COMPETENT AUTHORITY REPORT

THIABENDAZOLE (PT 8)

Document IIIA

Active Substance

Section 1: Applicant
Section 2: Identity
Section 3: Physical & Chemical Properties

Rapporteur Member State: Spain
May 2006

Section A1 Applicant

Annex Point IIA1

1.1 Applicant: **Syngenta European Center**

GU2 7YH Guildford
United Kingdom

Contact person: [redacted]
Syngenta European Office
Priestly Road
GU2 7YH Guildford
[redacted]

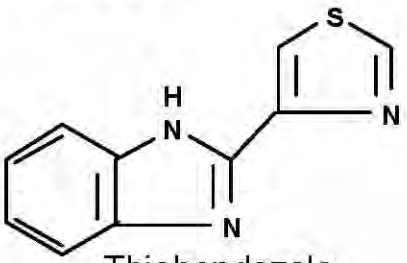
1.2 Manufacturer of Active Substance: **Syngenta Crop Protection AG**

CH - 4002 Basle
Switzerland

Location of plant: [redacted]

Contact point: Syngenta Crop Protection AG.
[redacted]

Section A2 Identity of Active Substance

Subsection (Annex Point)				Official use only
2.1	Common name	Thiabendazole		
2.2	Chemical name	IUPAC nomenclature :	2-(4-thiazolyl)-1H-benzimidazole	X1
2.3	Manufacturer´s development code number(s)	MK 360		
2.4	CAS No and EC numbers			
2.4.1	CAS-No	148-79-8		
2.4.2	EC-No	205-725-8		
2.4.3	CIPAC-No	323		
2.5	Molecular and structural formula, molecular mass			
2.5.1	Molecular formula	$C_{10} H_7 N_3 S$		
2.5.2	Structural formula	 Thiabendazole		
2.5.3	Molecular mass	201.26 g/mol		
2.6	Method of manufacture of the active substance	**CONFIDENTIAL INFORMATION**-data provided separately		
2.7	Specification of the purity of the active substance, as appropriate	**CONFIDENTIAL INFORMATION**-data provided separately		
2.8	Identity of impurities and additives, as appropriate	**CONFIDENTIAL INFORMATION**-data provided separately		
2.9	The origin of the natural active substance or the precursor(s) of the active substance	Not applicable		

Evaluation by Competent Authorities	
Date	**EVALUATION BY RAPPORTEUR MEMBER STATE** May 2005
Materials and Methods	[redacted]
Results and discussion	
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	
Remarks	[redacted]

Section A2.10
Annex Point IIA2.10

Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC

Subsection		Official use only
2.10.1 Human exposure towards active substance	The biocidal product is manufactured [redacted]. According to the TNsG Data Requirements, Ch.2, 2.10 and 6.6, for products manufactured outside the European Union, no details on this issue need to be included.	X1
2.10.1.1 Production i) Description of process ii) Workplace description iii) Inhalation exposure iv) Dermal exposure		
2.10.1.2 Intended use(s)		
1. Professional Users i) Description of application process ii) Workplace description iii) Inhalation exposure iv) Dermal exposure		
2. Non-professional Users including the general public (i) via inhalational contact (ii) via skin contact (iii) via drinking water (iv) via food (v) indirect via environment		
2.10.2 Environmental exposure towards active substance		
2.10.2.1 Production (i) Releases into water (ii) Releases into air (iii) Waste disposal		

Section A2.10 Annex Point IIA2.10	Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC

2.10.2.2 Intended use(s)

Affected compartment(s): water sediment air soil	
Predicted concentration in the affected compartment(s) water sediment air soil	

Evaluation by Competent Authorities	
EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	June 2005
Materials and methods	[redacted]
Conclusion	[redacted]
Reliability	
Acceptability	[redacted]
Remarks	

Section A3 Physical and Chemical Properties of Active Substance

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
3.1 Melting point, boiling point, relative density								
3.1.1 Melting point	EEC A.1	99.16 %	297-298 °C	Capillary tube method	Y	1	Pigeon, 1997	
3.1.2 Boiling point	EEC A.2. OECD 103	99.7 %	Thermal decomposition before the boiling point is reached	Differential scanning calorimetry	Y	0	Das, 2000	
3.1.3 Bulk density/ rel. density								
Relative density	EEC A.3.	99.16%	1.3989 g/cm^3	Pycnometer method	Y	1	Pigeon, 1997	
Bulk density	?	?	0.33 g/ml		?	3	?	**X1**
3.2 Vapour pressure	EEC A.4. OECD 104	99.7 %	4.6 · 10^{-7} Pa at 25°C (extrapolated)	Gas saturation method	Y	1	Widmer, 1999	
3.2.1 Henry´s Law Constant			calculated result: 1.4 · 10^{-6} Pa m^3 mol^{-1}	Water solubility at 20 °C; pH 7: 30 g/m^3 Vapour pressure at 20 °C: 2.0· 10^{-7} Pa			Burkhard, 2000	**X2**
3.3 Appearance								
3.3.1 Physical state	Visual test	99.8 %	fine crystalline solid (pure a.i.)		Y	1	Das, 2005	
		99.5 %	dry powder (tech. grade a.i.)		Y	1	Das, 2005	
3.3.2 Colour	Visual test	99.8 %	white (pure a.i.)		Y	1	Das, 2005	**X3**
		99.5 %	light-beige (tech. grade a.i.)		Y	1	Das, 2005	
3.3.3 Odour	Organoleptic test	99.8 %	odourless (pure a.i.)		Y	1	Das, 2005	
		99.5 %	odourless (tech. grade a.i.)		Y	1	Das, 2005	

Section A3 Physical and Chemical Properties of Active Substance

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
3.4 Absorption spectra								X4
UV/VIS		99.7 %	For the absorption maxima at 299 nm the molar extinction coefficient was determined to be 23213 l / mol · cm in neutral solution. No absorption maximum between 350 nm and 750 nm was observed.	Concentration and solvent: 1.4556 mg in 100 ml methanol Quartz cell : 10 mm pathlength	Y	1	Oggenfuss, 1999	
IR		99.7 %	Characteristic bands: ca. 3400-3500 cm^{-1} (N-H stretch) 1579 cm^{-1} (aromatic C-C) 1455 cm^{-1} (C=N in heterocycle) 1405 cm^{-1} (C-C in heterocycle)	KBr pellet	Y	1	Oggenfuss, 1999	
NMR		99.7 %	**^{1}H-RMN** Chem. Shift (ppm) N° of protons ca. 3.5 1 7.2 2 7.6 2 8.4 1 9.3 1	Solution in DMSO-D_6 Nucleus :^{1}H (300 MHz)	Y	1	Oggenfuss, 1999	
		99.7 %	**^{13}C-RMN** Chem. Shift (ppm): 115.2, 121.3, 123.3, 137.6, 146/147, 156.3	Solution in DMSO-D_6 Nucleus :^{13}C (75 MHz)	Y	1	Oggenfuss, 1999	

Section A3 Physical and Chemical Properties of Active Substance

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
MS		99.7 %	m / z 203 ^{34}S-isotope of molecular ion 201 M^+, molecular ion 174 M^+ - HCN 130 m/z 174 – CS 103 m/z 130 – HCN 90 m/z 130 – C_2NH_2 63 m/z 90 – HCN	Type of analyzer : ion trap Ionization mode : electron impact Detection : scan mode Ionizing energy : 70 eV	Y	1	Oggenfuss, 1999	
3.5 Solubility in water	*including effects of pH (5-9)*							
Water solubility 1	EEC A.6./ OECD 105	99.7 %	result: 31 mg/l temperature: 25 °C pH: 8.1	Flask method	Y	1	Das, 2001	
Water solubility 2	EEC A.6.	99.16 %	0.16 g/l at pH 4 0.03 g/l at pH 7 0.03 g/l at pH 10 Temperature: 20 °C	Flask method	Y	1	Pigeon, 1997	**X5**
3.6 Dissociation constant (-)	OECD 112	99.4 %	pk_{a1} = 4.73 pk_{a2} = 12.00 Temperature: 22.4 °C		Y	1	Book, 1988	
3.7 Solubility in organic solvents, including the effect of temperature on solubility	EEC A.6.	99.16 %	temperature: 20 °C n-heptane: < 0.01 g/l xylene: 0.13 g/l methanol: 8.28 g/l 1,2-dichloroethane: 0.81 g/l acetone: 2.43 g/l ethyl acetate: 1.49 g/l n-octanol: 3.91 g/l	Flask method	Y	1	Pigeon, 1997	
3.8 Stability in organic solvents used in b.p.			Thiabendazole is stable in organic solvents. Nevertheless, the biocidal product is not formulated					**X6**

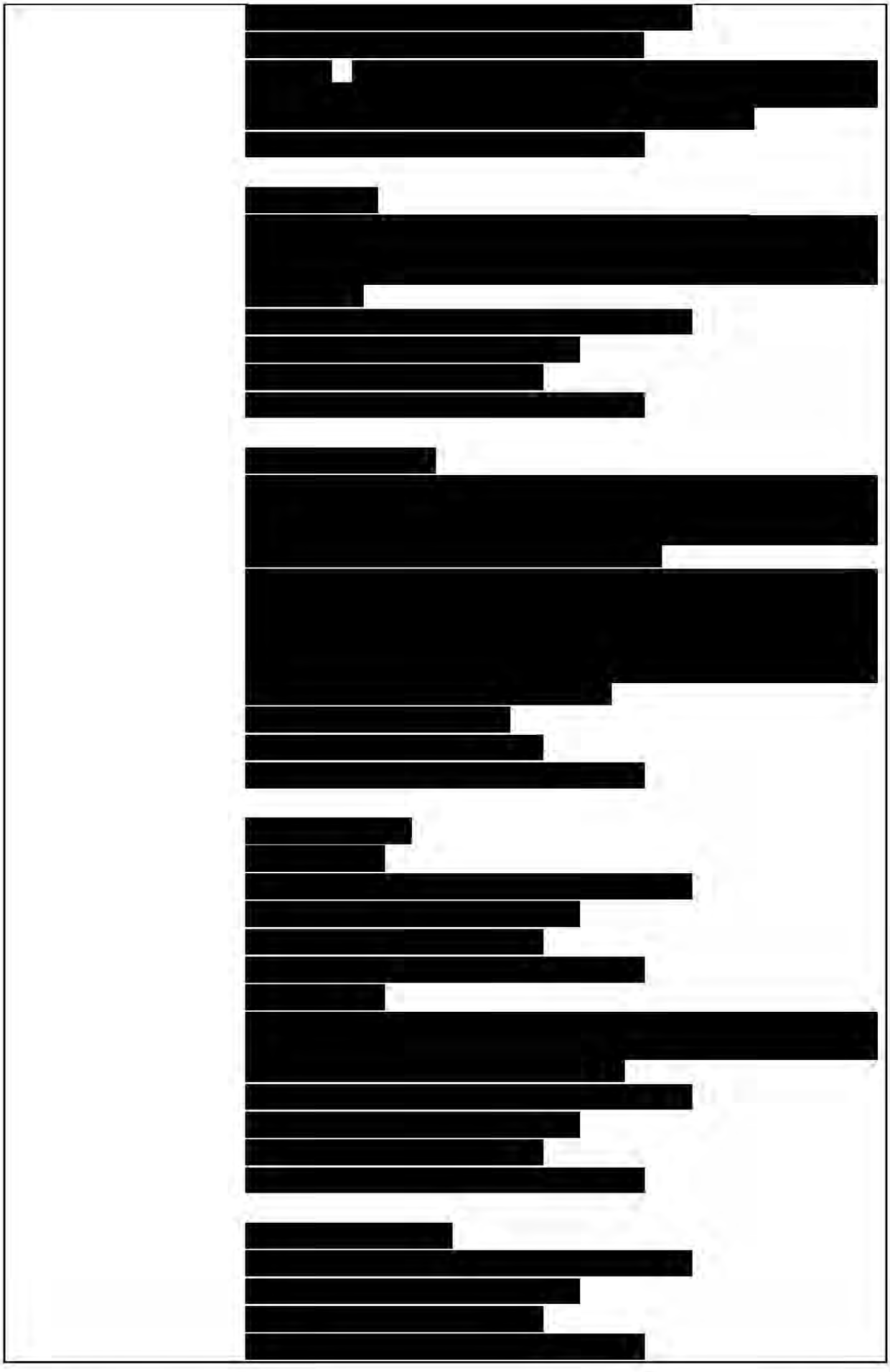
Section A3 Physical and Chemical Properties of Active Substance

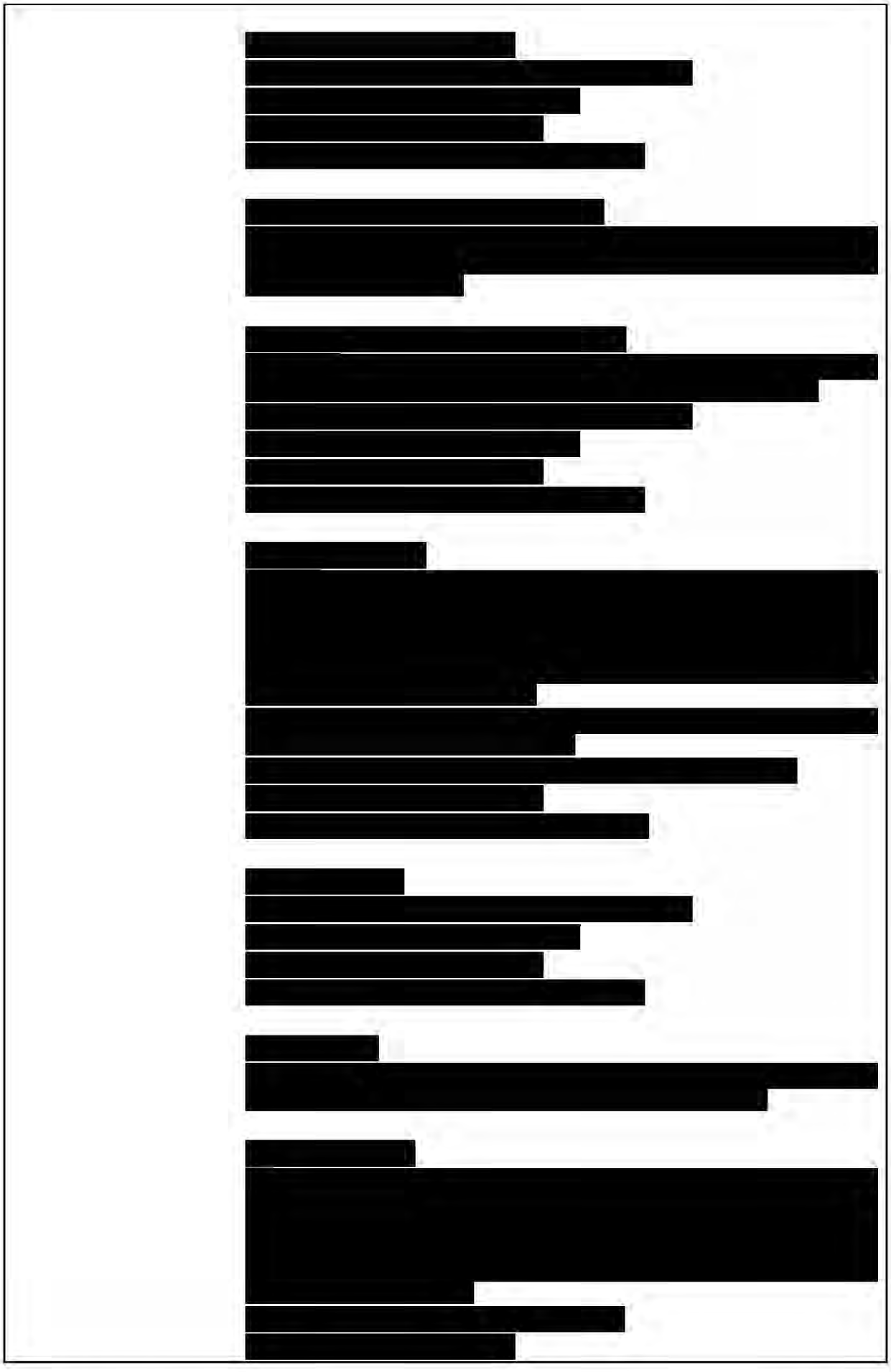
Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
and identity of relevant breakdown products			in organic solvents					
3.9 Partition coefficient n-octanol/water	*including effects of pH (5-9)*							
log Pow	EEC A.8.	99.16 %	temperature: 20 °C result: log P_{ow} = 1.62 at pH 4 log P_{ow} = 2.39 at pH 7 log P_{ow} = 2.40 at pH 10	Shake flask method	Y	1	Pigeon, 1997	**X7**
3.10 Thermal stability, identity of relevant breakdown products			Sublimation heat: 29.7 Kcal/mole. Sublimation pressure extrapolated at 25 °C: $4 \cdot 10^{-9}$ mm Hg Sublimation pressure extrapolated at 49 °C: $1.6 \cdot 10^{-7}$ mm Hg	Knudsen effusion technique	N		Boos 1973	
	OECD 113 EEC A.5.	99.5 %	The sample shows neither without nor with air any peak between room temperature and 150 °C		Y	1	Angly, 1999	**X8**
3.11 Flammability, including auto-flammability and identity of combustion products								
- **Flammability (solids)**	EEC A.10	99.16 %	The test substance is not considered highly flammable		Y	1	Pigeon, 1997	
- **Flammability (contact with water)**	EEC A.12	99.16 %	No gas		Y	1	Pigeon, 1997	
3.12 Flash-point	Not required for a solid substance							**X9**

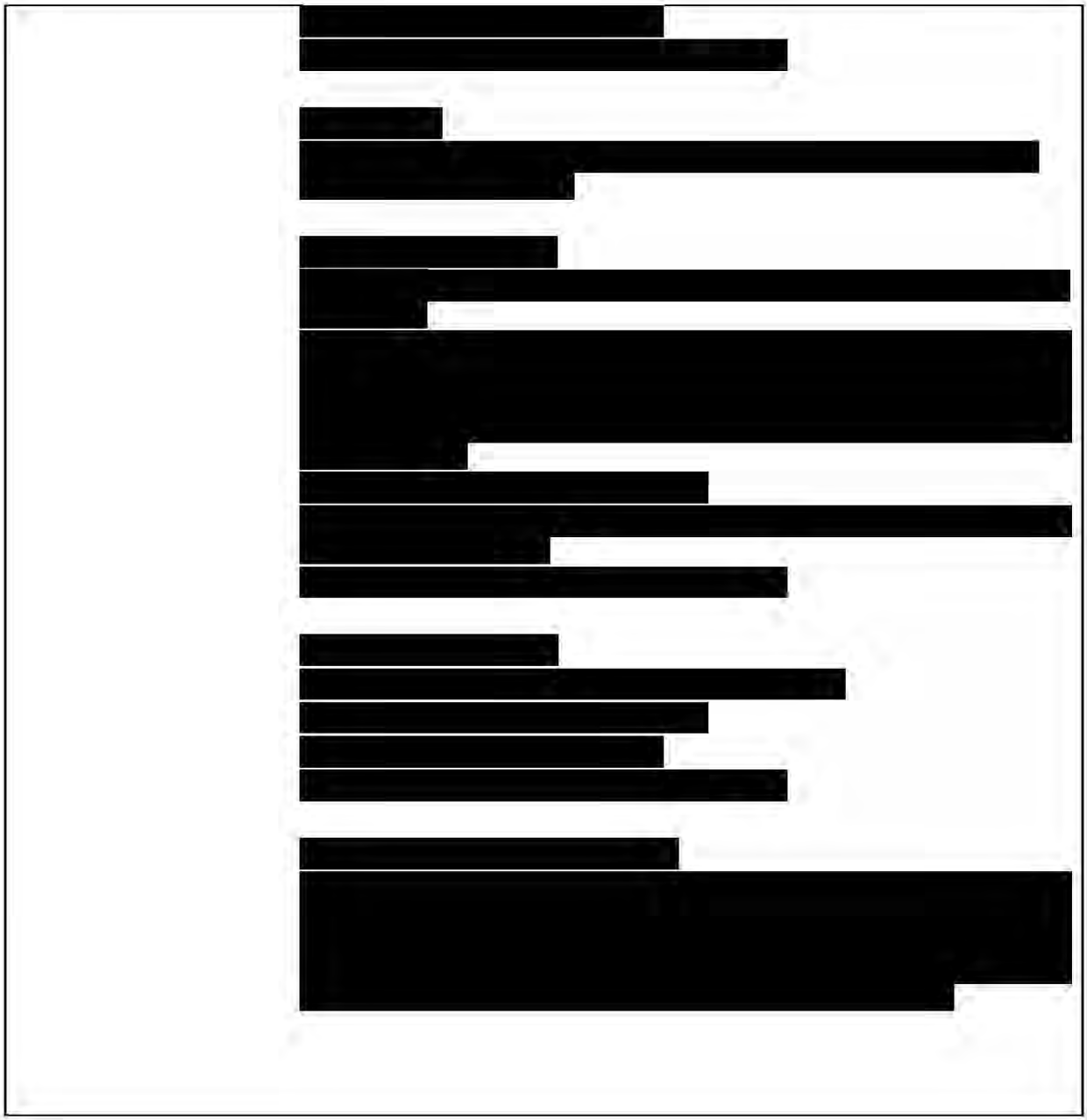
Section A3 Physical and Chemical Properties of Active Substance

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
3.13 Surface tension	EEC A.5 OECD No. 115	99.5 %	σ = 72.7 mN/m (90 % saturation concentration)		Y	1	Martin, 2000	**X10**
3.14 Viscosity	Not required for a solid substance							**X11**
3.15 Explosive properties	USA Code of Federal Regulations (CFR) 49, 173.53 Note: 4		Not considered explosive	Impact explosivity	Y	2	Welberry, 1988	**X12**
3.16 Oxidizing properties	EEC A.17.	99.5 %	Not oxidizing substance		Y	1	Jackson, 2002	
3.17 Reactivity towards container material	Unreactive (Packed in steel drums)							**X13**
	ASTM G31-72 (85)		No corrosion of the test specimens was observed		Y	1	Kundel, 2002	

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	May 2005
Comment	[redacted]
Evaluation of data submitted under section A3	[redacted]







COMPETENT AUTHORITY REPORT

THIABENDAZOLE (PT 8)

Document IIIA

Active Substance

Section 4: Analytical Methods for Detection and Identification

Rapporteur Member State: Spain
May 2006

Section A4.1/01 Analytical Methods for Detection and Identification

Identification of the active ingredient

Title of the Study:	Analytical Method AW-207/1-Thiabendazol-Content by HPLC chromatography

An analytical method (including validation) has been developed for determination of thiabendazole (MK 360)

Analytical Method	AW-207/1	(Dull, 1998)
Validation	Rep. N° 72794	(Dull, 1999)

Determination of active substance:

The active substance MK 360 is determined by liquid chromatography on a reversed phase C-18 column using UV detection at 254 nm. Quantification is done by comparison of peak areas to those of a reference solution.

Validation of the method:

Specificity: established; no interference between MK360, solvent and the organic by-products

Recovery: The recovery was tested using 3 weights of the active substance Range: 75 %, 100 % and 125 % of prescribed weight

The following mean value was found: 99.6 %

Linearity: The linearity was tested using 5 weights of the active substance. Range: 50 %, 75 %, 100 %, 125 % and 150 % of prescribed weight

The coefficient of variation was calculated to be 0.99998.

Accuracy: The accuracy of the method is established based on the findings for specificity, recovery and linearity.

Precision: The precision of the method is established based on the findings for repeatability and ruggedness.

Repeatability: The repeatability was determined with 5 individual subsamples of the same batch of MK360.

s_{rel} : 0.32 %

Ruggedness: Mean value of repeatability study: 99.5 %

Mean value of second laboratory: 99.4 %

Conclusion: The method is suitable for the specific and accurate determination of MK 360 with a good precision.

Compliance with GLP principles: Yes

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	May 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Remarks	

Section A4.1/02 Analytical Methods for Detection and Identification

Identification of the active ingredient, by-products and supplementary tests

Title of the Study:	Analytical Method AK-207/2-Thiabendazol-By-Products and Supplementary Test

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	May 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]le
Conclusion	[redacted]
Reliability	[redacted]ts
Acceptability	
Remarks	

98/8 Doc IIIA section No.	**4.1 / 03**	**Analytical methods for the determination of pure active substance and, where appropriate, for relevant degradation products, isomers and impurities of active substances and their additives (e.g. stabilisers)**
91/414 Annex Point addressed	**II 4.1 / 03;**	**Analytical methods for determination of active substance**

Title of the Study:	**HPLC method for the determination of Thiabendazole in simulated tank mixes, technical Thiabendazole and formulated Thiabendazole**
Dossier Reference:	4.1 /01,
Method number: Author:	M-021 Robert F. Peterson, Jr.
Name and address of testing facility:	Merck Research Laboratories, Hillsborough Road, Three Bridges, New Jersey 08887-0450, USA
Test substance:	Thiabendazole
Date of issue:	Analytical method: December, 1998 Validation: December, 1998
Compliance with GLP:	[X] Yes [ ] No, but complies with sound scientific principles
Reliability indicator	1

Test Sytems/ Findings

The total amount of thiabendazole is determined by HPLC using the external standardisation technique. The sample is dissolved in acetonitrile or methanol and analysed by ion-exchange chromatography for thiabendazole using UV detection at 305 nm. The precision (standard deviation/mean) of the assay was shown to be 1.8 - 3.9% for technical and formulated material. The standard calibration curve was shown to be linear over a range of concentrations (6-35 µ g/ml). The method is considered adequate for analysing the technical material, formulations of the active substance and tank mix suspensions of thiabendazole.

1.2	**Title**	HPLC method for the determination of Thiabendazole in simulated tank mixes, technical Thiabendazole and formulated Thiabendazole
1.3	**Report No.**	Method of Analysis M-021
1.4	**Lab. report No.**	not applicable
1.5	**Cross reference**	4.1/01
1.6	**Authors**	Robert F. Peterson, Jr., Research Fellow, Merck & Co., Inc.
1.7	**Date of report**	The final method report is still undergoing Merck Quality Assurance review.
1.8	**Published**	no
2.1	**Testing facility**	Merck Research Laboratories, Hillsborough Road, Three Bridges, New Jersey 08887-0450, USA
2.2	**Dates of experimental work**	18 September 1992 to 21 December 1992

3	**Objective**	To validate an HPLC method for the determination of thiabendazole in technical thiabendazole (Tecto Antimycotic A) and formulated thiabendazole (Mertect 340-F and Freshgard 555).
4.1	**Test substance**	Thiabendazole [2-(4-thiazolyl)-1H-benzimidazole], Composition: [redacted]
4.2	**Specification**	[redacted] active substance
4.3	**Storage stability**	not applicable
4.4	**Stability in vehicle**	test substance stable in vehicle
4.5	**Homogeneity in vehicle**	not applicable
4.6	**Validity**	method validated for the test substance in simulated tank mixes
5	**Vehicle/solvent**	Acetonitrile
6	**Physical form**	powder
7.1	**Test method**	Analytical method for the determination of Thiabendazole residues in simulated tank mixes, technical Thiabendazole and formulated Thiabendazole.
7.2	**Justification**	applicable for TBZ in simulated tank mixes
7.3	**Copy of method**	included in report
8	**Choice of method**	applicable for TBZ in simulated tank mixes
9	**Deviations**	none specified
10.1	**Certified laboratory**	inspected by U.S. EPA 1993
10.2	**Certifying authority**	U.S. EPA
10.3	**GLP**	The method validation portion of the study was conducted in compliance with (U.S.) EPA GLP
10.4	**Justification**	not applicable
11.1	**GEP**	not applicable
11.2	**Type of facility (official or officially recognized)**	not applicable
11.3	**Justification**	not applicable
12	**Test system**	**Sample**: Thiabendazole technical, formulated material or tank mix **Extraction:** diluted with acetonitrile or methanol and the Thiabendazole dissolved by sonication **Analysis**: The amount of Thiabendazole in the diluted mixture is determined using the external standardization technique by HPLC cation exchange chromatography (benzenesulfonic acid stationary phase) with UV detection at 305 nm. **Confirmation**: by comparison of the chromatographic retention time of thiabendazole in the final sample solution to the

			chromatographic retention time of thiabendazole in the HPLC standards.
13	Findings	**Limits of detection:**	< 0.1% active substance
		Limits of quantitation:	< 0.1% active substance
		Average concentrations:	98.22% for Tecto Antimycotic A (lot SSD-001), 43.48% for Mertect 340-F (lot RRX-113), and 4.62% for Freshgard 555 (lot 5276). Expected Thiabendazole concentrations in the different thiabendazole samples assayed were 98.5% for Tecto Antimycotic A (from MSDS), 42.28% for Mertect 340-F (from MSDS), 5% (nominal) for Freshgard 555.
		Coefficient of variation:	TECTO Antimycotic A: 3.85%; MERTECT 340-F: 1.78%; FRESHGARD 555: 3.53%
		Number of observations:	9
		Interferences:	no interferences for control samples and reagents used were observed.
14	Statistics	no statistical analysis was carried out, as it was considered unnecessary for interpretation of the results and therefore not required.	
15	References to publications	none	
16	Unpublished data	not applicable	

Evaluation and conclusions: The method is acceptable

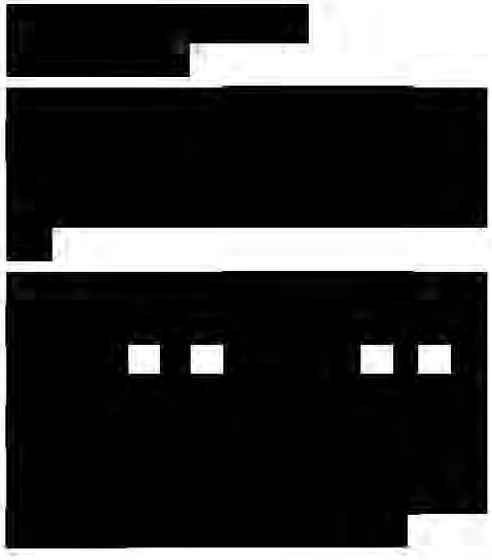
Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	May 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

98/8 Doc IIIA section No.	**4.1 / 04**	**Analytical methods for the determination of pure active substance and, where appropriate, for relevant degradation products, isomers and impurities of active substances and their additives (e.g. stabilisers)**
91/414 Annex Point addressed	**II 4.1 / 01**	**Analytical methods for determination of active substance**

Title of the Study:	**HPLC method for the determination of the Chlorinated Impurities in Thiabendazole**
Dossier Reference:	4.1 /02
Method number: Author: :	None Merck Manufacturing Division, MMD Standards & Administration, Merck & Co., Inc
Name and address of testing facility:	Merck Manufacturing Division, MMD Standards and Administration, Merck & Co., Inc., Rahway, New Jersey 07065, USA
Test substance:	Thiabendazole
Date of issue:	18 June 1993
Compliance with GLP:	[X] Yes [ ] No, but complies with sound scientific principles
Reliability indicator	1

[redacted]

3 [redacted]



[redacted]

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	May 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

98/8 Doc IIIA section No.	**4.2 / 01**	**Analytical methods including recovery rates and the limits of determination for the active substance, and for residues thereof, and where relevant in/on the following: (a) Soil**
91/414 Annex Point addressed	**II 4.2.2 / 01 & 03 & 05**	**Analytical methods for determination of residues – residues in soil**

Title of the Study	**Analytical Method: HPLC Method for the Determination of Thiabendazole and Benzimidazole in Soil.**
Dossier Reference:	4.2.2/01
Method Numbers: Author:	37853M Jim Fieser, Chemist II, Field and Analytical Chemistry Programs, ABC Laboratories, Inc.
Name and address of the testing facility:	Analytical Bio-Chemistry Laboratories, Inc., Field and Analytical Chemistry Programs, 7200 E. ABC Lane, Columbia, MO 65202-8015, USA
Test Substance:	Thiabendazole
Date of Issue:	4 April 1994
Compliance with GLP:	[X] Yes [ ] No, but complies with sound scientific principles
Reliability indicator	1

Test System/Findings

The analytical method can be used to determine residues of thiabendazole and the metabolite benzimidazole in soil. The soil sample is extracted with methanol/KOH followed by a second extraction of the residue with dimethylformamide/HCl, then partitioned into ethyl acetate and the extract purified by a series of acid/base liquid-liquid partitions. Ethyl acetate is evaporated, the residue dissolved in aqueous acetic acid and the solution analysed by HPLC on a C-8 column eluting with methanol/water (60/40) containing 0.1% ammonium acetate. Detection is by fluorescence.

Recoveries over the fortification at 0.01-1 mg/kg are in the range 80-92% (overall average recovery of 87%) for thiabendazole and 86-99% (overall average recovery of 92%) for benzimidazole. LOD of the analytical method for thiabendazole and benzimidazole in soil is 0.01 mg/kg and the limit of detection of 0.005 mg/kg.

1.2	**Title**	Analytical Method: HPLC Method for the Determination of Thiabendazole and Benzimidazole in Soil.
1.3	**Report No.**	92530
1.4	**Lab. report No.**	37853M
1.5	**Cross reference**	4.2.2/01
1.6	**Authors**	Jim Fieser, Chemist II, Field and Analytical Chemistry Programs, ABC Laboratories, Inc. Brian Jacobson, Team Leader/Study Director, Field and Analytical Chemistry Programs, ABC Laboratories, Inc.

1.7	**Date of report**	4 April 1994
1.8	**Published**	no
2.1	**Testing facility**	Analytical Bio-Chemistry Laboratories, Inc., Field and Analytical Chemistry Programs, 7200 E. ABC Lane, Columbia, MO 65202-8015, USA
2.2	**Dates of experimental work**	July 14, 1989 (Method validation results) August 7, 1989 to July 14, 1992 (Method recovery results from fortified control soil samples)
3	**Objective**	To validate an HPLC method for the determination of Thiabendazole and Benzimidazole in Washington soil. The analytical method was used to support the Merck study (No. 92530) entitled "Terrestrial Field Dissipation for Thiabendazole in Wheat."
4.1	**Test substance**	1. Thiabendazole [2-(4-thiazolyl)-1H-benzimidazole], Composition: [redacted] 2. Benzimidazole [1,3-benzodiazole], [redacted]%
4.2	**Specification**	[redacted] active substance
4.3	**Storage stability**	not applicable
4.4	**Stability in vehicle**	test substance stable in vehicle
4.5	**Homogeneity in vehicle**	not applicable
4.6	**Validity**	method validated for the test substance in Soil
5	**Vehicle/solvent**	methanol
6	**Physical form**	powder
7.1	**Test method**	Analytical method for the determination of Thiabendazole and Benzimidazole in soil. U.S. EPA Pesticide Assessment Guidelines, Subdivision N, Guideline Reference No. 164-1.
7.2	**Justification**	applicable for TBZ in Soil
7.3	**Copy of method**	included in report
8	**Choice of method**	applicable for TBZ in Soil
9	**Deviations**	none specified
10.1	**Certified laboratory**	inspected by U.S. EPA
10.2	**Certifying authority**	U.S. EPA
10.3	**GLP**	The method validation portion of the study was conducted in compliance with (U.S.) EPA GLP
10.4	**Justification**	not applicable
11.1	**GEP**	not applicable
11.2	**Type of facility (official or officially recognized)**	not applicable
11.3	**Justification**	not applicable

12	**Test system**	**Test object:**	soil
		Extraction:	by shaking the soil sample (20 g) in 1:1 6N hydrochloric acid/dimethylformamide (DMF). The extract is filtered into a separatory funnel and buffered to slightly basic pH with sodium hydroxide and sodium carbonate. The basic extract is then partitioned against ethyl acetate three times, and the combined ethyl acetate extracts rotary evaporated to near dryness (about 1 mL DMF remains). The residue is dissolved in 10% acetic acid in water.
		Analysis:	by reversed-phase HPLC with fluorescence detection.
		Confirmation:	The identity of thiabendazole and benzimidazole residues is confirmed by comparison of the chromatographic retention times of thiabendazole and benzimidazole in the final sample solution to the chromatographic retention times of thiabendazole and benzimidazole in the reference standard solutions.
13	**Findings**	**Limits of detection:**	0.005 mg/kg
		Limits of quantitation:	0.01 mg/kg
		Fortification levels:	0.01 mg/kg to 1 mg/kg
		Recovery:	Thiabendazole: 80 to 92%, overall average: 87% Benzimidazole: 86 to 99%, overall average: 92% Method recovery values from fortified samples analyzed concurrently with field samples are also reported. The overall average recoveries for Thiabendazole and Benzimidazole were 80 ± 8.7% (standard deviation) and 82 ± 7.3% (standard deviation), respectively (n = 59).
		Number of observations:	7
		Coefficient of variation:	Thiabendazole: 5.4% Benzimidazole: 4.5%
		Interferences:	from sample matrices for control samples and reagents were < 0.01 mg/kg (estimated) apparent TBZ and apparent Benzimidazole

14	**Statistics**	no statistical analysis was carried out, as it was considered unnecessary for interpretation of the results and therefore not required
15	**References to publications**	none
16	**Unpublished data**	not applicable

Evaluation and conclusions: The method is acceptable

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	May 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

98/8 Doc IIIA section No.	**4.2 / 02**	**Analytical methods including recovery rates and the limits of determination for the active substance, and for residues thereof, and where relevant in/on the following: (b) Air**
91/414 Annex Point addressed	**II 4.2.4 / 01 & 02**	**Analytical methods for determination of residues – residues in air**

Vapour pressure of the active substance (thiabendazole) is reported to be 4 x 10^{-9} h Pa (mm Hg). Analytical method for thiabendazole in air is not required as its vapour pressure does not exceed the trigger value of 1 x 10^{-5} h Pa (mm Hg).

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	May 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	
Reliability	
Acceptability	
Remarks	

98/8 Doc IIIA section No.	**4.2 / 03**	**Analytical methods including recovery rates and the limits of determination for the active substance, and for residues thereof, and where relevant in/on the following: (c) Water**
91/414 Annex Point addressed	**II 4.2.3 / 01 & 02 & 03**	**Analytical methods for determination of residues – residues in water**

Title of the Study	**Fluorescence Method for the Determination of Thiabendazole in Water**
Dossier Reference:	4.2.3/01, 4.2.3/02 (validation), 4.2.3/03 (validation surface water)
Method Number: Author:	Method of Analysis M-042 Joshua I. Justin
Name and address of the testing facility:	Merck Research Laboratories, Agricultural Department, Rahway, New Jersey 07065, USA
Test substance:	Thiabendazole
Date of issue:	27 April 1988
Compliance with GLP:	[ ] Yes [X] No, but complies with sound scientific principles
Reliability indicator	1

Test System/Findings

The analytical method is designed to monitor thiabendazole residues in groundwater and drinking water at residue levels as low as 0.05 µg/kg (0.05 µg/l). One litre of water, buffered to pH 7, is extracted with methylene chloride. The methylene chloride is evaporated and the residue partitioned between ethyl acetate and 0.1N HCl. Thiabendazole in the aqueous solution is determined spectrofluorometrically using an excitation wavelength of 306 nm and an emission wavelength of 360 nm. Thiabendazole recovery values obtained during method validation from control water samples fortified with 0.05 µg/kg to 0.5 µg/kg thiabendazole ranged from 88-106% (average recovery of 93%). LOD of the method for thiabendazole is 0.05 µg/kg and the estimated limit of detection of about 0.02 µg/kg.

1.2	**Title**	Fluorescence Method for the Determination of Thiabendazole in Water
1.3	**Report No.**	Method of Analysis M-042
1.4	**Lab. report No.**	not applicable
1.5	**Cross reference**	4.2.3/01
1.6	**Authors**	Joshua I. Justin, Agricultural Fellow, Merck & Co., Inc.
1.7	**Date of report**	27 April 1988 (Reformatted 13 September 1994)
1.8	**Published**	no
2.1	**Testing facility**	Merck Research Laboratories, Agricultural Department, Rahway, New Jersey 07065, USA
2.2	**Dates of experimental work**	13 June 1989 (Method validation)

3	**Objective**	To Validate an Analytical Residue Method for Thiabendazole in Water	
4.1	**Test substance**	Thiabendazole [2-(4-thiazolyl)-1H-benzimidazole], Composition: [redacted]	
4.2	**Specification**	[redacted] active substance	
4.3	**Storage stability**	not applicable	
4.4	**Stability in vehicle**	test substance stable in vehicle	
4.5	**Homogeneity in vehicle**	not applicable	
4.6	**Validity**	method validated for the test substance in Water	
5	**Vehicle/solvent**	0.1 N HCl	
6	**Physical form**	powder	
7.1	**Test method**	Analytical method for the determination of Thiabendazole residues in water	
7.2	**Justification**	applicable for TBZ in Water	
7.3	**Copy of method**	included in report	
8	**Choice of method**	applicable for TBZ in Water	
9	**Deviations**	none specified	
10.1	**Certified laboratory**	inspected by U.S. EPA 1993	
10.2	**Certifying authority**	U.S. EPA	
10.3	**GLP**	no	
10.4	**Justification**	GLP regulations not in effect at the time of the validation study	
11.1	**GEP**	not applicable	
11.2	**Type of facility (official or officially recognized)**	not applicable	
11.3	**Justification**	not applicable	
12	**Test system**	**Test object:**	buffered water sample (1 l at pH 7.0)
		Extraction:	by blending the water sample in methylene chloride. The methylene chloride extract is evaporated to dryness and the residue is dissolved and partitioned in ethyl acetate and 0.1N HCl.
		Analysis:	by spectrophotofluorometry using an excitation wavelength of approximately 306 nm and an emission wavelength of approximately 360 nm.
		Confirmation:	by comparison of the fluorescence (excitation and emission) spectrum of the final sample solution to the fluorescence spectrum of the processed thiabendazole standard.
13	**Findings**	**Limits of detection:**	0.02 µg/kg Thiabendazole

		(estimated)
	Limits of quantitation:	0.05 µg/kg Thiabendazole
	Fortification levels:	0.05 µg/kg to 0.5 ng/kg
	Recovery:	88 to 106% with an overall average recovery of 93%
	Coefficient of variation:	6.0%
	Interferences:	from the sample matrices for control samples and reagents subjected to the analytical procedure were < 0.02 µg/kg expressed as Thiabendazole.
14	**Statistics**	no statistical analysis was performed
15	**References to publications**	none
16	**Unpublished data**	not applicable

Evaluation and conclusions: The method is acceptable

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	May 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

98/8 Doc IIIA section No.	**4.2 / 04**	**Analytical methods including recovery rates and the limits of determination for the active substance, and for residues thereof, and where relevant in/on the following:** **(d) Animal and human body fluids and tissues**
91/414 Annex Point addressed	**II 4.2.1 / 01 & 02**	**Analytical methods for determination of residues – residues in and/or on plants, plant products, foodstuffs (of plant and animal origin), feeding stuffs**
Reliability indicator		1

Various studies are available covering this area – The findings are summarised

Test System/Findings

Animal Tissue: Fat/Skin

Spectrofluorometry – [redacted] (1987)

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	May 2005
Remarks	This test report was not included in Doc IV-A or in the corresponding Reference List. This report was requested to the applicant that answered that the study was not found. Therefore, the assessment of this analytical method could not be carried out. Nevertheless, there is an HPLC method developed and validated for the determination of thiabendazole and its metabolites in animal tissues.

Animal Tissue

HPLC

Thiabendazole (TBZ) and its animal metabolites 5-hydroxythiabendazole (5-OH-TBZ) and benzimidazole (BNZ) are released from the tissue using 6N HCl hydrolysis at 90-95°C for 24 hours. The solution is adjusted to pH 8, the TBZ, 5-OH-TBZ and BNZ extracted into ethyl acetate and the extract purified on a cation exchange solid phase extraction column. Quantitation of TBZ, 5-OH-TBZ and BNZ is performed by HPLC on a cation exchange column eluting with acetonitrile/phosphate buffer (25/75), pH 3.0-3.4. LOQ of the method is 0.1 mg/kg TBZ, 5-OH-TBZ and BNZ in the various tissues. The estimated limit of detection is 0.005 mg/kg for TBZ, and 0.01 mg/kg for 5-OH-TBZ and BNZ.

([redacted] 1994a)

Recovery values obtained by [redacted] and contract laboratories during method validation for chicken liver are shown below:-

Inter-Laboratory Recoveries of TBZ, 5-OH-TBZ and BNZ from chicken liver[a]

Fortification Level (mg/kg)	Recovery (%)
[redacted]	
A. TBZ:	

0.1 [a]	97, 100	115, 91, 88, 85
0.5	98, 93	90, 89
B. 5-OH-TBZ:		
0.1	84, 84	95, 82, 77
0.5	95, 92	93, 88
C. BNZ:		
0.1	82, 79	108, 90, 81, 78
0.5	100, 101	92, 90

[a] Control chicken liver samples contained < 0.02 mg/kg apparent residues of TBZ, 5-OH-TBZ and BNZ.

Recovery values obtained by [redacted] during method validation for pork kidney, chicken muscle and chicken skin/fat are shown below:-

Recoveries of TBZ, 5-OH-TBZ and BNZ from Pork Kidney, Chicken Muscle and Chicken Skin/Fat[a]

Fortification Level (mg/kg)	Recovery (%)		
	Pork Kidney	Chicken Muscle	Chicken Skin/Fat
A. TBZ:			
0.1	80, 81	85, 80	103, 81
0.5	98, 105	80, 86	88, 90
B. 5-OH-TBZ:			
0.1 [b]	95, 97	98, 101	86, 97
0.5	81, 89	85, 91	85, 85
C. BNZ:			
0.1	97, 100	86, 90	86, 84
0.5	98, 104	94, 93	91, 88

[a] Control animal tissue samples contained < 0.02 mg/kg apparent residues of TBZ, 5-OH-TBZ and BNZ.

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	May 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

Animal Tissue, Blood and Milk

Spectrofluorometry – [redacted], 1994b

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	May 2005
Remarks	[redacted]

Bovine Milk

HPLC

The milk sample containing residues of thiabendazole (TBZ) and 5-hydroxythiabendazole (5-OH-TBZ) is heated with concentrated HCl for four (4) hours at 85-90°C, the cooled solution adjusted to pH 8, extracted into ethyl acetate, the extract purified on a cation exchange solid phase extraction column and the purified solution assayed by HPLC on a cation ion exchange column eluting with acetonitrile/phosphate buffer (20/80) at pH 3.8. LOQ of the method is 0.05 mg/kg for TBZ and 5-OH-TBZ. The estimated limit of detection is 0.005 mg/kg.

([redacted] 1994)

Recovery values obtained by [redacted] and contract laboratories during method validation are shown below:-

Inter-Laboratory Recoveries of TBZ, 5-OH-TBZ and 5-NaSO4-TBZ from Raw Bovine Milk. [a]

Fortification Level (mg/kg)	Recovery (%)	
	[redacted]	[redacted]
A. TBZ:		
0.05	87, 92, 89, 90	--
0.4	91, 88,92,88	89, 90, 92, 90
2.0	96, 94, 103, 100	88, 92, 96, 98
B. 5-OH-TBZ:		
0.05	106, 100	--
0.4	109, 105	83, 81
2.0	101, 98	87, 86
C. 5-NaSO4-TBZ: [c]		
0.05	96, 104	--
0.4	102, 115	86, 88
2.0	108, 108	101, 102

[a] Control raw bovine milk contained < 0.01 mg/kg apparent residues of TBZ, 5-OH-TBZ and 5-NaSO4-TBZ.
[c] 5-NaSO4-TBZ was detected as 5-OH-TBZ after HCl hydrolysis.

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	May 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

Chicken Egg

HPLC

The egg sample containing residues of thiabendazole (TBZ), 5-hydroxythiabendazole (5-OH-TBZ) and benzimidazole (BNZ) is heated with 6N HCl for 24 hours at 90-95°C, the cooled solution adjusted to pH 8 and extracted into ethyl acetate, the extract purified on a cation exchange solid phase extraction column and the purified solution assayed by HPLC on a cation ion exchange column eluting with acetonitrile/phosphate buffer (25/75), pH 3.0-3.4.

LOQ of the method is 0.05 mg/kg for TBZ, 5-OH-TBZ and BNZ. The estimated limit of detection is 0.005 mg/kg for TBZ and 0.01 mg/kg for 5-OH-TBZ and BNZ.

([redacted] 1994c)

Recovery values obtained by [redacted] and contract laboratories during method validation are shown below:-

Inter-Laboratory Recoveries of TBZ, 5-OH-TBZ and BNZ from Chicken Egg[a]

Fortification Level (mg/kg)	Recovery (%)

	[redacted]	[redacted]
A. TBZ:		
0.05	90, 94	--
0.1	88, 86	75, 81
0.5	82, 73	89, 87
B. 5-OH-TBZ:		
0.05	84, 90	--
0.1	85, 81	76, 69
0.5	85, 79	86, 89
C. BNZ:		
0.05	95, 97	--
0.1	94, 93	87, 102
0.5	91, 89	103, 102

[a] Control chicken egg samples contained < 0.02 mg/kg apparent residues of TBZ, 5-OH-TBZ and BNZ.

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	May 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

Chicken Tissues and Egg

Spectrofluorometry

The tissue or egg sample is homogenised with a pH 4.5 aqueous buffer solution followed by incubation overnight with the enzyme glusulase to release 5-OH-TBZ.

The pH is adjusted to approximately 6.3 and any TBZ and 5-OH-TBZ are extracted with ethyl acetate. The ethyl acetate phase is extracted with 0.1 N HCl. The aqueous acid solution is adjusted to pH 7.2 and re-extracted with 0.1 N HCl, partitioned into ethyl acetate and determined individually in the same solution by spectrophotofluorometry. TBZ is determined using an excitation wavelength of 300-310 nm and an emission wavelength of 355-365 nm.

5-OH-TBZ is determined using an excitation wavelength of 340-345 nm and an emission wavelength of 415-425 nm. LOD of the method is 0.05 mg/kg for TBZ and 5-OH-TBZ in poultry tissue and eggs.

([redacted], 1990).

Recoveries of TBZ and 5-OH-TBZ from the various poultry products are shown below:-

Recoveries of TBZ and 5-OH-TBZ from Chicken Tissues and Eggs

Poultry Product	TBZ		5-OH-TBZ	
	Spike Level (mg/kg)	% Recovery	Spike Level (mg/kg)	% Recovery
Liver	**0.1-0.5**	**91-99**	**0.1**	**94-101**
Kidney	**0.1-0.5**	**94-98**	**0.1**	**94-98**
Muscle	**0.1-0.5**	**90-107**	**0.1**	**88-93**
Skin/Fat	**0.1**	**80-83**	**0.1**	**93-98**
Eggs	**0.1-0.2**	**82-98**	**0.3-0.4**	**87-106**

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	May 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

Human Serum

HPLC

The analytical method can be used to determine residues of thiabendazole (TBZ) and unconjugated and conjugated 5-hydroxythiabendazole (5-OH-TBZ) in human serum and to monitor the therapeutic use of TBZ in humans. An aliquot of the serum is buffered to pH 5.0, the enzyme mixture beta- glucuronidase added and the mixture incubated for 18 hours at 37°C. Acetonitrile is added, the mixture centrifuged and the supernatant analysed by HPLC for TBZ and 5-OH-TBZ on a C-18 column eluting with methanol/phosphate buffer (50/50), pH 7.0. Detection is by fluorescence. LOD of the method is 0.1 mg/kg for TBZ and 0.4 mg/kg for 5-OH-TBZ. Recoveries of TBZ from human serum fortified with 1-5 mg/kg of TBZ averaged 91%. Recoveries of 5-OH-TBZ from serum fortified with 6 -60 mg/kg of 5-OH-TBZ averaged 104%.

([redacted] 1982)

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	May 2005
Materials and Methods	[redacted]
Results and Discussion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]

COMPETENT AUTHORITY REPORT

THIABENDAZOLE (PT8)

Document III A

Active Substance

Section 5: Effectiveness against target organisms and intended uses

Rapporteur Member State: Spain

May 2006

Section A5 Effectiveness against target organisms and intended uses

Subsection (Annex Point)			Official use only
5.1	**Function (IIA5.1)**	Thiabendazole is a fungicide	
5.2	**Organism(s) to be controlled and products, organisms or objects to be protected (IIA5.2)**		
5.2.1	**Organism(s) to be controlled (IIA5.2)**	Threshold values in ppm.	X1
5.2.2	**Products, organisms or objects to be protected (IIA5.2)**	Freshly treated wood	X2
5.3	**Effects on target organisms, and likely concentration at which the active substance will be used (IIA5.3)**		
5.3.1	**Effects on target organisms (IIA5.3)**	Thiabendazole is a fungicide with protective and curative properties. Thiabendazole is active against many fungi of the classes: Ascomycetes, and Deuteromycetes. It is not active against fungi of the class of the Oomycetes and against most Alternaria spp. It inhibits the mitoses by binding to the tubuline and thus severely impairs fungal growth and development. The mode of action is the same as known for benomyl. Thiabendazole forms a protective deposit on the treated surface of fruits, tubers and roots and protects the goods from the damage caused by plant pathogenic fungi.	X3
5.3.2	**Likely concentrations at which the A.S. will be used (IIA5.3)** **PT1** **PTn**	Used as a 50% concentrate for industrial uses and as a 1% ready to use formulation for both Professionals and non Professionals	X4
5.4	**Mode of action (including time delay) (IIA5.4)**		
5.4.1	**Mode of action**	It inhibits the mitoses by binding to the tubuline and thus severely	

blue stain	Aureobasidium pullulans	<100	good
	Cladosporium cladosporioides	100-200	
moulds	Aspergillus niger	<400	good
	Trichoderma viride	<400	
soft rot	Chaetomium globosum	<400	good
	Humicola grisea	<400	

Section A5		Effectiveness against target organisms and intended uses	
		impairs fungal growth and development	
5.4.2	**Time delay**	Thiabendazole is a preventative fungicide	
5.5	**Field of use envisaged (IIA5.5)**		
	MG02: Preservatives	Wood preservative use (PT 8)	
	Further specification		
5.6	**User (IIA5.6)**	Thiabendazole containing products are used :	
	Industrial	For industrial wood preservation the application techniques are double-vacuum process and dipping.	
	Professional	For indoor (in situ) remedial wood preservation by professionals are mainly spraying, brushing and injection techniques.	**X5**
	General public	For do-it-yourself in situ treatment of wood (non-professional) the application techniques are brushing and spraying, both indoor and outdoor.	
5.7	**Information on the occurrence or possible occurrence of the development of resistance and appropriate management strategies (IIA5.7)**		
5.7.1	**Development of resistance**	Thiabendazole is considered effective as part of a total disease control programme. Proper handling during all phases of use as human medicine, crop production, harvest or storage product is equally important in the over-all effectiveness of a total disease control programme. Cases of resistance development have been noted for various applications under conditions of repeated usage in the absence of resistance management procedures. Cross resistance with other benzimidazole fungicides has also been noted. For wood treatment, it is seen to be used only in combinations.	
5.7.2	**Management strategies**	In areas where the presence of tolerance strains is confirmed, alternate control methods are recommended (e.g. alternation or combination with other fungicides having a different mode of action). For wood treatments, Thiabendazole should only be used in combination with other chemicals.	
5.8	**Likely tonnage to be placed on the market per year (IIA5.8)**	Approximately [redacted]	

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date	June 2005
Materials and methods	[redacted]
Conclusion	[redacted]
Reliability	
Acceptability	[redacted]
Remarks	[redacted]

COMPETENT AUTHORITY REPORT

THIABENDAZOLE (PT 8)

Document IIIA

Active Substance

Section 6: Toxicological and Metabolic Studies

Rapporteur Member State: Spain
May 2006

98/8 Doc IIIA section No.	6.1.1 / 01	Acute toxicity – Oral
91/414 Annex Point addressed	II 5.2.1 / 01	Acute toxicity - oral

1.2	Title	Thiabendazole Veterinary (Lot [redacted]): Acute Oral Toxicity Study in Rats
1.3	Report No.	81-2691
1.4	Lab. report No.	not applicable
1.5	Cross reference	5.2.1/01
1.6	Authors	[redacted]
1.7	Date of report	6 April 1981
1.8	Published	no
2.1	Testing facility	[redacted]
2.2	Dates of experimental work	23 March 1981 to 6 April 1981
3	Objective	to determine the acute oral toxicity of Thiabendazole in young adult male and female rats.
4.1	Test substance	Thiabendazole Veterinary for Preformed Suspensions, [redacted] pure by HPLC analysis
4.2	Specification	Lot [redacted]
4.3	Storage stability	within acceptable limits
4.4	Stability in vehicle	within acceptable limits
4.5	Homogeneity in vehicle	within acceptable limits
4.6	Validity	not applicable
5	Vehicle/solvent	the test compound was prepared as a suspension in 1% aqueous methylcellulose at a concentration of 50% (500 mg/ml)
6	Physical form	off-white powder
7.1	Test method	Acute Oral Toxicity Study in Rats
7.2	Justification	study complied with OECD guidelines according to the 1981 publication
7.3	Copy of method	not applicable
8	Choice of method	not applicable
9	Deviations	not applicable
10.1	Certified laboratory	as 10.3 - 10.4
10.2	Certifying authority	as 10.3 - 10.4
10.3	GLP	no
10.4	Justification	Study performed prior to the initiation of the GLP regulation
11.1	GEP	not applicable

11.2 Type of facility (official or officially recognized) not applicable

11.3 Justification not applicable

12 Test system

Animal species: rat [Crl:CD(SD) BR Strain]

Source: [redacted]

Number of animals: 10 males and 10 females per dose (100 animals in total)

Age: 6 to 7 weeks

Weight at initiation: 117 to 190 grams

Frequency of dosing: single dose

Dosage: 2222, 3333, 5000, 7500 and 11250 mg/kg

Administration: by gastric intubation using a metal catheter attached to a syringe

Physical examinations: frequently on the day of drug administration and daily thereafter for 14 days

Body weight: taken pretest and on days 7 and 12

Necropsy: animals were fasted on day 13 in preparation for necropsy on day 14

13 Findings

Doses	2222, 3333, 5000, 7500 and 11250 mg/kg
Mortality	No sex difference in toxicity was apparent. The majority of deaths occured overnight to 24 hours following drug administration. 3 deaths occured on Day 2.
Physical signs	Signs of drug effect were similar in males and females. Within 30 minutes at all dose levels decreased activity, bradypnea and ptosis were seen. Approximately 3 hours following drug administration a loss of righting reflex was observed at all dose levels. The duration of the loss of righting was about 24 hours. 2 surviving female rats at the 3333 mg/kg dose developed alopecia on Day 12.
Body weight	There were dose-related decreases in body weight gain for both sexes, particularly in those groups receiving 5000 mg/kg and above of thiabendazole. Body weight losses were found in males and females receiving 11250 mg/kg during Week 1. Thereafter, animals in this group had the expected increases in body weight.

Results: The LD50 values (based on 14-day mortality responses) are given below.

Species	Sex	Route	LD50 (95% Fiducial Limits) mg/kg
Rat	Male	Oral	5070 (3982 - 6389)
Rat	Female	Oral	4734 (3371 - 6541)

Conclusions: The results indicate that there is no significant sex-related difference in the acute oral toxicity of thiabendazole in the rat.

14 Statistics

Calculation of the 14-day LD50 values and their 95% fiducial limits was made by the method of Probit Analysis (D.J. Finney, 1971, Probit Analysis, Third Ed., Chapter 3-4, Cambridge University Press).

To determine significant difference in toxicity between male and female animals, the Mantel-Haenszel procedure was used (Mantel, N. and Haenszel, W., J. Natl. Cancer Inst. **22**: 719-748, 1959).

15 References to publications

none

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date February 2005

Materials and Methods [redacted]

Results and discussion [redacted]

Conclusion [redacted]

Reliability [redacted]

Acceptability [redacted]

Remarks [redacted]

98/8 Doc IIIA section No.	**6.1.2 / 01**	**Acute toxicity – Dermal**
91/414 Annex Point addressed	**II 5.2.2 / 01**	Acute toxicity – percutaneous

1.2	**Title**	Thiabendazole: Acute Dermal Toxicity Study in Rabbits
1.3	**Report No.**	86-5505
1.4	**Lab. report No.**	not applicable
1.5	**Cross reference**	5.2.2/01
1.6	**Authors**	[redacted]
1.7	**Date of report**	21 January 1987 - 8 August 1988
1.8	**Published**	no
2.1	**Testing facility**	[redacted]
2.2	**Dates of experimental work**	24 November 1986 to 8 December 1986
3	**Objective**	to evaluate the acute dermal toxicity of Thiabendazole in rabbits.
4.1	**Test substance**	Thiabendazole, [redacted]
4.2	**Specification**	product [redacted]
4.3	**Storage stability**	within acceptable limits
4.4	**Stability in vehicle**	not applicable
4.5	**Homogeneity in vehicle**	not applicable
4.6	**Validity**	not applicable
5	**Vehicle/solvent**	drug wetted with 0.9% saline (12 mls); animals' back
6	**Physical form**	off-white powder
7.1	**Test method**	24-hour dermal exposure to rabbits
7.2	**Justification**	study complied with OECD guidelines according to the 1981 publication
7.3	**Copy of method**	not applicable
8	**Choice of method**	not applicable
9	**Deviations**	not applicable
10.1	**Certified laboratory**	the study complied with GLP and the laboratory is subject to US EPA inspection
10.2	**Certifying authority**	the study complied with GLP and the laboratory is subject to US EPA inspection
10.3	**GLP**	yes
10.4	**Justification**	not applicable
11.1	**GEP**	not applicable

11.2 Type of facility (official or officially recognized) not applicable

11.3 Justification not applicable

12 Test system

Animal species: rabbit [New Zealand White Strain]

Source: [redacted]

Number of animals: 10 (5 males, 5 females)

Dosage: 2000 mg/kg

Administration: applied dermally to the shaved backs of the animals and occluded

Duration: 24 hours treatment, 15 days observation

General observations: twice daily

Necropsy: all animals examined grossly.

Histopathology: none

13 Findings

Dose	2000 mg/kg
Mortality	none
Clinical signs	no treatment-related
Gross postmortem observations	no treatment-related

Conclusions: In view of the above, the acute dermal LD50 of thiabendazole in the rabbit is >2000 mg/kg, the limit dose under EPA guidelines.

14 Statistics none used

15 References to publications none

16 Unpublished data not applicable

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

98/8 Doc IIIA section No.	6.1.3 / 01	**Acute toxicity – Inhalation**
91/414 Annex Point addressed	II 5.2.3 / 01	Acute toxicity - inhalation

1.2	**Title**	Acute Inhalation Toxicity Study in Rats.
1.3	**Report No.**	81-9003
1.4	**Lab. report No.**	not applicable
1.5	**Cross reference**	5.2.3/01
1.6	**Authors**	[redacted]
1.7	**Date of report**	23 October 1981
1.8	**Published**	no
2.1	**Testing facility**	[redacted]
2.2	**Dates of experimental work**	23 July 1981 to 7 August 1981
3	**Objective**	to determine the acute inhalation toxicity of Thiabendazole in a single 4 hour exposure in rats
4.1	**Test substance**	Thiabendazole, [redacted] purity (dry weight basis)
4.2	**Specification**	[redacted]
4.3	**Storage stability**	not applicable
4.4	**Stability in vehicle**	not applicable
4.5	**Homogeneity in vehicle**	not applicable
4.6	**Validity**	not applicable
5	**Vehicle/solvent**	not applicable
6	**Physical form**	white powder
7.1	**Test method**	Acute Inhalation Toxicity Study in Rats
7.2	**Justification**	complied with the OECD guidelines according to the 1981 publication
7.3	**Copy of method**	not applicable
8	**Choice of method**	not applicable
9	**Deviations**	not applicable
10.1	**Certified laboratory**	the study complied with GLP and the laboratory is subject to US EPA inspection
10.2	**Certifying authority**	the study complied with GLP and the laboratory is subject to US EPA inspection
10.3	**GLP**	yes
10.4	**Justification**	FDA GLP regulations issued on December 22, 1978 for compliance on and after June 20, 1979

11.1 GEP not applicable

11.2 Type of facility (official or officially recognized) not applicable

11.3 Justification not applicable

12 Test system

Animal species: rat (Sprague-Dawley strain)
Source: [redacted]
Number of animals: 20, 10 male, 10 female (5 per sex/group)
Dosage: 6.84 mg/l
Particle size: 4.15 ± 2.24 microns diameter
Administration: exposure to ambient air or thiabendazole aerosol
Duration: one four-hour exposure
General observations: prior to, during and immediately following exposure and twice daily
Histopathology: lungs, liver, kidneys and gross lesions

13 Findings

Dosage	6.84 mg/l
Clinical signs	all animals had squinted eyes, 2 animals had polypnea
Mortality	no mortality
Body weight development	slight decreases on Day 2 which rapidly reversed by Day 4
Histopathology	microscopic evaluation failed to reveal the presence of compound-related alterations

Results: LC50 for thiabendazole is >6.84 mg/l.

14 Statistics Student's t-test (Snedecor and Cochran, 1967)

15 References to publications not applicable

16 Unpublished data not applicable

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]

Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

98/8 Doc IIIA section No.	**6.1.4 / 01**	**Acute toxicity – Skin and eye irritation**
91/414 Annex Point addressed	**II 5.2.4 / 01**	Acute toxicity - skin irritation

1.2	**Title**	Skin Study in Rabbits
1.3	**Report No.**	61-3017
1.4	**Lab. report No.**	not applicable
1.5	**Cross reference**	5.2.4/01
1.6	**Authors**	[redacted]
1.7	**Date of report**	27 June 1961
1.8	**Published**	no
2.1	**Testing facility**	[redacted]
2.2	**Dates of experimental work**	14 June 1961 to 27 June 1961
3	**Objective**	to determine of Thiabendazole (L-585,216) is dermally irritating to the skin of rabbits
4.1	**Test substance**	Thiabendazole [redacted]: [redacted]
4.2	**Specification**	[redacted]
4.3	**Storage stability**	not applicable
4.4	**Stability in vehicle**	not applicable
4.5	**Homogeneity in vehicle**	not applicable
4.6	**Validity**	not applicable
5	**Vehicle/solvent**	saline added as a moistening agent
6	**Physical form**	powder
7.1	**Test method**	rabbit dermal irritation
7.2	**Justification**	complied with OECD guidelines according to the 1981 publication.
7.3	**Copy of method**	not applicable
8	**Choice of method**	not applicable
9	**Deviations**	not applicable

10.1	**Certified laboratory**	the study complied with GLP and the laboratory is subject to US EPA inspection
10.2	**Certifying authority**	the study complied with GLP and the laboratory is subject to US EPA inspection
10.3	**GLP**	no
10.4	**Justification**	study conducted prior to the issuance of the regulations
11.1	**GEP**	not applicable
11.2	**Type of facility (official or officially recognized)**	not applicable
11.3	**Justification**	not applicable
12	**Test system**	
	Animal species:	rabbit [New Zealand White Strain]
	Number of animals:	2 male, 2 female
	Administration:	applied dermally to the abraded backs of the animals
13	**Findings**	Thiabendazole was non-irritating to the abraded and intact skin of rabbits
14	**Statistics**	not applicable
15	**References to publications**	none
16	**Unpublished data**	no

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 2005
Materials and Methods	[redacted]
Results and discussion	
Conclusion	
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

98/8 Doc IIIA section No.	6.1.4 / 02	Acute toxicity – Skin and eye irritation

1.2	Title	Primary dermal irritation study in rabbits
1.3	Report No.	81-2692
1.4	Lab. report No.	not applicable
1.5	Cross reference	not applicable
1.6	Authors	[redacted]
1.7	Date of report	6 April 1981
1.8	Published	no
2.1	Testing facility	[redacted]
2.2	Dates of experimental work	23 March 1981 to 6 April 1981
3	Objective	to determine of Thiabendazole (Lot [redacted]) is dermally irritating to the skin of rabbits
4.1	Test substance	Thiabendazole Veterinary
4.2	Specification	[redacted]
4.3	Storage stability	not applicable
4.4	Stability in vehicle	not applicable
4.5	Homogeneity in vehicle	not applicable
4.6	Validity	not applicable
5	Vehicle/solvent	saline added as a moistening agent
6	Physical form	powder
7.1	Test method	rabbit dermal irritation
7.2	Justification	complied with OECD guidelines according to the 1981 publication.
7.3	Copy of method	not applicable
8	Choice of method	not applicable
9	Deviations	not applicable
10.1	Certified laboratory	the study complied with GLP and the laboratory is subject to US EPA inspection
10.2	Certifying authority	the study complied with GLP and the laboratory is subject to US EPA inspection
10.3	GLP	no
10.4	Justification	study conducted prior to the issuance of the regulations
11.1	GEP	not applicable
11.2	Type of facility (official or officially recognized)	not applicable

11.3	**Justification**	not applicable
12	**Test system**	
	Animal species:	albino rabbit [New Zealand White random]
	Number of animals:	3 male, 3 female
	Administration:	applied dermally to the abraded backs of the animals
13	**Findings**	Thiabendazole was non-irritating to the abraded and intact skin of rabbits
14	**Statistics**	not applicable
15	**References to publications**	none
16	**Unpublished data**	no

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

98/8 Doc IIIA section No.	**6.1.4 / 03**	**Acute toxicity – Skin and eye irritation**
91/414 Annex Point addressed	**II 5.2.5 / 01**	Acute toxicity - eye irritation

1.2	**Title**	Eye Irritation Study in Rabbits
1.3	**Report No.**	61-3018
1.4	**Lab. report No.**	not applicable
1.5	**Cross reference**	5.2.5/01
1.6	**Authors**	[redacted]
1.7	**Date of report**	27 June 1961
1.8	**Published**	no
2.1	**Testing facility**	[redacted]
2.2	**Dates of experimental work**	14 June 1961 to 27 June 1961
3	**Objective**	to determine of Thiabendazole [redacted] is ocularly irritating to the eyes of rabbits
4.1	**Test substance**	Thiabendazole, [redacted]
4.2	**Specification**	[redacted]
4.3	**Storage stability**	not applicable
4.4	**Stability in vehicle**	not applicable
4.5	**Homogeneity in vehicle**	not applicable
4.6	**Validity**	not applicable
5	**Vehicle/solvent**	a 10% concentration was prepared in saline
6	**Physical form**	powder
7.1	**Test method**	rabbit ocular irritation
7.2	**Justification**	according to Acute Toxicology SOP's
7.3	**Copy of method**	not applicable
8	**Choice of method**	not applicable
9	**Deviations**	the eye lid was closed for approximately one minute rather than one second as suggested in the guidelines. However, this deviation

		would tend to make the test more sensitive in detecting ocular initiation.
10.1	**Certified laboratory**	see 10.3 - 10.4
10.2	**Certifying authority**	see 10.3 - 10.4
10.3	**GLP**	no
10.4	**Justification**	study conducted prior to the issuance of the regulations
11.1	**GEP**	not applicable
11.2	**Type of facility (official or officially recognized)**	not applicable
11.3	**Justification**	not applicable
12	**Test system**	
	Animal species:	rabbit [New Zealand White Strain]
	Number of animals:	2 male, 2 female
	Dosage:	0.1 ml of suspension
	Administration:	administered to the eyes of the animals
	Duration:	one minute
	General observations:	during 14 days
13	**Findings**	slight transient injection of the vessels of the palpebral conjunctivae and sclera was observed, but was gone after two hours and during the remainder of the 14-day observation period. Therefore, Thiabendazole is considered minimally irritating to the eyes of rabbits.
14	**Statistics**	not applicable
15	**References to. publications**	none
16	**Unpublished data**	no

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 2005
Materials and Methods	[redacted]
Results and discussion	
Conclusion	
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

98/8 Doc IIIA section No.	**6.1.4 / 04**	**Acute toxicity – Skin and eye irritation**

1.2	**Title**	Primary Eye irritation study in rabbits
1.3	**Report No.**	81-2693
1.4	**Lab. report No.**	not applicable
1.5	**Cross reference**	not applicable
1.6	**Authors**	[redacted]
1.7	**Date of report**	6 April 1981
1.8	**Published**	no
2.1	**Testing facility**	[redacted]
2.2	**Dates of experimental work**	23 March 1981 to 6 April 1981
3	**Objective**	to determine ocular irritancy folowing a single instillation in the rabbit eyes
4.1	**Test substance**	Thiabendazole Veterinary
4.2	**Specification**	[redacted]
4.3	**Storage stability**	not applicable
4.4	**Stability in vehicle**	not applicable
4.5	**Homogeneity in vehicle**	not applicable
4.6	**Validity**	not applicable
5	**Vehicle/solvent**	not applicable
6	**Physical form**	powder
7.1	**Test method**	rabbit ocular irritation
7.2	**Justification**	not applicable
7.3	**Copy of method**	not applicable
8	**Choice of method**	not applicable
9	**Deviations**	not applicable
10.1	**Certified laboratory**	
10.2	**Certifying authority**	
10.3	**GLP**	no
10.4	**Justification**	study conducted prior to the issuance of the regulations
11.1	**GEP**	not applicable
11.2	**Type of facility (official or officially recognized)**	not applicable
11.3	**Justification**	not applicable
12	**Test system**	
	Animal species:	albino rabbit [New Zealand random]
	Number of animals:	5 male, 5 female

	Dosage:	One hundred mg of thiabendazole
	Administration:	administered into tha conjuntival sac of the left eye of each rabbit
	Duration:	one minute
	General observations:	during 14 days
13	**Findings**	instillation of the dry powder of thiabendazole into sac for one minute produced a slight conjuntival injection with a slight to moderate clear colorless discharge at 15 minutes. The discharge decreased to very slight at two hours and all eyes appeared normal at 24 hours
14	**Statistics**	not applicable
15	**References to. publications**	none
16	**Unpublished data**	no

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 2005
Materials and Methods	[redacted]
Results and discussion	Instillation of the dry powder of Thiabendazole into the conjunctival sac for one [redacted]
Conclusion	Thiabendazole produced only slight ocular irritation in rabbits. Flushing of the [redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

98/8 Doc IIIA section No.	**6.1.5 / 01**	**Acute toxicity – Skin sensitisation**
91/414 Annex Point addressed	**II 5.2.6 / 01**	Acute toxicity - skin sensitisation

1.2	**Title**	Thiabendazole: Cutaneous Sensitisation in the Guinea Pig
1.3	**Report No.**	66-0185
1.4	**Lab. report No.**	not applicable
1.5	**Cross reference**	5.2.6/02
1.6	**Authors**	[redacted]
1.7	**Date of report**	31 March 1966
1.8	**Published**	no
2.1	**Testing facility**	[redacted]
2.2	**Dates of experimental work**	unavailable
3	**Objective**	to investigate the cutaneous sensitisation potential of Thiabendazole
4.1	**Test substance**	Thiabendazole, [redacted]
4.2	**Specification**	[redacted]
4.3	**Storage stability**	within acceptable limits
4.4	**Stability in vehicle**	previously documented
4.5	**Homogeneity in vehicle**	previously documented
4.6	**Validity**	previously documented
5	**Vehicle/solvent**	a 0.1% suspension of thiabendazole prepared in physiological saline
6	**Physical form**	powder
7.1	**Test method**	not applicable
7.2	**Justification**	this study design does not meet the specifications of the US EPA Pesticide Assessment Guidelines but supports the conclusions of the other studies (86-9016 and the summary of 24 April 1990)
7.3	**Copy of method**	not relevant
8	**Choice of method**	not applicable
9	**Deviations**	not applicable
10.1	**Certified laboratory**	not applicable
10.2	**Certifying authority**	not applicable
10.3	**GLP**	no
10.4	**Justification**	study conducted prior to the issue of the regulations
11.1	**GEP**	not applicable
11.2	**Type of facility**	**(official or officially recognised)** not applicable

11.3 Justification not applicable

12 Test system

Animal species:	albino male guinea pigs
Number of animals:	13
Animal weight:	420 to 545 g
Dosage:	10 injections, the first at 0.05 ml and the remaining nine 0.1 ml. Two weeks after the 10th injection, a test injection was made of 0.05 ml of a freshly prepared thiabendazole suspension.
Administration:	intracutaneous injections at random in an area of the back and flanks with a #26 gauge hypodermic needle, three times a week
Observations:	readings of the diameter, height and colour of the reactions were made 1, 4 and 24 hours after the test injection and compared with similar readings taken after the first injection

13 Findings

Three guinea pigs died during the study. One was found dead 12 days after the initial injection. The remaining two died in the third week of the study. These deaths are not believed to be drug related. Isolated deaths among our stock animals were also noted at the time of this study.

In the remaining ten guinea pigs the reactions to test injections made two weeks after the tenth sensitising injection were no greater than those noted after the initial injection.

Conclusion: The above indicates that the guinea pigs had not become sensitised to thiabendazole.

14 Statistics none

15 References to publications none

16 Unpublished data not applicable

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]

Reliability	[redacted]
Acceptability	[redacted]
Remarks	

98/8 Doc IIIA section No.	**6.2 / 01**	**Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study**
91/414 Annex Point addressed	**II 5.1.1 / 01**	**Absorption, distribution and excretion in rats**

1.2	**Title**	Absorption, Metabolism and Excretion of Thiabendazole in Rats
1.3	**Report No.**	not applicable
1.4	**Lab. report No.**	not applicable
1.5	**Cross reference**	5.1.1/01
1.6	**Authors**	[redacted]
1.7	**Date of report**	1965
1.8	**Published**	no
2.1	**Testing facility**	[redacted]
2.2	**Dates of experimental work**	1965
3	**Objective**	To determine the absorption, excretion and distribution potential of thiabendazole, a broad spectrum anthelmintic given to male rats as a single oral dose.
4.1	**Test substance**	Thiabendazole [2-(4-thiazolyl)benzimidazole]
4.2	**Specification**	[redacted]
4.3	**Storage stability**	not applicable*
4.4	**Stability in vehicle**	expected to be stable*
4.5	**Homogeneity in vehicle**	expected to be homogenous*
4.6	**Validity**	not applicable*
5	**Vehicle/solvent**	not applicable*
6	**Physical form**	Off-white powder
7.1	**Test method**	extensively validated assay for absorption, excretion and distribution
7.2	**Justification**	no OECD guidelines were available, the assay was acceptable to regulatory agencies world wide
7.3	**Copy of method**	not applicable*
8	**Choice of method**	not applicable*
9	**Deviations**	not applicable*
10.1	**Certified laboratory**	not applicable*
10.2	**Certifying authority**	not applicable*
10.3	**GLP**	no
10.4	**Justification**	study conducted prior to GLP guidelines
11.1	**GEP**	not appplicable
11.2	**Type of facility (official or officially**	

recognized) not applicable

11.3 Justification not applicable

12 Test system

Animal Species: Holtzman rats

Number of animals: 8 male

Product: C^{14}: 6 animals
S^{35}: 2 animals

Dosage: 4 rats received 25 mg/kg
4 rats received 100 mg/kg

Administration: oral by feeding

General observations: after administration, animals were kept under observation during the study

13 Findings Maximum concentrations of radioactivity ranging between 15 mcg/ml and 21 mcg/ml occurred in 2 to 3 hours.

Dose level	Average in urine as percent of dose	Average in feces as percent of dose	Total ^{14}C eliminated in 48 hours
(mg/kg)	(%)	(%)	(%)
25	66	26	92
100	49	30	79

Table on page 41 of report WIL-146001

Urine: 25 mg/kg: average of 66% excreted in first 48 hours

100 mg/kg: average of approx. 80% in first 48 hours

Faeces: 25 mg/kg: average of 26% excreted in first 48 hours

Urinary radioactivity was high within 6 hours of thiabendazole-C14 administration indicating a rapid absorption of the compound.

Excretion of radioactivity virtually ceased within 2 to 3 days.

No traces of radioactivity was found in tissues of the 2 rats sacrificed 14 days after receiving the single dose.

14 Statistics none

15 References to publications Dominick J. Tocco, Charles Rosenblum, Christopher M. Martin, and Harry J. Robinson, Absorption, Metabolism and Excretion of Thiabendazole in Man and Laboratory Animals, Toxicology and Applied Pharmacology 9, 31-39 (1966).

16 Unpublished data not applicable

Evaluation by Competent Authorities

	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	March 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	Thiabendazole undergoes metabolic transformation by hydroxylation and [redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

* Note: A more recent metabolism study in rats as also submitted herein

98/8 Doc IIIA section No.	6.2 / 02	Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study
91/414 Annex Point addressed	II 5.1.1 / 01	Absorption, distribution and excretion in rats

1.2	Title	Thiabendazole: A Metabolism Study in Rats with ^{14}C-Thiabendazole
1.3	Report No.	WIL-146002
1.4	Lab. report No.	not applicable
1.5	Cross reference	5.1.1/02
1.6	Authors	[redacted]
1.7	Date of report	29 August 1990
1.8	Published	no
2.1	Testing facility	[redacted]
2.2	Dates of experimental work	10 August 1989 to 01 August 1990
3	Objective	To determine the disposition of 14C-Thiabendazole administered to rats and to determine the metabolism of the compound as a function of dose
4.1	Test substance	Thiabendazole (TBZ)
4.2	Specification	^{14}C-Thiabendazole [redacted]

Benzimidazole:	[redacted]
Benzimadazole-2-carboxylic acid	[redacted]
Benzimidazole-2-carboxamide	[redacted]
5-hydroxythiabendazole	[redacted]

4.3	Storage stability	within acceptable limits
4.4	Stability in vehicle	within acceptable limits
4.5	Homogeneity in vehicle	homogeneity of suspensions was within acceptable limits
5	Vehicle/solvent	0.5% aqueous methylcellulose
6	Physical form	powder
7.1	Test method	OECD guidelines according to the 1981 publication
7.2	Justification	not applicable
7.3	Copy of method	not relevant
8	Choice of method	not relevant
9	Deviations	not applicable
10.1	Certified laboratory	the study complied with GLP and the laboratory is subject to US EPA inspection

10.2	**Certifying authority**	the study complied with GLP and the laboratory is subject to US EPA inspection
10.3	**GLP**	yes
10.4	**Justification**	study conducted in accordance with EPA GLP standards
11.1	**GEP**	not applicable
11.2	**Type of facility (official or officially recognized)**	not applicable
11.3	**Justification**	not applicable

12 Test system

Animal species:	Charles River rats [Strain: Crl:CD®(SD)BR]
Source:	[redacted]
Number of Animals:	80 animals; 39 males and 41 females
Age:	males: 34-44 days females: 52-58 days
Dosage:	group 1: 29514 nCi/g group 2: 27370 nCi/g group 3: 28100 nCi/g group 4: 27423 nCi/g groups 1,2,4: target doses 25 mg/kg group 3: 400 mg/kg
Administration:	oral by gavage
Duration:	14 days at single daily dose, group 4 was also given a single oral pulse dose on day 15.
General observations:	twice daily check for overt toxicity; daily for clinical signs of toxicity
Body weights:	measured on receipt. For groups 1, 2 and 3, predose and at time of sacrifice For group 4, at randomization,on the eighth day of pre-conditioning, at the pulse dose and at sacrifice
Urine/feces:	collected on first day (hourly schedule): 0 to 4, 4 to 8, 8 to 12, 12 to 24 Then, collections daily
Blood:	at 7 days, 5-7 ml blood collected from euthanized rats
Organs analysed:	heart, lungs, spleen, both kidneys, liver, perineral fat, gonads uterus, muscle (leg), a portion of bone and brains
Cages:	after euthanization, washed with ethanol, then water. Washes combined and analyzed for ^{14}C.
14C measurement:	liquid scintillation metabolites: HPLC

13 Findings

Dose level	Average in urine as percent of dose	Average in feces as percent of dose	Total ^{14}C eliminated in 48 hours
(mg/kg)	(%)	(%)	(%)
26	67	26	93
418	53	12	65

- At low dose, most of the ^{14}C was eliminated in the first 24 hours after administration.
- At high dose, there was a lag period and the elimination of ^{14}C peaked on the second day after administration.
- The presence of ^{14}C-TBZ in the feces in the high dose group suggests that the system for absorption was overwhelmed.
- At the low dose level, the compound was absorbed, metabolized, conjugated and eliminated in urine.

At the high dose level, the compound was not completely absorbed and some parent compound passed through the gastrointestinal tract without being metabolized.

Results:

1. Disposition. When Thiabendazole was administered orally at doses of either 25 or 400 mg/kg about 70% was absorbed from the gastrointestinal tract and was eliminated through the urinary tract. The design of the study did not determine whether the portion eliminated in the feces had been absorbed.
2. 7 days after treatment, concentrations of residue were higher in some tissues than others. The residue which was present in tissues was not easily extracted. The use of ethanol, ethanol:water and dilute acid extracted minor portions of the residue. Residue levels in the low dose group ranged from 0.40 to 0.68 ppm and in the high dose group from 6.7 to 11.8 ppm.
3. The fate of the compound was not influenced by dose level. At both the high and low dose level the elimination patterns were similar. The average recovery of the ^{14}C-Thiabendazole administered to rats was 96.3%.
4. The fate of the compound was not influenced by continuous exposure to the compound. The amount of compound absorbed and eliminated did not change and the concentration of residues in tissues did not change.
5. Metabolism of the compound was found to be similar to that previously described in the scientific literature. At the low dose level, thiabendazole was almost quantitatively oxidized to form 5-hydroxythiabendazole, followed by conjugation to form the glucuronide and the sulfate of the 5-hydroxy metabolite. At the high dose level the ability of the animal to absorb the compound was overwhelmed and some of the parent compound was eliminated in the feces.

14 Statistics none

15 References to

publications

Tocco, D.J.; Buhs, R.P.; Brown, H.D.; Matzuk, A.R.; Mertel, H.E.; Harman, R.E.; Trenner, N.R. The Metabolic Fate of Thiabendazole in Sheep. J. Med. Chem. 1964, 7, 399-405.

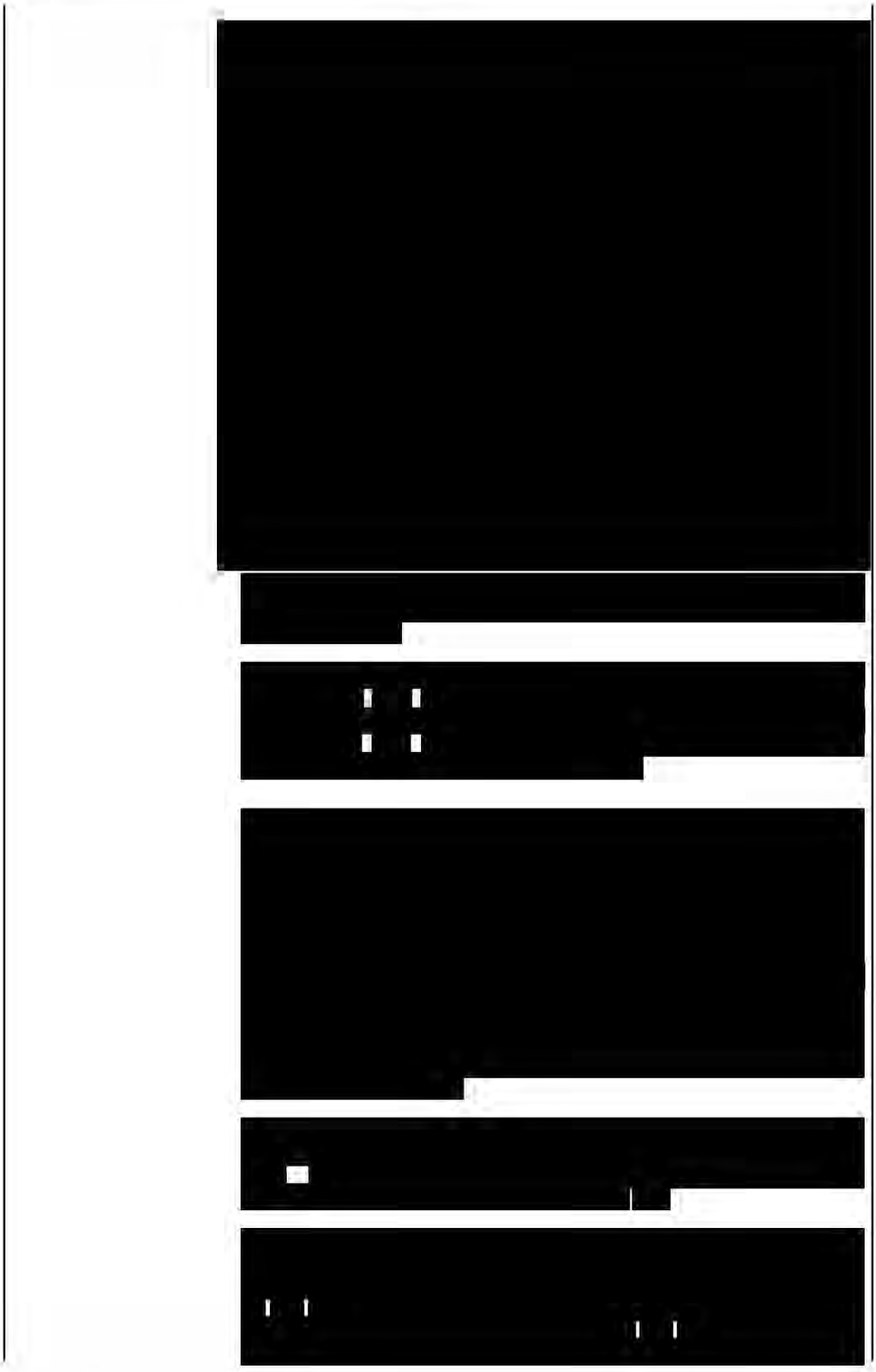
Tocco, D.J.; Egerton, J.R.; Bowers, W.; Christensen, V.W.; Rosenblum, C. Absorption, Metabolism, and Elimination of Thiabendazole in Farm Animals and a Method for Its Estimation in Biological Materials. J. Pharmacol. and Exptl. Therap. 1965, 149, 263-271.

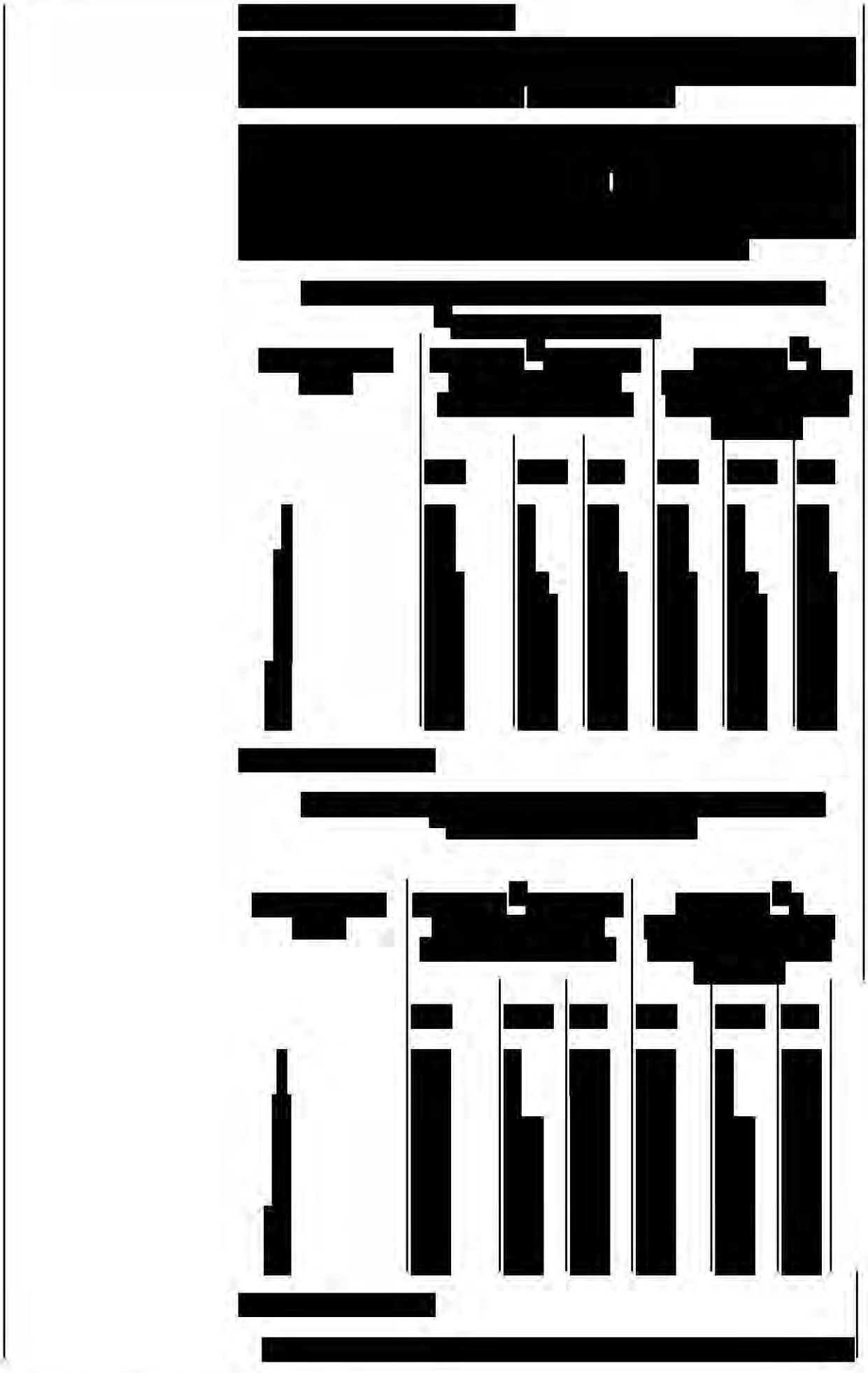
Tocco, D.J.; Rosenblum, C.; Martin, C.M.; Robinson, H.J. Absorption, Metabolism, and Excretion of Thiabendazole in Man and Laboratory Animals. Tox. and Applied Pharmacol. 1966, 9, 31-39.

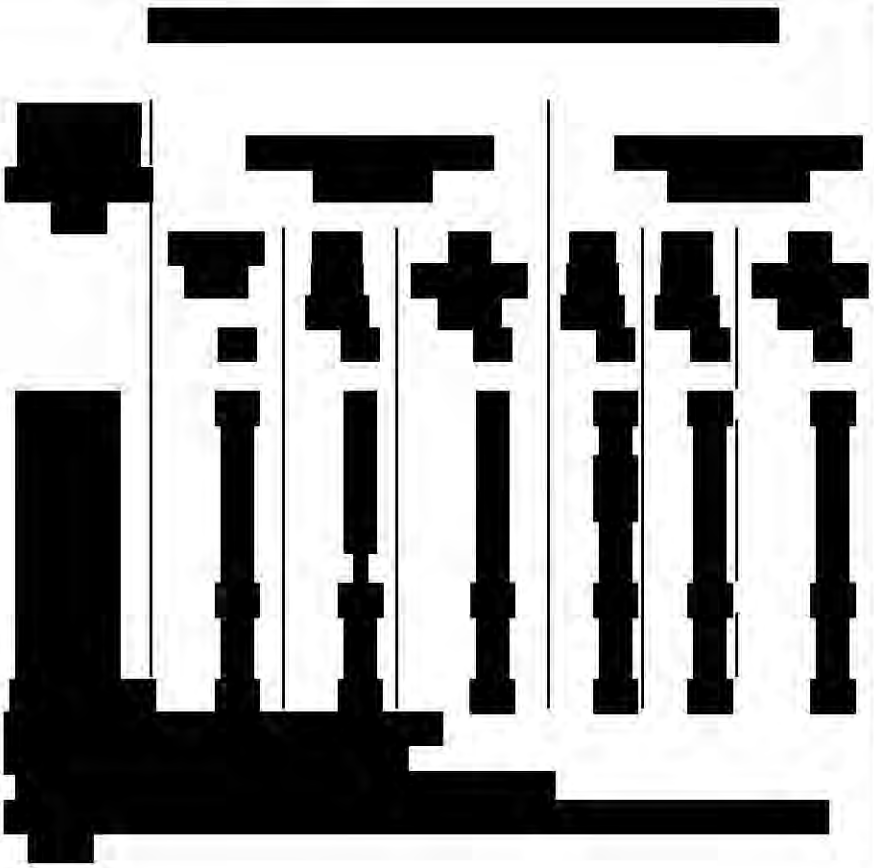
Levvy, G.A.; Conchie, J. Beta-Glucuronidase and the Hydrolysis of Glucuronides. In Glucuronic Acid, Free and Combined. Dutton, G.J., Ed., Academic Press, New York and London, 1966, pages 301-357.

16 **Unpublished data** not applicable

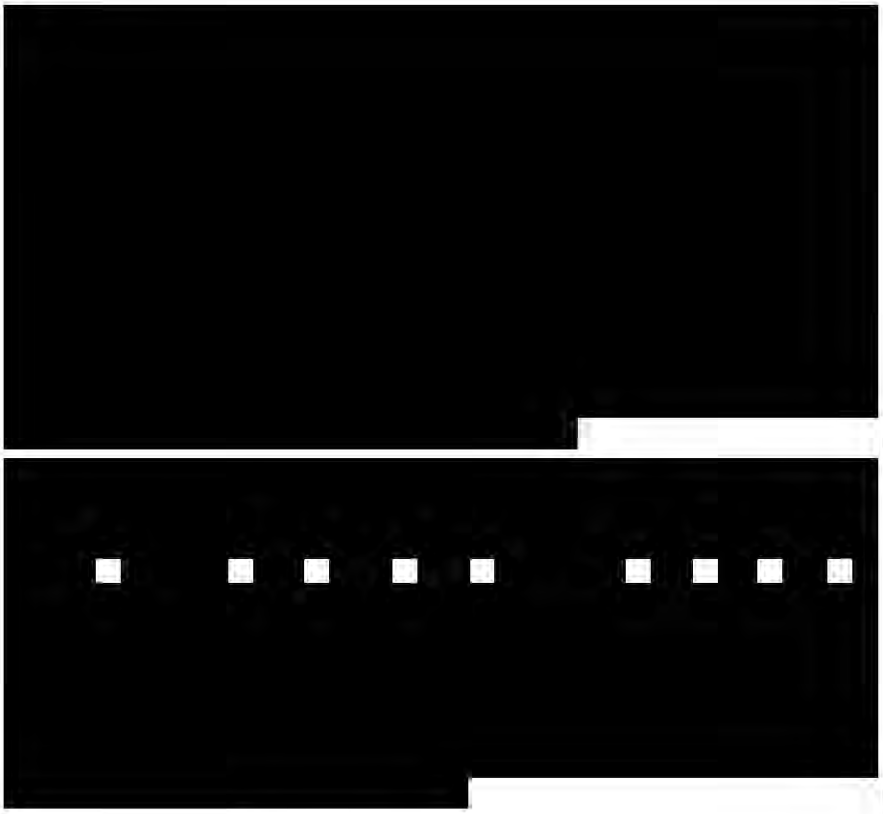
Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	May 2005
Materials and Methods	US EPA Pesticides Assessment Guidelines, Section 85-1
Results and discussion	[redacted]







Conclusion



Reliability
Acceptability
Remarks

98/8 Doc IIIA section No.	**6.3.1 / 01**	**Repeated dose toxicity (oral)**
91/414 Annex II Point addressed	**5.3.1 / 01**	Short-term toxicity - oral 28-day studies

1.2	**Title**	Thiabendazole: Six-Week Pilot Study in Mice
1.3	**Report No.**	TT #77-004-0
1.4	**Lab. report No.**	not applicable
1.5	**Cross reference**	5.3.1/01
1.6	**Authors**	[redacted]
1.7	**Date of report**	24 August 1977
1.8	**Published**	no
2.1	**Testing facility**	[redacted]
2.2	**Dates of experimental work**	02 February 1977 to 16 March 1977
3	**Objective**	estimate toxicity to select doses for a lifetime carcinogenic study
4.1	**Test substance**	Thiabendazole [redacted]
4.2	**Specification**	[redacted]
4.3	**Storage stability**	room temperature and stability confirmed by assays of the drug in the diet
4.4	**Stability in vehicle**	stability of drug in vehicle (diet) at room temperature for approximately 10 weeks determined
4.5	**Homogeneity in vehicle**	not performed in range-finding study
4.6	**Validity**	not applicable
5	**Vehicle**	diet -- Purina Lab Chow powdered and mixed with 1% by weight cottonseed and soybean oils (Wesson Oil, Hunt-Wesson Foods, Inc.)
6	**Physical form**	powder
7.1	**Test method**	six-week oral toxicity (drug in diet) study in mice
7.2	**Justification**	range-finding study for a carcinogenicity study
7.3	**Copy of method**	not applicable
8	**Choice of method**	not applicable
9	**Deviations**	not applicable
10.1	**Certified laboratory**	as 10.3 and 10.4
10.2	**Certifying authority**	as 10.3 and 10.4
10.3	**GLP**	no
10.4	**Justification**	range-finding purpose only
11.1	**GEP**	not applicable
11.2	**Type of facility**	

(official or officially recognized) not applicable

11.3 Justification not applicable

12 Test system

Animal species: Charles River CD-1 (HaM/ICR) mice

Source: [redacted]

No. of animals: 10 males and 10 females in each group; seven groups = 140 animals total

Age: young adults

Dosage (a.s.): 50, 150, 300, 600, and 900 mg/kg/day with two control groups (identical)

Administration: Oral by feeding

Duration: 6 weeks

General observations: daily for physical signs, although less detailed on weekends and holidays.

Food consumption: Determined once pretest and weekly during the study

Body weight: Twice pretest and once weekly during the study

Ocular examinations: None

Haematology, clinical chemistry, urinalysis, enzyme induction

assay: None

Gross pathology: None

Histopathology: None

13 Findings

Dosages:	Diet adjusted weekly to maintain dosage levels of 50, 150, 300, 600, or 900 mg/kg/day.
Clinical signs:	No drug-related physical signs were seen during the study.
Feed intake:	Decreased food intake compared to controls was seen in females and males given 600 or 900 mg/kg/day. In females, this only occurred during the first two weeks of the study.
Mortality:	No animals died during the study.
Body weight development:	Decreased body weight gain compared to controls occurred in males at 600 and 900 mg/kg/day. In females at these doses, decreased weight compared to controls was only seen in the first two weeks of the study.
Gross pathology:	None performed
Organ weights:	None performed

Conclusions: No treatment-related changes were seen at 50, 150, or 300 mg/kg/day. At 600 and 900 mg/kg/day, decreased food intake and weight gain compared to controls occurred; however, in females, this was only present during the first two weeks of the study.

14 Statistics none performed

15	**References to publications**	none
16	**Unpublished data**	not applicable

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	March 2005
Materials and Methods	[redacted]
	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

98/8 Doc IIIA section No.	**6.3.1 / 02**	**Repeated dose toxicity (oral)**
91/414 Annex Point addressed	**II 5.3.1 / 02**	Short-term toxicity - oral 28-day studies

1.2	**Title**	Thiabendazole: 5-Week Oral Toxicity Study in Rats
1.3	**Report No.**	86-9819 and 87-9809
1.4	**Lab. report No.**	not applicable
1.5	**Cross reference**	5.3.1/02
1.6	**Authors**	[redacted]
1.7	**Date of report**	15 June 1989
1.8	**Published**	no
2.1	**Testing facility**	[redacted]
2.2	**Dates of experimental work**	11 November 1986 to 10-12 December 1986 (86-9819) 13 January 1987 to 10-11 February 1987 (87-9809)
3	**Objective**	to assess the potential toxicity of Thiabendazole when administered orally for 1 month to rats
4.1	**Test substance**	Thiabendazole: [redacted]
4.2	**Specification**	TBZ: [redacted]
4.3	**Storage stability**	within acceptable limits
4.4	**Stability in vehicle**	stable 1 week at room temperature
4.5	**Homogeneity in vehicle**	concentration and uniformity were found to be within acceptable limits
4.6	**Validity**	concentration and uniformity were found to be within acceptable limits (as 4.5)
5	**Vehicle/solvent**	0.5% aqueous methylcellulose (400 cps) solution
6	**Physical form**	off-white powder
7.1	**Test method**	5-Week Oral Toxicity Study in Rats
7.2	**Justification**	conducted in accordance with the OECD recommended guidelines published in 1981
7.3	**Copy of method**	not applicable
8	**Choice of method**	not applicable
9	**Deviations**	not applicable
10.1	**Certified laboratory**	the study complied with GLP and the laboratory is subject to inspection by the Japanese regulatory authorities

10.2	**Certifying authority**	the study complied with GLP and the laboratory is subject to inspection by the Japanese regulatory authorities
10.3	**GLP**	yes
10.4	**Justification**	not applicable
11.1	**GEP**	not applicable
11.2	**Type of facility (official or officially recognized)**	not applicable
11.3	**Justification**	not applicable

12 Test system

Animal species: rat [SPF/VAF Crj: CD (SD) Strain]

Source: [redacted]

Number of animals: groups of 12 males, 12 females

Dosage: 50, 100, 200 and 800 mg/kg/day

Administration: orally by gavage

Duration: 28 to 31 days

General observations: Observed daily for mortality and physical signs with less detailed exams on weekends and holidays. Righting reflex was examined on 5 rats/sex/group during the pretest period and once a week during the study period

Histopathology: sections of the following tissues from all animals in the control, 200 and 800 mg/kg/day groups. Salivary gland, stomach, small intestine, large intestine, liver, pancreas, adrenal, thyroid (parathyroid when present in thyroidal sections), pituitary, kidney, urinary bladder, ovary, testis, uterus, prostate, skin (mammary gland when present in skin section), lung, heart, spleen, lymph node, thymus, bone marrow, bone, skeletal muscle, brain, spinal cord, nerve (sciatic), eye (with optic nerve).

In addition, thymus, bone marrow, spleen, thyroid glands and liver from all animals in the 100 and 50 mg/kg/day dose groups and selected grossly and/or ophthalmoscopically noted changes were also examined.

13 Findings

Dosages	0 - 50 - 100 - 200 and 800mg/kg/day
Clinical signs	physical signs of toxicity were noted in males and females at 800 mg/kg/day and included decreased activity, sedation, ataxia, recumbency, flaccidity, loss of righting reflex, apparent decreased skin temperature, piloerection, emaciation, rough hair coat and alopecia
Feed intake	200 and 800 mg/kg/day: decrease in feed intake
Mortality	800 mg/kg/day: treatment-related mortality: 8 males and 11 females died between Days 3 to 27

Body weight development	200 mg/kg/day: decrease in body weight gain in males and females of approximately 40 and 25% compared to controls 800 mg/kg/day: body weight losses occured in both sexes

Conclusion: the administration of thiabendazole to rats at 800 mg/kg/day for 5 weeks was considered to be surely toxic while the **NOEL** < 50 mg/kg/day.

14 Statistics

Hematological parameters, terminal body weight and organ weight data were analyzed for normality using the Wilk and Shapiro W statistic, and for homogeneity using the Levene Test; analysis of variance was by trend test at P = 0.05, with rankit transformation when necessary.

Data for body weight and food and food consumption for each sex were examined for linear, quadratic and average changes over time at the same level of significance.

Test for Homogeneity of Variances

Reference: Levene, H.: Robust Tests for Equality of Variances, Contributions to Probability and Statistics. Essays in Honor of Harold Hotelling, Stanford University Press, Stanford, Calif., 278-292, 1961.

Test for Normality of Data (Wilk and Shapiro's W statics)

References: Shapiro, S.S. and Wilk, M.B.: An Analysis of Variance Test for Normality (Complete Samples), Biometrika, 52: 591-611, 1965.

Reference: Wilk, M.B. and Shapiro, S.S.: The Joint Assessment of Normality of Several Independent Samples, Technometrics, 10: 825-839, 1965.

Reference: Shapiro, S.S. and Wilk, M.B.: Approximations for the Null Distribution of the W Statistic, Technometrics, 10: 861-866, 1968.

Reference: Shapiro, S.S. and Francia, R.S.: An Approximate Analysis FO Variance Test for Normality, J.A.S.A., 67: 215-216, 1972.

Reference: de Wet, T. and Venter, J.H.: Asymptotic Distributions of Certain Test Criteria of Normality, S. Afr. Stat. J., 6: 135-149, 1972.

Rankit Transformation

Reference: Harter, H.L.: Expected Values of Normal Order Statistics. Biometrika, 48: 151-165, 1961.

Trend (Dose-Response) Analysis

Reference: Tukey, J.W., Ciminera, J.L., and Heyse, J.F.: Testing the Statistical Certainty of a Response to Increasing Doses of a Drug, to be published in Biometrics, 1985.

15 References to publications none

16 Unpublished data not applicable

Evaluation by Competent Authorities
EVALUATION BY RAPPORTEUR MEMBER STATE

Date March 2005

Materials and Methods

[redacted]

Results and discussion

[redacted]

	[redacted]
Conclusion	[redacted]
Reliability	
Acceptability	
Remarks	

98/8 Doc IIIA section No.	**6.4.1 / 01**	**Subchronic oral toxicity test**
91/414 Annex Point addressed	**II 5.3.2 / 01**	Short-term toxicity - oral 90-day studies

1.2	**Title**	Fourteen-Week Oral Toxicity Study in the Albino Rat
1.3	**Report No.**	89-9014
1.4	**Lab report No.**	not applicable
1.5	**Cross reference**	5.3.2/01
1.6	**Authors**	[redacted]
1.7	**Date of report**	4 December 1989
1.8	**Published**	no
2.1	**Testing Facility**	[redacted]
2.2	**Dates of experimental work**	
		study initiation: 4 April 1989
		dosing initiation: 18 April 1989
		terminal necropsy: 18-21 July 1989
3	**Objective**	To investigate the potential toxicity of thiabendazole in rats during daily administration by oral gavage for a minimum of 90 days.
4.1	**Test substance**	(Thiabendazole)
4.2	**Specification**	Batch number [redacted]
4.3	**Storage stability**	was conducted and found to be within acceptable limits prescribed by GLP (documented in study)
4.4	**Stability in vehicle**	satisfactory
4.5	**Homogeneity**	
	in vehicle	satisfactory
4.6	**Validity**	not applicable
5	**Vehicle/solvent**	0.5% Methylcellulose (400 centipoises)
6	**Physical form**	powder
7.1	**Test method**	complied with US EPA Pesticides Assessment Guidelines
7.2	**Justification**	not applicable
7.3	**Copy of method**	not applicable
8	**Choice of method**	not applicable
9	**Deviations**	not applicable
10.1	**Certified laboratory**	the study complied with GLP and the laboratory is subject to US EPA inspection

10.2	**Certifying authority**	the study complied with GLP and the laboratory is subject to US EPA inspection
10.3	**GLP**	yes
10.4	**Justification**	not applicable
11.1	**GEP**	not applicable
11.2	**Type of facility (official or officially recognized)**	not applicable
11.3	**Justification**	not applicable

2 Test system

Animal species:	Rat - Sprague-Dawley Crl:CD®(SD) BR
Source:	[redacted]
No. of animals:	80 male, 80 female (4 groups of 20 animals/sex/group)
Age:	approx. 6 weeks at treatment initiation
Dosage:	25, 100 or 400 mg/kg/day
Administration:	oral by gavage
Duration:	14 weeks
General observations:	twice daily for mortality and signs of toxicity, complete physical examinations conducted weekly
Ophthalmology:	examinations performed on all animals pretest and again during week 13
Food consumption:	one week pretest and weekly during the treatment period
Body weight:	twice pretest and weekly during the treatment period
Hematology:	samples collected during weeks 6 and 13 from 10 animals/sex/group
	hematocrit, hemoglobin, platelet count, red blood cell count, white blood cell count (total and differential), Wintrobe's constants (MCV, MCH and MCHC calculated)
Histopathology:	all tissues from animals in groups 1 (control) and 4 (high-dose)
	thyroids, adrenals, spleen, lungs, liver, kidneys, stomach, skin and bone (distal end of femur and proximal end of tibia) from animals in groups 2 (low-dose) and 3 (mid-dose)
	aorta (thoracic), brain (cerebral cotex, cerebellum and medulla), colon, duodenum, epididymides, eyes, Harder's gland, heart (with segment of aorta attached), ileum, jejunum, lymph nodes (mandibular and mesenteric), mammary gland, optic nerves, ovaries, pancreas, pituitary, prostate, salivary glands, sciatic nerve, skeletal muscle, skin, spinal cord (cervical), testes, thymus, urinary bladder, uterus
Bone marrow smears:	all animals
Clinical biochemistry:	blood urea nitrogen (BUN), total protein, alkaline phosphatase (AP), glutamic pyruvic transaminase (GPT), glutamic oxaloacetic transaminase (GOT), albumin, A/G ratio

(calculated), total potassium, glucose, sodium, inorganic phosphate, cholesterol

Urinalysis: colour and appearance, pH, glucose, ketones, urobilinogen, blood, volume, specific gravity, protein, bilirubin, microscopy of centrifuged deposit, nitrite

samples collected during weeks 6 and 13 from 10 animals/sex/group

Gross pathology: all animals were fasted overnight and killed by carbon dioxide asphyxiation followed by exsanguination from the abdominal aorta.

Organ weights: all animals, fasted body weights of the following organs dissected free of fat: adrenals, brain, heart, kidneys, liver, lungs, ovaries, pituitary, prostate, spleen, testes, thyroids and parathyroids (lobes weighed together), uterus.

Paired organs were weighed separately, but reported together.

Organ weights relative to body weight and relative to brain weight were calculated for all animals.

13 Findings

Dosages	0 - 25 - 100 - 400 mg/kg/day
clinical signs	all doses: increase in alopecia/thin fur (2/2, 2/4, 5/10 in males/females in 25, 100 and 400 mg/kg/day, respectively)
Feed intake	100, 400 mg/kg/day: dose-related decrease in feed intake
Mortality	400 mg/kg/day: no mortality
Body weight development	100, 400 mg/kg/day: dose-related decrese in body weight gain (~11-14% and ~31-46% in both sexes for 100 and 400 mg/kg/day, respectively)
Haematology	100, 400 mg/kg/day: slight decrease in erythron (approx. 10%)
Clinical chemistry (blood)	400 mg/kg/day: increases up to 2-fold control values found in serum cholesterol
Urinalysis	400 mg/kg/day: slight decrease in pH levels, slight increase in bilirubin, urobilinogen and nitrite levels. Also darker colour urine.
Gross pathology	Focal darkening in areas of the stomach in a few mid and high-dose rats. Depressed and thickened areas in the stomach - high dose females.
Organ weights	100, 400 mg/kg/day: weight changes in stomach, liver, spleen, thyroid and kidney

Histopathology	100, 400 mg/kg/day: acanthosis and necrosis of the stomach, epithelium, hepatic centrilobular hypertrophy. Splenic pigmentation resembling hemosiderin in mid and high dose. Tubular degeneration in the kidneys only in high dose group. Thyroid follicular cell hypertrophy/hyperplasia in mid and high dose groups.

Conclusion: no deaths occured during the study and there were no treatment-related ophthalmic changes.

Several treatment-related changes in the mid- and high dosage groups:

* increased incidence of alopecia/thin fur
* decrease in body weight gain
* NOEL for effects on body weight and food consumption was 25 mg/kg/day
* decrease in erythron parameters
* NOEL for hematological changes was 25 mg/kg/day
* increase in serum cholesterol and slight increases in urinary bilirubin, urobilinogen and nitrate
* NOEL for these changes was 100 mg/kg/day
* histologic changes in the spleen, liver, thyroid, stomach and kidneys
* NOEL for histologic changes was 25 mg/kg/day

14 Statistics Individual data including body weights, food consumption, hemograms (excluding non-segmented neutrophils, monocytes, eosinophils and basophils of the WBC differentials) and clinical biochemistry data and absolute/relative organ weight data were subjected to calculation of group mean values with standard deviations and Trend (Dose-Response) Analysis.

15 References to publications R.N. Hill et al., Fund. and Appl. Toxicol. 12, 629-697, 1989.

16 Unpublished data not applicable

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	March 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]

[redacted]

Conclusion

Reliability

Acceptability

Remarks

98/8 Doc IIIA section No.	**6.4.1 / 02**	**Subchronic oral toxicity test**
91/414 Annex Point addressed	**II 5.3.2 / 01**	Short-term toxicity - oral 90-day studies

1.2	**Title**	A Fourteen Week Oral Toxicity Study in the Beagle Dog
1.3	**Report No.**	89-9010
1.4	**Lab. report No.**	not applicable
1.5	**Cross reference**	5.3.2/02
1.6	**Authors**	[redacted]
1.7	**Date of report**	17 January 1990
1.8	**Published**	no
2.1	**Testing facility**	[redacted]
2.2	**Dates of experimental work**	**Study initiation:** 23 February 1989 **Dosing initiation:** 28 March 1989 **Terminal Necropsy:** 27-29 June, and 3 July 1989
3	**Objective**	to investigate in dogs, the potential toxicity of Thiabendazole during daily oral administration for a minimum of 90 days
4.1	**Test substance**	Thiabendazole [redacted]
4.2	**Specification**	[redacted]
4.3	**Storage stability**	not applicable
4.4	**Stability in vehicle**	not applicable
4.5	**Homogeneity in vehicle**	not applicable
4.6	**Validity**	not applicable
5	**Vehicle/solvent**	compound was placed into 1/8 oz. J gelatin capsules (except for the first 8 days of treatment when 1/2 oz. J capsules were used)
6	**Physical form**	off-white powder
7.1	**Test method**	Oral Capsule Dog Toxicity Study
7.2	**Justification**	complied with OECD guidelines according to the 1981 publication
7.3	**Copy of method**	not applicable
8	**Choice of method**	not applicable
9	**Deviations**	not applicable
10.1	**Certified laboratory**	the study complied with GLP and the laboratory is subject to US EPA inspection

10.2	**Certifying authority**	the study complied with GLP and the laboratory is subject to US EPA inspection
10.3	**GLP**	yes
10.4	**Justification**	not applicable
11.1	**GEP**	not applicable
11.2	**Type of facility (official or officially recognized)**	not applicable
11.3	**Justification**	not applicable

12 Test system

Animal species:	Dog (*Canis familiaris*) - beagle
Source:	[redacted]
Number of animals:	16 males and 16 females, assigned to 4 groups
Age:	approx. 5-7 months at treatment initiation
Weight range:	6.9 to 8.6 kg males; 5.2 to 6.9 kg females, one day prior to treatment initiation
Dosage:	35, 75 or 150 mg/kg/day
Administration:	capsule
Duration:	14 weeks
General observations:	twice daily for mortality and signs of reaction to treatment (circa 1 and 6 hours post dosing), complete physical examinations conducted weekly
Ophthalmology:	funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examination conducted on all animals prior to start of treatment and during drug weeks 4 and 13. Alcon atropine (1%) solution was used to dilate the pupils.
Food consumption:	recorded daily, two weeks prior to treatment initiation and during the treatment period
Body weight:	weekly during pretreatment and treatment period, and fasted body weights measured prior to scheduled sacrifice
Cardiovascular studies:	Assessments conducted on all dogs once during pretreatment and in drug weeks 4, 9 and 12 for males and in drug weeks 5, 9 and 13 for females
Hematology:	hematocrit, hemoglobin, platelet count, red blood cell count, white blood cell count (total and differential), Wintrobe's constants (calculated), prothrombin time
Histopathology:	all tissues from animals in groups 1 (control) and 4 (high-dose)
	thyroids, adrenals, spleen, lungs, liver, kidneys, stomach, skin (from mammary region), bone, aorta (thoracic), brain (cerebral cortex, mid-brain, cerebellum and medulla), colon, duodenum, epididymides, esophagus, eyes, femur (distal 1/3), gallbladder, heart, ileum, jejunum, lymph nodes (mandibular and mesenteric), mammary gland (when present in skin section), optic nerves, ovaries, pancreas, pituitary, prostate, sciatic nerve,

skeletal muscle, spinal cord (cervical, thoracic, lumbar), testes, thymus, tongue, trachea, urinary bladder, uterus (horns and body).

In addition, testes, epididymides and prostate for all male dogs and the gallbladder, liver and kidneys for all dogs as well as all gross abnormalities were examined.

Clinical biochemistry: blood urea nitrogen (BUN), total protein, alkaline phosphatase (AP), glutamic pyruvic transaminase (GPT), glutamic oxaloacetic transaminase (GOT), albumin, A/G ratio (calculated), total bilirubin, chloride, calcium, potassium, glucose, sodium, inorganic phosphate, cholesterol, creatinine

Urinalysis: colour and appearance, pH, glucose, ketones, urobilinogen, blood, volume, specific gravity, protein, bilirubin, microscopy of centrifuged deposit, nitrite samples collected during weeks 4, 8 and 12 from all dogs

Gross pathology: all animals were fasted prior to schedules termination. Dogs were killed by an intravenous injection of sodium pentobarbital, followed by exsanguination from the axillary or femoral arteries For each animal, necropsy consisted of an external examination, including identification of all clinically recorded lesions and a detailed internal examination.

Organ weights: all animals, fasted body weights of following organs dissected free of fat: adrenals, brain, heart, kidneys, liver, lungs, ovaries, pituitary, prostate, spleen, testes, thyroids and parathyroids (lobes weighed together), thymus, uterus.Paired organs were weighed separately, but reported together.Organ weights relative to body weight and relative to brain weight were calculated for all animals.

13 Findings

Dosages	0 - 35 - 75 - 150 mg/kg/day
Clinical signs	dose dependent incidence of emesis in groups 3 and 4. Group 4 males and females exhibited salivation from drug week 2. No salivation in groups 1 or 2. Abnormal feces seen in animals from all groups and sexes. The frequencies observed for abnormal feces in each group were not considered to be related to treatment. 1 group 4 dog demonstrated head shaking, head tilt and loss of co-ordination during drug week 2. As there was no apparent progression of these signs, they were considered unlikely related to treatment. In control and/or treated groups, other clinical signs included minor skin lesions, redness and swellings and ocular discharge

Feed intake	during the first week of treatment, food consumption was reduced in both males and females from all groups, except for group 2 males. By Drug Week 3 food consumption was similar to controls.
Mortality	no deaths during the course of the study
Body weight development	during the first 2 weeks of treatment, animals had access to food for only 1 hour after treatment, slight reductions in weight gain were found in all treated groups. After the feeding regimen was changed in Drug Week 3, there was a marked improvement in the mean weight gain. Weight gain was considered similar for control and treated animals.
Ophthalmoscopy	no abnormalities of the eyes
Cardiovascular studies	no adverse or treatment-related effects
Hematology	the mean red blood count for the group 4 animals were low compared to controls during drug week 4, were still lower during drug week 8, but at drug week 12 the results were similar to controls. Decreases in red cell count may be related to food intake. Erythrocyte values for groups 2 and 3 were considered similar to controls. Other hematological parameters showed intergroup differences, but none were seen consistently or considered to have enough magnitude to indicate reaction to treatment
Clinical chemistry	no changes that indicated any effect of treatment
Urinalysis	no adverse effect attributable to treatment
Gross pathology	no gross findings which could be attributed to treatment
Organ weights	no treatment-related changes
Histopathology	gallbladder - very slight to slight cytoplasmic vacuolation of the epithelium in the mid- and high-dose groups

Conclusions: Emesis at doses of 75 and 150 mg/kg/day.

Decreased erythrocyte parameters at 150 mg/kg/day in weeks 4 and 8 which may have been related to transient decreases in food consumption.

The **NOEL** in this study was determined to be 35 mg/kg/day.

14 Statistics

Individual data including body weights, food consumption, hemograms (excluding non-segmented neutrophils, monocytes, eosinophils and basophils of the WBC differentials) and clinical biochemistries were subjected to calculation of group mean values with standard deviations. For hemograms and clinical biochemistries, the data for males and females were combined to obtain the mean and

standard deviation for each group and parameter, whereas for all other data the sexes were analyzed separately.

15	**References to publications**	none
16	**Unpublished data**	not applicable

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	April 2005
Materials and Methods	The study complied with GLP and the laboratory is subject to US EPA inspection
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

98/8 Doc IIIA section No.	**6.4.1 / 03**	**Subchronic oral toxicity test**
91/414 Annex Point addressed	**II 5.3.2 / 01**	Short-term toxicity - oral 90-day studies

1.2	**Title**	Thiabendazole: A 14-Week Dietary Toxicity Study in Rats
1.3	**Report No.**	90-9002
1.4	**Lab. report No.**	not applicable
1.5	**Cross reference**	5.3.2/03
1.6	**Authors**	[redacted]
1.7	**Date of report**	13 December 1990
1.8	**Published**	no
2.1	**Testing facility**	[redacted]
2.2	**Dates of experimental work**	15 February 1990 to 22 May 1990
3	**Objective**	To establish a no-effect level for clinically evident alopecia and to establish a maximum-tolerated dose for the subsequent dietary chronic toxicity/carcinogenicity study in this species
4.1	**Test substance**	Thiabendazole [redacted]
4.2	**Specification**	[redacted]
4.3	**Storage stability**	within acceptable limits
4.4	**Stability in vehicle**	confirmed for 3 weeks at room temperature
4.5	**Homogeneity in vehicle**	confirmed at lowest and highest concentrations
4.6	**Validity**	not applicable
5	**Vehicle/solvent**	Purina Certified Rodent Chow; Thiabendazole prepared in the diet
6	**Physical form**	off-white powder
7.1	**Test method**	in accordance with OECD recommended guidelines
7.2	**Justification**	not applicable
7.3	**Copy of method**	not applicable
8	**Choice of method**	not applicable
9	**Deviations**	no deviations which affected the quality or integrity of the study or the interpretation of the results in the report
10.1	**Certified laboratory**	the study complied with GLP and the laboratory is subject to US EPA inspection
10.2	**Certifying authority**	the study complied with GLP and the laboratory is subject to US EPA inspection

10.3	**GLP**	yes
10.4	**Justification**	not applicable
11.1	**GEP**	not applicable
11.2	**Type of facility (official or officially recognized)**	not applicable
11.3	**Justification**	not applicable

12 Test system

Animal species:	Sprague-Dawley [Strain: Crl:CD®BR]
Source:	[redacted]
Number of Animals:	126 animals; 50 males and 50 females
Age:	44 days at dosing
Dosage:	group 1: control group 2: 10 mg/kg/day group 3: 40 mg/kg/day group 4: 160 mg/kg/day group 5: 320 mg/kg/day
Administration:	in the diet
Duration:	at least 13 weeks
General observations:	twice daily check for mortality and moribundity;daily for obvious indications of toxic effect physical examinations and detailed clinical observations recorded once per week at each weighing interval
Body weights:	prior to initiation of treatment body weights and food consumption recorded weekly thereafter
Urine:	samples collected at Week 13 only, prior to blood collection
Blood:	during weeks 6 and 13, and repeat samples during Week 14
Organs weighed:	adrenals, brain, heart, liver,lungs, kidneys, ovaries, pituitary, prostate, spleen, testes, thyroid/parathyroids,uterus
Histology:	All tissues were examined microscopically from all high dose, control and early death animals with gross lesions and target organs (with the exception of kidneys which were examined from all groups but the 10 mg/kg/day males)examined for all groups.
Hematology:	cell morphology, corrected leukocyte count, erythrocyte count, hematocrit, hemoglobin, leukocyte count, leukocyte dfferential

	count, mean cell hemoglobin, mean cell hemoglobin concentration, mean cell volume, platelet count
Clinical chemistry:	alanine aminotransferase, albumin, albumin/globulin ratio, alkaline phosphatase, aspartate aminotransferase, blood urea nitrogen, calcium, chloride, creatinine, globulin, glucose, inorganic phosphorus, potassium, sodium, total bilirubin, total cholesterol, total protein, triglycerides
Urinalysis:	appearance, bilirubin, glucose, ketones, microscopic examination of sediment, occult blood, protein, specific gravity, volume

13 Findings

SURVIVAL/ADJUSTED SURVIVAL 14-WEEK DIETARY TOXICITY STUDY IN RATS														
Dose[1] / Sex[2]	Start	1	2	3	4	5	6	7	8	9	10	11	12	13
0 M	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
10 M	10/10	9/10	9/10	9/10	9/10	9/10	9/10	9/10	9/10	9/10	9/10	9/10	9/10	9/10
40 M	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
160 M	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
320 M	10/10	10/10	10/10	10/10	10/10	10/10	9/9	9/9	9/9	9/9	9/9	9/9	9/9	9/9
0 F	10/10	10/10	10/10	10/10	10/10	10/10	9/9	9/9	9/9	9/9	9/9	9/9	9/9	9/9
10 F	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	9/9
40 F	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
160 F	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
320 F	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	9/9

[1] in mg/kg
[2] "M" is Male, "F" is Female

SUMMARY INCIDENCE OF CLINICAL SIGNS - 14-WEEK DIETARY TOXICITY STUDY IN RATS										
	males					females				
OBSERVATION	group 1	group 2	group 3	group 4	group 5	group 1	group 2	group 3	group 4	group 5
hunched	0	0	0	0	0	0	0	1	0	0
thin	0	0	0	2	2	0	1	1	0	0
teeth cut	1	1	0	0	1	0	0	0	0	0
malocclusion	1	0	0	0	1	0	0	0	0	0
few or no feces	0	0	0	0	0	0	0	1	0	0
low body temperature	0	0	0	0	0	0	0	1	0	0
alopecia[a]	1	1	1	2	2	1	1	1	2	2
sores[a]	1	1	1	1	3	0	1	0	0	1
bloody crust[b]	0	0	0	1	2	1	0	0	0	1
lacrimation	1	0	0	1	2	0	0	1	1	0
chromodacryorrhea	2	0	0	1	0	1	2	1	0	1
exophthalmus	1	0	0	1	2	0	0	1	0	0
red[c]	1	0	0	0	0	0	0	0	0	1
pale[d]	0	0	0	0	0	0	0	1	0	0
swollen[e]	1	0	0	0	1	0	0	0	0	0
necrotic[f]	0	0	0	1	1	0	0	0	0	0
missing[g]	1	0	0	0	1	0	0	0	0	0

[a] various body locations
[b] nose, paws, eye
[c] paw, inguinal area(s)
[d] body
[e] paw, face
[f] eye
[g] digit, eye