Registration Decision RD2016-19

Isofetamid

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Registration Decision Statement[1] for Isofetamid

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is granting full registration for the sale and use of Technical Isofetamid Fungicide and Isofetamid 400 SC Fungicide, containing the active ingredient isofetamid, to control various *Botrytis* and *Sclerotinia* diseases on grape, lettuce (head and leaf), rapeseed, low growing berry and turfgrass on golf courses and sod farms.

This decision is consistent with the Proposed Registration Decision PRD2014-09, *Isofetamid*, which contains a detailed evaluation of the information submitted in support of this registration. The evaluation found that, under the approved conditions of use, the products have value and do not present an unacceptable risk to human health or the environment. See Appendix I for a summary of comments received during the consultation process as well as the PMRA's response to these comments.

Other Information

The relevant test data on which the decision is based (as referenced in PRD2014-09, *Isofetamid)* are available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa). For more information, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra.infoserv@hc-sc.gc.ca).

Any person may file a notice of objection[2] regarding this registration decision within 60 days from the date of publication of this Registration Decision. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticide and Pest Management portion of the Health Canada's website (Request a Reconsideration of Decision) or contact the PMRA's Pest Management Information Service

[1] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act.*

[2] As per subsection 35(1) of the *Pest Control Products Act.*

Appendix I Comments and Responses

1. Comment received:

On Page 32 of PRD2014-19, *Isofetamid* it indicates that the NOAEC for the Bobwhite Quail reproduction study is 276 mg a.i./kg diet. This is equivalent to approximately 25 mg a.i./kg-bw. The study endpoint listed on Page 82 also identifies the NOAEC for this study as 276 mg a.i./kg diet but the equivalent dose is listed as 6.05 mg a.i./kg-bw (females) and 7.88 mg a.i./kg-bw (males) rather than 25 mg a.i./kg-bw. Our concern is that a NOAEC of 6.05 mg a.i./kg-bw was used for the risk assessment rather than what appears to be the correct value of 25 mg a.i./kg-bw.

PMRA Response:

The NOAEC for the Bobwhite Quail was revised to 25 mg a.i./kg-bw. The endpoint had originally been considered as 94.3 mg a.i./kg diet (mean measured) which corresponds to 6.05 mg a.i./kg-bw (females) and 7.88 mg a.i./kg-bw (males) rather than about 25 mg a.i./kg-bw but was subsequently revised. The risk assessment has been updated accordingly. Despite this revision, using the revised endpoint of 25.2 mg a.i./kg bw/day (females – most sensitive endpoint), a reproductive risk still exists for small, medium and large sized birds (on-field, turf, maximum nomogram residues) and for small, insectivorous birds (on-field, turf, mean nomogram residues). This risk is mitigated by having the following statement on the label, "Toxic to birds and small mammals".

The revised Screening Level and refined RQs are as follows:

Screening Level Risk Assessment on Non-Target Species – Birds

	Toxicity (mg ai/kg bw/d)	**Feeding Guild (food item)**	**EDE (mg ai/kg bw)**	**RQ**
Small Bird (0.02 kg)				
Acute	200.00	Insectivore (small insects)	51.75	0.26
Reproduction	6.05	Insectivore (small insects)	51.75	2.07
Medium Sized Bird (0.1 kg)				
Acute	200.00	Insectivore (small insects)	40.38	0.20
Reproduction	6.05	Insectivore (small insects)	40.38	1.62
Large Sized Bird (1 kg)				
Acute	200.00	Herbivore (short grass)	42.14	0.21
Reproduction	6.05	Herbivore (short grass)	42.14	1.69

Further Characterisation Risk Assessment – birds – turf application (table incomplete shows only feeding guilds and bird sizes with RQs exceeding 1)

	Toxicity (mg ai/kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
			On-field EDE (mg ai/kg bw)	RQ	Off Field EDE (mg ai/kg bw)	RQ	On-field EDE (mg ai/kg bw)	RQ	Off Field EDE (mg ai/kg bw)	RQ
Small Birds (0.02 kg)										
Reproduction	25.20	Insectivore (small insects)	51.75	**2.07**	3.10	0.12	28.86	**1.16**	1.73	0.07
		Frugivore (fruit)	25.87	**1.04**	1.55	0.06	12.34	0.49	0.74	0.03
Medium Birds (0.1 kg)										
Reproduction	25.20	Insectivore (small insects)	40.38	**1.62**	2.42	0.10	22.52	0.90	1.35	0.05
Large Birds (1 kg)										
Reproduction	25.20	Herbivore (short grass)	42.14	**1.69**	2.53	0.10	14.96	0.60	0.90	0.04
		Herbivore (long grass)	25.73	**1.03**	1.54	0.06	8.40	0.34	0.50	0.02
		Herbivore (forage crops)	38.99	**1.56**	2.34	0.09	12.89	0.52	0.77	0.03

The endpoint table has been revised as shown below

2273911	Title: IKF-5411 ASSESSMENT TO DETERMINE THE EFFECTS ON REPRODUCTION IN THE BOBWHITE QUAIL	NOEC:276 mg a.i./kg-diet (mean measured); 25.2 mg a.i./kg-bw (females) and 26.8 mg a.i./kg-bw (males) LOEC:276 mg a.i./kg-diet (mean measured); 25.2 mg a.i./kg-bw Endpoint Effected: overall reproductive success, specifically, a reduced number of normal hatchlings

2. Comment Received :

On Page 34 of PRD2014-19, *Isofetamid*, it is states:

“Mammals - Further Characterization – turf applications

When mean nomogram residues were considered, there were no exceedances of the LOC for either on, or off-field scenarios for medium sized mammals feeding exclusively on grass.

It is expected that mammals will be exposed to a range of concentrations on food but effects are only expected to occur at the highest end of the residue concentration spectrum. Further refinements, such as bracketing the endpoints, were not required.

To summarize, some risk is expected to small, wild mammals via exposure from use of isofetamid on turf at the proposed maximum rate of 638 g a.i./ha and 8 applications spaced at 14 days apart (Table 15). Hazard statements will be required on the product label.”

The highlighted statement above references the risk characterization data in Table 15 for small mammals. The Risk Quotients (RQ) listed in this table for small mammals range from 0.0011 to 0.0153. These do not appear to support the need for a warning statement "Toxic to small wild mammals" on the label. Please indicate the LOC exceedance.

PMRA Response:

Please refer to Table 12 of PRD2014-19, *Isofetamid*. At the screening level, the risk quotient (RQ=1.43) was exceeded for medium sized herbivorous mammals (0.035 kg) in terms of reproductive risk. Although a further characterization was conducted, using mean nomogram residues, effects from exposure at the highest end of the residue spectrum cannot be ruled out and as such a hazard statement is required.

Please note that the risk quotients for small mammals are calculated using both on-field (treated area) and off-field estimated daily exposure (EDE). Off-field exposure will include all of the same assumptions as the on-field screening level assessment, with the exception of the application rate. The application rate will be equivalent to the predicted deposition from spray drift, which is calculated as the percentage of the maximum application rate expected to drift one metre downwind of the site of application. This percentage is dependent on the type of spray application and the droplet size expected and corresponds to the percentage drift that are currently used to calculate buffer zones. The off-field assessment for wild birds and mammals is not considered a refinement.

Additionally, default foliar half-lives are used to calculate exposure. At the screening level a default foliar half-life ($t_{1/2}$) of 35 days is used. If required, a default foliar half-life ($t_{1/2}$) of 10 days may be used to further characterize risk. In this case, the less conservative default foliar half-life of 10 days was used to calculate the risk quotients as a refinement for both on-field and off-field exposure.

3. Comment Received:

On Page 80 of PRD2014-19, *Isofetamid*, it states:

2273897	Title: DAPHNIA MAGNA REPRODUCTION STUDY OF IKF-5411 TECHNICAL	NOAEC: <0.39 mg ai/L LOAEC: 0.39 mg ai/L Endpoints affected: length, dry weight, and reproduction Most sensitive endpoint(s): length

The endpoints (NOAEC: <0.39 mg ai/L; LOAEC: 0.39 mg ai/L) for the *Daphnia* reproduction study are different than those indicated in the report. According to the report, the NOAEC is 0.81 mg ai/L and the LOAEC is 1.7 mg ai/L for the most sensitive endpoint - growth. Since the reported NOAEC of 0.81 mg ai/L was used in the risk assessments, we presume that the highlighted values indicated above are incorrect.

PMRA Response:

Statistical analysis was conducted using the negative control for comparison. William's Multiple Comparison test was used to determine the NOAEC mean length of 0.086 mg a.i./L and the LOAEC of 0.18 mg a.i./L. The most conservative endpoint was chosen from the statistical analysis.

Analysis ID	Endpoint	NOEL	LOEL	TOEL	PMSD	TU	Method
09-8434-3413	Hatching Success	0	>0		17.1%		Equal Variance t Two-Sample Test
01-9296-5596	Hatching Success	1.3	>1.3	NA	12.3%		Dunnett Multiple Comparison Test
10-6433-5036	Larval Survival	0	>0		13.2%		Equal Variance t Two-Sample Test
19-7108-6885	Larval Survival	0.68	1.3	0.9402	14.5%		Dunnett Multiple Comparison Test
03-9580-6026	Mean Dry Weight	0	>0		7.84%		Equal Variance t Two-Sample Test
21-2193-2650	Mean Dry Weight	0.18	0.35	0.251	6.92%		Dunnett Multiple Comparison Test
16-6056-8717	Mean Length	0	>0		2.58%		Equal Variance t Two-Sample Test
08-8379-7367	Mean Length	0.18	0.35	0.251	2.6%		Dunnett Multiple Comparison Test
15-1571-6101	Mean Length	0.086	0.18	0.1244	2.02%		Williams Multiple Comparison Test
03-8998-3109	Mean Wet Weight	0	>0		6.64%		Equal Variance t Two-Sample Test
19-6529-5639	Mean Wet Weight	0.18	0.35	0.251	6.61%		Dunnett Multiple Comparison Test

4. Comment Received:

On Page 80 of PRD2014-19, Isofetamid, it states:

2273899	Title: IKF-5411 TECHNICAL: A 96-HOUR FLOW-THROUGH ACUTE TOXICITY TEST WITH THE SALTWATER MYSID	Test: Flow-through 96-hr LC_{50} = 1.51 mg a.i./L, 95% C.I. = n/a NOEC = 0.64 mg a.i./L Endpoints effected: mortality

The endpoint for the acute mysid study (96-hr LC50 = 1.51 mg a.i./L, 95% C.I. = n/a) is different than that indicated in the report. According to the report, the 96-hour LC_{50} is 2.2 mg ai/L with a 95% confidence interval of 0.64–4.1 mg ai/L. Please clarify.

PMRA Response:

For the statistical evaluation of the 96 hour LC_{50} end point, the parameters of the data are as follows: Quantal, replicated (2 replicates) with two or more partial effects. As such a probit regression based on linear maximum likelihood was chosen for the end-point determination. The probed analysis found that the p(F) with 3 degress of freedom was 0.147. The p(F) is therefore > 0.05 suggesting that the slope of the relationship is not significantly different from zero. Due to the lacking of a concentration response, an LC_{50} could not be determined.

For the statistical evaluation of the 96 hour NOEC end point, the parameters of the data are as follows:

Testing of normal distribution was conducted by Shapiro Wilk's test, the test results indicate that the normality check was passed ($p > 0.05$) and that the treatment data did not significantly deviate from normal distribution.

Levene's Test on variance homogeneity was performed. The Levene test indicated variance in heterogeneity. A nonparametric tests is therefore required for the determination of the NOEC.

Test 1: Mann-Whitney U-test (Otherwise known as Wilcoxon Rank Sum). This test procedure failed as the number of replicates was too low.

The PMRA concludes that the LC_{50} could not be statistically determined and that the NOEC could not be statistically determined.

Based on mean measured concentrations, the 96-hour LC_{50} value was 1.51 mg a.i./L, 95% confidence intervals not determined. The no-mortality concentration and the NOEC were considered to be <0.31 mg a.i./L. The PMRA agrees with the methodology used to calculate the endpoint and the rationale for excluding the 96 hour mortalities in the 0.31 mg a.i./L test group.

DOC or TOC was not reported for the dilution water, therefore, the toxicity of IFK-5411 may be underestimated, and as such the study was classified as Reliable with restrictions. However, if these water quality parameters are provided and are deemed acceptable, the study can be upgraded.

5. Comment Received:

On Page 81 of PRD2014-19, *Isofetamid*, it is states:

2273905	Title: IKF-5411 TECHNICAL: AN EARLY LIFE-STAGE TOXICITY TEST WITH THE FATHEAD MINNOW	Growth (Length); (most sensitive endpoint): NOAEC: 0.086 mg ai/L LOAEC: 0.18 mg ai/L

The endpoints (NOAEC: 0.086 mg ai/L; LOAEC: 0.18 mg ai/L) for the Fathead Minnow early life-stage study are different than those indicated in the report. According to statistical analysis and the Study Director's conclusions, the NOAEC is 0.18 mg ai/L and the LOAEC is 0.35 mg ai/L for the most sensitive endpoint - growth. What was the basis of the PMRA endpoint selection for this study? Was a different statistical analysis conducted?

PMRA Response:

Statistical Method: The endpoints were statistically analyzed for hatching success, larval survival, wet weight, and mean length using CETIS version 1.8.7.12 statistical software with backend database settings implemented by EFED on 31 May 2013. Negative and solvent control data for each endpoint were compared using a two-sample t-test assuming equal variances. No differences were detected between controls and all subsequent analyses were conducted by comparing treatment data to the negative control only. Normality was assessed using the Shapiro-Wilks test and homogeneity of variance was tested using Bartlett's test. All endpoints met the assumptions of parametric statistics and were analyzed using Dunnett's Multiple

Comparison Test. Mean length exhibited a dose-dependent (linear) decreasing trend and was additionally analyzed using William's test. All analyses were based on mean measured exposure concentrations.

NOAEC: 0.086 mg ai/L
LOAEC: 0.18 mg ai/L

Endpoints affected: larval survival, mean length, mean wet and dry weight
Most sensitive endpoint(s): mean length

6. Comment Received:

On Page 87 of PRD2014-19, *Isofetamid*, it is states:

Organism	Exposure	PMRA Number	Endpoint value	EEC (mg a.i./L)	RQ	LOC exceeded?
Daphnia magna	Acute 48-h	2273896	LC_{50} = 2.35 mg a.i./L	0.53	0.226	No

The endpoint for the acute daphnia study (LC_{50} = 2.35 mg a.i./L) is different than that indicated in the report and in the table on page 80 of the PRD. The endpoint value should be EC_{50} = 4.7 mg ai/L.

PMRA Response:

The acute (96 hour) endpoint calculated for mysid was based on mean measured concentrations, with a 48-hour LC_{50} value of 4.7 mg a.i./L. The screening level risk assessment uses simple methods, conservative exposure scenarios and sensitive toxicity endpoints. For characterizing acute risk, acute toxicity values (LC_{50}, LD_{50}, and EC_{50}) from the relevant toxicity studies are divided by an uncertainty factor. The uncertainty factor is used to account for differences in inter- and intra-species sensitivity. Thus, the magnitude of the uncertainty factor depends on the group of organisms that are being evaluated (10 for fish, 2 for aquatic invertebrates e.g. *daphnia*). The EC_{50} is the effective concentration estimated to cause an effect to 50 percent of the test population. Similarly, the LC_{50} or LD_{50} is the lethal concentration or lethal dose estimated to cause mortality to 50% of the test population. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/(toxicity/uncertainty factor – if applicable)), and the risk quotient is then compared to the level of concern (LOC). The LOC =1 for all organisms with the exception of honeybees (acute LOC = 0.4) and beneficial terrestrial arthropods (LOC = 2).

Therefore, the endpoint used in calculating the risk quotient for *daphnia* was the 4.7 mg a.i./L ÷ 2 (uncertaintly factor) = 2.35 mg a.i./L.

7. Comment Received:

On Page 87 of PRD2014-19, *Isofetamid*, it is states:

Organism	Exposure	PMRA Number	Endpoint value	EEC (mg a.i./L)	RQ	LOC exceeded?
Mysid	Acute 96-h	2273899	EC_{50} = 0.755 mg a.i./L	0.53	0.71	No

The endpoint for the acute mysid study (EC_{50} = 0.755 mg a.i./L) is different than that indicated in the report. The endpoint value should be LC_{50} = 2.2 mg ai/L.

PMRA Response:

As per the response to question 4, the acute (96 hour) endpoint calculated for mysid was based on mean measured concentrations, with a 96-hour LC_{50} value of 1.51 mg a.i./L. The screening level risk assessment uses simple methods, conservative exposure scenarios and sensitive toxicity endpoints. For characterizing acute risk, acute toxicity values (LC_{50}, LD_{50}, and EC_{50}) from the relevant toxicity studies are divided by an uncertainty factor. The uncertainty factor is used to account for differences in inter- and intra-species sensitivity. Thus, the magnitude of the uncertainty factor depends on the group of organisms that are being evaluated (10 for fish, 2 for aquatic invertebrates e.g. mysid). The EC_{50} is the effective concentration estimated to cause an effect to 50 percent of the test population. Similarly, the LC_{50} or LD_{50} is the lethal concentration or lethal dose estimated to cause mortality to 50% of the test population. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/(toxicity/uncertainty factor – if applicable)), and the risk quotient is then compared to the level of concern (LOC). The LOC =1 for all organisms with the exception of honyebees (acute LOC = 0.4) and beneficial terrestrial arthropods (LOC = 2).

Therefore, the endpoint used in calculating the risk quotient for mysids was the 1.51 mg a.i./L ÷ 2 (uncertaintly factor) = 0.755 mg a.i./L.