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EEB In : 12/01/94
EEB Out :

To: Marion Johnson
Product Manager 10
Registration Division (7505C)

From: Anthony F. Maciorowski, Chief
Ecological Effects Branch/EFED (7507C)

Attached, please find the EEB review of...

Reg./File # : 264-LLN
Chemical Name : Fipronil
Type Product : Insecticide
Product Name : Chipco Gauntlet
Company Name : Rhone Poulenc
Purpose : Data review - new chemical

Action Code : 001 Date Due : 01/15/95
Reviewer : A. Bryceland

EEB Guideline/MRID Summary Table: The review in this package contains an evaluation of the following:

GDLN NO	MRID NO	CAT	GDLN NO	MRID NO	CAT	GDLN NO	MRID NO	CAT
71-1(A)			72-2(A)	43291719	Y	72-7(A)		
71-1(B)			72-2(B)			72-7(B)		
71-2(A)			72-3(A)	43291702	Y	122-1(A)		
71-2(B)			72-3(B)	43291701	Y	122-1(B)		
/1-3			72-3(C)			122-2		
71-4(A)			72-3(D)			123-1(A)		
71-4(B)			72-3(E)			123-1(B)		
71-5(A)			72-3(F)			123-2		
71-5(B)			72-4(A)			124-1		
72-1(A)			72-4(B)			124-2		
72-1(B)			72-5			141-1		
72-1(C)	43291718	Y	72-6			141-2		
72-1(D)						141-5		

Y=Acceptable (Study satisfied Guideline)/Concur
P=Partial (Study partially fulfilled Guideline but additional information is needed
S=Supplemental (Study provided useful information but Guideline was not satisfied)
N=Unacceptable (Study was rejected)/Nonconcur

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

To: Marion Johnson, PM10
Registration Division (7505C)

From: Anthony F. Maciorowski, Chief
Ecological Effects Branch
Environmental Fate and Effects Division (7507C)

Subject: Rebuttal Letter for Fipronil: Data Evaluation Records for the registration of Fipronil insecticide. (Fipronil Technical: sulfoxide 5-amino-1-[2,6-dichloro-4-trifluoromethly)phenyl]-4-[(1R,S)-(trifluoromethyl)sulyfinyl]-1H-pyrazole-3-carbonitrile

Ecological Effects Branch (EEB) has reviewed the data submitted by Rhone-Poulenc Ag Company in rebuttal letter regarding the data evaluation reviews (DER) for Fipronil insecticide.

1) M&B 46030: Acute Oral Toxicity (LD50) to the Red-Legged Partridge (MRID 429186-14), M&B 46030: Acute Oral Toxicity to the Pigeon (MRID 429186-13), M&B 46030 Technical: 14-Day Oral Acute Oral LD50 Study in House Sparrows (MRID 429186-18), and M&B 46030: Acute Oral (LD50) to the Pheasant (MRID 429186-15).

Registrant's Rebuttal: (excerpted from rebuttal letter of 6/12/94) These studies were all classified as supplemental because a non-standard test species was used. These non-standard species were tested to provide additional information on the toxicity of Fipronil. While there was no statement in the DER to require the studies to be repeated, Rhone-Poulenc would like to clarify that no new study will be performed even though these studies were classified as supplemental. The mallard duck and bobwhite quail, the species required to fulfill the guideline, have been tested.

Agency's Response: The non-standard test species studies (MRID#'s 429186-13, 14, 15, 18) do not have to be repeated.

2) EXP 60655A: 21-day Acute Oral LD50 Study in Bobwhite Quail (MRID 429186-19).

Registrant's Rebuttal: (excerpted from rebuttal letter of 6/12/94) This study was classified as supplemental because " the SEP states that routine tests must be conducted with the technical grade of the active ingredient". The technical grade material was tested (MRID 429186-17) and the study was reviewed and accepted as core prior to the review of this study with the formulated material. The guideline triggers for avian acute studies state that the formulated or typical end-use product (TEP) must be tested if the toxicity of the technical material is ≤50 mg/kg. Given that the LD50 of the technical material in bobwhite quail is 11.3 mg/kg, testing with the TEP was required. While there is no statement in the DER requiring the study to be repeated, Rhone-Poulenc requests that this study be upgraded to core since it is a required study and the only rejection factor was that the study was not performed with the technical grade material.

Agency's Response: This study (MRID 429186-19) will be upgraded to core based on 40 CFR 152.170 p.36.

3) M&B 46030 Technical: Toxicity and Reproduction Study in Bobwhite Quail (MRID 429186-22).

Registrant's Rebuttal: (excerpted from rebuttal letter of 6/12/94) This study was rejected because no treatment related effects were observed at the highest dose tested. According to the conclusion in the DER, this study must be repeated so that the test concentrations include the estimated environmental concentration (EEC=31 ppm) for Fipronil 1.5G. Further, that the range selected must generate an LOEC as well as NOEC without causing any mortality in the parent generation.

In the bobwhite quail reproduction study, doses were chosen based on preliminary trials and the existing bobwhite sub-acute dietary NOEC was 19.5 ppm, based on mortality, lethargy, diarrhea, and anorexia in the next higher dose (39 ppm) tested. Given that the NOEC in the sub-acute dietary was determined to be 19.5 ppm ai, only 9.5 ppm higher than the highest dose in the current reproduction study, it is unlikely that a new study could be performed with a higher dose that would result in a significantly different NOEC. Rhone-Poulenc believes that repeating this study to determine a LOEC, which is not usually in a risk assessment, does not justify the use of additional animals and resources.

In addition, Rhone-Poulenc disagrees with the statement that the EEC=31ppm. Fipronil 1.5G is a granular product proposed for application by in-furrow or t-band techniques in corn and Fipronil 0.5G is a granular product proposed for use by slit seeding application to turf. The Kenaga nomogram referenced in the DER is for determining residues on short grass or any

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other plant type utilized as food for avian species. The risk assessment performed with Fipronil, based on LD50s/sq.ft., shows that use of Fipronil on turf or corn does not result in the exceedence of a level of concern. In addition, there is maximum of two applications a year for Fipronil on turf and only one application to corn which results in little concern for chronic exposure.

In summary, since the known NOEC for the dietary feeding study with bobwhite quail is so near to the highest dose tested in the reproduction study Rhone-Poulenc feels that sacrificing additional animals and resources to repeat this study is not necessary to perform a valid risk assessment. EPA has stated that when the data in the reproduction study is questionable due to large dose intervals or other flaws in the performance of the test the NOEC, rather than the LEL, will be used in the risk assessment. If this study were to be repeated, the NOEC would be higher since the doses would have to increase compared to the current study. In order to save additional animals and resources, Rhone-Poulenc requests that the more conservative NOEC of 10 ppm ai, developed on the current bobwhite quail reproduction study, be used for the risk assessment purposes, that this study be upgraded to supplemental and that a waiver be granted for the repetition of this study.

Agency's Response: Kenaga provides an estimate for chronic exposure levels for granular products as an initial screen. Further if we examine the risk index for acute hazard, $LD50/ft^2$, in-row estimates do not exceed the LOC, however they approach the acute LOCs. The LD50/Sq.Ft. for the T-Band application is 0.41 mg/kg. This exceeds the LOC of 0.2 for restricted use and is close to the LOC trigger for the high acute risk hazard of 0.5. The acute single dose study had an LD50 of 11.3 mg/kg (c.i. = 9.2-13.9 mg/kg) and no NOEL. If the lower confidence limit is used the potential for acute hazard would be suggested. This coupled with the potential increase in exposure at endrows, implies that non-target organisms could be exposed to environmental residues approaching acute levels of concern. This would seem to support the estimates from Kenega, and imply that the potential for chronic effects needs to be defined better at levels which approach acute effect levels.

Additionally, according to the environmental fate data for anaerobic soil metabolism, the half-lives for Fipronil are 128 and 308 days in sandy loam soil and sandy soil, respectively. This data indicates that Fipronil is persistent and that there may be material present from a previous application when Fipronil is applied again. This has a potential to increase exposure to non-target organisms. The mammalian reproductive

data has not been reviewed yet.

This study, avian reproduction study 71-4(a), is to be repeated in order to determine the chronic no observable effect level (NOEC).

4) M&B 46030 - Toxicity to Duckweed, *Lemna gibba* (MRID 429186-56).

Registrant's Rebuttal: (excerpted from rebuttal letter of 6/12/94) This study was classified as supplemental because the "mean measured concentration was less than the required concentration". The study was run as a Tier 1 limit test due to the absence of effects in the preliminary study at a dose equivalent to what Rhone-Poulenc identified as the maximum use rate that would be requested for any registration. In this case, the measured concentration was equivalent to 0.13 lbs ai/acre. The proposed use rate for corn is 0.13 lbs ai/acre and the proposed use rate for turf is 0.025 lbs ai/acre. In both cases the measured concentration was equal to or greater than required for the proposed use pattern.

Rhone-Poulenc requests that this study be upgraded to core since it does meet the requirement for a Tier 1 Aquatic Plant Growth and Reproduction Study with the duckweed *Lemna gibba*.

Agency's Response: This study (MRID 429186-56) will be upgraded to core for the following reason; "The quantity of test substance to be tested should be the equivalent to the maximum label rate (in this case corn = 0.13 lbs ai/acre) as though it were applied to a surface of 15-cm or 6-inch water column. The application of 1 lb active ingredient per acre or 1.1 kg per hectare is equal to 735 parts per billion (ppb) in a 6-inch or 15-cm water column"[1].

The pounds active ingredient per acre in this case (corn) is 0.13. The following calculation indicates the maximum label rate as though the test substance were directly applied to a 6-inch or 15-cm water column:

0.13 lb ai/A X 735 ppb (as 1 lb ai/A in a 6-inch water col.) = 95.55 ppb (the maximum label rate for a 6-inch water column)

This 95.55 ppb would be 0.095 mg ai/l. The highest test concentration was 0.10 mg ai/l. Therefore, the test concentration was at a high enough level in this case. However if the use rate for Fipronil exceeds 0.13 lb ai/A this study would be considered supplemental and would not fulfill the guideline requirements due to the mean measured concentration being less than the required concentration.

5) M&B 46030 - Toxicity to The Freshwater Diatom, *Navicula pelliculosa* (MRID 429186-58).

Registrant's Rebuttal: (excerpted from rebuttal letter of 6/12/94) This study was classified as supplemental because the "mean measured concentration was less than the required concentration". The study was run as a Tier 1 limit test due to the absence of effects in the preliminary study at a dose equivalent to what Rhone-Poulenc identified as the maximum use rate that would be requested for any registration. In this case, the measured the measured concentration was equivalent to 0.16 lbs ai/acre. The proposed use rate for corn is 0.13 lbs ai/acre and the proposed use rate for turf is 0.025 lbs ai/acre. In both cases the measured concentration was equal to or greater than required for the proposed use pattern.

Rhone-Poulenc requests that this study be upgraded to core since it does meet the requirement for a Tier 1 Aquatic Plant Growth and Reproduction Study with the *Navicula pelliculosa*.

Agency's Response: This study (MRID 429186-58) will be upgraded to core for the following reason; "The quantity of test substance to be tested should be the equivalent to the maximum label rate (in this case corn = 0.13 lbs ai/acre) as though it were applied to a surface of 15-cm or 6-inch water column. The application of 1 lb active ingredient per acre or 1.1 kg per hectare is equal to 735 parts per billion (ppb) in a 6-inch or 15-cm water column"[1].

The pounds active ingredient per acre in this case (corn) is 0.13. The following calculation indicates the maximum label rate as though the test substance were directly applied to a 6-inch or 15-cm water column:

0.13 lb ai/A X 735 ppb (as 1 lb ai/A in a 6-inch water col.) = 95.55 ppb (the maximum label rate for a 6-inch water column)

This 95.55 ppb would be 0.095 mg ai/l. The test highest test concentration was 0.12 mg ai/l. Therefore, the test concentration was at a high enough level in this case. However if the use rate for Fipronil exceeds 0.16 lb ai/A this study would be considered supplemental and would not fulfill the guideline requirements due to the mean measured concentration being less than the required concentration..

6) M&B 46136 - Chronic Toxicity to Daphnids (*Daphnia magna*) Under Flow Through Conditions (MRID 429186-72).

Registrant's Rebuttal: (excerpted from rebuttal letter of 6/12/94) This study was classified as invalid because "both the dilution water control and the solvent control were

contaminated with high level of test material".

Mr. Don Suprenant, Springborn Laboratories, has addressed the issue of supposed contamination in the control solutions in his attached response. As he states, the apparent contamination is due to chromatographic interference and not to any cross-contamination with the treatment stocks. Since this was a static-renewal study and renewal occurred on day 0 and day 10, it is impossible to have contamination on day 21 but none on day 14, shortly after the treatment vessels were renewed. In addition, MB46136 is a metabolite of the active ingredient, Fipronil. In calculating the EEC for the parent compound and metabolites, the worst case EEC for MB 46136 for the highest proposed use of the product is still below the NOEC for the chronic daphnid study (0.12 µg ai/l in corn). The effect levels generated in this study would not be the most sensitive parameter in a risk assessment. This study, while not required, was performed to allow EPA to make a more informed decision concerning the active ingredient, Fipronil.

Rhone-Poulenc requests that this study be upgraded to core and that no repeat study be required. The reasons for the request are that the contamination could not have occurred on day 21 and not also have been observed on day 14 and the effect level of this metabolite will not influence the risk assessment.

Agency's Response: Table 1 information was excerpted from data submitted in the Springborn Laboratories study (Rept. # 91-8-3886 & MRID 429186-72);

Table 1 **Analytical Results**

Nominal Conc. µg ai/l	Day 0	Day 8	Day 14	Day 21
Solvent Control	3.4 0.54	0.26 0.22	<0.17 <0.17	0.41 3.6
Control	2.2 3.9	0.81 7.2	<0.17 <0.17	0.35 0.43

This study (MRID 429186-72) is invalid due to control contamination. Contamination was observed throughout the study (days 0 and 8) not just on day 21. This study does not need to be repeated because the test material was a soil metabolite and not the technical grade.

- "All control groups should be maintained in the same manner as test groups. However, control groups should be protected from airborne or other contamination by the test substance"[2].

7) The Chronic Toxicity of M&B 46030 to *Daphnia magna* Under Flow Through Conditions (MRID 429186-26).

Registrant's Rebuttal: (excerpted from rebuttal letter of 6/12/94) This study was classified as invalid because of high mortality in the dilution water control and variable measured concentrations.

Please refer to the attached memo from Mr. Suprenant, Springborn Laboratories, where he addressed both the issues of mortality in the dilution water control during the study and the variable measured concentrations. There was no significant mortality in the solvent control during the study and the mortality in the dilution water control did not occur until after day 15 of the test. No significant mortality occurred in any treatment level after day 15 so the effect level was determined by that time point. Comparing treatment level effects to the solvent control is more realistic since the treatment levels all contained the solvent. In addition, the mortality of 74% in the combined solvent and dilution water controls did meet the EPA Standard Evaluation Procedure Guideline (SEP) of no less than 70% survival, therefore the study should not be considered invalid.

Concerning the measured concentrations, ASTM states that analytical variability in a chronic study is unacceptable if the highest measured concentration divided by the lowest measured concentration for a treatment level exceeds two. In this study, the ratio of highest to lowest measured concentrations was ≤1.9, which meets guideline requirements.

Agency's Response: Table 2 information was excerpted from data submitted in the Springborn Laboratories study (Rept. # 90-01-3210 & MRID 429186-26);

Table 2 **Mortality Results (percent)**

Conc./Day:	1	2	4	7	10	12	14	15	18	19	21
Solvent Control	100	100	100	100	100	100	100	100	100	100	100
Control	100	100	100	100	95	93	93	93	63	53	50

° Criteria for test rejection; "30 percent of specimens in the controls (including solvent control) die;..."[3]

This study (MRID 429186-26) will not be updated to a core study because of excessive control mortality.

Additionally, regarding the variability of test concentrations:

1) The response from the registrant was that the highest measured concentration divide by the lowest concentration

was ≤1.9.
2) According to the data submitted the highest measured concentration for the 6.3 µg/l (nominal) was 6.4 µg ai/l on day 7 and the lowest measured concentration was < 0.44 µg ai/l on day 21.
3) ASTM says to take the highest measured concentration and divide by the lowest. If 6.4 is divided by 0.44 the answer is 14.545, and then this is greater than 2. Therefore according to ASTM "A life-cycle test with *D. magna* should be considered unacceptable if one or more of the following occurred .... the highest measured concentration of test material in fresh test solution in a treatment was more than twice the lowest treatment in the same treatment".[4]

In further regard to the subject of test concentration variability. It was noticed that between days 14 and 21, one of the 6.2 µg ai/l (nominal) concentration replicates, had went from 3.9 µg ai/l to less than 0.44 µg/l of test substance on day 21, according to the data submitted. The fact that one of the 6.2 µg ai/l replicates of a went from having a detectable amount (3.9 µg/l) of test substance to having an undetectable amount (<0.44 µg/l) indicates that the organisms of this replicate were not exposed to the test material for up to seven days.

The other question is that of the analytical instrumentation's minimum detection limits and the analytical results for the controls. Each day the control analyses show that the test substance was less than a certain amount and each amount is different for each day (ie; Day 0 <0.33µg/l, Day 7 <0.54µg/l, Day 14 <0.49µg/l, and Day 21 <0.44µg/l). Are these the minimum detection limits of the instrument, and if they are why are the minimum detection limits different on each day of analysis? Isn't a minimum detection limit a function of the type of instrument and the analyte? The agency would appreciate a clarification on this.

Furthermore, the analytical data table in the Springborn report, showed only two replicates for each concentration and control. The raw data that was submitted with this rebuttal letter had four replicates per concentration and control. Why are there only two analytical replicates when there are four replicates shown to be in the study? This study needs to be repeated to fulfill guideline requirements.

8) <u>(M&B 45950) - Chronic Toxicity to Daphnids (*Daphnia magna*) Under Flow Through Conditions (MRID 429186-70).</u>

<u>Registrant's Rebuttal:</u> (excerpted from rebuttal letter of

6/12/94) Please refer to the attached memo from Mr. Suprenant, Springborn Laboratories where he discusses the significance of the variable measured concentrations in light of the functioning diluter system. The apparent loss of material at the highest concentrations at the 7 day interval was most likely a function of the high binding capacity of Fipronil and its metabolites to food and other debris. In addition, the variability at day 21 was determined to be analyst error, not an absence of test material in the test solutions. Given the time involved in analyzing for M&B 45950, the test was ended and the diluter system was turned off before the problem was identified and resampling could occur.

M&B 45950 is a reduction product of the parent compound which is found in very low concentrations in laboratory studies and has not been found in field studies to date. The risk assessments performed for both corn and turf registration submissions have shown that there is no concern with this metabolite since none is formed in the field. This study, while not required was performed to allow EPA to make a more informed decision concerning the active ingredient, Fipronil.

Given that the diluter functioned properly during this study and that this is a metabolite of Fipronil that is not found in field samples, Rhone-Poulenc requests that this study be upgraded to supplemental and that no additional testing be required.

Agency's Response: This study (MRID 429186-70) will not be upgraded because measured concentrations were highly inconsistent. Two of the test concentrations decreased below the detection limit by test termination.

1) According to ASTM " the highest measured concentration of test material in fresh test solution in a treatment was more than twice the lowest treatment in the same treatment".
2) According to the data submitted the highest measured concentration for the 13 and 6.3 µg/l (nominal) were 17 (day 0) and 8.4 (day 0) µg ai/l, respectively. The lowest measured concentrations were both less than 0.43 µg ai/l on day 21.
3) ASTM says to take the highest measured concentration and divide by the lowest. The 6.3 µg/l (nominal) is 8.4 divided by 0.43 which is 19.534 this is greater than 2. The 13 µg/l is 17 divided by 0.43 which is 39.534 this is also greater than 2. Therefore according to ASTM "A life-cycle test with *D. magna* should be considered unacceptable if one or more of the following occurred .... the highest measured concentration of test material in fresh test solution in a treatment was more than twice the lowest treatment in the

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same treatment".[4]

Furthermore, the analytical data table in the Springborn report, showed only two replicates for each concentration and control. The raw data that was submitted with this rebuttal letter had four replicates per concentration and control. Why are there only two analytical replicates when there are four replicates shown to be in the study? This study does not need to be repeated because the test material was a soil metabolite and not the technical grade.

9) (M&B 46030) - Acute Toxicity Daphnids (*Daphnia magna*) During a 48-Hour Flow Through Exposure (MRID 429186-25).

Registrant's Rebuttal: (excerpted from rebuttal letter of 6/12/94) Briefly, ASTM states that 10% control mortality is acceptable for both static and flow-through studies while the EPA SEP states that mortality can only be 5% in flow-through tests. It is unclear why there is discrepancy between the SEP and ASTM when ASTM procedure are typically employed. In addition, a clear effect level was not compromised 10% mortality in the solvent control. Given that *Dapnia magna* is not the most sensitive species and thus, the effect level will not influence the risk assessment, and that ASTM allows for 10% control mortality during flow-through testing, Rhone-Poulenc request that this study be upgraded to core and that no repetition be required.

Agency's Response: This study (MRID 429186-70) will be upgraded to a core study.

If you have any questions about this review contact Andrew Bryceland at (703) 305-7347.

[1] Robert W. Holst, Pesticide Assessment Guidelines Subdivision J Hazard Evaluation Nontarget Plants (Washington, D.C.: USEPA EPA-540/9-82-020, 1982) 41.
[2] William Preston, Pesticide Assessment Guidelines Subdivision E Hazard Evaluation: Wildlife and Aquatic Organisms (Washington, D.C.: USEPA EPA-540/9-82-024, 1982).
[3] Miachel Rexrode, Hazard Evaluation Division Standard Evaluation Procedure *Daphnia magna* Life-Cycle (21-Day Renewal) Chronic Toxicity Test (Washington, D.C.: USEPA EPA-540/9-86-141, 1986).
[4] American Society for Testing Materials. 1992. Standard Guide for Conducting Renewal Life-Cycle Toxicity Tests with Daphnia magna. E1193 -87. (Philadelphia, PA, 1992).
[5] Elizabeth Zucker, Hazard Evaluation Division Standard Evaluation Procedure Acute Toxicity Test for Freshwater Invertebrates (Washington, D.C.: USEPA EPA-540/9-85-005, 1985).