

“safe.” Section 408(c)(2)(A)(ii) of the FFDCA defines “safe” to mean that “there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information.” This includes exposure through drinking water and in residential settings, but does not include occupational exposure. Section 408 of the FFDCA (b)(2)(C) requires EPA to give special consideration to exposure of infants and children to the pesticide chemical residue in establishing a tolerance and to “ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue. . . .” Additionally, section 408(b)(2)(D) of the FFDCA requires that the Agency consider “available information” concerning the cumulative effects of a particular pesticide’s residues and “other substances that have a common mechanism of toxicity.”

EPA performs a number of analyses to determine the risks from aggregate exposure to pesticide residues. First, EPA determines the toxicity of pesticides. Second, EPA examines exposure to the pesticide through food, drinking water, and through other exposures that occur as a result of pesticide use in residential settings.

IV. Toxicological Profile

Consistent with section 408(b)(2)(D) of the FFDCA, EPA has reviewed the available scientific data and other relevant information in support of this action and considered its validity, completeness, and reliability and the relationship of this information to human risk. EPA has also considered available information concerning the variability of the sensitivities of major identifiable subgroups of consumers, including infants and children.

Based on the toxicology data cited and the limited exposure to humans and domestic animals, there is a reasonable certainty that no harm will result from aggregate exposure to IMMGV to the U.S. population including infants and children to residues of IMMGV when used as viral pest control agent to control the Indian Meal Moth on all food commodities. This includes all anticipated dietary exposures and all other exposures for which there is reliable information. The Agency has arrived at this conclusion based on the long history of research, use and safety of testing baculoviruses which is documented in the public scientific literature (Refs. 1–5). IMMGV is a

naturally occurring organism to which some environmental and dietary exposure is likely to be common for most individuals. The conclusion of safety is further supported by the lack of toxic or pathogenic effects on test animals at high doses (data submitted by the registrant, MRID numbers 453070–01, 450662–07, and 450662–08). Baculoviruses have been described in the scientific literature for approximately 40 years. In addition to their natural occurrence, these viruses have a long history of safe use as bioinsecticides. Baculoviruses have been studied extensively in both laboratory and field experiments, which have shown that the virus host range is limited to arthropods. IMMGV has been shown to be very restricted in its insect host range. No toxicological or pathogenic effects produced by the baculovirus itself, have been observed in mammals, birds, fish or plants. The lack of mammalian toxicity at high levels of exposure to IMMGV demonstrates the safety of the product at levels well above maximum possible exposure levels anticipated in the crops. There has been a significant amount of research performed on baculoviruses and numerous scientific references are available which describe the biology of these viruses, their host range, and their mode of action. Toxicity studies submitted in support of this tolerance exemption include the following:

1. *Acute oral toxicity/pathogenicity (453070–01)*. Thirteen male (254–321 grams (g)) and 13 female (160–208g) albino rats were divided into three groups and treated with 0.1 milliliter (mL) of the test substance. Treatment was administered by oral gavage with at least 1×10^8 viral particles per animal. No deaths occurred in any of the test animals. Other than diarrhea during the first few hours following dosing, there were no other apparent clinical symptoms. Based upon the data there were no significant adverse effects reported upon doses of at least 1×10^8 viral capsules. The toxicity category was deemed Toxicity Category IV.

2. *In vitro mammalian cell viral infectivity in mammalian cells (450662–08)*. Human WI–38 and WS1 cell cultures and African green monkey CV–1 cell cultures were exposed to 1×10^6 units of the test substance. The cell cultures were observed daily for 21 days following inoculation for virus induced cytopathic effects. The test preparation was shown to be highly infectious and cytopathic to the target *Plodia interpunctella* larva. No differences were seen between the virus treated nor the solvent treated control cell cultures with respect to any cytopathic endpoint

at any time post-inoculation. Based on the data, there was no evidence that the virus could infect any of the three mammalian cell lines.

3. *In vitro mammalian cell viral induced cytotoxicity (450662–07)*. Human WI–38 and WS1 cell cultures and African green monkey CV–1 cell cultures were exposed to 1×10^6 units of IMMGV technical (IMMGV) for 1 hour. The cell cultures were then washed, refed with virus-free medium, incubated for 8 days, fixed, stained and the number of colonies counted. The test preparation was shown to be highly infectious and cytopathic to the target *Plodia interpunctella* larva although analysis determined that the actual number of viral capsules used was only 42% of the target value. No differences were seen between the virus treated and the solvent treated control cell cultures with respect to cloning efficiency in any of the three cell lines. Based on the data, there was no evidence that the test substance was cytotoxic to any of the three mammalian cell lines.

4. *Acute eye irritation (450662–09)*. The test substance was instilled in the eyes of four males and two female adult New Zealand albino rabbits at approximately 0.04 g/eye ($\sim 7.14 \times 10^9$ viral capsules). Animals were acclimated for 11 days and before treatment their eyes were checked for normalcy using ophthalmic fluorescein and an ultraviolet (UV) lamp. The right eye of each animal was treated and the other eye served as a control. No deaths occurred. Clinical signs noted included conjunctivitis, corneal opacity and iritis, all of which cleared within 4 days of treatment. The toxicity from this study was deemed Toxicity Category IV.

5. *Data waivers*. Data waivers were requested for the following studies:

i. *Acute dermal toxicity*. This study was waived based upon the lack of toxicity in animals dosed orally (453070–01) and more importantly cells inoculated with viral pest control agent (450662–07 and 450662–08). Cell culture infectivity and cytotoxicity assays demonstrated that there were no toxic effects to mammalian cell lines (human lung, human endothelial and primate renal cell lines) when inoculated with doses of IMMGV. Cell culture assays provide valuable information on the ability of the viral pest control agent to infect, replicate in, transform or cause toxicity in mammalian cell lines. Thus, this assay is the most likely indicator of evaluating the toxicity of a viral pest control agent. Unlike the oral, dermal and inhalation routes of exposure, these barriers (exposure conditions) do not exist in cell culture assays as the host cell is completely exposed, thus,