

Cry34Ab1 and Cry35Ab1 proteins are not considered toxic.

#### IV. Aggregate Exposures

In examining aggregate exposure, section 408 of the FFDCA directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures, including drinking water from ground water or surface water and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

##### *Dietary Exposure*

Exposure via the skin or inhalation is not likely since the plant-incorporated protectant is contained within plant cells, which essentially eliminates these exposure routes or reduces these exposure routes to negligible. Oral exposure, at very low levels, may occur from ingestion of processed corn products and, potentially, drinking water. However a lack of mammalian toxicity and the digestibility of the plant-incorporated protectants have been demonstrated. The use sites for the Cry34Ab1 and Cry35Ab1 proteins are all agricultural for control of insects. Therefore, exposure via residential or lawn use to infants and children is not expected. Even if negligible exposure should occur, the Agency concludes that such exposure would present no risk due to the lack of toxicity demonstrated for the Cry34Ab1 and Cry35Ab1 proteins.

#### V. Cumulative Effects

Pursuant to FFDCA section 408(b)(2)(D)(v), EPA has considered available information on the cumulative effects of such residues and other substances that have a common mechanism of toxicity. These considerations included the cumulative effects on infants and children of such residues and other substances with a common mechanism of toxicity. Because there is no indication of mammalian toxicity to these plant-incorporated protectants, we conclude that there are no cumulative effects for the Cry34Ab1 and Cry35Ab1 proteins.

#### VI. Determination of Safety for U.S. Population, Infants and Children

##### *A. Toxicity and Allergenicity Conclusions*

The data submitted and cited regarding potential health effects for the Cry34Ab1 and Cry35Ab1 proteins include the characterization of the expressed Cry34Ab1 and Cry35Ab1 proteins in corn, as well as the acute oral toxicity, heat stability, and *in vitro*

digestibility of the proteins. The results of these studies were determined applicable to evaluate human risk and the validity, completeness, and reliability of the available data from the studies were considered.

Adequate information was submitted to show that the Cry34Ab1 and Cry35Ab1 test materials derived from microbial cultures were biochemically and functionally similar to the protein produced by the plant-incorporated protectant ingredients in corn. Production of microbially produced protein was chosen in order to obtain sufficient material for testing.

The acute oral toxicity data submitted support the prediction that the Cry34Ab1 and Cry35Ab1 proteins would be non-toxic to humans. When proteins are toxic, they are known to act via acute mechanisms and at very low dose levels (Ref. 3). Since no treatment-related adverse effects were shown to be caused by Cry34Ab1 and Cry35Ab1 proteins, even at relatively high dose levels (greater than 5,000 mg/kg based upon a dosage of a 1:4.6 ratio mixture of (54% pure) Cry34Ab1 and (37% pure) Cry35Ab1 proteins and greater than 2,000 mg/kg for an equimolar mixture (1:3) of the pure proteins), the Cry34Ab1 and Cry35Ab1 proteins are not considered toxic. This is similar to the Agency position regarding toxicity and the requirement of residue data for the microbial *Bacillus thuringiensis* products from which this plant-incorporated protectant was derived. See 40 CFR 158.740(b)(2)(i). For microbial products, further toxicity testing and residue data are triggered by significant acute effects in studies such as the mouse oral toxicity study to verify the observed effects and clarify the source of these effects (Tiers II and III).

Although Cry34Ab1 and Cry35Ab1 expression level data were submitted, residue chemistry data were not required for a human health effects assessment of the subject plant-incorporated protectant ingredients because of the lack of mammalian toxicity. Both: (1) Available information concerning the dietary consumption patterns of consumers (and major identifiable subgroups of consumers including infants and children); and (2) safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of food additives, are generally recognized as appropriate for the use of animal experimentation data were not evaluated. The lack of mammalian toxicity at high levels of exposure to the Cry34Ab1 and Cry35Ab1 proteins demonstrates the safety of the product at

levels well above possible maximum exposure levels anticipated in the crop.

The genetic material necessary for the production of the plant-incorporated protectant active ingredients are the nucleic acids (DNA, RNA) which comprise genetic material encoding these proteins and their regulatory regions. The genetic material (DNA, RNA) necessary for the production of Cry34Ab1 and Cry35Ab1 proteins in corn have been exempted under the blanket exemption for all nucleic acids (40 CFR 174.175).

##### *B. Infants and Children Risk Conclusions*

FFDCA section 408(b)(2)(C) provides that EPA shall assess the available information about consumption patterns among infants and children, special susceptibility of infants and children to pesticide chemical residues and the cumulative effects on infants and children of the residues and other substances with a common mechanism of toxicity. In addition, FFDCA section 408(B)(2)(C) also provides that EPA shall apply an additional tenfold margin of safety for infants and children in the case of threshold effects to account for prenatal and postnatal toxicity and the completeness of the database unless EPA determines that a different margin of safety will be safe for infants and children.

In this instance, based on all the available information, the Agency concludes that there is a finding of no toxicity for the Cry34Ab1 and Cry35Ab1 protein and the genetic material necessary for their production. Thus, there are no threshold effects of concern and, as a result, the provision requiring an additional margin of safety does not apply. Further, the provisions of consumption patterns, special susceptibility, and cumulative effects do not apply.

##### *C. Overall Safety Conclusion*

There is a reasonable certainty that no harm will result from aggregate exposure to the U.S. population, including infants and children, to the Cry34Ab1 and Cry35Ab1 proteins and the genetic material necessary for their production. This includes all anticipated dietary exposures and all other exposures for which there is reliable information. The Agency has arrived at this conclusion because, as discussed above, no toxicity to mammals has been observed for the plant-incorporated protectants.