



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

008393

APR 25 1991

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Memorandum

Subject: Azadirachtin Biochemical Pesticide. Product
Chemistry Data in Support of Registration.
MRID Nos. 416264-01 through -18.
416269-01 through -19.
416263-01 through -13.
DEB Nos. 7326, 7752 and 7753.
DP Bar Code 158246, 158247, 158249.

From: Michael S. Metzger, Chemist
Special Review Section 2
Chemistry Branch 2 - Reregistration Support
Health Effects Division (H7509C) *Michael S. Metzger*

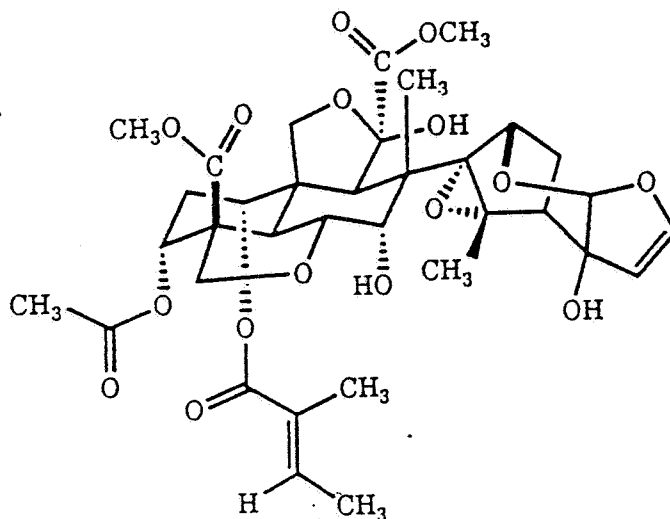
Thru: Francis B. Suhre, Section Head
Special Review Section 2
Chemistry Branch 2 - Reregistration Support
Health Effects Division (H7509C) *Francis B. Suhre*

To: P. Hutton / W. Nelson, PM 17 Team
Registration Division (H7505C)

and

Thomas McClintock, Ph.D.
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

Native Plants Incorporated (NPI) submits Product Chemistry data for the pesticide azadirachtin [dimethyl (2aR,3S,4S,4aR,5S,7aS,-8S,10R,10aS,10bR)-octahydro-3,5,8,10-tetrahydroxy-4-methyl-4-[(1aR,2S,3aS,6aS,7S,7aS)-3a,6a,7,7a-tetrahydro-6a-hydroxy-7a-methyl-2,7-methanofuro[2,3-b]oxireno[e]oxepin-1a(2H)-yl]-1H,7H-naphtho[1,8-bc:4,4a-C']difuran-5,10a(8H)-dicarboxylate,10-acetate 8-[(E)]-2-methylcrotonate] (see structure on next page) to fulfill the requirements of Subdivision M for biochemical pesticides. Fifty volumes of data were submitted. Much of the information submitted pertains to the End-Use products Azatin[™] EC and Azatin[™]-Plus EC and is deferred for review to the Registration Division. Information which pertains to Azatin[™] Technical is reviewed below by guideline number.



AZADIRACHTIN

151-10 Product Identity and Disclosure of Ingredients

PRODUCT IDENTITY

Product Name: Azatin[™] Technical
 Company Code Number: NPI-720

CONFIDENTIAL STATEMENT OF FORMULA (CSF)

A CSF for Azatin[™] Technical was submitted and is included at the end of the Confidential Appendix.

INFORMATION ON INGREDIENTS

Information on active ingredient:

CAS Registry Number: 11141-17-16.
 Molecular/Empirical formula: $C_{35}H_{44}O_{16}$
 Molecular weight: 720
 Chemical name: Azadirachtin (see full chemical name above)
 Structure: see above
 Source of biochemical: *Azadirachta indica* (Neem tree)
 Mode of action: insect feeding - deterrent properties
 (information taken from published article)
 Azatin[™] Technical contains 10% active ingredient by weight.

✓ No information in this submission directly addresses the issue of ingredients, other than azadirachtin, in the technical product. A published article was provided,

Jacobson, M. (Editor). 1988. *The Neem Tree - Volume 1*. pp. 19-46. CRC Press Inc., Boca Raton, FL.

This article discusses the Neem tree from which the technical material is extracted, but provides no information regarding the technical material itself. A small amount of additional information is provided in MRID No. 416264-05 which discusses formation of an unintentional ingredient (see the Confidential Appendix under Section 151-12). The discussion states that other unintentional ingredients are not expected. The submitter also supplies a list of "Substances Isolated from Neem Trees" which is included in the Confidential Appendix.

CBRS Response to 151-10:

The data submitted do not adequately address the requirements of 151-10. Since numerous data requirements are not satisfied by this submission, we will not reiterate the Guidelines here but refer the submitter to the Pesticide Assessment Guidelines, Subdivision M, Section 151-10. In particular, the requirements for information on impurities must be addressed [Sections 151-10(c)(2)(i-viii), 151-10(c)(3), 151-10(c)(1)(i-vi) for any biochemicals present other than azadirachtin], a CSF must be submitted for Azatin[®] Technical which contains all required information on the active ingredient as well as impurities in the technical product [Section 151-10(b)], and additional information regarding the host range and the mode of action must be provided [151-10(c)(1)(vi)].

We note that identification of components and determination of certified limits for all components present at $\geq 0.1\%$ (as required by the Guidelines) for an extract of this type may not be feasible because of the large number of components which may be present, and because of the large batch to batch variation which likely occurs. However, at a minimum, chromatographs must be supplied in which all major peaks are identified, and certified limits must be determined for these peaks taking into account the batch to batch variation resulting from different neem seed sources, different manufacturing processes, and any other factor which may affect the percentages of these impurities in the technical material. Additionally, the weight percentage of the impurities which have been identified in the technical material must be provided. Should TOX consider it necessary that additional information regarding the identity and levels of impurities be provided, these data will also be required. (Note: the toxicological studies submitted for Azadirachtin utilized the technical material, NPI-720; personal communication with T. McClintock, Ph.D., 3/19/91.) We refer the submitter to the Pesticide Assessment Guidelines, Subdivision D (Product Chemistry), Sections 61, 62, and 63 for additional information. Additional information regarding manufacturing process, analysis

of samples, and determination of certified limits is included below and in the Confidential Appendix.

151-11: Manufacturing Process

A description of the manufacturing process is provided for Azatin[®] Technical. See the Confidential Appendix for details.

CBRS Response to 151-11:

The submitted information is not adequate to fulfill the requirements for Manufacturing Process. See CBRS Response to 151-11 in the Confidential Appendix for additional details.

151-12: Discussion of the Formation of Unintentional Ingredients

A brief discussion of the formation of unintentional ingredients was provided. See the Confidential Appendix to this review for additional information.

CBRS Response to 151-12:

We cannot determine the adequacy of the discussion of the formation of unintentional ingredients until additional information regarding the manufacturing process is provided. However, it is unlikely that the information submitted fulfills the requirements of 151-12 since the product is extracted from the seeds of Neem trees, and the presence of extraneous host residues are likely. We refer the submitter to the Guidelines (151-12) for information on what types of chemical components must be considered in this discussion. We note that the published article regarding the chemistry of Neem trees provides some interesting and potentially useful information which might be useful to the submitter in putting together this discussion, but the article alone is not sufficient to fulfill the data requirement since it refers to the Neem tree rather than the technical product.

151-13: Analysis of Samples

Information regarding analysis of samples for Azatin[®] Technical has been submitted and is discussed in the Confidential Appendix.

CBRS Response to 151-13:

The requirements for 151-13 have not been satisfied. See the Confidential Appendix for details.

151-15: Certification of Ingredient Limits

Information has been submitted and is discussed in the Confidential Appendix.

CBRS Response to 151-15:

✓ The requirements for 151-15 have not been satisfied. See the Confidential Appendix for details.

151-16: Analytical Methods for Certified Limits

A description of the analytical method used to determine azadirachtin in the technical product was provided. See the Confidential Appendix for details.

CBRS Response to 151-16:

The information provided is not adequate to fulfill the requirements of 151-16. Analysis of the technical product, not analytical grade material, must be demonstrated, and the method(s) must be capable of determining azadirachtin as well as any other component for which certified limits are required (see Section 62-2 of Subdivision D of the Pesticide Assessment Guidelines for information regarding establishment of certified limits). We refer the submitter to Subdivision M (Section 151-16) and Subdivision D (Product Chemistry, Section 62-2 and 62-3) of the Pesticide Assessment Guidelines for further information. We note that supporting raw data must be submitted (e.g. chromatographs).

151-17: Physical and Chemical Properties

A discussion of the information submitted for Physical and Chemical Properties is provided in the Confidential Appendix. Adequate data were submitted to fulfill the following requirements for Azatin Technical:

- Color
- Physical state
- Odor
- Melting point
- pH

Data were submitted but were found deficient for the following properties (see Confidential Appendix for details):

- Density
- Solubility
- Stability

Data are required but were not submitted for Azatin[™] Technical for the following properties (see the Pesticide Assessment Guidelines, Subdivision M, Section 151-17, Subdivision D, Sections 63-9 and 63-11):

Vapor pressure
Octanol-water partition coefficient

CBRS Response to 151-17:

Data remain outstanding for the physical/chemical properties listed above. See the Confidential Appendix for details.

Conclusions and Recommendations

Adequate data were submitted to fulfill the requirements for the following Sections of Subdivision M of the Pesticide Assessment Guidelines for Azatin[™] Technical:

151-17 for Color, Physical state, Odor, Melting point, and pH.

As discussed in detail above and in the Confidential Appendix, additional data are required for the following Sections of Subdivision M:

151-10
151-11
151-12
151-13
151-15
151-16
151-17 for Density, Solubility, Stability, Vapor pressure, and Octanol-water partition coefficient.

We defer review of materials related to End-Use products to the Registration Division.

CBRS recommends against registration of this product due to the outstanding Product Chemistry data discussed above.

Attachment: Confidential Appendix

cc without attachment: Circu

cc with attachment: M. Metzger (CBRS), Azadirachtin SF, RF, C...
Furlow (PIB/FOD, H7506C)

RDI:F.Suhre:FS:3/18/91:RDS:3/19/91

H7509C:CBRS:M.Metzger:MM:Rm810f:CM#2:3/21/91

CONFIDENTIAL APPENDIX

(NOT INCLUDED)