Proposed Re-evaluation Decision PRVD2024-02

Natamycin and its Associated End-use Products

Consultation Document

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Proposed re-evaluation decision

Under the *Pest Control Products Act*, all registered pesticides must be re-evaluated regularly by Health Canada's Pest Management Regulatory Agency (PMRA) to ensure that they continue to meet health and environmental safety standards and continue to have value. The re-evaluation considers data and information from various sources such as information from pesticide manufacturers, incident reports, and other regulatory agencies. Health Canada applies internationally accepted risk assessment methods, risk management approaches and policies to all re-evaluations.

This document presents the proposed regulatory decision for the re-evaluation of natamycin, including any proposed amendments (risk mitigation measures) to protect human health and the environment, as well as the science evaluation on which the proposed decision is based.

Natamycin is registered to suppress dry bubble disease in mushroom production facilities. It is also registered for use as a preservative for samples of milk used in analytical testing laboratories. Currently registered products containing natamycin are listed in Appendix I.

Natamycin, also known as pimaricin, is a naturally-occurring antimycotic substance, produced by the soil bacterium *Streptomyces natalensis*, *Streptomyces lydicus*, and *Streptomyces chattanoogensis*. Natamycin prevents the germination of fungal spores. It is an important tool for mushroom growers to control integrated dry bubble disease management. It is also important to the dairy industry to preserve milk samples in analytical testing laboratories. Natamycin is also a food preservative that is approved and used in more than 150 countries around the world. Based on the current use pattern, natamycin has value in providing a pest management solution, and the potential risks to human health (dietary, occupational, and bystander) and the environment (aquatic and terrestrial organisms) are considered to be acceptable when products containing natamycin are used according to proposed label updates.

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law. The key risk-reduction measures being proposed for natamycin to address the potential risks identified in this re-evaluation are as follows:

- Updates to precautionary and first aid statements
- Updates to storage and disposal statements
- Resistance management statement for mushroom use

Refer to Appendix II for all proposed label updates.

Under the authority of the *Pest Control Products Act* and based on an evaluation of currently available scientific information, products containing natamycin (Appendix I) are being proposed for continued registration in Canada, with the proposed updates to label directions (Appendix II).

All products containing natamycin registered in Canada are subject to this proposed re-evaluation decision. This document is subject to a public consultation,[1] during which written comments and additional information may be submitted to PMRA Publications. The final re-evaluation decision will be published taking into consideration the comments and information received during the consultation period.

Next steps

The public, including the registrants and stakeholders, are encouraged to submit written comments and additional information during the 90-day public consultation period upon publication of this proposed re-evaluation decision.

All comments received during the 90-day public consultation period will be taken into consideration in preparation of the re-evaluation decision document,[2] which could result in revised risk mitigation measures. The re-evaluation decision document will include the final re-evaluation decision, the reasons for it and a summary of comments received on the proposed re-evaluation decision with Health Canada's responses.

Other information

When Health Canada makes its re-evaluation decision, it will publish a Re-evaluation Decision on natamycin (based on the Science Evaluation of PRVD2024-02). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room.

Additional scientific information

Additional scientific data are not required at this time.

[1] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

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

Science evaluation

1.0 Use description

Natamycin is a preventative fungicide, registered to suppress dry bubble disease in mushrooms. It is also registered for use as a preservative for milk samples used in analytical testing laboratories. As a preservative for milk samples in laboratories, the product is a tablet that is dispensed automatically or with a handheld dispenser. For mushroom facility uses, the product is applied in the irrigation water to the surface of the prepared mushroom bed as a surface drench. The product is diluted in a recirculating irrigation tank and applied by hose with an irrigating hand wand to the surface of the prepared mushroom bed as a surface drench. Treatment is conducted in an enclosed growing room with growing stacked beds and applied moving from top to bottom. A total of two applications may be applied, once at casing and once at pinning, at a rate of 2.0 mL product per square meter. Used compost and casing must be steamed in the mushroom house prior to disposal outside of the mushroom growth facility.

2.0 Human health assessment

Natamycin is of low acute toxicity via the oral, dermal, and inhalation routes, minimally-irritating to the eyes, slightly irritating to the skin, and not a dermal sensitizer. Natamycin is considered to be non-mutagenic in a bacterial reverse mutation assay and in an in vitro mammalian chromosomal aberration assay. No toxicological reference values are established. Therefore, a qualitative approach was taken for the health assessment for natamycin.

For classification of eye irritation potential according to current standards, available eye irritation studies were re-assessed. Based on the re-assessment of the available information, technical grade active ingredient labels, do not require signal words on the principal display panel and precautionary statements on the secondary display panel.

When used as a preservative for milk samples, occupational exposure could occur when workers handle the end-use product. Workers are required to wear a long-sleeved shirt, long pants, chemical-resistant gloves, protective eyewear (goggles or face shield), shoes and socks during mixing, loading, clean-up and repair when handling the product. Potential risk from the use is considered acceptable under the current conditions of use.

For mushroom facility uses, occupational exposure is expected to be mainly by the dermal route during mixing, loading, and conducting postapplication activities, such as harvesting, and handling of used compost and casing. Workers are required to wear a long-sleeved shirt, long pants, waterproof gloves, shoes and socks during mixing, loading, application, clean-up and repair. For postapplication, workers must wear a long-sleeved shirt, long pants, waterproof gloves, socks and shoes. Other precaution and hygiene statements on the label require the user to wash hands thoroughly with soap and water after handling, and to remove contaminated clothing and wash clothing before reuse. Personal protective equipment are proposed to be updated to meet current standards. Potential risk from mixing, loading, application and postapplication activities is considered acceptable with the proposed label updates.

Bystander and residential exposure is not expected as the commercial application of natamycin in mushroom facilities and analytical testing laboratories are expected to be limited to authorized personnel only. Therefore, risk to bystander and residential exposure is considered as acceptable.

Natamycin is registered for food uses. Food residue exposure to natamycin from consumption of treated mushrooms is not expected to be of concern as conservative exposure estimates show that it will not appreciably increase the dietary exposure to natamycin beyond what is currently expected from its use as a food additive. Additionally, based on the registered use patterns for natamycin, the label has the necessary mitigative measures to limit contamination of drinking water and exposure is expected to be negligible. For the use as a preservative of milk samples, the treated milk samples are used for analytical testing laboratories, not for consumption. And therefore, dietary exposure from the use as a preservative of milk samples is not expected.

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential, and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal, and inhalation). Residential (dermal and inhalation) and drinking water exposure are not expected based on the registered use pattern for natamycin. When natamycin is used according to the label directions, the aggregate risk from potential dietary (food and drinking water) and non-occupational exposures is considered acceptable. Therefore, an aggregate exposure assessment is not required.

The *Pest Control Products Act* requires that Health Canada consider the cumulative exposure to pest control products with a common mechanism of toxicity. Accordingly, an assessment of potential common mechanism of toxicity with other pesticides was undertaken. For the current evaluation, PMRA did not identify information indicating that natamycin shares a common mechanism of toxicity with other registered pest control products. Therefore, there is no requirement for a cumulative health risk assessment at this time.

Antimicrobial resistance

Although fungal resistance to natamycin and other polyene antifungal agents has been induced both in vitro and in vivo, it is unlikely and has not been observed to occur as a result of the pesticidal uses of natamycin as these uses do not present the conditions for the extreme selective pressure for resistance to develop. Even if natamycin resistant variants were to occur, these variants grow poorly, exhibit decreased pathogenicity, are unable to compete in the environment and tend to revert back to normal growth and susceptibility in the absence of the selective pressure. Exposure to the registered products (Brotab Milk Preservative and Zivion M) will be limited, both in duration and frequency of use. Hence, their use will not present a continuous selective pressure. Furthermore, natamycin is not permitted for use as a therapeutic or veterinary drug in Canada and its use is declining in other countries.

Therefore, the risk of antimicrobial resistance (AMR) when the registered end-use products (Brotab Milk Preservative and Zivion M) are used according to the updated label instructions is acceptable. New uses of natamycin, however, may require further assessment.

As of 7 November 2023, no human or domestic animal incidents involving natamycin had been submitted to the PMRA.

3.0 Environment assessment

The available information on the environmental fate suggests that natamycin is not volatile. It is stable to hydrolysis, and degrades rapidly in sunlight. Natamycin is not considered as a Track 1 substance as it does not meet all the Track 1 criteria as per the Toxic Substances Management Policy, specifically, it is not expected to persist or bioaccumulate in the environment.

For use as a preservative for milk samples in analytical testing laboratories, small amounts of natamycin are used and disposed of, potential environmental exposure and potential risk, is considered negligible.

For use in mushroom facilities, the product is applied as a surface drench (see Section 1 for detailed use description). The spent medium/compost must be steamed within the mushroom house at the end of each production, prior to disposal, resulting in negligible natamycin residues. Exposure of non-target organisms to natamycin from mushroom houses/production facilities is considered negligible under the current conditions of use, and the potential risks to the environment are considered to be acceptable.

Label instructions on the proper treatment and disposal (in other words, heating the medium for no less than 12 hours at 65ºC or greater) of the mushroom medium should minimize exposure to the environment and any potential risks. Standard storage statements and disposal statements are proposed to be added to all product labels to meet current labelling standards.

As of 7 November 2023, no environment incidents involving natamycin had been submitted to the PMRA.

4.0 Value assessment

Natamycin is a preventative fungicide and have acceptable value. It binds with ergosterol in the fungal cell membrane and disrupts its integrity or function. Resistance is not known to this fungicide. In Canada, natamycin is registered to suppress dry bubble disease in mushrooms. Natamycin is an important tool for mushroom growers to control integrated dry bubble disease management. It is also registered for use as a preservative for milk samples in testing laboratories to determine the quality of milk.

Appendix I Registered products containing natamycin in Canada[1]

Table 1 Products containing natamycin subject to proposed label amendments

Registration number	Marketing class*	Registrant	Product name	Formulation type	Active ingredient** (%)
22612	T	Advanced Instruments Inc.	Pimaricin Technical	Dust or powder	PIM 85
30520	T	DSM Food Specialties B.V.	Natamycin TGAI	Solid	PIM 91.02
28530	C	Advanced Instruments Inc.	Brotab Milk Preservative	Tablet	PIM 1.62 BND 42.63
30521	C	DSM Food Specialties B.V	ZIVION M	Suspension	PIM 10.34

[1] As of 1 February 2024, excluding discontinued products or products with a submission for discontinuation.
* T = Technical grade active ingredient; C = Commercial
**PIM = Natamycin; BND = Bronopol

Appendix II Proposed label updates for products containing natamycin

Information on labels of currently registered products should not be removed unless it contradicts the label statements provided below.

1. Technical grade active ingredient:

1.1 Replace the term "guarantee" with "active ingredient".

1.2 Based on a classification of minimally-irritating to the eyes, currently registered technical grade active ingredient products containing natamycin no longer require the following label statements:

On primary display panel the following signal words:
"DANGER - EYE IRRITANT"

On the Secondary display panel under **PRECAUTION**:
"Severely irritating to the eye; DO NOT get in eyes"

1.3 All registered natamycin product labels must include standard first aid statements as per the new PMRA Guidance Document, *First Aid Labelling Statements* (Canada, 2022).

1.4 The following statement must be included in a section entitled **STORAG**E:
"Store this product away from food or feed."

1.5 The following statement must be included in a section entitled **DISPOSAL**:

"Canadian manufacturers should dispose of unwanted active ingredients and containers in accordance with municipal and provincial regulations. For additional details and clean-up of spills, contact the manufacturer and the provincial regulatory agency."

2. Commercial class products:

2.1 Replace the term "guarantee" with "active ingredient".

2.2 Under the **PRECAUTIONS** section, precautionary label statements should be updated to meet current standards:

When used as a preservative for milk samples: Workers are required to wear a long-sleeved shirt, long pants, chemical-resistant gloves, protective eyewear (goggles or face shield), shoes and socks during mixing, loading, clean-up and repair when handling the product.

For mushroom facility uses: Workers are required to wear a long-sleeved shirt, long pants, waterproof gloves, shoes and socks during mixing, loading, application, clean-up and repair. For postapplication activities including data gathering, harvesting, and handling of used compost and casing, workers must wear a long-sleeved shirt, long pants, waterproof gloves,

socks and shoes.

2.3 All registered natamycin product labels must include standard first aid statements as per the new PMRA Guidance Document, *First Aid Labelling Statements* (Canada, 2022).

2.4 The following statement must be included in a section entitled **STORAGE**:

"Store this product away from food or feed"

2.5 Add the following statement to a section entitled **DISPOSAL**:

For recyclable containers:

DO NOT reuse this container for any purpose. This is a recyclable container, and is to be disposed of at a container collection site. Contact your local distributor/dealer or municipality for the location of the nearest collection site. Before taking the container to the collection site:

1. Triple- or pressure-rinse the empty container. Add the rinsings to the spray mixture in the tank.

2. Make the empty, rinsed container unsuitable for further use.

If there is no container collection site in your area, dispose of the container in accordance with provincial/territorial requirements.

For returnable containers:

DO NOT reuse this container for any purpose. For disposal, this empty container may be returned to the point of purchase (distributor/dealer).

For containers that can be refilled for the user by the distributor/dealer:

For disposal, this container may be returned to the point of purchase (distributor/dealer). It must be refilled by the distributor/dealer with the same product. DO NOT reuse this container for any other purpose.

Disposal of unused, unwanted product:

For information on disposal of unused, unwanted product, contact the manufacturer or the provincial/territorial regulatory agency. Contact the manufacturer and the provincial/territorial regulatory agency in case of a spill, and for clean-up of spills."

3. **For product registered for mushroom use, add the following statement to a section entitled DIRECTIONS FOR USE:**

"DO NOT allow releases, effluent or runoff from mushroom houses containing this product to enter lakes, streams, ponds or other waters."

4. For commercial class end-use product registered for use in mushroom facilities (Reg. No. 30521).

4.1 add Site of Action Grouping and Identification Symbol on the front panel

GROUP	48	FUNGICIDE

4.2 the following statement must be included in a section entitled **RESISTANCE MANAGEMENT RECOMMENDATIONS**

For resistance management, ZIVION M contains a Group 48 fungicide. Any fungal population may contain individuals naturally resistant to ZIVION M and other Group 48 fungicides. A gradual or total loss of pest control may occur over time if these fungicides are used repeatedly in the same location. Other resistance mechanisms that are not linked to site of action but specific for individual chemicals, such as enhanced metabolism, may also exist. Appropriate resistance-management strategies should be followed.

To delay fungicide resistance:

- Where possible, rotate the use of ZIVION M or other Group 48 fungicides with different groups that control the same pathogens.
- Use tank mixtures with fungicide from a different group that is effective on the target pathogen when such use is permitted.
- Fungicide use should be based on an integrated disease management program that includes scouting, historical information related to pesticide use and crop rotation and considers host plant resistance, impact of environmental conditions on disease development, disease thresholds, as well as cultural, biological and other chemical control practices.
- Where possible, make use of predictive disease models to effectively time fungicide applications.
- Monitor treated fungal populations for resistance development. Notify DSM Food Specialties B.V. if reduced sensitivity of the pathogen to ZIVION M is suspected.

If disease continues to progress after treatment with this product, do not increase the use rate. Discontinue use of this product, and switch to another fungicide with a different site of action, if available.

- Contact your local extension specialist or certified crop advisors for any additional pesticide resistance-management and/or IPM recommendations for specific crops and pathogens.

For further information and to report suspected resistance, contact (company representatives) at (toll free number) or at (Internet site).

References

Published information

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