Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Consultation Document G96-01

Tebufenozide

The active ingredient tebufenozide and formulated product Mimic® 240 LV Forestry Insecticide, for control of larval Lepidoptera, are proposed for registration.

This document provides a summary of data reviewed and the rationales for the proposed regulatory decisions concerning Mimic® 240 LV Forestry Insecticide and the active ingredient tebufenozide.

This document has been prepared in keeping with the ongoing efforts of the Pest Management Regulatory Agency (PMRA) to regulate pest control products in an open and transparent manner.

The PMRA will accept written comments on this proposal up to February 15, 1996 and expects to make a final regulatory decision by March 1, 1996. Please forward all comments to:

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Introduction

Tebufenozide, a new active ingredient, is an Insect Growth Regulator (IGR) in the chemical family benzoic acid hydrazide. An aqueous flowable formulation containing 240 g/L of tebufenozide, Mimic® 240 LV Forestry Insecticide, for use in forests and woodlands, is proposed for registration. Tebufenozide has a novel mode of action in that it mimics the action of the insect molting hormone, ecdysone, in larval Lepidoptera (caterpillars), by initiating an unsuccessful (lethal) molt in the larvae. Larvae stop feeding within hours of ingestion of a toxic dose; death occurs in three to seven days.

Chemistry Assessment

Specifications, methods of analysis, microcontaminant analysis, and quality control data of the pilot plant production were reviewed and were found acceptable. Once full-scale production of tebufenozide is initiated, supplementary chemistry data will be submitted and reviewed.

Health Assessment

Toxicology: In the rat, orally administered (by gavage) single doses (3 or 250 mg/kg bw) of ^{14}C-tebufenozide (labelled in either the t-butyl, A- or B-ring group) were rapidly absorbed and excreted. The excretion profiles were similar, regardless of the position of the ^{14}C-label, dose level, sex or whether the rats were pre-treated with 30 ppm dietary non-labelled tebufenozide for two weeks. A mean total of 87-104% of the administered dose was excreted within 48 h of dosing, primarily via the faeces which accounted for >90% of the ^{14}C-label excreted. Only minor amounts (<1-8% of dose) were excreted in urine and trace amounts (<0.1-0.4% of dose) were eliminated in expired air (as $^{14}CO_2$ and organic volatiles) from rats dosed with [^{14}C-t-butyl]-tebufenozide. At 3 mg/kg bw, systemic absorption was calculated to be 35-39% of the total dose; 30-34% was excreted in the bile and ~5% in the urine. At 250 mg/kg bw, only about 4% of the administered dose was absorbed and metabolized. Tissue retention of ^{14}C-radioactivity was very low; <1 and #0.01% of the dose were retained at 3 and 250 mg/kg bw, respectively, at 7 days post-dose. The highest concentrations were found in the liver, fat and kidneys. The tissue ^{14}C-distribution profiles were consistent with the pharmacokinetic data and indicated that the ^{14}C-radioactivity associated with the A-/B-ring label was cleared more rapidly from the tissues than that associated with the t-butyl label.

^{14}C-tebufenozide was extensively metabolized in rats. The majority of ^{14}C-radioactivity excreted in faeces was in the form of unabsorbed (parent) tebufenozide, accounting for ~60 and >90% of the given dose at 3 and 250 mg/kg bw/day, respectively. No unchanged parent compound was detected in the urine. There were no significant qualitative differences in the metabolite profiles between the different ^{14}C-labelled versions of tebufenozide, the high and low doses, sexes, or rats with or without pre-treatment with dietary tebufenozide (30 ppm) for two weeks. In general, the whole-molecule metabolites identified (total of 13-15) in the urine, faeces and bile were identical. The major route of metabolism of tebufenozide appeared to be the oxidation of benzylic carbons (A-/B-ring) of the molecule to provide a number of oxidized metabolites with various combinations of oxidation state at the three carbon centres oxidized. One exception was RH-2703 which was produced by oxidation of the non-benzylic carbon, the terminal C on the A-ring ethyl group.

In acute studies, tebufenozide technical was of low oral toxicity (LD_{50} >5,000 mg/kg bw) to rats and mice and low dermal (LD_{50} >5,000 mg/kg bw) and inhalation toxicity (LC_{50} 4.3 mg/L) to rats. Tebufenozide technical was found to be non-irritating to the skin and minimally irritating to the eyes of male New Zealand White (NZW) rabbits, and it was not a skin sensitizer in the guinea pig.

In acute studies, tebufenozide 240 LV formulation (Mimic® 240 LV containing 24% a.i.) was of low toxicity to rats when given via the oral, dermal or inhalation route. The oral LD_{50} was >5,000 mg/kg bw, the dermal LD_{50} was >2,000 mg/kg bw and the inhalation LC_{50} was >1.33 mg/L (equivalent to

>0.32 mg a.i./L). Tebufenozide 240 LV formulation was found to be mildly irritating to the skin and to the eyes of NZW rabbits, and it was not a skin sensitizer in the guinea pig.

In acute studies, tebufenozide metabolites (RH-111788, RH-96595, RH-120970, RH-089886 or RH-112651) were of low toxicity to mice when given acutely via the oral route. The oral LD_{50} of these tebufenozide metabolites in mice was >5,000 mg/kg bw.

Repeated short-term oral administration of tebufenozide technical to mice (2-week, 13-week), rats (2-week, 4-week and 13-week) and dogs (2-week, 6-week, 13-week and 52-week) resulted primarily in haematotoxic effects - mild regenerative haemolytic anaemia and compensatory responses from the haematopoietic tissues. Based on haematotoxicity, the No Observable Adverse Effect Level (NOAEL)/No Observable Effect Level (NOEL) was 35.3 mg/kg bw/day for mice (13-week), 13.1 mg/kg bw/day for rats (13-week) and 1.9 mg/kg bw/day for dogs (13-week and 52-week combined). The dog appeared to be the most sensitive species for short-term toxicity.

Repeated short-term (4-week) dermal application of tebufenozide technical to rats resulted in no evidence of treatment-related systemic toxicity at dose levels up to 1,000 mg/kg bw/day. The NOEL was >1,000 mg/kg bw/day for rats.

In long-term rodent dietary studies, the NOEL for chronic systemic toxicity was 7.8 mg/kg bw/day for mice (based on a slightly reduced survival rate and mild regenerative haemolytic anaemia at higher dose levels) and 4.8 mg/kg bw/day for rats (based on decreased body weight and food consumption and mild regenerative haemolytic anaemia at higher dose levels). Tebufenozide technical was not oncogenic in the mouse or the rat under the conditions of the studies.

Tebufenozide technical (and its metabolites) had been adequately tested for mutagenicity and/or genotoxicity in a standard series of in vitro and in vivo assays and the results were negative. It was concluded that tebufenozide technical (and its metabolites) did not demonstrate any genotoxic and/or mutagenic potential under the conditions tested.

In a rat reproduction study (two generation, one litter per generation), the NOEL for parental toxicity was 0.7 mg/kg bw/day based on increased severity of pigment deposition in the spleen (F_0 and F_1 females) at the next higher dose of 9.7 mg/kg bw/day. At the highest dose of 142.2 mg/kg bw/day, additional signs of parental toxicity were reduced mean body weight and food consumption (F_0 and F_1 males only) during pre-mating, and increased splenic extramedullary haematopoiesis (both sexes and generations). Signs of reproductive toxicity were evident at 142.2 mg/kg bw/day: decreased mean number of implantation sites (F_1 females), prolonged gestation period (F_1 females), a slightly higher number of pregnant females with total resorption (both generations) and a small increase in the number of dams (F_1 generation) dying during delivery. The NOEL for reproductive toxicity was 9.7 mg/kg bw/day.

In two rat teratogenicity studies, the NOAEL for maternal toxicity was 1,000 mg/kg bw/day, the highest dose level tested. At 1,000 mg/kg bw/day, there was a slight reduction in mean body weight gain and food consumption at initiation of dosing; the decreases were transient and reversible, and therefore were not considered to be toxicologically significant. There were no treatment-related reproductive or teratogenic effects at any dose level. The NOEL for embryo-fetotoxicity and teratogenicity in the rat was 1,000 mg/kg bw/day, the highest dose level tested in the studies. In two rabbit teratogenicity studies, there were no treatment-related mortalities or clinical signs of maternal toxicity, no adverse effects on reproductive parameters and no evidence of teratogenic potential at any dose level. The NOEL for maternal and embryo-fetal toxicity and teratogenicity in the rabbit was 1,000 mg/kg bw/day, the highest dose level tested in the studies.

In summary, the primary target site of tebufenozide toxicity was the peripheral haematopoietic system and the main toxicological end-point, consistent across all species tested, was mild regenerative

haemolytic anaemia with compensatory responses from the haematopoietic tissues. Technical tebufenozide was of low acute toxicity to the mouse via the oral route and to the rat via the oral, dermal or inhalation route. Pharmacokinetic and metabolism studies in the rat revealed that the compound was only partially absorbed, rapidly excreted and that there were no signs of bioaccumulation in any tissue/organ examined. Tebufenozide was not oncogenic in the mouse or in the rat, and it did not demonstrate any mutagenic/genotoxic potential in vitro or in vivo. There was no evidence of any teratogenic potential in the rat or the rabbit and no effect on reproduction except at a high dose level that elicited parental toxicity.

Drinking Water Exposure: No monitoring data were found on residues of tebufenozide in surface, ground or drinking water. Based on the environmental data presented, tebufenozide is not expected to pose a significant health risk through drinking water.

Occupational Exposure: Based on a Health Canada assessment, selected data from surrogate exposure studies were combined with estimates from the Pesticide Handlers Exposure Database (PHED) to yield exposure estimates for airblast and aerial application. The replicates derived from the PHED assessment are considered representative of the proposed use of Mimic® 240 LV. Aerial application exposure estimates for the mixer/loader and applicator (pilot) were 0.017 and 0.015 mg/kg bw/day, respectively. Exposure estimates were based on workers wearing gloves (except pilot), long pants, and long-sleeved shirts.

Risk Assessment: An acceptable daily intake (ADI) of 0.019 mg tebufenozide/kg bw has been estimated based on the overall NOEL of 1.9 mg/kg bw/day (50 ppm) for haematotoxicity in the 13- and 52-week feeding studies in the dog using a 100-fold safety factor.

An objective concentration for tebufenozide in drinking water, using the estimated ADI of 0.019 mg/kg bw, can be calculated as approximately 0.09 mg/L, assuming an adult consumer with a 10% allocation of drinking water.

The use pattern of tebufenozide indicates a short-term occupational exposure of several days per year. Dermal exposure is regarded as the major route of exposure for airblast and aerial application. Given the likely route and duration of exposure, the 4-week rat dermal toxicity study with a NOEL of 1,000 mg/kg bw/day was considered most appropriate for occupational risk assessment purposes. The risk assessment indicated that, provided Mimic® 240 LV is used according to label directions, the margin of safety (MOS) for occupational exposure would be acceptable.

Environmental Assessment

In laboratory experiments, tebufenozide was relatively non-volatile from moist soil and water surfaces and did not bioaccumulate in fish and mammals tested. Based on laboratory and field studies, the likelihood of deleterious effects on beneficial non-target arthropods, following the use of tebufenozide, is predicted to be minimal. Tebufenozide is unlikely to pose a risk to soil microorganisms, earthworms, birds, wild mammals, fish, amphibians, aquatic plants and most aquatic invertebrates including crayfish, copepods, rotifers, insects and the mysid shrimp.

Tebufenozide was shown to have the potential for residue carryover into the next season in forest soil, forest litter and conifer needles, following application at the proposed maximum label rates. Tebufenozide would be classified as moderately persistent in forest pond water in Ontario and was shown to partition into and accumulate in bottom sediments in a forest pond, and to persist at 393 days after treatment. The potential for tebufenozide residues to continue to accumulate in aquatic sediments following annual applications is unknown. Tebufenozide could present a risk to some aquatic invertebrates, i.e., cladocerans and molluscs, following application at the proposed maximum label rates.

To address the above concerns, and identified data gaps, the applicant has agreed to provide data on the effects of tebufenozide on freshwater and terrestrial species of molluscs, terrestrial plants and honey bee larvae, and additional large-scale forestry dissipation data. Research to determine the potential for residue carryover in foliage to provide a second year of control of forest pests must also be conducted. Additional studies on the effects of tebufenozide on birds, amphibians and non-target terrestrial insects will be submitted and reviewed on a supplementary basis. In order to establish more scientifically-based buffer zones, empirical drift data from aerial application should be generated.

Based on an assessment of the environmental safety of tebufenozide, a temporary registration of the forestry use is acceptable while supplementary data are being generated and with the required "Environmental Precautions" added to the Mimic® 240 LV label (see Appendix 1).

Value Assessment

Mimic® 240 LV Forestry Insecticide is an effective insecticide that would be an asset in forest pest management programs. Some further work is required to optimize application rates and volumes for operational programs. Therefore, a temporary registration is recommended for those uses meeting a satisfactory assessment. Efficacy data were reviewed and the information established that the product has merit and value for the following uses with appropriate labelling:

- Control of eastern spruce budworm with a maximum application of 70 g a.i./ha applied when the insect is between the third and sixth instar. A second application of 70 g a.i./ha may be required to ensure adequate coverage.
- Control of jack pine budworm with a maximum application of 70 g a.i./ha applied when the insect is between the third and fifth instar. A second application of 70 g a.i./ha may be required to ensure adequate coverage.

Acceptable claims for control are: corrected insect population reduction was greater than or equal to 70%; residual populations did not exceed 2.5 larvae per branch; and defoliation of the treated host tree should not exceed 25% or should be less than 50% of that defoliation caused by an untreated population of similar size.

Proposed Regulatory Decision

The PMRA is recommending a "Restricted" class temporary registration for Mimic® 240 LV Forestry Insecticide. This will allow further environmental and efficacy data to be generated when the product is used under operational conditions. The use pattern will be for use in forests and woodlands to control spruce budworm and jack pine budworm. (see label in Appendix 1). Although maximum rates for both pests have been determined, further work is required to optimize application rates and volumes for operational programs.

Mitigative labelling (Environmental Precautions) is required to provide acceptable margins of safety for the identified environmental risks to aquatic invertebrates and includes the establishment of buffer zones to mitigate possible aquatic impacts. Suggested buffer zones are included in Appendix 2.

Label of Mimic® 240 LV Forestry Insecticide

MIMIC® 240 LV

FORESTRY INSECTICIDE

RESTRICTED

FOR CONTROL OF EASTERN SPRUCE BUDWORM AND JACK PINE BUDWORM
IN FORESTS AND WOODLANDS

READ LABEL BEFORE USING

CAUTION
EYE AND SKIN IRRITANT

GUARANTEE- Tebufenozide..... 240 g/L

REGISTRATION NO. PEST CONTROL PRODUCTS ACT

KEEP OUT OF REACH OF CHILDREN

NET CONTENTS
10 L

ROHM AND HAAS CANADA INC.
2 MANSE ROAD
WEST HILL, ONTARIO
M1E 3T9
1-800-268-4201

Mimic® 240 LV forestry insecticide has a novel mode to action in that it mimics the action of the insect molting hormone, ecdysone, in larval Lepidoptera (caterpillars). Larvae stop feeding within hours of ingestion of a toxic dose of Mimic® 240 LV and soon thereafter begin to undergo an unsuccessful (lethal) molt. Actual mean time to mortality is somewhat dependent on the physiology of the target species and on the local environmental conditions, but is generally three to seven days.

Mimic® 240 LV is effective against larval Lepidoptera.

Mimic® and the flask symbol are trademarks of Rohm and Haas Company, Philadelphia, Pa., registered in Canada under which Rohm and Haas Canada Inc. has been registered as user.

NOTICE TO USER: This control product is to be used only in accordance with the directions on this label. It is an offence under the *Pest Control Products Act* to use a control product under unsafe conditions.

NATURE OF RESTRICTION: This product is to be used only in the manner authorized; contact local pesticide regulatory authorities about use permits that may be required.

RESTRICTED USES

Forestry Use: Ground/Aerial Application for sites greater than 500 ha.
Woodlands Use: Aerial Application for sites 500 ha or less.

DIRECTIONS FOR USE:

Apply Mimic® 240 LV forestry insecticide for the control of eastern spruce budworm and jack pine budworm in conifer forests and woodlots. This product may be applied by air or by ground equipment.

Eastern Spruce Budworm

> Apply when the insect larvae are between the third and sixth instar (at bud flush for spruce and/or balsam fir). A second application may be required to ensure adequate coverage.

Jack Pine Budworm

> Apply when the insect larvae are in the third to fifth instar (at this time the shoots or candles have elongated and the needles have started to separate). A second application may be required to ensure adequate coverage.

The recommended application rate is 290 millilitres of Mimic® 240 LV per hectare. For aerial application, use a spray volume with enough water as the carrier to provide uniform coverage. Uniform coverage of the foliage is essential to provide maximum protection from defoliation.

Before using this product, consult your local Canadian Forestry Service office or forestry authority and Rohm and Haas Canada Inc. for information on timing, method of application, and concentration of spray mixtures.

PRECAUTIONS:

KEEP OUT OF REACH OF CHILDREN

CAUTION, MAY IRRITATE EYES AND SKIN. WEAR PROTECTIVE CLOTHING (LONG TROUSERS, LONG-SLEEVED SHIRTS), IMPERVIOUS GLOVES AND SPLASH GOGGLES DURING ALL MIXING, LOADING AND APPLICATION. WEAR A CARTRIDGE RESPIRATOR DURING APPLICATION. PROTECTIVE CLOTHING SHOULD BE WASHED BEFORE RE-USE.

ENVIRONMENTAL PRECAUTIONS:

DO NOT CONTAMINATE WATER BY CLEANING OF EQUIPMENT OR DISPOSAL OF WASTES. DO NOT APPLY WHEN WEATHER CONDITIONS FAVOUR DRIFT OR RUN-OFF FROM AREAS TREATED.

DO NOT APPLY DIRECTLY TO AQUATIC SYSTEMS. THIS PRODUCT IS TOXIC TO CERTAIN AQUATIC INVERTEBRATES. TO MITIGATE IMPACT ON THESE ORGANISMS, PROVINCIAL REGULATORY AUTHORITIES SHOULD BE CONSULTED TO ESTABLISH APPROPRIATE BUFFER ZONES BETWEEN TREATMENT BLOCKS AND AQUATIC SYSTEMS.

AQUATIC SYSTEMS INCLUDE ALL RIVERS DESIGNATED AS DOUBLE-SIDED AND ALL LENTIC (STANDING) WATER BODIES, INCLUDING IMPOUNDMENTS, BEAVER PONDS AND BOG PONDS THAT APPEAR ON THE MOST RECENT 1:50,000 TOPOGRAPHIC MAP OF THE AREA TO BE TREATED, OR AS IDENTIFIED BY MORE UP-TO-DATE DATA (E.G., GIS SYSTEMS) IN THE PARTICULAR JURISDICTION AND APPROVED BY PROVINCIAL REGULATORY AUTHORITIES. LENTIC (STANDING) WATER BODIES THAT DO NOT APPEAR ON A 1:50,000 TOPOGRAPHIC MAP OF THE TREATMENT AREA, OR A MORE UP-TO-DATE DATA SYSTEM, BUT ARE VISIBLE FROM THE AIR DURING PRETREATMENT RECONNAISSANCE FLIGHTS SHOULD ALSO BE INCLUDED, WHERE POSSIBLE.

FIRST AID:

IF IN EYES:	FLUSH EYES WITH LARGE AMOUNTS OF WATER FOR AT LEAST 15 MINUTES. CONSULT A PHYSICIAN IF IRRITATION PERSISTS.
IF INHALED:	MOVE SUBJECT TO FRESH AIR.
IF ON SKIN:	WASH AFFECTED SKIN AREAS WITH SOAP AND WATER AND CONSULT PHYSICIAN IF IRRITATION OCCURS. REMOVE CONTAMINATED CLOTHING PROMPTLY AND WASH BEFORE RE-USE.
IF SWALLOWED:	DILUTE BY GIVING TWO GLASSES OF WATER TO DRINK AND CALL A PHYSICIAN OR POISON CONTROL CENTRE. NEVER GIVE ANYTHING BY MOUTH TO AN UNCONSCIOUS PERSON.

TOXICOLOGICAL INFORMATION:

IF SWALLOWED EMESIS IS RECOMMENDED.

STORAGE:

STORE IN A COOL, DRY AREA. DO NOT CONTAMINATE WATER, FOOD OR FEED BY STORAGE OR DISPOSAL. AVOID CONTAMINATION OF STREAMS, LAKES AND PONDS. PESTICIDE WASTES ARE TOXIC. IMPROPER DISPOSAL OF EXCESS PESTICIDE, SPRAY MIXTURE OR RINSATE IS PROHIBITED.

PESTICIDE DISPOSAL:

1. RINSE THE EMPTIED CONTAINER THOROUGHLY AND ADD THE RINSINGS TO SPRAY MIXTURE IN THE TANK.
2. FOLLOW PROVINCIAL INSTRUCTIONS FOR ANY REQUIRED ADDITIONAL CLEANING OF CONTAINER PRIOR TO ITS DISPOSAL.
3. MAKE EMPTY CONTAINER UNSUITABLE FOR FURTHER USE.
4. DISPOSE OF CONTAINER IN ACCORDANCE WITH PROVINCIAL REQUIREMENTS.
5. FOR INFORMATION ON THE DISPOSAL OF UNUSED, UNWANTED PRODUCT AND THE CLEANUP OF SPILLS CONTACT THE PROVINCIAL REGULATORY AGENCY OR THE MANUFACTURER.

SPILL AND LEAK PROCEDURES:

DIKE AND CONTAIN SPILL WITH INERT MATERIAL (E.G. SAND, EARTH). TRANSFER LIQUID TO CONTAINERS FOR RECOVERY OR DISPOSAL AND SOIL DIKING MATERIAL TO SEPARATE CONTAINERS FOR DISPOSAL. KEEP SPILLS AND RUNOFF OUT OF MUNICIPAL SEWERS AND OPEN BODIES OF WATER. DO NOT TAKE CONTAMINATED CLOTHING HOME TO BE LAUNDERED.

LIMITATION OF WARRANTY:

SELLER'S GUARANTEE SHALL BE LIMITED TO THE TERMS SET OUT ON THE LABEL AND, SUBJECT THERETO, THE BUYER ASSUMES THE RISK TO PERSONS OR PROPERTY ARISING FROM THE USE OR HANDLING OF THIS PRODUCT AND ACCEPTS THE PRODUCT ON THAT CONDITION.

Suggested buffer zones (in metres) for Mimic® 240 LV when applied aerially to forests using a C188 Agtruck with AU4000 Micronairs

The following table provides some appropriate buffer zones for Mimic® 240 LV application by air. Buffer zones assume the use of a C188 Agtruck with AU4000 Micronairs and vary with windspeed, aircraft height and block width. They were developed by Dr. Robert Mickle of the Atmospheric Environment Service of Environment Canada at Downsview, Ontario, based on the Interdepartmental Task Force on Pesticide Drift (ITFPD) data base. As more data are generated, the buffer zone numbers can be further defined and modified.

	block width (metres)					
	100	250	500	1,000	1,500	2,000
windspeed 6.1 kph aircraft height 31.6 m	buffer zone width (metres)					
one application @ 70 g a.i./ha	0	10	15	25	40	40
two successive applications @ 70 g a.i./ha	50	60	80	110	130	160
windspeed 12.6 kph aircraft height 36.7 m	buffer zone width (metres)					
one application @ 70 g a.i./ha	5	40	80	130	140	150
two successive applications @ 70 g a.i./ha	125	175	220	280	320	350