Public Release Summary
on

Evaluation of the new active

THIACLOPRID

in the new product

Calypso 480 SC Insecticide

National Registration Authority
for Agricultural and Veterinary Chemicals

November 2001

Canberra
Australia

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Graeme Barden
National Registration Authority for Agricultural and Veterinary Chemicals
PO Box E 240
KINGSTON ACT 2604

Ph: 02 6272 3898
Fax: 02 3272 3218

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 (Worksafe Australia) 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 *Ag Manual: The Requirements Manual for Agricultural Chemicals* and *Ag 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

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
a.i.	active ingredient
ARfD	Acute Reference Dose
bw	bodyweight
^{o}C	Degrees Celsius
d	day
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
EA	Environment Australia
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
EUP	End Use Product
F_0	original parent generation
F_1	first offspring generation
FAO	Food and Agriculture Organisation of the United Nations
g	gram
h	hour
ha	hectare
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
L	Litre
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
LOEC/LOEL	Lowest Observed Effect Concentration/Level
mg	milligram
mL	millilitre
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
NOEC/NOEL	No Observable Effect Concentration/Level
PPE	Personal Protective Equipment
ppm	parts per million
Q-value	Quotient-value
s	second
SC	Suspension Concentrate
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
µg	microgram

INTRODUCTION

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed application of the chemical thiacloprid as a foliar spray to (commercially grown) camellias, maybush and roses for the control of aphids. It also seeks public comment prior to the chemical product being registered and approved for use in Australia.

Responses to public consultation will be considered prior to registration of the products detailed in this document. They will be taken into account by the NRA in deciding whether the product should be registered and in determining appropriate conditions of registration and product labelling.

Copies of the full technical reports on public health, occupational health & safety, environmental impact and residues in food are available on request.

The NRA must receive written comments by 4 December 2001 for the attention of:

Mr Graeme Barden
Agricultural and Veterinary Chemicals Evaluation
National Registration Authority
PO Box E240
Kingston ACT 2604
FAX: 02 6272 3218

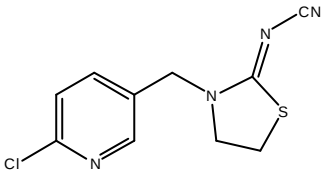
CHEMISTRY AND MANUFACTURE

Active constituent

The active constituent thiacloprid has the following properties:

Common name (ISO):	Thiacloprid
Chemical name (IUPAC):	N-{3-[(6-chloro-3-pyridinyl)methyl]-1,3-thiazolan-2-yliden} cyanamide
Chemical name (CAS):	Cyanamide, [3-[(6-chloro-3-pyridinyl)methyl]-2-thiazolidinylidene]
CAS Registry Number:	111988-49-9
Empirical formula:	$C_{10}H_9ClN_4S$
Chemical family	Chloronicotinyl insecticide
Molecular weight:	252.73
Physical form:	crystalline powder
Colour:	pale yellow
Odour:	weak characteristic odour
Melting point:	136^{o}C
Density:	1.46g/cm^3 at 20^{o}C
Octanol/water partition coefficient:	P_{ow} = 18, Log P_{ow} 1.26 at 20^{o}C
Vapour pressure:	3 x 10^{-10} Pa at 20^{o}C
	8 x 10^{-10} Pa at 25^{o}C

Structural formula:



Summary of the NRA's Evaluation of thiacloprid

The Chemistry and Residues Evaluation Section of the NRA has evaluated the chemistry aspects of thiacloprid (manufacturing process, quality control procedures, batch analysis results and analytical methods) and found them to be acceptable.

Thiacloprid is a new active constituent and there are no FAO specifications available for thiacloprid.

On the basis of the data provided it is proposed that the following minimum compositional standards be established for thiacloprid:

Active constituent	*Minimum content*
Thiacloprid	Not less than 985 g/kg

Other characteristics of thiacloprid (toxicology, environmental fate *etc*. are covered in subsequent sections of this Public Release Summary.

PRODUCT

Calypso 480 SC Insecticide

Formulation type:	Suspension Concentrate
Active constituents concentration:	480 g/L thiacloprid

Physical and Chemical Properties of the Product

Telone Soil Fumigant

Physical state:	Liquid, suspension
Colour:	Light brown
Odour:	Weak, characteristic
Specific gravity:	1.19 g/cm^3 at 20^{o}C
Dynamic viscosity:	η = 120.1 mPa s at 20^{o}C
PH	7.4
Flash point:	No flash point up to the boiling point (100^{o}C)
Flammability/autoignition:	No ignition temperature up to 600^{o}C
Storage stability:	The applicant provided storage stability data demonstrating that the product will be stable for at least 2 years when stored under ambient conditions (30^{o}C).

Summary of the NRA's Evaluation of Calypso 480 SC Insecticide

The Chemistry and Residues Evaluation Section of the NRA has evaluated the chemistry aspects of Calypso 480 SC Insecticide (manufacturing process, quality control procedures, batch analysis results, analytical methods and storage stability) and found them to be acceptable.

TOXICOLOGICAL ASSESSMENT

Summary

The product Calypso 480 SC Insecticide is a suspension concentrate formulation containing the active ingredient thiacloprid at 480 g/L. Calypso 480 SC Insecticide is intended for use in controlling aphids on ornamental plants. Thiacloprid is new to the Australian market and is closely related to imidacloprid, a compound that has been registered for some time.

After ingestion, thiacloprid is rapidly absorbed, widely distributed within the body, extensively metabolised and excreted mainly in the urine. Thiacloprid was of moderate acute oral and inhalation toxicity and low acute dermal toxicity. It was not a skin irritant or a skin sensitiser, but it was a slight eye irritant. Based on information from toxicity studies using a very similar formulation, Calypso 480 SC Insecticide was considered to have a similar toxicological profile except that it was not considered to be an eye irritant.

In repeat dose studies the liver was considered to be the primary target organ. The activity of enzymes of detoxication in the liver was higher after ingestion, inhalation and skin exposure to thiacloprid and the activity of a liver enzyme involved in steroid hormone synthesis was higher after ingestion. Effects on other organs such as the thyroid and adrenals were considered to be secondary to the effects on the liver and related to the increased liver enzyme activity. In whole lifetime studies, a higher incidence of thyroid and uterine tumours were observed in rats and a higher incidence of ovarian tumours was observed in mice. These tumours were considered to be related to the increased liver enzyme activity occurring over a whole lifetime and were not considered to be predictive of an increased likelihood of cancer development in humans. In addition, a range of tests showed that thiacloprid did not damage genetic material.

In reproduction studies in rats, difficulties giving birth were observed at high concentrations in some studies, but a clear no effect concentration was identifiable. There were no developmental effects observed in rat or rabbit pups in the absence of any detectable toxicity to the mother and there were no observations indicative of a specific neurotoxic effect in rats.

Based on an assessment of the toxicology, it was considered that there should be no adverse effects on human health from the use of this product when used in accordance with the label directions.

Evaluation of toxicology

The toxicological database for thiacloprid, which consists primarily of toxicity tests conducted using animals, is quite extensive. In interpreting the data, it should be noted that toxicity tests generally use doses that are high compared with likely human exposures. The use of high doses increases the likelihood that potentially significant toxic effects will be identified. Findings of adverse effects in any one species do not necessarily indicate such effects might be generated in humans. From a conservative risk assessment perspective however, adverse findings in animal species are assumed to represent potential effects in humans, unless convincing evidence of species specificity is available. Where possible, considerations of the species-specific mechanisms of adverse reactions weigh heavily in the extrapolation of animal data to likely human hazard. Equally, consideration of the risks to human health must take into account the likely human exposure levels compared with those, usually many times higher, which produce effects in animal studies. 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 (ADI and ARfD) at which no adverse health effects in humans would be expected.

Toxicokinetics and Metabolism

After oral administration of 1 mg/kg bw in rats, absorption of radiolabelled thiacloprid was rapid with approximately 60-80% of the administered dose being absorbed and peak plasma concentrations occurred 1-1.5 hours after dosing. Absorption was lower at 100 mg/kg bw and peak plasma concentrations were achieved at 3-4 hours after dosing. Results from autoradiography and kinetic studies show that radioactivity was distributed widely throughout the body with the kidney, liver, lung, adrenals, thyroid, spleen, gastrointestinal tract (plus contents) and skin containing the highest residues 48 hours after administration. Generally the pattern of distribution was similar with respect to dose and sex. However, 48 hours after a dose of 100 mg/kg bw, tissue residues were higher and females had significantly higher tissue residues than males. Plasma concentrations of thiacloprid were higher throughout gestation when compared with non-pregnant animals. Thiacloprid was extensively metabolised with some 25 metabolites identified and metabolic transformations included C and N

hydroxylation, S oxidation and methylation, oxidative ring cleavage and methylene bridge cleavage, glucuronic acid and pentose sulfate and glycine conjugations. Excretion was relatively rapid with >90% of administered doses excreted within 48 hours. Urinary excretion was the major route of excretion of radioactivity (60-80%) regardless of dose, sex or route of administration. Faecal excretion accounted for up to 39% of the administered dose and radioactivity excreted via exhaled air was minimal (<1%).

Acute Studies

Thiacloprid technical was of moderate acute oral toxicity in both fasted (LD_{50}=836 mg/kg bw in males and 444 mg/kg bw in females) and non-fasted (LD_{50}=621 mg/kg bw in males and 396 mg/kg bw in females) rats. It was of moderate acute inhalation toxicity (LC_{50} >2535 mg/m^3 in males and 1223 mg/m^3 in females) in rats with some sex differences observed. It was of low acute dermal toxicity (LD_{50}>2000 mg/kg bw) in rats and it was not a skin irritant in rabbits or a skin sensitiser in guinea pigs. It was a slight eye irritant in rabbits.

Based on results from toxicity studies conducted using a very similar formulation, Calypso 480 SC Insecticide (480g/L thiacloprid) was considered to be of moderate acute oral toxicity (between 500 and 2000 mg/kg bw in males and between 200 and 500 mg/kg bw in females) and low acute dermal toxicity (LD_{50}>4000 mg/kg bw) in rats. It was not an eye or skin irritant in rabbits and it was not a skin sensitiser in guinea pigs.

Short-Term Studies

In a two-week study in which mice were fed 0, 50, 200, 2000 and 10,000 ppm thiacloprid, water intake was lower in males at 2000 and 10,000 ppm. Cholesterol was lower in males at 10,000 ppm and bilirubin and albumin were lower in females at 10,000 ppm. Liver weights were higher at 2000 and 10,000 ppm and enzymes of detoxication were induced in liver at ≥ 2000 ppm. Hepatocellular hypertrophy was observed in males at ≥ 200 ppm and in females at 2000 and 10,000 ppm and a higher incidence of fatty change was observed in the livers of both sexes at 2000 and 10,000 ppm.

In a three-week study in which mice were fed 0, 100, 1000 and 10,000 ppm thiacloprid, water intake was lower in females at 10,000 ppm and body weights were lower in males at 10,000 ppm. Liver weights were higher in both sexes at 1000 and 10,000 ppm with enlarged livers observed only in males at 10,000 ppm.

In a two week study in which rats were given 0, 5, 10, 20, 60 and 120 mg/kg bw/day thiacloprid by gavage, one male at 120 mg/kg bw/day had decreased reactivity and females at 60 and 120 mg/kg bw/day had reduced defecation. Food consumption was lower in males at 60 and 120 mg/kg bw/day and water consumption was higher in females at 120 mg/kg bw/day. Body weight was lower in both sexes at 60 and 120 mg/kg bw/day. Blood leukocyte count was slightly lower and erythrocytes were slightly higher at 120 mg/kg bw/day. AST and ALT were higher in both sexes at 120 mg/kg bw/day and cholesterol was higher in both sexes at 60 and 120 mg/kg bw/day. Alkaline phosphatase activity and phosphorus were higher in females at 60 and 120 mg/kg bw/day and urea was higher in males at 120 mg/kg bw/day. Phase I and phase II enzyme activities in the liver where induced in a dose-dependant manner in males at ≥ 20 mg/kg bw/day and in females at 60 and 120 mg/kg bw/day. Adrenals were slightly discoloured in females at 120 mg/kg bw/day. Liver weights were higher at 60 and 120 mg/kg bw/day with increased liver cell division observed in a few rats. A “cytoplasmic change” and hepatocellular hypertrophy were observed in the liver of both sexes at 120 mg/kg bw /day and “cytoplasmic change” was observed in females at 60 mg/kg bw/day. Total cell count was lower in the spleen of males at 120 mg/kg bw/day and in the lymph nodes of females at ≥ 20 mg/kg bw/day. Splenic macrophages were activated in males at 60 and 120 mg/kg bw/day, but had lower rates of activation in all groups of treated females. Macrophages from lymph nodes were slightly activated at ≥ 20 mg/kg bw/day. Cell proliferation in the liver was higher and cell proliferation in the kidney was lower in females at 120 mg/kg bw/day.

In a two week study in which rats were fed 0, 25, 100, 500 and 2000 ppm thiacloprid, constipation and lower body weights were observed in both sexes at 2000 ppm. Food consumption was transiently lower and water consumption was higher in females at 2000 ppm. GGT, TSH, cholesterol and bile acids were higher at 2000 ppm and enzymes of detoxication in the liver were induced at 500 and 2000 ppm. Liver lobulation and higher liver weights were observed at 2000 ppm and hepatocellular hypertrophy was observed at 500 and 2000 ppm. Increased fat deposition in the liver was observed in males at 2000 ppm. Increased mitosis was observed in the thyroid of males at 500 and 2000 ppm with follicular hypertrophy observed in males at 2000 ppm.

In an inhalation study in which rats were given 0, 2, 20 and 200 mg/m^3 thiacloprid (5 x 6 hour exposures daily), bradypnea, laboured breathing, tremor, piloerection, reduced motility and mydriases were observed for up to a day after each exposure. Front paw grip strength was higher at 20 and 200 mg/m^3 and food consumption and body weights were lower at 200 mg/m^3. Plasma protein was higher in males and glutamate dehydrogenase and bile salts were lower in females at 200 mg/m^3. Hepatic O- and N-demethylase activities were higher in both sexes at 200 mg/m^3 and hepatic cytochrome P-450 and triglycerides were higher in males at 200 mg/m^3. Small

thymus and enlarged livers were observed in males at 200 mg/m^3 and black spleens were observed in females at 20 and 200 mg/m^3. Thymus weights were lower and liver weights were higher in both sexes at 200 mg/m^3. All effects had resolved by the end of a two-week recovery period.

In an inhalation study in which rats were given 0, 2, 20 and 200 mg/m^3 thiacloprid (5 x 6 hour exposures/week for 4 weeks), bradypnea, laboured breathing, tremor, piloerection, reduced motility, atony, rales, miosis and mydriases were observed mainly during the first week of treatment. Severe respiratory distress and decreased body weight gain were observed at 200 mg/m^3 and therefore the highest dose was reduced to 100 mg/m^3 after the first week. Signs of respiratory distress continued throughout the study at 100 mg/m^3. Body weights were lower in males at 200 mg/m^3. Alkaline phosphatase, glucose and phosphorus were higher at 200/100 mg/m^3 and cholesterol and bile acids were higher in females at 200/100 mg/m^3. Hepatic N-demethylase activity was higher in males at 20 and 200/100 mg/m^3 and O-demethylase activity and cytochrome P-450 content were higher at 200/100 mg/m^3. Liver weights were higher in both sexes at 200/100 mg/m^3 and thyroid weights were higher in males at 20 and 200/100 mg/m^3. Follicular hypertrophy in the thyroid was observed in males at 200/100 mg/m^3 and hepatocellular hypertrophy was observed in males at ≥ 20 mg/m^3 and in females at 200/100 mg/m^3.

In a four-week study thiacloprid was applied to the skin of rats at doses of 0, 100, 300 and 1000 mg/kg bw/day. Liver weights were higher at 1000 mg/kg bw/day with hepatocellular hypertrophy observed at 300 and 1000 mg/kg bw/day in males and at 1000 mg/kg bw/day in females. Follicular hypertrophy in the thyroid was observed in both sexes at 1000 mg/kg bw/day. Hypertrophy in the liver and thyroid of males at 1000 mg/kg bw/day were partially reversible after a two-week recovery period.

In a ten-week study in which dogs were fed 0, 100, 300, 1000 and 2500 ppm thiacloprid, the dietary concentration in the 1000 ppm group was slowly increased to 2500 ppm by day 38 of the study. Food consumption and body weight were lower in females at 2500 ppm. ALT was transiently higher in males at 2500 ppm and creatinine and urea were higher in both sexes at 1000 and 2500 ppm. Serum T_3 was elevated and T_4 was transiently lower in females and hepatic enzymes of detoxication were induced in both sexes at 2500 ppm. "Cytoplasmic" changes in hepatocytes were observed in both sexes at 2500 ppm and in females at 1000 ppm and fatty changes in the liver were observed in males at 2500 ppm. Prostate weights were higher in males at 1000 and 2500 ppm.

After consuming thiacloprid at 0, 50, 250, 1250 and 6250 ppm in the diet for up to 14 weeks, food intake was slightly higher in male mice at 1250 and 6250 ppm and water intake was lower in both sexes at 6250 ppm. Body weights were lower and triglycerides were higher in males, plasma cholesterol was lower in both sexes and protein and albumin were lower in females at 6250 ppm. Bilirubin was lower in both sexes at 1250 and 6000 ppm. Hepatic N-demethylase activity was higher and hepatocellular hypertrophy was observed in males at ≥ 250 ppm and in females at 1250 and 6250 ppm and cytochrome P-450 content and liver weights were higher in both sexes at 1250 and 6250 ppm. Kidney weights were higher and the number of autophagic vacuoles in the proximal tubules was lower in males at 1250 and 6250 ppm. The number of advanced corpora lutea was lower, interstitial glands were activated and adrenal weights were higher in females at 1250 and 6250 ppm and vacuolation in the adrenal X-zone was observed in all treated groups of females. A NOEL could not be established since increased vacuolation in the X-zone of the adrenal cortex was observed in all treated groups of females. The LOEL was 50 ppm (27.2 mg/kg bw/day).

Thiacloprid at 0, 25, 100, 400 and 1600 ppm was fed to rats for up to 13 weeks with a 5-week recovery period for animals at 0 and 1600 ppm. Water consumption was lower in males and body weights were lower in both sexes at 1600 ppm. Clotting time was shorter in females and cholesterol and creatinine were higher in males at 1600 ppm. Cholesterol was higher in females and protein was higher in both sexes at 400 and 1600 ppm. Blood T_3 was transiently higher in all treated groups of males but remained higher for the duration of treatment only at 1600 ppm and T_4 was transiently higher in males at 400 and 1600 ppm. Hepatic cytochrome P-450 content and phase I and phase II enzyme activities in the liver were higher at 400 and 1600 ppm. Urinary sodium and calcium were higher in males at 1600 ppm. Thyroid weights were higher in males at 1600 ppm and liver weights were higher in males at 400 ppm and in both sexes at 1600 ppm. Hepatocellular hypertrophy was observed at 400 and 1600 ppm with a fine granular or vesicular cytoplasm in liver cells observed at 1600 ppm in both sexes and fatty changes observed in males at 1600 ppm. Macrophages from the spleen were slightly activated in both sexes and mitogen stimulation was higher in males at 1600 ppm. At the end of recovery, all effects were returning towards control levels. The NOEL was 100 ppm (7.3 mg/kg bw/day in males and 7.5 mg/kg bw/day in females) based on changes in clinical chemistry, liver enzyme activities and histopathology observed at ≥ 400 ppm.

After consuming thiacloprid at 0, 250, 1000 and 4000 ppm in the diet for up to 15 weeks, dogs at 4000 ppm had severely reduced food intake and body weight gains after vomiting consumed food. Therefore treatment ceased at 4000 ppm and recommenced at day 15 at a dose of 2000 ppm. Food intake was transiently lower at 2000 ppm

and body weight gains were lower in males at 2000 ppm. Plasma urea and thyroxine binding capacity were higher and thyroxine was lower in both sexes at 1000 and 2000 ppm. Cholesterol was higher and ALT was inconsistently higher in some females at 2000 ppm. Enzymes of detoxication in the liver were generally higher at 2000 ppm, but 7-ethoxyresorufin deethylase activity was lower in males at 2000 ppm and in females at 1000 and 2000 ppm. Prostate weights were higher with associated prostatic hypertrophy at 1000 and 2000 ppm. "Prominent" Leydig cells and degenerated spermatocytes in testes and/or epididymides were observed at 2000 ppm. Uterus weights were higher at 2000 ppm. The NOEL in this study was 250 ppm (equal to 8.9 mg/kg bw/day) based on histopathological effects observed in prostate and slight effects on clinical chemistry and liver enzymes at 1000 and 2000 ppm.

Long-Term Studies

In a chronic/carcinogenicity study mice consumed thiacloprid at 0, 30, 1250 and 2500 ppm in the diet for up to 107 weeks. Although males at 2500 ppm tended to have a higher food intake, body weights were lower. Leucocyte counts were higher in males at 1250 and 2500 ppm and transiently higher in females at these doses. Adrenal weights were higher in females at 2500 ppm after one year but not after two years. Liver weights were higher at 1250 and 2500 ppm. The number of vacuoles in the proximal tubules of the kidney was lower in males at 2500 ppm after one year but not after two. In the liver, hepatocellular hypertrophy was observed in both sexes at 1250 and 2500 ppm, fatty change and degeneration were observed in males at 1250 and 2500 ppm and fatty change was observed in females at 2500 ppm and necrosis was observed in both sexes at 2500 ppm. Vacuolation in the mesenteric and mandibular lymph nodes was observed in both sexes at 1250 and 2500 ppm. Vacuolation in the X-zone of the adrenal cortex, the incidence of eosinophilic, leutinised cells in the ovarian stroma and surrounding adipose tissue and the incidence of benign ovarian luteomas were higher at 1250 and 2500 ppm. Based on higher leucocyte count, higher liver weight, histopathological changes and a higher incidence of benign ovarian tumours observed at 1250 and 2500 ppm, the NOEL was 30 ppm (5.7 mg/kg bw/day in males and 10.9 mg/kg bw/day in females).

In a chronic/carcinogenicity study rats consumed thiacloprid at 0, 25, 50, 500 and 1000 ppm in the diet for up to 107 weeks. Food consumption and body weight gains were lower in both sexes and water intake was transiently lower in males at 500 and 1000 ppm. Water consumption was lower in females at 1000 ppm. TSH was higher at 500 and 1000 ppm in males and at 1000 ppm in females. In males alkaline phosphatase tended to be lower and protein, bilirubin and cholesterol tended to be higher. AST tended to be lower in both sexes and triglycerides lower in females at 1000 ppm. Water clefts in the lens cortex were observed in males at ≥ 50 ppm and in females at 500 and 1000 ppm and opacity in the lense and retrolenticular area were higher in females at ≥ 50 ppm. Generally phase I and phase II liver enzymes were induced at ≥ 50 ppm in both sexes. At 1000 ppm, liver weights were higher in both sexes and hepatocyte vacuolation was observed in males. Hepatocellular hypertrophy, "cytoplasmic changes" and mixed cell foci were observed in males at ≥ 50 ppm and females at ≥ 500 ppm. Liver necrosis was increased in females at ≥ 500 ppm. Thyroid follicular hypertrophy was increased in males at ≥ 50 ppm and females at ≥ 500 ppm and in some groups was associated with colloid alteration, pigment and follicular hyperplasia. Thyroid follicular adenomas were observed in males at 500 and 1000 ppm. Uterine nodules were observed at 1000 ppm and a higher incidence of ovarian cysts and uterine adenocarcinoma and adenosquamous carcinoma occurred at 500 and 1000 ppm. A higher incidence of focal Leydig cell hyperplasia, cholesterol clefts in the pituitary and increased haematopoiesis in the marrow of femur and sternum were observed in males at 500 and 1000 ppm. "Turbid eyes" and lens degeneration were observed in females at 500 and 1000 ppm and retinal atrophy was observed in females at ≥ 50 ppm. Skeletal muscle was atrophic in females at 500 and 1000 ppm and muscle degeneration and mononuclear cell infiltration were observed in females at 1000 ppm. Sinus histocytosis was observed in the mesenteric lymph nodes of both sexes at 1000 ppm. Sciatic nerve degeneration in both sexes and radicloneuropathy and cholesterol clefts in the spinal chord of females were observed at 500 and 1000 ppm. Based on hepatic enzyme induction and histopathological changes in the liver and thyroid, the NOEL in this study was 25 ppm, equal to 1.2 mg/kg bw/day.

After consuming thiacloprid at 0, 40, 100, 250 and 1000 ppm in the diet for 52 weeks, female dogs at 1000 ppm had lower feed intake and males at 1000 ppm had lower plasma T_4. Kidney weight was higher after six months in males at 1000 ppm but not after a year and prostate weights were higher after a year at 1000 ppm. Hepatocellular cytoplasmic changes were observed in males at 1000 ppm after six months but not after a year. The severity of pigment deposition in the proximal tubules of the kidney was increased at 1000 ppm. The NOEL was 250 ppm (equal to 8.9 mg/kg bw/day in males and 8.3 mg/kg bw/day in females).

Reproduction and Developmental Studies

In a two generation dose range finding study rats were fed thiacloprid at 0, 100, 400 and 1600 ppm in the diet. Food consumption and body weight gain were lower at 1600 ppm in F_0 generation adults of both sexes. Reproduction was not affected. Pup body weight gain was lower at 1600 ppm and pup survival was lower in

association with cannibalisation at 1600 ppm. Hepatocellular hypertrophy and hepatocyte cytoplasm with a "ground glass" appearance were observed in both F_0 and F_1 generations at 1600 ppm. Increased mitosis in the liver was also observed in F_1 animals at 1600 ppm. Follicular hypertrophy in the thyroid was observed in F_0 generation adults at 400 and 1600 ppm and in the F_1 generation at 1600 ppm.

In the main two generation reproduction study, rats were fed thiacloprid at 0, 50, 300 and 600 ppm in the diet. Dystocia (difficulty giving birth) was observed in F_0 dams at 300 and 600 ppm leading to their death or sacrifice. Body weight gain was lower in adults of both generations at 600 ppm. A higher incidence of stillbirths was observed in all treated groups of the F_1 generation and at 50 and 600 ppm in the F_2 generation without an obvious dose relationship. The number of live births, pup survival and pup body weights were lower at 600 ppm in both generations. Liver weights were higher in F_0 males and F_1 females at 300 and 600 ppm and thyroid weights were higher in F_0 females at 300 and both sexes 600 ppm. In adults in both generations a higher incidence of hepatocytomegaly and hypertrophy of the follicular cells of the thyroid were observed at 300 and 600 ppm. Hepatocyte necrosis was also seen in F_0 females at 300 and 600 ppm. The NOEL for toxicity to adults and reproduction toxicity was 50 ppm (equal to approximately 3.5 mg/kg bw/day in males and 4.2 mg/kg bw/day in females) based on dystocia, increased liver and thyroid weights and histopathological effects in adults at 300 and 600 ppm.

In a one generation study aimed at evaluating the reproducibility of dystocia and stillbirths, rats were fed thiacloprid at 0, 25, 300 or 1000 ppm in the diet for 10 weeks prior to mating, during mating and until sacrifice of males after mating and females after weaning of litters. Five dams died and one was sacrificed at 1000 ppm without a cause of death being established. Four dams at 1000 ppm died during gestation, two after having begun birth. Body weight of dams at 1000 ppm was lower throughout the study. The incidence of stillbirths was similar in control and treated groups. Pup survival and body weights were lower and the incidence of "weak" pups was higher at 1000 ppm. Liver and thyroid weights of dams were higher at 1000 ppm. There were no effects on reproduction and maternal toxicity at 300 ppm (equal to 26 mg/kg bw/day) based on dystocia and lower pup body weights and clinical signs observed at 1000 ppm.

In order to investigate possible causes of dystocia and stillbirths, rats were fed thiacloprid at 0 and 1000 ppm in the diet for 10 weeks prior to mating, during mating and until sacrifice of males after mating and females on gestation days 21 or 22. Three treated dams died during gestation, one after delivering part of a litter. Food consumption and body weight were lower in females prior to mating and body weight remained lower at sacrifice. Measurement of cervical collagen concentrations demonstrated that the cervix of treated rats was firmer on days 13, 15 and 17 of gestation but no significant differences were noted later in gestation. Cervical extensibility, uterine contractile responses, uterine electrical activity, intrauterine pressure, uterine $alpha_1$ adrenergic receptor concentration and uterine wet and dry weights and water content were similar in control and treated groups. The number of foetuses per litter was lower and vaginal weight was higher in treated dams.

In order to further investigate possible dystocia, mated female rats were given thiacloprid by oral gavage at doses of 0, 17.5, 35 and 60 mg/kg bw/day on gestation days 18-22. Treatment related deaths occurred at 35 and 60 mg/kg bw/day on gestation day 20-22. Clinical signs included hypoactivity, chromorhinorrhea and clear vaginal discharge at 35 and 60 mg/kg bw/day. Dystocia was not observed. Lower body weight gain and food consumption were observed in all treated groups of dams. Stillbirths were higher at 35 and 60 mg/kg bw/day. In the dams, lower body weight gain and food consumption were observed at all tested doses. There were no effects on reproduction toxicity at 17.5 mg/kg bw/day based on stillbirths observed at 35 and 60 mg/kg bw/day.

In another investigation of dystocia and stillbirths, rats were fed thiacloprid at 0 and 800 ppm in the diet for 10 weeks prior to mating, during mating and until sacrifice of males after mating and females on gestation days 16 or 22 or day 2 postpartum. Two treated females did not start or did not complete parturition. Body weight of treated dams was lower. At the end of the premating period cholesterol, ALT, potassium and globulin were higher and glucose was lower in treated females and triglycerides and lipaemic index were lower on gestation day 18. Steroid hormone levels (estradiol, progesterone, corticosterone) and luteinising hormone were elevated in treated rats, whereas there was no effect on other measured serum hormone levels (prolactin, follicle stimulating hormone). Cytochrome P-450 levels and O and N-demethylase activities in liver of treated females were higher throughout the study. Uterine and cervical prostaglandin, liver and uterine glutathione and uterine oestrogen and progesterone were similar in control and treated animals. Liver weight was higher and hepatocytomegaly was observed in all treated females throughout the study and an electron micrograph showed proliferation of the smooth endoplasmic reticulum in hepatocytes from treated females.

Thiacloprid was administered to pregnant rats by gavage at 0, 2, 10 or 50 mg/kg bw/day on gestation days 6 through 19. Water consumption and urination tended to be higher and food consumption and body weight gains were lower at 50 mg/kg bw/day. Post-implantation losses were higher and foetus weight was lower at 50 mg/kg bw/day. At 50 mg/kg bw/day, there was a higher foetal incidence of incomplete or unossified bones in a variety

of skeletal locations including proximal and distal phalanges, metacarpals, sternebrae, thoracic vertebral body, parietal and interparietal bones and supraoccipital bone. A higher foetal incidence of enlarged fontanelle, wavy ribs, asymmetrical sternebrae and limb dysplasia were also observed at 50 mg/kg bw/day. The NOELs for maternal and foetal toxicity were 10 mg/kg bw/day based on lower maternal body weight gain, post-implantation losses, lower foetal body weight and skeletal effects in foetuses at 50 mg/kg bw/day.

Thiacloprid was administered to pregnant rabbits by gavage at 0, 2, 10 or 45 mg/kg bw/day on gestation days 6 through 28. Two dams at 45 mg/kg bw/day aborted. Water intake and urination were lower at 45 mg/kg bw/day. Defecation and food consumption were lower and body weight losses were higher at 10 and 45 mg/kg bw/day. Gravid uterine weights were lower and post-implantation losses were higher at 45 mg/kg bw/day. A lower proportion of male foetuses was observed at 45 mg/kg bw/day and foetal body weights were lower at 10 and 45 mg/kg bw/day. At 45 mg/kg bw/day, there was a higher incidence of incomplete or unossified bones in a variety of skeletal locations including phalanges, metacarpals, calcanei, cervical and caudal vertebrae and hyoid bone and a higher incidence of arthrogryposis, 13^{th} rib and supernumerary lumbar vertebrae with 13^{th} rib. The NOELs for maternal and foetal toxicity were 2 mg/kg bw/day based on lower feed intake and bodyweight gains in dams and lower foetal body weights at 10 and 45 mg/kg bw/day.

Genotoxicity

Thiacloprid was not mutagenic with or without metabolic activation in a bacterial reverse mutation assay or in a forward mutation assay using mammalian cells *in vitro*. It did not increase the frequency of chromosomal aberrations and did not induce unscheduled DNA synthesis in mammalian cells *in vitro*. It did not induce micronuclei in an *in vivo* mouse micronucleus assay.

Special Studies

In an acute neurotoxicity study rats were given thiacloprid by oral gavage at doses of 0, 22, 53 and 109 mg/kg bw. Tremors, decreased activity, ataxia, dilated pupils, "body cool to touch", stained urine and ptosis of eyelids were observed in males and females at 109 mg/kg bw, primarily on the day of dosing. Body weight was lower in males at 109 mg/kg bw. Treatment related effects in the functional battery observations were restricted to the day of dosing with some effects e.g. clonic tremors occurring at all doses. Similarly, effects on motor and locomotor activity were restricted to the day of dosing with effects occurring in males at 100 mg/kg bw and at all doses in females. In a supplementary study, rats were given thiacloprid by oral gavage at doses of 0, 3.1 and 11 mg/kg bw. Lower motor and locomotor activity were observed in females at 11 mg/kg bw.

In a subchronic neurotoxicity study, rats were given y thiacloprid at 0, 50, 400 and 1600 ppm in the diet for 13 weeks. Body weights and food consumption were lower at 1600 ppm. There were no neurotoxic effects at any tested dose.

The plant metabolites KKO 2254 and WAK 6999 had LD_{50}'s of >2000 mg/kg bw in males and females and neither were mutagenic in bacterial reverse mutation assays.

Thiacloprid was a very weak inhibitor of thyroid peroxidase activity (IC_{50} >870 µM) and hydrolysis products of thiacloprid did not inhibit thyroid peroxidase *in vitro*. Plasma extracts from untreated and thiacloprid treated rats had similar effect on thyroid peroxidase activity *in vitro*.

In a study of aromatase inhibition, mice were fed dietary thiacloprid at 0, 10, 30, 250 and 2500 ppm for 13 weeks. Decreased reactivity and increased motility were observed at 250 and 2500 ppm and food consumption was lower at 2500 ppm. Plasma progesterone and liver weights were higher at 2500 ppm. Hepatic aromatase activity was higher and vacuolation in the X-zone of the adrenal cortex was observed at 250 and 2500 ppm. Co-treatment with mecamylamine (a nicotine mimic) slightly reduced the severity of some of the effects of thiacloprid treatment.

Rats were fed dietary thiacloprid at concentrations of 0, 100 and 1000 ppm for 4 weeks and, in a second study, female rats (10/group) were fed dietary thiacloprid at concentrations of 0, 100, 200, and 500 ppm for 4 weeks to examine aromatase induction and thiacloprid toxicokinetics. Body weights were lower in males at 1000 ppm and in females at 500 and 1000 ppm. Food consumption was lower in males at 100 and 1000 ppm and females at 1000 ppm. Liver weights were higher in both sexes at 1000 ppm and in females at 500 ppm. Hepatic aromatase was induced at ≥ 200 ppm and ovarian aromatase activity was similar in control and treated groups. Plasma thiacloprid concentrations were relatively constant in males and increased proportionally with dose. In females, peak plasma concentrations occurred at day eight, remaining at this concentration for the duration of the study and the increase in plasma concentration was slightly greater than the increase in oral dose.

Ovarian and hepatic aromatase activities were measured in tissues taken from females in a one-generation reproduction study examining dystocia and stillbirths (0 and 800 ppm). Ovarian aromatase activity was similar in control and treated groups during premating and gestation. However, on day 2 of lactation aromatase activity in treated rats remained high whereas activity in the control group was decreased. Liver aromatase activity in the treated group was approximately double that in the control group at the end of the premating period.

Thiacloprid was a very weak inhibitor of 7-ethoxycoumarin deethylation activity in both rat and dog microsomes *in vitro* with IC_{50} >100µM and thiacloprid did not inhibit the hydroxylation of testosterone (IC_{50} >1000 µM). Other results supplied in this study (details of methodology not supplied) show that feeding rats thiacloprid at dietary concentration of 100 ppm for two weeks increased the hydroxylation of testosterone at several positions suggesting the induction of several different cytochrome P-450 isotypes.

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.

On the basis of its toxicity, the NDPSC has included thiacloprid in schedule 6 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). There are provisions for appropriate warning statements and first-aid directions on the product label.

NOEL/ADI

The Acceptable Daily Intake is that quantity of an agricultural compound that can safely be consumed on a daily basis for a lifetime and is based on the lowest NOEL obtained in the most sensitive species. This NOEL is then divided by a safety factor that reflects the quality of the toxicological database and takes into account the variability in responses between species and individuals.

The ADI for thiacloprid was established at 0.01 mg/kg bw/day mg/kg bw/day based on a NOEL of 1.2 mg/kg bw/day in a 2-year dietary study in rats and using a 100-fold safety factor in recognition of the extensive toxicological database available for thiacloprid.

Acute Reference Dose (ARfD)

The acute reference dose is the maximum quantity of an agricultural or veterinary chemical that can safely be consumed as a single, isolated, event. The ARfD is derived from the lowest single or short term dose which causes no effect in the most sensitive species of experimental animal tested, together with a safety factor which reflects the quality of the toxicological database and takes into account the variability in responses between species and individuals.

The highest acute dose of thiacloprid at which no evidence of toxicity was detected was 3.1 mg/kg bw in an acute neurotoxicity study in rats. The ARfD was established at 0.03 mg/kg bw on the basis of this NOEL and using a 100-fold safety factor.

RESIDUES ASSESSMENT

At this point in time, the applicant only seeks use on commercially grown camellias, maybush and roses. As such, no assessment of thiacloprid residues in foods was required.

ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

At this point in time, the applicant only seeks use on commercially grown camellias, maybush and roses. As such, no assessment of trade aspects of thiacloprid residues in foods was required.

OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Summary

NOHSC has conducted a risk assessment on Calypso 480 SC Insecticide containing thiacloprid at 480 g/L as a suspension concentrate for use on camellias, maybush and roses to control aphids. Workers can safely use Calypso 480 SC Insecticide when it is handled in accordance with the control measures indicated in this assessment.

Thiacloprid has moderate acute oral and inhalation toxicity in rats. It is not a skin irritant but a slight eye irritant in rabbits. Thiacloprid is not a skin sensitiser in guinea pigs.

Thiacloprid is not on the NOHSC *List of Designated Hazardous Substances*. The applicant has classified thiacloprid and Calypso 480 SC Insecticide as hazardous, according to the NOHSC *Approved Criteria for Classifying Hazardous Substances*.

Technical grade thiacloprid is manufactured overseas and will be imported into Australia. The end-use product (EUP) will be formulated in Australia and packed in 1, 5, 10 and 20 L high-density polyethylene (HDPE) bottles or drums.

Calypso 480 SC Insecticide will be applied to camellias, maybush and roses by tractor mounted and hand held devices. The maximum application rate is 10 mL EUP in 100 L of water, with a minimum spray volume of 1000 L/ha. For perennials, a maximum of 3 sprays are recommended in a year.

Based on the risk assessment, cotton overalls buttoned to the neck and wrist, elbow-length PVC or nitrile gloves and a disposable fume mask should be worn when preparing the spray. When using the prepared spray, cotton overalls buttoned to the neck and wrist, and elbow-length PVC or nitrile gloves should be worn.

The final product label requires the following statement:

RE-ENTRY

"Do not allow entry into treated areas until the spray has dried. When prior entry is necessary, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use."

Assessment of occupational health & safety

Thiacloprid is not on the NOHSC *List of Designated Hazardous Substances*. The applicant has classified thiacloprid and Calypso 480 SC Insecticide as hazardous according to the NOHSC *Approved Criteria for Classifying Hazardous Substances*.

The following risk phrases apply for thiacloprid:
R20 Harmful by inhalation
R22 Harmful if swallowed
R40 Limited evidence of a carcinogenic effect
R48 Danger of serious damage to health by prolonged exposure
R63 Possible risk of harm to the unborn child

Thiacloprid will be manufactured overseas as a yellowish crystalline powder. It has moderate oral and inhalation toxicity in rats. Thiacloprid is not a skin irritant but a slight eye irritant in rabbits. It is not a skin sensitiser in guinea pigs.

Based on results of a similar formulation, the TGA has concluded that Calypso 480 SC Insecticide will have moderate acute oral and low dermal toxicity in rats. It is not an eye or a skin irritant in rabbits, and not a skin sensitiser in guinea pigs. No acute inhalation toxicity studies were conducted on the product or the similar formulation.

Formulation, repackaging, transport, storage and retailing

The end-use product (EUP) will be formulated in Australia from the imported active ingredient and will be packed in 1, 5, 10 and 20 L high-density polyethylene (HDPE) containers.

Storemen, transport workers, laboratory staff, formulators and packers will handle the active constituent and the product. The submission contains sufficient information on the categories of workers, nature of work done and prevention of worker exposure required for workplace assessment.

Use and exposure

Calypso 480 SC Insecticide is indicated for the control of aphids in camellias, maybush and roses. It will be applied to camellias, maybush and roses by tractor mounted and hand held devices. The maximum application rate is 10 mL EUP in 100 L of water, with a minimum spray volume of 1000 L/ha. A maximum of 3 sprays per year is recommended for perennials.

The main routes of exposure are dermal, inhalation and ocular. Categories of workers that can be exposed to the product are mixer/loaders, ground applicators, clean-up personnel and re-entry workers.

There are no available worker exposure data on Calypso 480 SC Insecticide. NOHSC used the UK Predictive Operator Exposure Model (POEM) to estimate applicator exposure to Calypso 480 SC Insecticide.

These estimates in conjunction with toxicology data demonstrated that the use of clothing, gloves and fume mask during mixing / loading, and clothing and gloves during spraying is necessary to protect workers from acute and repeated exposure.

Entry into treated areas

Workers entering treated areas can be exposed to product residues and degradation products during crop management activities and harvesting.

Based on generic foliar residue data, NOHSC recommends a restricted entry period until the spray has dried. When prior entry is necessary, cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves should be worn to reduce exposure.

Recommendations for safe use

Users should follow the instructions and Safety Directions on the product label. Safety Directions include the use of cotton overalls buttoned to the neck and wrist, elbow-length PVC or nitrile gloves and disposable fume mask when preparing the spray and use of cotton overalls buttoned to the neck and wrist, and elbow-length PVC or nitrile gloves when using the prepared spray.

The PPE recommended should meet the relevant Standards-Australia.

Re-entry statement

"Do not allow entry into treated areas until the spray has dried. When prior entry is necessary, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use."

Conclusion

NOHSC supports the registration of thiacloprid in Calypso 480 SC Insecticide at 480 g/L as a suspension concentrate, for use on camellias, maybush and roses.

Calypso 480 SC Insecticide 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 thiacloprid and Calypso 480 SC Insecticide MSDS.

ENVIRONMENTAL ASSESSMENT

Summary

Thiacloprid is stable to hydrolysis at pH values of 5-9 and 25°C and not expected to photodegrade significantly in water with a half-life of about 324 d. The DT_{50} for photodegradation on sandy loam thin layers was 74 d with the amide KKO 2254 as the major product. Metabolism in aerobic soils was rapid with DT_{50} and DT_{90} values of 0.4-2.6 and 12-29 d four soils. Mineralisation to CO_2 after 100 d was ≤34% of the originally applied amount. KKO 2254 was the main metabolite (peaking at 74% at 3 DAT) in three soils while the sulfonic acid metabolite WAK 6999 (peaking at 20% at 60 DAT) was predominant in another soil. Estimated DT_{50} values for KKO 2254 were 32-142 d and 16-79 d for WAK 6999. Biodegradation in anaerobic conditions was much slower with a calculated half-life of thiacloprid of >1 year with the major metabolite of KKO 2254. In two mostly aerobic, natural sediment-water systems, thiacloprid disappeared from the water column with half-lives of 3 and 11 d whereas the whole system half-lives were 20 and 12 d, respectively, with KKO 2254 as the major metabolite.

K_{OC} values for thiacloprid in six soils were 261-870 mL/g indicating medium to low mobility. KKO 2254 was of medium mobility (166-438 mL/g) while WAK 6999 showed very high mobility (12-28 mL/g) in five soils. A 60-d aged residue leaching study confirmed this, as WAK 6999 was the main component in the leachate accounting for 19% of the originally applied amount. This was confirmed in lysimeter studies in which only WAK 6999 was recovered in the leachate three years after application of thiacloprid for two years. Computer modelling showed conflicting results with WAK 6999 predicted at 2.2 µg/L in the leachate in one scenario but <0.001 µg/L in another. Despite a low vapour pressure, the loss of about 12% from soil and 15% from tomato plant surfaces after 24 h was attributed to volatilisation. Dissipation in the field was relatively quick with DT_{50} and DT_{90} values for thiacloprid of 3.4-27 and 31-91 d, respectively, in the top 10 cm of soil. However, the longest DT_{90} value of 508 d indicated the persistence of total residues in one soil. On only one occasion were any parent thiacloprid or metabolite found in the 20-30 cm deep soil layer. The relatively low log K_{OW} of 1.26 suggests a low potential for bioconcentration or bioaccumulation.

Thiacloprid was generally of low acute toxicity to birds although a single unverified study indicated high toxicity to Japanese quail. A chronic reproduction study found mallard ducks most sensitive with NOEC and LOEC values of 48 and >140 mg a.i./kg food, respectively. A six-week study on Japanese quail showed NOEC and LOEC values of 157 and 485 mg a.i./kg food, respectively, but was only run for six weeks compared to 20 weeks for the mallards. Thiacloprid was at best moderately toxic to rainbow trout and bluegill sunfish with 96-h EC_{50} values of <9.25 mg a.i./L. The metabolite KKO 2254 was at worst slightly toxic to both fish with 96-h LC_{50} >78.6 mg/L. Parent thiacloprid was also slightly toxic to trout early life stages with 97-d NOEC and LOEC values of 0.24 and 0.48 mg a.i./L, respectively. Amphipods (96-h EC_{50} of 24.5 (20.2, 29.7) µg a.i./L) and midge larvae (28-d NOEC and LOEC values of 1.0 and 1.8 µg a.i./L, respectively) were about 1000X more sensitive than daphnids. At least 28 d were required before concentrations reduced to 1.0 µg a.i./L and no adverse effects were seen on midge larvae introduced to containers initially treated at 2.8 µg a.i./L. An outdoor mesocosm study showed that affected invertebrates required 98 d to recover from an initial concentration of 1.0 µg a.i./L. KKO 2254 was slightly toxic to amphipods with a 96-h EC_{50} of 16.1 (10.4, 28.1) mg/L and had no effect on midges at 0.1 mg/L after 28 d. Freshwater green algae and duckweed were both not sensitive to thiacloprid or the metabolites KKO 2254 and WAK 6999.

Thiacloprid was moderately to slightly toxic to earthworms in 14-d exposures but an application rate of 62.5 g a.i./ha significantly reduced the number of juvenile worms after 56 d. Although no significant impact of two applications of 250 g a.i./ha 7 d apart was found on the earthworm fauna in a natural grassland, the subsampling methodology may have obscured any trend. Honeybees were not sensitive to thiacloprid in acute oral and contact tests and semi-field tests. When actively foraging bees were sprayed directly with 178-188 g a.i./ha, there was no adverse effect lasting >7 d on mortality, behaviour or brood development, although there was an inconclusive effect on honey stores in the hive. Carabid and rove beetles were at worst only slight affected (5% mortality) when sprayed once or twice with 150-187.5 g a.i./ha in field studies despite sensitivity in laboratory tests. Ladybird beetles were highly sensitive in laboratory exposures (LOEC of 0.96 g a.i./ha) and significantly impacted in semi-field tests at 60 g a.i./ha. Spiders were adversely affected by 187.5 g a.i./ha after 14 d while the 30-d LC_{50} to green lacewings was 58.1 (29.7, 177.7) g a.i./ha when exposed to residues and fresh sprays on bean seedlings. Predatory mites were adversely affected at 60 g a.i./ha in the laboratory but were at worst temporarily affected (four week recovery) when treated in apple orchards at 176-202 g a.i./ha. Parasitic wasps were sensitive to 60-69.7 g a.i./ha in laboratory and field studies but not to sprays of 0.25 g a.i./L in an orchard. A concentration of 2.57 mg a.i./kg soil dw did not affect soil respiration but caused an adverse but tolerable effect on nitrogen turnover at 28 DAT.

The expected limited use pattern of Calypso 480 SC Insecticide on ornamental plants will preclude significant contamination of soil and water resulting in low exposure to nontarget animals and plants. Therefore the hazard from this use pattern is expected to be low. Should the applicant seek to extend the use pattern to agricultural food crops in the future, a more comprehensive environmental hazard assessment will need to be undertaken at that time.

Environmental Assessment

Environmental Exposure

Calypso 480 SC Insecticide is proposed for the control of aphids on camellias, maybush and roses according to the label directions at an application rate of 10 mL EUP/100 L water. Given the concentration of thiacloprid of 480 g a.i./L EUP, this equates to an application rate of 0.048 g a.i./L water. The label instructs to "apply as a thorough cover spray at first sign of insect infestation". The company suggested the most likely use scenarios would be spot treatments of ornamental flowers, shrubs and trees showing aphid infestations. At a usual spray volume of 1,000 L/ha, an estimated application rate would be 48 g a.i./ha.

Calypso 480 SC Insecticide is a Group 4A insecticide for resistance management and the label states not to apply this product in consecutive sprays by alternating with another registered aphicide from at least one other group. There is no maximum number of sprays given for this use pattern and the company commented that because of the product's effectiveness against aphids, it is unlikely that infested plants would be sprayed more than once a year but to be conservative, two sprays per year could occur. For confined environments such as glasshouses, annuals are not to be sprayed more than once for any one crop while perennials should alternate with another aphicide with a maximum of three sprays in any 12 month period.

Environmental Chemistry and Fate

Abiotic transformation

Thiacloprid is stable to hydrolysis at pH values of 5-9 and 25°C with >95% parent compound remaining after 30 d in these conditions. Photolysis in water is also not expected to be a major degradation pathway as the half-life was estimated to be about 324 d under midsummer conditions. Computer modelling confirmed this with a direct photolysis half-life of >1 year. The DT_{50} for thiacloprid on sandy loam soil thin layers was equivalent to 74 d at midsummer conditions with KKO 2254 as the major degradate (up to 24% of the originally applied amount) in both irradiated and dark control samples.

Biotic transformation

Thiacloprid degraded rapidly with DT_{50} values of 0.4-2.6 d in four soils; the corresponding DT_{90} values were 11.7-29.0 d. Mineralisation to CO_2 after 100 d was 6.5-33.6% of the originally applied amount with no volatiles found. The main metabolite was the amide KKO 2254 which peaked at 73.8% at 3 DAT. In only the sandy soil the sulfonic acid metabolite WAK 6999 was found at a maximum of 19.7% at 60 DAT. Computer modelling of these results showed a DT_{50} for KKO 2254 of 32-142 d and DT_{90} of 106-473 d.

WAK 6999 was also degradable with highly variable DT_{50} and DT_{90} values of 16-79 d and 54-262 d, respectively. The main metabolite of this degradation was WAK 7747, which peaked at 18% in one soil, and a sulfonic acid amide accounting for a maximum of 23% in two other soils.

Biodegradation in anaerobic conditions was much slower with a calculated half-life of thiacloprid of >1 year (64-74% of the originally applied radioactivity remaining at 360 DAT of which 89% was found in the sediment). The major metabolite was KKO 2254 at a maximum of 14.2% at 360 DAT.

In two natural sediment-water systems incubated in the laboratory under mostly aerobic conditions, parent compound was quickly removed from the water column by degradation and/or partitioning to sediment with half-lives of 2.9 and 10.8 d. Half-lives for degradation from the whole sediment-water system were 20.3 and 12.1 d, respectively, with KKO 2254 as the only metabolite recovered in quantities >10% of the originally applied amount. Thiacloprid partitioned to the sediment with peaks after 3 d of about 10 and 51% of the dose. The portion of bound residues in the sediments increased with the progressing incubation period from about 0.2-0.4% at day 0 to about 17 and 32% at 100 DAT.

Mobility

The K_{OC} values for thiacloprid in six soils were 261-870 mL/g indicating medium to low mobility in soil. Desorption tests showed that 15-67% of the adsorbed amount was desorbed again. The K_{OC} values of KKO 2254 were 166-438 mL/g (medium mobility) while those for WAK 6999 were 11.9-28.2 mL/g (very high mobility) in five soils. For thiacloprid residues that had been aerobically aged for 60 d and then leached with water, the main component in the leachate was WAK 6999 accounting for 18.5% of the originally applied amount. The majority of the radioactivity (73%) remained in the top 5 cm of the soil columns.

In field lysimeters (sandy loam with grass cover) treated twice with thiacloprid at 365-400 g a.i./ha (two week interval) per year for two years and then leached with 794-923 mm/year, neither the parent compound nor its main metabolite KKO 2254 were detected in the leachates (348-418 L/year) at any time. WAK 6999 was the major residue measured at 6.9 µg/L in the leachate in the second year. After three years, no radioactive residues were found below 40 cm depth and the main portion (~49%) of residues was in the top 20 cm.

Computer modelling using PELMO software found a maximum annual concentration of WAK 6999 in the leachate of 2.2 µg/L after a loamy sand with grass cover was treated with 90 g a.i./ha twice at a two week interval; neither parent nor KKO 2254 were expected to exceed 0.001 µg/L in the leachate. However, similar modelling of two applications of 108 g a.i/ha to tomato plants showed no expected leaching of >0.001 µg/L below 1.45 m.

Volatilisation of about 12% from soil and 15% from tomato plant surfaces after 24 h was reported under field conditions. Although the vapour pressure for thiacloprid is low, the intensity of sunlight and higher temperature was given as the reason for the higher than expected volatilisation.

Field dissipation

After application of 288 g a.i./ha to bare soil in a field dissipation study, the DT_{50} and DT_{90} values for thiacloprid were 3.4-27 and 31-91 d, respectively, in the top 10 cm of soil. However, the longest DT_{90} value of 508 d indicated the persistence of total residues in one soil. No residues were detected in the 20-30 cm deep soil layer. In another study with the same application rate to bare soil, the DT_{50} and DT_{90} values were 10-16 and 35-53 d, respectively. The DT_{90} for total residues was 196-258 d and on only one occasion was any parent thiacloprid or metabolite found in the 20-30 cm deep soil layer.

Bioconcentration and Bioaccumulation

The relatively low log K_{OW} of 1.26 suggests a low potential for bioconcentration or bioaccumulation.

Environmental Toxicology

Birds

Thiacloprid was practically non-toxic to adult bobwhite quail in a single oral dose exposure with an LD50 of 2,716 (1,540, 248,553) mg a.i./kg bw and in a 5-d dietary test with the LC_{50} most likely between 5,000 and 10,000 mg a.i./kg food. However, an unverified (the company should submit this study) single oral dose LD50 of 49 mg a.i./kg bw would indicate high toxicity to Japanese quail. This result was not confirmed in 5-d dietary exposures in which the LC_{50} was approximately 2,500 mg a.i./kg food (slightly toxic). Thiacloprid was also practically non-toxic to mallard ducklings with a 5-d LC_{50} of >5,000 mg a.i./kg food.

Chronic reproduction studies found mallards most sensitive with NOEC and LOEC values of 48 and >140 mg a.i./kg food, respectively. Japanese quail were next sensitive (157 and 485 mg a.i./kg food, respectively) with bobwhite quail the least sensitive (466 and >466 mg a.i./kg food, respectively). However, if the Japanese quail experiment had been run for longer than only six weeks similar to the other two tests of 20-23 weeks, effects at lower concentrations may have been observed.

Fish

The 96-h LC_{50} for young rainbow trout was 30.5 (27.0, 34.1) mg a.i./L (slightly toxic) but symptoms of toxicity were observed in all fish at all concentrations indicating a 96-h EC_{50} of <5.0 mg a.i./L for sublethal effects. This was also true for bluegill sunfish with a 96-h LC_{50} most likely between 16.7 and 28.4 mg a.i./L but with a 96-h EC_{50} of <6.2 mg a.i./L, which is at best moderately toxic. In bluegill exposed to formulated thiacloprid (as opposed to the TGAC as before), the 96-h LC_{50} was 80.7 (35.5, 144) mg a.i./L but moderate toxicity was shown by the EC_{50} of <9.25 mg a.i./L. The metabolite KKO 2254 was at worst slightly toxic to both bluegill (96-h LC_{50} >78.6 mg/L) and rainbow trout (96-h LC_{50} of >79.4 mg/L).

Thiacloprid was only slightly toxic to rainbow trout early life stages as 97-d NOEC and LOEC values were 0.24 and 0.48 mg a.i./L, respectively, based on length and weight. The relatively high acute/chronic ratio (calculated as LC_{50}÷NOEC) of 127 suggests a different mode of action between the acute and chronic effects.

Aquatic invertebrates

Aquatic invertebrates, such as amphipods (*Hyalella azteca*, 96-h EC_{50} of 24.5 (20.2, 29.7) µg a.i./L) and midge larvae (*Chironomus riparius*, 28-d NOEC and LOEC of 1.0 and 1.8 µg a.i./L, respectively), were about 1000X more sensitive to thiacloprid than *Daphnia magna* in acute and chronic exposures. The 28-d EC_{50} of thiacloprid 480 SC to chironomids was 1.64 (1.43, 1.87) µg a.i./L based on emergence in another study. At least 28 d and concentrations reduced to 1.0 µg a.i./L were required before no adverse effects were seen on midge larvae introduced to containers initially treated at 2.8 µg a.i./L. Invertebrates were also sensitive in an outdoor pond mesocosm study where all affected species (Ephemeroptera, Nematocera, Ceratopogonidae and Chaoboridae) recovered by 98 DAT when exposed to an initial concentration of 1.0 µg a.i./L. The metabolite KKO 2254 was slightly toxic to amphipods with a 96-h EC_{50} of 16.1 (10.4, 28.1) mg/L and had no effect on midges at 0.1 mg/L after 28 d.

Aquatic plants

Thiacloprid was only slightly toxic to two freshwater green algae (120-h E_bC_{50} of 60.6 mg a.i./L (confidence limits not specified) to *Pseudokirchneriella subcapitata* and 72-h E_bC_{50} of 44.7 mg a.i./L to *Scenedesmus subspicatus*) while the metabolite KKO 2254 was practically non-toxic in 96-h exposures (E_bC_{50} and E_rC_{50} >100 mg/L to *P. subcapitata*). The metabolite WAK 6999 was similarly non-toxic to *S. subspicatus* with both E_bC_{50} and E_rC_{50} >100 mg/L. The 15-d NOEC and LOEC of parent thiacloprid to duckweed were 46.8 and 95.4 mg a.i./L, respectively, which is only very slightly toxic.

Terrestrial invertebrates

Thiacloprid was moderately to slightly toxic to earthworms in 14-d laboratory exposures with the most sensitive NOEC and LOEC values of 0.32 and 1.0 mg a.i./kg soil dw, respectively. An application rate of 62.5 g a.i./ha significantly reduced the number of juvenile worms after 56 d. Although no significant impact of two applications of 250 g a.i./ha 7 d apart was found on the earthworm fauna in a natural grassland, the subsampling methodology was inefficient and may have introduced additional variability and obscured any trend.

Thiacloprid was moderately to relatively non-toxic to honeybees in 48-h oral and contact laboratory experiments. When freshly treated alfalfa (200 g a.i./ha) was placed into the cages for 24-h, mortality was slight (<7%) but significantly different from controls. Actively foraging bees sprayed with 178-188 g a.i./ha were not adversely affected in one experiment but slightly affected with recovery by 7 DAT in another. The second experiment also showed no effect on brood development and an inconclusive effect on honey stores in the hive.

Carabid beetles were adversely affected at 100 g a.i./ha in a worst-case 14-d exposure laboratory study, but only slightly affected (5% mortality) when sprayed twice at 150 g a.i/ha (7 d interval) and confined in cages in an oat field for 20 d. A single spray of 187.5 g a.i./ha caused significant reductions in viable young rove beetles after 83 d when housed on quartz sand but had no effect when a natural loamy sand was used (presumably due to biodegradation although microbial activity was not assessed). Ladybird beetles showed similar sensitivity to applications as low as 0.96 g a.i./ha in laboratory conditions for 65 d and semi-field exposures showed 60 g a.i./ha could reduce populations by 80% after 69 d.

Spiders were adversely affected by 187.5 g a.i./ha after 14 d while the 30-d LC_{50} to green lacewings was 58.1 (29.7, 177.7) g a.i./ha when exposed to residues and fresh sprays on bean seedlings. Predatory mites showed statistically increased mortality and reduced reproductive capacity compared to controls when exposed to freshly dried residues at 60 g a.i./ha in the laboratory for 14 d. When apple orchards were treated twice at 181 g a.i./ha with an interval of 34 d, mite populations were temporarily reduced but recovered by four weeks after the second application. However, in two other field studies in apple orchards, two applications of 176-202 g a.i./ha caused no measurable adverse effects.

Under laboratory conditions, all parasitic wasps exposed to freshly dried residues at 69.7 g a.i/ha were moribund or dead after 48 h. Parasitisation efficiency was reduced by 39% when wasps were caged on outdoor wheat crops freshly treated at 60 g a.i./ha. Another study showed 35-49% reduction in emerged adult wasps when apple seedlings containing parasitised host eggs were sprayed with 0.25 g a.i./L and incubated in a greenhouse but showed no effect when seedlings were exposed to the weather in an orchard.

Soil nitrification and respiration

Soil respiration processes were not affected by 2.57 mg a.i./kg soil dw whereas this concentration caused an adverse but tolerable effect on nitrogen turnover at 28 DAT. Thiacloprid has low bactericidal activity as shown by the 30-minute EC_{50} of 6,330 mg a.i./L in an activated sludge.

Environmental Hazard

Estimated Environmental Concentrations

For the use pattern of controlling aphids on camellias, maybush and roses, the label states to apply 10 mL EUP/100 L water (0.048 g a.i./L water) as a thorough cover spray at first sign of insect infestation. Given a usual spray volume of 1,000 L/ha, a representative application rate would be 48 g a.i./ha. The company suggested the most likely use scenarios would be spot treatments of ornamental flowers, shrubs and trees showing aphid infestations.

Use of thiacloprid in glasshouses is not expected to result in any significant soil or water contamination.

Hazard to Terrestrial and Aquatic Organisms

Despite the toxicity of thiacloprid to various sensitive organisms (eg. aquatic invertebrates, ladybird beetles, spiders, green lacewings and parasitic wasps), their exposure to thiacloprid is expected to be severely limited from the use pattern of Calypso 480 SC Insecticide on camellias, maybush and roses and relatively low application rate of 48 g a.i./ha. As little or no contamination is expected of nontarget soil and water, there is also no significant expected hazard to terrestrial and aquatic organisms.

Desirable Vegetation

As thiacloprid is proposed for use on ornamental plants, has a low toxicity to freshwater green algae and duckweed and is not expected to significantly contaminate nontarget areas, the hazard of Calypso 480 SC Insecticide use to nontarget vegetation is not expected to be high.

Conclusions and Recommendations

Bayer Australia Limited has applied for registration of a new product, Calypso 480 SC Insecticide, which contains the new active constituent thiacloprid at 480 g a.i./L. The product will be marketed as suspension concentrate for the control of aphids on ornamental plants at a maximum application rate of 10 mL EUP/100 L water (0.048 g a.i./L water). Thiacloprid is a Group 4A insecticide for resistance management and the label states not to apply this product in consecutive sprays by alternating with another registered aphicide from at least one other group. There is no maximum number of sprays given for this use pattern. For confined environments such as glasshouses, annuals are not to be sprayed more than once for any one crop while perennials should alternate with another aphicide with a maximum of three sprays in any 12 month period.

The expected limited use pattern of Calypso 480 SC Insecticide on ornamental plants will preclude significant contamination of soil and water resulting in low exposure to nontarget animals and plants. Therefore the hazard from this use pattern is expected to be low.

There are several issues that will need to be addressed if this chemical is to be extended to other uses. However, to complete our assessment for this use on camellias, maybush and roses, the company has commented on the report, and agreed to the recommended label statements.

EFFICACY AND SAFETY ASSESSMENT

Proposed use pattern

The applicant proposes that thiacloprid be used as a foliar spray to control aphids on commercially grown camellias, maybush and roses in all States. Detail of the use pattern can be seen in the Directions For Use tables in the following section (Labelling Requirements).

Calypso 480 SC Insecticide will be available in 1 L, 5 L, 10 L and 20 L plastic bottles or drums.

The proposed rate of use is 10 mL/100L of water.

On the basis that the product is not intended for use on food crops at this time, Withholding Periods will not be required.

Evaluation of efficacy data

Data presented by Bayer Australia Limited support claims that when used commercially grown ornamental crops, Calypso 480 SC Insecticide will adequately control aphids.

The data were adequate (with appropriate discussion) to demonstrate efficacy of the product when used according to the proposed label instructions.

Phytotoxicity

Phytotoxicity was not observed in efficacy trials conducted on roses, camellias or maybush (*Spiraea* sp.).

LABELLING REQUIREMENTS

Draft label

POISON

KEEP OUT OF REACH OF CHILDREN

READ SAFETY DIRECTIONS BEFORE OPENING OR USING

Calypso® 480 SC Insecticide

Active Constituent: 480 g/L THIACLOPRID

GROUP 4A INSECTICIDE

For the control of aphids on camellias, maybush and roses

1 Litre
5 Litres
10 Litres
20 Litres

Directions for use

Crop	Pest	Rate	Critical Comments
Camellias Maybush Roses	Aphids	10 mL/100 L	Apply as a thorough cover spray at first sign of insect infestation.

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

General Instructions

Mixing

Prior to pouring, shake container vigorously, then add the required quantity of Calypso 480 SC to water in the spray vat while stirring or with agitators in motion.

Insecticide Resistance Warning

GROUP	4A	INSECTICIDE

For insecticide resistance management, Calypso is a Group 4A insecticide. Some naturally occurring insect biotypes resistant to Calypso and other Group 4A insecticides may exist through normal genetic variability in any insect population. The resistant individuals can eventually dominate the insect population if Calypso and other Group 4A insecticides are used repeatedly. The effectiveness of Calypso on resistant individuals could be significantly reduced. Since occurrence of resistant individuals is difficult to detect prior to use, Bayer Australia Limited accepts no liability for any losses that may result from the failure of Calypso to control resistant insects. Calypso may be subject to specific resistance management strategies. For further information contact your local supplier, Bayer representative or local agricultural department agronomist.

Insecticide Resistance Management Strategy for aphids: Do not apply Calypso in consecutive sprays. Alternate with another registered aphicide from at least one other group, eg Nitofol (Group 1A).
Confined environments such as glasshouses: Annuals: Do not apply more than one spray of Calypso to any one crop. Perennials: Alternate with a registered aphicide from at least one other group. Use a maximum of three sprays in any 12 month period.

Re-entry

Do not allow entry into treated areas until the spray has dried. When prior entry is necessary, wear 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 Livestock

DO NOT graze any treated area, or cut for stock food.
DO NOT feed produce harvested from treated area to animals, including poultry.

Protection of Wildlife, Fish, Crustaceans and Environment

This product is very highly toxic to aquatic invertebrates. DO NOT contaminate streams, rivers or waterways with the chemical or used containers.

Storage and Disposal
(1 litre label)
Store in the closed, original container in a cool, well ventilated area. Do not store for prolonged periods in direct sunlight. Rinse container before disposal. Add rinsings to spray tank. Do not dispose of undiluted chemicals on site. Dispose of at a local authority landfill. If no landfill is available, bury the container below 500 mm in a disposal pit specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots. Empty containers and product should not be burnt.
(other pack sizes)
Store in the closed, original container in a cool, well ventilated area. Do not store for prolonged periods in direct sunlight. Triple or preferably pressure rinse container 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 bury empty containers in a local authority landfill. If no landfill is available, bury the containers below 500 mm in a disposal pit specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots. Empty containers and product should not be burnt.

Safety Directions
Poisonous if swallowed. When opening the container and preparing spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing), elbow-length PVC or nitrile gloves and a disposable fume mask. When using the prepared spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing), elbow-length PVC or nitrile gloves. Wash hands after use. After each day's use wash gloves and contaminated clothing.

First Aid
If poisoning occurs contact a doctor or Poisons Information Centre (131126).

For further information refer to the Material Safety Data Sheet for the product.

Liability
This product must be used strictly as directed. Bayer Australia Limited may not be liable for loss or damage arising from failure to follow directions for use.

Calypso® is a registered trademark of Bayer AG MN
NRA Approval Number: (not yet determined)

Bayer Australia Limited emergency contact
1800 033 111
Australia wide, 24 hours

Bayer Australia Limited
875 Pacific Highway
Pymble NSW 2073
Telephone (02) 9391 6000
www.bayercrop.com.au

GLOSSARY

Active constituent	The substance that is primarily responsible for the effect produced by a chemical product.
Acute	Having rapid onset and being of short duration.
Carcinogenicity	The ability to cause cancer.
Chronic	Of long duration.
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 octanol water partitioning 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.

References

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