

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).

The Agency has considered the product characterization data showing expression levels of Cry1F protein in cotton seed exposure levels of consumers (and major identifiable subgroups of consumers) to the pesticide chemical residue and to other related substances. These considerations include dietary exposure under the tolerance exemption and all other tolerances or exemptions in effect for the plant-incorporated protectants' chemical residue, and exposure from non-occupational sources. 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 cottonseed oils 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 Cry1F protein 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 Cry1F protein. Refer to the *Bacillus thuringiensis* Reassessment BRAD dated October 15, 2001.

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, EPA concludes that there are no cumulative effects for the Cry1F protein.

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

A. Toxicity and Allergenicity Conclusions

The product characterization data are acceptable for Cry1F protein expressed in cotton. The Agency was able to determine that the Cry1F protein expressed in cotton was the same protein as the Cry1F expressed in corn which is covered by an existing tolerance exemption (40 CFR 180.1217). Also the Cry1F protein produced by microbial culture was biochemically and functionally similar to the protein produced by the plant-incorporated protectant in cotton. Therefore, the Agency was able to bridge mammalian toxicity data from a previous submission for Cry1F protein expressed in corn to cover the mammalian toxicity studies required for Cry1F protein expressed in cotton. These studies are the acute oral toxicity (MRID numbers 446911-01 and 450201-18), heat stability, amino acid homology (MRID numbers 452749-01 and 449717-01) and *in vitro* digestibility (MRID number 447149-03) studies.

The data submitted and cited regarding potential health effects for the Cry1F protein include the characterization of the expressed Cry1F protein 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.

The acute oral toxicity data submitted supports the prediction that the Cry1F protein 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. 1). Since no effects were shown to be caused by Cry1F protein, even at relatively high dose levels (>5,050 mg test substance/kg body weight; 576 mg Cry1F/kg body weight), the Cry1F protein is 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 Cry1F expression level data were required for an environmental fate

and effects assessment, 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: available information concerning the dietary consumption patterns of consumers (and major identifiable subgroups of consumers including infants and children); and 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. The lack of mammalian toxicity at high levels of exposure to the Cry1F protein demonstrates the safety of the product at levels well above possible maximum exposure levels anticipated in the crop. Refer to the *Bacillus thuringiensis* Reassessment BRAD dated October 15, 2001. Its 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 Cry1F protein in cotton has 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 data base 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 Cry1F protein and its genetic material necessary for its production in or on cotton. 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