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Pharma Research
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REPORT

ON

A REPEATED-DOSE (30 DAYS) ORAL TOXICITY STUDY

OF OCTOPIROX IN BEAGLE DOGS

REPORT No. 400/76

September 1, 1976

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Index

	Page
Summary	2
Survey	3
Preliminary Remarks	4
Method	5
Results	11
Figures	Figures
Body weight development etc.	1 - 2
Individual Values	Tables
Hematological findings	3 - 18
Serum findings	19 - 26
Enzyme activities	27 - 34
Urinalyses	35 - 50
Electrocardiographic findings	51 - 58
Organ weights	59 - 62
Appendix	Appendix
Composition of feed	I
Composition of killing agent T 61-Hoechst	II
Report on experimental pathology	III

Report on a repeated-dose (30 days) oral toxicity study of Octopirox in Beagle dogs

Summary:

In a 30-day toxicity study the anti-dandruff-agent Octopirox (= H 72 6146 A) was administered in doses of 16, 40 or 100 mg per kg body weight, mixed with food, to groups of 2 male/2 female pure-bred Beagle dogs from our own breeding. A fourth group of 2 male/2 female Beagle dogs was not treated and served as control.

All dogs lived up to the scheduled end of the study.

The following results were obtained in this study:

the food consumption was normal in all dogs, the general state of health was good, and the body weight development of the treated dogs corresponded with that of the control animals. The other clinical investigations, including ECG, the laboratory findings and the post mortem examinations did not reveal any substance-induced pathological changes.

Survey:

Compound:	Octopirox (H 72 6146 A)
Category:	Anti-dandruff-agent
Species:	English Beagle dog
No. of animals per group:	2 ♂/2 ♀
Route:	Oral, mixed with food
Dosage:	0, 16, 40, 100 mg/kg body weight
Duration of study:	30 days
No. of treatments:	30
Beginning of study:	April 13 and 14, 1976
Last treatment:	May 12 and 13, 1976
Killing:	May 13 and 14, 1976

Persons responsible:

Study director:	Dr. Brunk
Hematology:	Dr. Brunk/Dr. Schultes
Clinical chemistry:	Dr. Wicha/Dr. Hajdú
Histology:	Dr. Deutschländer/Prof. Kief
Industrial toxicology:	Dr. Weigand
Head of department:	Prof. Kramer

Preliminary Remarks:

Compound:	Octopirox (H 72 6146 A) Batch E002 anti-dandruff agent
Experimental animals:	Pure-bred English Beagle dogs from our own breeding, breed: HOE:BEAK. Age of male and female dogs at the beginning of the study: 8 months. Mean body weight of male dogs at the study: 14.4 kg (12.8 - 15.7 kg) Mean body weight of female dogs at the beginning of the study: 13.1 kg (11.3 - 14.3 kg).
Groups and dosages:	The doses administered in this study had been chosen after exploratory studies. Group I: 2 males, 2 females control, untreated Group II: 2 males, 2 females 16 mg/kg Group III: 2 males, 2 females 40 mg/kg Group IV: 2 males, 2 females 100 mg/kg
Duration of study and route of administration:	Octopirox was given daily (7 times a week) for 30 days, mixed with the food, at the midday feeding. The control animals were not treated.

I. METHOD:

1. Maintenance and Feeding

The dogs were kept in individual boxes in climatized (18°C) kennels with open-air runs for the groups. They received a standard diet (Latz FF, mfr.: Latz Purina GmbH, for composition see Appendix I) in daily portions of 850 g (males) or 650 g (females). In addition, each dog received an individual feeding of 150 g minced meat per day.

Water was provided ad libitum in automatic watering troughs.

Dogs which had not consumed all of their food two hours after feeding were recorded. The amount not consumed until the following morning was weighed.

2. Clinical Investigations:

2.1 Assessment of general state of health:

Daily.

2.2 Determination of body weight:

Once a week.

2.3 Behaviour:

Daily observation.

2.4 Reflex response:

The flexor, patellar, anal, cutaneous, corneal, pupillary, blinking, placing (visual and tactile) and righting reflexes were examined prior to the first treatment and at the end of the study.

2.5 Eye examinations:

The eyes were examined by means of an Okulus hand slit lamp and a Kowa fundus camera RC2 (direct ophthalmoscopy) prior to the first treatment and at the end of the study.

In this assessment the examination of cornea, anterior chamber, iris/pupil, lens, vitreous body and fundus of the eye was included.

2.6 Examination of hearing:

Simple noise test for assessment of hearing, performed prior to the first treatment and the end of the study.

2.7 Examination of teeth:

Prior to the first treatment and at the end of the study.

2.8 Examination of visible mucous membranes:

Prior to the first treatment and at the end of the study.

3. Laboratory tests:

For all tests, the blood samples were withdrawn from the vena cephalica antebrachii or from the vena saphena parva of the animals which had been fasted for 18 - 20 hours. For the determination of the coagulation time a marginal ear vein was punctured. With the exception of the last-mentioned parameter, all other hematological examinations were performed with EDTA blood.

3.1 Hematological examinations:

The blood samples were withdrawn prior to the beginning of the study (preliminary values) and at the end of the study (final values) and were then examined.

In these examinations the following parameters were determined:

erythrocytes leukocytes	Coulter Counter,model ZF	mil./mm^3 thous./mm^3
hemoglobin content	Counter(hemoglobinometer)	g/100 ml blood
coagulation time	Capillary method acc. to SCHALM (at 18°C)	min.
hematocrit	acc. to WINTROBE	% of whole blood
BSR	acc. to WINTROBE, uncorrected 1-hour value	mm/hour
reticulocyte count	Brilliant cresyl blue staining acc.to BEGEMANN	% of erythrocytes
thrombocyte count	Coulter Counter, model ZF	100,000/mm^3 blood
Heinz bodies	Nile blue chloride staining	
different blood count	Panoptic staining acc. to PAPPENHEIM	

3.2 Clinical chemistry examination:

3.2.1 Serum analyses:

At the times of examination listed in 3.1, the following parameters were determined in all dogs:

sodium	mmol/l	by means of Auto-analyzer Technicon SMA 6/60
potassium	mmol/l	
inorg.phosphorus	mmol/l	
uric acid	umol/l	
bilirubin	umol/l	
creatinine	umol/l	
urea-N	mmol/l	BUN Analyzer,Beckman
calcium	mmol/l	Ca-Analyzer 940, Corning
chlorides	mmol/l	Chloride Titrator, Aminco

3.2.2 Serum glucose determination:

The serum glucose level was assessed by means of the Glucose Analyzer Beckman (Values in mmol/l).

3.2.3 Enzyme activities:

By means of a Bichromat Analyzer ABA-100, ABBOTT, the follwing parameters were determined at the times of examination listed in 3.1:

SGOT	acc. to KARMEN	U/l serum
SGPT	acc. to KARMEN	U/l serum
alk.phosphatase	acc. to BESSEY-LOWRY	U/l serum

3.3 Urinalyses:

At the times of examination given in 3.1, the follwing parameters were determined in the pooled urine of each animal:

specific weight	areometric method	
pH value	special indicator paper from Merck, Darmstadt	
appearance and colour		
sediment	new methylene blue staining	
protein	Combi-Uristix^{R}	
glucose	Combi-Uristix^{R}	Ames Miles GmbH Frankfurt
bilirubin	Ictotest	
hemoglobin	Combi-Uristix^{R}	

4. Physiological Examinations:

4.1 Elextrocardiographic examinations:

Prior to the beginning of the study and at the end of the study an electrocardiogram of the standing dog in lead II was recorded by means of a Hellige Simpliscriptor T 20, feed: 50 mm/sec. Pulse rate, PQ-, QRS- and QT-time and pattern of activity were evaluated.

5. Post Mortem Examinations:

The dogs were killed with an intravenous injection of 0.2 ml killing agent T 61-Hoechst (for composition see Appendix II) and were exsanguinated by opening of the carotid artery.

All animals (groups I - IV) were killed on the day after the last treatment.

5.1 Dissection:

Subsequently to the killing, the animals were dissected and examined macroscopically.

5.2 Organ weights:

The following organs were weighed:

heart	spleen	ovaries/testis
lungs	brain	adrenals
liver	pituitary	thyroid
kidneys	pancreas	

5.3 Histological examinations:

Sections of the following organs or parts of organs were fixed in formalin and/or Carnoy's solution and were submitted to histological examination:

heart	pancreas	testis/ovaries
lungs	thymus	epididymis/uterus
liver	pituitary	prostate
kidneys	cerebrum	stomach
spleen	cerebellum	jejunum
adrenals	eye with optic nerve	colon
thyroid	urinary bladder	bone marrow (fixed in Schaffer's solution)

II. RESULTS:

All dogs lived up to the scheduled end of the study.

1. Food Consumption:

The amount of food offered was always consumed rapidly and completely.

2. Clinical Findings:

2.1 General state of health:

The general state of health of the dogs was always good. Experiment-related disorders were not observed.

2.2 Body weight development: (Table and Figures 1 and 2)

A slight weight gain was observed in all dogs. The course of the body weight curves of the treated dogs of all dosage groups corresponded to that of the control animals.

The nutritional state of all dogs was good.

Table: Body weight in kg

Dose	Dog No.		Beginning of study	End of study	Difference
Control	558	♂	14.0	14.8	+ 0.8
	559	♂	14.7	15.4	+ 0.7
	566	♀	13.1	13.8	+ 0.7
	567	♀	14.1	14.8	+ 0.7
16 mg/kg	560	♂	12.8	13.9	+ 1.1
	561	♂	15.1	15.9	+ 0.8
	568	♀	13.5	14.5	+ 1.0
	569	♀	11.3	12.1	+ 0.8
40 mg/kg	562	♂	14.8	15.5	+ 0.7
	563	♂	14.3	15.3	+ 1.0
	570	♀	12.0	12.7	+ 0.7
	571	♀	12.4	13.3	+ 0.9
100 mg/kg	564	♂	15.7	16.2	+ 0.5
	565	♂	14.0	14.6	+ 0.6
	572	♀	13.9	14.5	+ 0.6
	573	♀	14.3	15.2	+ 0.9

2.3 Behaviour:
N.A.D.

2.4 Reflex response:
N.A.D.

2.5 Eye findings:
N.A.D.

2.6 Hearing:
N.A.D.

2.7 Teeth:
N.A.D.

2.8 Visible mucous membranes:
N.A.D.

3. Laboratory Findings:

3.1 Hematological findings: (Individual Values 3-18)
The hematological findings revealed no deviation from the physiological norm.

3.2. Clinical chemistry findings:

3.2.1 Serum findings: (Individual Values 19-26)
No pathological values were measured.

3.2.2 Serum glucose level: (Individual Values 19-26)
Only physiological concentrations were measured.

3.2.3 Enzyme activities: (Individual Values 27-34)
All values measured were within the physiological norm.

3.3. Urinalyses: (Individual Values 35-50)
N. A. D.

4. Physiological Examinations:

4.1 Electrocardiographic findings: (Individual Values 51 - 58)
The evaluation of the electrocardiograms revealed no substance-related changes in any of the dogs.

5. Post Mortem Findings:

5.1 Macroscopic organ findings:
Substance-induced organ changes were not observed.

5.2 Organ weights: (Individual Values 59 - 62)
All organ weights were normal.

5.3 Microscopic organ findings: (Report by Prof.Kief/ Dr. Deutschländer, Appendix III)
The histological examination revealed that in this study Octopirox did not cause any morphologically demonstrable organ changes.

September 1, 1976

Pharmaceutical Research/Toxicology
of
HOECHST AG

signed:

Dr. Brunk
Clinical toxicology

Dr. Weigand
Industrial toxicology

Prof. Kramer
Head of department

Figure 1: Body weigl evelopment after treatment \ : Octopirox
30-day oral toxicity study; species: English Beagle dog; 2 males per group

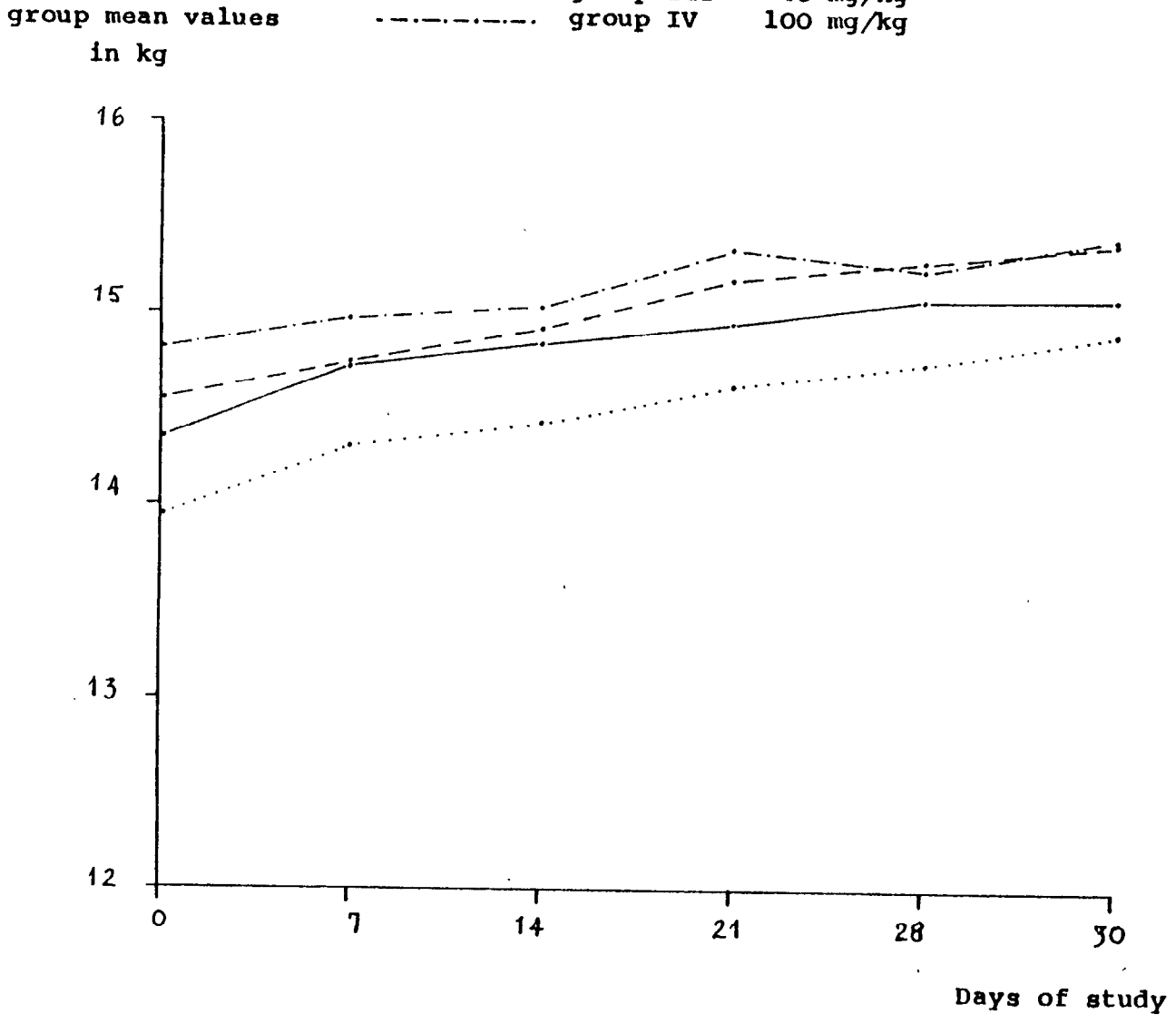
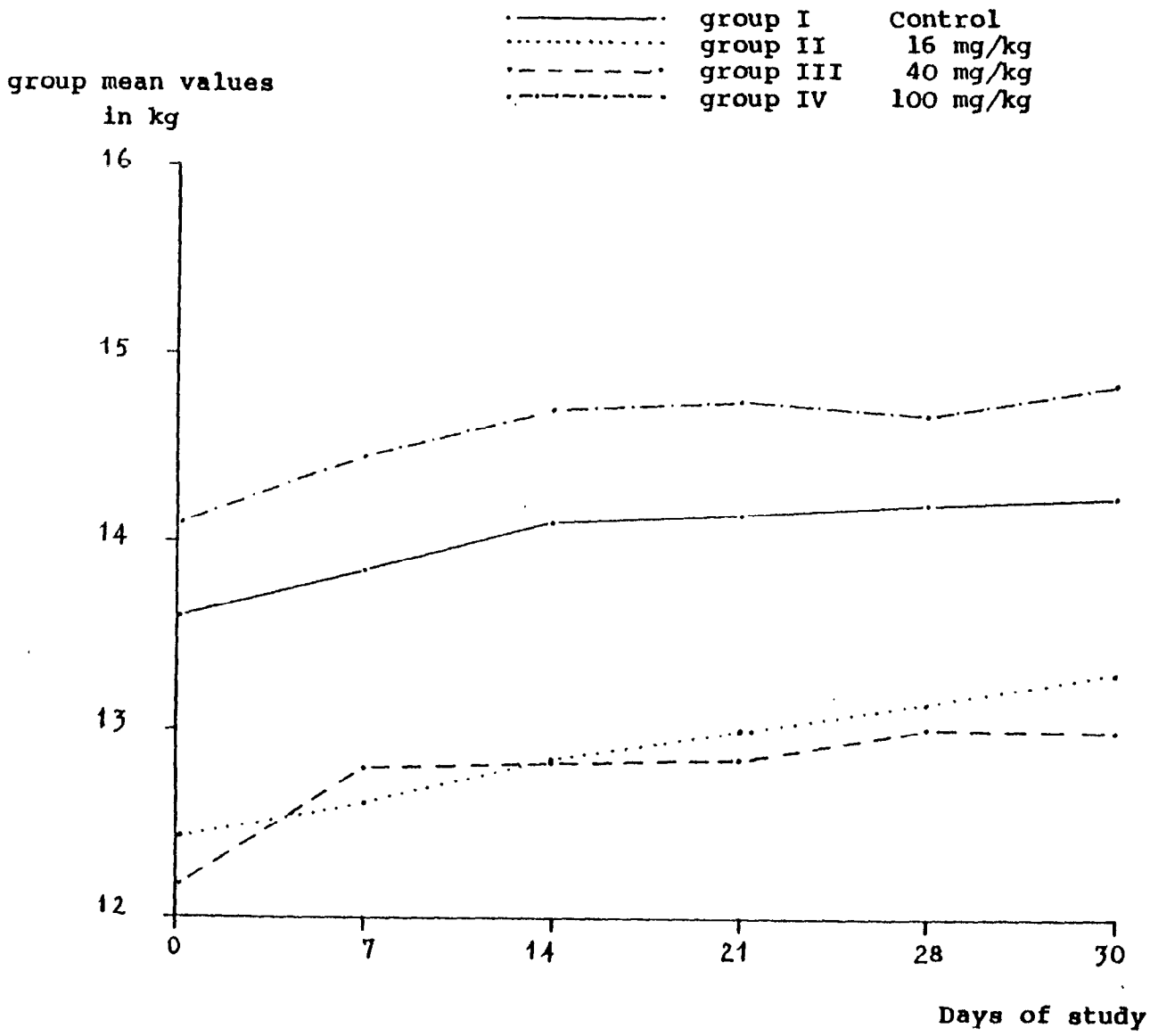


Figure 2: Body weight development after treatment with Octopirox
30-day oral toxicity study; species: English Beagle dog; 2 females per group



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Hematological Findings

Compound: Octopirox

Dose: Control

Administration: untreated

Species: Beagle, English

Week: Preliminary value

Animal No.	Sex	RBC 10^6	HB g%	PCV %	Retic. ‰	Heinz B.	Sed. Rate mm/h	Platelets 10^3	Coag. T. min.
558	M	7.12	17.0	50	4	Ø	0	255	1
559	M	6.19	14.6	49	2	Ø	0	255	1
566	F	5.92	16.4	48	3	Ø	0	308	1
567	F	6.37	16.3	47	3	Ø	0	271	1

00004

Hematological Findings

Compound: Octopirox

Dose: Control

Administration: untreated

Species: Beagle, English

Week: Preliminary value

Animal No.	Sex	WBC	Band	Neutro Segm.	Eos	Baso	Lympho	Mono
		10^3	%	%	%	%	%	%
.	.	.	.	.	.	.	.	.
558	M	8.9	-	54	5	-	41	-
559	M	6.2	-	51	2	-	47	-
566	F	9.7	1	52	1	-	46	-
567	F	8.2	1	62	1	-	36	-

00005

Hematological Findings

Compound: Octopirox

Dose: 16 mg/kg

Administration: orally in feed

Species: Beagle, English

Week: Preliminary value

Animal No.	Sex	RBC	HB	PCV	Retic.	Heinz B.	Sed. Rate	Platelets	Coag. T.
		10^6	g%	%	‰		mm/h	10^3	min.
560	M	5.75	15.1	48	1	Ø	0	324	1
561	M	6.56	16.5	49	2	Ø	0	271	1
568	F	6.29	16.7	50	1	Ø	0	250	1
569	F	6.23	14.7	47	0	Ø	0	313	1

00006

Hematological Findings

Compound: Octopirox

Dose: 16 mg/kg

Administration: orally in food

Species: Beagle, English

Week: Preliminary value

Animal No.	Sex	WBC	Band	Neutro Segm.	Eos	Baso	Lympho	Mono
		10^3	%	%	%	%	%	%
.	.	.	.	.	.	.	.	.
560	M	7.2	-	54	7	-	39	-
561	M	9.7	1	47	11	-	41	-
568	F	8.6	-	70	7	-	23	-
569	F	6.9	-	65	2	-	33	-

Hematological Findings

Compound: Octopirox

Dose: 40 mg/kg

Administration: orally in food

Species: Beagle, English

Week: Preliminary value

Animal No.	Sex	RBC	HB	PCV	Retic.	Heinz B.	Sed. Rate	Platelets	Coag. T.
		10^6	g%	%	‰		mm/h	10^3	min.
.	.	.	.	.	.	.	.	.	.
562	M	6.29	16.1	46	2	Ø	0	245	2
563	M	6.63	16.3	50	3	Ø	0	302	1
570	F	6.35	15.0	47	1	Ø	0	308	1
571	F	5.65	14.4	47	2	Ø	0	308	2

00008

Hematological Findings

Compound: Octopirox

Dose: 40 mg/kg

Administration: orally in food

Species: Beagle, English

Week: Preliminary value

Animal No.	Sex	WBC	Band	Neutro Segm.	Eos	Baso	Lympho	Mono
		10^3	%	%	%	%	%	%
.	.	.	.	.	.	.	.	.
562	M	7.8	2	50	6	1	40	1
563	M	7.9	1	53	5	-	41	-
570	F	8.5	1	52	1	-	45	1
571	F	6.8	1	57	1	-	41	-

00009

Hematological Findings

Compound: Octopirox

Dose: 100 mg/kg

Administration: orally in food

Species: Beagle, English

Week: Preliminary value

Animal No.	Sex	RBC	HB	PCV	Retic.	Heinz B.	Sed. Rate	Platelets	Coag. T.
		10^6	g%	%	‰		mm/h	10^3	min.
.	.	.	.	.	.	.	.	.	.
564	M	6.97	16.5	49	1	Ø	0	261	1
565	M	6.67	16.2	48	2	Ø	0	266	2
572	F	6.41	17.2	51	0	Ø	0	255	1
573	F	6.12	16.0	48	0	Ø	0	276	1

00010

Hematological Findings

Compound: Octopirox

Dose: 100 mg/kg

Administration: orally in food

Species: Beagle, English

Week: Preliminary value

Animal No.	Sex	WBC	Band	Neutro Segm.	Eos	Baso	Lympho	Mono
		10^3	%	%	%	%	%	%
564	M	8.3	-	68	5	-	27	-
565	M	9.1	-	70	1	-	29	-
572	F	6.1	-	49	4	-	46	1
573	F	7.3	-	55	3	-	41	1

Hematological Findings

Compound: Octopirox

Dose: Control

Administration: untreated

Species: Beagle, English

Week: Final value

Animal No.	Sex	RBC	HB	PCV	Retic.	Heinz B.	Sed. Rate	Platelets	Coag. T.
		10^6	g%	%	‰		mm/h	10^3	min.
.	.	.	.	.	.	.	.	.	.
558	M	6.93	17.1	51	2	Ø	0	224	2
559	M	6.51	15.6	48	2	Ø	0	235	2
566	F	5.38	14.7	49	2	Ø	0	245	2
567	F	6.32	16.5	49	2	Ø	0	203	2

Hematological Findings

Compound: Octopirox

Dose: Control

Administration: untreated

Species: Beagle, English

Week: Final value

Animal No.	Sex	WBC	Band	Neutro Segm.	Eos	Baso	Lympho	Mono
		10^3	%	%	%	%	%	%
558	M	8.5	-	69	1	-	30	-
559	M	5.8	-	56	9	-	35	-
566	F	7.8	-	59	1	-	40	-
567	F	7.9	-	64	2	-	34	-

Hematological Findings

Compound: Octopirox

Dose: 16 mg/kg

Administration: orally in food

Species: Beagle, English

Week: Final value

Animal No.	Sex	RBC	HB	PCV	Retic.	Heinz B.	Sed. Rate	Platelets	Coag. T.
		10^6	g%	%	‰		mm/h	10^3	min.
560	M	6.62	16.1	51	0	Ø	0	245	2
561	M	6.10	15.3	48	1	Ø	0	229	1
568	F	6.03	17.0	49	1	Ø	0	224	1
569	F	5.41	15.3	49	0	Ø	0	255	2

Hematological Findings

Compound: Octopirox

Dose: 16 mg/kg

Administration: orally in food

Species: Beagle, English

Week: Final value

Animal No.	Sex	WBC	Band	Neutro Segm.	Eos	Baso	Lympho	Mono
		10^3	%	%	%	%	%	%
560	M	7.7	-	56	5	-	39	-
561	M	7.8	-	53	4	-	43	-
568	F	7.3	-	52	6	-	42	-
569	F	5.8	-	55	1	-	44	-

00015

Hematological Findings

Compound: Octopirox

Dose: 40 mg/kg

Administration: orally in food

Species: Beagle, English

Week: Final value

Animal No.	Sex	RBC 10^6	HB g%	PCV %	Retic. ‰	Heinz B.	Sed. Rate mm/h	Platelets 10^3	Coag. T. min.
562	M	6.01	15.1	45	1	Ø	0	203	1
563	M	6.06	15.2	45	1	Ø	0	235	2
570	F	6.57	16.3	48	0	Ø	0	271	2
571	F	5.70	15.4	47	3	Ø	0	266	2

00016

Hematological Findings

Compound: Octopirox

Dose: 40 mg/kg

Administration: orally in food

Species: Beagle, English

Week: Final value

Animal No.	Sex	WBC	Band	Neutro Segm.	Eos	Baso	Lympho	Mono
		10^3	%	%	%	%	%	%
.	.	.	.	.	.	.	.	.
562	M	9.0	-	71	-	-	29	-
563	M	8.7	-	54	3	1	42	-
570	F	7.7	-	59	-	-	41	-
571	F	7.4	-	58	1	-	41	-

09017

Hematological Findings

Compound: Octopirox

Dose: 100 mg/kg

Administration: orally in food

Species: Beagle, English

Week: Final value

Animal No.	Sex	RBC	HB	PCV	Retic.	Heinz B.	Sed. Rate	Platelets	Coag. T.
		10^6	g%	%	‰		mm/h	10^3	min.
.	.	.	.	.	.	.	.	.	.
564	M	6.23	15.3	48	1	Ø	0	250	1
565	M	6.03	15.7	49	2	Ø	0	224	1
572	F	6.31	16.3	49	1	Ø	0	214	1
573	F	6.43	16.8	50	2	Ø	0	229	2

00018

Hematological Findings

Compound: Octopirox

Dose: 100 mg/kg

Administration: orally in food

Species: Beagle, English

Week: Final value

Animal No.	Sex	WBC	Band	Neutro Segm.	Eos	Baso	Lympho	Mono
		10^3	%	%	%	%	%	%
.	.	.	.	.	.	.	.	.
564	M	6.6	-	68	7	-	25	-
565	M	5.0	-	54	2	1	43	-
572	F	5.4	-	52	3	-	45	-
573	F	6.5	-	59	3	-	38	-

00919

Clinical Chemistry

Compound: Octopirox

Dose: Control

Administration: untreated

Species: Beagle, English

Week: Preliminary value

Animal No.	Sex	Sodium mM/l	Potassium mM/l	Inorg. Phosphorus mM/l	Uric Acid uM/l	Bilirubin (total) uM/l	Creatinine uM/l	Calcium mM/l	Chloride mM/l	BUN mM/l	Glucose mM/l
558	M	150	4.6	1.60	40	5.0	73	2.6	107	4.1	4.6
559	M	149	4.8	1.65	30	4.5	82	2.6	109	5.1	4.5
566	F	151	4.9	1.52	42	4.0	74	2.7	107	3.2	5.0
567	F	148	4.8	1.48	36	5.5	82	2.6	107	4.0	4.9

00020

Clinical Chemistry

Compound: Octopirox

Dose: 16 mg/kg

Administration: orally in food

Species: Beagle, English

Week: Preliminary value

Animal No.	Sex	Sodium mM/l	Potassium mM/l	Inorg. Phosphorus mM/l	Uric Acid uM/l	Bilirubin (total) uM/l	Creatinine uM/l	Calcium mM/l	Chloride mM/l	BUN mM/l	Glucose mM/l
560	M	150	5.0	1.58	28	5.0	70	2.5	97	4.3	5.1
561	M	150	4.9	1.60	28	4.5	73	2.7	90	3.2	4.8
568	F	149	4.5	1.42	34	6.0	73	2.5	108	4.1	5.5
569	F	149	5.5	1.54	34	4.0	86	2.7	107	5.0	4.9

Clinical Chemistry

Compound: Octopirox

Dose: 40 mg/kg

Administration: orally in food

Species: Beagle, English

Week: Preliminary value

Animal No.	Sex	Sodium mM/l	Potassium mM/l	Inorg. Phosphorus mM/l	Uric Acid uM/l	Bilirubin (total) uM/l	Creatinine uM/l	Calcium mM/l	Chloride mM/l	BUN mM/l	Glucose mM/l
562	M	151	4.8	1.65	32	5.0	72	2.5	108	3.5	4.8
563	M	152	5.0	1.70	34	4.0	75	2.6	107	3.6	4.4
570	F	152	5.8	1.62	40	4.5	80	2.5	110	3.9	5.3
571	F	151	4.8	1.72	40	4.5	80	2.6	108	4.6	5.2

0002

Clinical Chemistry

Compound: Octopirox

Dose: 100 mg/kg

Administration: orally in food

Species: Beagle, English

Week: Preliminary value

Animal No.	Sex	Sodium mM/l	Potassium mM/l	Inorg. Phosphorus mM/l	Uric Acid uM/l	Bilirubin (total) uM/l	Creatinine uM/l	Calcium mM/l	Chloride mM/l	BUN mM/l	Glucose mM/l
564	M	150	4.7	1.62	40	5.0	82	2.6	111	3.7	5.2
565	M	151	4.7	1.54	40	4.5	80	2.5	110	5.2	4.6
572	F	151	5.0	1.54	34	5.0	82	2.6	110	5.3	5.3
573	F	151	4.7	1.60	36	4.0	76	2.6	101	4.8	5.5

Clinical Chemistry

Compound: Octopirox

Dose: Control

Administration: untreated

Species: Beagle, English

Week: Final value

Animal No.	Sex	Sodium mM/l	Potassium mM/l	Inorg. Phosphorus mM/l	Uric Acid uM/l	Bilirubin (total) uM/l	Creatinine uM/l	Calcium mM/l	Chloride mM/l	BUN mM/l	Glucose mM/l
558	M	153	4.3	1.66	40	5.0	90	2.6	102	8.5	6.0
559	M	152	4.8	1.72	36	5.0	85	2.6	106	6.3	5.7
566	F	151	4.5	1.62	38	5.0	70	2.5	102	4.9	6.0
567	F	152	4.7	1.73	32	6.0	82	2.6	98	5.4	6.2

00024

Clinical Chemistry

Compound: Octopirox

Dose: 16 mg/kg

Administration: orally in food

Species: Beagle, English

Week: Final value

Animal No.	Sex	Sodium mM/l	Potassium mM/l	Inorg. Phosphorus mM/l	Uric Acid uM/l	Bilirubin (total) uM/l	Creatinine uM/l	Calcium mM/l	Chloride mM/l	BUN mM/l	Glucose mM/l
560	M	153	4.9	1.68	34	5.0	68	2.7	102	5.5	6.7
561	M	152	4.7	1.64	36	4.0	84	2.7	101	5.0	5.7
568	F	153	4.6	1.55	32	4.5	84	2.6	101	5.6	5.9
569	F	152	4.7	1.52	34	5.5	90	2.6	101	6.7	5.9

Clinical Chemistry

Compound: Octopirox

Dose: 40 mg/kg

Administration: orally in food

Species: Beagle, English

Week: Final value

Animal No.	Sex	Sodium mM/l	Potassium mM/l	Inorg. Phosphorus mM/l	Uric Acid uM/l	Bilirubin (total) uM/l	Creatinine uM/l	Calcium mM/l	Chloride mM/l	BUN mM/l	Glucose mM/l
.	.	.	.	.	.	.	.	.	.	.	.
562	M	151	4.5	1.48	38	5.0	82	2.4	100	4.9	5.9
563	M	151	4.7	1.52	36	5.0	93	2.6	98	6.6	6.0
570	F	153	4.6	1.48	40	4.5	8 5	2.6	105	5.9	6.1
571	F	154	4.6	1.80	40	5.0	135	2.6	100	10.9	6.4

00026

Clinical Chemistry

Compound: Octopirox

Dose: 100 mg/kg

Administration: orally in food

Species: Beagle, English

Week: Final value

Animal No.	Sex	Sodium mM/l	Potassium mM/l	Inorg. Phosphorus mM/l	Uric Acid uM/l	Bilirubin (total) uM/l	Creatinine uM/l	Calcium mM/l	Chloride mM/l	BUN mM/l	Glucose mM/l
564	M	147	4.5	1.75	36	4.5	88	2.5	103	6.1	6.2
565	M	149	4.7	1.60	36	5.0	92	2.5	103	5.6	5.8
572	F	151	4.7	1.62	34	5.5	90	2.6	107	5.9	6.2
573	F	153	4.4	1.83	34	5.0	93	2.6	99	7.0	6.1

Clinical Chemistry

Compound: Octopirox

Dose: Control

Administration: untreated

Species: Beagle, English

Week: Preliminary value

Animal No.	Sex	GOT U/l	GPT U/l	Alk. Phos. U/l	GLDH U/l
558	M	11	28	148	
559	M	12	24	166	
566	F	10	25	168	
567	F	7	25	145	

00028

Clinical Chemistry

Compound: Octopirox

Dose: 16 mg/kg

Administration: orally in food

Species: Beagle, English

Week: Preliminary value

Animal No.	Sex	GOT U/l	GPT U/l	Alk. Phos. U/l	GLDH U/l
560	M	13	29	166	
561	M	8	21	187	
568	F	6	23	197	
569	F	10	16	123	

00029

Clinical Chemistry

Compound: Octopirox

Dose: 40 mg/kg

Administration: orally in food

Species: Beagle, English

Week: Preliminary value

Animal No.	Sex	GOT U/l	GPT U/l	Alk. Phos. U/l	GLDH U/l
562	M	11	33	179	
563	M	13	21	178	
570	F	10	20	136	
571	F	10	17	130	

Clinical Chemistry

Compound: Octopirox

Dose: 100 mg/kg

Administration: orally in food

Species: Beagle, English

Week: Preliminary value

Animal No.	Sex	GOT U/l	GPT U/l	Alk. Phos. U/l	GLDH U/l
564	M	11	34	114	
565	M	11	27	127	
572	F	8	45	144	
573	F	8	34	144	

Clinical Chemistry

Compound: Octopirox

Dose: Control

Administration: untreated

Species: Beagle, English

Week: Final value

Animal No.	Sex	GOT U/l	GPT U/l	Alk. Phos. U/l	GLDH U/l
558	M	8	22	79	
559	M	9	30	74	
566	F	7	21	95	
567	F	7	20	73	

00032

Clinical Chemistry

Compound: Octopirox

Dose: 16 mg/kg

Administration: orally in food

Species: Beagle, English

Week: Final value

Animal No.	Sex	GOT U/l	GPT U/l	Alk. Phos. U/l	GLDH U/l
560	M	11	22	104	
561	M	9	17	100	
568	F	10	19	129	
569	F	11	12	69	

00033

Clinical Chemistry

Compound: Octopirox

Dose: 40 mg/kg

Administration: orally in food

Species: Beagle, English

Week: Final value

Animal No.	Sex	GOT U/l	GPT U/l	Alk. Phos. U/l	GLDH U/l
562	M	9	20	116	
563	M	7	13	100	
570	F	10	13	85	
571	F	7	16	76	

00034

Clinical Chemistry

Compound: Octopirox

Dose: 100 mg/kg

Administration: orally in food

Species: Beagle, English

Week: Final value

Animal No.	Sex	GOT U/l	GPT U/l	Alk. Phos. U/l	GLDH U/l
564	M	8	19	73	
565	M	10	19	77	
572	F	9	21	112	
573	F	9	34	114	

Urinalysis

Compound: Octopirox

Dose: Control

Administration: untreated

Species: Beagle, engl.

Week: Preliminary value

Animal No.	Sex	Appearance	Color	Spec. Grav.	pH	Sediment
558	M	slightly turbid	yellow	1.055	6.2	20,30,50,70,72,90
559	M	clear	yellow	1.054	6.2	20,30,50,70,72,90
566	F	slightly turbid	yellow	1.046	6.4	10,30,70,72,90
567	F	slightly turbid	yellow	1.053	6.2	20,30,70,72,90

00036

Urinalysis

Substance: Octopirox

Dose: Control

Route: untreated

Species: Beagel, engl.

Time: Preliminary value

Animal No.	Sex	Protein	Glucose	Hemoglobin	Bilirubin	Ketone Bodies
558	M	Ø	Ø	Ø	Ø	-
559	M	Ø	Ø	Ø	Ø	-
566	F	Ø	Ø	Ø	Ø	-
567	F	Ø	Ø	Ø	Ø	-

Urinalysis

Compound: Octopirox

Dose: 16 mg/kg

Administration: orally in food

Species: Beagle, engl.

Week: Preliminary value

Animal No.	Sex	Appearance	Color	Spec. Grav.	pH	Sediment
560	M	clear	bright yellow	1.031	6.2	10,20,30,50,70,72,90
561	M	slightly turbid	yellow	1.048	6.4	10,20,30,50,70,72,73,90
568	F	clear	yellow	1.039	6.4	10,20,30,36,70,72,90
569	F	slightly turbid	yellow	1.033	6.2	20,30,70,72,90

00938

Urinalysis

Substance: Octopirox

Dose: 16 mg/kg

Route: orally in food

Species: Beagle, engl.

Time: Preliminary value

Animal No.	Sex	Protein	Glucose	Hemoglobin	Bilirubin	Ketone Bodies
560	M	Ø	Ø	Ø	Ø	-
561	M	Ø	Ø	Ø	Ø	-
568	F	Ø	Ø	Ø	Ø	-
569	F	Ø	Ø	Ø	Ø	-

00039

Urinalysis

Compound: Octopirox

Dose: 40 mg/kg

Administration: orally in food

Species: Beagle, engl.

Week: Preliminary value

Animal No.	Sex	Appearance	Color	Spec. Grav.	pH	Sediment
562	M	clear	yellow	1.044	6.4	10,20,30,36,50,70,72,73,90
563	M	clear	yellow	1.047	6.4	10,20,30,50,70,72,90
570	F	clear	yellow	1.053	6.2	10,20,30,70,72,90
571	F	clear	yellow	1.046	6.2	10,20,30,36,70,72,90

00040

Urinalysis

Substance: Octopirox

Dose: 40 mg/kg

Route: orally in food

Species: Beagle, engl.

Time: Preliminary value

Animal No.	Sex	Protein	Glucose	Hemoglobin	Bilirubin	Ketone Bodies
562	M	Ø	Ø	Ø	Ø	-
563	M	Ø	Ø	Ø	Ø	-
570	F	Ø	Ø	Ø	Ø	-
571	F	Ø	Ø	Ø	Ø	-

Urinalysis

Compound: Octopirox

Dose: 100 mg/kg

Administration: orally in food

Species: Beagle, engl.

Week: Preliminary value

Animal No.	Sex	Appearance	Color	Spec. Grav.	pH	Sediment
564	M	slightly turbid	yellow	1.051	6.4	10,20,30,50,70,72,73,90
565	M	clear	yellow	1.056	6.4	20,30,50,70,72,90
572	F	slightly turbid	yellow	1.055	6.2	20,30,70,72,90
573	F	slightly turbid	yellow	1.050	6.4	20,70,72,90

00042

Urinalysis

Substance: Octopirox

Dose: 100 mg/kg

Route: orally in food

Species: Beagle, engl.

Time: Preliminary value

Animal No.	Sex	Protein	Glucose	Hemoglobin	Bilirubin	Ketone Bodies
564	M	Ø	Ø	Ø	Ø	-
565	M	Ø	Ø	Ø	Ø	-
572	F	Ø	Ø	Ø	Ø	-
573	F	Ø	Ø	Ø	Ø	-

00043

Urinalysis

Compound: Octopirox

Dose: Control

Administration: untreated

Species: Beagle, engl.

Week: Final value

Animal No.	Sex	Appearance	Color	Spec. Grav.	pH	Sediment
558	M	clear	yellow	1.048	6.7	20,30,50,70,72,73,90
559	M	slightly turbid	yellow	1.041	6.6	20,30,50,70,72,90
566	F	clear	yellow	1.042	6.6	10,30,70,72,90
567	F	clear	yellow	1.042	6.6	20,70,72,73,90

00044

Urinalysis

Substance: Octopirox

Dose: Control

Route: untreated

Species: Beagle, engl.

Time: Final value

Animal No.	Sex	Protein	Glucose	Hemoglobin	Bilirubin	Ketone Bodies
558	M	Ø	Ø	Ø	Ø	-
559	M	Ø	Ø	Ø	Ø	-
566	F	Ø	Ø	Ø	Ø	-
567	F	Ø	Ø	Ø	Ø	-

00045

Urinalysis

Compound: Octopirox

Dose: 16 mg/kg

Administration: orally in food

Species: Beagle, engl.

Week: Final value

Animal No.	Sex	Appearance	Color	Spec. Grav.	pH	Sediment
560	M	slightly turbid	yellow	1.058	6.2	10,20,31,36,50,72,91
561	M	clear	yellow	1.035	6.4	30,50,72,90
568	F	clear	bright yellow	1.035	6.2	10,30,36,70,72,90
569	F	clear	yellow	1.042	6.4	20,30,72,90

00046

Urinalysis

Substance: Octopirox

Dose: 16 mg/kg

Route: orally in food

Species: Beagle, engl.

Time: Final value

Animal No.	Sex	Protein	Glucose	Hemoglobin	Bilirubin	Ketone Bodies
560	M	Ø	Ø	Ø	Ø	-
561	M	Ø	Ø	Ø	Ø	-
568	F	Ø	Ø	Ø	Ø	-
569	F	Ø	Ø	Ø	Ø	-

Urinalysis

Compound: Ocotpirox

Dose: 40 mg/kg

Administration: orally in food

Species: Beagle, engl.

Week: Final value

Animal No.	Sex	Appearance	Color	Spec. Grav.	pH	Sediment
562	M	clear	yellow	1.031	6.9	10,21,30,50,70,72,90
563	M	clear	yellow	1.041	6.4	10,20,30,36,50,70,72,90
570	F	slightly turbid	yellow	1.047	6.2	20,30,70,72,90
571	F	clear	yellow	1.036	5.8	20,30,36,70,90

00048

Urinalysis

Substance: Octopirox

Dose: 40 mg/kg

Route: orally in food

Species: Beagle, engl.

Time: Final value

Animal No.	Sex	Protein	Glucose	Hemoglobin	Bilirubin	Ketone Bodies
562	M	Ø	Ø	Ø	Ø	-
563	M	Ø	Ø	Ø	Ø	-
570	F	Ø	Ø	Ø	Ø	-
571	F	Ø	Ø	Ø	Ø	-

00049

Urinalysis

Compound: Octopirox

Dose: 100 mg/kg

Administration: orally in food

Species: Beagle, engl.

Week: Final value

Animal No.	Sex	Appearance	Color	Spec. Grav.	pH	Sediment
564	M	clear	yellow	1.033	7.2	20,30,50,70,72,73,90
565	M	clear	yellow	1.049	6.4	20,50,70,72,91
572	F	clear	yellow	1.050	6.2	20,30,36,72,90
573	F	clear	yellow	1.040	6.4	10,20,30,70,72,73

00050

Urinalysis

Substance: Octopirox

Dose: 100 mg/kg

Route: orally in food

Species: Beagle, engl.

Time: Final value

Animal No.	Sex	Protein	Glucose	Hemoglobin	Bilirubin	Ketone Bodies
564	M	Ø	Ø	Ø	Ø	-
565	M	Ø	Ø	Ø	Ø	-
572	F	Ø	Ø	Ø	Ø	-
573	F	Ø	Ø	Ø	Ø	-

Elektrokardiographische Untersuchungen

Substanz: H 72 6146 A (Kontrolle) (Octopirox)

Dosis:

Applikation: p.o. im Futter

Tierart: Beagle-Hund, engl.

Woche: Vorwert

Tier-Nr.	G	Herzfrequenz Schläge/Min.	PQ-Zeit in Sek.	QRS-Zeit in Sek.	QT-Zeit in Sek.
558	M	120	0.12	0.05	0.20
559	M	110	0.12	0.05	0.18
566	F	120	0.10	0.05	0.18
567	F	160	0.12	0.04	0.18

Elektrokardiographische Untersuchungen

Substanz: H 72 6146 A (Octopirox)

Dosis: 16 mg/kg

Applikation: per os im Futter

Tierart: Beagle-Hund, engl.

Woche: Vorwert

Tier-Nr.	G	Herzfrequenz Schläge/Min.	PQ-Zeit in Sek.	QRS-Zeit in Sek.	QT-Zeit in Sek.
560	M	185	0.08	0.04	0.16
561	M	130	0.12	0.04	0.18
568	F	130	0.11	0.045	0.18
569	F	140	0.12	0.04	0.18

Elektrokardiographische Untersuchungen

Substanz: H 72 6146 A (Octopirox)

Dosis: 40 mg/kg

Applikation: per os im Futter

Tierart: Beagle-Hund, engl.

Woche: Vorwert

Tier-Nr.	G	Herzfrequenz Schläge/Min.	PQ-Zeit in Sek.	QRS-Zeit in Sek.	QT-Zeit in Sek.
562	M	115	0.12	0.045	0.18
563	M	115	0.10	0.04	0.18
570	F	150	0.10	0.04	0.18
571	F	95	0.12	0.04	0.18

Elektrokardiographische Untersuchungen

Substanz: H 72/6146 A (Octopirox)

Dosis: 100 mg/kg

Applikation: per os im Futter

Tierart: Beagle-Hund, engl.

Woche: Vorwert

Tier-Nr.	G	Herzfrequenz Schläge/Min.	PQ-Zeit in Sek.	QRS-Zeit in Sek.	QT-Zeit in Sek.
565	M	90	0.12	0.05	0.21
564	M	110	0.14	0.05	0.20
572	F	105	0.12	0.04	0.20
573	F	150	0.11	0.04	0.18

Elektrokardiographische Untersuchungen

Substanz: H 726146 A (Kontrolle) (Octopirox)

Dosis:

Applikation: per os im Futter

Tierart: Beagle-Hund, engl.

Woche: Endwert

Tier-Nr.	G	Herzfrequenz Schläge/Min.	PQ-Zeit in Sek.	QRS-Zeit in Sek.	QT-Zeit in Sek.
558	M	110	0.14	0.04	0.18
559	M	110	0.10	0.04	0.16
567	F	110	0.12	0.04	0.18
566	F	110	0.10	0.04	0.14

00056

Elektrokardiographische Untersuchungen

Substanz: H 72 6146 A (Octopirox)

Dosis: 16 mg/kg

Applikation: per os im Futter

Tierart: Beagle-Hund, engl.

Woche: Endwert

Tier-Nr.	G	Herzfrequenz Schläge/Min.	PQ-Zeit in Sek.	QRS-Zeit in Sek.	QT-Zeit in Sek.
560	M	150	0.08	0.04	0.17
561	M	100	0.12	0.04	0.19
568	F	110	0.10	0.04	0.20
569	F	130	0.11	0.04	0.18

Elektrokardiographische Untersuchungen

Substanz: H 72 6146 A (Octopirox)

Dosis: 40 mg/kg

Applikation: per os im Futter

Tierart: Beagle-Hund, engl.

Woche: Endwert

Tier-Nr.	G	Herzfrequenz Schläge/Min.	PQ-Zeit in Sek.	QRS-Zeit in Sek.	QT-Zeit in Sek.
562	M	70	0.12	0.04	0.20
563	M	160	0.10	0.04	0.15
570	F	110	0.10	0.04	0.18
571	F	90	0.12	0.04	0.18

00058

Elektrokardiographische Untersuchungen

Substanz: H 72 6146 A (Octopirox)

Dosis: 100 mg/kg

Applikation: per os im Futter

Tierart: Beagle-Hund, engl.

Woche: Endwert

Tier-Nr.	G	Herzfrequenz Schläge/Min.	PQ-Zeit in Sek.	QRS-Zeit in Sek.	QT-Zeit in Sek.
564	M	90	0.12	0.05	0.20
565	M	70	0.12	0.04	0.21
572	F	110	0.12	0.05	0.18
573	F	110	0.11	0.05	0.18

00059

Body weight, Organ weight

in g

Species: Beagle, English

Compound: Octopirox

Dose: Control

Administration: untreated

Animal No.	Sex	Body wt. g	Heart g	Lungs g	Liver g	Kidneys g	Spleen g	Brain g	Pancreas g	Testicles/ Ovary g	Adrenals g	Pituitary g	Thyroid g
558	M	14750.0	108.0	133.0	429.0	58.0	69.0*	99.0	29.0	19.0	0.980	0.097	0.854
559	M	15400.0	114.0	137.0	488.0	58.0	46.0	97.0	32.0	20.0	0.908	0.099	0.765
566	F	13760.0	120.0	105.0	396.0	67.0	122.0*	89.0	30.0	0.904	0.991	0.097	0.938
567	F	14750.0	104.0	111.0	441.0	51.0	84.0*	85.0	27.0	0.916	0.875	0.096	0.901

* coagulation

00069

Body weight, Organ weight

Compound: Octopirox

Dose: 16 mg/kg

in g

Administration: orally in food

Species: Beagle, English

Animal No.	Sex	Body wt.	Heart	Lungs	Liver	Kidneys	Spleen	Brain	Pancreas	Testicles/ Ovary	Adrenals	Pituitary	Thyroid
.	g	g	g	g	g	g	g	g	g	g	g	g	g
560	M	13900.0	112.0	115.0	415.0	53.0	38.0	87.0	28.0	15.0	0.974	0.089	0.799
561	M	15900.0	120.0	121.0	418.0	63.0	63.0*	92.0	29.0	17.0	0.808	0.098	1.062
568	F	14500.0	110.0	130.0	447.0	57.0	46.0	87.0	25.0	0.778	1.118	0.082	1.098
569	F	12100.0	102.0	109.0	323.0	44.0	81.0*	80.0	27.0	0.697	0.798	0.093	0.722

* coagulation

00061

Body weight, Organ weight

in g

Compound: Octopirox

Dose: 40 mg/kg

Administration: orally in food

Species: Beagle, English

Animal No.	Sex	Body wt. g	Heart g	Lungs g	Liver g	Kidneys g	Spleen g	Brain g	Pancreas g	Testicles/ Ovary g	Adrenals g	Pituitary g	Thyroid g
562	M	15500.0	123.0	147.0	422.0	67.0	85.0*	92.0	20.0	22.0	0.849	0.078	0.863
563	M	15250.0	115.0	122.0	434.0	61.0	65.0*	83.0	32.0	18.0	1.150	0.083	0.926
570	F	12700.0	106.0	108.0	382.0	48.0	34.0	82.0	27.0	0.790	0.851	0.086	0.733
571	F	13300.0	100.0	111.0	361.0	51.0	71.0	88.0	24.0	0.608	0.921	0.104	0.533

* coagulation

00062

Body weight, Organ weight

Compound: Octopirox

Dose: 100 mg/kg

in g

Administration: orally in food

Species: Beagle, English

Animal No.	Sex	Body wt. g	Heart g	Lungs g	Liver g	Kidneys g	Spleen g	Brain g	Pancreas g	Testicles/ Ovary g	Adrenals g	Pituitary g	Thyroi g
564	M	16200.0	134.0	139.0	426.0	70.0	47.0*	83.0	34.0	19.0	0.962	0.100	0.971
565	M	14600.0	115.0	136.0	438.0	53.0	42.0*	94.0	25.0	22.0	0.905	0.090	0.792
572	F	14500.0	120.0	125.0	382.0	51.0	36.0	86.0	32.0	0.704	1.087	0.084	1.141
573	F	15150.0	120.0	141.0	447.0	58.0	105.0*	91.0	17.0	0.806	1.182	0.075	1.142

* coagulation

Composition of the prepared food Latz FF

Manufacturer: Latz Purina GmbH
5350 Euskirchen
Federal Republic of Germany

Composition:

55.5 %	Cereals
14.4 %	Animal protein fodder
14.0 %	Oil cake
7.4 %	Fat
3.2 %	Mineral fodder
2.5 %	Dried vegetables
1.0 %	Whey powder
1.0 %	Yeasts
1.0 %	Vitamin pre-mix
100.0 %	

Vitamin A	24,000 I.U. per kg
Vitamin D_3	2,000 I.U. per kg
Vitamin E	24 mg per kg

Content of critical constituents:

21.0 %	Raw protein
11.0 %	Raw fat
1.0 %	Calcium
0.7 %	Phosphorus

PREPARATION FOR KILLING ANIMALS

T-61 HOECHST®

Composition (per 1 ml)

200 mg	N-[2-(m-methoxyphenyl)-2-ethylbutyl-(1)]-γ--hydroxybutyramide
50 mg	4,4'-methylene-bis-(cyclohexyltrimethylammonium iodide)
5 mg	4'-butylaminobenzoyl-2-dimethylaminoethanol hydrochloride

Hoechst

Hoechst Aktiengesellschaft
Pharma Research
Exp. Pathology

Appendix III

REPORT

ON

THE MACROSCOPIC AND MICROSCOPIC EXAMINATION OF DOGS

AFTER A REPEATED-DOSE (30 DAYS) ORAL TREATMENT WITH OCTOPIROX

July 2, 1976

Vorsitzender des Aufsichtsrats: Karl Winnacker · Vorstand: Rolf Sammet, Vorsitzender; Kurt Lanz, stellv. Vorsitzender; Erhard Bouillon, Rudolf Frank, Enrique Hartung, Wolfgang Hilger, Willi Hoerkens, Josef Nowotny, Wolfgang von Pölnitz, Otto Ranft, Hans Reintges, Jürgen Schaafhausen, Hans Schlachter, Klaus Weissermel · Sitz der Gesellschaft: Frankfurt (M) · Handelsregister: Frankfurt (M) Abt. B Nr. 14500

Report on the macroscopic and microscopic examination of dogs after repeated-dose (30 days) oral treatment with Octopirox

The inner organs of 8 male/8 female Beagle dogs were submitted to histological examination. Groups of 2 male/2 female dogs had received a daily dose of 16, 40 or 100 mg Octopirox per kg body weight with their food for 30 days. Two male and female dogs were not treated and served as controls. On the day after the last treatment the animals were killed and dissected.

Macroscopic findings:

Macroscopic examination of the animals at dissection revealed no substance-induced changes. Several dogs of the lowest and median dosage group showed ascarides in the small intestine. In one of these dogs grey-white dots were found in the renal cortex.

Microscopic findings:

Microscopic examination also revealed no substance-induced organ changes. Kupffer-cell proliferations in the liver and glycoproteid-containing casts in the renal papilla were observed in control and treated animals. In the renal cortex of one dog of the median dosage group a small scarred area was observed which was - just like the grey-white dots of another dog - attributed to parasites. Lipid and iron metabolism, spermiogenesis and follicle ripening were not influenced by Octopirox.

The examinations have shown that in this study Octopirox did not lead to morphologically demonstrable organ changes.

July 2, 1976 signed:
Dr. Deu

Prof. Kief Dr. Deutschländer

Individual macroscopic and microscopic findings:

(30-day oral toxicity study in dogs)

Frozen sections, stained with Fat red 7 B, of heart, liver, adrenals and kidneys were fixed in formalin and submitted to microscopic examination. Sections of heart, lungs, liver, spleen, adrenals, kidneys, cerebrum, cerebellum, testis, epididymis, prostate, ovaries, uterus, pancreas, pituitary, thyroid, stomach, small and large intestine, thymus, urinary bladder and retina with optic nerve were fixed in Carnoy's solution, embedded in paraplast and stained with H & E. Sections of heart, liver, kidneys, lungs, spleen, cerebrum and cerebellum were, in addition, submitted to PAS and Prussian blue staining.

Beginning of the study:	April 13/14, 1976
End of study:	May 12/13, 1976
Killing:	May 13/14, 1976

Controls to Octopirox

Dog No. 558 (S 708/76) ♂

Macroscopic findings:

N.A.D.

Microscopic findings:

Kidneys: Individual glycoproteid containing, partially Fat red-positive casts in the papilla.

All other organs N.A.D.

Dog No. 559 (S 709/76) ♂

Macroscopic findings:

N.A.D.

Microscopic findings:

Liver: Individual Kupffer-cell proliferations.

Kidneys: Several glycoproteid containing casts in the papilla.

All other organs N.A.D.

Dog No. 566 (S 710/76) ♀

Macroscopic findings:

N.A.D.

Microscopic findings:

Liver: Several Kupffer-cell proliferations.

Kidneys: Numerous glycoproteid-containing, partially Fat red-positive casts in the papilla.

All other organs N.A.D.

Dog No. 567 (S 711/76) ♀

Macroscopic findings:

N.A.D.

Microscopic findings:

Liver: Isolated Kupffer-cell proliferations.

Kidneys: Numerous glycoproteid-containing casts in the papilla.

All other organs N.A.D.

16 mg Octopirox per kg body weight

Dog No. 560 (S 712/76) ♂

Macroscopic findings:

N.A.D.

Micorscopic findings:

Liver: Individual Kupffer-cell proliferations.

Kidneys: Individual glycoproteid-containing casts in the papilla, otherwise N.A.D.

All other organs N.A.D.

Dog No. 561 (S 713/76) ♂

Macroscopic findings:

A small amount of ascarides in the small intestine, otherwise N.A.D.

Microscopic findings:

Liver: Individual Kupffer-cell proliferations.

Kidneys: Several glycoproteid casts in the papilla, otherwise N.A.D.

All other organs N.A.D.

Dog No. 568 (S 714/76) ♀

Macroscopic findings:

Isolated grey-white dots in the renal cortex, and isolated ascarides in the small intestine.

Microscopic findings:

Kidneys: Several glycoproteid casts in the papilla, otherwise N.A.D.

All other organs N.A.D.

Dog No. 569 (S 715/76) ♀

Macroscopic findings:

N.A.D.

Microscopic findings:

Kidneys: Several glycoproteid casts in the papilla.

All other organs N.A.D.

40 mg Octopirox per kg body weight

Dog No. 562 (S 716/76) ♂

Macroscopic findings:

Isolated ascarides in the small intestine.

Microscopic findings:

Pituitary: One cyst in the ciliated epithelium.

All other organs N.A.D.

Dog No. 563 (S 717/76) ♂

Macroscopic findings:

Isolated ascarides in the small intestine.

Microscopic findings:

Kidneys: A small subcapsular area with atrophic parenchyma in the state of scarificatic otherwise N.A.D.

All other organs N.A.D.

Dog No. 570 (S 718)76) ♀

Macroscopic findings:

N.A.D.

Microscopic findings:

Liver: Several Kupffer-cell proliferations.

All other organs N.A.D.

Dog No. 571 (S 719/76)♀

Macroscopic findings:

N.A.D.

Microscopic findings:

Liver: Several Kupffer-cell proliferations.

All other organs N.A.D.

Bone marrow findings:

A tissue sample from a median sternal segment of each dog was embedded in methacrylate and cut undecalcified after previous alcohol-formalin fixation and was then histologically examined. The sections were submitted to Giemsa and Ladewig-Prussian blue staining.

The sections examined did not reveal any pathological morphological changes. The cells of hematopoiesis showed normal maturation, and the megacaryocytes exhibited normal configuration. Osseous and osteoid parts of the spongiosa and the cells of bone metabolism showed normal distribution.

100 mg Octopirox per kg body weight

Dog No. 564 (S 720/76) ♂

Macroscopic findings:

N.A.D.

Microscopic findings:

Liver: Isolated Kupffer-cell proliferations.

All other organs N.A.D.

Dog No. 565 (S 721)76) ♂

Macroscopic findings:

N.A.D.

Microscopic findings:

Liver: Individual Kupffer-cell proliferations

Kidneys: Individual glycoproteid casts in the papilla.

All other organs N.A.D.

Dog No. 572 (S 722/76) ♀

Macroscopic findings:

N.A.D.

Microscopic findings:

Liver: Individual Kupffer-cell proliferations

Kidneys: Numerous glycoproteid-containing, partially Fat red-positive casts in the papilla, otherwise N.A.D.

All other organs N.A.D.

Dog No. 573 (S 723/76) ♀

Macroscopic findings:

N.A.D.

Microscopic findings:

Liver: Individual Kupffer-cell proliferations

Kidneys: Several glycoproteid-containing, parti Fat red-positive casts in the papilla.

All other organs N.A.D.

June 23, 1976

Dr. Deu