can be obtained from www.bayercropscience.com.au.

EXCLUSION OF LIABILITY

This product must be used strictly as directed, and in accordance with all instructions appearing on the label and in other reference material. So far as it is lawfully able to do so, Bayer CropScience Pty Ltd accepts no liability or responsibility for loss or damage arising from failure to follow such directions and instructions.

APVMA Approval No.: 61224/xxxx

IMPORTANT: READ THIS BOOKLET BEFORE USE

Bayer CropScience

DIRECTIONS FOR USE

Restraints

Do not apply by air.

DO NOT apply when wind speed is less than 3 or more than 20 kilometres per hour at the application site.

DO NOT apply with smaller than MEDIUM spray droplets according to ASAE S572 definition for standard nozzles.

DO NOT apply if there are aquatic and wetland areas including aquacultural ponds or surface streams and rivers within 140 metres downwind from the application area.

CROP	PEST	RATE	WHP	CRITICAL COMMENTS
Brassica vegetables (broccoli, Brussels sprouts, cabbage, cauliflower, kohlrabi)	Diamondback moth (*Plutella xylostella*), cabbage white butterfly (*Pieris rapae*), heliothis (*Helicoverpa* spp)	150-200 g/ha or 20 g/100 L	3 days (H)	Monitor crops and commence insecticide applications once local economic spray thresholds are reached. Apply up to 3 sequential applications of Belt 240 WG at 7 to 14 day intervals (for diamondback moth, refer to additional comment below regarding application windows). Use the higher application rate and/or shorter application interval (7 to 10 days) during periods of high pest pressure or rapid crop growth. **Always add a non-ionic surfactant at appropriate label rates.** Further treatments should be made with alternate mode of action insecticides, as necessary, and in accordance with resistance management strategies. Belt 240 WG is compatible with integrated pest management (IPM) production systems. **Diamondback moth:** Refer to the current CropLife Australia insecticide resistance management strategy for application windows for this product in your region.
	Soybean looper (*Thysanoplusia orichalcea*)	100-150 g/ha or 15 g/100 L		

NOT TO BE USED FOR ANY PURPOSE OR IN ANY MANNER CONTRARY TO THIS LABEL UNLESS AUTHORISED UNDER APPROPRIATE LEGISLATION

WITHHOLDING PERIODS

Harvest (H)

Brassica vegetables: **DO NOT HARVEST FOR 3 DAYS AFTER APPLICATION**

Grazing (G)

Brassica vegetables: **DO NOT USE ON BRASSICAS GROWN FOR FORAGE OR FODDER. DO NOT GRAZE TREATED BRASSICA CROPS.**

Export of treated produce

Growers should note that MRLs or import tolerances may not exist in all markets for edible produce treated with Belt 240 WG. If you are growing edible produce for export, please check with Bayer CropScience Pty Ltd for the latest information on MRLs and import tolerances before using Belt 240 WG.

GENERAL INSTRUCTIONS

Insecticide Resistance Warning

GROUP	28	INSECTICIDE

For insecticide resistance management Belt 240 WG Insecticide is a Group 28 insecticide.

Some naturally occurring insect biotypes resistant to Belt 240 WG and other Group 28 insecticides may exist through normal genetic variability in any insect population. The resistant individuals can eventually dominate the insect population if Belt 240 WG or other Group 28 insecticides are used repeatedly. The effectiveness of Belt 240 WG on resistant individuals could be significantly reduced. Since occurrence of resistant individuals is difficult to detect prior to use, Bayer CropScience Pty Ltd accepts no liability for any losses that may result form the failure of Belt 240 WG to control resistant insects.

Belt 240 WG may be subject to specific resistance management strategies. For further information contact your local supplier, Bayer CropScience representative or local agricultural department agronomist.

Mixing
Shake the container well before using. Partially fill the spray tank with clean water and add the required volume of product to the water whilst agitating. Add non-ionic surfactant, then top up the tank with clean water to the required volume. Belt 240 WG should be applied as soon after mixing as possible.

Application
Ground application
Thorough coverage of the crop is essential. Do not apply when conditions are unsuitable for water-based spray applications. Avoid high temperatures, strong winds, inversion conditions, imminent rain or any conditions that may reduce the quality of spray coverage or result in drift from the target area.

A non-ionic surfactant / wetting agent (e.g. Agral 600) MUST be used when applying Belt 240 WG to brassica crops. Apply at a rate of 0.01% v/v.

Apply in sufficient water, with correct nozzles and pressure to achieve medium spray droplets as defined in ASAE S572, and using suitable application parameters (boom height, speed etc) to ensure thorough coverage of the target area. If using rates per 100 L, aim to spray plants to "point of run-off" stage, thoroughly covering all plant surfaces.

Aerial application
DO NOT apply by air.

Compatibility
Belt 240 WG may be mixed with the following crop protection products: Blue Shield® DF, Bayfidan® 250 EC, Confidor® 200 SC and Kocide® 350 DF. For the latest information on the compatibility of Belt 240 WG with other products, contact your local Bayer CropScience Area Manager or your local reseller.

PRECAUTIONS
Re-entry
Do not allow entry into treated areas until the spray has dried, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT
Very toxic to aquatic invertebrates.
Overspray or drift to aquatic habitats should be avoided.
Do not apply under weather conditions or from spraying equipment which could be expected to cause spray to drift onto adjacent areas, particularly wetlands, water bodies or watercourses.
Do not contaminate dams, waterways or drains with the product or its container.

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Bayer CropScience

(Label code)

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GLOSSARY

Active constituent	The substance that is primarily responsible for the effect produced by a chemical product.
Acute	Having rapid onset and of short duration.
Carcinogenicity	The ability to cause cancer.
Chronic	Of long duration.
Codex MRL	Internationally published standard maximum residue limit.
Desorption	Removal of an absorbed material from a surface.
Efficacy	Production of the desired effect.
Formulation	A combination of both active and inactive constituents to form the end use product.
Genotoxicity	The ability to damage genetic material
Hydrophobic	Water repelling
Leaching	Removal of a compound by use of a solvent.
Log P_{ow}	Log to base 10 of octonol water partioning co-efficient.
Metabolism	The conversion of food into energy
Photodegradation	Breakdown of chemicals due to the action of light.
Photolysis	Breakdown of chemicals due to the action of light.
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body.
Toxicology	The study of the nature and effects of poisons.

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Footnote:
Updated versions of these documents are available on the APVMA website http://www.apvma.gov.au.

APVMA PUBLICATIONS ORDER FORM

To receive a copy of the full technical report for the evaluation of flubendiamide in the products Belt 480 SC Insecticide and Belt 240 WG Insecticide, please fill in this form and send it, along with payment of $30 to:

Colin McCormack
Pesticides Contact Officer
Australian Pesticides and Veterinary Medicines Authority
PO Box E240
Kingston ACT 2604

Alternatively, fax this form, along with your credit card details, to:
Colin McCormack at 02 6210 4776.

Name (Mr, Mrs, Ms, Dr)_____

Position _____

Company/organisation _____

Address _____

Contact phone number (___) _____

I enclose payment by cheque, money order or credit card for $_____

Make cheques payable to 'Australian Pesticides and Veterinary Medicines Authority'.

___ Bankcard ___ Visa ___ Mastercard

Card number _____/_____/_____/_____ Expiry date ...../...../.....

Signature_____ Date _____