Health Canada / Santé Canada

Pest Management Regulatory Agency / Agence de réglementation de la lutte antiparasitaire

2008-2521

DEC 16 2009

Stephen A. Nicholson
Valent BioSciences Canada, Ltd.
2704 Orser Road
Elginburg, ON K0H 1M0

Dear Mr Nicholson:

Re: Notice of Objection – RVD2008-18 *Bacillus thuringiensis*

We have carefully reviewed your Notice of Objection, filed in July of 2008, regarding the Health Canada Pest Management Regulatory Agency (PMRA) decision to continue the registration of *Bacillus thuringiensis* (RVD2008-18). We are aware of your long-standing interest in *Bacillus thuringiensis*, and continue to make every effort to answer your questions and address your concerns.

Under the *Pest Control Products Act*, any person who believes there is a scientific basis for reconsideration of a decision to which subsection 28(1) applies can file a Notice of Objection within 60 days of the publication of the decision. Objections are expected to focus on the scientific basis of the decision related to health and environmental risks, the value of the pesticide and the need for this decision to be taken to an external panel of experts for consideration of the scientific argument presented in the Notice and to obtain advice to the Minister in that regard.

When a notice of objection is filed, a team of PMRA scientists, who were not involved in the original decision, is established. The team considers the scientific basis for the objection and determines if the criteria for the establishment of a review panel have been met.

Criteria for establishing a review panel include:

a. whether the information in the notice raises scientifically founded doubt as to the validity of the evaluation or re-evaluation of the health and environmental risks and the value of the pesticide; and
b. whether the advice of a panel of expert scientists would assist in addressing the objection.

.../2

Many of the concerns you raised in your objection were addressed during the extensive review and consultation process for the re-evaluation of *Bacillus thuringiensis*, and in our previous communications with you previously. Our team of PMRA scientists has carefully and extensively reviewed your questions and concerns, and has responded to each item separately in the attached document with information that was considered in the re-evaluation decision of *Bacillus thuringiensis*. The team did not identify any scientifically founded doubt with respect to the validity of the PMRA re-evaluation decision in the information you provided in your objection. As a result this notice of objection does not fulfill the criteria to establish a review panel to reconsider the decision for continued registration of *Bacillus thuringiensis*. However, some statements will be amended on the product labels, as outlined in the attached detailed response.

We trust that the information provided in the attached detailed response provides some clarity to the issues you raised. The PMRA continues to put human health and the environment at the forefront of our regulatory activities, and will only register products for which there is reasonable certainty that no harm will result from their use as directed, including *Bacillus thuringiensis*.

Sincerely,

Marion Law
Chief Registrar
PEST MANAGEMENT REGULATORY AGENCY

Attachment:
Detailed Response to Notice of Objection

Attachment: A
Sub. No. 2008-2521

Detailed Response to Notice of Objection – RVD2008-18 *Bacillus thuringiensis*

The notice of objection, filed under subsection 35(1) of the *Pest Control Products Act* (PCPA), by Mr. Stephen Nicholson regarding the re-evaluation decision for *Bacillus thuringiensis* has now been reviewed and assessed in accordance with the Act and Regulations.

The following information was received and reviewed in support of the notice of objection:

- Attachment to notice of objection (rationale)

Issues raised in the Notice of Objection are **bolded**, PMRA responses are not.

1) Aquatic Statement

The proposed label language wording is unacceptable and if applied, will result in severely limiting the ability of protection managers to protect the nation's forested lands. The proposed wording in not supported by fact and ignores over 30+ years of successful aerial applications to North American forests.

Research work conducted by Charles Buckner, Peter Kingsbury, Steve Holmes, and David Kreutzweiser amongst others has shown that impact to aquatic habitats is negligible. (Numerous references available)

Operational assessments conducted in Quebec by the provincial Ministry of Resources, and in Ontario by the provincial Ministry of Natural Resources in the 1980's support the conclusions drawn by these researchers.

Additionally reference texts such as by Glare and O'Callaghan, (2000) and the World Health Organization (1999) would indicate that PMRA's proposed wording regarding aquatic habitats is not supported by science.

As indicated in the PACR document, since health risks associated with drinking water and Bt are negligible, and aquatic habitat impacts are minimal or non-existent, the statement as proposed is unjustified and not based on fact or in science.

Additionally, PMRA's misuse of GPS/GIS terminology in identifying aquatic habitats underscores its lack of understanding of current forest protection technology.

Proposed Wording:

Delete all references to 'lotic' and 'lentic' as this adds a degree of complexity and interpretation not required for label purposes. In layman terms, water is either standing, running, or frozen; do not complicate the issue.

Amend first sentence of current wording as follows:

'Avoid direct application to sensitive aquatic habitats... ...estuaries or marine habitats.'

The statement, "Do not apply directly to aquatic habitats ...", was intended to prevent all aquatic uses (direct applications) of Btk-based products since there are no registered aquatic uses for this microbial pest control agent. The intent was not to limit indirect aquatic applications which may occur during forestry applications, especially in small aquatic habitats that are intermingled in forests. As noted in the Re-evaluation Decision Document, RVD2008-18, *Bacillus thuringiensis*, PMRA recognized that the statement could have alternate meanings to other jurisdictions so the following alternate statement was drafted in consultation with stakeholders:

"As this product is not registered for the control of pests in aquatic systems, DO NOT use to control aquatic pests."

The previous statement will no longer be required on the label. In addition, the PMRA will no longer require the following statement under the "Directions for use" section since it makes reference to sensitive aquatic habitats:

"BEFORE AERIAL APPLICATIONS TO FORESTS - Consult the most recent provincially approved topographic maps of the area to be treated (1: 50,000) or more up-to-date information (e.g. GPS systems) to identify sensitive aquatic habitats. Sensitive aquatic habitats include:

a) All running (lotic) and standing (lentic) water bodies, including impoundments, beaver ponds and bog ponds, that appear on the map or GPS system;
b) Running (lotic) and standing (lentic) water bodies that do not appear on the map or GPS system but are visible from the air."

2) Personal Protective Equipment

Again, the proposed label language is not supported by fact. Research conducted regarding exposure levels of agricultural workers to microbial compounds is not applicable to forestry applications. It also misrepresents the risks involved to the public, especially regarding the use of Btk to protect forested residential areas.

Protection program managers are placed in an awkward situation with this proposed requirement; all studies show, and PMRA agrees that Btk is of minimal risk to people, yet PMRA is mandating the use of significantly more stringent PPE. This sends a definite mixed message that will only make a program manager's duties more difficult.

Forestry applications use fully formulated products, handled through closed-loop loading systems. In a typical forestry season, ground workers loading aircraft etc are exposed to the products in a liquid form, and only for a brief time when opening tank hatches etc. There is no particulate matter and no reason for a NIOSH -95 series type respirator.

Contrary to PMRA's statement, NIOSH-approved respirators ARE more intrusive and threatening in appearance.

This requirement will only serve to increase anxiety of residents and bystanders living in residential forested areas that are being sprayed with Btk.

Proposed Wording:

Delete in entirety all references to NIOSH-95 respiratory equipment. Current label language is acceptable.

The current PMRA policy on the requirement of a dust/mist filtering respirator mask (MSH/NIOSH approval number prefix TC-21C) or a NIOSH-approved respirator with any N-95, R-95, P-95 or HE filter for biological products was largely adopted due to hygienic/sensitization concerns associated with the use of large concentrations of micoorganisms as well as harmonization activities such as joint reviews under North American Free Trade Agreement (NAFTA). In some cases, masks/respirators may also be required as a result of acute mammalian testing (i.e., pulmonary studies).

Microbial pest control products contain numerous biological macromolecules associated with not only the microbial pest control agent, but those associated with possible microbial contaminants, and growth medium constituents as well. Many of these biological materials could, in theory, induce allergies in susceptible individuals via a number of possible routes of exposure. PMRA is aware of standard OECD and U.S. EPA test methods for evaluating the sensitization potential of products, however, these methods only measure the sensitization potential of compounds on a small number of test animals via the dermal/intradermal route. Since these studies do not include a larger number of animals to account for natural variation in any given population and only measure the sensitization potential of samples via the dermal/intradermal route (e.g., not inhalation or intranasal routes), they do not entirely address PMRA's concerns with these types of product. PMRA is also aware of growing evidence that, at certain exposure and/or at certain periods of life, exposure to some microorganisms may be beneficial and may even reduce the risk for allergies. These findings, however, are not definitive meaning that some individuals can still develop allergies despite early exposure to bacteria. In addition, some researchers noted that, if B-cells were already primed to produce IgE antibodies, microbial antigens could still stimulate those B-cells and thus exacerbate existing allergic conditions. Also, positive sensitization reactions were reported in several dermal sensitization studies conducted on previously registered and currently registered products (see "Dermal sensitization studies" below) despite the limitations noted above.

The PMRA would like to add that the requirement for a NIOSH-approved respirator/mask is also justified by findings in acute pulmonary studies. Acute pulmonary studies conducted on various *B. thuringiensis*-based products have demonstrated severe effects at high doses (i.e., $\geq 10^8$ colony forming units per animal; see "Pulmonary studies" below). Although these effects are not expected to occur following a single operational exposure, the observed persistence of *B. thuringiensis* in the lungs could lead to an accumulation of spores in the lungs of applicators, and handlers/mixers through repeated exposure during an entire use season. The above-noted respirators/masks can significantly reduce the accumulation of this microorganism in the lungs of workers in situations where inhalation exposure is likely. The petitioner, however, has noted that the requirement for a respirator/mask is unnecessary if closed-loop transfer systems are used to load the product onto aircrafts. The PMRA has carefully considered this comment and has

decided to make the following changes to the aerial application instructions *B. thuringiensis*-based products:

- the handler requirement for a NIOSH-approved respirator/mask and eye goggles may be waived when handlers use closed systems to load *B. thuringiensis*-based products onto aircrafts;
- when reduced personal protective equipment is worn, the respirator/mask and eye goggles must be immediately available for use in the event of an emergency such as a spill or equipment breakdown; and

- as noted in the Re-evaluation Decision Document, RVD2008-18, the requirement for eye goggles may be waived entirely if indicated by eye irritation test data or an acceptable rationale.

As a result, the following aerial application instructions and precautions will be required on all *B. thuringiensis*-based products that have aerial applications:

> "**Aerial Application Instructions:**
> Apply only by fixed-wing or rotary aircraft equipment that has been functionally and operationally calibrated for the atmospheric conditions of the area and the application rates and conditions of this label.
>
> Label rates, conditions and precautions are product-specific. Apply only at the rate recommended for aerial application on this label. Where no rate for aerial application appears for the specific use, this product cannot be applied by any type of aerial equipment.
>
> Ensure uniform application by using appropriate marking devices and/or electronic guidance equipment.
>
> **Use Precautions:**
> Apply only when meteorological conditions at the treatment site allow for complete and even coverage. Apply only when meteorological conditions are in compliance with local and/or provincial authorities.
>
> **Operator Precautions:**
> DO NOT allow the pilot to mix product to be loaded onto the aircraft. However, loading of premixed product with a closed system is permitted. It is desirable that the pilot have communication capabilities at each treatment site at the time of application.
>
> The field crew and the mixer/loaders must wear the personal protective equipment described in the PRECAUTIONS section of this label. When handlers/loaders use closed systems to load the product onto the aircraft, the handler requirement for eye goggles and a NIOSH-approved respirator/mask with any N-95, R-95, or P-95 filter for biological products may be waived. When reduced personal protective equipment is worn, the respirator/mask and eye goggles must be immediately available for use in an emergency such as a spill or equipment breakdown.
>
> All personnel on the job site must wash hands and face thoroughly before eating and drinking. Protective clothing must be washed before reuse.

Decontaminate aircraft cockpits and vehicle cabs if contamination occurs.

Product Precautions:
Read and understand the entire label before opening this product. If you have questions, call the manufacturer at [insert toll free number] or obtain technical advice from the distributor or from your provincial agricultural or forestry representative. Application of this specific product must meet and/or conform to the aerial uses and rates on this label."

With regards to concerns with the cost and the public perception of NIOSH-approved respirators/masks, PMRA is aware of these concerns and would like to note that the Agency's primary concern on this matter is the health and safety of all handlers, mixers/loaders, and applicators. The PMRA would also like to clarify its response to this concern in RVD2008-18 by adding that some NIOSH-approved N-95 masks look almost identical to regular dust masks and are thus not any more intrusive or threatening in appearance.

Dermal sensitization studies

PMRA 1381470	2000. Skin Sensitization Study in Guinea Pigs, DACO: M4.6.
PMRA 1193164	Human Health and Safety Testing, Reporting of Hypersensitivity Incidents, Dermal Sensitization Study in Guinea Pigs, Final Report, Completed December 8, 1997
PMRA 1208220	Dermal Sensitization Study of Dipel R6AF in Guinea Pigs (L08151-B), DACO: 4.6.6.
PMRA 1247735	Hypersensitivity Study on Teknar in the Guinea Pig, DACO: 4.6.6.
PMRA1169441	Dermal Sensitization – Guinea Pig, DACO: 4.2.6

Pulmonary studies

PMRA 1174032	Acute Pulmonary Toxicity/Pathogenicity Study of Dipel Technical Material (Bacillus thuringiensis var Kurstaki) in Rats, Final Report, DACO: M4.2.3.
PMRA 1174179	Four-Week Subacute Inhalation Toxicity Study in Guinea Pigs. Dipel. Final Report. Ocotber 17, 1973. DACO: M4.2.3.
PMRA 1381464	1988, Murine Pulmonary Toxicity of Bacillus thuringiensis sp. Microbial Pesticides, DACO: M4.2.3.
PMRA 1465204	1990, Acute Pulmonary Toxicity / Pathogenicity Study of Vectobac Technical Material (Bacillus thuringiensis var. israelensis) in Rats, Document 5, DACO: M4.2.3.

PMRA 1174389	Acute Pulmonary/Pathogenicity Study in Rats, DACO: M4.2.3.
PMRA 1225754	Acute Pulmonary Toxicity and Infectivity to Rats, DACO: 4.2.3, 4.6.3.

Note: These study reports are available in the PMRA Reading Room.

3) Precautionary Statement – Sensitization

This is being fully addressed by my regulatory colleagues. My concern is that the approach taken by PMRA to add 'boiler plate' language to all pesticide labels is not flexible enough to be responsive to individual products. All registered pesticides do not pose the same risks, so blanket language is unacceptable and ignores product-specific research. Furthermore, if PMRA does not accept the science supporting this issue, again the risks of using such products will be, in the public's eye, unacceptable.

Proposed Wording:

As per Valent BioSciences Corporation submission.

PMRA's policy on the sensitization potential of various microbial pest control agents is described in PMRA's response to the petitioner's concern on the requirement of personal protective equipment.

To address the objector's original concern on PMRA's flexibility on sensitization labelling, the PMRA has reviewed some data and would consider new data to re-evaluate the requirement for product labeling, however, appropriate data are difficult to generate for microbial pest control agents (for additional details see PMRA's response to the objector's concern on the requirement of personal protective equipment), especially new ones with little or no history of use without widespread reporting of adverse effects. That said, *B. thuringiensis*-based products have a long history of use in many countries, including Canada and the United States. This long period of use has indeed generated some alternative sources of data in support of *B. thuringiensis*, especially Btk. Some of these data were in fact considered and discussed in the Proposed Acceptability for Continuing Registration, PACR2006-09, *Re-evaluation of Bacillus thuringiensis*. As noted in PACR2006-09, no increases in health effects were observed during large-scale Btk spray programs conducted in Auckland, New Zealand, southern Vancouver Island, British Columbia, and Seattle, Washington, in 1996, 1999 and 2000, respectively. These data, however, were not considered for the removal of sensitization statements on product labels at the time of re-evaluation. As a result, PMRA has conducted a re-assessment of the sensitization potential of *B. thuringiensis* which considered the detailed rationale provided by Valent BioSciences Corporation.

According to the information and data supplied by Valent BioSciences Corporation, no adverse health effects or respiratory reactions to *B. thuringiensis* were reported in numerous workers exposed to Btk and *B. thuringiensis* subsp. *israelensis* (Bti). In some cases, however, positive skin test reactions and specific IgE and IgG antibodies to spore extracts of *B. thuringiensis* were observed. These observations, according to Valent BioSciences's rationale, do not necessarily

indicate a symptomatic state, but are rather indicative of previous exposure to these microbial organisms. The objector has also provided a number of published studies which note that, at certain exposure and/or at certain periods of life, exposure to some microorganisms may be beneficial and may even reduce the risk for allergies. These findings, however, are not definitive meaning that some individuals can still develop allergies despite early exposure to bacteria. In addition, some researchers noted that, if the immune system was already primed to produce allergies, microbial antigens could exacerbate existing allergic conditions. Also, positive sensitization reactions were reported in several dermal sensitization studies conducted on previously registered and currently registered products (see "Dermal sensitization studies" in PMRA's response to the objector's concern on personal protective equipment) despite despite limitations in study protocols.

Considering all the available data on *B. thuringiensis* at this time, PMRA has determined that *B. thuringiensis* has some potential to induce sensitizations reactions in previously unsensitized individuals. As a result, all product labels must include the statements, "Potential Sensitizer" and "May cause sensitization." on the principal and secondary display panels.

4) Resistance Management

Again, a broad brush approach by PMRA that it not supported by fact. Resistance is NOT an issue in forest applications, and there are few alternate products available if a program manager wished to follow PMRA's recommendations.

In reviewing the original PACR Re-evaluation Document, there is no indication of any concerns re resistance management. It can also be argued that in consideration of 30+ years of application to forests, resistance has never occurred. Resistance has been noted twice, and in isolated conditions (once on an island, and once in a storage silo); a quick scan of the literature would indicate the fallacy of such a recommendation.

Proposed Wording:

Delete this section as it is non-applicable."

The potential for development of resistance to *Bacillus thuringiensis* subsp. *kurstaki* (BTB) has been demonstrated for several different species of Lepidoptera in laboratory studies. Development of resistance resulting from operational use of pest control products containing this active ingredient under field conditions has been documented for at least two species (diamondback moth, *Plutella xylostella*, in fields the USA and other countries, and cabbage looper, *Trichoplusia ni*, in greenhouses in Canada). The development of resistance may be unlikely under current use patterns for forestry applications, but it is prudent to include resistance management statements on the labels of pest control products and they are required on all end-use product labels except for homeowner/residential uses. The fact that resistance historically has not been an issue in forest applications does not preclude the possibility that it might become an issue in the future. It should be noted that the resistance management statements are only recommendations and include a description of the key condition under which resistance is likely to develop (repeated use in the same site). Users should recognize that repeated use of insecticides in the same site is not normal practice in current forest pest management, so the resistance management recommendations would not normally apply to use in forestry, although repeated application in the same site cannot be completely ruled out, even for forestry

applications. In addition, some products are currently registered for both forestry applications and for agricultural uses, for which resistance management is a greater concern.