

# **REGULATORY REVIEW DECISION FOR**

# PYMETROZINE AND ITS ASSOCIATED END-USE

# PRODUCTS

## Pest Control Products Board 2022©

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#### **1.0. Introduction**

Following initial authorization on use of pest control products, regulatory authorities all over the world may review the status of authorization routinely or when new information becomes available that a pest control product has safety concerns. The process of review must be based on the existing laws and regulations.

Pursuant to Regulation 11(2b) of the Pest Control Products (Registration) Regulations of 1984 of the Pest Control Products Act (PCPA), the Pest Control Products Board (PCPB) initiated a review of Pymetrozine and Pymetrozine based end use products based on new information that Pymetrozine was a suspected human carcinogen category 2. (Source EU)

#### 2.0. Main objectives of the review

- I. Review existing scientific data in view of establishing the weight of evidence if any that supports the safety concerns.
- II. Make recommendations for consideration by the Board.

#### 3.0. Uses of Pymetrozine

#### 3.1. Mode of action of Pymetrozine

Pymetrozine belongs to the pyridine azomethines insecticide chemical group. It acts on sensillae in the chordotonal organ TRPV channel modulators by blocking the nerve impulse to the brain. Physiologically, it appears to act by preventing the insects from inserting their stylus into the plant tissue.

As of 30<sup>th</sup> April 2022, there were 2 registered pest control products containing Pymetrozine as the active ingredient (<u>Appendix III</u>). Pymetrozine end-use products registered in Kenya are formulated as water dispersible granules and suspension concentrates.

#### 3.2. Registered uses of Pymetrozine based products in Kenya

Pymetrozine end use products are registered for use in Kenya as an insecticide for the control of aphids and whiteflies on Roses; cabbage aphids on Kales; and aphids and thrips on French beans.

#### 3.3. Quantities of Pymetrozine based products imported 2016-2021

A total of 11,658Kgs have been imported over the last 6 years (2016-2021).

Table 1: Quantities of Pymetrozine based products imported 2016-2021

	2016	2017	2018	2019	2020	2021	Total
Quantities	270	3240	1810	1618	3720	1000	11658
imported (Kgs)							

#### 4.0. Data considered in the review

To evaluate the identified aspects of concern, PCPB considered currently available relevant scientific information, data submitted by the applicants to support approval of the individual products in Kenya, initial information provided by stakeholders, various regulatory decisions made around the world including FAO/WHO Joint Meeting on Pesticide Residues, the European Union, the United States Environmental Protection Agency, Health Canada, Australia Pesticide and Veterinary Medicine Authority.

A summary of the regulatory decisions is presented in <u>Appendix I</u> while appendix II represents information collected from stakeholders.

#### **5.0 Methodology of the review**

In compliance with the constitution of Kenya on the bill of rights, and public participation, the Board wrote a circular to the local agents and the public notifying them of the intended review and called for any information that would assist the reviewers in arriving at the correct decision. The feedback was to be received within 90 days from the date of notification.

This was followed by a call for experts from Government institutions that included the Universities, Toxicological society of Kenya, KALRO, and KePHIS etc. After evaluation of the applications, four external experts were selected to team up with experts from PCPB.

Four active ingredients were reviewed and reports made and later submitted to the board of management. The board recommended that the outcome of the review be subjected to a second round of public participation.

#### **6.0: Outcome of the review**

#### **6.1.** Potential for carcinogenicity to humans

The main target organ of Pymetrozine upon short-term and long-term exposure in rats and mice is Liver. Long-term studies in both rats and mice provided evidence of treatment-related tumours in the liver at the highest dose level tested in both mice and rats. A slightly increased incidence in benign hepatoma or carcinoma or combined hepatoma and carcinoma was also seen at the second highest dose level in female rats and male mice.

Mechanistic studies induced xenobiotic metabolizing enzymes and stimulating hepatocyte cell proliferation in mice, with weak tumour promoting activity for thyroid in rats.

#### 6.2. Potential for reproductive toxicity

In a 90-day study in which dogs received Pymetrozine in the diet, the following adverse effects were noted: thymic atrophy, testicular tubular atrophy, reduced spermatogenesis, hepatocellular necrosis and inflammatory changes in several organs. In a 1-year study in dogs, effects observed were reduced testes weights, increased cholesterol, and reduced haemoglobin.

#### 6.3. Hazard assessment

Pymetrozine showed a low acute toxicity in rats or mice, was not irritant and not sensitising. After repeated exposure, the target organs were the liver (in all species), the erythrocytes and the testes in rats and dogs.

The triazine containing metabolites CGA-294849 (4-amino-6-methyl-1,2,4-triazine-3,5 (2H,4H)-dione) and GS-23199 (6-methyl-1,2,4-triazine-3,5(2H,4H)-dione) are likely to be of

toxicological concern. These compounds are azapyrimidines and analogist of thymine and uracil. The uracil analogue of GS-23199 is a mutagen. The metabolite GS-23199 can serve as a marker for CGA-215525, CGA-249257, and CGA-294849 for risk assessment purposes. These compounds are all "azauracils' 'that may lea d to the carcinogenic nature of Pymetrozine (EPA, 2000).

#### 6.4. Dietary risk assessment

Residue data from supervised residue trials for Fulfil 25 SC on French beans and Chess 50 WG on French beans and kales was evaluated to determine whether residues of Pymetrozine will exceed the MRLs of the registered crops when used as per Kenyan GAP. The evaluation show that there is likelihood that the EU MRLs will be exceeded. Codex MRLs for Pymetrozine have not been set, JMPR did not reach a conclusion on Pymetrozine residue definition.

Data gaps were identified on metabolites of toxicological concerns, especially on processed plant products which may pose consumer safety risk. Consumer risk assessment was, therefore, not conclusive.

#### 6.5. Fate and behaviour in soil and water

In soil, phototransformation of Pymetrozine is not expected to be a major route of transformation. Pymetrozine is moderately mobile to immobile in soil, while its transformation products are moderately to very highly mobile in soil. Pymetrozine is stable to hydrolysis at pH 7 but undergoes hydrolysis under acidic conditions resulting in two major transformation products, CGA 215525 (4-amino-6-methyl-4,5-dihydro-1,2,4-triazin-3 (2H)-one) and CGA 300407 (nicotinaldehyde). In water, phototransformation of Pymetrozine is a major route of transformation with a half-life of 2.1 days. (EFSA, 2014).

#### 6.6. Effects on non-target organisms

Pymetrozine has been determined to be of low acute toxicity to birds, aquatic organisms, mammals, and bees. The metabolites of Pymetrozine proved to be either non-toxic or less toxic to aquatic standard test species compared to the parent compound except CGA300407 with a higher toxicity to fish and daphnids. Considering the low acute levels of toxicity and

exposure of surface water, all metabolites can be considered as not relevant for the aquatic environment.

Pymetrozine has a low potential for bioconcentration in fish (log POW -0.19 at 25°C, pH 7 and its more polar metabolites have log POW << 3) and is not readily biodegradable (biodegradation of 2% in 29 days). This active substance exhibited long term toxicity to daphnia from a 21-day reproduction study where the NOEC was found to be 0.0251 mg a.s /L. Therefore Pymetrozine has been classified as H410 chronic category 1 (NOEC is  $\leq$  0.1 mg/L).

#### **6.7. Incident reports**

As of 30<sup>th</sup> October 2022, there were no incidents relating to the human health or environmental aspects of concern reported.

#### 7.0. Proposed review decision for Pymetrozine

The outcome of evaluation of available scientific information related to the aspects of concern indicates that potential human health and environmental risks for Pymetrozine are unacceptable under current conditions of use.

The review showed that Pymetrozine had safety concerns due to being a possible carcinogen category 2, risk to operators and aquatic environment (chronic toxicity) as well as possible risk to consumers.

Unique mode of action for Pymetrozine: Physiologically, it appears to act by preventing the insects from inserting their stylus into the plant tissue. This mode of action is unique and the product may be useful in resistance management to alternate with the registered products.

There were data gaps on toxicology of metabolites in the technical dossiers submitted to PCPB.

There is a likelihood that maximum residue levels on French beans and kales would be exceeded using Kenyan GAP. The consumer risk assessment based on the parent molecule

Pymetrozine was acceptable, however, there were data gaps on the two metabolites of toxicological concern and therefore the consumer risk assessment was not conclusive.

The risk to the outdoor worker and operator was found to be acceptable for Chess 50WG while it was an unacceptable for Fulfil 25SC.

The risk was acceptable for indoor use (Roses) for both CHESS 50WG and FULFIL 25SC. The worker exposure for FULFIL 25SC was unacceptable.

Pymetrozine is moderately mobile to immobile in soil while its metabolites are moderately to highly mobile in soil and water leading to high potential exposure through drinking water and edible crops.

Alternative pest control products (conventional and biopesticides) are registered for similar uses on the same crops in Kenya. A number of conventional and biopesticides are registered for use in Kenya for similar uses on the same crops, such as Acetamiprid, Alphacypermethrin, Zetacypermethrin, Abamectin, Bifenthrin, Malathion, Diazinon, Imidacloprid, Diafenthiuron, Deltamethrin, Sulfoxaflor, Thiocyclam, Thiamethoxam, Methomyl, Lufenuron etc. However some of the possible alternative products are subject of review.

#### 8.0. Proposed risk reduction measures

- 1. Immediate withdrawal of all uses of Pymetrozine-based end-use products on edible crops and outdoor ornamentals.
- 2. Restricted to use on indoor non-edible crops.
- 3. Not for use near water bodies.
- 4. PPE requirement of a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, application, clean-up and repair to minimise exposure.
- 5. Include on the Label statement: "suspected of causing cancer", "suspected damaging of fertility or unborn child" and "very toxic to aquatic life with long lasting effects"
- 6. Restrict pack size to >10Kg or 10L

 The registrant should address the concerns raised on worker exposure in indoor use for the product FULFIL 25SC.

#### 9.0. References

The list of pest control products https://www.pcpb.go.ke/on-crops/

 $\underline{https://www.pcpb.go.ke/wpcontent/uploads/2020/10/guidance\_on\_dossier\_evaluation\_for}$ 

\_the\_registration.pdf

 $\underline{https://portal.apvma.gov.au/pubcris; jsessionid=8vK6ipNLLVvooxHjfEqgUY5?p\_auth=m}$ 

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https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2014.3817 (accessed 22nd

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https://www.fao.org/fileadmin/templates/agphome/documents/Pests\_Pesticides/JMPR/Re port2014/5.26\_PYMETROZINE\_279\_.pdf (accessed 22<sup>nd</sup> November 2021)

## APPENDIXES

## Appendix I: Summary of international regulatory decisions

Country/Region	Regulatory decision	Classification	Mitigation measures
European Union	<ul> <li>Withdrawal of authorisations by 30 April 2019 Max period of grace: 30 January 2020The following was review</li> <li>high potential for the representative uses assessed to result in groundwater exposure above the parametric drinking water limit of 0.1 µg/l by the toxicologically relevant metabolite CGA371075 in all pertinent groundwater scenarios</li> <li>adverse effects on endocrine organs but could not be concluded with data submitted</li> </ul>	Carcinogen category 2; Reproductive toxicant category 2; Chronic aquatic category 3	EU MRL adjusted to the limit of detection (0.02mg/kg)
United States of America	Approved	Likely human carcinogen	<ul> <li>Prohibit application on vulnerable soils to address the drinking water risk estimates from groundwater that drive the dietary and aggregate risks</li> <li>Application rate reductions and reduction in annual maximum number of applications to address surface water and drinking water risk estimates</li> <li>prohibition on use within 900 feet of drinking water well</li> <li>Prohibit aerial application to address occupational mixer/loader risks</li> <li>Requiring respirators to address the occupational handler risks</li> </ul>

Country/Region	Regulatory decision	Classification	Mitigation measures
			• Amend labels to include advisory spray drift language to address the risks to invertebrates, birds, and mammals
			<ul> <li>Risk Mitigation for Dietary Risk:</li> <li>Groundwater mitigation (leaching) for all except container-grown ornamentals</li> <li>To mitigate potential cancer risk from application of Pymetrozine to plants grown in-ground, the EPA is requiring the prohibition of Pymetrozine application to plants grown on vulnerable soils, defined as having all three of the following characteristics: 1) sandy soil (&gt;60% sand content) as water movement is faster, 2) less than 3% organic matter content (Soil with low organic matter content has greater leaching potential, because organic matter binds some chemicals and keeps them from moving through the soil profile. Organic matter also aids in water retention), and 3) shallow depth to groundwater (less than 30 feet).</li> <li>Reduce application rates maximum annual application rate for ornamentals grown outdoors</li> <li>Occupational (handler) Require respirator for mixer/loader of aerial and chemigation applications</li> </ul>

Country/Region	Regulatory decision	Classification	Mitigation measures
Canada	Approved	likely human carcinogen	<ul> <li>All outdoor uses of Pymetrozine were proposed for cancellation.</li> <li>Prohibition of effluent or runoff from greenhouses containing Pymetrozine to enter aquatic</li> <li>The potential cancer risk of Pymetrozine (occupational) is considered to be acceptable with the following proposed risk mitigation measures: <ul> <li>PPE requirement of a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, application, clean-up and repair.</li> <li>For greenhouse ornamentals grown for cut flowers to minimize exposure to post application workers: A limit of 1000 L spray solution per hectare; and a reduction of the maximum application rate from 10 g a.i./100 L to 8.5 g a.i./100 L.</li> <li>For greenhouse vegetables: To improve clarity, a maximum spray volume of 2000 L/ha is proposed.</li> </ul> </li> </ul>
JMPR Evaluation	Evaluated, 2014		conclusion not reached based on the data provided; No codex MRL set
Australia	approved		Restricted to two applications per crop and not for use with backpack sprayers e.g. vegetables

N 0	Comments	Respondent
1.	<ul> <li>a) Our markets require that we export pest free products which will be difficult to achieve without some of their active ingredients.</li> <li>b) Our resistance management strategies require that we avoid overreliance on the same active ingredients. We need to have a wider selection option to enable us to achieve a working pesticide rotation program.</li> <li>c) We are restricted by the markets on the number of chemicals we can spray on our crops, removing these ingredients will leave us with very limited choices which may result in pest and disease build up beyond economic threshold hence will have negative impact on our business.</li> <li>We are writing to request for retention of some very important active ingredients in our crop protection program.</li> <li>We recognize the effects that pesticides have on the ecosystem and need to use them responsibly.</li> </ul>	Hadithi Plants (K) Limited, Fairy Flowers (K) Limited & Lathyflora (K) Limited
	However, we are already restricted on most active ingredients that we cannot use on our products by the market. Further, we are also under pressure to export pest and disease-free products. Removing some of these products will strain our production process which will have a great negative impact on our business.	
2.	We have adopted Crop protection management strategies, which ensure responsible use of pesticides and guarantee minimal negative impact to people and environment.	Africalla Kenya LTD

3.	Essential for aphid control esp. in situations where foliar neonics are restricted.	Kenya Flower Council
4.	We can do without Pymetrozine	Equinox Flowers
5.	We are not using Pymetrozine	P. J. DAVE Flowers LTD
6.	No immediate suitable alternatives.	Finlays Flowers
7.	The safety of Pymetrozine-based products can be demonstrated, and adequate mitigation measures can allow for a safe use of this product in Kenya.	Syngenta Kenya
8.	Active ingredient that must be withdrawn immediately. Proposed withdrawal in Kenya should be based on: 1) Carcinogenicity 2) Reproductive toxicity	BIBA-K, KOAN, RODI, RTFI

	Product particulars	Active ingredient	Registered uses
1.	CHESS 50 WG Water Dispersible Granules PCPB(CR)0944	Pymetrozine 500g/Kg	Insecticide for the control of aphids and whiteflies on Roses; cabbage aphids on Kales & bean aphids on French beans.
2.	FULFIL 25SC Suspension concentrate PCPB(CR)1464	Pymetrozine 250g/L	Insecticide for the control Thrips, Aphids and Whitefly on Roses, and thrips on French beans

### Appendix III: Registered Pest Control Products Containing Pymetrozine