11/12/91

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

008802

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

Subject: Review of Acute Pulmonary Toxicity/Pathogenicity Data and Addendum to Manufacturing Process in Support of an EUP/Registration of Bacillus thuringiensis var. aizawaii, ABG-6305 Technical Powder,

To: Mike Mendelsohn/Phil Hutton, PM-17
Insecticide-Rodenticide Branch

From: Rita Briggs, Ph.D., Chemist RB
Science Analysis and Coordination Branch (SACB)
Health Effects Division (H7509C)

Through: Reto Engler, Ph.D.,
Senior Science Advisor, HED

DATA REVIEW RECORD

Product Name: Bacillus thuringiensis (Berliner) var. aizawaii, ABG-6305
ID No: 000275-IA
Synonym: CenTari XENTARI
Caswell No: 066
HED Project: 1-2335
MRID No: 419748-01 - Acute Pulmonary Tox/Path/Infectivity
419748-10 - Addendum to Manufacturing Process (MRID No. 41722501)

BACKGROUND/ACTION REQUESTED

Toxicology and product analysis data were previously submitted and reviewed by HED (see memo. R.Briggs to M. Mendelsohn, April 24, 1991) in support of seven EUP

applications for the use of Bacillus thuringiensis var. aizawai technical powder (ABG-6305) and formulated end-use product (ABG-6314). At the time of the initial submission, Abbott requested that pulmonary data for B.t. var. kurstaki or B.t. var. israelensis be bridged to partially fulfill toxicological requirements for the new strain of B.t. var. aizawaii; SACB concurred that B.t. var. aizawaii is sufficiently similar in identity to B.t. var. kurstaki to warrant bridging of such data. However, the registrant has now submitted an acute pulmonary toxicity/pathogenicity/infectivity study on B.t. var. aizawaii, ABG-6305 as well as a description of a proposed modification to the manufacturing process. Registration Division has requested SACB's comments on the submitted data as well as on questions arising from the initial review. These issues are addressed below.

CONCLUSIONS

1. **Modifications to Manufacturing Process:** It is SACB's opinion that the proposed modifications to the manufacturing process do not incur any undue health risks.
2. **Acute pulmonary toxicity/pathogenicity/infectivity study:** Data submitted indicate that the TGAI, at a concentration of 6.4×10^8 CFU/kg body weight (approximately 1.65 to 1.81×10^8 CFU/animal) is non-toxic and non-infective. A pattern of clearance from the lungs also was clearly established indicating that the test material is non-persistent.
3. **Analytical Method for Quantification of Delta-endotoxin:** It is SACB's opinion that the analytical method, i.e. SDS-Page and densitometry, used to quantify delta-endotoxin is an acceptable method.
4. **Certified Limits:** SACB believes that comments on the range of certified limits for the inert ingredients in MP and EP preferably should be made by the section that normally does the reviews, i.e. Precautionary Review Section, Registration Support Branch.
5. **Food Tolerance Exemption:** the toxicological data submitted on the technical grade material permits SACB to support an exemption from a tolerance for this strain of Bacillus thuringiensis var. aizawaii provided conditions in 40 CFR 180.1011 are met.
6. **Data Requirements for the technical MP:** SACB does not see the need for any additional studies on the manufactured product (MP) since the components of the MP have been tested either in due course of fulfilling data requirements for the technical grade active ingredient (TGAI) or the end-use product (EP).
7. **Data Requirements for Registration:** It is SACB's opinion that the acute toxicity data submitted for the previous EUPs, along with the present acute pulmonary toxicity study, fulfill acute toxicity requirements for registration of Bacillus thuringiensis var. aizawaii technical powder (ABG-6305). However, as reported in the 'Conclusions' section in April 24 memo, data from the HPLC assay to determine presence of beta-exotoxin and storage stability data are still outstanding. These should be submitted before SACB can fully support registration.

MODIFICATIONS TO MANUFACTURING PROCESS ** CBI (151A-11)**

(Addendum to MRID# 419748-10) **MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED**

SACB DISCUSSION: SACB does not anticipate any adverse health risk resulting from the modifications made to the manufacturing process.

DATA EVALUATION REPORT (152A-1)

008802

Reviewed by: Rita Briggs, Ph.D., Chemist, SACB/HED RB

Secondary Reviewer: Roy Sjoblad, Ph.D., Microbiologist, SACB/HED RRS

Study Type: Acute Pulmonary Toxicity/Infectivity/Pathogenicity - Rat

MRID No: 419748-01

Caswell No: 066

Test Material : Bacillus thuringiensis var. aixawaii, ABG-6305 Technical Powder

Synonyms: Centari

Project No: 901292D/ABT 143-2/AC

Sponsor: Abbott Laboratories

Testing Facility: Huntington Research Centre Ltd., Cambridge, England

Title of Report: Acute Pulmonary Toxicity and Infectivity/ Pathogenicity to Rats of Bacillus thuringiensis ABG-6305

Authors: John N. Carter

Study Completed: February 12, 1991

Conclusion: Based on the results from the acute pulmonary tox/path/infect. study , SACB does not anticipate any unreasonable risk resulting from exposure to the test substance via the pulmonary route. A single dose of 1.65-1.81 x 10^8 CFU/animal was non-toxic, non-infective, and cleared from the lungs within 3 days after administration.

Classification: Acceptable

I. STUDY DESIGN

Test Material: Bacillus thuringiensis var. aizawaii, ABG-6305 was used at a concentration of 6.77 x 10^{10} CFU/g.

Test Animal: Crl:CD^R (SD)BR VAF Plus rats were obtained from Charles River U.K. Ltd., Kent, England. The animals weighed between 246-304 g and were 7-10 weeks of age at the time of dosing on Day 1.

Methods: Twenty-three female and twenty-three male rats used in the study were assigned to seven treated groups (Group A-G) and two control groups (Groups H and J). Each test group consisted of six animals (3/sex). Group H (shelf control) and Group J (untreated controls housed in a separate room) each contained four animals (2/sex).

The test material was suspended and diluted in sterile water to a concentration of 5.3×10^8 CFU/ml. Each treated rat received, via a single intratracheal instillation, approximately $1.65 - 1.81 \times 10^8$ CFUs in a volume of 1.2ml/kg. body weight.

The animals were observed daily for clinical signs of toxicity. Body weights were recorded on Days 1, 4, 8, 15, 22, 36 and 50. At the time of sacrifice, post-mortem examinations were conducted and samples of blood, brain, lungs, liver, spleen, kidney, mesenteric lymph node, and caecal contents were removed except in the case of Group A and Group I on Day 1 when only lung samples were taken.

II. RESULTS

No mortality and no treatment-related clinical signs of toxicity occurred during the course of the study. All animals gained weight throughout the experimental period and by the end of the study group mean body weights of treated animals were comparable to those of the control animals.

No macroscopic abnormalities were observed at the time of sacrifice.

A pattern of clearance from the lung was established. One hour following administration, viable organisms recovered from the lungs of treated animals ranged from approximately 6×10^3 to 1.5×10^4 CFUs. At Day 3, five of the six animals had non-detectable levels of the organism; the sixth animal had very low levels (40 CFUs). The lungs were clear of test material thereafter.

Bacillus thuringiensis, ABG-6305 also appeared to be non-infective. The organism was detected at very low levels in the kidneys of two animals (19 CFU/g and 1.45×10^2 CFU/g) on Day 7, and in the spleen of one animal on each of Day 7 (87 CFU/g) and Day 14 (58 CFU/g).

III. SACB DISCUSSION

A single intratracheal instillation of Bacillus thuringiensis, ABG-6305, at a concentration of 6.4×10^8 CFU/kg body weight, produced no deaths or clinical signs of toxicity. Weight gains in treated animals were comparable to controls and no macroscopic abnormalities were noted at necropsy. The test material was non-infective and a pattern of clearance from the lungs was established.