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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: August 11, 1981

SUBJECT: Gibberellins As Biorational Pesticides. Scheme for human hazard evaluation of Gibberellin - Gibberellic Acid toxicity data/Toxicology Branch/HED

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The procedure contained in this memorandum for hazard evaluation of Gibberellic Acid - Gibberellin toxicity data has been approved for use by Toxicology Branch/HED. Gibberellins have been designated Biorational Pesticides, and should be reviewed accordingly.

Rationale for Classification of Gibberellic Acid - Gibberellins as Biorational Pesticides

Gibberellins do fit the Supart M Biorational Pesticide definition; they are of biological origin (except for synthesized Gibberellins), they are usually species or group specific and the mode of action is other than frank toxicity.* Subpart M Guidelines limit Biorational Pesticides to application rates of 20 g or less per acre; some Gibberellins are used at rates as high as 210 g per acre.

The only Gibberellin for which a fairly complete toxicity profile is available is Gibberellin A_3 (Gibberellic Acid); teratogenic and mutagenic studies are lacking.

Although Gibberellins may be classified as Biorational Pesticides, they should be registered by EPA; Toxicology Branch cannot predict or anticipate the potential toxicity of all present and future Gibberellins without toxicity data, or predict all future inert ingredients contained in formulations.

*Gibberellins are plant growth regulating substances that are associated with plant tissues.

However, in view of the fact the Gibberellins may be classed as Biorational Pesticides, human hazard evaluation may be conducted according to Subpart M Guideline requirements which consist of a battery of short-term, acute type tests. Subacute or chronic studies would be required only if Tier 1 testing indicated hazard potential.

Since approximately 14 different Gibberellins are known to exist and tolerance exemption requests for additional Gibberellins may be anticipated plus the impossibility of estimating human hazard(s) presented by unlimited application rates, a systematic approach to Gibberellin hazard assessment is proposed.

Definition of Terms Used in a Hazard Assessment Scheme for Gibberellins

1. Naturally Occurring Gibberellins - Naturally occurring plant growth regulators isolated from plant tissues that exhibit the gibbane molecular skeleton.

2. Synthetic Gibberellins - Some Gibberellins may be synthesized artifically; such Gibberellins may or may not be identical to naturally occurring Gibberellins.

3. Complete Toxicity Data Base - This term refers to a toxicity profile developed according to Subpart F hazard assessment Guidelines for conventional chemical pesticides.

4. Incomplete Toxicity Data Base - This term refers to an incomplete toxicity profile developed according to Subpart F hazard assessment Guidelines.

5. Subpart M Tier 1 and Tier 11 Toxicity Tests (See proposed Guidelines for Registering Pesticides in the U.S., Subpart M. Draft of Septmember 29, 1980, for detailed explanation of tests).

Tier 1 Tests

LD_{50} Determination	Species	Test Substance
Oral	Rat	Formulated Product
Dermal	Rat or Mouse	Formulated Product
Inhalation	Mouse, Rabbit or Guinea Pig	Formulated Product

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Irritation	Species	Test Substance
ocular, primary	Rabbit	Formulated Product
dermal, primary	Guinea Pig or Rabbit	Formulated Product
Hypersensitivity		
non-immediate	Hamster or Guinea Pig	Formulated Product

Mutagenicity Tests

(Modification of Subpart M 9/29/80 Draft Guidelines)

a. Bacterial assay for reverse gene mutation (Ames assay)

b. A DNA damage/repair assay in E. coli, or other appropriate organism for which a substantial body of testing of repair-deficient mutants exists.

Cellular Immune Response		
(Modification of Subpart M 9/29/80 Draft Guidelines)	Mouse	Technical Agent

a. Blood cell counts (RBC, WBC differentials). Performed on day 0, and 14 days post treatment.

b. Serum protein determined by electrophoresis performed on day 0 and 14 days post treatment. Include amounts of albumin, and globulin fractions (to determine any alteration in specific antibody fractions).

Tier 11 Tests

Oncogenic Test	Newly weaned mouse, newly weaned rat	Technical Agent
Subchronic Oral	Mouse, rat or dog; 90 day test	Technical Agent
Subchronic Dermal	Rabbit or guinea pig (species not tested in primary Tier 1 test)	Technical Agent
Subchronic Inhalation	Rat	Technical Agent

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	Species	Test Substance
Cellular Immune Response	Mouse, antibody formation; cell mediated response	Technical Agent
Teratogenicity Test	Two species from rat, mouse, hamster, rabbit	Technical Agent

Hazard Assessment Scheme for Gibberellins Designated Biorational Pesticides

The human hazard assessment scheme for Gibberellins presented below separates naturally occurring and synthetic Gibberellins applied at 20 g or less per acre, and those applied at more than 20 g per acre rates:

1. Naturally occurring, or synthetic Gibberellins that are shown to be identical to naturally occurring Gibberellins - complete or partial (incomplete) toxicity data base available.

   a. Used at less than 20 g per acre.

      i. Complete tox. data base available - exempt from tolerances (clear inerts)

      ii. Incomplete tox. data base - require Subpart M Tier 1 tests.

      If results indicate lack of toxicity - exempt from tolerance (clear inerts). If results indicate hazard potential(s) - require Subpart M Tier 11 tests.

   b. Application rate more than 20 g per acre.

      A. Residue data indicates no significant increase above natural Gibberellin background levels.

         i. Complete tox. data base available No tox. data required - exempt from tolerances (clear inerts).

         ii. Incomplete tox. data base - require Subpart M Tier 1 tests.

         If results indicate lack of toxicity - exempt from tolerance (clear inerts).

         If results indicate hazards potential(s) require Subpart M Tier 11 tests.

B. Residue data indicates significant increase above natural Gibberellin levels.

i. Complete tox. data base available.

If residue data estimated exposure levels are equal to or less than tox. test animal exposure - exempt from tolerance (clear inerts)

If residue data estimated exposure levels greater than tox. test animal exposure - require Subpart M Tier 1 tests, using animal dose levels equivalent to intended use exposure levels.
Animal test results negative - exempt from tolerance (clear inerts).
Animal test results positive - require Subpart M Tier II tests.

ii. Incomplete tox. data base.

Require Subpart M Tier 1 tests. Animals dosed at intended use exposure levels (based on residue levels).

Animal results negative - exempt from tolerance (clear inerts).

Animal results positive - require Subpart M Tier 11 tests.

2. Naturally occurring Gibberellins for which EPA does not have a toxicity data base.

a. Used at 20 g or less per acre.

i. Require Subpart M Tier 1 tests - if tox. tests data indicate lack of toxicity - exempt from tolerance (clear inerts).

ii. If animal tox. tests indicate hazard potential - require Subpart M Tier 11 tests.

b. Used at more than 20 g per acre application rate.

1. Require Subpart M Tier 1 tests using animal dose levels indicated by estimated exposure data, based on residues.

If no toxicity indicated - exempt from tolerances (clear inerts).

If animal tox. tests indicate hazard potential - require Subpart M Tier 11 tests.

3. Synthetic Gibberellin(s) which have not been shown to be identical to naturally occurring Gibberellin(s)

The actual differences or deviation of a specific synthetic Gibberellin from a naturally occurring Gibberellin counterpart will be determined on a case by case basis.

a. If a synthetic Gibberellin is found to be essentially identical (as per RD SOP for me too technicals) to a naturally occurring Gibberellin counterpart, Subpart M biochemical Biorational Tier 1 testing only will be required; provided no toxic potential is indicated by such tests.

b. If a synthetic Gibberellin is found to be significantly different from a naturally occurring Gibberellin counterpart, indicating concern for human hazard potential, a human hazard evaluation according to Subpart F (as for conventional pesticides) will be required.

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