I. GENERAL INFORMATION

A. File Number

NADA 110-048

B. Sponsor

SmithKline Animal Health Products
Division of SmithKline Beckman Corporation
1600 Paoli Pike West
Chester, PA 19380

C. Proprietary Name

Valbazen®

D. Established Name

albendazole

E. Amount of Active Ingredient

11.36% Suspension (113.6 mg/mL)

F. Dispensing Status

Over the Counter (OTC)

G. Dosage Regimen

Ten (10) mg of albendazole per kg of body weight (4.45 mg/lb) administered orally with a suitable syringe.

H. Route of Administration

Oral

I. Indication

Exactly from label

J. Effect of Supplement

Cattle anthelmintic for the removal and control of the following endoparasites infecting cattle:

1. Liver flukes:

   Fasciola hepatica (adults)

2. Tapeworms:

   Moniezia benedeni, M. expansa (heads and segments)

3. Lungworms:

   Dictyocaulus viviparus (adults and 4th stage larvae)

4. Stomach worms:

   Barberpole worm: *Haemonchus contortus, H.Placei* (adults and 4th stage larvae)
   Brown stomach worm: *Ostertagia ostertagi* (adults, 4th stage larvae,4th stage inhibited larvae)
   Small stomach worm: *Trichostrongylus axei* (adults and 4th stage larvae)

5. Intestinal worms:

   Hookworm: *Bunostomum phlebotomum* (adults)
   Threadnecked intestinal worm: *Nematodirus spathiger, N. helvetianus* (adults, 4th stage larvae)
   Small intestinal worms: *Cooperia oncophora, C. punctata* (adults, 4th stage larvae)
   Bankrupt worm: *T. colubriformis* (adults)
   Nodular worm: *Oesophagostomum radiatum* (adults)

II. EFFECTIVENESS

Albendazole is an effective antiparasitic agent with broad spectrum activity against gastrointestinal and other nematodes, as well as cestodes and trematodes. Based on preliminary data, developmental research in cattle was conducted in a series of ten dose titration and 14 dose confirmation efficacy trials in 11 different geographic locations in the United States as well as internationally. Doses of 2.5 to 45 mg albendazole per kg body weight, given orally, were used in these studies, and the most effective dose of albendazole for use in cattle was 10 mg/kg.

Albendazole, in a suspension formulation, was administered orally as a drench, and was evaluated for efficacy using the controlled test, as recommended by the Center for Veterinary Medicine in its "Guidelines for Evaluation of Bovine Anthelmintics". Briefly stated, a certain number of infected cattle remain untreated, the remainder receive medication. After a suitable period of time post treatment (usually five to seven days, but longer in some circumstances), treated and untreated (control) animals are killed and necropsied. Remaining parasites are identified and counted for each animal.

In these studies the animals were either experimentally or naturally infected with one or more species of nematodes, cestodes, and/or trematodes. The claim for each major parasitic species is supported by adequate and well controlled studies.

Efficacy was expressed in percent removal of worms as compared to controls. The percent removal was calculated as follows:

Percent Removal of Parasites = (N)* Control - (N) Treated / (N) Control X 100

* (N) = Number of Parasites

Efficacy of albendazole was in the 90% range for each parasite claimed. Data from all major controlled efficacy studies were analyzed statistically using non-parametric procedures. The results supported the conclusion that when given orally to cattle at 10 mg/kg body weight, albendazole is a effective anthelmintic with a wide spectrum of activity against adult and larval stages of gastrointestinal roundworms, lungworms, tapeworms and liver flukes infecting cattle.

The investigator and efficacy against individual parasitic species are given in Tables 1,2,3 and 4.

Table 1 Summary of Dose-Titration Studies
Efficacy of Albendazole Against Adult Parasites

Parasite	**Dose (Range)**	**% Removal (Range)**	**Investigator**
F. hepatica	7.5-45 mg/kg	75-100	Bell, Malone
M. expansa	2.5-20 mg/kg	97-100	Ciordia
D. viviparus	5-20 mg/kg	99-100	Cheney, Theodorides
H. contortus	2.5-10 mg/kg	17-97	Benz, Theodorides
O. ostertagi	2.5-10 mg/kg	97-100	Benz, Smeal, Theodorides
T. axei	2.5-10 mg/kg	98-100	Benz, Theodorides
T. colubriformis	2.5-10 mg/kg	100	Theodorides
C. oncophora	2.5-10 mg/kg	29-100	Benz, Theodorides
C. punctata	2.5-7.5 mg/kg	45-99	Benz
N. spathiger	2.5-10 mg/kg	91-100	Theodorides
B. phlebotomum	2.5-10 mg/kg	95-100	Theodorides
Oe. radiatum	2.5-10 mg/kg	100	Benz, Theodorides

Table 2 Summary of Dose-Titration Studies
Efficacy of Albendazole Against Fourth Stage Nematode Larvae

Parasite	**Dose (Range)**	**% Removal (Range)**	**Investigator**
D. viviparus	5-10 mg/kg	91-100	Cheney
H. contortus	2.5-10 mg/kg	96-99	Theodorides
O. ostertagi	2.5-10 mg/kg	7-99	Erasmus, Smeal, Theodorides
T. axei	2.5-10 mg/kg	99-100	Theodorides
C. oncophora	2.5-10 mg/kg	99-100	Theodorides
C. punctata	2.5-10 mg/kg	94-100	Erasmus
N. spathiger	2.5-10 mg/kg	85-99	Theodorides

Efficacy of Albendazole Against Inhibited Fourth-Stage Larvae

Parasite	**Dose (Range)**	**% Removal (Range)**	**Investigator**
O. ostertagi	7.5-10 mg/kg	92-98	Smeal

Table 3 Summary of Dose-Titration Studies Efficacy of Albendazole Against Cestodes and Adult Nematodes

Parasite	**Dose (Range)**	**% Removal (Range)**	**Investigator**
F. hepatica	10 mg/kg	87	Foreyt
M. expansa	7.5 mg/kg	100	Johns
M. benedeni	5 mg/kg	100	Williams
D. viviparus	5 mg/kg	99-100	Sheldon, Worley
D. viviparus	7.5 mg/kg	99-100	Cheney, Downey, Theodorides
H. contortus	5 mg/kg	79-81	Benz
H. placei	7.5 mg/kg	99-100	Courtney, Johns, Williams
O. ostertagi	5 mg/kg	98	Williams
O. ostertagi	7.5 mg/kg	95-100	Courtney, Downey, Duncan, Johns, Williams
T. axei	5 mg/kg	100	Williams
T. axei	7.5 mg/kg	99-100	Courtney, Downey, Johns
C. punctata	5 mg/kg	100	Williams
C. punctata	7.5 mg/kg	97-99	Courtney, Downey
C. oncophora	7.5 mg/kg	99-100	Downey, Duncan, Johns
Nematodirus spp.	7.5 mg/kg	100	Duncan, Johns
N. helvetianus	5 mg/kg	98	Worley
N. helvetianus	7.5 mg/kg	87-99	Downey
T. colubriformis	5 mg/kg	100	Williams
T. colubriformis	7.5 mg/kg	100	Johns
B. phlebotomum	5 mg/kg	96	Williams
Oe. radiatum	5 mg/kg	100	Williams
Oe. radiatum	7.5 mg/kg	100	Johns

Table 4 Summary of Dose-Confirmation Studies Efficacy of Albendazole Against Fourth Stage Nematode Larvae

Parasite	Dose (Range)	% Removal (Range)	Investigator
D. viviparus	7.5 mg/kg	95	Cheney
H. placei	5 mg/kg	92	Williams
O. ostertagi	5 mg/kg	92	Williams
O. ostertagi	7.5 mg/kg	93	Williams
T. axei	5 mg/kg	92	Williams
C. punctata	5 mg/kg	86	Williams
C. punctata	7.5 mg/kg	99	Downey
N. helvetianus	7.5 mg/kg	98	Downey

Efficacy of Albendazole Against Inhibited Fourth-Stage Larvae

Parasite	Dose (Range)	% Removal (Range)	Investigator
O. ostertagi	7.5 mg/kg	84-92	Downey, Duncan, Williams

Location of Investigators given in Tables I, II, III and IV

Dr. R. Bell, College Station, TX
Dr. G. Benz, Auburn, AL
Dr. J. Cheney, Ft. Collins, CO
Dr. H. Ciordia, Experiment, GA
Dr. C. Courtney, Gainesville, FL
Dr. N. Downey, Castleknock, Ireland
Dr. G. Duncan, Glasgow, Scotland
Dr. F. Erasmus, Isando, S. Africa
Dr. W. Foreyt, Pullman, WA
Dr. D. Johns, N.S.W., Australia
Dr. T. Kistner, Corvallis, OR
Dr. J. Malone, Baton Rouge, LA
Drs. C. & J. Sheldon, Casa Grande, AZ
Dr. M. Smeal, N.S.W., Australia
Dr. V. Theodorides, W. Chester, PA
Dr. J. Williams, Baton Rouge, LA
Dr. D. Worley, Bozeman, MT

A. Dose Titration

Dose titration studies were carried out to determine the dose of albendazole needed to control trematodes, cestodes, gastrointestinal and pulmonary nematodes. Approximately 400 cattle were used, three fourths of which were treated with albendazole and the remaining cattle served as untreated controls. An oral suspension formulation was utilized with dosages ranging from 2.5 to 45 mg/kg. Accepted husbandry practices were duplicated with respect to breeds of cattle, diets, and grazing conditions. Standard procedures were followed for allocating, dosing, collecting samples, enumerating and identifying parasites, and performing necropsies. The parasitic infections were experimentally induced in five of the trials and naturally

acquired in the remaining five trials. Based on the data collected, an optimum effective dose of 10 mg/kg albendazole per kg body weight was determined.

Dose Titration Study

R.R. Bell
Texas A & M University
College Station, TX

Study A-217

This trial was conducted in cattle with a natural infection of *F. hepatica*, using the oral suspension. The cattle were obtained from two sources: 30 yearling steers from Sealy, Texas and 45 animals ranging from year old calves to aged cows from Brazoria, Texas. Prior to treatment, the animals were weighed and randomly allocated to five groups (15 animals per group). Four of the groups were treated with a single oral dose of 15, 25, 35 or 45 mg/kg of albendazole. The fifth group was left untreated and served as controls. The cattle were held on dry lot for three weeks and then necropsied. The percent removal of the worms listed below was recorded for each dose level. No adverse reaction occurred.

	% Removal			
Parasite	**15 mg/kg**	**25 mg/kg**	**35 mg/kg**	**45 mg/kg**
F. hepatica adult	96	98	98	100

All treatment groups were statistically significantly better than the control group ($p<0.0001$). The Wilcoxon rank sum test indicated that there was not sufficient evidence to conclude that 25 mg/kg is better than 15 mg/kg ($p=0.1020$). A regression analysis via the arc sine transformation on the percentage of zeros counted at each dose (6.7% at 0, 40% at 15, 60% at 25, 86.7% at 35 and 93.3% at 45 mg/kg) is statistically significant ($p<0.0001$).

Dose Titration Study

J.B. Malone
Louisiana State University
Baton Rouge, Louisiana

Study A-303

Cattle were obtained from farms with a history of endemic fascioliasis. Infection was confirmed in each animal by fecal examination for liver fluke ova. Twenty-two animals were divided into three groups of seven or eight animals each and treated with a single dose of albendazole suspension at 7.5, 10 or 15 mg/kg. An additional group of eight animals was left untreated and served as controls. The results are given below. No adverse reaction which was attributable to albendazole administration was reported.

Parasite	% Removal		
	7.5 mg/kg	**10 mg/kg**	**15 mg/kg**
F. hepatica adult	77	94	88

Dose Titration Study

R.R. Bell
Texas A & M University
College Station, Texas

Study A-226

The animals on this study were selected from a Texas herd in which clinical fascioliasis had been diagnosed. The 40 animals selected varied from two years to aged. The cattle were individually weighed and randomly allocated to four groups of ten cattle each. Three of the four groups were given a single oral dose of albendazole suspension at 7.5, 10 or 15 mg/kg. The remaining group of ten animals was untreated. Each group was held in a separate dry lot for one month. Thereafter, the animals were necropsied and the percent removal listed below was recorded. No adverse reaction occurred.

Parasite	% Removal		
	7.5 mg/kg	**10 mg/kg**	**15 mg/kg**
F. hepatica adult	98	99	98

All dose levels were statistically significantly better than the controls ($p<0.001$). There was no evidence to indicate any difference between the dose levels by the Wilcoxon rank sum test. The regression via the arc sine transformation on the percentage of zeros at each dose (10% at 0, 20% at 7.5, 40% at ten and 50% at 15 mg/kg is statistically significant ($p=0.0136$).

Dose Titration Study

J.M. Cheney
Colorado State University
Fort Collins, CO

Study A-224

Thirty five calves were experimentally infected with *D. viviparus*. The infection was so severe that a number of animals died before and after treatment. In order to have ten animals in the control group, five animals which died and were necropsied nearest to the treatment date were included with the controls. The remaining calves were treated with a single oral dose of albendazole suspension at 5.0 mg/kg (nine calves), 7.5 mg/kg (eight calves) or 10.0 mg/kg (eight calves). At necropsy, the percent removal of adult and fourth stage larvae was as follows. No adverse reaction was reported.

Parasite	% Removal		
	5 mg/kg	**7.5 mg/kg**	**10 mg/kg**
D. viviparus adult	100	100	99
D. viviparus larvae	100	100	91

Dose Titration Study

M.G. Smeal
Veterinary Research Station
New South Whales, Australia

Study IA-005

This study was designed as a dose titration study to determine efficacy against the inhibited larvae of *O. ostertagi.* Eighteen steers naturally infected with nematodes were divided into three groups of six animals each. One group received no albendazole and served as a control. The other two groups received a single oral dose at either 7.5 mg/kg or 10 mg/kg. At necropsy, the results were as follows. No adverse reaction was reported.

Parasite	% Removal	
	7.5 mg/kg	**10 mg/kg**
O. ostertagi adult	98	99
O. ostertagi 4th stage larvae	87	98
O. ostertagi 4th stage inhibited larvae	92	98

Dose Titration Study

V.J. Theodorides
Applebrook Center
West Chester, PA

Study A-200

Thirty-five calves, experimentally infected with gastrointestinal nematodes, were divided into four groups. Three of the groups were treated with a single oral dose of albendazole suspension at 2.5, 5.0 or 10.0 mg/kg (ten, eight, and nine calves, respectively). The fourth group of eight calves remained untreated and served as a control. At necropsy, the following results were recorded. No adverse reaction was reported.

Parasite	% Removal		
	2.5 mg/kg	**5 mg/kg**	**10 mg/kg**
H. contortus adult	79	96	97
H. contortus larvae	96	99	99
O. ostertagi adult	97	99	100
O. ostertagi larvae	99	99	99
T. axei adult	100	100	100
T. axei larvae	100	99	99
N. spathiger adult	91	98	100
N. spathiger larvae	85	97	99
C. oncophora adult	99	100	100
C. oncophora larvae	99	99	100
B. phlebotomum adult	99	95	100
T. colubriformis adult	100	100	100
T. colubriformis larvae	99	100	100
Oe. radiatum adult	100	100	100

For *H. contortus*, the 5.0 mg/kg dose is better than the 2.5 mg/kg dose (p=0.0019) and the 10.0 mg/kg dose is statistically better than the 5.0 mg/kg dose (p=0.0446). Therefore, the optimal dose for this species of parasite is between 5.0 and 10.0 mg/kg.

Dose Titration Study

H. Ciordia
University of Georgia
Experiment, GA

Study A-219

A total of 412 calves from five farms was screened to obtain 60 calves having fecal samples positive for *M. expansa*. The calves were divided into five groups (12 calves per group). One group served as an untreated control and the remaining four groups received a single dose of albendazole suspension at 2.5, 5.0, 10.0 or 20.0 mg/kg, respectively, Fourteen days later the animals were necropsied. The percent removal in the treatment is given below. No adverse reaction was reported.

Parasite	% Removal			
	2.5 mg/kg	**5 mg/kg**	**10 mg/kg**	**20 mg/kg**
M. expansa adult	97	97	100	100

Dose Titration Study

G.W. Benz
Auburn University
Auburn, AL

Study A-215

A total of 39 calves, experimentally infected with gastrointestinal parasites, was divided into four groups. Three of the groups received albendazole suspension as a single oral dose of 2.5, 5.0 or 7.5 mg/kg (ten, ten and nine calves respectively). The fourth group of ten calves remained untreated and served as a control. The following results were reported. No adverse reaction was observed.

	% Removal		
Parasite	**2.5 mg/kg**	**5 mg/kg**	**7.5 mg/kg**
H. contortus adult	17	48	83
O. ostertagi adult	99	99	99
T. axei adult	98	99	99
C. oncophora adult	29	93	100
C. punctata adult	45	91	99
Oe. radiatum adult	100	100	100

For *H. contortus* the 2.5 mg/kg dose and the 5.0 mg/kg dose are not statistically better than the controls (p=0.2981 and p=0.3372 respectively). Likewise, there is not sufficient evidence to demonstrate that the 5.0 mg/kg dose is better than the 2.5 mg/kg dose, however, the data do indicate that the 7.5 mg/kg dose is better than the 5.0 mg/kg dose (p=0.465). This study confirms the data from the previous study (Theodorides, A-200) via, that the optimal dose for *H. contortus* is between 5.0 and 10.0 mg/kg.

Dose Titration Study

V.J. Theodorides
Applebrook Center
West Chester, PA

Study A-213

A total of 39 calves was experimentally infected with *D. viviparus* and divided into four groups. One group of 11 calves remained untreated, the other groups received a single oral dose of albendazole suspension at 5, 10 or 20 mg/kg (nine, ten and nine calves, respectively). At necropsy, 35 days after experimental infection, all adult lungworms were removed in the treated groups. No adverse reaction was observed.

	% Removal		
Parasite	**5 mg/kg**	**10 mg/kg**	**20 mg/kg**
D. viviparus adult	100	100	100

Dose Titration Study

F.P.G. Erasmus
Terenure Research Farm
Isando, S. Africa

Study SA 75/10

This study was designed as a dose titration study against larval stages of gastrointestinal nematodes. Friesland calves, five to six months old were experimentally infected with larvae of *O. ostertagi* and *C. punctata*. One group of nine calves received no albendazole and served as a control. The other four groups received a single oral dose of albendazole suspension at either 2.5, 5.0, 7.5 or 10.0 mg/kg (five, 11, three, and five calves respectively). The calves were necropsied 20 to 26 days after treatment and the worms in the treated calves were removed as follows. No adverse reaction was reported.

	% Removal			
Parasite	**2.5 mg/kg**	**5 mg/kg**	**7.5 mg/kg**	**10 mg/kg**
O. ostertagi larvae	7	61	86	97
C. punctata larvae	94	99	100	100

B. Dose Confirmation

Confirmation of the dose selected for gastrointestinal and pulmonary nematodes, trematodes and cestodes was ascertained in 14 controlled trials. A total of 284 cattle were used, approximately one half of which were treated with albendazole and the remaining cattle served as untreated controls. Infections were acquired naturally in eight (8) of the trials and were experimentally induced in four (4) of the trials, along with two (2) trials in which an experimental infection was superimposed on an existing natural infection. All of the cattle were necropsied and parasites remaining were recorded.

Dose Confirmation Study

W.J. Foreyt
Washington State University
Pullman, WA

Study AX 5059

Twenty cattle from a fluke enzootic area in southern Idaho were selected based on the presence of five or more fluke eggs per gram of feces. The cattle were divided into two groups of ten each. One group received a single oral dose of albendazole suspension at 10 mg/kg; the other group was left untreated and served as a control. At necropsy, the percent removal of the worms was recorded and is given below. No adverse reaction was observed.

	% Removal
Parasite	**10 mg/kg**
F. hepatica adult	87

Dose Confirmation Study

G.L. Duncan
University of Glasgow
Glasgow, Scotland

Study IA-009

Ten calves of mixed breed with natural infections of gastrointestinal nematodes were divided into two equal groups. One group was left untreated, the other received a single oral dose of albendazole suspension at 7.5 mg/kg. At necropsy, the results were as follows. No adverse reaction was reported.

	% Removal
Parasite	**7.5 mg/kg**
O. ostertagi adult	100
O. ostertagi 4th stage inhibited larvae	89
C. oncophora adult	100
Nematodirus spp. adult	100

Dose Confirmation Study

D.E. Worley
Montana State University
Bozeman, MT

Study A-229

A total of 21 calves was experimentally infected with *D. viviparus* and divided into two groups. One group of ten calves was treated with a single 5 mg/kg dose of albendazole suspension. The other group of 11 calves served as an untreated control. All 11 control calves were infected with adult lungworms; there were no adult lungworm recovered from any of the treated calves. No adverse reaction was observed.

	% Removal
Parasite	**5 mg/kg**
D. vivparus adult	100

Dose Confirmation Study

C.H. Courtney
University of Florida
Gainesville, FL

Study AX-5223

A total of 21 yearling crossbred beef cattle with natural infections were divided into two groups. One group of ten animals received a single oral dose of albendazole at 7.5 mg/kg; the other group of 11 animals served as an untreated control. At

necropsy, the results given below were recorded. No adverse effect associated with the albendazole treatment was observed.

	% Removal
Parasite	**7.5 mg/kg**
H. placei adult	100
O. ostertagi adult	98
T. axei adult	100
C. punctata adult	99

Dose Confirmation Study

V.J. Theodorides
Applebrook Center
West Chester, PA

Study A-214

Six calves were experimentally infected with *D. viviparus* and equally divided into two groups. One group received no albendazole; the other received a single oral dose of albendazole suspension at a dose of 7.5 mg/kg. At necropsy, five days later, the worm count in the controls was an average of 44.3 worms per animal, there were no worms in the treated calves. No adverse reaction was reported.

	% Removal
Parasite	**7.5 mg/kg**
D. viviparus adult	100

Dose-Confirmation Study

C. Williams
Louisiana State University
Baton Rouge, Louisiana

Study A-253

A group of 32 newly weaned calves with natural infections was selected. An experimental infection of *T. colubriformis* and *T. axei* was superimposed on the existing natural infections of cestodes and gastrointestinal nematodes. The calves were divided into two groups of 16 each. One group remained untreated, the other group received a single oral dose of albendazole suspension at 5 mg/kg. The results were reported as follows. No adverse reaction was observed.

Parasite	% Removal 5 mg/kg
H. placei adult	99
H. placei larvae	92
O. ostertagi adult	98
O. ostertagi larvae	92
T. axei adult	100
T. acei larvae	92
C. punctata adult	100
C. punctata larvae	86
T. colubriformis adult	100
B. phlebotomum adult	96
Oe. radiatum adult	100
M. benedeni adult	100

Dose-Confirmation Study

J. M. Cheney
Colorado State University
Fort Collins, Colorado

Study A-266

Thirty calves were experimentally infected with *D. viviparus*, and divided into three groups of 10 calves each. One group received no albendazole; the other two received a single oral dose of albendazole suspension at 7.5 mg/kg administered either 5 days or 21 days after experimental infection, respectively. At necropsy, the lungworm count in the controls was an average of ll6 worms per animal. No adverse reaction was observed.

Parasite	% Removal 7.5 mg/kg
D. viviparus adult	99
D. viviparus larvae	95

Dose Confirmation Study

J.C. Williams
Louisiana State University
Baton Rouge, Louisiana

Study A-278

The existence of an infection with *O. ostertagi* in the inhibited larval stage was predetermined by necropsy and examination of seven animals from a herd of steer calves at the Red River Valley Experiment Station. Twenty four animals were selected from the herd and divided into two groups of 12 animals each. One group received no albendazole, while the other received a single oral dose of 7.5 mg/kg. At necropsy, removal of the various stages of *O. ostertagi* was reported as follows. No adverse reaction was observed.

Parasite	% Removal 7.5 mg/kg
O. ostertagi adult	99
O. ostertagi 4th stage larvae	93
O. ostertagi 4th stage inhibited larvae	84

Dose Confirmation Study

C.M. & J.J. Sheldon
Central Arizona Veterinary Laboratory, Inc.
Casa Grande, Arizona

Study A-5002

A total of 22 feeder calves naturally infected with *D. viviparus* was divided into two groups of 11 animals each. One group was treated with a single oral dose of albendazole suspension at a dose of 5 mg/kg. The other group remained untreated and served as a control. At necropsy, lungworms were recovered from nine of the control animals; there was an average of 43.2 worms per animal. In the treated group only a single adult lungworm was found in one of the 11 calves. No adverse reaction was observed.

Parasite	% Removal 5 mg/kg
D. viviparus adult	99

Dose Confirmation Study

D.E. Worley
Montana State University
Bozeman, Montana

Study A-5012

This study was conducted to confirm the efficacy of albendazole against *N. helvetianus.* Twenty animals with natural infections of *N. helvetianus* were divided equally into two groups of ten. One group was treated with a single oral dose of albendazole suspension at 5 mg/kg. The other group served as an untreated control. The following results were reported. No adverse reaction was observed.

Parasite	% Removal 5 mg/kg
N. helvetianus adult	98

Dose Confirmation Study

N.E. Downey
Agricultural Institute
Dunsinea Research Center
Castleknock, Ireland

Study IA-010

Sixteen calves with natural infections of *O. ostertagi* were divided into two groups (eight calves per group). One group remained untreated; the other group received a single oral dose of albendazole at 7.5 mg/kg. The results were as follows. No adverse reaction was reported.

	% Removal
Parasite	**7.5 mg/kg**
O. ostertagi adult	99
O. ostertagi 4th stage inhibited larvae	92
T. axei adult	99
C. oncophora adult	99
C. punctata adult	97
C. punctata larvae	99
N. helvetianus adult	99
N. helvetianus larvae	98
D. viviparus adult	100

Dose Confirmation Study

N.E. Downey
Agricultural Institute
Dunsinea Research Center
Castleknock, Ireland

Study IA-011

Four calves with natural infections of gastrointestinal nematodes were treated with 7.5 mg/kg of albendazole suspension and post mortem worm counts were compared to those of four untreated controls with comparable infections. The results were as follows. No adverse reaction was reported.

	% Removal
Parasite	**7.5 mg/kg**
O. ostertagi adult	95
O. ostertagi 4th stage inhibited larvae	90
C. oncophora adult	100
N. helvetianus adult	87
D. viviparus adult	100

Dose Confirmation Study

G.W. Benz
Auburn University
Auburn Alabama

Study A-300

A total of 43 calves was experimentally infected with one of two different strains of *H. contortus* (Merck isolate, or USDA isolate). The calves were divided into four

groups; one group had ten animals and the remaining three groups had 11 animals each. One group of ten infected with the Merck isolate, and one group of 11 infected with the USDA isolate, remained untreated and served as controls. The infected calves in the remaining two groups were given a single oral dose of albendazole suspension at 5 mg/kg. At necropsy, the results were as follows. No adverse reaction was reported.

	% Removal
Parasite	**5 mg/kg**
H. contortus - Merck isolate	81
H. contortus - USDA isolate	79

Dose Confirmation Study

D.R. Johns
SmithKline Research Station
Cobbitty, New South Wales, Australia

Study AUST 77/2

An experimental infection of *H. placei, T. axei, T. colubriformis, C. oncophora,* and *Oe. radiatum* was superimposed on existing natural infections of gastrointestinal nematodes in 11 head of cattle. One group of six animals received a single oral 7.5 mg/kg dose of albendazole; the remaining five animals were left untreated and served as controls. At necropsy, the results were as follows. No adverse reaction was reported.

	% Removal
Parasite	**7.5 mg/kg**
H. placei adult	100
O. ostertagi adult	100
T. axei adult	100
T. colubriformis adult	100
C. oncophora adult	100
Nematodirus spp. adult	100
Oe. radiatum adult	100
M. expansa adult	100

C. Clinical Field Trials

Well-documented clinical field trials were conducted in the United States according to an approved protocol which was modified to accommodate the parasite(s) of interest and local management conditions. Groups of cattle with at least a moderate worm infection, as determined by egg counts in their feces, were selected. Approximately the same numbers of animals were treated with albendazole or were left untreated, as controls. Worm eggs in fecal samples were counted before and after treatment, and animals were visually observed for side effects.

Thirteen investigators studied albendazole suspension in 12 states. They treated cattle of various breeds and compared them to untreated controls. Investigators, trial locations and numbers of animals in these studies are tabulated on the following

pages. The results of these clinical field trials confirm the results of the controlled studies indicating elimination or reduction of fecal egg counts in virtually all treated cattle. The recommended treatment was found to be safe and practical under field conditions.

CLINICAL FIELD TRIALSWITH ALBENDAZOLE SUSPENSION IN CATTLE
LIVER FLUKES
United States

Study #	**Investigator/ Location**	**Total No. of Animals**	**No. of Treated**	**No. with Fluke eggs Before Treatment**	**No. with Fluke eggs After Treatment**	**No. of Controls**	**No. with Fluke eggs Before Treatment**	**No. with Fluke eggs After Treatment**
A-231	Dr. Hall Caldwell, ID	101	51	41	29	50	39	34
A-236	Dr. Drake Reno, NV	70	36	36	8	34	34	21
A-237	Dr. Bradley Gainesville, FL	142	71	71	59	71	71	57
A-239	Dr. Malone Baton Rouge, LA	48	24	24	20	24	24	24
A-240	Dr. Bell College Sta., TX	30	16	15	1	14	14	13
A-267	Dr. Bradley Halopaw, FL	104	52	43	17	52	49	49
A-274	Dr. Drake Reno, NV	67	33	24	15	34	28	28

CLINICAL FIELD TRIALS WITH ALBENDAZOLE SUSPENSION IN CATTLE
TAPEWORMS
United States

Study #	Investigator/ Location	Total No. of Animals	No. of Treated	No. with Tapeworm eggs Before Treatment	No. with Tapeworm eggs After Treatment	No. of Controls	No. with Tapeworm eggs Before Treatment	No. with Tapeworm eggs After Treatment
A-246	Dr. Ciordia Experiment, GA	56	29	29	1	27	27	12
A-241	Dr. Troutt Blacksburg, VA	13	6	6	2	7	7	3

CLINICAL FIELD TRIALSWITH ALBENDAZOLE SUSPENSION IN CATTLE
LUNGWORMS
United States

Study #	Investigator/ Location	Total No. of Animals	No. of Treated	No. with Lungworm Larvae Before Treatment	No. with Lungworm Larvae After Treatment	No. of Controls	No. with Lungworm Larvae Before Treatment	No. with Lungworm Larvae After Treatment
A-228	Dr. Taylor Stevensville, MT	53	24	10	3	29	13	7
A-248	Dr. Quinn Helena, MT	40	20	9	8	20	7	6
A-281	Dr. Sheldon Casa Grande, AZ	100	50	24	0	50	20	4
A-313	Dr. Sheldon Texarkana, TX	167	84	6	1	83	14	9

CLINICAL FIELD TRIALSWITH ALBENDAZOLE SUSPENSION IN CATTLE GASTROINTESTINAL NEMATODES
United States

Study #	**Investigator/ Location**	**Total No. of Animals**	**No. of Treated**	**No. with Nematode eggs Before Treatment**	**No. with Nematode eggs After Treatment**	**No. of Controls**	**No. with Nematode eggs Before Treatment**	**No. with Nematode eggs After Treatment**
A-228	Dr. Taylor Stevensville, MT	48	22	22	12	26	26	5
A-234	Dr. Caley Manhattan, KS	44	25	25	23	19	19	6
A-241	Dr. Troutt Blacksburg, VA	55	27	27	20	28	28	28
A-245	Dr. Todd Madison, WI	43	24	24	3	22	22	20
A-296	Dr. Jordon Stillwater, OK	46	24	24	3	22	22	20
A-274	Dr. Drake Reno, NV	64	32	32	1	32	32	14
A-281	Dr. Sheldon Canadian, TX	167	83	50	8	84	59	58
A-359	Dr. Bradley Gainesville, FL	24	12	10	2	12	9	8

III. TARGET ANIMAL SAFETY

Studies to evaluate the safety of albendazole in cattle were conducted at SmithKline Animal Health Products Research Laboratories in West Chester, PA; French's Forest, Brookvale, Australia; and Isando, Transvaal, South Africa as well as in the laboratories of independent investigators in the United States and other countries.

Acute Oral Toxicity Study of Albendazole in Cattle

Investigator:

P.C. Van Schalkwyk, T.L. Geyser, and M. Recio
SmithKline Animal Health Products
Isando, Transvaal, South Africa

Study A-78/5

Purpose: The objective of this study was to identify the "toxic syndrome" characterized by responses of the target animal to the administration of toxic doses of albendazole.

Methods: Twenty ruminating calves weighing 175 to 520 pounds were selected for this study. Albendazole suspension was administered orally to groups of four cattle as a single oral dose of 22.5, 45.0, 112.5 or 150.0 mg/kg. A similar group of four calves served as an untreated control. After the administration of the compound, the animals were observed daily for 14 days.

Results: No symptoms other than soft feces were seen in two animals which received 45 mg/kg dose. At the two higher doses toxic symptoms included decreased activity and anorexia followed by a severe watery diarrhea. Subsequently, one animal in each of these two dose groups died. Necropsy changes consisted of fibrinous peritonitis and ascites, hydrothorax and acute pleuritis, congestion of the abomasum and acute enteritis.

Conclusion: The dose at which no overt effect was observed in cattle in this study is 45 mg/kg; i.e., 4.5 times the highest recommended therapeutic dose.

Toxicity Study of Albendazole in Cattle

Investigator:

J.C. Killeen, Jr. and W.E. Rinehart
Bio/dynamics Inc.
East Millstone, NJ

Study A-75-1241

Purpose: The objective of this study was to determine the maximum tolerated dose of albendazole in cattle.

Methods: A single dose of albendazole (suspended in 0.5 Methocel) was administered orally by drench to Aberdeen Angus cattle (weighing 300 to 700 pounds), at levels of

75 (two male and two female), 106 (two male and two female), 150 (two male and two female) or 300 mg/kg (one male and one female). After the administration of the compound, all animals were retained for a 14 day observation period followed by necropsy of all survivors.

Results: At the highest dose, 300 mg/kg, both animals died; one at five and the other, six days after dosing. A syndrome of anorexia, lethargy, recumbency, and slight weight loss was observed in both animals prior to death. Similar signs, along with rough hair coat, occurred in one male which received the 150 mg/kg dose and in one male and one female which received the 106 mg/kg dose. All animals, including those which died, were necropsied. There was no macroscopic tissue change considered related to drug administration, therefore, no histologic examination of the tissues was performed.

Conclusion: The maximum tolerated dose in this study was 75 mg/kg.

Acute Oral Toxicity Study in Fasciolized Cattle

Investigator:

J.H. Schafer, Elars
Bioresearch Laboratories, Inc.
Fort Collins, CO

Study A1003

Purpose: The objective of this study was to determine potential toxic effects of albendazole when administered to cattle eight weeks after artificial infection with *F. hepatica*.

Methods: Sixteen head of cattle, weighing 450 to 620 pounds, were randomly divided into four groups of two males and two females, each. Two of the groups were experimentally infected with *F. hepatica*; the other two groups remained uninfected and served as controls. Eight weeks after infection, one non infected group and one infected group were given a single oral dose of 45 mg/kg of albendazole. Thereafter, all animals were observed for four weeks and then necropsied.

Results: Prior to treatment sorbitol dehydrogenase (SDH) and glutamate dehydrogenase (GDH) serum levels in the infected groups rose during the first few weeks of the study while gamma glutamyl transpeptidase (GGTP) levels rose sharply at eight weeks following infection. One week after albendazole administration, significantly lower SDH and GGTP serum levels were observed in the infected treated animals (i.e., these values returned to normal pre infection levels) as compared to the non-treated infected group. Hematocrit values remained essentially within normal range in all groups throughout the study. Appetites of all animals were good throughout the study. No adverse clinical sign was noted in any animal prior to or following administration of albendazole. No macroscopic nor histopathologic change occurred which was considered related to albendazole administration.

Conclusion: Administration of albendazole at 4.5 times the recommended therapeutic dose produced no evidence of toxicity in animals infected with *F. hepatica*.

Tolerance Study of Albendazole in Cattle

Investigator:

V.J. Theodorides
SmithKline Animal Health Products
Applebrook Center
West Chester, PA

Purpose: The objective of this study was to determine the potential toxic effects of albendazole when administered weekly for eight consecutive weeks.

Methods: Three Hereford cows, weighing 565 to 680 pounds, received a single oral dose of 75 mg/kg of albendazole suspension, once weekly for eight consecutive weeks. Three other Hereford cows were left untreated and served as controls. Ten days after the initial dose and at bi-weekly intervals thereafter, blood samples were drawn from each animal and assayed for alkaline phosphatase, serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transaminase, serum bilirubin, albumin and globulin. All surviving treated animals were necropsied two weeks following the last dose of albendazole.

Results: One animal died spontaneously six days after receiving the fifth dose of albendazole. The macroscopic changes observed at necropsy were indicative of pneumonia; however, extensive autolysis precluded meaningful histopathologic examination and definitive diagnosis. No adverse clinical sign was observed in the other two animals; no clinicopathologic or histopathologic change occurred which was attributable to albendazole administration.

Conclusion: Administration of 75 mg/kg of albendazole at weekly intervals for eight weeks was well tolerated by the cattle.

Five Day Subacute Oral Toxicity Study with Albendazole in Cattle

Investigator:

J.C. Killeen,Jr. and W.E. Rinehart
Bio/dynamics Inc.
East Millstone, NJ

Study A75-1242

Purpose: The objective of this study was to assess the toxicity of albendazole when administered daily for five consecutive days.

Methods: Twenty four Aberdeen Angus cattle weighing 300 to 700 pounds were selected for this study. Albendazole, suspended in 0.5% Methocel, was administered orally to groups of 3 males and 3 female cattle for five days at levels of 7.5, 25.0 or 40.0 mg/kg per day. A similar group of three males and three females were untreated and served as a control. The animals were examined before and after treatment for clinical signs of toxicity by observation, hematology and clinical chemistry tests. Two males and two females from each group were necropsied 24 hours after the last dose. The remaining animals were retained for a nine day observation period and then

necropsied. The untreated controls and the animals in the highest treatment group and the livers from the animals in the mid dose group were also examined for histopathologic signs of toxicity.

Results: Three animals, one control and two receiving 40 mg/kg/day died spontaneously prior to termination. These animals were necropsied and death was considered to have been caused by repeated trauma induced by the speculum used for intubation each day.

Conclusion: Evaluation of all in life (physical observations, body weight, hematology, and clinical chemistry) and post mortem parameters did not reveal any change considered related to the administration of albendazole.

Four reproductive safety studies were conducted in pregnant cows which received either single or multiple doses of albendazole suspension at various stages of gestation.

Reproductive Studies of Albendazole in Cattle

Investigator:

V.J. Theodorides
SmithKline Animal Health Products
Applebrook Center
West Chester, PA

Study A-2001

Purpose: The objective of this study was to determine the effects of albendazole on the embryo when administered to mated cows during the first 61 days of gestation.

Methods: Two groups of 27 Hereford cows, two to three years old, received multiple oral doses of 25 mg/kg of albendazole suspension either on days seven and 14 of gestation or on days 21, 31, 41, 51 and 61 of gestation. An additional group of 27 Hereford cows which served as a control was treated once with 25 mg/kg of albendazole approximately 30 days prior to calving in order to evaluate the drug for a possible abortifacient effect.

Results: Albendazole administration at 2.5 times the highest recommended therapeutic dose had no significant effect on duration of pregnancy, incidence of assisted delivery or stillborn calves or weight of the calves at birth. No abnormal calf was born. The pregnancy rates at 60 days after first mating were 85% for controls, 63% for cows treated twice on days seven and 14 of gestation and 85% for cows treated with multiple doses on days 21, 31, 41, 51 and 61 of gestation.

Reproductive Safety of Albendazole in Cattle

Investigator:

V.J. Theodorides
SmithKline Animal Health Products
Applebrook Center

West Chester, PA

Study A-2002

Purpose: The objective of this study was to determine the effects of albendazole on the early embryo when administered to heifers seven and 14 days after insemination.

Methods: A group of 71 Hereford virgin heifers, 18 to 24 months old, received two 15 mg/kg doses of albendazole seven and 14 days respectively, after breeding. A similar group of 71 heifers received placebo and served as a control.

Results: The number of heifers which became pregnant in the treated group (62) was slightly less than in the control group (67), and there was a lower first service conception rate, 61% treated versus 72% in the control group.

Reproductive Safety of Albendazole in Cattle

Investigator:

V.J. Theodorides
SmithKline Animal Health Products
Applebrook Center
West Chester, PA

Study A-2002

Purpose: The objective of this study was to determine the effects of albendazole on the early embryo when administered to heifers either seven or 14 days after insemination.

Methods: Groups of 90 or more heifers (Hereford and/or Black White face), 18 to 24 months old, received a single oral dose of albendazole suspension at 25 mg/kg on either day seven or 14 of gestation. A similar group of heifers remained untreated and served as a control. All animals were bred only once.

Results: The conception rates were 75% for controls, 61% for heifers treated on day seven of gestation and 8% for heifers treated on day 14 of gestation.

Conclusion: Based on these three studies, an adequate margin of safety (i.e., three to five times the recommended dose of 10 mg/kg) when administered during the first month after mating has not been established. Therefore, a cautionary statement contraindicating use of the product during the first 45 days of pregnancy is included in the labeling.

Reproductive Safety of Albendazole in Cattle

Investigator:

D.R. Johns and M.J. Edwards
SmithKline Animal Health Products
Cobbity, New South Wales, Australia

Study A-2017

Purpose: The objective of this study was to determine the effects of albendazole when administered during early pregnancy on conception rates following estrus and ovulation synchronization.

Methods: For this study, 159 Hereford heifers, 15 to 20 months of age, were divided into four groups of 39 or 40 animals each. Estrus was synchronized, using an intramuscular injection of cloprostenol, and the heifers were artificially inseminated. In each of the four groups one half of the heifers received four 10 mg/kg doses of albendazole seven, 14, 28 and 42 days after artificial insemination; the remaining animals in each group received 30 mL of water and served as controls.

Results: At 100 days post insemination 36 of the 79 treated heifers were pregnant i.e., a conception rate of 45.5%; 34 heifers out of the 80 controls were pregnant representing a conception rate of 41.5%. Using the Chi Square test the difference was not statistically significant.

Conclusion: Treatment with albendazole suspension at a dose of 10 mg/kg administered four times during early gestation (viz on days seven, 14, 28 and 42) had no detrimental effect on the conception rate of the heifers.

Investigations of the Effect of Albendazole on Spermatogenesis, Quality of Semen and Libido in Treated Bulls

Investigator:

W.E. Berdntson, B.W. Pickett and P.J. Chenoweth
Animal Reproduction Laboratory
Colorado State University
Fort Collins, CO

Study A-2000

Purpose: The objective of this study was to determine the effects of albendazole on spermatogenesis, seminal quality and libido in bulls.

Methods: A single oral dose of 22.5 mg/kg of albendazole suspension was administered to 12 two year old Hereford and/or Angus bulls. 14 bulls of similar age, weight and breed were untreated and served as controls. The following parameters were measured over a 70 day period following treatment: scrotal circumference, libido, spermatozoal ejaculate, initial and post thaw motility, total solids, acrosomal integrity (post thaw), and plasma testosterone. Groups of treated and control bulls were castrated on days seven, 28, 49 and 70 post treatment and total testicular weight, weight of the tunical albuginea (testicular capsule), testicular parenchymal weight, epididymal weight, and number of spermatids were determined as well as quantitative testicular histology.

Results: There was no adverse effect of spermatozoal production, spermatozoal output, quality of freshly ejaculated or frozen semen, libido, or serum testosterone levels in the treated bulls.

Conclusion: Treatment with albendazole suspension at a dose of 22.5 mg/kg (i.e., 2.25 times the highest recommended therapeutic dose) exerted no detrimental effect on the treated bulls.

IV. HUMAN SAFETY

A. Toxicity and Teratogenicity Tests

Toxicity and teratogenicity studies were done to determine potential hazards to human health when food derived from treated animals is ingested.

Three Month Oral Toxicity Study in Rats

Investigator:

J.C. Killeen, Jr. and W.R. Rapp
Bio/dynamics Inc.
East Millstone, NJ

Study 75-1109

Methods: Albendazole was administered daily in the diet to equisexual groups of 40 Long Evans strain rats for three months at dose levels of 2, 10 or 30 mg/kg/day. A similar group of rats received the basal diet only and served as a control.

Results: Evaluation of physical observation, body weight and food consumption data, laboratory studies (hematology, clinical chemistry, and urinalysis), organ weights, organ/body weight ratios and histologic examination of tissues did not reveal any effect attributable to treatment with albendazole.

Conclusion: The no effect level in this study was 30 mg/kg/day.

Three Month Oral Toxicity Study of Albendazole in Dogs

Investigator:

J.C. Killeen, Jr. and W.R. Rapp
Bio/dynamics Inc.
East Millstone, NJ

Study 75-1110

Methods: Albendazole was administered daily to equisexual groups of eight beagle dogs via gelatin capsules for three months at doses of 2, 10 and 30 mg/kg. A similar group of dogs received empty gelatin capsules and served as a control.

Results: Erythrocytes cholinesterase activity was statistically significantly lower in the high dose males than controls at months one and three. However, no pharmacologic effect or histopathologic change was noted that could be attributed to a depression or inhibition of cholinesterase activity. In addition, no similar change which was statistically significantly different from control was noted in the

females. It was concluded; therefore, that the depression of the cholinesterase in the high dose males was attributable to extreme variation in the assay procedure. Evaluation of general observations of body weight and food consumption data, hematology, urinalysis, organ weights, organ/body weight ratios and histologic examination did not reveal any effect attributable to the administration of albendazole.

Conclusion: The no effect level in this study was 30 mg/kg/day.

Six Month Oral Toxicity Study of Albendazole in Dogs

Investigator:

I.W. Daly and G.K. Hogan
Bio/dynamics Inc.
East Millstone, NJ

Study A-1018

Methods: Twenty four male and 24 female beagle dogs were equally distributed into four groups of six animals/sex/group and given 0, 5, 30 or 60 mg/kg of albendazole daily in gelatin capsules for six months. Hematology, clinical chemistry and cholinesterase evaluations were performed pretest and at monthly intervals. Brain cholinesterase was evaluated at termination. Urinalysis was performed pretest and at two, four and six months. Ophthalmoscopic examinations were conducted pretest and at termination. At the end of the experiment the animals were killed and the tissues from all dogs were evaluated histopathologically.

Results: Several toxic responses were seen among the high dose dogs. These included hematologic dyscrasia, reduced body weight gains, slightly higher liver weights, significant decreases in both the absolute and relative weights of the testes, hypocellular bone marrow, and one undiagnosed death. The only effect seen among the mid-dose (30 mg/kg/day) dogs was a reduced white blood cell count and no evidence of toxicity was noted in any of the low dose dogs.

Conclusion: The dose of 5 mg/kg/day of albendazole was established as the no effect level.

Chronic Oral Carcinogenicity Study of Albendazole in Rats

Investigator:

I.W. Daly and A.L. Knezevich
Bio/dynamics Inc.
East Millstone, NJ

Study A-1022

Methods: Albendazole was administered daily in the diet at dose levels of 3.5, 7.0 or 20.0 mg/kg to male and female F1a rats (Charles River CD, derived from F0 generation given albendazole at dose levels of 1.0, 2.5 or 5.0 mg/kg/day for

approximately 60 days prior to mating and throughout the mating, gestation, lactation and post weaning segments of the study). One hundred rats per sex per group were used. Two additional groups of 100 rats of each sex received unmedicated diet and served as controls. All surviving male rats were terminated at week 121 and all surviving female rats at week 122.

Results: Evaluation of ophthalmology, physical observations, body weight, food consumption, urinalysis, terminal organ and organ/body ratios did not reveal any effect attributable to the administration of albendazole. Mean total leukocyte and segmented neutrophil counts were slightly reduced in the high dose males at 22 and 24 months and in the high dose females at 24 and 28 months. Slight decrease was observed in these parameters in the high dose males and females at some earlier bleeding intervals; however, these changes were not consistent over time and were within the range of values observed in one or more of the control groups. The other hematologic parameters evaluated were unremarkable in the treated males and females throughout the study. Mean alkaline phosphatase values were slightly increased in the high dose males at three and six months, but not during the remainder of the study. Mean cholesterol values were slightly elevated in the high dose females at three, six, 12, 18, 24 months and at the termination of the study. Other clinical chemistry parameters were unremarkable. Histopathologic evaluation of the tissues revealed testicular degenerative lesions and liver vacuolation among the high dose rats; however, the incidence observed was within the range occurring in the historical control data of this laboratory. Analysis of the neoplasm data focused attention on an increase of histiocytic sarcomas primarily in the male and on the increase of uterine endometrial stromal polyps and sarcomas.

Conclusion: Histiocytic sarcomas are spontaneous, commonly occurring, lymphoreticular tumors appearing with a rate that is highly variable from study to study. The increase in all groups in this study was within historical control range, and the incidence in the control groups was at the low end of the range. In addition, if the histiocytic sarcomas were combined with the lymphoreticular/hematopoietic tumors, as is commonly and acceptably done, the apparent increase disappears. The above considerations lead to the conclusion that the slight increase in the incidence of histiocytic sarcomas was not considered to be biologically significant. Uterine endometrial stromal tumors, particularly polyps, are spontaneous, common tumors, highly variable in incidence. The incidence in all groups is within the range of historical control data. In view of the highly variable historical incidence of combination with the sarcomas, was not considered to be biologically significant. Albendazole was determined not to be carcinogenic in the rat. The no observed effect level is 7 mg/kg/day.

Chronic Oral Carcinogenicity Study of Albendazole in Mice

Investigator:

I.W. Daly and A.L. Knezevich
Bio/dynamics Inc.
East Millstone, NJ

Study A-1024

Methods: Albendazole was administered daily in the diet to male and female Charles River CD-1 mice at dose levels of 25, 100 or 400 mg/kg. One hundred mice per sex per group were used. Two additional groups of 100 mice of each sex received unmedicated diet and served as controls. All surviving mice were terminated after 25 months on test.

Results: No compound related changes were seen in general appearance and behavior, physical observations or mortality. The high dose males and females exhibited reduced mean erythrocyte counts and elevated mean platelet counts throughout the study. These effects were more pronounced in the females than in the males. During months three to 18, mean leukocyte counts were slightly decreased in the high dose males, as compared to the controls, at most bleeding intervals. However, during the last six months of the study this trend reversed and the high dose males exhibited total leukocyte counts which were, for the most part, slightly elevated relative to control. With few exceptions, the differences from control mice were not statistically significant. The patterns noted in the mean erythrocyte, total leukocyte and platelet counts of the high dose males and females were considered suggestive of a treatment related effect. At necropsy, the incidence of high dose males with flaccid and/or small testes and high dose females with endometrial polyps of the uterus was increased compared to controls. Microscopically, bilateral degeneration of the tubular germinal epithelium of the testes of the high dose males and cytoplasmic vacuolation of centrilobular hepatocytes of the liver in the high dose males and females were considered treatment related. There were no other histopathologic findings which were attributable to the administration of albendazole.

Conclusion: Albendazole was demonstrated not to be a carcinogen in mice in this study. Based on the drug related changes seen in the livers of the male and female mice, in the testes of the male mice and the uterus of the female mice, 25 mg/kg/day was established as the no effect level for this study.

Three Generation Reproduction Study of Albendazole in Rats

Investigator:

R. Schroeder and W.E. Rinehart
Bio/dynamics Inc.
East Millstone, NJ

Study A-1007

Methods: Albendazole was administered in the diet at fixed concentrations of 0, 30, 75 or 150 ppm to Long Evans rats continuously for three successive generations. Each parental generation (F0, F1 and F2) consisted of 12 males and 24 females.

Results: No drug related effect was seen in mating, pregnancy or fertility indices, offspring viability at birth, litter survival to weaning or pup sex distribution data. At the high dose a slight, although statistically significant, decrease in mean gestation length was noted in the first pregnancies of the F0 generation. During

the ensuing lactation interval (F1a litters) a statistically significant decrease in pup survival indices on days zero to four and four to 21 was noted in this same group. For the remainder of the study (F1b litters, F1 and F2 generations) the gestation length and pup survival data for the high dose group were comparable to control. No drug related effect on gestation length or pup survival occurred in the low or mid dose groups. Mean pup body weight data during lactation were comparable between the controls and the low and mid dose groups throughout the study. In the high dose group, mean pup body weights during lactation tended to be slightly lower than control throughout most of the study, with the exception of the F2a litter, for which mean pup weights were slightly higher than controls. Gross necropsy examination of the adults (F0, F1 and F2) and offspring did not reveal any change attributable to administration of albendazole.

Conclusion: A no effect level of 150 ppm was established for albendazole in this study.

Perinatal and Postnatal Study of Albendazole in Rats

Investigator:

D.E. Johnson and J.L. Schardein
International Research & Development Corp.
Mattawan, MI

Study A-1026

Methods: Albendazole was administered orally by gavage as a single daily dose to groups of 25 pregnant Charles River CD rats at doses of 5, 20 or 40 mg/kg. An identical group of rats received the vehicle only (0.5% aqueous Methocel) and served as a control. Nineteen rats in each group were treated on days 16 to 20 of gestation while the remaining six were treated from day 16 of gestation through day 20 of lactation. All dams were allowed to deliver and the resulting litters were culled to ten pups (five males, five females, if available) and evaluated for developmental and behavioral parameters. Maternal criteria evaluated includes maternal body weight gain, appearance and behavior, survival, gestation length, parturition, fertility and uterine observations. Offspring evaluations included gross examinations for external malformations, viability, sex ratios, weight gain and neuropharmacologic tests at weaning.

Results: There was no observable treatment related effect at either the low or mid dose levels. Decreased viability and external and skeletal malformations were observed at the high dose (40 mg/kg/day). At the high dose there was a statistically significant decrease in mean pup body weight on days zero, four, 12 and 21 of lactation and decreased survival of the pups during lactation. A slight decrease in mean maternal body weight gain was observed in the high dose dams during lactation days zero through four.

Conclusion: The no effect level in this study is concluded to be 20 mg/kg/day.

Teratogenicity Study of Albendazole in Rats

Investigator:

J.C. Killeen, Jr. and W.R. Rapp
Bio/dynamics Inc.
East Millstone, NJ

Study A-2008

Methods: Albendazole (doses of 0, 2, 5, 10 or 30 mg/kg/day) was given by gavage to groups of 20 mated female Long Evans rats from days six through 15 of gestation. Fetuses were delivered by Caesarean section on day 20 of pregnancy. Behavior and general condition, food consumption and body weight were monitored for the dams. Live and dead fetuses, resorption, and implantation sites were counted. The fetuses were weighed, their sex determined and they were examined for external appearance and detectable abnormalities. Approximately two-thirds of the fetuses were processed for determination of skeletal abnormalities and the remaining for soft tissue malformations.

Results: Embryotoxic effects at the 30 mg/kg/day dose level were noted in all in life parameters. The number of dams with viable fetuses and the number of viable fetuses within a litter were significantly less and resorption greater than in the control. Fetal weight and size were also markedly less than control. A definite teratogenic effect of the drug as evidenced by an increased incidence of skeletal and soft tissue malformations also occurred at the high dose level. Small increases in malformations at lower dose levels were observed that indicated possible teratogenicity but a dose related pattern was not evident.

Conclusion: Albendazole at 30 mg/kg/day appears to be fetotoxic and teratogenic in rats. The increased incidence of malformations in the other treated groups did not occur in a dose related pattern. The nature of the malformations precluded determination of a no effect level. The following study was used to determine the no effect level.

Teratogenicity Study of Albendazole in Rats

Investigator:

J.C. Killeen, Jr. and W.R. Rapp
Bio/dynamics Inc.
East Millstone, NJ

Study A-2010

Methods: This study was conducted as a follow up to the preceding Study A-2008. Albendazole was administered by gavage to groups of mated Long Evans rats (19, 20 or 21 rats per group) at doses of 0, 0.5, 2.0, 5.0 or 10.0 mg/kg/day from days six through 15 of pregnancy.

Results: At 10 mg/kg/day albendazole was embryotoxic and teratogenic. At the lower dose levels (0.5, 2.0 or 5.0 mg/kg/day) there was no evidence of either maternal or fetal toxicity, nor was there any effect on the reproductive

parameters, fetal viability, size or sex. There was no indication of teratogenicity in either the soft tissue or skeletal examinations.

Conclusion: The no effect level in this species is 5 mg/kg/day.

Teratogenicity Study of Albendazole and Metabolites in Rats

Investigator:

D. Martin and P. Delatour
Ecole Nationale Veterinaire
de Lyon, Charbonnieres, France

Methods: Albendazole or one of its ten identified metabolites was administered by gavage to groups of mated female albino Sprague-Dawley (OFA strain) rats from day eight through 15 of pregnancy. In order to insure good comparison of one compound against another, the daily dose administered was equimolar rather than equal in weight. In the case of albendazole the doses administered (MX10-4g/kg) ranged from 5.3 to 13.25 mg/kg. A similar group of female rats served as a control. Fetuses were delivered on the 21st day of pregnancy by Caesarean Section. Parameters studied in this experiment were similar to those in the other rat teratology studies.

Results: At doses of 6 mg/kg and lower, albendazole impaired neither the general health of the mothers nor the intrauterine development of the fetuses. At doses greater than 6 mg/kg, albendazole and its sulfoxide metabolite were embryotoxic and produced teratogenic effects. No embryotoxic or teratogenic effect was noted following administration of the other metabolites of albendazole.

Conclusion: The no effect level for albendazole and its sulfoxide metabolite for the parameters studies was 6 mg/kg/day.

Teratogenicity Study of Albendazole in Rabbits

Investigator:

J.C. Killeen, Jr. and W.R. Rapp
Bio/dynamics Inc.
East Millstone

NJ - Study A-2009

Methods: Albendazole (0,2,5,10 or 30 mg/kg/day) was administered by gavage to groups of 15 mated New Zealand White rabbits from day seven through 19 of pregnancy. The parameters studied in this experiment were similar to those in the rat teratology study.

Results: At the highest dose (30 mg/kg/day) albendazole was maternally toxic, embryotoxic and induced teratogenic effects. This was manifested by a higher mortality rate in the does, as compared to controls, a significantly lower number of viable fetuses with a concomitant increase in the number of resorption, slightly lower fetal weight and size at birth, and the occurrence of ectrodactyly in all viable

fetuses. At the 10 mg/kg/day dose albendazole was embryotoxic. The observations in the other groups which received albendazole were comparable to the controls or within the historical control range established for this laboratory.

Conclusion: The no effect level for the parameters studied was determined to be 5 mg/kg.

Teratogenicity Study of Albendazole in Mice

Investigator:

J.C. Killeen, Jr. and W.R. Rapp
Bio/dynamics Inc.
East Millstone, NJ

Study A-2011

Methods: Albendazole (doses of 0,2,5,10 or 30 mg/kg/day) was administered by gavage to groups of mated female Charles River COBS mice (21 to 26 mice per group) from day six through 15 of pregnancy. The parameters studied in this experiment were similar to those in the rat and rabbit teratology studies.

Results: The administration of albendazole did not impair the general health of the mothers nor the intrauterine development of the fetuses at any dose level. The mean numbers of corpora lutea, implantation sites, and viable fetuses in all treated groups were comparable to control. The percentages of fetuses live, dead and reabsorbed, the mean fetal weights and sex ratios indicated no drug related effect. Likewise, there was no evidence of albendazole induced embryotoxic or teratogenicity in this species.

Conclusion: The no effect level for the parameters studied in this experiment was 30 mg/kg/day.

B. Calculation of Albendazole Acceptable Daily Intake

1. Studies considered in establishing a tolerance:

Study	**No Effect Level**
Carcinogenicity study in rats	7.0 mg/kg/day
Carcinogenicity study in mice	25.0 mg/kg/day
Six month dog study	5.0 mg/kg/day
Three Generation Reproduction in Rats	150 ppm
Peri/Postmatal Reproduction in Rats	20.0 mg/kg/day
Rat Teratology	5.0 mg/kg/day
Rabbit Teratology	5.0 mg/kg/day
Mouse Teratology	30.0 mg/kg/day

2. Safe Concentration for Albendazole Residues:

   The no observed effect level for establishing the safe concentration of the total residues of albendazole is 5 mg/kg/day. This is based on the teratogenic effect in the rat teratology study. The rat is considered the most sensitive species

and the teratology study the most sensitive study. Therefore, with a 1000 fold safety factor, the safe concentration for albendazole residues is:

Albendazole Acceptable Daily Intake (ADI) = 5 mg/kg/day (NOEL) / 1000 fold safety factor = 0.005 mg/kg/day

Safe Concentration in Muscle
= ADI x 60 kg(weight of average human) / 0.5 kg/day(daily consumption of meat)
= 0.005 mg/kg/day x 60 kg / 0.5 kg/day = 0.6 ppm

This is the safe concentration for albendazole residues in muscle derived from treated cattle. Safe concentration of albendazole residues in edible tissues other than muscle is as follows:

Tissue	Consumption Factor	Safe Concentration
Liver	2	1.2 ppm
Kidney	3	1.8 ppm
Fat	4	2.4 ppm

C. Total Residue and Metabolism Studies

The levels of total drug related residues of albendazole (ABZ) in the tissues of cattle treated with ^{14}C-albendazole were determined in four studies which varied by dose level, withdrawal schedule, and class of cattle treated. The studies are outlined below, and the animals in each received a single oral dose of the radiotracer by capsule.

Study No. I

Dose: 20 mg/kg (twice the recommended dose)
Total Number and class of cattle in study: 12 male and female ruminating calves
Withdrawal schedule: 1, 4, 6, 10, 20 and 30 days post dosing

Study No. II

Dose: 15 mg/kg (1.5 times the recommended dose)
Total Number and class of cattle in study: 12 male and female ruminating calves
Withdrawal schedule: 1, 4, 6, 12, 14 and 20 days post dosing

Study No. III

Dose: 27.5 mg/kg (2.75 times the recommended dose)
Total Number and class of cattle in study: 8 male and female ruminating calves
Withdrawal schedule: 2, 40 and 60 days post dosing

Study No. IV

Dose: 10 mg/kg

Number and class of cattle in study: 15 mature brood cows
Withdrawal schedule: 60, 90, 120, 150 and 180 days post dosing

Tissue samples of muscle, liver, kidney and fat from each of the animals were radioassayed for total drug related residues. The results from the four studies are shown collectively in the two tables that follow.

Total Radioactivity (ppm) in the Edible Tissues of Cattle Receiving the Indicated Dose of ^{14}C-Albendazole

Tissue	Dose	1 Days Post Dosing	2 Days Post Dosing	4 Days Post Dosing	6 Days Post Dosing	10 Days Post Dosing	12 Days Post Dosing	14 Days Post Dosing	20 Days Post Dosing
Muscle	20 mg/kg	7.9 ± 0.3		0.07 ± 0.05	0.06 ± 0.01	0.05 ± 0.006			0.03 ± 0.001
Muscle	15 mg/kg	4.8 ± 0.57		0.06 ± 0.11	0.04 ± 0.001			0.02 ± 0.006	0.02 ± 0
Liver	27.5 mg/kg		24.1 ± 4.8						
Liver	20 mg/kg	29.0 ± 3.5		8.20 ± 1.0	6.76 ± 1.6	3.57 ± 0.07			1.15 ± 0.17
Liver	15 mg/kg	22.5 ± 3.0		5.98 ± 0.06	4.33 ± 0.54		2.47 ± 0.21	1.84 ± 0.22	1.21 ± 0.23
Kidney	20 mg/kg	21.7 ± 7.9		4.40 ± 1.0	3.19 ± 0.61	1.93 ± 0.45			0.63 ± 0.14
Kidney	15 mg/kg	15.6 ± 2.5		2.15 ± 0.91	1.76 ± 0.18		0.85 ± 0.28	0.98 ± 0.24	0.41 ± 0.13
Fat	20 mg/kg	0.4 ± 0.5		0.04 ± 0.01	0.02 ± 0.001	0.01 ± 0.001			<0.01 ± 0.001
Fat	15 mg/kg	1.76 ± 0.04		0.21 ± 0.06	0.08 ± 0.01		0.07 ± 0.01	0.03 ± 0.004	0.04 ± 0.02

Total Radioactivity (ppb) in the Edible Tissues of Cattle Receving the Indicated Dose of ^{14}C-Albendazole

Tissue	Dose	30 Days Post Dosing	40 Days Post Dosing	60 Days Post Dosing	90 Days Post Dosing	120 Days Post Dosing	150 Days Post Dosing	180 Days Post Dosing
Muscle	10 mg/kg			10.4 ± 3.5	10.6 ± 4.6	8.3 ± 1.0	5.6 ± 2.1	6.5 ± 1.4
Muscle	20 mg/kg	20.0 ± 1.0						
Muscle	27.5 mg/kg			10 ± 10				
Liver	10 mg/kg			278.7 ± 46.8	105.8 ± 20.1	89.5 ± 39.2	45.0 ± 19.0	25.5 ± 7.1
Liver	20 mg/kg	420 ± 70						
Liver	27.5 mg/kg		260*	110 ± 70				
Kidney	10 mg/kg			62.3 ± 22.0	29.2 ± 9.3	27.5 ± 1.8	20.1 ± 8.6	18.9 ± 5.5
Kidney	20 mg/kg	250 ± 60						
Kidney	27.5 mg/kg			40 ± 30				
Fat	10 mg/kg			4.8 ± 2.6	4.0 ± 2.2	2.1 ± 0.6	1.6 ± 0.5	2.3 ± 0.97
Fat	20 mg/kg	<10 ± 1						
Fat	27.5 mg/kg			37 ± 4				

Liver and kidney from cattle in the residue studies described above were subjected to wet chemistry procedures to establish the profiles of ^{14}C-albendazole metabolites present in those samples. A number of extraction procedures were used with liver and kidney tissue which varied in the extraction solvent and the use of sample pretreatment with enzymes or acid hydrolysis. The techniques used to isolate and quantitate metabolites included thin layer chromatography, autoradiography, and reverse isotope dilution.

In general, the qualitative profiles of the major metabolites present in the liver and kidney were very similar regardless of the profiling procedure used. There were, however, significant variations in the amounts of the individual metabolites observed because metabolite stability and solubility parameters varied. The greatest single factor affecting the quantitative profile was the use of acid hydrolysis, which released metabolites, particularly the 2-aminosulfone metabolite, from the bound residue present in liver.

At one day withdrawal, 52% of the ^{14}C-albendazole residues present in cattle liver was freely extractable into ethylacetate. By four days of withdrawal, the percentage of freely extractable residues had declined to about 3% of the total

radioactivity in liver. These results established that freely extractable residues of albendazole were present in significant amounts only at short withdrawal times. By four days post dosing the majority of the residue (about 97%) was present as bound residue.

The use of more vigorous extraction procedures, particularly the use of acid hydrolysis as noted earlier, effected the release of increasing amounts of drug related residues from the bound residue. This effort resulted in the isolation and identification of parent albendazole and its sulfoxide, sulfone, and 2-albendazole major metabolites in liver tissue. Two minor metabolites, the 2-aminosulfoxide and the hydroxypropylsulfone, were also shown to be present but in small amounts and only at short withdrawal times. The table below presents the quantitation of the major metabolites as percentages of the extractable radioactivity present in liver tissue. The extractable radioactivity in the samples ranged between 17% and 66% of the total radioactivity present in the tissue depending upon the extraction procedure used and the length of the withdrawal time.

Percentages of the Major ^{14}C-Albendazole Metabolites in the Extractable Radioactivity Present in Cattle Liver

Days Post Dosing	ABZ	ABZ Sulfoxide	ABZ Sulfone	ABZ 2-Amino-Sulfone
1	27%	38%	12%	<1%
4	NQ*	NQ	12%	10%
6	-	10%	13%	28%
10	-	-	13%	35%
12	-	12%	12%	18%

NQ* = Present but not quantitated

Metabolite patterns of albendazole in kidney tissue were obtained using procedures similar to those used with liver. At 24 hours post dosing a pattern was shown to consist of unchanged albendazole and the same three major and two minor metabolites that were present in liver tissue. By ten days post dosing, the albendazole 2-aminosulfone was the only metabolite present.

Metabolic profiles of albendazole in the urine of rats and mice were also determined using similar extraction procedures. The following table presents the quantitation of the major metabolites as percentages of the extractable radioactivity present in urine. The extractable radioactivity ranged between 39% and 82% of the total radioactivity present in urine depending upon the extraction procedure used.

Percentages of the Major ^{14}C-Albendazole Metabolites in the Extractable Radioactivity Present in 0-24 Hour Urine of Rats and Mice

Species	ABZ	ABZ Sulfoxide	ABZ Sulfone	ABZ 2-Amino-Sulfone	ABZ Hydroxypropylsulfones Metabolite E	ABZ Hydropropylsulfones Metabolite G
Rat	2	5	27	15	14	24
Mouse	<1	1	29	4	22	30

A comparison was made of the metabolite patterns present in cattle liver and kidney with those present in the urine collected from the rats and mice. The comparison showed that parent albendazole and all other metabolites identified at any time period in cattle liver and kidney were also present in the urine of the laboratory species. Therefore, the test species were exposed to all of the metabolites shown to be present in the liver and kidney from cattle treated with albendazole.

D. Marker Residue, Target Tissue, and Rm (Tolerance) for Albendazole in Cattle

The data in the tables of total residue values shown on two of the previous pages established that liver contains the highest levels of total drug related residues of albendazole and that it is the tissue in cattle from which residues are the slowest to deplete to the safe concentration. These observations suggested liver as the likely choice of target tissue for albendazole in cattle.

The metabolism data, summarized in Section C., confirmed liver as the target tissue and led to the selection of the 2-aminosulfone metabolite as the marker substance. Those data demonstrated that the 2-aminosulfone metabolite was present in sufficiently high concentration and had the proper depletion characteristics in liver to serve as the marker substance in that tissue.

The Rm (tolerance) for albendazole was set from data obtained from the analysis of liver tissue from cattle in total residue study Nos. 2 and 4. The livers from the cattle in those studies were assayed for the 2-aminosulfone marker by the determinative assay of the regulatory method. The method involves a one hour hydrolysis of the liver samples with 6N HCl, as discussed in Section E. The hydrolysis step releases the marker substance from the non freely extractable (bound) residue as a consistent proportion of the total residue.

The livers in study No. IV were obtained at 60, 90, 120, 150 and 180 days post dosing from cattle which received a 10 mg/kg dose of ^{14}C-albendazole. When assayed by the determinative procedure, the livers contained the 2-aminosulfone marker at levels averaging 19.3% of the total residue present (range: 13.7% to 23.6%). The livers in study No. II were obtained at 4, 6, 12 and 14 days post dosing where the cattle received a 15 mg/kg dose of the radio-labelled drug. When these livers were assayed, the concentration of the 2-aminosulfone marker averaged 18.0% of the total residue (range: 17.0% to 20.3%).

These results demonstrated that, when measured by the determinative procedure, the 2-aminosulfone metabolite represents approximately 18% of the total residue present in liver tissue through the period of four to 180 days post dosing, regardless of the dose administered. Based on that relationship, a value of 0.2 ppm was assigned as the Rm (tolerance) for the albendazole marker in cattle liver. That value is the level of the 2-aminosulfone metabolite (the marker substance) expected to be present in liver (the target tissue) when the total residues of albendazole in that tissue have depleted to the safe concentration of 1.2 ppm (0.2 ppm ‰ 18% of 1.2 ppm).

E. Regulatory Methods for Residues

Albendazole Determinative Assay Procedure

The determinative assay for measuring residues in liver from cattle treated with albendazole is based on the measurement of the marker substance, the 2-aminosulfone metabolite, by high performance liquid chromatography (HPLC) with fluorescence detection.

Homogenized cattle liver (2.5 g) is fortified with the internal standard, hydrolyzed in 6N hydrochloric acid, adjusted to pH 8.0-9.5 with sodium carbonate and extracted with ethyl acetate. The albendazole marker and internal standard are back extracted into 1N hydrochloric acid and the ethyl acetate removed by aspiration. The aqueous phase is adjusted to pH 8.0-9.5 with sodium carbonate, and then extracted with toluene, which is removed by aspiration. The aqueous phase is applied to a SEP-PAK C_{18} cartridge where the compounds of interest are retained and subsequently eluted with ethyl acetate. The ethyl acetate eluate is concentrated to dryness. The residue is reconstituted in water/methanol, filtered, and the marker residue quantified using HPLC.

The quantitative sensitivity of the method is 25 ppb.

Albendazole Confirmatory Assay Procedure

The confirmatory procedure for albendazole may be performed on the same sample extract obtained for the determinative HPLC analysis described above. The dry residue from the water/methanol filtrate from that procedure is treated to form the t-butyl dimethylsilyl (t-BDMS) derivative which is then subjected to GC/MS analysis. The mass spectral analysis monitors for the presence of three ions that are characteristic of the t-BDMS derivative of the marker residue. The presence of albendazole residues in the sample of cattle liver is confirmed when the relative intensities of those three ions agree to within ± 10% of standard samples.

Validation

A method trial of the determinative and confirmatory procedures was satisfactorily completed by FDA and USDA laboratories. The validated regulatory methods for residues of albendazole are filed in the Food Additives Manual on display in FDA's Freedom of Information Public Room (Room 12A-30, 5600 Fishers Lane, Rockville, MD 20857).

F. Marker Residue Depletion Study and Calculation of a Withdrawal Time

Depletion of the marker residue following administration of albendazole in the suspension formulation was determined in a study utilizing 32 head of beef cattle. The animals each received a single oral dose of albendazole suspension at 10 mg/kg. The cattle were euthanized in groups of eight (four heifers and four steers per group) at 20, 24, 28 or 32 days post dosing.

The livers (target tissue) were collected at the time of slaughter and were assayed for the marker residue (the 2-aminosulfone metabolite) using the determinative procedure. The results are presented in the table below.

Residue Levels (ppb) of the Albendazole Marker Residue in the Livers of Cattle Following a 10 mg/kg Dose of the Suspension Formulation of Albendazole

	20 Days Post Dosing	**24 Days Post Dosing**	**28 Days Post Dosing**	**32 Days Post Dosing**
Number of Animals	8	8	8	8
Average ppb	131 ± 31	113 ± 20	77.7 ± 18	51.9 ± 10

A statistical analysis of the depletion data using the upper tolerance limit containing a 99 percentile of the population with 95% confidence limits yielded a withdrawal period of 24 days. A withdrawal time of 27 days is used for labeling purposes with the albendazole suspension in order to have a single common withdrawal time for the various oral dosage forms of albendazole being developed.

G. Safety to Handler

The drug was also evaluated for untoward effects which might result from physical contact with it:

Albendazole was not irritating when applied directly to abraded or non abraded rabbit skin (500 mg applied to each side). Similarly, no irritation was observed in either non irrigated (non washed) or irrigated eyes of any rabbit immediately, 24, 48 or 72 hours after instillation of 100 mg of albendazole.

A single oral dose of 3000 mg/kg of albendazole failed to produce death when administered to mice. This dose represents approximately 300 times the highest recommended therapeutic dose.

The studies demonstrated that the drug would have no ill effects on persons handling it if it is used according to label recommendations.

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of Section 512 of the Act and demonstrate that albendazole (Valbazen®) is safe and effective when administered as an oral suspension at a dosage level of 10 mg/kg body weight to cattle for the indications stated in the product labeling.

In the initial Threshold Assessment of albendazole the Agency assigned albendazole to Category D. This assessment was based upon literature reports that structurally similar benzimidazoles gave positive responses in mutagenicity assays. Additionally in 1981, the Agency concluded that because of the high score assigned to albendazole negative mutagenicity tests would not remove it from the requirements for carcinogenicity testing in two rodent species. Consequently, albendazole underwent chronic carcinogenicity testing in the mouse and rat.

The submitted data including negative carcinogenicity studies in two rodent species are adequate to satisfy the Agency's food safety requirements. The safe concentrations for total albendazole in uncooked edible beef tissues are: 0.6 ppm in muscle, 1.2 ppm in liver, 1.8 ppm in kidney and 2.4 ppm in fat. A regulatory tissue residue method has been developed for the determination of the marker compound, the 2-aminosulfone metabolite, with a tolerance of 0.2 ppm in cattle liver.

The Agency concludes that adequate directions for use have been written for the proposed over the counter use of this broad spectrum anthelmintic which is indicated for the removal and control of parasites commonly occurring in cattle.

VI. ATTACHMENTS

Box label
Case labels
Bottle labels

Copies of these labels may be obtained by writing to the:

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.