DEC 13, 1991

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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Registration of Azadirachtin Biochemical Pesticide: SACB Review of Supplemental Information for Product Chemistry Data and Toxicity Studies (HED Project Nos. 1-1717 and 1-2399; I.D. No. 000275-AO; MRID Nos. 419232-00 through -20, Caswell No. 594A)

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JTMc 11/19/91

TO: Phil Hutton/Willie Nelson (PM-18)
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THROUGH: Reto Engler, Ph.D,
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Attached are the Product Chemistry/Identity and Mammalian Toxicology Chapters for azadirachtin, a biochemical insecticide extracted from the seeds of the Neem tree proposed for the use on ornamental plants and vegetable seed crops for the control of whiteflies, aphids, certain scale insects, mealy bugs, and fungus gnats.

ACTION REQUESTED: To support the registration of azadirachtin Product Chemistry and Mammalian Toxicology data was submitted by AgriDyne Technologies Inc. (formerly Native Plants Incorporated) and reviewed by SACB and CBRS, respectively (see 4/25/91 memorandum from M. Metzger to W. Nelson/T. McClintock and 5/30 memorandum from J. T. McClintock to P. Hutton/W. Nelson). SACB and CBRS noted several deficiencies and requested additional information and data to fulfill the requirements of Subdivision M for Product Chemistry and Mammalian Toxicology. In response to these cited deficiencies AgriDyne Technologies Inc. submitted additional data and information to HED for review. CBRS and SACB have reviewed this information and data and have summarized the results below.

STUDY SUMMARIES:

Product Identity/Chemistry

Adequate information and data were submitted to fulfill the requirements of Subdivision M Series 151A-12, and -17 (melting

point, Ph, vapor pressure and photostability only). The following information is required for Series 151A-10, -11, -13, -15, -16, -17 (physical properties; see 11/12/91 memorandum from M. Metzger to W. Nelson/T. McClintock for specific details).

151A-10. Product Identity. CAS Registry Numbers for impurities are required. For full registration (AgriDyne Technologies Inc. must identify and establish certified limits for all **major** impurities at levels **greater than 1%** in any production batch of technical or **greater than 0.3%** in the end-use product.

151A-11. Manufacturing Process. A step-by-step detailed description of the **new** manufacturing process to be used to produce the end-use product must be provided (only a flow diagram was provided).

151A-13. Analysis of Samples. A significant number of impurities at greater than 1% were not identified. **Major** impurities in any batch should be identified and upper certified limits established. Additional deficiencies are noted in the Confidential Appendix (see page 10 and 11 of 17).

151A-15. Certification of Ingredient Limits. Revised CSFs for the end-use product must be submitted. For full registration all **major** impurities present in any batch at levels **greater than 1%** must be identified and upper limits established (see Confidential Appendix for specific details).

151A-16. Analytical Methods for Certified Limits. Standard curves must be provided for azadirachtin for the five batches of technical material discussed in MRID No. 419232-03 (see Confidential Appendix for specific details).

151A-17. Physical and Chemical Properties. Physical and chemical properties must be submitted for a sample manufactured by the new manufacturing process (see page 9-14 of 11/12/91 memorandum for specific details).

SACB DISCUSSION: AgriDyne Technologies Inc. has submitted spectral data which are sufficient to identify all but approximately six components (major impurities) at greater that 1% in the technical material. In light of the fact that AgriDyne Technologies Inc. has submitted extensive information and data on the identity of most of the major impurities and based on the low toxicity observed for azadirachtin technical, SACB would recommend that each production batch be evaluated by intraperitoneal (IP) injection. Each production lot, prior to the addition of other materials, could be tested by IP injection into each of five laboratory mice followed by cage-side observation for 7 days. This approach would eliminate any possible concerns which might arise due to batch to batch variation in the relative percentages of impurities. Since a production batch using the new manufacturing process has yet to be evaluated SACB would also recommend that production batches from the previous manufacturing process be compared to production

batch(es) produced using the new manufacturing process for percent a.i. and levels of impurities.

Mammalian Toxicology Studies

151B-10. Acute Oral Toxicity Study in Rats. The information and/or data submitted previously was not adequate to fulfill the requirements of 151B-10 (see 5/30/ memorandum from J. T. McClintock to P. Hutton/W. Nelson). This study was classified as CORE Supplementary. However, since the registrant submitted the appropriate information/data to address the noted deficiencies this study has been upgraded to CORE Minimum. Toxicity Category III.

Limit Test. This study has been upgraded to CORE Minimum since the registrant submitted information on the percent purity of the test compound. Toxicity Category IV.

It should be noted that differences were observed in both oral studies (i.e. observed mortality). These differences should be discussed by the registrant since the Agency will classify the test material based on the most sensitive study (i.e. Toxicity Category III).

151B-11. Acute Dermal Toxicity Study in Rabbits. The original submission did not include percent purity of the a.i. or individual animal data. Since this information was submitted the study has been upgraded to CORE Minimum. Toxicity Category III.

Limit Test. This study was also upgraded to CORE Minimum since the registrant submitted the appropriate information on the percent purity of the test material. Toxicity Category III.

152B-12. Acute Inhalation Toxicity Study in Rats. Since several deficiencies were noted (i.e. percent a.i. in the test material, individual body weight and clinical data) this study was classified as CORE Supplementary. This study has now been upgraded to CORE minimum (Toxicity Category III) since the registrant has submitted the appropriate data and information.

152B-14. Primary Dermal Irritation Study in Rabbits. Technical. SACB requested information on the test material, individual animal data, and clinical observations. The appropriate information and data has been submitted by the registrant. This study has now been upgraded to CORE Minimum, Toxicity Category IV.

Formulated Product. Based on the submitted information and data which was requested by SACB this study has been upgraded to CORE Minimum, Toxicity Category II (Mild irritant).

152B-15. Dermal Sensitization Study in Guinea Pigs. This study was previously judged CORE Supplementary because no positive controls were used; and inappropriate methods were used to rank the sensitization potential of azadirachtin. A Dermal Sensitization Study has now been submitted using 1-Chloro-2,4-Dinitrobenzene as

a positive control. It should be noted that this study was not performed in conjunction with the previous study using azadirachtin as the test material and no effort was made to compare both substances.

152B-16. Hypersensitivity Incidents. All incidents must be reported to the Agency.

152B-18, Immunotoxicity; 152B-20, 90-Day Feeding (1 species); 152B-21, 90-Day Dermal (rat); 152B-22, 90-Day Inhalation (rat); and 152B-23, Teratogenicity (1 species). Due to low volume/minor use and lack of noted toxicity of the subject compound these studies have been waived. However, in the event that the application rate exceeds 20 gram active ingredient per acre (as currently proposed) resulting in higher exposure, SACB/HED would reevaluate these waiver requests and consider implementing any of the remaining Tier I studies.