ENVIRONMENTAL PROTECTION AUTHORITY
To Obtain Approval to Import or Manufacture the Pesticide, Tetraniliprole

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Company: Bayer New Zealand Limited
Contact Name: Tonde Kaitano, Regulatory Scientific Manager
Name of substance: Permission to Import a Pesticide, Vayego (Tetraniliprole)
Application number: APP203605

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A. Introduction:

Tetraniliprole (Trade name: Vayego) is a member of a class of insecticides, the Anthranilic diamides, which also includes: broflanilide, chlorantraniliprole, cytranliniprole, cyclaniliprole, cyhalodiamide, flubendiamide and tetrachlorantraniliprole. Of these organo-chemicals, chlorantraniliprole and cyrantraniliprole, in particular, have been characterized, and, due to their ‘ultra-high efficiency’, low ‘non-specific’ toxicity, and broad spectrum of activity, have been applied throughout the World for controlling targeted insect populations. Tetraniliprole, a related product, has not yet been approved for distribution.

These pesticides bind to Ryanodine Receptors* (RyRs) in the endoplasmic reticulum and sarcoplasm reticulum (SR) of cells in diverse species, including Insectivore, Piscine through Mammalia, to disrupt intra-cellular modulation of calcium (Ca^{2+}), particularly in muscle and neuronal cells. Notably, the RyRs, occurring as three isomers, RyR1, RyR2 and RyR3, are ubiquitous and highly conserved, signifying their fundamental physiological roles in the development, survival and continuance of life.

RyR1 and calcium serve crucially important functions in cellular processes and homeostasis. RyR1 regulates non-voltage calcium channels, that on binding of an anthranilic diamide (e.g. tetraniliprole), invokes a rapid, unregulated release of Ca^{2+} from stores in the lumen of the SR, into the cell’s cytosol. This quick influx of Ca^{2+} disrupts intra-cellular homeostasis and invokes rapid contraction and seizure of skeletal muscles and then death of faunal targets (1).

RyR1, and the related and equally ubiquitous, inositol 1,4,5-triphosphate receptors (IPsR) present in the cell’s endoplasmic/sarcoplasmic reticulum (ER/SR), are related structurally and physiologically. The two protein complexes are each encoded by three distinct genes, and the respective protein domains form, on assembly, similar tetrameric, Ca^{2+}-permeable channels that lead to large conductance of calcium ions. Further, structurally analogous protein domains of RyRs are inter-changeable functionally with their IPsR counterparts, thereby enabling assembly of Ca^{2+}-channel chimaeras. Also, individual channel sub-types can exhibit discrete cellular distributions and expression in distinct regions of different tissues, and, in turn, Ca^{2+} release can be modulated by different factors thereby further defining specific and diverse roles of intra-cellular Ca^{2+} signals. Consequently, RyR- and IPsR-channels control a broad array of physiological processes, in adults and during development; including gene transcription, cell-fate, exocytosis, neuron function and muscle contraction.
B. Ryanodine Receptors:

Ryanodine is a highly toxic diterpenoid derived from Ryania speciosa (Salicaceae), a South American plant that yields an extract used originally as an insecticide. Pure ryanodine binds with very high affinity to the ‘open-form’ of the intra-cellular receptor family, RyR1, RyR2 and RyR3, and thereby locks calcium channels into a half-open position and allows Ca^{2+} stored in the endoplasmic reticulum and sarcoplasmic reticulum to flood into the cell cytoplasm. When these events occur in skeletal, smooth and cardiac muscles, even at low nano-molar concentrations, they undergo massive contractions, and higher levels invoke complete seizure, in insect and mammalian cells. The effect is definitive - Ryanodine has an LD_{50} of 0.1, 0.09, 0.8 and 0.7 ug/ml, respectively, in the mouse, house fly, adult cockroach and locust (nymph). The compound is classified very toxic to bees and aquatic life. The sensitivity to ryanodine reflects the compound’s extremely high-binding affinity in target cells.

A dramatic Ryanodine-induced Ca^{2+}-release occurs from the endoplasmic reticulum of sub-microvilli in photoreceptors of the compound eyes (ommatidia) of drone bees (Apis mellifera, New Zealand) (6,9).

The three isomers of RyRs are expressed differentially in various tissues. RyR1 acts predominantly in skeletal muscle cells, RyR2 in cardiac myocytes, and RyR1, RyR2 and RyR3 serve roles in different regions of the brain in invertebrate and vertebrate species, insects to humans. Also, RyRs function in promoting secretion of insulin by the pancreas and production of bile acid by the gall bladder. The three isomers, in turn, are regulated by modulators that bind to specific domains of the respective RyRs to enhance or inhibit their roles in Ca^{2+} release. Modulators of RyR functions comprise the Bcl-2 protein family, calmodulin, Ins-P_{3}, polycystins and presenilins, which, on binding to specific protein domains, cause conformational changes and thereby alter or block Ca^{2+}-channel permeability (5).

The RyRs are associated with multiple diseases - humans express >400 RyR1-mutation variants of which many may be silent, whereas others will prove to be associated with specific diseases. Presently known RyR-associated diseases comprise malignant hyperthermia (4), central core disease (5) and neurodegeneration (6), including Alzheimer’s Disease, Parkinson’s Disease and Spinocerebellar Ataxia (4,5).

Modulation of Ca^{2+}-channel permeability determines a broad array of finely tuned biochemical and physiological functions. Disruption of singular or complementary biochemical processes by tetraniiliprole, a highly toxic substance, has detrimental effects on cells, tissues and organs.

C. Key issues:

1) Tetraniiliprole is being proposed for the control of coddling moth, leaf-rollers and other pests in pome fruit, stone fruit and grapes; and likewise proposed for controlling cabbage white butterfly larvae, leaf miner, diamond-back moth larvae and other pests in vegetable and forage brassicas,

2) Tetraniiliprole binds with high-affinity to the isoforms of Ryanodine Receptors, RyR1, RyR2, RyR3, present in the endoplasmic reticulum and/or sarcoplasmic reticulum of target cells, present in all invertebrate through vertebrate species studied through the present time,

3) Target cells comprise smooth, skeletal and cardiac muscle; neuronal cells of the brain and other neural cell types, pancreas, gall bladder and photoreceptors in the eye (Humans and honey bees),

4) Ryanodine Receptors comprise large (>500,000 Daltons) tetrameric complexes embedded in the reticular membranes, that, along with modulatory and regulatory proteins, form canals for Ca^{2+} to flow from reticulum-based storage sites into the cell cytoplasm, for regulating intra-cellular metabolism, and, via hormones and neural signals, regulate the physiological functions of other cells, tissues and organs,

5) Ryanodine Receptors are ubiquitous and highly conserved among evolutionary diverse fauna, under-scoring their central and essential roles in biochemical, endocrinological, physiological processes,

6) Ryanodine Receptors, in humans, have succumb to numerous mutations (hotspots), some of which have been identified with neurological degeneration - Alzheimer’s Disease, Parkinson’s Disease,
Spino cerebellar Ataxia; raising the possibility of complications ensuing from acute and/or chronic exposure to tetraniliprole,

7) Tetraniliprole, chlorantraniliprole and cyantraniliprole, three related pesticides, have elicited resistance over time, by rapid selection for polymorphisms in genes encoding for the Ryanodine receptors, need to be addressed,

8) Need to establish broad margins (>50 meters) around crop fields, set limits on suitable weather conditions, and avert helicopter spraying, to avoid pesticide strikes on nearby apiaries and crops,

9) Lack of hard data addressing the toxicity of Tetraniliprole on Honey bees and moths pollinating nearby native and exotic flowering plants and trees - contrary to the claim, bees prefer field margins,

10) Provide convincing data on the toxicity of tetraniliprole against birds, honey bees and other insects; including identifying and assessing the possible toxic effects of all breakdown products.

D. Notes:

a) The three-dimensional structure of the tetrameric, RyR- and IP3-R-Ca2+-channels, based on X-ray crystallography, are shown with the carboxyl-termini projecting as a pore through the membrane into the lumen of the endoplasmic/sarcoplasm reticulum.[10] The necessary conformational changes are described that allow or block passage of Ca2+ ions through the channels.

b) The genes encoding RyRs have been characterised for Heliothis virescens (Tobacco budworm), Myzus persicae (Green peach aphid), Aphis gossypii (Melon aphid), Peregrinus maidis (Corn hopper), Drosophila melanogaster (Fruit fly), and, more recently, Plutella xylostella (Diamond-back moth).

E. References


**Name:** Tetraniliprole

**PubChem CID:** 56602311

**Tetraniliprole:** 1-(3-Chloro-2-pyridinyl)-N-(4-cyano-2-methyl-6-((methylamino)carbonyl)phenyl)-3-((5-(trifluoro-methyl)-2H-tetrazol-2-yl)methyl)-1H-pyrazole-5-carboxamide

**Molecular Weight:** C_{22}H_{16}ClF_{3}N_{10}O_{2}

**Molecular Weight:** 544.883 g/mol