CASWELL FILE

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MAY 22 1985

MEMORANDUM

SUBJECT: Gibberellic Acid (Gibberellin A_3). Acc. No. 071422
EPA # 9E2145.
CAS No. 467.

FROM: William S. Woodrow, Ph.D.
Section VII, Toxicology Branch
Hazard Evaluation Division (TS-769C)

ABK for Bill Woodrow 5/21/85

TO: Hoyt Jamerson (43)
Registration Division (TS-767C)

W S Burnam 5.21.85

THRU: Albin B. Kocialski, Ph.D.,
Supervisory Pharmacologist
Section VII, Toxicology Branch
Hazard Evaluation Division (TS-769C)

ABK 5/21/85

The petitioner, IR-4 National Director Dr. R. H. Kupelian, on behalf of the IR-4 Technical Committee and all the State Agricultural Experiment Stations, requests the exemption from the requirement of tolerances for Gibberellin A_3 when used as a plant growth regulator in or on the raw agricultural commodities artichokes, blueberries, citrus fruits, grapes, hops, leafy vegetables, pome fruits, stone fruits, sugarcane, sugarcane fodder, and sugarcane forage. Requests to exempt Gibberellin A_3 from the application limitation of 20 g or less per acre, and to waive the requirement for any remaining Gibberellin A_3 toxicity data were also made.

Recommendations:

1. The requested exemption from the requirement of tolerances for gibberellic acid (Gibberellin A_3) used as a plant growth regulator in or on artichokes, blueberries, citrus fruits, grapes, hops, leafy vegetables, pome fruits, stone fruits, sugarcane, sugarcane fodder, and sugarcane forage is not toxicologically supported. According to 40 CFR Part 158 "Data Requirements for Pesticide Registration; Final Rule" published

in the Federal Register, Wednesday, October 24, 1984, for Biochemical Pesticides, the following toxicity data for Gibberellin A_3 is not available and must be submitted (see page 4 this report for full list of biochemical pesticide data requirements):

Required data

a) Primary eye irritation study

b) Primary dermal irritation study

c) Studies to detect genotoxicity

A gene mutation test; such as an acceptable Ames Salmonella/reverse mutation assay.

A structural chromosome aberration test; such as a mammalian cell culture Sister Chromatid Exchange, or mouse heritable translocation test.

A test for other genotoxic effects; such as a microbial DNA damage and repair test.

d) An acute inhalation study

Conditionally required data

Teratogenicity study in one mammalian species.

2. New toxicity data reviewed in the present report:

a. Ames Salmonella/microsome mutagenic assay.

Not mutagenic.

Classification: Supplementary Data (no proof that maximum possible challenge concentration of GA_3 was used, and it was not clear whether a negative control was included). Additionally no raw data was provided,

b. 90-Day subchronic feeding study with GA_3 in rats and mice.

No significant toxic effects in rats.

Stomach inflammation in male and female mice at the 5% and 2.5% dose level, stomach inflammation in male and female mice at the 2.5% dose level.

Apparent NOEL Rats - 5.0% gibberellic acid (HDT)

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NOEL-weight depression - mice:

females - 5.0% gibberellic acid. (HDT)
males - 5.0% gibberellic acid. (HDT)

Classification (mouse and the rat studies) - Supplementary Data:

(Rat study - No hematology, blood chemistry or urinalysis data, and;

Mouse study - Histopathologic data not reported at the lower dose levels of 1.25, 0.62 or 0.31% of the diet).

c. Tumorigenicity of Gibberellin A_3 in mice. Gibberellin A_3 was not tumorigenic in mice.

Classification: Supplementary Data (Preliminary Report - Innes Study).

3. The label signal word is satisfactory.

Background Information:

A tolerance of 0.15 ppm for Gibberellin A_3 has been established for a number of RACs.

[Quoted from 40 CFR, 1983 pp. 225]

§180.224 Gibberellins; tolerances for residues:

Commodity	Parts per million
Artichokes	0.15 (N)*
Blueberries	0.15 (N)
Citrus fruits	0.15 (N)
Grapes	0.15 (N)
Hops	0.15 (N)
Leafy vegetables	0.15 (N)
Stone fruits	0.15 (N)
Sugarcane	0.15 (N)
Sugarcane fodder	0.15 (N)
Sugarcane forage	0.15 (N)

*(N) = Negligible residues.
[End of quotation]

The petitioner states the following requests in the summary portion of what they call "Second Amendment to Petition 9E 2145, proposing an Exemption from a Tolerance For Residues of the Naturally Occurring Plant Growth Regulator, Gibberellic Acid (GA_3)," Acc. No. 071422:

1. That the 20 g/acre application rate for GA_3 be waived; the petitioner cites 40 CFR §162.45 C;

2. That all remaining toxicity data gaps for GA_3 be waived; based on the toxicity data previously submitted to the Agency, and toxicity data included in the present (Acc. No. 071422) document submitted.

3. That an exemption from the requirement of a tolerance be granted "for only those crops for which negligible tolerances have been established, and for pome fruits."

Gibberellins have been designated "biochemical" pesticides because they fulfill most of the important biochemical pesticide definition criteria: They are naturally occurring, their mode of action is other than frank toxicity (modify plant growth). However, for some uses Gibberellins are applied at more than 20 grams per acre. At present, EPA Guidelines place a limit of 20 grams per acre on pesticides to be considered as biochemical pesticides.

40 CFR Part 158 (Biochemical Pesticide Data Requirements: Vol. 49 (FR Wednesday, October 24, 1984), lists the following Tier I No. 207 Toxicity data study requirements:

Required studies

Acute oral toxicity
Acute dermal toxicity
Acute inhalation toxicity
Primary eye irritation
Primary dermal irritation
Studies to detect genotoxicity

Conditionally required studies

90-Day feeding (1 mammalian species)
Teratogenicity (1 mammalian species)

Gibberellic Acid (GA_3) toxicity studies previously submitted to TOX Branch, EPA:

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These data were listed by Dr. William E. Parkin, Toxicology Branch, EPA Pesticides Tolerances Division, in an August 4, 1972 memo to Drew M. Baker, Pesticides Control Branch, EPA Pesticides Tolerances Division:

Test	Species	Compound	Result
Acute oral	Mouse	Gibberellic acid in CMC	LD_{50} > 25.0 g/kg
		Gibberellic acid in dilute NaOH	LD_{50} 15.1 g/kg
		Gibberellic acid spray dried	LD_{50} 6.3 g/kg
	Rat	Gibberellic acid in CMC	LD_{50} > 15.0 g/kg
		Gibberellic acid in dilute NaOH	LD_{50} > 15.0 g/kg
	Dog	Gibberellic acid spray dried	LD_{50} > 0.5 g/kg
5-month feeding study	Rat	Na salt	Body weights decreased at 400 ppm
15-week feeding study	Rat	5% Gibberellic acid	No effect
90-day feeding study	Dog	Na salt	No effect at 1000 mg/kg
4 1/2-week feeding study	Rat	Na salt	No effect at 1000 mg/kg
90-day gavage study	Rat	Gibberellic acid	No effect at 1 g/kg
212-375-day feeding study	Rat	Gibberellic acid	No effect at 10,000 ppm
202-day feeding study	Rat	Gibberellic acid	No effect at 10 ppm
398-day feeding study	Rat	Gibberellic acid	No effect at 100 ppm

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Test	Species	Compound	Result
187-day capsule study	Dog	Gibberellic acid	No effect at 0.2 mg/kg
385-day capsule study	Dog	Gibberellic acid	No effect at 1 mg/kg
385-day feeding study	Dog	Gibberellic acid	No effect at 0.5 mg/kg for 187 days - raised to 10 mg/kg for additional 198 days
2-year carcinogenicity	Rat	Gibberellic acid	Negative
Reproduction study	Rat	Na salt	Negative

The attached scheme for human hazard evaluation of Gibberellin - Gibberellic Acid toxicity data, and consideration of GA_3 toxicity data available to the Agency indicates that additional toxicity data are necessary for GA_3:

1. For GA_3 used at less than 20 g/acre (list of additional required data):

   a. Acute dermal toxicity
   b. Primary eye irritation
   c. Primary dermal irritation
   d. Acute inhalation study

   e. Studies to detect genotoxicity

      1. Gene mutation (an acceptable Ames test)
      2. Structural chromosome aberration test
      3. Other genotoxic effects; such as a microbial DNA damage and repair test

   f. An acceptable teratogenicity study (required on a conditional basis).

2. If GA_3 is used at more than 20 g/acre (list of additional required data):

   The toxicity studies shown above (under 1. GA_3 used at less than 20 g/acre) are required, plus residue data for each intended crop use (if GA_3 is used at more than 20 g/acre) (see attached R.B. Perfetti memorandum).

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NOTE: In the event that adverse toxicological effects are determined by the toxicity tests described above, or that residue data show GA_3 levels significantly above natural GA_3 levels, further toxicity testing as outlined in the scheme for human hazard evaluation of Gibberellin-Gibberellic Acid toxicity data may be required.

Review of Data:

1. McCann, Joyce, Edmund Choi, Edith Yamasaki, and Bruce N. Ames. Detection of Carcinogens in the Salmonella/Microsome Test: Assay of 300 Chemicals. Proc. Nat. Acad. Sci. U.S.A. Vol. 72, No. 12, pp. 5135-5139, December 1975.

Conclusion:

Unacceptable Data (proof that a maximum cell tolerated challenge dose was used was not evident, also, it was not clear whether a negative (vehicle) control was included).

2. Repeated 14-Day Dose Toxicity of Gibberellic Acid in Fischer 344 Rats and B6C3F, Mice. Sponsor: Abbott Labs., Chicago, IL. Tester: EG & G Mason Research Institute. Contract #78-67-106002, October 19, 1979.

Test Material - Gibberellic acid (GA_3)

A. Range-finding study

Five animals per sex per dose per species (rat and mouse) were fed gibberellic acid at 0.62%, 1.25%, 2.5%, 5.0%, and 10.0% of animal feed for 14 days. A sixth group of animals (rat and mouse) were fed diet without the added test chemical, to serve as control animals:

% Gibberellic acid in diets	Numbers of Animals			
	Mice		Rats	
	M	F	M	F
0.62	5	5	5	5
1.25	5	5	5	5
2.5	5	5	5	5
5.0	5	5	5	5
10.0	5	5	5	5
0.0	5	5	5	5

Animals were observed 2x daily for clinical symptoms. Body weight determinations were made on days 0, 7, and 14.

Results:

No mortality. The only clinical observations were loss

of hair and some scrotal lesions. Gross necropsies did not indicate compound or dose related abnormalities.

Weight depression in treated animals compared to controls was observed (in excess of 10%), in 2.5% male rats and 10.0% female rats.

Based on weight depression findings, doses for further subchronic testing in rats and mice were selected: 2.5%, 1.25%, 0.62%, 0.31%, and 0.16% plus diet controls.

Classification:

Supplementary Data

B. 90-Day Subchronic Feeding Toxicity Study of Gibberellic Acid in Fischer 344 Rats and B6C3F$_1$ Mice.

Sponsor: Tracor Jitco, Inc. Tester: EG & G Mason Res. Institute, Worcester, Mass. Report No. MRI-TRA 31-80-56, August 14, 1980.

Test Material: Technical gibberellic acid (gibberellin A_3).

Fischer 344 rats and B6C3F$_1$ mice were fed gibberellic acid diets for 14 weeks as follows:

[Quoted from the tester's report]

Group	Dose (%)	No. Animals on test	
		F344 Rats	B6C3F$_1$ Mice
52 AM	0.31	10	10
52 AF	0.31	10	10
52 BM	0.62	10	10
52 BF	0.62	10	10
52 CM	1.25	10	10
52 CF	1.25	10	10
52 DM	2.50	10	10
52 DF	2.50	10	10
52 EM	5.00	10	10
52 EF	5.00	10	10
52 M	Diet control	10	10
52 F	Diet control	10	10
	Total	60M, 60F	60M, 60F

[End of quotation from tester's report]

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Animal diets were prepared on a weekly basis; the chemical was weighed, added to an aliquot of meal in a mortar and mixed as a premix. The premix was then added to the remaining meal and blended in a mechanical blender for 15 minutes. Chemical and dosed feed was stored at 0 ± 5°C. A sample of each formulation was submitted for quality control analysis; duplicate samples (10 g) from 3 places in the blenders of the highest and lowest concentrations of dosed feed were analyzed.

Animals were subjected to a 15-day quarantine period. Prior to study initiation, animals were segregated by weight. Clinical observations were made twice daily. Individual animal weights were recorded weekly.

Control animals received lab chow only.

After 14 weeks on test, urine samples were collected from all control animals and from the 5.0% treated animals; the tester's protocol also states that "at the end of 13 weeks 18-hour urine collections were conducted on all treated and control animals." The urine samples were pooled, measured and sealed. Blood samples were collected from the 2.5%, the 5.0% and diet control animals (presumably also at 13 weeks of test). Urine and serum samples were stored at -60°C.

Rats which died or were killed at study termination received a complete gross necropsy; tissues were fixed in formalin. Tissues normally routinely examined were:

gross lesions and tissue masses	
mandibular lymph node	
mammary gland	testes
skin	uterus
stomach	lungs and bronchi
brain	pancreas
thymus	spleen
trachae	kidneys
salivary gland	adrenals
sternbrae	bladder
thyroid	pituitary
parathyroid	spinal chord
small intestine	eyes
colon	ovaries
liver	heart
prostate	esophagus

In addition to the organs listed for histopathological examination for rats, gall bladders of mice were examined grossly and histopathologically.

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Results - Rats

Compound consumption and weight gain: male rats consumed progressively less food and consequently less compound than comparable female treatment groups when measured at weeks 4, 8 and 12, however, no significant weight gain or depression was observed for any treatment group compared to control rats.

Clinical observations were largely soft stools, diarrhea in 1 of 10 animals per group, excepting the top group (5% of diet), when two animals showed "tail bends" (the tester does not define the term tail bends.)

The test protocol stated that blood samples were taken from the 2.5%, 5.0% and control animals at 13 weeks, or at test termination, however, no hematology or blood chemistry test results were reported.

Results of urine sample analyses were not reported.

Feed analysis for gibberellic acid indicated lower doses (0.31, 0.62, and 1.25%) were within 10% of the target concentrations. However, in one instance the intended 2.5% dose was low by 11% error, and in one instance the highest dose tested (intended 5% of diet) fell 15% lower than the intended concentration.

Various pathological observations, such as discolored lungs, small liver masses, granular spleen surfaces and filled uterine horns did not appear to be dose or compound related.

No hyperplasia or neoplasms were observed by histopathological examination. Most of the rats, including those in the control group, exhibited mild peribronchial murine pneumonia. Also, most of the male mice, including controls, had patchy cardiac myolysis.

Conclusions - (Rat Study)

Since no hematology, blood chemistry, or urinalysis results were presented for the 14-week rat feeding study, it is impossible to make definite conclusions about the subchronic effects of gibberellic acid on rats. The clinical observation "tail bends" should have been explained.

An apparent NOEL (no significant adverse effects of any type), was 5.0% gibberillic acid in the diet (HDT).

Results - Mice

Food and compound consumption decreased somewhat for male and female treated mice, however, comparable slight body weight gains were observed in all groups of male and female mice.

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NOEL - weight depression:

female mice - 5.0% % gibberellic acid.

male mice - 5.0% % gibberellic acid.

Clinical observations such as alopecia and bite wounds were noted in scattered instances in both male and female mice, and did not appear to be dose or compound related.

Seven of 10 male and 7 of 10 female mice at the 5.0% dose level showed chronic stomach inflammation of the mucosal lining, and 2 of 10 male and 5 of 10 female mice at this dose level exhibited acute inflammation of the stomach mucosal lining. Three of ten male mice and 8 of 10 female mice at the 2.5 % diet treatment level with gibberellic acid exhibited chronic inflammation of the stomach mucosal lining. Three of the 10 female mice also exhibited acute stomach inflammation. One female mouse exhibited acute and chronic liver inflammation at the 2.5 % dose level.

NOTE: No histopathological data for male or female mice were presented for the 1.25%, 0.62% or the 0.31% dose levels, therefore, it is not possible to determine the effect(s) of Gibberellin A_3 at dose levels below the 2.5% diet level.

Conclusions (Mouse Study)

$B6C3F_1$ mice exhibited stomach inflammation in females at the 5% dose level, and stomach inflammation in males at the 5% dose level and in males and females at the 2.5% dose level.

No other significant toxic effects were noted, including hyperplasia or neoplastic findings.

It is impossible to establish NOEL or LEL dose levels for stomach inflammation effects; data below the 2.5% were not reported for either males or females (1.25%, 0.62% or 0.31% dose levels).

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Classification

Rat Study - Supplementary Data. (No hematology, blood chemistry, or urinalysis results were reported. The stated "tail bends" adverse clinical observation should be explained.)

Mouse study - Supplementary Data. (The only significant toxic effects were chronic and acute stomach inflammation in male and female mice at the 2.5 and 5% dose levels; however, histopathologic findings [of any kind] were not reported for the 1.25, 0.62, or the 0.31% dose levels.)

3. Bioassay of Pesticides and Industrial Chemicals for Tumorigenicity in Mice: A Preliminary Note. J.R.M. Innes, B.M. Ulland, Marion G. Balerio, L. Petrucelli, L. Fishbein, E.R. Hart, A.J. Palotta, R.R. Bates, H.C. Falk, J.J. Gant, M. Klein, I. Mitchell, and J. Peters. Journal of the National Cancer Institute, Vol. 42, No. 6, June, 1969.

Test Material - Technical Gibberellic Acid (Gibberellin A_3)

This study report is preliminary in nature; early results of a large scale screen using 130 pesticides and industrial compounds for tumorigenicity in mice.

Two hybrid strains of mice were used:

a. (c57BL/6X C3H/Anf) F_1, designated strain X

b. (c57BL/6X AKR) F_1, designated strain Y

The two strains of mice were exposed separately to the test compound and positive and negative control chemicals by either single subcutaneous injection, or by continuous oral administration.

Prior to study initiation, maximally tolerated doses were determined in mg/kg of body weight by selecting maximal dose levels that resulted in zero mouse mortality.

The selected maximally tolerated dose was administered daily by stomach tube beginning when mice were 7 days of age until the mice were 4 weeks old. After the chemicals were mixed directly with the diet, no vehicle was used. The compound concentration was calculated according to animal body weights and food consumption for 4-week-old mice. The same concentration of compound was maintained throughout the 18-month study period.

The surviving animals were necropsied after 18 months of observation; an external examination was made and a thorough

examination of thoracic and abdominal cavities, with histologic examination of major organs and of all grossly visible lesions.

The individual positive controls and experimental groups were compared with the grouped negative controls. The authors state that this chi-square analysis presents a corrected relative risk which is a measure of the tumor incidence among the treated mice as compared to the controls. The analysis was performed with four tumor groupings: hepatomas, pulmonary tumors, lymphomas, and total mice with tumors. The significance test of each sex-strain subgroup and their various combinations were analyzed by the Mantel-Haenszel procedure, and the combined relative risk uses of the weighted geometric mean[2] with the 1/2 corrections used throughout.

Results and Conclusions:

The current results presented in this preliminary study seem to indicate that gibberellic acid (Gibberellin A_3) was not tumorigenic when fed to two different hybrid strains of laboratory mice for a period of 18 months.

Classification: Supplementary Data

Tox Chem. No. 467 (gibberellin A_3 only) gibberellic acid

File Last Updated --

Current Date 4/10/85

Study/Lab/Study #/Date	Material	EPA Accession No.	Results		TOX Category	Core Grade
(These "old" tox. data begin about 1960.)						
Acute oral, mouse		114828 (pp7F0544)	Gibberellic acid in CMC	LD_{50}>25.0 g/kg		
			Gibberellic acid in dilute NaOH	LD_{50} 15.1 g/kg		
			Gibberellic acid spray dried	LD_{50} 6.3 g/kg		
Acute oral, rat		"	Gibberellic acid in CMC	LD_{50}>15.0 g/kg		
			Gibberellic acid in dilute NaOH	LD_{50} 15.0 g/kg		
Acute oral, dog		"	Gibberellic acid	LD_{50}>5 g/kg		
			Gibberellic acid spray dried	LD_{50}>0.5 g/kg		
5-month feeding study, rat		"	Na salt	Body weights decreased at 400 ppm		
15-week feeding study, rat		"	5% Gibberellic acid	No effect		

Tox Chem. No. 467 gibberellic acid A_3 File Last Updated -- Current Date 4/10/85

Study/Lab/Study #/Date	Material	EPA Accession No.	Results		TOX Category	Core Grade
90-day feeding study, dog		114828 (7F0544)	Na salt	No effect at 1000 mg/kg		
4 1/2-week feeding study, rat		"	Na salt	No effect at 1000 mg/kg		
90-day gavage study, rat		"	Gibberellic acid	No effect at 1 g/kg		
212-375-day feeding study, rat		"	Gibberellic acid	No effect at 10,000 ppm		
202-day feeding study, rat		"	Gibberellic acid	No effect at 10 ppm		
398-day feeding study, rat		"	Gibberellic acid	No effect at 100 ppm		

Tox Chem. No. 467 (gibberellic acid only) File Last Updated -- Current Date 4/10/85

Study/Lab/Study #/Date	Material	EPA Accession No.	Results		TOX Category	Core Grade
187-day capsule study, dog		114828 (7F0544)	Gibberellic acid	No effect at 0.2 mg/kg		
385-day capsule study, dog		"	Gibberellic acid	No effect at 1 mg/kg		
385-day feeding study, dog		"	Gibberellic acid	No effect at 0.5 mg/kg for 187 days and 10 mg/ kg for 198 days		
2-year carcinogenicity, rat		"	Gibberellic acid	Negative		
reproduction study, rat		"	Na salt	Negative		

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

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

FROM: William S. Woodrow, Ph.D.
Toxicology Branch/HED (TS-769)

TO: William Burnam, Acting Chief
Toxicology Branch/HED (TS-769)

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 Biochemical Pesticides, and should be reviewed accordingly.

Rationale for Classification of Gibberellic Acid - Gibberellins as Biochemical Pesticides

Gibberellins do fit the Subpart M Biochemical 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 Biochemical 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 Biochemical 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.

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However, in view of the fact the Gibberellins may be classed as Biochemical Pesticides, human hazard evaluation may be conducted according to 40 CFR Part 158 Data Requirements (FR Wednesday October 24, 1984, which consist of a battery of short-term, acute type tests, one subacute feeding study, and one teratology study. Chronic studies would be required only if Tier I 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 artificially; 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 I, Tier II, and Tier III Toxicity Tests (See 40 CFR Part 158 EPA Data Requirements for Pesticide Registration, FR Wed. Oct. 24, 1984).

   Tier I Tests:

	Species	Test Substance
Acute Oral	Rat	Formulated Product
Acute Dermal	Rat or Mouse	Formulated Product
Acute Inhalation	Mouse, Rabbit or Guinea Pig	Formulated Product
Ocular, primary irritation	Rabbit	Formulated Product

Dermal, primary irritation	Guinea Pig or Rabbit	Formulated Product
Non-immediate hypersensitivity	Hamster or Guinea Pig	Formulated Product

Mutagenicity Tests

a. Gene mutation test; such as an Ames Salmonella/reverse mutation assay.

b. Structural chromosome aberration test; such as a mammalian cell culture Sister Chromatid Exchange, or Mouse Heritable Translocation test.

c. A test for other genotoxic effects; such as a microbial DNA damage and repair test.

90-day Feeding	1 mamm. species	Technical agent
Teratogenicity	1 mamm. species	Technical agent
Tier II Tests:	mammalian mutagenicity tests	
Tier III Tests:	Chronic exposure (feeding) Oncogenicity	

Hazard Assessment Scheme for Gibberellins Designated Biochemical 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 40 CFR Part 158 Tier I tests.

If results indicate lack of toxicity - exempt from tolerance (clear inerts). If results indicate hazard potential(s) - require 40 CFR Part 158 Tier II tests.

b. Application rate more than 20 g per acre.

A. Residue data indicate 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 40 CFR Part 158 Tier I tests.

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

If results indicate hazard potential(s) require 40 CFR Part 158 Tier II tests.

B. Residue data indicate 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 40 CFR Part 158 Tier I 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 40 CFR Part 158 Tier II tests.

ii. Incomplete tox. data base.

Require 40 CFR Part 158 Tier I tests. Animals dosed at intended use exposure levels (based on residue levels).

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

Animal results positive - require 40 CFR Part 158 Tier II 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 40 CFR Part 158 Tier I tests - if tox. test data indicate lack of toxicity - exempt from tolerance (clear inerts).

      ii. If animal tox. tests indicate hazard potential - require 40 CFR Part 158 Tier II tests.

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

      1. Require 40 CFR Part 158 Tier I 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 40 CFR Part 158 Tier II tests.

3. Synthetic Gibberellin(s) which have been shown to be not 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, 40 CFR Part 158 Biochemical Tier I 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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