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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

DATE: JUNE 27, 2006

MEMORANDUM

Subject: Agency's Response to the Registrant Response for Acute Neurotoxicity and repeated Exposure Inhalation Study and determination of Inhalation MOE* and Developmental Toxicity Reviews for:

Chemical: **Belclene 350**
Tri-n-butyl tetradecyl phosphonium chloride
EPA Reg. No.: 5185-UOO
DP Barcode: D325778
Decision: 346393
PC 128824

From: S. L. Malish, Ph.D., Toxicologist, S. L. Malish 6/29/06
Risk Assessment and Science Support Branch (RASSB) Antimicrobials Division (AD)[7510C]

To: Velma Noble, PM 31
PM Team Reviewer, Drusilla Copeland
Regulatory Management Branch
Antimicrobials Division [7510C]

Thru: Nader Elkassabany, Ph.D., Team Leader, Nader Elkassabany 7/3/06
Team One, RASSB/AD [7510C]

and

Norman Cook, Chief, RASSB/AD [7510C] 7/5/06

Synonym: TK 12 780/2, tri-n-butyltetradecylphosphonium chloride, tributyl tetradecyl phosphonium chloride, TTPC, Bellacide 350

FORMULATION:

Active Ingredient:

	% weight
Tri-n-butyl tetradecyl phosphonium chloride	50% a.i.

Applicant: Ciba Geigy, Ltd, Basle, Swizerland

Uses: Tri-n-butyl tetradecyl phosphonium chloride (TTPC) is an organo-phosphorous ionic chemical that is proposed as a new active ingredient as a biocide for the control of algae, bacteria and fungi in air washers, industrial scrubbing systems, recirculating cooling towers, and process water including cooling towers, evaporative coolers, brewery pasterizers, can warmers, hydrostatic sterilizers, non-food contact pulp and paperboard processter and enhanced oil recovery systems. Two new product formulations have been proposed, Bellacide 350 whis is a 50% a.i. and Bellacide 355 which is 5% a.i. (but used at a higher rate).

ACTION REQUESTED:

With regard to the chemical substance, Tri-n-butyl tetradecyl phosphonium chloride, evaluate the toxicological studies for a 1) developmental rat study (MRID 46721703), and 2) developmental rabbit study (46721704), 3) Respond to registrant letter (MRID 467217-02) with regard to performing an acute neurotoxicity study, and a repeated exposure inhalation study and 4) prepare toxicology endpoints for risk assessment incorporating this new data.

Results:

Note: All results and conclusions are in accord with the conclusions of the Memorandum of the Antimicrobial Division Toxicology Endpoint Selection Committee (ADTC), June 7, 2006 **.

A. Developmental Studies

The following developmental studies were upgraded to **Acceptable/ Guideline** with new information supplied by the sponsor. This studies were not included in the Toxicology Endpoints for Risk Assessment for other studies were deemed more important.

Below are the executive summaries for the rabbit and rat developmental studies:

1. Prenatal Developmental Toxicity Study - Rat; OPPTS 870.3700 [83-3a]; OECD 414.

EXECUTIVE SUMMARY: In a developmental toxicity study (MRIDs 00133048, 40680704, 46721703) Belclene® 350 [tri-n-butyltetradecylphosphonium chloride (TTPC) (50% a.i.)] was administered to 24 Tif:RAIf(SPF) female rats/dose by gavage at dose levels of 0, 20, 60 and 120 mg/kg bw/day from days 6 through 15 of gestation. This is equivalent to 0, 10, 30 and 60 mg ai/kg/day, which was verified by the registrant.

There were two spontaneous deaths in the high-dose group dams (days 9 and 14), which could be treatment-related. In addition, another high dose animal died on day 15 of pregnancy due to an intubation error. Dyspnea was present in a mid-dose and 4 high-dose (60 mg ai/kg/day) animals on day 15, and vaginal bleeding was observed in one mid-dose female on day 15. Maternal body weight was significantly reduced in the high dose group on days 9, 12, 15, and 18. Maternal body weight gain was also significantly reduced between treatment days 6-15 and throughout the entire study (days 0-20) in the high-dose group. Mean food consumption was significantly reduced during gestational days 6-11 for both the mid- and high dose groups, and for gestational days 11-16 for the high dose group. There was no difference between control and treated groups for the number of females with implantations, and number of implantations/female. There were no abortions at any level. **The maternal LOAEL is 60 mg ai/kg bw/day, based on significantly decreased body weight, body weight gain, and food consumption. The maternal NOAEL is 30 mg ai/kg bw/day.**

Embryonic and fetal deaths were not statistically different from controls. There were no other soft tissue changes noted. The major sign of fetal toxicity was an increased incidence of incomplete ossification of the 5th sternebra observed in the mid (30 mg ai/kg/day) and high (60 mg ai/kg/day) dose groups by day 21. The percentage of incomplete ossification of the 5th sternebra (analyzed by litter changes) was 12/22 (54.5%), 13/24 (54.2%), 18/22 (81.8%) and 17/19 (89.5.0%) for the control, low, mid and high dose groups, respectively. **The developmental LOAEL is 30 mg ai/kg /day, based on an increased incidence of incomplete ossification of the fifth sternebrae. The developmental NOAEL is 10 mg ai/kg /day.**

This study is classified as **ACCEPTABLE-GUIDELINE**, and fulfills the guidelines specified by OPPTS 870.3700.

2. Prenatal Developmental Toxicity Study - Rabbit; OPPTS 870.3700 [83-3a]; OECD 414.

EXECUTIVE SUMMARY: In a developmental toxicity study [MRID 40680705, MRID 46721704 and MRID 00133048], Belclene 350 (50% ai, batch/lot 006) was administered to 20 chinchilla rabbits/dose by gavage at dose levels of 0, 7.5, 22.5, or 45 mg/kg/day from days 6 through 18 of gestation (i.e., gd 6-18). These doses are equivalent to 0, 3.75, 11.25, and 22.5 mg ai/kg/day, respectively, which was confirmed by the registrant.

Treatment-related effects at 11.25 and 22.5 mg ai/kg/day include statistically significant decreased body weight gain during gestational days 6-18 and significantly decreased food consumption during gestational days 6-11. **The maternal LOAEL is 11.25 mg ai/kg/day,**

based on significantly decreased body weight gain and food consumption. The maternal NOAEL is 3.75 mg ai/kg/day.

Developmental findings occurred at 11.25 and 22.5 mg ai/kg/day. Treatment-related effects at 22.5 mg ai/kg/day include statistically decreased fetal weight and an increase compared to the control in the incidence of delayed ossification of the hindlimb phalangeal nuclei. At 11.25 mg ai/kg/day, there was a significant decrease in male fetal weight and an increase compared to the control in the incidence of delayed ossification of the hindlimb phalangeal nuclei. **The developmental LOAEL is 11.25 mg ai/kg/day, based on an increased incidence of delayed ossification of hindlimb phalangeal nuclei, and significantly decreased fetal body weight for males. The developmental NOAEL is 3.75 mg ai/kg/day.**

The study is classified as **ACCEPTABLE-GUIDELINE** and fulfills the guideline requirements of OPPTS 870.3700.

B. Physical Properties

As noted in your response, the vapor pressure of this substance is very low, namely 3.75×10^{-8} mg Hg at 39° C not 24 mm Hg as noted in the original ADTC memo. The sponsor has also withdrawn the chemical for use in decorative fountains and, therefore, the data gap requesting a 28 day inhalation study is negated as well as the Short-term and Intermediate-Term Inhalation Exposure scenario in the toxicology end points for risk assessment.

C. References to Tri-n-butyl tetradecyl phosphonium chloride being a Cholintesterase Inhibitor and the possibility of performing an acute neurotoxicity study

Tri-n-butyl tetradecyl phosphonium chloride is an organophosphate, but it is ionic and not an ester. It, therefore, would not have the properties of an organophosphate cholinesterase inhibitor. Albeit, neurotoxicity was seen in the 90 day oral toxicity study (hunched posture and foaming/mucus salivation); the mechanism of this effect is unknown. For this reason the ADTC is of the opinion that an acute neurotoxicity study is required.

D. Toxicology Endpoints for Risk Assessment

These endpoints (Table 1) as promulgated by the ADTC have been attached and have incorporated the information contained in you letter to us (see above).

Table 1. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION FOR TTPC

Exposure Scenario	Dose Used in Risk Assessment UF	Target MOE for Risk Assessment	Study and Toxicological Effects
Acute and Chronic Dietary	Risk assessment not required based on use pattern		
Non-Dietary Occupational/Residential Exposures			
Incidental Oral Short-Term (1-30 days) and Intermediate-Term (1–6 months) (Residential)	**NOAEL** = 8.66 mg. a.i./kg/day	Target MOE = 100 (Residential) (10x interspecies extrapolation, 10x intrapecies variation)	90 Day Rat Drinking Water Study LOAEL = 27.2 mg a.i./kg/day for males and 32.3 mg a.i./kg/day for females based on various clinical signs and significantly reduced weight and reduced food and water consumption
Dermal Short-Term (1-30 days) and Intermediate-Term Dermal (1-6 months) (Occupational/Residential)	**NOAEL (oral)** = 8.66 mg a.i./kg/day (dermal absorption rate = 100% of oral absorption)	**Target MOE** = 100 (Residential and Occupational) (10x interspecies extrapolation, 10x intrapecies variation)	90 Day Rat Drinking Water Study LOAEL = 27.2 mg a.i./kg/day for males and 32.3 mg a.i./kg/day for females based on various clinical signs and significantly reduced weight and reduced food and water consumption
Dermal Long-Term (6 months – lifetime) (Occupational/Residential)	Risk assessment not required based on use pattern		
Inhalation Short-Term (1-30 days), Intermediate-Term (1-6 months) and Long-Term (6 months-lifetime) (Occupational/ Residential)	Risk assessment not required based on use pattern		
Cancer	No cancer data available for TTPC		

References

*Bellacide 350, EPA product No. 5185-UOO:
Registrant Response for Acute Neurotoxicity and repeated Exposure Inhalation Study and Determination of Inhalation MOE.
Study Identification BLBCRSP0501,
Study Author: John A. Todhunter, Ph.D.
Study Compiled at: SRS International Corporation
7700 Leesburg Pike
Falls Church, VA 22043
Study Completion Date: December 19, 2005
Bio-Lab, Inc., P.O. Box 300002, Lawreceville, GA 30049
MRID: 467217-02

** June 7, 2006 Memorandum on Tri-n-butyl tetradecyl phosphonium chloride (Revised Report of the Antimicrobials Toxicology Endpoint Selection Committee (ADTC) from Timothy F. McMahon to Norm Cook