



EPA REGISTRATION DIVISION COMPANY NOTICE OF FILING FOR PESTICIDE PETITIONS PUBLISHED IN THE FEDERAL REGISTER

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TEMPLATE:

EcoPhage LTD.

4F9112

EPA has received a pesticide petition (4F9112) from EcoPhage LTD., 3 Pinchas Sapir St., Ness Ziona, Israel 7403626 requesting, pursuant to section 408(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a(d), to amend 40 CFR part 180 to establish an exemption from the requirement of a tolerance for residues of Bacteriophage active against *Xanthomonas campestris* pv. *vesicatoria*_EcoPhage and Bacteriophage active against *Pseudomonas syringae* pv. *tomato*_EcoPhage under 40 CFR when used as an active ingredient for in or on all food or feed commodities in pesticide formulations. EPA has determined that the petition contains data or information regarding the elements set forth in section 408 (d)(2) of FFDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1. *Plant metabolism.*

2. *Analytical method.* An analytical method is not required for enforcement purposes since EcoPhage is seeking to establish an exemption from the requirement of a tolerance without any numerical limitations.

3. *Magnitude of residues.* NA-Remove

B. Toxicological Profile

1. *Acute toxicity.* Bacteriophages are the most abundant group of biological entities on the planet, are naturally occurring viruses that are found in soil and water and

in association with plants and animals. Bacteriophages are obligate parasites of bacteria, which means they attach to, infect, and reproduce in bacteria, and are host-specific for bacteria, with specific bacteriophage attacking only one bacterial species and most frequently only one strain within a bacterial species. As such, bacteriophage's do not attack other beneficial bacteria. In addition, there is no evidence for bacteriophage's infecting any life form except bacteria, even though, for instance, life forms such as humans and other animals commonly consume bacteriophages found in water, on plant surfaces, and in food.

No toxicological studies are available on the strains of bacteriophages included in Bacteriophage active against *Xanthomonas campestris pv. vesicatoria*_EcoPhage and Bacteriophage active against *Pseudomonas syringae pv. tomato*_EcoPhage. Several peer-reviewed scientific papers have been submitted and summarized on similar bacteriophages for each toxicity guideline. EcoPhage requests a waiver of the toxicological data requirements for the Bacteriophage active against *Xanthomonas campestris pv. vesicatoria*_EcoPhage and Bacteriophage active against *Pseudomonas syringae pv. tomato*_EcoPhage based on the several references showing the lack of adverse effects, host specificity, and lack of evidence of pathogenicity against anything other than bacteria.

2. *Genotoxicity*. NA-Remove

3. *Reproductive and developmental toxicity*. NA-Remove

4. *Subchronic toxicity*. NA-Remove

5. *Chronic toxicity*. NA-Remove

6. *Animal metabolism*. NA-Remove

7. *Metabolite toxicology*. NA-Remove

8. *Endocrine disruption*. NA-Remove

C. *Aggregate Exposure*

1. *Dietary exposure*. The intended use of Bacteriophage active against *Xanthomonas campestris pv. vesicatoria*_EcoPhage and Bacteriophage active against *Pseudomonas syringae pv. tomato*_EcoPhage is an application for the purpose of the control and prevention of bacterial blight and bacterial speck on peppers and tomatoes. So dietary exposure to this active ingredient is possible.

i. *Food*. Residues remaining after treatment may be reduced because bacteriophages are sensitive to ultraviolet light and heat. Even if residues persist on food commodities, bacteriophages are already common in plant materials and food and likely consumed regularly without reports of associated human health hazards. Further, bacteriophages are host specific and results of toxicological testing indicate no risk to human health from consuming Bacteriophage active against *Xanthomonas campestris pv. vesicatoria*_EcoPhage and *Pseudomonas syringae pv. tomato*_EcoPhage do not produce recognized toxins, enzymes, or virulence factors normally associated with mammalian

invasiveness or toxicity.

ii. *Drinking water.* As Bacteriophage active against *Xanthomonas campestris pv. vesicatoria*_EcoPhage and Bacteriophage active against *Pseudomonas syringae pv. tomato*_EcoPhage are intended for application to tomatoes and peppers in the environment, the potential for these bacteriophages to enter surface water or ground water is practically non-existent. However, exposure to humans from residues of Bacteriophage active against *Xanthomonas campestris pv. vesicatoria*_EcoPhage and Bacteriophage active against *Pseudomonas syringae pv. tomato*_EcoPhage in drinking water as a result of pesticidal use is considered unlikely. The proposed end-use product with this active ingredient is applied at low use rates that would not be expected to increase levels of the microbe above natural levels. If the bacteriophages do remain in the environment, they will degrade rapidly without the presence of the target host bacterium. Additionally, should the bacteriophage find their way into water intended for human consumption and that is treated, they would not tolerate the conditions water is subjected to in a drinking water facility (including flocculation, chlorination, pH adjustments, UV exposure, filtration, and high temperatures). Additionally, numerous bacteriophages have been isolated from water and waste water sources indicating humans are already exposed to bacteriophages similar to those seeking an exemption from tolerance by EcoPhage.

2. *Non-dietary exposure.* Bacteriophages belonging to the Caudovirales order are naturally occurring and found worldwide. As a pesticidal active ingredient, bacteriophages have historically been applied to combat bacterial plant pathogens, such as *Xanthomonas* and *Pseudomonas* species. Due to the use patterns and low application rates, there will not likely be a significant increase in exposure over the background levels of Bacteriophage active against *Xanthomonas campestris pv. vesicatoria*_EcoPhage and Bacteriophage active against *Pseudomonas syringae pv. tomato*_EcoPhage in agricultural crops. Furthermore, there is no evidence of any concern for inhalation or dermal toxicity at various levels of exposure than would be expected to be encountered by a typical agricultural applicator. Lastly, given that these phages only infect *Xanthomonas* and *Pseudomonas* plant pathogens and there is no recognized relationship that exists between the phage genus and any pathogen of humans and animals, no adverse effects to humans from inhalation or dermal exposure to the widespread use of bacteriophage's have been reported or are anticipated.

D. Cumulative Effects

EcoPhage has not found Bacteriophage active against *Xanthomonas campestris pv. vesicatoria*_EcoPhage and Bacteriophage active against *Pseudomonas syringae pv. tomato*_EcoPhage to share a common mechanism of toxicity with any other substance and Bacteriophage active against *Xanthomonas campestris pv. vesicatoria*_EcoPhage and Bacteriophage active against *Pseudomonas syringae pv. tomato*_EcoPhage do not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, EcoPhage does not find to have a common mechanism of toxicity with other substances. EcoPhage concludes no cumulative effects associated with Bacteriophage active against *Xanthomonas campestris pv. vesicatoria*_EcoPhage and Bacteriophage active against *Pseudomonas syringae pv. tomato*_EcoPhage need to be considered.

E. Safety Determination

1. *U.S. population.* Based on the acute toxicity and pathogenicity data previously discussed and the use of bacteriophages as a microbial pesticide for approximately 18 years without reported adverse effects to humans, EcoPhage concludes that there is a reasonable certainty that no harm will result other U.S. population, including infants and children, from aggregate exposure to the residues of Bacteriophage active against *Xanthomonas campestris pv. vesicatoria*_EcoPhage and Bacteriophage active against *Pseudomonas syringae pv. tomato*_EcoPhage. This included all anticipated dietary exposures and all other exposures for which there is reliable information. EcoPhage concludes that the data and information available on Bacteriophage active against *Xanthomonas campestris pv. vesicatoria*_EcoPhage and Bacteriophage active against *Pseudomonas syringae pv. tomato*_EcoPhage do not demonstrate toxic, pathogenic, and/or infective potential to mammals. Thus there are no threshold effects of concern, as a result an additional margin of safety is not necessary.

2. *Infants and children.* NA-Remove

F. International Tolerances

EcoPhage is not aware of any country requiring a tolerance for Bacteriophage active against *Xanthomonas campestris pv. vesicatoria*_EcoPhage and Bacteriophage active against *Pseudomonas syringae pv. tomato*_EcoPhage nor have any CODEX Maximum Residue Levels been established for any food crops at this time.