Public Release Summary
on

Evaluation of the new active

SEMDURAMICIN

in the product

AVIAX BROAD SPECTRUM COCCIDIOCIDAL FEED ADDITIVE PREMIX

National Registration Authority
for Agricultural and Veterinary Chemicals

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FOREWORD

The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) 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 NRA works in close cooperation with advisory agencies, including the Department of Health and Family Services (Chemicals and Non-prescription Drug Branch), Environment Australia (Risk Assessment and Policy Section), the National Occupational Health and Safety Commission and State departments of agriculture and environment.

The NRA 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 NRA 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 NRA's publications *Vet Manual: The Requirements Manual for Veterinary Chemicals* and *Vet Requirements Series.*

This Public Release Summary is intended as a brief overview of the assessment that has been completed by the NRA 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 NRA. Alternatively, the reports can be viewed at the NRA Library Ground Floor, 22 Brisbane Avenue, Barton, ACT.

The NRA welcomes comment on the usefulness of this publication and suggestions for further improvement. Comments should be submitted to the Executive Manager—Registration, National Registration Authority for Agricultural and Veterinary Chemicals, PO Box E240, Kingston ACT 2604.

CONTENTS

LIST OF ABBREVIATIONS AND ACRONYMS

ADI	Acceptable Daily Intake (for humans)
bw	body weight
CAS	Chemical Abstract Services
cm	centimetre
CO_2	Carbon dioxide
EUP	End Use Product
g	gram
ha	hectare
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
ISO	International Standards Organisation
kg	kilogram
Koc	organic carbon partitioning coefficient
K_{ow}	octanol/water partition coefficient
kt	kilotonne
LC/MS	liquid chromatography/mass spectroscopy
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
LOQ	Limit of Quantitation
m	metre
mg	milligram
MIC	Minimum Inhibitor Concentration
mL	millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Dietary Intake
NHMRC	National Health and Medical Research Council
NOEC/NOEL	No Observable Effect Concentration/Level
PPE	Personal Protective Equipment
ppm	parts per million
PVC	Polyvinyl chloride
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
t	tonne
TGAC	Technical Grade Active Constituent
WHP	Withholding Period

INTRODUCTION

This publication provides a summary of the data reviewed, and an outline of regulatory considerations for the use of the chemical semduramicin as a coccidiostat in broiler chickens. The information provided herein presents only the conclusions reached by various reviewers after consideration of the scientific database. Copies of the full technical reports on public health, occupational health & safety, environmental impact and residues in food are available on request.

The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) has completed an assessment of the data submitted by the applicant in support of this use of semduramicin and now invites public comment before deciding whether to approve this product for use in Australia. The information contained in the document is provided for public comment.

The deadline for comments is 4 September 2001. Comments should be sent to:

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Applicant

Pfizer Animal Health
38-42 Wharf Road
West Ryde NSW 2114

Justification for use

AVIAX BROAD SPECTRUM COCCIDIOCIDAL FEED ADDITIVE PREMIX is intended for us in broiler chickens as an anticoccidial for the control of coccidiosis caused by *Eimeria* spp.

Product details

AVIAX BROAD SPECTRUM COCCIDIOCIDAL FEED ADDITIVE PREMIX contains 50g/kg semduramicin and is to presented as a multiwall 25 kg bag. The formulation of the product takes place at the Pfizer Plant in West Ryde, NSW.

Semduramicin is currently registered for use as an anticoccidial in Peru, Argentina, Brazil, Mexico, Malaysia, Singapore, Venezuela, Saudi Arabia, Algeria, Chile, Uruguay, Ecuador, Colombia. Korea, Poland, Bolivia, Guatemala, Nicaragua, El Salvador, Panama, USA, Dominican Republic, Costa Rica, Kenya, Japan, Turkey, Indonesia, Canada, South Africa, New Zealand and Honduras.

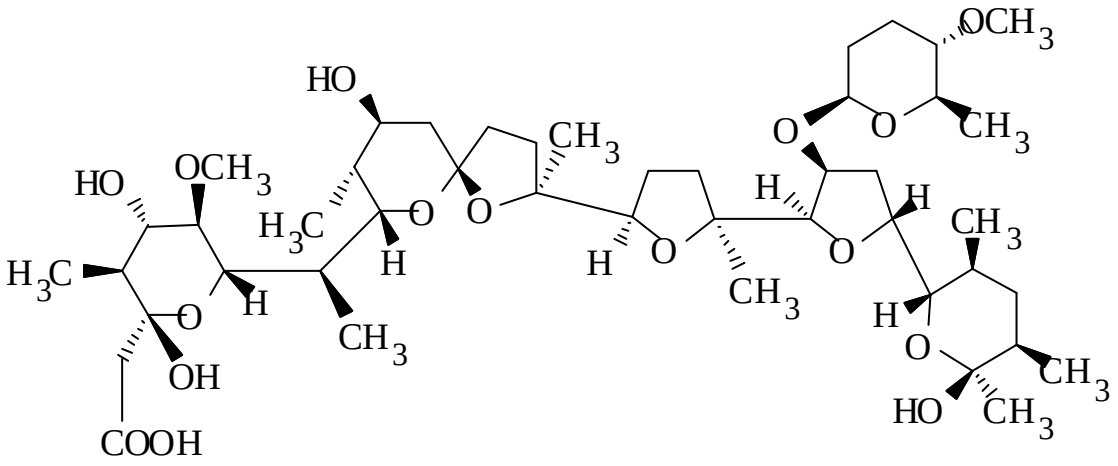
CHEMISTRY AND MANUFACTURE

Active constituent

The chemical active constituent is semduramicin and has the following properties:

Common name (ISO):	semduramicin sodium
Chemical name:	(3R,4S,5S,6R,7S,22S)-23,27-didemethoxy-2,6,22-tridemethyl-5,11-di-O-demethyl-6-methoxy-22-[[(2S,5S,6R)-tetrahydro-5-methoxy-6-methyl-2H-pyran-2-yl]oxyl]Lonomycin A, sodium salt
CAS Registry Number	113378-31-7
Empirical formula:	$C_{45}H_{76}O_{16}$ (free acid), $C_{45}H_{75}O_{16}$ Na(sodium salt)
Molecular weight:	894.50 (as sodium salt)
Physical form:	powder
Colour:	brown
Odour:	Faint "fermentation" odour.
Density:	0.2 to 0.3 $g.cm^{-3}$
n-octanol / water partition coefficient (K_{OW}):	log K_{OW} 2.21 (pH 9) to 2.58 (pH 6).
Vapour pressure at 25^{O}C:	Non-volatile. Vapour pressure is expected to be < 10^{-8} at 20^{O}C.

Structural formula:



Formulated product

Formulation type:	veterinary feed additive
Active constituent concentration:	semduramicin sodium 51.3 g/kg (as the mycelial)

Physical and chemical properties of the product

Physical appearance and colour:	uniform light tan coloured finely ground meal
Odour:	mild odour typical of rice hulls
Melting/softening point:	decomposes before melting
Boiling point and vapour pressure:	not applicable
Volatile materials:	no specific data. Expected to be low at 100^{o}C
Flashpoint:	non flammable
Specific gravity:	0.5 (bulk density)
Solubility in water:	forms a slurry in water
Corrosiveness:	not corrosive

Storage stability:	The applicant provided storage stability data demonstrating that the product is stable for at least 2 years when stored under at or below 30^{o}C (room temperature) in multi-walled bags.

TOXICOLOGICAL ASSESSMENT

Summary

Semduramicin, a veterinary premix, is an anticoccidial agent that disrupts the function of cell membranes and as a consequence of this action adversely affects the development of coccidia. Coccidia are protozoan parasites, which cause disease in a number of species including chickens. Semduramicin is available in two forms, crystalline and mycelial. Crystalline semduramicin is purified from the mycelial form, which remains associated with the mycelial mass of the fungi from which it is produced. The product to be registered, AVIAX BROAD SPECTRUM COCCIDIOCIDAL FEED ADDITIVE PREMIX which contains semduramicin (mycelial) at 50 g/kg, is to be used for the control of coccidiosis (the disease caused by coccidia) in broiler chickens. An extensive toxicological database exists for the crystalline form of semduramicin and a number of studies have been performed on the mycelial form to demonstrate its toxicological equivalence.

Semduramicin is of high acute oral and inhalational toxicity, is slightly irritating to the eye and abraded skin, but is not irritating to intact skin and is not a skin sensitiser. The product, AVIAX BROAD SPECTRUM COCCIDIOCIDAL FEED ADDITIVE PREMIX is expected to have moderate acute oral toxicity, low dermal toxicity, low inhalational toxicity but should not sensitise skin. It may have the potential to cause moderate eye irritation.

In repeat dose studies, muscle degeneration occurring in dogs and rats following dietary exposure to semduramicin was considered secondary to its effect on cell membranes. Although semduramicin caused damage to the peripheral nervous system and effects on the eyes of dogs following dietary exposure, similar effects were not reported in rodents. There was no evidence to suggest that semduramicin has potential to cause cancer or reproductive or birth defects. Metabolism studies indicate that semduramicin is absorbed following oral dosing and undergoes limited metabolism.

Four week and 3-month studies in the rat and dog and a reproduction and fertility study in the rat with mycelial semduramicin, did not reveal any substantial toxicological differences between the mycelial and crystalline forms of semduramicin.

Based on an assessment of the toxicology and the likely residue levels, it was considered that no adverse effects on human health from the proposed use of the product was likely.

Assessment of toxicology

The toxicological database for semduramicin conducted using animals, is quite extensive. In interpreting the data, it should be noted that toxicity tests generally use doses, which are high compared to likely human exposures. The use of high doses increases the likelihood that potentially significant toxic effects will be identified. Toxicity tests should also indicate dose levels at which the specific toxic effects are unlikely to occur. Such dose levels as the No-Observable-Effect-Level (NOEL) are used to develop acceptable limits for dietary or other intakes at which no adverse health effects in humans would be expected. Semduramicin is available in two forms, crystalline and mycelial. Crystalline semduramicin is purified from the mycelial form, which remains associated with the mycelial mass of the fungi from which it is produced. Studies have been conducted on both purified and mycelial semduramicin.

Toxicokinetics and metabolism

Metabolism studies indicate that semduramicin is absorbed following oral dosing and distributed to the liver. Metabolites identified in the liver, excreta and bile were closely related to semduramicin.

Acute studies

Semduramicin sodium was of high acute oral toxicity in mice and rats with LD_{50} values estimated to be between 25 to 50 mg/kg in mice, and 50 to 100 mg/kg and 5 to 20 mg/kg in male and female rats respectively, and was of high acute inhalational toxicity (LC_{50} values (male/female): 82/53 mg/m^3) in rats. It was slightly irritating to the eye and to abraded skin in rabbits, but was not irritating to intact rabbit skin and was not a dermal sensitiser in guinea pigs.

Acute studies conducted with a formulation containing semduramicin at a similar concentration to the product to be registered suggests that the product will be of low acute inhalational toxicity and not a skin sensitiser. Although no other acute toxicity studies conducted with the product were provided, based on the acute toxicity and concentration of semduramicin and the non-active constituents, the product is expected to be of moderate acute oral toxicity and to be a moderate eye irritant. The potential for the product to produce acute dermal toxicity is considered low as it is a dry formulation and the high molecular weight of semduramicin would impede dermal absorption.

Repeat dose studies

Repeat dose studies suggest that the dog is the most sensitive species. In dogs, muscle degeneration and necrosis, and damage to the peripheral nervous system which may have been associated with overt signs of neurotoxicity (difficulty in standing and walking) occurred following dietary doses of crystalline semduramicin at 4 mg/kg bw/day for 5 to 12 weeks or mycelial semduramicin at doses equivalent to 2 mg/kg bw/day of semduramicin. However similar findings were not evident in dogs following dietary semduramicin doses at up to 1 mg/kg bw/day of the mycelial form for 3 months or of the crystalline form for approximately 53 weeks. Degeneration of cardiac muscle was reported in mice following dietary doses of the crystalline form at 10 mg/kg bw/day for 92 days. The mechanism of cellular/tissue toxicity was stated to be characteristic of other antiparasitic compounds and involved disruption of cell membrane function.

Ocular effects also occurred in dogs following dietary doses of the crystalline form at 1 mg/kg bw/day for durations of 182 and 373 days, however similar effects were not reported in other species. In dogs, semduramicin was found to increase the heart rate, strengthen the contraction of the heart, and to affect the peripheral vascular system.

In rats, effects on the liver (liver cell enlargement, and accumulation of fat) occurred following dietary exposure to crystalline semduramicin at 1.12 and 2.24 mg/kg bw/day for 5 weeks. However, dietary exposure at up to 2 mg/kg bw/day for 104 weeks failed to cause similar effects. In rats treated with mycelial semduramicin in the diet at up to 2.0 mg/kg bw/day for one month no adverse effects were noted. In rats treated at the same level for 3 months the females at the highest dose ate less and, together with females at 1 mg/kg bw/day, gained less weight. Mild inflammatory changes were observed in the liver and Harderian gland of both sexes.

In mice following dietary doses of crystalline semduramicin at the highest exposure level, 10 mg/kg bw/day, for 21 months, the incidence of Harderian gland adenoma was increased. In the absence of a Harderian gland in humans the significance of this finding to humans is not known. In addition, semduramicin, both crystalline and mycelial, was not found to damage genetic material in bacterial or mammalian cells and there was no evidence to suggest that semduramicin was carcinogenic.

Reproduction and developmental studies

In a reproduction study conducted in rats in which animals were continuously exposed to crystalline semduramicin via the diet for 3 generations, there were no effects on the reproductive system. In developmental studies conducted in rats and rabbits, although skeletal anomalies occurred at non-maternotoxic doses, the anomalies were characteristic of those associated with delayed development, and were most likely secondary to subclinical maternotoxicity. Similar anomalies were reported at maternotoxic doses, however there was no evidence to suggest that semduramicin was teratogenic.

A single generation reproduction study in rats with mycelial semduramicin given in the diet at doses equivalent to up to 2.0 mg/kg bw/day of semduramicin crystalline, found that females ate less and gained less weight and that pup weights at the highest dose were reduced. Physical and behavioural development of the pups and reproduction in adults were normal however.

Genotoxicity studies

In a number of genotoxicity studies conducted with semduramicin sodium, or mycelial semduramicin, there was no evidence to suggest that semduramicin damages genetic material.

Public health standards

Poisons Scheduling

The National Drugs and Poisons Schedule Committee (NDPSC) considered the toxicity of the product and its active ingredients and assessed the necessary controls to be implemented under States' poisons regulations to prevent the occurrence of poisoning.

The NDPSC recommended that semduramicin be listed in poisons schedule 7 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). However, given the product containing only 5% of semduramicin was found to be less acutely toxic, poisons schedule 6 was recommended for veterinary feed premixes containing 5% or less of semduramicin.

There are provisions for appropriate warning statements and first-aid directions on the product label.

NOEL/ADI

The most sensitive species tested was the dog with a NOEL of 0.3 mg/kg bw/day. In order to calculate the acceptable daily intake (ADI) for humans, a safety factor is applied to the NOEL in the most sensitive species. The magnitude of the safety factor is selected to account for uncertainties in extrapolation of animal data to humans; variation within the human population; the quality of the experimental data; and the nature of the potential hazards. Using a safety factor of 100, an ADI of 0.003 mg/kg bw/day was established.

RESIDUES ASSESSMENT

Chemical residues in food

The residue data and use pattern supported a NIL slaughter withholding period (WHP) in chickens following semduramicin use at 25 g /tonne of finished feed. The product will not be used in the feed of birds laying eggs or that may in the future lay eggs for human consumption. Data from 5 metabolism and 7 residue trials were considered. The data show that when AVIAX BROAD SPECTRUM COCCIDIOCIDAL FEED ADDITIVE PREMIX is used in accordance with the label, the proposed MRLs for semduramicin should not be exceeded and consumption of tissues from treated animals is unlikely to result in dietary intake of semduramicin exceeding the established Acceptable Daily Intake (ADI).

Metabolism studies

Studies in chickens, dogs and rats were submitted for consideration. The major residue detected was the parent compound.

Chickens

Radioactivity levels depleted rapidly after withdrawal of the chickens from medicated feed, approaching LOQ by 36 hours. The highest residues of total radioactivity were found in liver. The major component of the residue was parent compound (~50% 6 hours after withdrawal) with no metabolite accounting for more than 9% of total radioactivity.

Dogs and rats

Studies in dogs and rats showed that parent compound accounted for 21% - 80% of radioactivity present in the liver 6 hours after withdrawal. Metabolite profiles from rat liver were similar to those from chicken liver. Significant amounts of the A-ring O-desmethyl product (54% - 67% of radioactivity) were identified in dogs. No other metabolite accounted for more than 5% of total radioactivity in dogs.

Analytical methods

Two methods were presented, a HPLC method for the determination of semduramicin in liver, and a LC/MS method for the determination of semduramicin in liver, kidney, muscle and fat/skin. Both methods used similar extraction procedures. The LC/MS method presented is acceptable for the determination of semduramicin residues in poultry tissue for residue trial purposes. Due to the limited availability of LC/MS instruments in Australia this method may not find routine use. The HPLC method used in the residue studies is acceptable for the quantitation of semduramicin residues in poultry liver for both trial and enforcement purposes. The HPLC method should be readily adaptable for use with other tissue types. The data submitted demonstrate acceptable stability of incurred residues in samples stored at –20 °C for up to 436 days.

Limits of quantification

The limit of quantification for the LC/MS method is 0.05 mg/kg in all tissues. The limit of quantitation for the HPLC method is 0.025 mg/kg in liver.

Residue definition

The data support a residue definition of **semduramicin,** as the parent compound is the major residue present in chickens.

Residue trials

Seven studies were submitted for consideration.

Muscle, liver and kidney: No semduramicin residues were detected above LOQ in muscle tissue at a dose rate of 37.5 ppm (1.5x proposed dose rate). Liver residues complied with the proposed MRL of 0.5 mg/kg after withdrawal from feed containing either the crystalline or mycelial form of semduramicin at 25 ppm. Residues accumulate to a lesser extent in kidney than liver, and residues in kidney did not exceed 0.2 mg/kg at a dose rate of 37.5 ppm (1.5x proposed dose rate).

Skin and fat: Data for residues in fat independent of skin were not presented. Metabolism studies indicated that most of the residue in the skin + fat fraction may be associated with the fat (higher TRR in fat than skin + fat). Although the product is to use the mycelial form of semduramicin, skin + fat residue data from 1 experiment in which birds were administered either the crystalline or mycelial form of semduramicin in the feed at 37.5 ppm were presented. Six hours after withdrawal (approximating the normal delay from withdrawal to slaughter) skin + fat residues in the six birds treated with the mycelial form of semduramicin were below 0.2 mg/kg. Three birds treated with the crystalline form exhibited semduramicin residues above 0.2 mg/kg. The establishment of a semduramicin MRL for chicken fat/skin of 0.5 mg/kg is recommended to encompass the data obtained with crystalline semduramicin.

Australian MRLs

The semduramicin MRLs proposed herein for Australia are:

Compound		Food	MRL (mg/kg)
PM	0840	Chicken meat	*0.05
		Chicken liver	0.5
		Chicken kidney	0.2
		Chicken fat/skin	0.5

Withholding Period Statements

The recommended withholding period statement is

MEAT: NIL

Dietary intake

The dietary intake calculation shows that, using the total Australian population dietary intake figures, the calculated National Estimated Dietary Intake (NEDI) for semduramicin does not exceed the Australian ADI for semduramicin of 0.003 mg/kg/day, and is thus safe for human consumption.

Australia produced ~600 kt of poultry carcasses in 1998 with a value of ~$1020million. Exports of poultry carcasses in 1998 totalled ~ 23 kt, or 4% of production[1]. About 90% of the exported product is frozen, with some 80% of that being cuts and offal[2]. Other products exported include flours, meals, pellets and greaves of poultry meat/meal[3].
Major export destinations for Australian poultry product in 1996 are shown below. The export market is dynamic, with France importing ~$1.1million worth of Victorian product in 1999/2000)[4], and the USA being a notable destination for poultry product from Queensland in 1997/1998.

Top 10 export destinations for Australian poultry product, May 1995 to April 1996[5].

Country	$A million	Tonnes
Hong Kong	7.9	7935
China	2.5	2678
South Africa	2.2	1810
Vanuatu	0.9	457
Wallis & Futuna Is	0.7	307
Kiribati	0.7	346
Nauru	0.6	255
Sri Lanka	0.5	547
Tuvalu	0.4	198
New Caledonia	0.3	149
Total top ten	**16.6**	**14682**
All countries	**19.2**	**15269**

Codex MRLs
Codex has not considered semduramicin.

Implications for trade
Semduramicin has widespread use overseas. Where MRLs have been established overseas they are similar to those proposed for Australia. Because the only major export market for Australian chicken product known to have a semduramicin use is South Africa and the only market to have MRLs established is the USA, the registration of AVIAX BROAD SPECTRUM COCCIDIOCIDAL FEED ADDITIVE PREMIX in Australia has the potential to unduly prejudice trade. For this reason, it is proposed to add a trade advice statement to the label, such as the one below:

> *NOTE: The withholding period stated on this label applies only to product destined for the Australian domestic market. Some export markets apply different standards. If necessary, details of overseas standards should be obtained prior to use of this product.*

[1] ABARE (2001). Australian Commodity Statistics 2000.
[2] Kennedy J (1999). Chickenmeat export opportunities. *11th Australian Poultry & Feed Convention 10-13 October 1999.*
[3] http://www.statedevelopment.qld.gov.au/export/industry/agribusiness/capability/#Poultry
[4] http://www.nre.vic.gov.au/web/root/domino/cm_da/nrenti.nsf/frameset/NRE+Trade+and+Investment?OpenDocument21/02/2001
[5] ABS, June 1996, in submission Part 5B (1997) p 5.0081

OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Summary
Semduramicin is not on the NOHSC List of Designated Hazardous Substances. Pfizer Animal Health Pty Ltd has classified semduramicin as a hazardous substance and assigned the following risk phrases:

R26 Very toxic by inhalation
R28 Very toxic if swallowed

Substances containing semduramicin are hazardous when it is present in concentrations =0.1%.

It is a white to off-white powder. In experimental animals, it has high acute oral and inhalation toxicity. In rabbits, it is a slight irritant to the eye and abraded skin, but is not irritating to intact skin. It is not a skin sensitiser in guinea pigs.

Pfizer Animal Health has determined that AVIAX BROAD SPECTRUM COCCIDIOCIDAL FEED ADDITIVE PREMIX is a hazardous substance. Based on the amount of semduramicin and calcium carbonate in the EUP, the Therapeutic Goods Administration has concluded that AVIAX BROAD SPECTRUM COCCIDIOCIDAL FEED ADDITIVE PREMIX may be of moderate oral toxicity and a moderate eye irritant. It is a light tan powder with a faint odour typical of rice hulls. It is packed into 25 kg multi-wall bags composed of either heat-sealed polyethylene liner inside a woven polypropylene outer bag or four Kraft paper piles and one polyethylene ply.

Formulation and packaging of the product should be carried out under air extraction. Formulators and packers should wear appropriate protective equipment such as overalls, gloves and dust masks. Advice on safe handling of the technical grade active constituent (TGAC) and end use product (EUP) during routine formulation and end use is provided in the Material Safety Data Sheet (MSDS) for semduramicin and the product.

Based on the toxicity of semduramicin and the non-active ingredients of the product, AVIAX BROAD SPECTRUM COCCIDIOCIDAL FEED ADDITIVE PREMIX can be expected to be of moderate acute oral toxicity and a moderate eye irritant. It is not expected to be a skin irritant or skin sensitiser. End users should follow the instructions and safety directions on the product label, which include the use of cotton overalls, hat, PVC gloves, goggles and a disposable dust mask.

Formulation, transport and sale
Pfizer Animal Health Pty Ltd will formulate the product in Australia, with approximately 10 workers potentially exposed to semduramicin. Engineering controls, such as dust extraction, are in place to protect the production and maintenance personnel.

Transport workers, store persons and retailers will only handle the packaged product. They could only become contaminated if the packaging were breached.

Advice on safe handling of semduramicin and the product during routine formulation and use is contained in the respective MSDS.

End use

The product will be mixed with chicken feed at the rate of 500 g AVIAX BROAD SPECTRUM COCCIDIOCIDAL FEED ADDITIVE PREMIX to each tonne of feed, equivalent to 25 g semduramicin per tonne finished feed (0.0025%). The finished feed will be fed continuously to chickens as the sole ration from day one to slaughter.

Mixing of the product with the feed will be carried out at feed mills. There are approximately 25 feed mills with an average of six workers in each mill. Exposure would occur at the time of sampling and weighing out the premix by feed mill operators and when adding this to the mixer. There will be virtually no on-farm mixing of the product.

The primary routes of occupational exposure will be through skin contamination and inhalation of product/feed dust.

No worker exposure studies were available, so a qualitative risk assessment was conducted. The EUP is an eye irritant and workers will require eye protection when handling the premix. The average particle size of the EUP is above the inspirable range, however, the dust may be a physical irritant, therefore a dust mask is recommended during handling of the premix.

On assessing the health risk from repeated exposure, it was recommended that overalls and gloves be worn during handling of the premix to minimise skin contamination.

Re-handling of treated animals

AVIAX BROAD SPECTRUM COCCIDIOCIDAL FEED ADDITIVE PREMIX is for oral administration, so a restricted handling interval is not necessary.

Recommendations for safe use

Australian workers involved in formulation and packing of AVIAX BROAD SPECTRUM COCCIDIOCIDAL FEED ADDITIVE PREMIX should be protected by proper engineering controls, such as dust extraction and recommended PPE.

End users should follow the instructions and Safety Directions on the product label. Safety Directions include the use of overalls, hat, elbow-length PVC gloves, goggles and a disposable dust mask.

The PPE recommended should meet the relevant Standards Australia standard specified below:

> AS 2161-1978 Industrial Safety Gloves and Mittens (Excluding Electrical and Medical Gloves)
>
> AS 1337-1992 Eye Protection for Industrial Applications
>
> AS/NZS 1715-1994 Selection, Use and Maintenance of Respiratory Protective Devices and AS/NZS 1716-1994 Respiratory Protective Devices
>
> AS 3765-1990 Clothing for Protection Against Hazardous Chemicals

Semduramicin should be labelled in accordance with NOHSC *National Code of Practice for Labelling of Workplace Substances*. Pfizer Animal Health has produced MSDS for semduramicin and AVIAX BROAD SPECTRUM COCCIDIOCIDAL FEED ADDITIVE PREMIX. The MSDS should contain information relevant to Australian workers, as outlined in the NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets*. Employers should obtain the MSDS from the supplier and ensure that their employees have ready access to it.

AVIAX BROAD SPECTRUM COCCIDIOCIDAL FEED ADDITIVE PREMIX can be used safely if handled in accordance with the instructions on the product labels. Additional information is available in the MSDS for semduramicin and the product.

ENVIRONMENTAL ASSESSMENT

Summary
Semduramicin sodium is relatively rapidly hydrolysed under acid conditions but is relatively stable under neutral and alkaline conditions. The TGAC is rapidly decomposed by aqueous photolysis but degradation is likely to proceed via an indirect photolysis mechanism such as photoinduced degradation by a reactive chemical species. Aerobic degradation in soils indicates that the TGAC is moderately persistent with a half-life to CO_2 of 42-104 days. Degradation products do not tend to accumulate as the compound and its degradation products are mineralised to CO_2. Semduramicin sodium is immobile in soils with low sand content but is more mobile as sand content increases. Binding of semduramicin sodium appears to be strongest to the mineral fraction of soils rather than to organic matter. Semduramicin sodium was determined to be less able to leach from clay soils but exhibits a potential for leaching from sandy soils.

Semduramicin is considered slightly toxic to fish, daphnia and algae. The TGAC is not toxic to earthworms and soil microbes but is moderately toxic to seedling growth. The ecotoxicity of semduramicin sodium suggests that the greatest area of concern is to plants and freshwater algae.

The active is to be used as a feed additive for broiler chickens with environmental release occurring through the spreading of contaminated manure on fields as fertiliser. The expected environmental concentration of semduramicin in either soil or run-off waters is significantly lower than the concentrations shown to be toxic to soil microbes, earthworms, plants and various fish species, daphnia and algae tested. Semduramicin could potentially leach to groundwater in very sandy soils particularly if water tables are shallow.

Environmental fate
Semduramicin sodium is an anticoccidial for the control of coccidiosis in broiler chickens. Semduramicin is in a class of polyether ionophorous compounds and is used in the early stages of the *Eimeria* life cycle affecting the development of sporozoites, trophozoites and schizonts. Semduramicin is produced in a fermentation process using the bacterium *Actinomadura roseorufa* Huang sp. nov. and the fermentation broth including the semduramicin containing mycelium is spray dried to form a powder. Data indicate that the production process kills the bacterium and the imported product should not contain viable material such as spores. The product is formulated as mycelial semduramicin with non-active ingredients as a 5% premix for use in compounding broiler chicken feeds. Use of the compound is on a continual basis from day one of age until slaughter at day 40 and complete feeds containing 25 ppm semduramicin are the sole ration. Environmental exposure is from spreading contaminated manure on fields as a fertiliser.

Metabolism
The drug, semduramicin sodium, undergoes rapid metabolism by chickens with approximately 7% of the administered dose excreted unchanged. When incorporated in complete feed at 25 ppm, the concentration of semduramicin sodium in fresh manure of chickens is 1.6 ppm average. One metabolite has been shown to be active in tests for biological activity of ionophores and is present at a concentration of 2.1 ppm in excreta. This represents a total of 3.7 ppm of material biological activity as an ionophore of a total of 25 ppm. An analysis of metabolism using radiolabelled TGAC showed the metabolites are polar substances detected at levels of <0.1 ppm. The most abundant metabolites have been identified as O-desmethyl derivatives (A ring and G ring) of the active. A ring opened product

has also been tentatively identified. The liver is the organ with highest residue levels and semduramicin sodium and its metabolites are readily expelled in excreta.

Hydrolysis

Aqueous hydrolysis was determined using sterile solutions containing 10 ppm semduramicin sodium in pH 5, 6, 7, 8 and 9 aqueous buffers. Semduramicin sodium hydrolyses under acidic conditions with a half-life of 11-36 days, being more readily hydrolysed at lower pH. It is moderately stable in neutral conditions, half-life 90 days, and in alkaline conditions with half-lives from 77-115 days. The test was conducted at 25°C over a 29 day period and errors associated with half-lives >29 days will be relatively large. The identity of hydrolysis products was not given in the study. Additional evidence of hydrolysis can be obtained from control samples (dark) from photolysis experiments where the only degradation path is via hydrolysis. Half-lives were obtained at 34°C and were 13.7 days (pH 6), 31.2 days (pH 7) and 17.4 days (pH 9). The drug is expected to undergo hydrolysis in the environment and is more susceptible under acidic conditions.

Photolysis

The rate of photodegradation of semduramicin in aqueous solutions was determined using 10 ppm semduramicin in pH 6, 7 and 9 aqueous buffers at 34°C±2 over 187 hours. The semduramicin sodium concentration decreased rapidly in aqueous buffered solutions with the rate of decrease more rapid at lower pH. Solutions of semduramicin sodium had half-lives of 3.55 days (pH 6), 4.38 days (pH 7) and 5.66 days (pH 9) at 34°C. Half-lives were determined using continuous exposure to simulated sunlight. Reported half-lives for 12 hour exposures are double the experimentally determined half-lives.

Photodegradation is likely to proceed by an indirect photolysis mechanism such as photoinduced degradation by a reactive chemical species. The identity of the photodegradation products was not determined in the study.

Soil degradation

Aerobic degradation was tested on three soil types using radiolabeled active and indicates that semduramicin sodium is moderately persistent with a half-life for mineralisation to CO_2 of 42-104 days. A CO_2 plateau was not reached by day 66 and the study extended to 94 days. Degradation rates had still not plateaued and errors associated with half-lives >94 days will be large. A maximum of 63.5% of applied radioactivity was detected as $^{14}CO_2$ and volatiles in silty clay loam after 66 days. The maximum applied radioactivity detected as $^{14}CO_2$ and volatiles after 94 days was 52% in clay loam and 40.3% in clay soils. Tests were conducted using 25 ppm semduramicin, which is higher than the expected concentration in soil from normal use.

Mobility in soil

The adsorption/desorption characteristics of semduramicin sodium was determined by a shaking flask equilibrium technique using three soil types of different physico-chemical properties in contact with aqueous solutions. The adsorption and desorption processes were described by the Freundlich isotherm equation. Tests were run over 72 hours to reach equilibrium. The sorption coefficients (Kads) ranged from 4.65 to 25.7 and the desorption coefficients (Kdes) ranged from 2.41 to 16.2. The coefficients based on organic carbon content of the soils (K_{OC}) ranged from 150 to 1750 for sorption and from 79 to 1100 for desorption. A K_{OC} value of 150 indicates a compound with high mobility in soil whereas

values of 1400 and 1750 indicate a low degree of mobility. However, given the relative levels of organic matter in the soils tested it would appear that silt or clay content is the critical factor in determining the degree of sorption of semduramicin. In very sandy soils semduramicin is likely to be highly mobile.

Soil leaching potential was investigated using ^{14}C-semduramicin in a soil column method at the equivalent of 50-70 cm of rainfall. The amount of semduramicin sodium detected in the leachate ranged from 78-83% in Thoresby loamy sand and 64-71% in Alconbury sandy clay loam. Distribution coefficients (Kd) for the soils are 0.98 $mL.g^{-1}$ for Alconbury and 0.21 $mL.g^{-1}$ for Thoresby soils indicating greater mobility in the coarser Thoresby soil with a lower organic content.

Sorption to soils may be due to binding to minerals especially in clay soils which have a large surface area. Where the active is spread in soils with high sand content the active has a potential to leach into groundwater particularly where such soils overly shallow watertables.

Field dissipation

No studies were submitted for soil and water. A study was undertaken using three crop species, lettuce, beetroot and spring wheat, reared indoors under controlled conditions. Crops were grown to maturity over 84-132 days with the semduramicin applied 14 days before crops were planted. There is little uptake of the active from soil with levels measured being just above the limit of detection except for straw obtained from spring wheat.

Accumulation and bioaccumulation

Accumulation in soils and bioaccumulation is not expected under normal use.

Environmental effects

Birds and vertebrates

No studies were undertaken for birds and other vertebrates. Safety during feeding to chickens (target animal), turkeys and horses was determined for oral intake.

Aquatic species

Tests were conducted on four aquatic species including two fish species, one invertebrate species and one fresh water algal species. The 96 hour LC50 for rainbow trout (*Onchorhynchus mykiss*) was 32 ppm and the NOEC was 11 ppm. Significant mortality was observed at test concentrations of 30 and 50 ppm. For bluegill (*Lepomis macrochirus*) the 96 hour LC50 was 38 ppm and the NOEC was 13 ppm. Cumulative mortality at 96 hours was 50% at both 22 and 37 ppm concentrations. The LC50 was determined by moving average angle analysis but this is not considered the best method for statistical analysis of these results. A probit analysis is generally considered to be more reliable for this data type. Semduramicin is considered slightly toxic to both rainbow trout and bluegill.

The 48 hour EC50 for immobilisation of water flea (*Daphnia magna*) was 38 ppm and the NOEC was 19 ppm. Immobile organisms were recorded at 48 and 31 ppm concentrations. Semduramicin is considered to be slightly toxic to *Daphnia magna*. Toxicity tests for semduramicin sodium against the freshwater green alga, *Selenastrum capricornutum*, gave an MIC of 19 ppm and NOEL of 10 ppm. The maximum growth rates (μ_{max}) averaged 1.23 day^{-1} occurring between days 0-3. At the NOEL concentration of 10 ppm μ_{max} averaged 1.14

day^{-1} between day 1-5 and for 19 ppm (MIC) was 0.92 day^{-1} with delayed growth and maximum growth rates occurring between days 3-9. Growth of *Selenastrum capricornutum* was completely inhibited at concentrations >39 ppm. Semduramicin is slightly toxic to *Daphnia magna* and *Selenastrum capricornutum*.

Terrestrial species

No studies were undertaken for predator species, parasites and bees which is acceptable due to the low expected exposure under normal use.

Tests were conducted on a single soil invertebrate, the earthworm *Eisenia foetida*, and a range of soil microbes including representative soil bacteria (*Clostridium novyi, Bacillus stearothermophilus* and *Flavobacterium meningosepticum*), ascomycetes (*Trichoderma viride*), moulds (*Penicillium italicum*) and blue-green algae (*Nostoc* sp.). An LC50 of between 100-1000 ppm and an NOEC of 100 ppm was determined for earthworms in artificial soil. The minimum inhibitory concentration (MIC) determined for soil microbes was >100 ppm in all cases. Two further tests indicated no effect on the microbes responsible for nitrification in soil at 112 ppm and no impact on organisms responsible for anaerobic degradation of sewage sludge at 25 ppm.

Plants

The effect of semduramicin sodium was studied for six crop plants including both monocotyledons, rye (*Lolium perenne*), wheat (*Triticum aestivum*) and corn (*Zea mays*) and dicotyledon species, cucumber (*Cucumis sativus*), soybean (*Glycine max*) and pinto bean (*Phaseolus vulgaris*). Germination, root elongation and seedling growth were examined. The NOEC in monocotyledons was lowest in ryegrass, 0.31 ppm with reduced survival, shoot length and weight at 2.2 ppm and highest in corn, 2.2 ppm with reduced survival at 4.2 ppm and lowered root weight at 7 ppm. Wheat has an NOEC of 0.77 ppm with reduced shoot length and weight at 2.2 ppm and reduced survival at 4.2 ppm. For the dicotyledon species the lowest NOEC was observed in soybean, 0.31 ppm was reduced shoot length at 0.77 ppm. No other effects were observed at the highest concentration of 2.2 ppm. Cucumber and pinto beans both had an NOEC of 0.77 ppm with reduced shoot weight and length observed at 2.2 ppm for cucumber and reduced root weight at 2.2 ppm for pinto beans.

Results for soybeans are conflicting. Germination was statistically reduced at 1 ppm in preliminary test but no effect on germination was observed in the definitive test at test concentrations of 0.36 and 2.2 ppm. As a result reliable NOEL and NOEC values for soybean are not available. The NOEC values for seed germination and root elongation of the five other species tested ranged from 13 ppm (Pinto bean germination) to 86 ppm (corn germination).

Environmental hazard

Test calculations indicate that manure from medicated chickens would result in low drug concentrations when applied to soil as a fertiliser. The highest potentially toxic total residue levels that could result from typical use are approximately 0.223 ppm in soil and 3.24 ppm in surface waters under worst case conditions. At a lower application rate of 11 $t.ha^{-1}$ and dilution with uncontaminated litter the concentration is expected to be 0.08 ppm in soil and 1.17 ppm in water. If only biologically active residues are considered then a 20 $t.ha^{-1}$ application of contaminated manure would result in soil concentrations of 0.03 ppm which would result, under worst case conditions, in a concentration in surface waters of 0.48 ppm. In the environment the active constituent is removed by degradation in soil, hydrolysis and

photodegradation, and no accumulation of the active is expected over time.

Soil dwelling organisms are most likely to be exposed from the application of contaminated manure as fertilizer. However, the expected environmental concentration of semduramicin and residues in soil is significantly lower than the concentrations shown to be toxic to soil microbes and earthworms. Consequently impacts on populations of these organisms are not anticipated. Exposure of birds and terrestrial mammals to the active will be very low as the amount applied in contaminated manure is low; in addition few species are expected to frequent cultivated areas where manure has been applied. Maximum projected concentrations in the environment are lower than concentrations affecting germination and growth of plants and seeds so phytotoxic effects are not anticipated.

In run-off waters the concentration of residues is likely to be significantly lower than the concentrations shown to be toxic various fish species, daphnia and algae tested. Application rates to soil are low and residues in run-off is expected to be diluted by sorption to uncontaminated soils. Extreme worst case projected concentrations in the aquatic environment are lower than concentrations required to have an adverse effect on the most susceptible aquatic organism tested. There is a possibility of contamination of groundwater where contaminated manure is applied to very sandy soils which overlie shallow watertables. However, leaching is considered unlikely because semduramicin is expected to sorb strongly to bedding material and manure and will be subject to degradation in the chicken shed and during any storage before spreading.

Hazard from the formulation, handling and disposal is low as formulation takes place in controlled areas and any spills will be small, being limited by the small pack size. Feed spillage is unlikely to contribute to any significant environmental release of the active.

Conclusion

The use of semduramicin sodium is not expected to have a significant impact on the environment when used as directed. The potential exists for some adverse effects where contaminated manure is applied to very sandy soils either through leaching to groundwater or through collection of run-off water in small bodies of water. While this appears unlikely the applicant should agree to keep the National Registration Authority and Environment Australia informed if any such incidents occur in Australia. In addition, if the use of semduramicin increases significantly or if any extension of use is required then field dissipation data from sandy soils will be required.

EFFICACY AND SAFETY ASSESSMENT

Scientific experts from the State Departments of Agriculture/Primary Industries assessed the submitted scientific studies and found them to be sufficient to support the proposed label claims for this product.

Semduramicin is a polyether ionophorous compound and like other members of this class has utility for the control of coccidiosis. The principal mode of action relates to its ability to form a lipophilic complex with various cations, principally sodium, potassium and calcium, and transport these through cell membranes. This action distorts trans-membrane ion gradients, damaging cells and ultimately rupturing cell walls. Semduramicin acts principally early in the *Eimeria* life cycle and affects the development of sporozoites, trophozoites and schizonts. For use as a feed additive anticoccidial it has the following claim:

For the prevention of coccidiosis in broiler chickens caused by *Eimeria acervulina, E. brunetti, E. maxima, E. necatrix, E. praecox* and *E. tenella*

Efficacy of semduramicin against *Eimeria* spp at the recommended label dose of 25 ppm was established in a series of dose determination and confirmation studies comprising:

- Battery studies
  - 42 studies using product based on purified semduramicin and involving a broad range of individual field isolates of *E. tenella* (10 isolates), *E. acervuline* (11 isolates), *E. maxima* (8 isolates), *E. necatrix* (3 isolates), *E. brunetti* (4 isolates) and *E. mivati/mitis* (6 isolates) conducted in the US and UK.
  - 15 studies using product based on purified semduramicin and mixed species inocula involving naturally occurring mixtures of *Eimeria* spp (*E. acervulina, E. brunetti, E. maxima, E. necatrix, E. praecox* and *E. tenella)* conducted in the US and the UK.
  - 6 studies using product based on the mycelial form of semduramicin and involving individual field isolates of *E. tenella* (2 isolates), *E. acervuline* (2 isolates), *E. maxima* (2 isolates) conducted in the US.
- Floor pen studies
  - 15 studies using product based on purified semduramicin and mixed species inocula involving naturally occurring mixtures of *Eimeria* spp (*E. acervulina, E. brunetti, E. maxima, E. necatrix, E. praecox* and *E. tenella* conducted in the US, UK and Europe.
  - 1 study using product based on purified semduramicin and mixed species inocula involving naturally occurring mixtures of *Eimeria* spp (*E. acervulina, E. maxima,* and *E. tenella)* conducted in New Zealand.
  - 3 studies using purified semduramicin and mixed species inocula involving naturally occurring mixtures of *Eimeria* spp (*E. acervulina, E. maxima,* and *E. tenella)* conducted in Australia.

Efficacy of semduramicin in the product AVIAX BROAD SPECTRUM COCCIDIOCIDAL FEED ADDITIVE PREMIX was further confirmed in the field with extensive studies with product based on purified semduramicin under commercial growing conditions-in the US involving 3 studies with 107, 600 broiler chickens, and in New Zealand involving 3 studies with 97,000 broiler chickens. Confirmatory field studies in Australia were conducted under

simulated commercial growing conditions involving 2 studies with 12,000 birds. Bioequivalence of product based on purified semduramicin or the mycelial form of semduramicin was confirmed with commercial field studies in South Africa involving -5 studies with 115,000 broiler chickens.

No adverse effects were recorded in any of the dose determination, dose confirmation or field studies. In addition, margin of safety studies and compatibility studies demonstrated the product to be safe when tested at levels up to 75ppm or if administered concurrently with commonly used feed additives or water medications. The safety of semduramicin in non-target species such as turkeys and horses was also demonstrated.

POISON
KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS BEFORE OPENING OR USING
FOR ANIMAL TREATMENT ONLY

AVIAX*
Broad Spectrum Coccidiocidal
Feed Additive Premix

Semduramicin 50 g/kg
as semduramicin sodium 51.3 g/kg

For the prevention of coccidiosis caused by *Eimeria acervulina, E. brunetti, E. maxima, E. mitis, E. necatrix, E. tenella* and *E. praecox* in broiler chickens

DIRECTIONS FOR USE

RESTRAINTS
DO NOT USE in birds which are producing or may in the future produce eggs or egg products for human consumption.

Add 500 g of AVIAX premix to each tonne of chicken feed. This produces a semduramicin level of 25 g/tonne in the finished feed which should be fed continuously as the sole ration.

AVIAX premix must be thoroughly mixed into the feed. It is recommended that each 1 kg of premix intended for a 2 tonne feed blend be extended with 9 kg of ground meal which is then added gradually to the feed blend.

PRECAUTIONS
1. For use in broiler chickens.
2. Do not allow consumption by any other animals or birds, as toxicity may occur
3. Care must be taken not to exceed the recommended use level of 25 g/tonne of semduramicin

Note: Medicated feed must be labelled with Restraints and Precautions.

WITHHOLDING PERIOD
MEAT: NIL
EGGS: DO NOT USE in birds which are producing or may in the future produce eggs or egg products for human consumption.
The withholding period stated on this label applies only to product destined for the Australian domestic market. Some export markets apply different standards. If necessary, details of overseas standards should be obtained prior to use of this product.

SAFETY DIRECTIONS: Poisonous if swallowed. Will irritate the eyes. Avoid contact with eyes and skin. When opening the container and mixing into stockfeed, wear cotton overalls buttoned to the neck and wrist and a washable hat, elbow length PVC gloves, goggles and a disposable dust mask. If product in eyes, wash it out immediately with water. After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water. After each day's use wash gloves goggles and contaminated clothing.

For further information consult the product Materials Safety Data Sheet (MSDS).

FIRST AID: If poisoning occurs, contact a doctor or Poisons Information Centre.
Phone Australia 131126 New Zealand 03 4747000

DISPOSAL: Render empty bags unusable by puncturing or tearing, and dispose of them by burial beneath at least 500mm of soil in a disposal pit located away from water courses

Licensed under the Animal Remedies Act 1967, No 6122
NRA Approval Number 48882/_____

Store below 30°C (Room Temperature) in a dry place

Batch No: Expiry Date:

Phibro Animal Health
17 Amax Avenue, Girraween, NSW, 2145

Licensed to and distributed in New Zealand by
NRM Feeds Ltd
100 Carlton Gore Road, Newmarket, Auckland.
*Phibro trademark 25 kg NET

GLOSSARY

Active constituent	The substance that is primarily responsible for the effect produced by a chemical product.
ADI	The daily intake of a chemical, which, during an entire lifetime, appears to be without appreciable risk to the health of the consumer.
Acute	Having rapid onset and of short 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
Leaching	Removal of a compound by use of a solvent.
LOQ	The level below which an analytical method is unable to accurately quantify the substance being measured.
Metabolism	The conversion of food into energy
MRL	The maximum concentration (in mg/kg) of a chemical reside that is legally permitted in a food commodity
MSDS	A document that describes the properties and uses of a substance, that is, identity, chemical and physical properties, health hazard information, precautions for use and safe handling information.
NOEC	The next lowest concentration in the concentration test series from the lowest-observed-effect concentration.
NOEL	The highest concentration or amount of a substance to cause no detectable alteration of morphology, functional capacity, growth development or life span of the most sensitive test organism.
Photodegradation	Breakdown of chemicals due to the action of light.
Photolysis	Breakdown of chemicals due to the action of light.

Safety directions	Phrases that give directions for the safe handling and storage of a chemical and use of personal protective equipment.
TGAC	The commercial grade of an active constituent as it comes from the manufacturing plant and before it has been formulated.
Toxicokinetics	The study of the movement of toxins through the body.
Toxicology	The study of the nature and effects of poisons.
WHP	The minimum recommended interval that should elapse between the last application of a formulated product to an animal, and the slaughter thereof.

References

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NRA PUBLICATIONS ORDER FORM

To receive a copy of the full technical report for the evaluation of semduramicin in the product AVIAX BROAD SPECTRUM COCCIDIOCIDAL FEED ADDITIVE PREMIX please fill in this form and send it, along with payment of $30 to:

Sue Scales
Agricultural and Veterinary Chemicals Evaluation Section
National Registration Authority for Agricultural and Veterinary Chemicals
PO Box E240
Kingston ACT 2604

Alternatively, fax this form, along with your credit card details, to:
Sue Scales at (02) 6272 5249.

Name (Mr, Mrs, Ms, Dr)_____

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

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