CHEMOTHERAPY OF RODENT MALARIA EVALUATION OF DRUG ACTION AGAINST NORMAL AND RESISTANT STRAINS INCLUDING EXO-ERYTHROCYTIC STAGES

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FINAL REPORT

by

WALLACE PETERS, MD, DSc

December 1978



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US ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

Fort Detrick, Frederick, Maryland 21701

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Department of Parasitology / Liverpool School of Tropical Medicine Pembroke Place Liverpool L3 5QA, UK

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A procedure has been developed in conjunction with WHO for the screening of blocd and tissue schizontocides with prolonged activity. Details of the Screening procedure are included with this report. A fluorescent technique is being developed to identify long acting compounds which possess tissue schizontocidal activity.

Investigations of polymer matrix preparations to prolong the antimalarial activity of pyrimethamine and sulphadiazine continue. A more reliable and technologically simpler method of preparing the drug-matrix polymers has been developed.

Further studies on the mode of action of chloroquine are reported.

The present programme in Liverpool will terminate at the end of September 1979 when the Principal Investigator will transfer his activities to the London School of Hygiene and Tropical Medicine.

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ADDENDUM

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1. INTRODUCTION

During the year under review we have continued to evaluate new WRAIR compounds with special reference to causal prophylactic agents, to drug potentiation and to the development of a screening procedure to detect agents with prolonged activity. We have continued the investigation of WRAIR compounds received in 1977 together with a further 12 compounds sent this year. (This makes a total of 371 compounds examined to date.)

Biochemical work has been delayed during the year because of technical difficulties that have necessitated the cloning of our rodent malaria strains that are being employed in this work, and a shortage of small animal accommodation pending reconstruction work to improve our animal rooms.

In October 1978 the Principal Investigator took the opportunity of his presence in Washington to visit WRAIR for discussions on the progress of this programme.

2. CYCLICAL PASSAGE OF RODENT MALARIA STRAINS

In order to carry out work on long-acting compounds we are now maintaining <u>P. yoelii yoelii 17X as well as P. y. nigeriensis in cyclical passage</u>. Every precaution is taken to ensure that there is no accidental cross contamination, including a periodical check on enzyme markers.

3. CHEMOTHERAPY STUDIES

3.1 Blood schizontocides

Apart from the specially selected compounds used in the development of the screen for long-acting compounds we have examined 3 8-aminoquinolines and 2 other compounds of structures so far unidentified to us. WR 226,296 was highly active sc and po against <u>P. berghei</u> in the 4-day test. WR 232,584 was also active but less po than sc. WR 235,485 was very active sc and po against the N, NS and RC lines, but the P line was markedly resistant to it, especially sc. WR 212,293 and 233,637 showed insignificant activity at 30 mg/kg and will be examined at higher doses. These data are summarised in Table 1 and detailed in Tables 2 through 6.

3.2 Causal prophylaxis

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We have examined the causal prophylactic properties of 33 WRAIR compounds. The data on these are summarised in Table 7, and detailed in Tables 8 through 58. Of the 8-aminoquinolines, the most active was WR 221,527 when given po. WR 228,456 is another salt of this compound which is slightly less active. Note that the data given have not been adjusted to take account of the molecular weights, and no primaquine index has therefore been calculated yet. Included in the compounds studied are several, such as the quinazolines WR 141,871, 159,412 and 180,872 that were provided primarily for studies on repository activity (see Addendum). It will be noted from the individual cata sheets that many of these compounds did exhibit residual activity in the causal prophylaxis test, e.g. the Mannich bases WR 194,965 and 228,258.

3.3 Screening system for drugs with prolonged activity

A procedure has now been worked out for the detection of prolonged antimalarial activity in candidate antimalarials. Details are given in an Annex to this report. A further development of the procedure is being examined at the present time to distinguish between true action on excerpthrocytic schizogony from delayed activity against first (or later) generation asexual erythrocytic stages.

We were fortunate in being able to benefit from discussions with Dr. A. Ager of Miami on this project during i is visit to Liverpool in April this year. It is hoped that Dr. Ager's laboratory will the over this system or modify it if necessary for use in screening the large number of candidate compounds with possible repository activity in the WRAIR inventory.

An examination of the series of compounds provided by WRAIR in this procedure, using diformyl dapsone (DFD) as a control, has shown clear residual activity in the pyridine methanol WR 172,435 (4 x DFD), the phenanthrene methanol WR 171,669 (3 x DFD) and the quinazoline WR 180,872. (It is encouraging to note that in this work which was carried out "blind", i.e. the nature of the compound was unknown to the staff reforming the tests, WR 6798 gave precisely the same result as the DFD control.)

3.4 New drug delivery systems

We have continued our studies on the use of drug-polymer matrix preparations to obtain a prolongation of antimalarial effect with standard antimalarial compounds. Our original experimental system, employing implants prepared from silastic tubing filled with the powdered antimalarial compound has been discontinued, since such capsules were profligate in the use of compounds, up to 50 mg being used in each. Comparison of the results obtained with 'tubing' implants and polymerdrug 'mixture' implants also showed that the latter were more effective. ないというないので、ための

3.4.1 Implants prepared from siloxane-drug mixtures

Siloxane-drug mixtures have been prepared with a number of standard antimalarials as described in the last Annual Report. Further work has continued with pyrimethamine, sulphadiazine and latterly, sulphadoxine incorporated into silicone rubber matrices and employed experimentally. Attention has been paid to the design of experiments for the evaluation of residual antimalarial action since two major aspects of the protocol previously employed were considered unreliabie; the first related to the fact that during the course of an experiment mice were of different ages and body weight at the time of challenge (all mice received implants on Day 0 and were challenged at intervals thereafter) and the second was the possible effect of host immunity on parasitaemia in animals which were repeatedly challenged with infected mouse erythrocytes. In the revised protocol which has been adopted during the past year, groups of mice receive implants on Days 0, -28 to + 140 at 28 day intervals and all groups are challenged on Day + 168. Groups of control, untreated mice are also set up on Day 0. Thus all mice are of the same age at the time of infection and receive a single parasite challenge. With this system it has been found that a 200 mg implant containing 1 mg pyrimethamine base protects mice for > 5 < 6 months.

3.4.2 Impiants prepared from biodegradable polymer-drug mixtures

Mixtures of pyrimethamine, sulphadiazine and cycloguanil in biodegradable matrices have been prepared by Professor Graham, Strathclyde University, Scotland. Difficulties were encountered initially in preparing mixtures with pyrimethamine but 24 mg implants of this mixture (30% pyrimethamine base) protected mice against P. berghei challenge for > 3 months.

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A more reliable and technologically simpler method of preparing matrixpyrimethamine mixtures has now been developed and preliminary tests have revealed that 50 mg implants containing 20% pyrimethamine Lase protect mice for > 56 days. A full trial of these preparations is in progress.

Preparations containing 10% and 30% sulphadiazine in a biodegradable matrix have been obtained. Preliminary tests with these mixtures have given encouraging results and further evaluation is in progress.

Considerable attention has been focussed on the use of injectable, powdered formulations of biodegradable polymers containing sulphadiazine and pyrimethamine The different grades of particle supplied were of $> 53 < 96 \mu$, $> 96 < 250 \mu$ and $> 100 < 250 \mu$ diameter. Colloidal preparations of particles were prepared in carboxymethyl cellulose and administered sc at doses from 0.5-5 mg/20 g body weight. The results obtained with the injectable biodegradable matrix-drug powders have shown that the residual effect of these preparations is much less than that obtained with an equivalent dosage in pellet form. This is probably related to a more rapid release of the antimalarial from such powders, and agrees with results obtained by Wise et al. (J. Pharm. Pharmac. (1978), 30, 686-689). Quantitative studies on the rates of release of antimalarials from the various preparations employed have not been possible because radio-labelled compounds have not been available. A source of radio-labelled sulphadoxine has now been obtained and it is hoped that radio-labelled pyrimethamine will be made available for our use through the WHO TDR Programme. It is also intended to develop an <u>in vitro</u> bioassay for the determination of the serum levels of pyrimethamine, sulphadiazine and sulphadoxine using P. falciparum in vitro cultures.

In addition to work on pyrimethamine and sulphadiazine a limited amount of work has also been performed with cycloguanil hydrochloride-biodegradable polymer mixtures. No powder preparations have been tested but with solid implants the residual effect of \sim 50 mg implants containing 30% cycloguanil was < 14 days.

3.4.3 Sustained release from Alzet^R osmotic minipumps

Experiments using WR 99,210 (LIV/1019) and primaquine phosphate released from osmotic minipumps were described in the previous Annual Report (December 1977).

A comparison has been made between the antimalarial effects of equivalent dosages of primaquine phosphate administered once daily by sc injection and continously by constant release from the osmotic minipumps to determine if the use of a slow release preparation could result in a reduction in the total dosage of primaquine required to control parasitaemia.

On D+3 of infection with <u>P. berghei</u> N strain, Alzet^K osmotic minipumps (of 170 μ l capacity and a flow rate of 1μ l/hr) containing solutions of 4.125, 8.25 and 16.5 μ g/ μ l respectively of primaquine phosphate were implanted in three groups of mice. Three further groups of mice received primaquine at 5, 10 and 20 mg/kg, sc, daily from D+3 for 7 days. A release of 4.125 μ g/hr from osmotic minipumps in a 20 g mouse is equivalent to a total daily dosage of 5 mg/kg. The experiment therefore included three paired groups of mice receiving primaquine phosphate at daily dosages of 5, 10 and 20 mg/kg for a 7 day period.

The results of this experiment (graphically illustrated in Figures 1, 2 and 3) demonstrate that the antimalarial effect of primaquine phosphate was similar in mice treated daily and in those which received drug continuously. A fulminating infection was observed in mice receiving 5 mg/kg daily and 4.125 μ g/hr, there being a slightly greater antimalarial effect in mice receiving the drug by daily injection. A plasmodistatic effect was observed during the period of treatment at 10mg/kg daily and 8.25 μ g/hr and a plasmodicidal effect with elimination of parasites by D+7 resulted from treatment with 20 mg/kg and 16.5 μ g/hr.

These results and those from a duplicate experiment indicate that no reduction in the total dosage of primaquine phosphate required for the treatment of malaria infections may be achieved by the employment of slow release preparations.

3.5 Drug potentiation

We have completed studies on the potentiation of the blood schizontocidal activity of WR 158,122 by dapsone and by sulphadexine, both of which are shown in Tables 59 and 60, and Figures 4 and 5 exhibit a marked degree of potentiation. In view of research that has been undertaken elsewhere (Dynatech R/D Corp) on the incorporation of WR 158,122 and sulphadiazine into biodegradable polymers these data give encouragement for the extension of polymer studies with one ' or other mixtures of these compounds.

3.6 Mode of action of chloroquine and mefloquine

It has been suggested that the death of the chloroquine-treated malarial parasite is caused by intercalation of chloroquine into the parasite's nucleic acid. To investigate this, parasites were treated with radioactively-labelled chloroquine for one hour in vitro and the amount of radioactivity associated with the TCA-insoluble fraction of the parasitised cells was measured. The first two experiments of this kind indicated substantial retention of chloroquine in the TCA-insoluble fraction with more of the chloroquine associated with protein than with nucleic acid. However, in three further experiments carried out in identical manner, virtually no radioactivity was found in either the protein or the nucleic acid fractions. Whether these conflicting results were due to artefacts or to a change in the chloroquine sensitivity of the parasite due to the abnormally high temperature in the animal house cannot at present be determined. At the end of these experiments it was found that the enzymes of the parasite were no longer those of the chloroquine-sensitive N strain, but those of the chloroquine-resistant NS line. Experiments will be resumed when improvements to the animal house permit the preparation of an indisputably cloned strain.

4. CONCLUSIONS AND RECOMMENDATIONS

Our current year's work has continued to provide useful data concerning the value of the newer 8-aminoquinolines as causal prophylactic agents. Further work is required on a technique to distinguish definitively in rodents between true causal prophylaxis and the delayed blood schizontocidal action of some of these compounds. This will link in well with the extension of our work on the technique of evaluating long-acting drugs which has made good progress during the current year.

With the pending completion of construction work on improved small animal accommodation and the production of clones of the strains of <u>Plasmodium</u> needed for further biochemical studies on drug resistance, it is anticipated that experiments on the mode of action of chloroquine and mefloquine using radiolabelled material will continue early in the new year.

A fluorescent technique is being developed for the detection of small numbers. of tissue schizonts as part of the screening procedure referred to above. Sera obtained in immunised rabbits have so far not been of sufficiently high titre to give consistent results. Our studies on the prolongation of antimalarial action of various drugs by their incorporation in polymers will be continued, using any WRAIR compounds that may be suggested. Potentiating drug combinations will also be examined in such formulations.

The Principal Investigator will transfer his activities in October 1979 when he leaves Liverpool to take over the Chair of Medical Protozoology at the London School of Hygiene and Tropical Medicine. Funds have been requested from WRAIR to permit completion of the oresent programme up to the end of September 1979 in Liverpool. Early in the new year it is hoped to have a further meeting with WRAIR to negotiate possible further collaboration.

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APPENDICES 6.

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Table 1	Summary of blood schizontocidal studies in 4 day test against <u>Plasmodium berghei</u> .
Tables 2-6	Detailed 4-day tests of 5lood schizontocidal action
Table 7	Summary of causal prophylactic tests against Plasmodium yœlii nigeriensis
Tables 8-58	Details of causal prophylactic tests
Table 59	ED ₉₀ of WR 158,122 and DDS alone or in combination. Data in mg/kg sc in 4-day test (see Figure 4)
Table 60	ED ₉₀ of WR 158,122 and sulphadoxine alone or in combination. Data in mg/kg sc in 4-day test (see Figure 5).
Figures 1-3	A comparison of the response of <u>Plasmodium berghei</u> to primaquine phosphate following drug administration by repeated daily injections via mini osmotic pumps.
Figure 4	WR 158,122 and DDS – ED ₉₀ values when compounds are used alone or in combination in varying proportions.
Figure 5	WR 158, 122 and sulphadoxine - ED ₉₀ values when compounds are used alone or in combination in varying proportions.

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Comp.	GNAD	4 3 3 4 3	à			4 4		· v ·	IRAIN	1	: 	,	1	i.				CMMEN
WR NO.	ON NI	koute	1 D 50	1 1020	ED ₀ N	130	LL 90	20	1 060		D ₉₀	0,	D90	0,5 0	ED ORA	<u> </u>		
226296AA		S S	0.3	0.8														
BG44452	1961	od	0.1	0.4														
232584 AA	1541	ů	0.8	3.8														
BH 05361		õ		_Ā			+											
235485 AA		Š	0.7	2.5	2.4	0.1	2.5	1.0 6	5.0 2	6.0								
BH 35570	1571	od	1.0	2.3	2.3	1.0	1.5	0.7 1	0.1	4.8				+				
212293 AB		SC		>30					<u></u>					_				
BH 49943	0601			1			†		 			 		 				
233637 AB	1 501	SC		ñ														
BH 49596	1601								 									
							<u> </u>											
																TAB	LE 1	

	or NUMBER	LIV 139	9.1	PARAS	SITE (SUB) SPECIES	P. D. berghei
	-	KOUTE		Istration : j.p.	/s.c.;p.o.	
	Strain	Daily dose mg/kg D0 - D +3	No. of mice	No. of experiments	Mean control porosite rate %	Treated PR% x 100 Control PR% x 100
	÷	0.03	5			100 ± 2.5
		0.1	5		-	88.9±7.3
	Nsc	0.3	5		-	75.5±13.3
		1.0	5		-	8·8 ± 3·6
		Ø.	10		36.0	
Ē	ED ₅₀ (range)	(7.0-1.0)6.0	·			
	ED ₉₀ (range)	0.8(0.3-1.8)				
		Resistance factor 90			•	
	· · · · · · · · · · · · · · · · · · ·	0.03	5		_	73.2 ± 11.4
11111111111111111111111111111111111111		0.1	5			65.0±11.2
	N p.o.	0.3	5	1	-	50.1 ± 12.1
STATES IN		1.0	5		-	1.0±0.3
ACTORNAL PROPERTY OF		ø	10	•	36.0	
a and a state	ED ₅₀ (range)	0.1(0.04-0.4)				
Service and	ED ₉₀ (range)	0.4(0.1-1.2)	<u> </u> .			
generalista en entre		Resistance factor ₉₀				
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COMPOUN or NUMBE		541	PARAS	SITE (SUB) SPECIES	P.b.berghei
	Route	e of admin	istration : j.p.	/socuip.oo	·
Strain	Daily dose mg/kg D0 - D +3	No. of mice	No. of experiments	Mean control porasite rate %	Treated PR% Control PR% x 100
	0.03	5		_	100 ± 2.2
	0.1	5			90.2±4.3
N sc	0.3	5		-	68.1 ± 3.0
	1.0	5			51.3 ± 5.1
	ø	10		36.0	
ED ₅₀ (range)	0.8(0.4-1.3)	, .	•		•
ED ₉₀ (range)	3.8(1.9-6.2)				
	Resistance factor 90				
• • • • • • • • •	0.03	5		-	93.5 ± 3.6
	0.1	5		-	96.3 ± 2.6
N po.	0.3	5	1	_	99.8 ± 5.2
	1.0	5		-	85.4 ± 5.9
	Ø	10		36.0	
ED ₅₀ (range)					
ED ₉₀ (range)	> 1.0 Resistance				
LIVEPPOC TROPICAL	DL SCHOOL OF MEDICINE	I DATE	E - DEC 1978	PRINCIPAL INVESTIGA	TOR PROF. W. PETERS

	COMPOUN or NUMBER	D NAME BH 355		PARAS	SITE (SUB) SPECIES	P. b. berghiei
		Koure		Isiration : Jap.	/ Socu/ P. O.s	
	Strain	Daily dose mg/kg D0 - D +3	No. of mice	No. of experiments	Mean control parasire rate %	Treated PR% Control PR% x 100
		0.1	5		-	93.9 ± 3.9
		0.3	5		-	85.4 ± 4.7
	Ν	1.0	5	. 	-	50.7 ± 16.6
		3.0	5			4.2 ± 2.9
AVESSE		ø	10		36.5	
	ED ₅₀ (range)	0.7(0.4-1.5)		•		
	ED ₉₀ (range)	2.5(1.4-5.7)				
		factor 90 1.0				
	· · · · . · . · · · · · · · · · · · · ·	0.1	5			96.3 ± 6.9
		0:3	5		-	97.9 ± 5.6
	NS	1.0	5		_	61.3 ± 17.1
		3.0	5		-	5.3 ± 2.7
		Ø	10	a	45.6	
	ED ₅₀ (range)	1.1(0.8-1.6)	1			
	ED ₉₀ (range)	2.4(1.7-3.7) Resistance	 			
	LIVERPOC TROPICAL	DL SCHOOL OF	DATE	' DEC 1978	PRINCIPAL INVESTIGA	ATOR PROF. W. PETERS

COMPOU cr NUMBI	WR 235 BH 355 BH 355 ER LIV 15	(BLOOD 485 AA 570 71	SCHIZONTOC	CIDES) SITE (SUB) SPECIES	P.b. Derchei
	Route	e of admin	istration : j.p.	/s.c./0.c.	- 1
Strain	Daily dose ma/kg D0 - D +3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% x 100
	011	5		-	94.4±10.4
	0.3	5			88.3±9.6
RC	1.0	5			73.5± 13.4
	3.0	5		_	6.5 ± 2.9
	ϕ	10	•	4.6	
ED ₅₀ (range)	0.8(0.5-2.6)				
ED ₉₀ (range)	2.5(1.5-7.0) Resistance factor 90 1.0				
•	0.1	5		_	87.3± 16.3
	5،0	5		_	62.1 ± 18.8
P .	1:0	5	<u> </u>	-	62.3 ± 19.0
	3.0	5		-	53.0 ± 1.9
·	Ø	10	•	19.0	
ED ₅₀ (range) ED ₉₀ (range)	$\frac{2.2(0.5-5.8)}{65(14->100)}$ Resistance factor 90 26	[Interp	olated graph	cally]	
LIVERPO TROPICA	OL SCHOOL OF AL MEDICINE	DATE	E - DEC 1978	PRINCIPAL INVESTIGA	TOR PROF. W. PETERS

	· ,	SUMMA	RY OF AN	NTIMALARIAL	DRUG TESTS	TABLE 4c
	. ,		(BLOOD	SCHIŻONTOC	(IDES)	
		WR 235	485 A	A	•	
	COMPOUN	D NAME LIV 15	71	ይላይላል	TTE (SUIR) SPECIES	P. b. berahei
		Route	of admin	istration · i A		
2	Strain	Daily dose mg∕kg D0 - D +3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% × 100 Control PR%
			• •			
	÷-	0.4				100 ± 4,3
		0.3 .	S		-	91.1 ± 5.3
N						
IN		1.0	5	 	-	783 ± 51
		3.0	5		-	5.4 ± 2.2
		Ø	10		36.5	
ED 5	(ronge)	1.0(0.6-1.9)	<i>•</i> • •			
ED9	0 (range)	2.3(1.3-4.2)				
		factor 90 1.0				
	1					
• 、 • •	· · · · · ·	0.1	5			93.5 1 4.5
		0.3	5		~	91.0 ± 4.5
NIC	2		¥			L
		1.0	5	<u> </u>	-	61.4±13.1
		3.0	17)		~	4.4 ± 2.0
		4			:	<u> </u>
ED	co (rance)	ψ	-10	•	42.6	
ED,		0.9(0.6-1.7)				
<u> </u>	<u> </u>	<u>2.3(1.5-4.)</u> Resistance				
		factor 901.0				
	LIVERPOO		['. \ TE	- DEC 1978	PRINCIPAL	TOP PROF. W. PETERS
	IKUPICAL		DATE		IINVESTIGA	
SA .						

	COMPOUN or NUMBER	SUMMA WR 235 BH 354 LIV 15 Route	RY OF AN (BLOOD 9985 A 570 7) of admin	NTIMALARIAL SCHIZONTOC A PARAS istration : i.e.	DRUG TESTS CIDES) SITE (SUB) SPECIES	TABLE 4d
	Strain	Daily dose mg/kg D0 - D +3	No. of mice	No. of experiments	Mean control porasite rate %	Tre ited PR% × 100 Control PR% × 100
		01	5		-	82.6±10.9
		0:3	5		_	76.5±12.5
C	RC	1.0	5		-	59.1±18.0
	. ·	3.0	S		-	1.3 ± 0.8
		ø	10		4.6	
	ED ₅₀ (range)	0.5(0.3-1.7)	<i>ı</i>			
	ED ₉₀ (range)	1.5(0.9-4.7)				·
		Resistance factor 90 0 7				
	• • • • •	0.1	5			100 ± 2.2
		٤.0	5		_	93.0 ± 4.4
	P	1.0	5		-	94-1 ± 8.4
Stand Ritico		3.0	5			65.2 ± 9.4
	· · ·	ø	10	•	19.0	
	ED ₅₀ (lange)	3.4(0.9-5.7)				
		111.0(3.2-18.8) Resistance factor ₉₀ 4.8				
	LIVERPOO TROPICAL	L SCHOOL OF MEDICINE	DATE	- DEC 1978	PRINCIPAL INVESTIGA	TOR PROF. W. PETERS

		, .	
SUMMARY	OF ANTIMALAR	HAL DRU	IG TESTS

(BLOOD SCHIZONTOC/DES)

TABLE 5

W	R 2	121	29	BAB
•		_		

COMPOUND NAME BH 49943

or NUMBER

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LIN/1590 PARASITE (SUS) SPECIES . P.D. Derghei

Route of edministration : inf. in

Strain	Daily dose mg/kg D0 - D +3	No. of mice	No. of experiments	Mean control porosine rate %	Treated PR% Control PR% × 100
	1.0	5		_	84.3 ± 61
	3.0	5		-	88.6 ± 4.2
N	10.0	5			75.0 ± 7.7
	30.0	5		-	86.6 ± 4.7
	ø	10		49.0	
ED ₅₀ (range)					
ED ₉₀ (range)	> 30.0				
	Resistance factor 90				
٠					·
	· · · · · · · · · · · · · · · · · · ·		·		۰
				1	
,					
ED _{ao} (rance)			•		
ED ₉₀ (range)					
	Resistance factor ₉₀				
LIMERPOO TROPICAL	l school of Medicine	DATE-	D.EC 1978. «	PRINCIPAL INVESTIGA	TOR PROF. W. PETERS

SUMMARY OF ANT'MALARIAL DRUG TESTS

WR 233637 AB

THE PART OF STREET, SAME

TABLE

6

			SCHIZONIO(C(DEC)	
	WR 233	3637 AE	3		
	ND NAME LIV / 1	592 591	PARA	SITE (SUB) SPECIES	P. D. Derohei
OF NOMBER	\ • ⊽ ***•{*•	· · · · · • •	• • • • •	······································	······································
	Koute	e of admin	istration : int	ومستوع زرون ا	
Strain	Daily dose	No. of	No. of	Mean control	Treatea PR% x 100
	mg/kg D0 - D ÷3	mice	experiments	parasive rate %	Control PR%
	1.0				
		3			94.62 2.8
	3.0	5		_	9.5 + 2.9
		3	· · ·		74.2 7 1.0
N	10.0	E		_	
• •	10.0	5		<u> </u>	7 T I I I I I I I I I I I I I I I I I I
	30.0	-		-	203 + 0 4
	1 30.0	5		1	18'S I 5'4
	Ø	10		49.0	
ED ₅₀ (range)			<u> </u>		
ED _{oo} (range)	<u>\</u>				
	> 30.0	i T			
	factor 90				
•		Ì			1 1
) 9 1
		1	1	·	<u> </u>
		• •			
			<u> </u>		
ED ₅₀ (range)			·		
ED ₉₀ (range)		-			
	Resistance	-			
	factor 90	; 1			
. 1			•	251010104	
	MEDICINE	DATE	' DEC 1978	. IN EST GA	ATOR PROF. W. PETERS
			•	•	
- 				٠	

TABLE 7					
furan		Nil at 30	30 po	1507	93133AC BB59627
DFD		Nil at 30	30 po	1506	67'98AL AF50013
dapsone		Nil at 30	30 po	1505	448AG AG28874
pyridine methanol	Residual activity only	Present at 3 Marked at 30	30 po	1504	180409AC BE99420
=		ΪŇ	3-10 po	14.76	230388AA BG81580
=		Nil at 30	30 po	1455	ZN44030
=		Nil	3-10 po	1392	BE16967
E		Nii	3-10 po	1451	ZN42821
		N:I	3-10 sc	1451	ZN42821
=	Inactive at 30 mg/kg po	1	1.	1449	ZU3608AA ZN42125
=	Inactive at 30 mg/kg sc	9	I	1449	203608AA ZN42125
=		ΠŻ	3 po	1439	2:21527AB BG48898
₩ 95 C ++ 124-4	Inactive at 30 mg/kg po	ïŻ	ł	1428	212579AB BG48969
=		Nii	3-10 po	1413	228456AA BG62807
=		- 1	3 bo	1402	228002AA BG58199
=	Inactive at 30 mg/kg po	1	8	1399	227681AA BG56612
=		ĨŻ	10-30 po	1437	218335AA BE66930
8-aminoquinoline		ĪŽ	10-30 po	1348	218335AA BE66930
Type of Compound	Comment	Residual action at active dose	Minimum fully active dose (mg/kg x 1)	LIV No.	. WR No.

Number (Number ($\frac{M(M)}{00000}$) ($\frac{M(M)}{00000}$)Equival ($\frac{M(M)}{00000}$)Type of Compound ($\frac{M(M)}{00000}$)2 $10-30po$ Nilfuran3 $10-30po$ Nilfuran1 $3po$ Nilfuran2 $10-30po$ Nilfuran1 $3po$ Nilfuran2 $0.31pc$ Nilfuran2 $0.3-1pc$ Nilfuran2 $0.3-1pc$ Nilfuran3 $1-3tc$ Nilfuran3 $1-3tc$ Nil at 1"3 $0.10.3pc$ Nil at 1"4 $3tc$ Present at 1"5 $10-30tc$ Monded at 30Residual activity only6 $10-30tc$ Monded at 30Residual activity only7 $30tc$ Nil at 30Monded at 307 $30tc$ Nil at 30Monded at 308 $10-30tc$ Monded at 30Residual activity only7 $30tc$ Nil at 30Monded at 309 $10-30tc$ Monded at 30Monded at 309 $10-30tc$ Monded at 30Monded at 309 $10-30tc$ Monded at 30Monded at 309 $10-30tc$ Nil at 30Monded at 309 <th></th> <th>••••</th> <th></th> <th></th> <th></th>		••••			
608 $10-30\mathrm{po}$ Nilfuen610 $10-30\mathrm{po}$ Nilmenoclone610 $10-30\mathrm{po}$ Nilmenoclone611 $3\mathrm{po}$ Nilclociguonil611 $3\mathrm{po}$ Niltriazine612 $0.3-1\mathrm{sc}$ Nilmenoclone612 $0.3-1\mathrm{sc}$ Nilmenoclone613 $0.1-0.3\mathrm{po}$ Nilmenoclone613 $1-3\mathrm{sc}$ Nilmenoclone614 $3\mathrm{sc}$ Nil at 1menoclone615 $1-3\mathrm{sc}$ Nil at 1menoclone616 $3\mathrm{sc}$ Present at 1menoclone616 $10-30\mathrm{sc}$ Merked at 30Residual activity onlymenoclone616 $10-30\mathrm{sc}$ Merked at 30Residual activity onlymenoclone616 $10-30\mathrm{sc}$ Nul at 30Residual activity onlymenoclone616 $10-30\mathrm{sc}$ Nul at 30Residual activity onlymenoclone616 $10-30\mathrm{sc}$ Nul at 30Residual activity onlymenoclone617 $30\mathrm{sc}$ Nil at 30Nil at 30minocyc.me618 $3-10\mathrm{sc}$ Nil at 30Nil at 30minocyc.me619 $3-10\mathrm{sc}$ Nil at 30Nil at 30minocyc.me	V No.	Minimum fully active dose (ma/ka x 1)	Residual action at active dose		Type of Compound
50010-30 poNilmenoclone51010-30 poNilclociguanil5113 poNiltrazine5120.3-1 scNilmenoclone5130.3-1 poNilmenoclone5130.3-1 poNilmenoclone5143 scPresent at lmenoclone5151-3 scNil at lmenoclone5143 scPresent at lmenoclone51510-0.3 poNil at lmenoclone51610-30 scMerked at 30Residual cativity only51610-30 scMerked at 30Residual cativity only51610-30 scMerked at 30Residual cativity only51730 poMerked at 30Residual cativity only51810-30 scNil at 30merked at 3051730 poNil at 30merked at 305183-10 scNil at 30merked at 3051930 poNil at 30merked at 3051730 poNil at 30merked at 305183-10 scNil at 30merked at 305193-10 scNil at 30mirked at 305183-10 scNil at 30mirked at 305183-10 scNil at 30mirked at 305193-10 scNil at 30mirked at 305193-10 scNil at 30mirked at 305193-10 scMirked at 30mirked at 305193-10 scMirked at 30mirked at 30<	508	10-30.po	ĪŻ		furan
[310] $10-30\mathrm{po}$ Nilclociguanil[511] $3\mathrm{po}$ Niltriazine[512] $0.3-1\mathrm{sc}$ Niltriazine[513] $0.3-1\mathrm{sc}$ Niltriazine[513] $0.3-1\mathrm{sc}$ Niltriazine[513] $1-3\mathrm{sc}$ Niltriazine[513] $0.1-0.3\mathrm{po}$ Niltriazine[514] $3\mathrm{sc}$ Present of 1triazine[515] $10-30\mathrm{sc}$ Marked radResidual activity only[516] $10-30\mathrm{sc}$ Marked radResidual activity only[517] $30\mathrm{po}$ Present of 10triazine[518] $10-30\mathrm{sc}$ Present of 10triazine[517] $30\mathrm{po}$ Nil et 30Residual activity onlytri[518] $10-30\mathrm{sc}$ Nil et 30Nil et 30[517] $30\mathrm{po}$ Nil et 30Nil et 30[518] $3-10\mathrm{sc}$ Nil et 30Nil et 30[519] $3-10\mathrm{sc}$ Nil et 30Nil et 30[519] $3-10\mathrm{sc}$ Nil et 30Nil et 30[518] $3-10\mathrm{sc}$ Nil et 30Nil et 30[519] 3	1509	î 0-30 po	I.I.N		menoctone
[51] $3po$ Nilinterime[52] $0.3-1$ scNilquinazoline[51] $0.3-1$ scNilmil[51] $0.3-1$ scNilmil[51] $0.3-1$ scNilmil[51] $1-3$ scNilmil[51] $0.1-0.3$ poNilmil[51] 3 scPresent et lmil[51] 3 scPresent et lmil[51] $3po$ Nilmil[51] $10-30$ scPresent et l0mil[51] $10-30$ scPresent et l0mil[51] $10-30$ scPresent et l0mil[51] $10-30$ scPresent et l0mil[51] $10-30$ scNil et 30mil[51] 30 poNil et 30mil[51] 30 poNil et 30mil[51] $3-10$ scNil et 30mil[51] $3-10$	1510	10-30 po	I:Z		clociguanil
I512 $0.3-1$ scNilquinazolineI512 $0.3-1$ poNilNil"I513 $1-3$ scNil ar 1""I513 $1-3$ scNil ar 1""I513 $0.1-0.3$ poNil ar 1""I514 3 scPresent ar 1""I514 3 scPresent ar 1""I514 3 poNil ar 3Residual activity only"I515 $10-30$ scMarked ar 30Residual activity only"I515 $10-30$ scMarked ar 30Residual activity only"I516 $10-30$ scMarked ar 30Residual activity only"I516 $10-30$ scNil ar 30Nil activity only"I517 30 poNil ar 30Nil ar 30"I518 30 poNil ar 30Nil ar 30"I518 $3-10$ poNil ar 30Nil ar 30"I519 $3-10$ poNil ar 30Nil ar 30"I518 $3-10$ poNil ar 30Nil ar 30"I519 $3-10$ poNil ar 30Nil ar 30Nil ar 30I510NNNN	1511	3 ро	ïż		triazine
1512 $0.3-1$ poNil at 1"1513 $1-3$ scNil at 1"1513 $1-3$ scNil at 1"1514 3 scPresent at 1"1514 3 poNil at 3"1515 $10-30$ scMarked at 30Residual activity only"1515 $10-30$ scMarked at 30Residual activity only"1516 $10-30$ scNil at 30""1517 30 poNil at 30""1517 30 poNil at 30""1518 $3-10$ scNil at 30""1518 $3-10$ scNil at 30""1518 $3-10$ poNil at 30""1518 $3-10$ poNil at 30"1518 $3-10$ poNil at 30"1518 $3-10$ poNil at 30"1518 $3-10$ poNil at 30"1519 $3-10$ poNil at 30"1518 $3-10$ poNil at 30"1519 $3-10$ poNil at 30"1519 $3-10$ poNil at 30"1519 $3-10$ poNil at 30"1519 $3-10$ poNil at 30Nil at 301519 $3-10$ po <t< td=""><td>1512</td><td>0.3-1 sc</td><td>īž</td><td></td><td>quinazoline</td></t<>	1512	0.3-1 sc	īž		quinazoline
ISI3 1-3 sc Nil at 1 " ISI3 0.1-0.3 po Nil at 1 " ISI4 3 sc Present at 1 " ISI4 3 sc Present at 1 " ISI5 10-30 sc Marked at 30 Residual activity only Mannich base ISI5 10-30 sc Marked at 30 Residual activity only " ISI6 10-30 sc Marked at 30 Residual activity only " ISI6 10-30 sc Marked at 30 Residual activity only " ISI6 10-30 sc Marked at 30 Residual activity only " ISI6 10-30 sc Marked at 30 Isi at 30 " ISI7 30 sc Nil at 30 " " ISI7 30 ps Nil at 30 " " ISI8 3-10 ps S10 sc Isi at 30 "	1512	0.3-1 po	Ξ. Ž		1
1513 $0.1-0.3 \operatorname{po}$ Nil at 1"1514 $3 \operatorname{sc}$ Present at 1"1514 $3 \operatorname{sc}$ Present at 1"1515 $3 \operatorname{po}$ Nil at 3Residual activity only"1515 $10-30 \operatorname{sc}$ Marked at 30Residual activity only"1516 $10-30 \operatorname{sc}$ Marked at 30Nerked at 30"1517 $30 \operatorname{sc}$ Nil at 30Nil at 30"1518 $3-10 \operatorname{sc}$ Nil at 30Nil at 30"1518 $3-10 \operatorname{pc}$ Nil at 30""1518 $3-10 \operatorname{pc}$ Nil at 30""1518 $3-10 \operatorname{pc}$ Nil at 30""	1513	1- 3 sc	Nil at 1		=
15143 scPresent at 1"15143 poNil at 3"151510-30 scMarked at 30Residual activity only"151530 poMarked at 30Residual activity only"151610-30 scPresent at 10""151610-30 scPresent at 10""151610-30 scPresent at 10""151610-30 pcPresent at 10""151730 scNil at 30Soloo"151730 scNil at 30""15183-10 pcNil at 30Nil at 30"15183-10 pcNil at 30Nil at 30"15183-10 pcNil at 30NN15183-10 pcNNN15183-10 pcNNN15183-10 pcNNN15183-10 pcNNN15183-10 pcNNN15183-10 pcN	1513	0.1-0.3 po	Nil at 1		
15143 poNil at 3"151510-30 scMarked at 30Residual activity onlyMannich base151530 poMarked at 30Residual activity only"151610-30 scMarked at 30Residual activity only"151610-30 poMarked at 30Residual activity only"151610-30 poMarked at 30""151730 scNil at 30""151730 scNil at 30""15183-10 poNil at 30""15183-10 poNil at 30""15183-10 poNil at 30""	1514	3 sc	Present at 1		Ŧ
151510-30 scMarked at 30Residual activity onlyMannich base151530 poMarked at 30Residual activity only"151610-30 scMarked at 30Residual activity only"151610-30 scMarked at 30""151730 scNil at 30""151730 scNil at 30""15183-10 scNil at 30""15183-10 sc10 sc""15183-10 pc10 sc10 sc"15183-10 pc10 sc10 sc10 sc151910 sc10 sc10 sc10 sc151910 sc10 sc10 sc10 sc151910 sc10 sc10	1514	3 po	Nil at 3		Ξ
1515 30 po Marked at 30 Residual activity only " 1516 10-30 sc Present at 10 " " 1516 10-30 po Marked at 30 " " 1516 10-30 po Present at 10 " " 1517 30 sc Nil at 30 " " 1517 30 po Nil at 30 " " 1517 30 po Nil at 30 " " 1518 3-10 sc Nil at 30 " " 1518 3-10 po Nil at 30 " "	1515	10-30 sc	Marked at 30	Residual activity only	Mannich base
1516 10-30 sc Present at 10 Marked at 30 " 1516 10-30 po Present at 10 Marked at 30 " 1517 30 sc Nil at 30 " 1517 30 sc Nil at 30 " 1517 30 po Nil at 30 " 1518 3-10 sc 3-10 po " 1518 3-10 po " "	1515	30 po	Marked at 30	Residual activity only	=
1516 10-30 po Present at 10 Morked at 30 " 1517 30 sc Nil at 30 miscellaneous 1517 30 po Nil at 30 " 1518 3-10 sc " " 1518 3-10 po " "	1516	10-30 sc	Present at 10 Marked at 30		-
1517 30 sc Nil at 30 miscellaneous 1517 30 po Nil at 30 " 1518 3-10 sc " " 1518 3-10 po " "	1516	10-30 po	Present at 10 Marked at 30		=
1517 30 po Nil at 30 1518 3-10 sc minocycte 1518 3-10 po "	1517	30 sc	Nil at 30		miscellaneous
1518 3-10 sc minocycte 1518 3-10 po "	1517	30 po	Nil at 30		2
1518 3-10 po	1518	3-10 sc			minocycie
	1518	3-10 po	•		=

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New Alexandre Ale	SARAN AND AND AND AND AND AND AND AND AND A	and a state of the			
WR No.	LIV No.	Minimum fully active dose (mg/kg x 1)	Residual action at active dose	- Comment	Type of Compcund
231033AA BG89086	1520	10-30 sc	Marked at 10	Residual activity only	8-an:inoquinoline
231033AA BG89086	1520	10-30 po	Present at 10 Marked at 30	Residual activity only	-
231138AA BG89362	1521	30 sc	Nil at 30		naphthyridinone
231138AA BG89362	1521	30 po	Nil at 30		=
1 99507A8 BD24062	1522	1	ŧ	Inactive at 30 mg/kg sc	8-aminoquinoline
199507AB BD24062	1522	8	ŧ	Inactive at 30 mg/kg po	=
230837AA BG85408	1524	30 sc	Nil at 30		miscellaneous
230837AA BG85408	1524	10-30 po	liN		=
27653AD AH07834	1525		9	Inactive at 30 mg/kg sc	RC ₁₂
27653AD AH07834	1525	8	5	Inactive at 30 mg/kg po	RC ₁₂
232584AA BH05361	1541	10-30 sc	Nil		8-aminoquinoline
232584AA BH05361	1541	10-30 po	ΪŻ		Ξ
					TABLE 7 (contd.)

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TIGATOR: PROFESSOR W TABLE 8	ACIFAL INVENT		Ś	م) وت کا	日日三	:YUY:	jal act	RFSID	_
			Q mg/ks	10-30	/E DOSE			MINIM	_
Fully achive	ଏଜ.୫ ^	ZI L		3.80	2:4	3/3		0/3	30.0
Inactive	r Ö I				ي ج			3/3	0.0
Inactive	1 0.54			•	2.11			3/3	3.0
				3.98	5.68	5/S		2/S	Ø
COX COX	Frephylocue Activity	Resi-Jural Ácityity	$(h - f) = \frac{(b - a)(e - a)}{(c - a)} - (b - c)$. 'e'	ы Ч Ч	× ×.	×		img/kg
		VAI UES	(a = 2) ACTIVITY	P P	GMP 29	ATE A		PA -	DOSE
Stheft NG		(S: P. Z. Digar	PARATTE (JUK) SPECH		S TFW MICE	021: 0	₩AT! H	Staf 2	
TIME ALL TR. DATE: TO	, pr	A110N1 4	POSITE OF SOMETING		02H 108	1 4 80	NOHVX	FRLFM	-,,-
BOTHENC. BECKED			AA 268812 M	1348	۲ ۰ ۰٬۷۰			002	•
8E/1/21 .1.VG	Tres Lassen buckets . Low and early a state of the mean			BR649	iest NO.	SIX a Mr.	AI 14 CT	CANS	
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	CAUSAL 140	There a X	is iest >	0: •	x 640	, A				84.1.21.71
- •	DRUG				F64		WK 218335 AA			BOTHENC, BEGG
7 6	FREFAXATIO	1 · · · ·	- - - - - - - - - - - 	0			POLITE OL COMPLIST	ALONS 4	d.	OWE AFTER DATE OF
	. FR 11 184 A 14	باري،	O HWA	Mic F			PARA UTE (NIR) SPECH	S: P Aired		OW PRANS
DOSE	PATENCO	Y RATE	G	AP 2%			<u>(a = 2) ACTIVITY</u>	VAI UES		
mg/ kg	c°/ _T ° XC	· CX/TX	î,în	ى	; /e.	$(\mathbf{p} - \mathbf{f}) = \int_{-\infty}^{\infty} (\mathbf{p} - \mathbf{f})$	$\frac{-\alpha)(e - \alpha)}{(e - \alpha)} - (b - \alpha)$	Residial Áctivity	Frophylacie Activity	CON
Ø	5/5	s/s	S.68		3.98					
3 O	3/3		5.35						1 0.33	Inachive
0.01	3/3		4.90						84:0-	Inactive
30.0	0/3	3/3	×i<		4.63			NIL	× 8.32	Fullyactive
	•									A ≈ ∼uα⊅gadé
	MINIMUM F	η η Ας	TIVE DOS		0-90	mg/kg				
	RFSIDUAL A	стуну:	Ξ,Ζ	at	ር' 0 ጠ	· 64/ 6		and Sel	JCIFAL INVEST	IGATOR: PROFESSOR W
										TABLE 9
					ı					
المعادية والمحالية المحالية المح			i i i i i i i i i i i i i i i i i i i							
	and the second secon	ter and at the second second second	And		A PASSA A CARL A					

				and the second	e.	لمراجع میں اور	1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1	and south the second	ين المراسم الم موالية المراسم ا	A. S. S. S. S. S. S. S. S. S.
							··· ··	•	- ,	· · · · · ·
TABLE 10				•						
TIGATOR: PROFESSOR W.	JCIPAL INVES	A: XA	ائ گ	/وس 30	il at	Z	:VnY:	AI ACT	RFSIDU	_
			ნა/რმ	1	DSE	IIVE DO	ΓΙΥ ΑΟ	JM FUI	MINIM	
Inactive	- 0.05	NIL		4 20		5.63	3/3		3/3	30,0
Inactive	0.45					6.13			3/3	0.01
Inachise	0					5.68			3/3	3.0
				86.5	~	5.63	s/s		5/2	Ø
COMK	Prophylacue Activity	Kesi-jual Áctivity	$(h - f) = \int \frac{(b - a)(e - a)}{(c - a)} - (b - a)$.)e.	ىد	<u>}</u>	C ^X /T ^X	с I ×	c ^c / _T ⁰	mg/kg
		VAI UES	(a = 2) ACTIVITY	d	3MP 2%		2ATE	702	PÁ I t	DOSE
StkAid- NiG		.S: <u>P. y. auguri</u>	PARATTE (SUM) SPECI		V Mic.E	C 11	:150	H 1179	18 H A I A	
NON ALLES THER HOW	, br,	بسكيتها وMO(IA)	POINT OF TOMINISH		0, 5	કરા. છેી	~	~(;.1)	FRI LAW	
90111. NO. BG36612			W 127681 AA	6661					DRUC.	•
9A11, 12.1.78				66649	:ON	S IESI	XVIII	, IC 2 24.1	C ANSAI	

								A A A A A A A A A A A A A A A A A A A		
	с, USAi ¹⁶⁷	X V 17 +	IS : ES I >	ίΟ. Β	Ř 646					8 F · I · 8 I · J · 84
				, ^.1	1402	WK	228002 AA			101111 MON 84 581
	TKLEA (MIN)	** **	ું પુરૂ નગર	ວ. ≁`	-	HO.	H OF SOME IS RA	41.0%5	à.	Dividine de la IM.C
the state of the s	« FR 1-31 A.1	:130H	C TFW	Mıć.E		I And	a ufe (sub) specific	3: P	· • >51 म	S.kArd N.C
DOSE	PATENCY	Y RATE	19	MP 2%			(a 2) ACTIVITY	VAI UES		
mg/kg	c ^c / _T ., xc	CX/TX	f.h	ىد	. ə/	$(h - f) - \frac{1}{2} (f - a)(f $	$\left(\frac{\alpha}{2}\right)^{-1} = (p \cdot \alpha)^{-1}$	Resident Activity	Frephyleeve Activity	03
Ø	4/S		5.82							
0 Y	* ¹ / ¹		%.8<							Achue
0.	2/3		C0.6<							Acrive
3.0	2/3		06.6<	-						Active
9										
	MINIMUM	ULY ACT	IIVE DO	SE	۵ ۵ ۵	€¥∕£m				
	RFSIDUAL A	стуну:						PREV	ICIPAL INVEST	IGATOR: PROFESSOR V
	* 1/3 DIED									
					٠		·			TABLE 11
	j -									
		and the second	A CALIFORNIA SA CALIFORNIA	ALC AND ALC	2012月1月1日初至			経営の行動を含む		artikere some for the second

								ine and the second	A CONTRACT OF	
						1. 1. 1.		·	-	· · · · · · · · · · · · · · · · · · ·
TABLE 12				`				DEAD	3/2	
IGATOR: PROFESSOR W	ACIFAL INVEST	PRS		63/6	at 10.	lin	:γnγ:	AL. ACT	RFSIDUJ	
			ლდ	3-10	SE	IIVE DC		IN FUI	MINIM	
									•	
>LDioe						•			°/3 *	30.0
Fully active	£8:t <	NIL		3.51		ž	3/3		%3	0.0
Hchive A Marine	> 5:09					70.114			۲ <u>ع</u>	3,0
				EF.S		513	5/2		5/S	Ø
NOC COM	Frephyleciu Activity	Residual Activity	$(h - f) - \frac{(b - a)(e - a)}{(c - a)} - (b - a)$	°/e	ع	ۍ ^۲	CX/T×	×	c°/ _T o	mg/kg
		VALUES	(a = 2) ACTIVITY	4	3MP 2%		RATE		PÁ II	DOSE
Sikaid: NiG	iens's	5: <u>P. , aigar</u>	PARA STE (SUB) SPECH		Ι Μις.Ε	Ć TFW	1301	к АТ!	V FR 158	age water a survey of the
TIME AL (P MERCHON	cd,	ALION: H	ROUTE OF FOMI-FISTE		0 ⁷ H,	eer, öQ,	<u>۲</u> ۲	NOILA	PRLPA%.	
BOTHENO. BG 6280			WR 228456AA	5141	۲. <i>۰</i> ۷/				URIJG.	
1. 5.1-78				3R 647	Ö N	IS IEST	X 5 ⁽)	Č ž		
					NAME AND ADDRESS OF					

	r AulsAi	INCONTA.	XIS LES	NO	BR 64	£					86-1-21	
•	DRIG.			1.27	1425	'n	CIZ W	gy sest			BOTHENC, BG48	96
	₽RLFA×⊿		∿eer, öΩ	O,H			5 milOz	N SOMETISTR	41:0''': 4:	·›d	TAN ALTER TAUEN	Ő
	~ FR 1 FBK	ATE MOST:	011-0	M Mić E			PARAUTE	F (548) SPECIES	S. P. K. algere		SikArd NiG	× 14.100 -
DOSE	PATE	NCY RATE		GMP 2%	P - 0		- p)	- 2) ACTIVITY	VAI UFS			
mg/kg	C°/ _T °		Lx Lx	<u>م</u>	, e	. (h - f)	$-\left \frac{(b - a)(e - a)}{(c - a)} \right $	i (ω · q) - [Residual Áctivity	Prophylaciuc Activity	<u></u>	N C
Ø	5/2	S/S	\$ 2.6	60	80°5							ار فر مرا ^ر یا
3.0	3/3		5.6	~						10.0 -	Inactive	5
0.0	3/3		6.16							0.48	Inactive	. ANT CAR
30.0	3/3	3/3	9 6-13		4.58				NIL	0.49	Inactive	
	•											
	OWINIW	M FULLY AG	CTIVE D	OSE	1	ц	ნა/მ					
	RFSIDUA	N. ACTIVITY	ź	i at	S S S S S S S S S S S S S S S S S S S	છ/છ.			1284 	ICIPAL INVENT	IGATOR: PROFESSOR	∧ ~
					•						TABLE 13	
	· · · · · · · · · · · · · · · · · · ·											

1.1.1. 120

	CAUSAI		コメメリシ	S IESE A	<u>40</u> .	BR 64	ſ,				8E11/5 1:VG
	- 31 J. W. J.				I	438	-	W 221 527 AB			BOTHENC, BG488
	FREEAW	2010	9≮-	ອດເ. ທີ່ໄ, 🖓	°, ℃			POLITE OF COMPANY	ALIONS 4	, br	OULS INTE ALLIV INT
	v IR 14 B	H HV	(),¦;	с њи	Mić E		,	PARAUTE (NB) SPECIE	S: P. V. alger	· .×i+++	StkA M. NG
DOSE	PATE	NCY R	ATE -	6	MP 2%	d		(a = 2) ACTIVITY	VAI UFS		
mg/kc	g (c ^o / _T o		c×/.tx	ų, tr	ى	ر'. د / د	$(h - f) = \frac{1}{2}(h - f)$	$\frac{-\alpha}{(c-\alpha)} - (b-\alpha)$	<u>Řesidual</u> Áctivity	Prophylacus Astivity	S.
Ø	5/5		5/S	t.9		÷H S					2025
3.0 3	*0/3			×4						E8.F <	Fully achive
0.0	%** %		3/3	>14		4.03			NIC	₹8.۲ <	Fully active
30.0	%3										> LD.00
	ł 										
	MINIM	UM FUI	TY ACT	IVE DO:	SE	3	бж∕бш				
	KESIDUX	AL. ACT DIED	ivny:	1.2	at t) <u>en</u> 0	J.		PRSP	ACIFAL INVEST	IGATOR: PROFESSOR
	E/C ++	1 DIED	۵				·				TABLE 14
	 : .										

	CAUSAL	ПУН ДО й І	a XIS 1E	SI NO:	BR	939						8E/1/EC. JIVG	
	SRUG.			· · ·	4	64		w W	03608 A	4		10101 NO. ZN 431	1
	PRLPAKA	:NOH	l veer.	80, H ₂ O				nor	SIL-IWOY IO	IPAIJONE +p/a	ud./.	TAME AFFIRE AND FOR	4
	VFR (1-8k/	ATF HOST	Ω̈́.	IFW MIC	щ			PARA	71E (5438) SPEC	JCS: P. y. niger	ieus.	SikAiti: NiG	. A
DOSE	PATEN	ICY RATE		GMP 2	ч р.				(a = 2) ACTIVI	ry values			
mg/kg	c°/ _T o	x) VX	/T× Γ	ېا P	U` 	e	(h - f) -	(<u>b - a)(e</u> (c - ($(\alpha \cdot q) - \frac{(r)}{(r)}$	Residual Activity	Prophylectic Activity	CON	Ny -
æ	4/4	3/	3 2	£	ñ	فع							1. A. M. M. C. M 1. M.
3,0 10	3/3		Ň	Ē	 						- 0.56	Inactive.	1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1
0.01	3/3		Ŝ	S							~ 0.23	Inuctive .	ગમર્ટ છે. ત્વડો બદ્ધ
30.0	3/3	°.	/3 5.	45	ŝ	4				NIL	- 0.28	Inachive .	
													and Constitution
													1
													MF 1996
_	MIN:MUM	M FULLY /	ACTIVE	DOSE .		1	/6m	kg				- -	an a
	RESIDUAL		<i>⊷</i> ∵	ti'l at	о м	<u>و</u>	<u>الع</u>			PRi	NCIPAL INVEST	IGATOR: PROFESSOR W	а. >
												[ABLE 15	

La come	C.A.USAI	⋎⋖Ћл⋴⊖аа	US LEST NO.	BRESI	_0		ter versioner and the second		84/1/6C . JIAO
v =44.)	DRIJG.		i.·V,	1449	WR	203 608 AA			80111 F NO. ZN 4212
	PRLPAKA	x1	veer. 80, 11 ₂ 0		10:	ITE OF ADMIMIST	AllON: 40	, bo	HMI ALTP INTERIOU
	`v FR 11 86	All HOST:	O TEW MIC	ш	PAR	kasite (sua) specie	S: P. V. nigrai	jensis j	SikAid: NG
DOSE	PATE	NCY RATE	GMP 2	4 %		(a = 2) ACTIVITY	VAI.UES		
mg/kg	c°/r^{0}	$x c \frac{c^{x}}{r}$	х ^f /h b	^ر /و	$(h - f) = \frac{1}{2} \left(\frac{b - a}{b}\right)$	$\frac{(e - \alpha)}{-\alpha} - (b - \alpha)^{\frac{1}{2}}$	Kesidual Áctivity	Prophylectic Activity	COMA
Ø	4/4	3/3	5-73	3.62					
ŝ	3/3		5:48					-0.25	Inuctive.
0.01	3/3		5:38					-0.35	Inactive .
ନ୍ତି	2/3	3/3	5.4	3.58			NIL	- 0.29	Inactive.
		2 040 0 ¹⁰⁰ - 1140 0100 - 1140							
	NINIMU	IM FULLY AC	TIVE DOSE	1	mg/kg				
	RFSIDUA	AL ACTIVITY:	Nil ar	30 mg	. ويا/		PRIN	ICIPAL INVEST	IGATOR: PROFESSOR W.
							·		TABLE 16

AXIS 1EST 140: BA E-4-6 DAYT, 18-1-38 LVX HAST MR 2192874 AA 00111 FNC. ZN42883 LVX HAST MR 2192874 O'L-4-1-1 MR 1112 LI-18 LVX LVX HAST MR 219281 O'L-4-1-1-1 MR 1112 LI-18 LVX LVX LVX LVX MR 219281 O'L-4-1-1-1 MR 21011 L G TEV MUE LMAX-TF (VIA) STFC1/S. F. 2-09241 MR 11-1 MU 0 L G TEV MUE LMAX-TF (VIA) STFC1/S. F. 2-09241 MR 11-1 MU 0 L G TEV MUE LMAX-TF (VIA) STFC1/S. F. 2-09241 MA 11-1 COMM L G TEV MUE LMAX-TF (VIA) STFC1/S. F. 2-09241 MA 11-1 MA 11-1 L G TEV MUE LMAX-TF (VIA) STFC1/S. F. 2-09241 MA 11-1 MA 11-1 L S 282 P P P P L L L L L L L S 282 P P P P L L L L L L L L L L L L L L L L L L L L L L L L L <th>1.AXIS TEST NO. BR 646 IV./ 1451 WR 219 I. Ween 60, 4₂0 B1, C TEW MICE BACK</th> <th></th> <th></th>	1.AXIS TEST NO. BR 646 IV./ 1451 WR 219 I. Ween 60, 4 ₂ 0 B1, C TEW MICE BACK		
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	L.V./ 1451 WR 219 L.V./ 1451 WR 219 L. C.TFW MICE BARAUT		8E-1-81 JUVG
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Tweet 60, H ₂ O C TFW MicE	9874 AA	MOULENC. ZN 4282
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	LE CIEW MICE EARAUT	OF ADMIT IS IPAL OCH HE CARA	WOH ATTE ATTY W'L
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$		IF (Stal) SPECIES: P. P. Digreteries	SikAii L. NiG
$\sqrt{1}$ f_{n} h_{n} z_{n} $(n - s_{1} - \frac{1}{2}(s - \frac{1}{2}) - (s - \sigma_{1})$ $Fersihvlerik. COMM S:82 A_{c1viy} A_{c1viy} A_{c1viy} S:82 A_{c1viy} A_{c1viy} S:82 A_{c1viy} A_{c1viy} N148 A_{c1viy} N14 A_{c1viy} N4 A_{c1viy} N14 A_{c1viy} N14 A_{c1viy} N14 A_{c1viy} N14 A_{c1viy} ACTIVE DOSE A_{c1viy} ACTIVE DOSE A_{c1viy} ACTIVE DOSE A_{c1viy} ACTIVE DOSE A_{c1viy} N: Ni at 3o' <$	E GMP 2% P (a	= 2) ACTIVITY VALUES	
5.82 Achive >14- Achive >14- Achive >14- Fullyactive	$\frac{x}{\sqrt{Tx}} \frac{f}{f}h$ b $\frac{c}{e}$ (h - f) $\frac{(b - \alpha)(e - \alpha)}{(c - \alpha)}$	a) - (b · a) Residual Prophylacii Activity Activity	COMM
ylta8 Active >14 Active >14 Eulylactive Active Dose Boundaria Active Dose Britation Active Dose Failugation Active Dose Britation	5.82		žebrča -
>14 Eullyactive	211.48		Achue
>14 Fully audre >14 Fully audre Active bose 310 Active bose 310 Active bose 310 Prive in at 30 (previous data) PRINCIPAL INVESTIGATOR: PROFESSOR W.	>14		Fully active
ACTIVE DOSE 310 mg/kg ACTIVE DOSE 310 mg/kg Y: Nil at 30 (purious data) R:INCIPAL INVESTIGATOR: PROFESSOR W. TABLE 17 TABLE 17	>14		Fullyactive
ACTIVE DOSE 3-10mg/kg ACTIVE DOSE 3-10mg/kg Y: Nil at 30 (previous data) R:NCIFAL !NVESTIGATOR: PROFESSOR W.			
ACTIVE DOSE 3-10mg/kg Y: Nil at 30 (puious data) TABLE 17 TABLE 17			
ACTIVE DOSE 3-10. mg/kg Y: Nil at 30 (perious data) TABLE 17 TABLE 17			
Y: Nil at 30 (purious data) PRINCIPAL INVESTIGATOR: PROFESSOR W. TABLE 17 TABLE 17	/ ACTIVE DOSE 3\O mg/kg		*222.02.02.24
TABLE 17	ITY: Nil at 30 (perious data)	PRINCIPAL INVE	STIGATOR: PROFESSOR W.
	,		TABLE 17

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								-	 	
2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2										
IGATOR: PROFESSOR W	ICIFAL INVESI	N:24		ivious data)	so (pe	Nil at 3	VIIY:	ALACT:	KESIDU	
				Q mg∕kg	3-1	VE DOSE .	LY ACTI	JM FUIL	MINIM	
			-							
Fully achive						4 ~			€/٥	30.0
Fully active						>14			o/3	0.01
Active					 i	F\$;8<			2/3	3.0
						5.82	,	1	4/5	Ø
CON	Prophylociuc Activity	Residual Áctivity	$\frac{\alpha}{\alpha} \frac{(e - \alpha)}{(e - \alpha)} - (p - \alpha)$	(h - f) = (f - f)	;` `;`	ب ^ہ	ت×'لم	U X	^{ر ۲} ٬۰	mg/kg
		<u>VAI UFS</u>	(a - 2) ACTIVITY		d %	GMP 2	AT:		PAT	DOSE
SikArd Nic		5: P	ARA J'TE (NIR) SPECH		ي.	C TFW Mic); +; (1. 41.	ግ በየ ብ አ	
WE AFTER THE FOR	. d	AI 0% ++	OTH OL SOMEDSIE	£1		1, 80, H ₂ O	いて	4.(P×EFA ⇔	
8014 F NC. ZN 4287			WY THE GIR W	۲. ۲.	, 14S	···!			ડ્રાશ્કાર.	Tr.e.
84.1.81 .31A0		100 Mar 11-19 (Mar 100) Mar 10-19 (Mar 10-19)		546	BR 6	IESI NO.	SIXVIV	-	CAUSAİ	

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	с Ausai	нДОлт	; X & 17.1	S LEST NO	αΩ 	R 647						8 E/1/S 'J(V()
	SHRG				1	පුලුව		NG W	AA 19F 2			HOTHENC, BEIGO
	PkLFAKA	1-1-2-11	a.~ 1	er. 80, 4 ₇ 0	در			nilOa	OL FOMITISI	PALOVIC HEA	t d	OFF STREET BY WIL
	*11 H 11 Å	SF HV	;1;(Ć TrW Mo	Ш			PARAS	TF (34.14) SPFCI	r. p. e , - , - , - , - , - , - , - , - , -		SikArid, NiG
DOSE	PATE	NCY RA	\TE	GMP	2% P			(a	- 2) ACTIVITY	r VALUES	-	
mg/kg	c [°] / _T 0	ر ×	c ^x , _T x	h h	ى_	, , , ,	(+ - t) -	$\frac{(p-\alpha)(e-\alpha)}{(c-\alpha)}$	α) - (p · α)	Reși-juul Ácîivity	Prophylaciic Activity	COM
Ø	5/5		5/5	ti.9		ft.S						
3.0	3/3			5.62							1 0.55	Inactive
0.0	5/ع			>14					-		£8.F <	Fully active
30.0	6/ع	f	3/3	× 4		3.62				NIL	€8·F <	Fully active
												0
	NINIW	I'IN FUIT	Y ACTI	VE DOSE	сı,	0	/6ш	Į,g				
_	RESIDUA	I. ACIN	/IIY:	Nil at	м М	ا/ وس د	م			PRI	ACIPAL INVESTI	IGATOR: PROFESSOR W.
											-	ABLE 19

1.45
								The second second	······································	
TABLE 20		· · ·								
IGATOR: PROFESSOR W.	icipal invest	41284	J.	/ Em 01	ar 12	Nii	WITY:	AL ACT	KFSID1.	
			mg/kg	>30	DSE	IVE DO	LY ACI	JM FUI	MINIM	
			-							
Active	> 5,50	NIL		3.St		>11.6	3/3		¹ /3	30.0
l hackive	- 0.0 -					619			3/3	0 0
hachie	10.62					5.55	 		3/3	9 9
ering in a				FF.5		tig	5/5		5/5	8
WWO()	Frophylaciic Activity	Residical Áchivity	$(h - f) - \frac{(b - a)(e - a)}{(c - a)} - (b - a)$	°/e	ى	<u>,</u>	ر× / ۲×	ر : ×	c^{c}/T^{0}	mg/kg
		VALUES	(a = 2) ACTIVIT	6 P	3MP 24		ATE		PÁTE	DOSE
SikArid, Nic		ts: <u>P. V. aigar</u> i	PARASTE (SUR) SPEC		V Mic.E	ố TEV	:150	H 118,	1841 84 ^.	
TAME ALL FR. DATE: HONE	'n.	PALIONE HILL	PORT OF TOM FISH		0. T	ငေး ပဲ()	* -	****	PREFAX	
BOTA SULADO			A ISFSIC W	1455	、				SH13G	
84/1/S JIG			Γŗ	BR 64	ON	is lest	X v 17.0	.i., 1	CAUSAI	
					A DESCRIPTION OF THE OWNER OF THE					

-						A CONTRACT AND A CONTRACT							
	CAUSA!	IdO aid	TUAX	S iEST	NO:	5R 64	E		en of Maria January, en en Var en		nie w la constante a const	NET A MARKEN KANKANA ANA ANA ANA ANA ANA ANA ANA AN	DATE: 5/1/78
	DRUG.					1476	Δ	-	WR 2303	588 AA			BOTHE NO. BC BISE
	₽₿Е₽₳₦₼	NOIN	: Í we	ser, 80,	H ₂ O				ROUTE OF A	DMINISIP.	AlloN: 44	/,pr	TIME AF LEP. I NEECOO
	VFR IFBK	ATF H	osr:	ð tfw	MICE				PARASITE (S	UM) SPECIE	S: <u>P. y. niger</u>	iensis	sikaiN: Nic
DOSE	PATE	NCYR	ATE	5	:MP 2%	٩			(a = 2)	ACTIVITY	VALUES		
mg/kg	c°/ _T °	UX X	c ^x / _T x	t L		c/e	ب	- t) - (t-	- α)(e - α) (c - α) -	(p ·· q)	Residual Activity	Prophylaciic Activiły	Ö
8	5/5		5/5	たいの		tt.S							
9.0 .0	2/3			8 -8<								> 2.25	Active
0.0	0/3		 	× 4			<u></u>					£8.F <	Fully active
30.0	o/3			<u>4</u> 4		3.4.	4				NIL	58-F <	Fully active
												ale day of the second)
									-				
	MINIM				DSE	3-1	0	mg/kg					
_	RESIDU	AL. ACI	יאטאן.	ĨŻ	4	30		ଣ			1X	NCIPAL INVES	rigator: professor v
													TABLE 21
	· · · · · · · · · · · · · · · · · · ·												
AN CONTRACTOR	N. S.		SERVICE REPORT	ALAST CONTRACTOR		NH SHOW	Contraction of the second	NUT GENERAL STATE	ALL STATISTICS AND ALL ALL STATISTICS AND ALL STATI	South R. Minishi	WANTER AND	「「「「「「「」」」」	

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A STATE AND A S	<u>।</u> শিল্প	216231	ギャワ	5 LEST ⁿ	<u> </u>	BRGE	đ			the restar is a first second by welling a second by the		8E/1/81 JUV0
	ં પ્રાપ્ત:				ł ł	504		WK 18	0409 AC			BOTHENO, BESSATC
	iklfa	41-17-4	24	ier, 80, 1	0.1			2018 11102	OL SOMETS P	ALON: HIM	, d	NON A 1811 BALLY IN'L
	NH 11 AL ^.	11-1124	51:0	Ó TFW	Mić.F			FARA S	IF (5.M) SPECIE	S: P. V. Napad	5,5514	SikAily Nic
DOSE	PÀ IL	NOV B	∆TE	5	MP 2%			<u>p)</u>	= 2) ACTIVITY	VALUES		
mg/kg	c^{o}/t^{o}	L X	ت×1⁄±×	ĥ	٩	ر. رو	(y - t)	$-\left \frac{(b-a)(e-a)}{(c-a)}\right $	$\frac{1}{2} (o \cdot q) - (\overline{o}$	Residual Áctivity	Prophylaciic Activity	COMN
Ø	5/5	3/3	5/ 5	5.41	4.50	4.65						
3.0	2/3			9.60		SE.F	- 61.4	2.50 + 5	. <u>35</u> -2.50]	2.65	1:54	
0.0	3/3			97.6		7-60	3.85 -	[2.50 × 5.	60 - 2.50	2.89	96.0	Activity mainly vesig
30.0	3/3			10.11		10.50	5.60-	[2.50 × 8.5	[a: 2-	5.68	- 0.08	
								-				
	MINIM	UM FUI	ιΥ ΑСΤ	IVE DO	SE	>30	E .	g/kg				
	RFSIDU	AL ACT	іупу:	Per	tent a	カ	24/ Su			4:24	ICIPAL INVEST	IGATOR: PROFESSOR W.
-	* 1/3 -	DICD										TABLE 22
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TABLE 23		` •								
IGATOR: PROFESSOR W	ucipal invest	r: A: N	[kg	و م	9 7 7	ii Z	λυλί	AI. AC	RESIDI	_
			mg/kg	30	OSE	CTIVE D	ι.LΥ Ασ	IUM FU	MINIM	
			-							
жжж э ў ,										
Active.	3.91	NIL		ود.4	.œ	~ 33	3/3		2/3	30.0
Active .	2.37				00	ţ			3/3	10.0
Inactive .	88.0				Ø	ب و			3/3	ů. O
				4.60	Ŧ	ů V	s/s		s/s	Ø
COMN	Prophylectic Activity	Residual Activity	$\left[(p - i) - \frac{(c - a)}{(p - a)(e - a)} - (p - a) \right]$	ر د (e	م.	× t	χ.	X	c°/ _T o	mg/kg
•		VALUES	(a = 2) ACTIVITY	4	GMP 2%		RATE	ENC.Y	PAI	DOSE
SikAid: NiG	5 . 5 . 5 . 5 . 5 . 5 . 5 . 5 . 5 . 5 .	S: P nigrai	PARAUTE (SUB) SPECIE		W Mic E	Q II	:1501	₩A11 +	4 I B I I	
TIME AL (FR. LINEPOLY)	, br,	کا ۵۱،۵۵۰ مرتب	ROUTION TO PUDA		0 H.O	งอรา. ผู้ไ		10.1V	PRLFAX	
10111 L NO. 44.2884			WR 448 AG	ISOS	L.v./				Catho.	
3 8L.1.81.7tV0			đ	BR 65	: ON I	XIS IES	NH A	гожг х	יגטאדי	
						inerstation of the second s		Survey and	A Star Star	Sandara Ash

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	A deve	المعارية الم	Si x v	ET N	<u>ତ</u> . ଜ	3R 653	4			-	861181 H.V.
	-6:26.				.	206	۹ ۲	JA 865		-	PUTTE NO. AF 500
	1 KEFA C		しいやい	··. 80, H	0,		HEOZ	CI SUMPLISE	AI 004	ġ.	MOLEN AND AND MOL
	R 11 R	.(ч. П.А.	.:	I M IL C	Mic E		1 ARA 1	ાર (ંહાક) કામ્લોન	S. P	·	S.R.A. L. N.C.
DOSE	PAIE	NUL PATE		GŇ	AP 2%	d)	<u>a = 2) ACTIVITY</u>	VAI UFS		
mg/kg	c?/ ₁₀		/.T.	ĥ	فحو	;/e	$(h - f) - \frac{1}{2}(h - a)(e - a)$	$\frac{1}{2} - \alpha$ - (p - c)	Recidint Activity	Frephylaciu Autiviiy	ŴO.?
B	5/5	<u>i</u>	Ś	5.41		460					
3.0	3/3			5.56						0.15	Inactive
0.0	3/3			6.22						0.81	Inactive
30.0	3/3	ิตั	(3	8.58		4.06			NiL	£1,5	Achive
							-				
	WINIW	M FULLY	ACTIN	VE DOS	* : بو	Э О	6.Yom				3. 18 m June 1. m Bar
	RESIDUA	AL ACTIVIT	۲. ۲.	1:1 2	с М	1/5~	ள			ACIFAL INVESTI	GATOR: PROFESSOR W
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			to be a compared to be compared to be a compared to be a compared to be a								

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a Sing the state	CASSAL 1	XVIPPLE	IS IESI	NC.	Seesa	<u>لہ</u>				8 L · 1 · 81 · 1: VG
	in the			, ^, <u>'</u>	Liv 15	to	WR 93133 AC		-	101111 MOL BB 5962
	P. K. F. X. K. A.	57 - T. ().	وتوريد وال	ບ ະ			PORT OF STANDIST	ALO'S HIL		NOR A NO 24 IV IW'I
<u> </u>	× 18 11 81 *	::(יויו	Ϋ́ Η Ο	/ Mić E			EARA L'IT (LER) SPECIE	S: F		SikArt Nic
DOSE	PATEL 4	TY RATE		3MP 2%	d		<u>(a = 2) AC TIVITY</u>	VAI UES	3	
mg/kg	c°/r°		×.	ىد	5, 	- (j - ų)	$-\left \frac{(b-a)(e-a)}{(c-a)} - (b-a) \right $	kreijiul Áctivity	Frephylacius Astivity	MOC:
Ø	5/s	5/5	5.4		4.60					
3.0	3/3		16.5						05.0	Inactive
0 0	3/3		5.38						-0.03	Inactive
30.0	3/3	3/3	7.95		4.48			NIC	2.54	Active
										, vi4i
							-			A. 10 - 1 - 2 - 2 - 2 - 2 - 2 - 2 - 2 - 2 - 2
										e - 22 84493
	WIWIWIW	FULLY AC	TIVE DC	JSE	V 30	Sm	j/kg			*******************************
	RESIDUAL.	ACTIVITY:	īž	ar i	50 50	G.		E 24	JCIPAL JNVEST	GATOR: PROFESSOR W
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			and the second second		Sale-op-						
	1 IVSBX1	121111	SIX V	IEST N	0. B	R680	^				841 4 1 FE . 1140
	DRUK 3				× · · · · ·	805		ar 179305 Ad		-	SOLIF NO. BE4733
	PREPARAT	1.().) vec	36. 80, H	0,			ROULE OF SUMPRISE	ALIONS H	.pc	I'MI VI I'L INLES I'NON
	_18118C∆	15010-11	<u>.</u>) TFW A	ά ις.Ε			PARASUE (505) SPECI	S: F. Z. aigeri	1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1	SikAidi Nic
POSE	PATEN	CY RATE		<u></u>	AP 2%			(a ≈ 2) ACTIVITY	VAI.UES	3	
mg/kg	C°/ _T "		ΎT×	J.	ىك	ر 'e	(h - f) -	$\frac{(\mathbf{b}-\alpha)(\mathbf{e}-\alpha)}{(c-\beta)} - (\mathbf{b}-\alpha)$	Residual Áctivity	Prophyleciuc Activity	WWOC)
Ø	s/s	ัก	/3 (SF. d		3.%					a france is
3.0	3/3			4.43						- 2.30	Inachise.
00	*£/1			9.54						18.5 <	Pehve.
30.0	o/3	<u>s</u>	3	.4		3.92			NIL	حد ج ۲	Fully active.
											-
	VOWINIW	ላ ቶሀቤረ	ACTN	VE DOS	с Э	1	V ⁶ ш0.	kg			
	RFSIDUAL	ACTIVIT	<u>۲</u>	lin	ち	30	وعا/ور		41.84	ACIPAL INVENT	GATOR: PROFESSOR W.
	* 1/3 D	G								-	ABLE 26
	-						· · · · · · · · · · · · · · · · · · ·				
				AND DESCRIPTION OF THE OWNER OF T							

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25.y ⁻	C.AUSAI	HC 44	1XA N ⁴	S LEST		3865	Q					14/4/ 48 JIV
	:ગ્રહ્માઉ.				(· · · ·)	509		WR 498	08 AC			SETTE EN. NN THIOR
- *	PREPARE	P-O-IV	1 ~6	ser. 80, 5	o, ⁺			soure or	ALSH-IMOR	ABONE HIT	, be	TIMI ALTER INFRUM
	.^ FR 118ŀ	ATL 11	051:	O TEW	Mić.E			PARASILE	(21:14) SPECIF	S: F. V. aigar		SikAid: NiG
DOSE	PATL	NCY R	ATE	<u>ق</u>	MP 2%	d		(a =)	2) ACTIVITY	VALUES		
mg/kg	c°/ _T 0	L X	c ^x / _T x	f Jh	ع	د/e	(h - f) -	$\left \frac{(b-a)(e-a)}{(c-a)}\right $	- (p ·· q)	Residual Áctivity	Prophyleciic Activity	COMV
Ø	5/S		3/3	643		3.86						
ю м	3/3			5.83							-1-90	Incubive.
0.01	2/3			ନ୍ମ - ୫<							<06'I<	Active.
30.0	o/3		3/3	>14		3.82				NIL	F2.F<	Fully Active.
								-				
	MINIMC	JM FUL	ΓΥ ACT	IVE DO	SE	10 - 0	Ç	/kg				
	RFSIDUA	N ACTI	νηγ.	ĨZ	at	30 5	وما/و			PR	ACIPAL INVEST	IGATOR: PROFESSOR W.
												TABLE 27
	, ,											
	ALC AND	ALC: NO.	世界が大学校	or an arrive	and the second second	a contraint			C. C. M. K. C. M. K. C. M. K. C. M. K.			

		······································							• •	
TABLE 28										
TIGATOR: PROFESSOR W.	ACIPAL INVES	98.1 1	ويا	30 mg	il ar	Z	יייזי:	AI ACI	RESIDU	
			mg/kg	10-30	DSE	rive do	TLY AC	UM FUI	MINIM	
			-						1	
Fully active.	+2.F <	NIL		3.98		¥ 4	3/3		٤/٥	0 0 0 0 0 0 0
Inachive.	1-08					5.65			3/3	0.01
Inactive.	52.0 -					6.48			3/3	Э, О
				3 8 8		5F.9	3/3	1	5/S	Ø
COM	Prophylactic Activity	Residual Áctivity	$(h - f) - \frac{b - a(e - a)}{b - a} - (b - a)$) (e	ع	Å.	С,′,тх		c°/ _T o	mg/kg
		VALUES	(a = 2) ACTIVITY		3MP 2%		ATE -		1 Þá 1	DOSE
SikAital Mic	letts: s	S: <u>F. y. nigar</u> i	PARASTE (SUB) SPECH		/ Mic.E	O IFW	051:	P EV3	V FR 113	
TIME AFTER THEFT HON	od,	AION: Prime	ROUTE OF THAT		H,O	cer, 60,	~ - 	A140 A	PR EFAX	
BOTHENO. AM 3327			G-65835 W	1510	ί.··,				ંગલાયું :	
84/4/ to .1100				38680	NO.	IS TEST	X V 17.FI	Jean I	ላግሌ	ting .

						Base Street					
	ואאטערט	HC M	TAAN!	I ISEL S	NO:	5868 0	0				84/4/48 . JIAO
	ઝહ્યાલ.					ISI		WR 99210 AE			BOTH F NO. AW 236
	PkLFARA	1-0-1	- 20	ser, 80, 1	0,H			ROUTE OF JUMPINE	المكري ة :الأOذاله ^م	, pc	TIME AFTER THE ECTION
****	V FR 11 81.	ATF H	:1SC	С ТғW	Mić.E			PARASTE (SUM) SPEC	ES: <u>P. Y. nigar</u>	ieuses	Sikaid: NG
DOSE	PÀTEI	NOY R	ATE	ى	MP 2%	d		(a = 2) ACTIVITY	(VALUES		
mg/kg	c°/ _T o	L X	c ^x / _T x	f/h	ى	ر/e	(+ - t) - ([-	$\frac{-\alpha)(e-\alpha)}{(c-\alpha)} - (b \cdot \alpha)$	Residual Activity	Prophylactic Activity	CON
Ø	s/s		3/3	£F.3		3.86					
3.0	د/٥			¥ 4						+2.F.<	Fully active
0.0	0/3			<u>×</u>						£2.F <	Fully active
30.0	<u>ج/ع</u>		3/3	4		3.78			NIL	トム・ドィ	Fully active
											•
	UMINIM	IM FUL	LY ACT	IVE DO	SE	m V	mg/kg				
	RESIDUA	IL ACTI	ı∨nY:	II.V	at	30	શ્ય/ ઈ		PR:1	ACIPAL INVEST	IGATOR: PROFESSOR W
											TABLE 29

									[!	
IIGATOR: PROFESSOR W	icipal. Inves	PRS					۲۲:	L ACTIVI	RFSIDUA	_
				mg/kg	N. 10 10	DOSE	ACTIVE	Μ ΕυιιΥ	NINIW	
Fully achive .						4	~		0/3	30.0
Fully active.						4	~		0/3	0.01
Fully active.						4	×		0/3	3.0
						63	வ்		4/S	ଷ
COX	Prophylactic Activity	Residual Áctivity	$\left[\frac{e-\alpha}{-\alpha}\right] - (b-\alpha)$	$(h - f) - \frac{b - a}{c}$	د. در	ہ ب	×, T×		c°/ _T °	mg/kg
		VALUES	(a = 2) ACTIVITY		4 %	GMP 24		VCY RAT	PA IE	DOSE
SikAid: NiG	5 (51)-51	rs. <u>P. V. aiger</u>	ASTE (SUR) SPECH	ЯАч		FW MicE	<u>ي</u> ۲	8000 EV	VIR II RI	
NOU ALM ALL AVI	Ł	A DONE #//	PE OF SOMITIST	20		60, 4, Ü	14861	1+0 4:	PRLFAXA	
BOTHENC, AX2684			141871 AB	WR	1S12	I. • • /			DRUG.	
85.2.5 JIAU				3	BR 65	SI NO.	IAXIS IF	DecOPER	(AUSAI	Listen a

DRUG. $i.v.'$ ISIZ WR HAI B71 AB PREPARATION: $i.vecr. a0, H_2O$ ROUTH OI AD ROUTH OI AD VERTBRATH HOST: O THW MALE ROUTH OI AD ROUTH OI AD VOSE PALENCY RATE $GMP 2y_0$ RAASTE (SUB) SPEC POSE PALENCY RATE $GMP 2y_0$ $P(-1) = \frac{1}{(c-0)} = \frac{1}{(c-0)} = \frac{1}{(b-c)} = \frac{1}{(c-0)} $	AliOhi + ///m IS: F nigrrieus: Kesidual Prophylaciu. Activity Activity 0.03 - 1.12 0.88 - 1.53	WOTHENC. AX 2484
PREPARATION: LACC. B0. H_2 O ROUTE OF CITAIN TION: ROUTON: ROUTON: ROUTON: ROUTON: ROUTON: ROUTINE	ES: F. V. aigrrieuse S: F. V. aigrrieuse Residual Prophylectul Activity Activity 0.03 - 1.12 0.88 - 1.57	TIME ALTER THEFT TOP
VFR IFBRATH HOST: O THW MACE PARASHF (SUB) SPEC $DOSE$ PATHINCY RATE $GMP 2\% P$ $(d - 2) ACTIVIT$ mg/kg C^{c}/T^{O} XC C^{r}/T^{X} $f_{1}h$ b $(d - 2) ACTIVIT$ mg/kg C^{c}/T^{O} XC C^{r}/T^{X} $f_{1}h$ b $(d - 2) ACTIVIT$ mg/kg C^{c}/T^{O} XC C^{r}/T^{X} $f_{1}h$ b $(p - g) - (b - g) - (b - g)$ $(b - g) - (b - g)$ 0 S/S $3/3$ $3/3$ 6.48 4.33 4.28 $(b - g) - (b - g) - (b - g)$ $(b - g) - (b - g) - (b - g)$ 0 $2/S$ $3/3$ $3/3$ 5.43 4.34 -1.05 $(c - g) - (b - g) - (b - g) - (b - g)$ 0 $2/3$ $3/3$ 5.43 4.34 -1.05 $(c - g) - (b - g) - (c - g) -$	CS: F. V. Aigrrieuses Residual Prophylacius Activity Activity 0.03 - 1.12 0.88 - 1.57	SIKARA MUG
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	VAIJUES Residual Prophylactic Activity 0.07 - 1.12 0.88 - 1.57	IN ACTV E
mg/kg C^{2}/T^{1} X^{C} C^{X}/T^{X} $f_{1}h$ b $f_{1}e^{-1}$ $b^{-1}e^{-1}$ $b^{-1}e^{-1}$ $b^{-1}e^{-1}$ $b^{-1}e^{-1}$ $b^{-1}e^{-1}$ $b^{-1}e^{-1}e^{-1}$ $b^{-1}e^{$	Residual Prophylaciu Activity Activity 0.07 - 1.12 0.88 - 1.57	C.OMN
Ø 5/5 3/3 3/3 6.48 4.33 4.28 0.1 2/3 3/3 5.43 4.34 -1.05 - 2.33 133 0.3 2/3 3/3 5.80 5.15 -0.68 - 2.33	ES.1 - E0.0	INACTVE
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	21.1 - F0.0 21.1 - F0.0	INACTIVE
0.3 2/3 * 3/3 5.80 5.15 -0.68 - 2.33	£5.1 - 88.0	
		i、ACFV格 ・
· 0 0/3 3/3 2/4 4-51 752 - 233 × 2.6 - 2.33	FI-F SE-O	FULLY ACAVE
MINIMUM FULLY ACTIVE DOSE . 0:3 1.0 mg/kg		
RESIDUAL ACTIVITY, NIL AT -1 mg/kg	PRINCIPAL INVEST	TIGATOR: PROFESSOR W
* 1/3 DIED		TABLE 31
		*

			VALUE							
	r AUSAL Far	1 X V 1/ +1.j	S 1531 >	 -	8 R 6 51	ß				10411. 3.2.78
•2 ⁻	DRUG.			, ^.i	1512	WR	80 1F8 141			BOTHENC AX2LSA
	PREFAMENCO	- × -	ક છેલું પ્રચં	0,1		Ör	HE OF SOMICIES P	ALONS 4/	č.	MON AND AN IN AND
	v JR (18) ∆11 -	: 15071	Ó TEW	Mid.E		P.A.	Aste (sta) sherifi	5: P Y 255763	• • • • • • • • • • • • • • • • • • • •	skart NG
DOSE	I PATENCY	RATE	15	MP 2%	d		(a = 2) ACTIVITY	VAI UES	ar san b 'Y an san 'Y an an 'Y an 'Y an an an 'Y an	
mg/kg	c ^c /t ^a xc	CX/TX	f.h	ى	; (e	$(h - t) - \frac{1}{2} (b - \alpha)$	$\frac{\overline{(e-\alpha)}}{-\alpha} - (b-\alpha)$	Řesidual Áctivity	Frephylacite Activity	WO'
Ø	4/S		5.69							
30	o/3		× 4							Fully achive.
0.01	0/3		41							Fully active.
30.0	°/3		×14				¢			Fully achive.
										•
							-			
	MINIMUM FC		live do:	SE	V 3 0	mg/kg				••••••••••••••••••••••••••••••••••••••
	RESIDIAL AC	TIVEY:						413A	ICIPAL INVEST	IGATOR: PROFESSOR W
										TABLE 32
								· ·		

	CAUSAI	HUCISI	SIXAJY.	S LEST N	0: B	R 667						DATE. 113.138
and the second	DRUG.				51 // ···	215		WR 14	41871 AB			BOTHENC. AX 265
	PREPA#A	NON:	1 ve	er. 80, H	0			nor	F OF PDMP BSH	PALIONI: ++++++++++++++++++++++++++++++++++++	sd,	THE ALLER INFECTION
	V FR 1F8K	ATI' HO	51: (O TEW I	Nic.E			PARAS	ITE (SUB) SPECIA	ES: P. v. niger	iensis *	SikAijd: Nic
DOSE	PATE	NCY RA	Τ ^Γ	4 S	AP 2% P				(<u>a = 2) ACŤIVITY</u>	VALUES		
mg/kg	c°/ _T u	ں ×	cx/tx	f,h	ىد	°/e	(h - f	$-\frac{1}{(c-c)}$	$\frac{1}{\alpha}$ - $\frac{1}{\alpha}$ - $\frac{1}{\alpha}$ - $\frac{1}{\alpha}$	Residual Áctivity	Prophylactic Activity	S.
R	5/S	3/3	3/3	6.48	4.33	4.28						-
1.0	£/٤		2/3*	6.25		4.65	0.23-	233 x 2.6	<u>25</u> - 2:33]	ୡଢ଼୕ଡ଼	- 0.15	INACTIVE
ю. О	2/3		2/3	>843		0F.4	1.95-	2:33 × 2.	70 - 2.33	0.44 44	1.51	Active
<u>o</u>	6/3		3/3	× 4		95.4	7.52-	[2.33 × 2 2.28	- <u>2</u>	0.49	50.F	FULN ACTIVE
												· · · · ·
	, , , , , , , , , , , , , , , , , , ,							-				* * **********************************
												- - -
	NMINIM	TIN FULL	Y ACTI	IVE DOS	بو		0	tey/bu				- -
\$ +	RFSIDGA	I ACIN	/ITY:	NIL	. AT	1	64/1			134	ICIPAL INVEST	IGATOR: PROFESSOR
	* /3 DI	IED										TABLE 33
									AND THE PARTY PARTY PARTY IN THE PARTY INTERPARTY IN		TO SALAR AND A SALAR AND AND AN AND AND AND AND AND AND AND	

				Section 2					
2	IX V Dardo	S :Est >	Ć.	g 658				n vor men og skale skriver i vere en men og skriver i det skoleren	8. 1.81 J.V.
			1	213	3	R 159412 AC	¥		NOTH F NO. 6659
1 V V V	12	- (Jo . 105	0.1		ž	otte or some iste	AL 016 + 10	ŧ	1. 44 24 15 11.4 10 1
1 × 1	: :(.(.))	C IFW	Mit.E		74	ARA STE (SUB) SPECIF	S: F. V. alitic		ON THARS
TENC	Y RATE	15	MP 2% P	 .		(a = 2) ACTIVITY	VALUES		
×		f_h	ى),e	$(\mu - i) = \frac{1}{(p - i)}$	$\frac{\alpha}{\alpha} \frac{(e-\alpha)}{(e-\alpha)} - (b-\alpha)$	Residual Áctivity	Frophylactic Activity	
1		5.69							-
		¥ 4							Fullyactive
		<u>×</u> 4							Fully active
		×14.							Fully active
									-
		 				-			
MUMI	FULLY ACT	IVE DO	SE∧	0	mg/kg				
JUAL.	4CIIVITY:						4: XA	ACIPAL INVEST	IGATOR: PROFESSOR
									TABLE 34
:		*. 					· · · · · · · · · · · · · · · · · · ·		
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TEST NO. BR670	11/ 1513 WK 159412 AC BOTHEND. BOTHEND. BOTHEND.	1, 80, H ₂ O	TFW MICE PARASITE (SUB) SPECIES: P. v. nigerieusis StkAtivi: NiG	<u>GMP 2% P (a = 2) ACTIVITY VALUES</u>	$f_{h} = \frac{c}{c} \left(h - f \right) - \frac{b - a}{c} \left(- a \right) - (b - a) - $	85-5 BES 05-5	5.87 3.25 0.15 - [1.79 - 1.74] 0.06 0.09 Inachue.	0.58 3.67 0.86- [1.74 × 1.67 - 1:74] - 0.11 0.97 machine.	10.87 3.70 545 - [1:34 × 1:70 - 1:34] - 0:04 > 5.19 Active .			/E DOSE! = 3 mg/kg	Nil ar 1 mg/kg PRINCIPAL INVESTIGATOR: PROFESSOR W	TABLE 35		
9670	513				·/e (h -	3.79	3.85 0.15-	3.67 0.86-	3-70545-	ang tang pang tan Pa		n. L	ویا /وس			
51 NO: B	1.1/1	0.H.O	W MICE	GMP 2% P	<u>م</u>	45.6 G	t.	8	83			DOSE I	lil ar I.			
ALAXIS TES		l veen â	151: O'TI	15	CX/TX FA	3/3 5:7	3/3 5.8	3/3 6/6	3/3 >00			Y ACTIVE I	/ITY: N			
AL PROPH		KAHON:	BEATE HO	THNCY RA		3/3						TIN FOUT.	JAL ACTIN			
CAUSA	DRUG	PREPAN	VER H-6	I A T	g C°/ _T °	5/2	3/3	e/e	2,3		 	VINIW	RESIDI			
		Self.com	Colora	DOSE	mg/k	B	ō	Ó Ý	• •							

		· ·						• • •	<u>}</u>	
TARLE 36	ACIPAL INVEN					••				
	1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.		mg∕kg	0 ×	DOSE .	CTIVE	ייינייע ודא איז	JM FU	WINIW	
•										
Fully active					4	7			c/3	30.0
Fully active	÷					×			0/3	0 0
Fully active					4	<u>,</u>			0/3	3:0
					ଟ୍ୱ	ů.			4/S	Ø
	Frephylactic Activity	Kesidual Activity	$(h - f) - \left[\frac{(b - \alpha)(e - \alpha)}{(c - \alpha)} - (b - \alpha) \right]$,e ,'e	ى 	t t	×)	U X	c°/r°	mg/kg
		VAI UES	<u>(a = 2) ACTIVITY</u>	₩ Þ	GMP 2		PATE_	Y UN	PAT	DOSE
subat. No		15: P. 4. attra	PARA ATE (SHB) SPECH	t 9 3	EW Mic	5	:15CH		~ FR 1F8	29 4 De regense
1. MI AL PR 114 14 14	;d	AI 0514 4	POUT OF STANDER		0 [°] H 09	م عروب ف	-	0	FREFA.	
BOTHENC, BB598			WR 159412 AC	1513					oktiG.	
84.1.81 JUVG			ſ	BR 651	SL NO.	×iS lE	ダレッ、	5 at 1	NUSA!	
						And the second second				

CAUSAL PROPERTY BRIEBART CON- LIR HEINEATH CON- LIR HEINEATH CON- LIR HEINEATH CON- CO/3 3/3 3/ 2/3 3/3 3/ 2/3 3/3 3/ 2/3 3/3 3/ 2/3 3/3 3/ 2/3 3/ 2/3 3/ 2/3 3/ 3/ 2/3 3/ 2/3 2/	AXIS LEST NO. BR 670	TALE AC ALL AC ALL AC ACLE AC ACLE AC ACLE ACLE	Tweer 80, 4, O ROULE OF SOMATISPATIONS WITH D. A. M. APPE THE THE PORT	· O TEW MICE PARASSITE (SEW) SPECIES: P. V. AGRITHULLA R STRATS . NIC	<u>GMP 2% P</u> (a = 2) ACTIVITY VALUES	$\int T^{x} \left[f_{y} \right]_{1} = b = \frac{c}{2} \left[e - (h - f) - \int (b - a) (b - a) - (b - a) \frac{1}{2} \right] = \frac{Resided}{Resided} = \frac{Prephylociec}{Resided} = \frac{COMM}{Resided}$	8 5:35 3:74 3:79	3 $8:33$ $3:39$ $2:61 - \left[\frac{1:74 \times 1:39}{1:79} - 1:74\right]$ Ni1 $22:61$ Slightly active.	3 > 14 3.96 > 8.28 - [1.74 × 1.96 -1.74] 0.17 > 8.11 Fullyactive.	$\begin{vmatrix} 3 \\ 5 \\ 5 \\ 5 \\ 6 \\ 6 \\ 6 \\ 6 \\ 6 \\ 6 \\ 6$		ACTIVE DOSE	Y: Nil al 1 mg/kg. CHESCOR W.	TABLE 37	
CAUSAL PROJUCTION RAIS IEST NO. DRUG INVERTINE RELAVATION INSERTATION INSERTANT OF INSERTANCE INVERTINE $\frac{Pattericy RATE}{C/TU} \times C$ Trimmund $\frac{Pattericy RATE}{C/TU} \times C$ C/Trime $\frac{Pattericy RATE}{C/T} \times C$ C/Trime $\frac{Pattericy RATE}{C/$	୦୮୬ ନଥ	1513	rc	<u>ι</u> .	<u>d</u>	$\frac{1}{2} \int e^{-\frac{1}{2}} \left[(h - f) - \int \frac{1}{2} \left[\frac{h}{2} - \frac{1}{2} \right] \right]$	8E.E 4	3-36 2.61 - [1-3	3.96 > 8.28 - [1.	4.09 > 8.28 - [-		0.1 - 0.3. mg/kg	· 64/6m		
CAUSAL INCULLAA ATE INUG INUG INUG INUG INUG INUG INUG INUG	is lest NO.	, <u>``</u>	reen 80, 4 , O	O TEW MICE	1 GMP 29	FF	5.5 GF:2	\$6:33	× 4	× 4	 	 TIVE DOSE	Nil ap		
CAUSAI DRUG FREEAVA VIRHEAVA VIRHEAVA VIRHEAVA	Xalibeitost		1-04-14	411-11/312	VCY RATE	×u ⁽ , ¹ , ¹ ,	3/3 3/3	<i>دا</i> د	e/e	ele		 M FULLY AC	: XUAADY -		
		DUNC:	FKLFAKA	^ {\\ [+] \\ \\ -	PATEN	C°/T ¹⁰	5/S	2/3	e/0	ę'з		MINIMU	RESIDUA		

									in the second			
	CAUSAI	NC 40	4/LAXIS	S LEST N	÷.	3866	Ŋ					DATE: 24/2/78
	DRUG.				L:V/ 1	1514		WR 180	SA2 AC			BOTHE NO. BDOD
	PREPARA	NOIL	1 we	ier. 80, ⊱	4 ² 0			ROUTE O	ADMINISIP	Alion: ip/ac/	set,	TIME AFTER I NFECTIO
(1 2);55778788	V FR j F Bix	ATH H(:1SC	Ő TFW	MICE			PARASITE	(SUM) SPECIE	S: <u>P. y. nigeri</u>	ensis	Sikain: NiG
DOSE	PATE	NCY R	ATE	G	MP 2%	4		= D)	2) ACTIVITY	VALUES		
mg/kg	c°/rº	с Х	c ^x / _T x	f_h	٩	°/e	- (J - H)	$\frac{(b-a)(e-a)}{(c-a)}$	- (p a)	Residual Activity	Prophylectic Activity	8
Ø	4/5	3/3	s/s	66.3	3.91	16.5						
0. 0.	0/3		3/3	>14		5.30]-1E-E<	1.91 × 3.3C	[16.1-7	1.39	>6.3 ೩	Fully active . Some res
0.0	0/3		3/3	>14		8.40]-1F.F <	1.91 × 5.40	[16.1	3.49	>4.22	Marked residual activ
30.0	o/3		o/3	>14		4 /<]-IF.F<	1.91 × 12.00 1.91	[16.1	> 10.09	1	Prophylactic activity ma
2) - 20) - 1 - 7 - 20												residual activity.
								-				C
	MINIMU	im ful	LY ACT	IVE DO	SE	0.00	6w	A-5				- 2. erányiny
~ <u></u>	RESIDUA	N. ACTI	ΥΠΥ:	C.	sent	ar 1	وماوس			PRIM	ICIPAL INVEST	IGATOR: PROFESSOR
									·		-	ABLE 38
	: 	· · · · · · · · · · · · · · · · · · ·										

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AND SPECIAL

URUG. PKEPAKATIC VIRIFBKATI DOSE PATENCY mg/kg C ⁰ /T ⁰ XC	on: Iw HOSI:			•					
PIKEPAKATIO VIRITBIKATI DOSE PATENCY mg/kg C^{0}/T^{0} XC	en iversite		- -	514		WK 180872 A	.)		BOTHENO. BD 05
$\frac{\sqrt{18} 11 \cdot 1$	HOS1:	cer. 80, H	ي ر			ROULE OF ADMINIS	IRAIION: 41-	od,Á	TIME ALLER ONFFUR
$ \begin{array}{c c} \text{PATENCY} \\ \text{rg/kg} & C^{0}/T^{0} & XC \\ \hline \hline \hline $		Ó TԻW A	MIC E			PARASITE (SUB) SPEC	JES: P. v. niger	ieusis	Sikaist: Nic
rg/kg C ^o / _T o XC	₹ RATE	U.S	AP 2% P			(a = 2) ACTIVIT	<u>Y VAI.UES</u>		
Ø 4/5 3/	· c ^x / _T x	f,h	ع	°/e	(h - f)	$-\left \frac{(b-a)(e-a)}{(r-a)}-(b-a)\right $	Residual Áctivity	Prophylactic Activity	
	3 515	ଟେ.୨	3.91	16.5					
3.0 0/3	3/3	× 4		4.30	- 15:5	[1 91 × 2.30 -1.91]	0.39	>7.32	Fully active.
o.o %3	3/3	41<		2.10	-1554	16.1- 01-2 × 16.1	61.1	> 6.52	Fully active . Some re
0.0 0/3	3/3	× 4		ର ଜ	- 15:5<	1.91 × 4.19 1.91 - 1.91	2.28	> 5·43	Filly active. Marked m
						-			
MINIMUM F	υι.LY ΑCT	IIVE DOSI	ب	33	Ε	9, ¹ kg			-
RFSIDUAL A	CTIVITY:	Nil al	ء س ح	وعااود			PR:1	NCIPAL INVEST	IGATOR: PROFESSOR
								·	TABLE 39

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			A CALLER AND A SA								
	INSUM)	ન્દ્રાત્ કર્સન	コメイマ	5 1EST P	ر ک. ۲	RUCE	ŧ٨				8E 24/27
	: દ્વારા દુ:					513		WK 1949651	Ł		SULLE NO. BG SA
	PKLFAKA	NI ON	1 20	ier. 80, F	0,4			ROUTE OF JOMIN	SIRA BONE +/ag	<u>.</u>	TIME ALTER UNFFORM
	V FR (18k	भा गए	5.1:	O TFW	Mić.E			PARASITE (SUB) SPF	CHS: F. Y. nigro		sikarde Nic
DÕSE	PATH	ちょう ちょうしょう	\TE [™]	15	AP 2% F			(a = 2) ACTIV	ITY VALUES		94
mg/kg	c ^c / _T o	UX X	c×/ _T ×	f,h	ى	,e ;;	(h - f) -	$-\left \frac{(b-a)(b-a)}{(c-a)}-(b-a)\right $	Residual Activity	Prophylactic Activity	CON
Ø	4/5	3/3	5/5	6:39	3.91	3.91					
3.0	3/3		3/3	5.49		3.95	-08.0-	[16.1 - 56.1 × 16.1]	0.0 40.0	-0.84	Inachive
0.0	3/3		3/3	5.99		4.20	-06:0-	[161- 02.2x 161]	0.29	0.59 1	Inachive
0 0 0	<u>%</u>		3/3	<u> </u>		11.61	-1F.F<	[161-11.01×16.1]	. 8.20	- 0.49	All achistry residual
								-			
	MINIM	IM Full	ΙΥ ΑСΤ	IVE DO:	se ic	0.30	D	j∕kg			-
	RFSIDUA	N ACT	VirY:	Mark	ed at		. وما/ و		PR:1	ACIPAL INVEST	IGATOR: PROFESSOR W
											TABLE 40a

	CAUSAL 190	X 4 17 11	(S 1ES F	2.0. 6	2 8690				CATE, 5/6/78
	Sthe			, ^.'!	1525	W 27653 M	0		SOTHE NO. AHOR
	PKEFARATIO	*-	eer, 80, 5	Û. T		PIMON IO HIDOR	SPALOPIS	, d. c	WW VI HE DALE TON
	1. FR 1 FBK AT1	HOST:	O TFW	Μιζ.Ε		PARASUF (SUM) SP	CITS: F. <u>Z. aigre</u>		ON TRAFT
DOSE	PATENCY	RATE	5	MP 2%		(a = 2) ACTIV	ITY VALUES	-	
mg/kg	c°/ _T u XC	, , , , , , , , , , , , , , , , , , ,	î. A	ع	;/e	$(\mathbf{h}-\mathbf{f}) = \left \frac{(\mathbf{b}-\mathbf{a})(\mathbf{e}-\mathbf{a})}{(\mathbf{c}-\mathbf{a})} - (\mathbf{b}-\mathbf{a}) \right $	Residinal Activity	Frephylectuc Activity	WOC)
Ø	5/S	5/5	5.40		3-89 A				
3.0	3/3		5:26					1-0- 4-0-	Inactive
0.0	3/3		5.21					61.0-	Inactive
30.0	3/3	3/3	S-73		3.88 88:E		Ţ.Ż	0:33	Inactive
1									
									514 9 <u>(</u> 146 - 44
	MINIMUM FO	JULY ACT	TIVE DO	SE	1	6y/6.0			5,000 4 5,000 4 5,000
	RFSIDUAL AC	: ለዓለብ	īZ	et.	30 mg/	الاح الح	1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1	ACIPAL INVEST	GATOR: PROPESSOR WA
									TABLE 406
							·		
				Utiné ana k					

DRUG, PATENCY RATE	XIS LEST NO:	•				•
DOSE PATENCY RATE		BR66	ũ			86/86/78 JUV
LIR H BKATL 1001.	~	1515	WK 194965 AG		•	BOTHF NO. BG DE 22
DOSE PATENCY RATE	I veer 80 420		ROUTE OF LOWITIST	ALEONS 4	þ	I'MI VI ILE THEFT ION
DOSE PATENCY RATE	C IFW MiCL	ш	PARASUE (SUR) SPECIE	S: F. V. aigned		SikAid. Nie
	(3MP 2	4 %	(a = 2) <u>ACTIVITY</u>	VALUES		
	T ^x ^f /h b	, 'e	$(h - f) = \frac{1}{(c - a)} \left(\frac{b - a}{(c - a)} - (b - a) \right)$	Resi-Jual Ácâivity	Prophylectic Activity	COMA
Ø 4/5 3/3 5/5	5 6-29 3.9	16.5 16				
3.0 1/3	5.21	3.98	$\left[16.1 - \frac{16.1}{36.1 \times 16.1}\right] - 80.1 - 10.1$	Foro	S1·1-	Inactive .
10.0 3/3	6.35	5.20	0.06- [1.91 × 3.20 - 1.91	1.29	-1.23	linachue.
30.0 2/3 2/3	5.S6	211-44	-0.73 - [1.9.1 × 9.44 -1.91	7.53	- 8.26	All activity residual.
						2 - 2
WINIMUM FULLY A	CTIVE DOSE .	OC A	mg/kg			
RESIDUAL AC OVINY	r: Marked	at 30 .	. ويا اوس		ACIPAL INVEST	IGATOR: PROFESSOR W
						TABLE 41

TABLE 42								DIED	* 2/3	
rigator: Professor W.	ycipál, invest	PR.1	, prevent at 10 mg/kg.	ar 30	wed a		ידראיי	al. ACI	RESIDUA	
			-							
? Fully active. Narked residual activity	> 2.16	د ه. م	> 8.18- [1.86× 8.03 - 1.86]	60-01		>14	3/3		°/3	30.0
Active, Some residual	×4.92	2:35	>7:27-[16:1]-1:86]	6.32	6	>13.0	3/3		1/3	0. 0
Slightly active .	1.39	11.0	1.50- [1.86x 2.00 -1.86]	4.02		ся т т	3/3		5/S	0 0
				u Q	3.86	5.89	5/S	3/3	8/8	Ø
COMN	Prophyleciic Activity	Residual Áctivity	$(h - f) = \left[\frac{(b - a)(e - a)}{(c - a)} - (b \cdot a) \right]$	°,'e	عـ	¥.	CX/TX	С Х	c°/ _T 0	mg/kg
		VALUES	(a = 2) ACTIVITY	٩	3MP 2%		ATE	ENCY R	PÀTI	DOSE
Sikaith Nic	ieusis	Cs: P. v. niger	PARASITE (SUB) SPECIE		/ Mic.E	Ó IFW	051:	i (TZA	, IR 158	
TIME AF FR. I NEF. RON	J.	A BOPE 4/44	ROUTE OF ADMINISTE		H, O	eer. 80,	×	NONA	PREPAR	
BCTILE NO. BC BS			AR 238358 AB	1516					DRUG.	
1041F. 15/21/78				BREES	NO:	IS TEST	ХАЛЧ	JO41 I	CAUSA	Ś.
					ALCONTRACTOR	and the second	Printaryan Lan			

			and a second		d						
AUSAL (POPERA) auto		ŝ	Ś	IEST N	<u>0</u> .	X	~4				BERGISI ING
JKUG. KEPAKA HON- I	- 7 0	-	ve∢	ь 60 H		0		ROUTE OF ADMINISTR	AliONis aprim.	, br	TIME AFTER THE FUTURE
v (R 1588AT) +00513	TE (CS)	<u></u>	0	TEW A	AiC.E			PARASITE (SUM) SPECIE	S: P. V. Aigeri	1	SikAiti, Nico
PATENCY RATE	ĊŶ ŖĂŢĘ	1 14.		GN	AP 2% F			(a = 2) ACTIVITY	VALUES		
c°/T° xc c^{\times}/T°		$ \langle \rangle $	· >_	f./h	به ا) e	q) - (; - y)	$\frac{-\alpha}{(c-\alpha)} - (b-\alpha)$	Resi-jual Áctivíty	Prophylactic Activity	COMN
8/8 3/3 5/	13 5/		Ś	5.83	3.86	16.5					
2/3 3/	3,		3 1	4F.0		4.81	4.92 - [-	1.91 - 1.86	88.0	4.04	Active .
1/3 [*] 3/	3/		m	3.90		5.90	8.08 - []	1.91 - 1.86	56.1	6.13	Active. Some residual a
0/3 2,	5		m M	4		Yo.67	-] - 81.8<	1981 - 1987 - 1.86	>6.59	> 1.59	Fully active. Manhed residue
		1									
								-			
			<u> </u>								
MINIMUM FULLY A	ላ ተጣር ላ	A	CTN	/E DOS	н Ш	0-3(Q mg/kg				
kesidujal activity * 3/3 died	ACTIVITY IED	7		reser	ratl	ě	m (64)6	wheed at 30 mg/	Kg.	ACIPAL INVEST	IGATOR: PROFESÇOR W.
))	1										TABLE 43
							ويلامهم فالمتحرك فالمتاب المحاط والمحاط والمحاص والمحاص والمحاط والمحاط والمحاص والمحاط والمحاص و	a fallowing the structure of the second second second to the second second second second second second second s	xxxxxxxxxxxxxxxxxxxxxxxxxxxxx	the second state state of the second	ai di di fitti da sectara sectara di secto sectara di ana di ana

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1ABLE 44 *								
FIGATOR: PROFESSOR W	ACIPAL INVEST		. G.	1 30 mg/	Nil at	AUNIY:	RFSIDIJAL A * 1/3 DIEI	
- -			mg/kg	230	TIVE DOSE	FULY AC	WINIW	1 - 1
y								
			-					
Achve.	4.23	Nil		4.48	lo.oS	3/3	2/3	30.0
Active .	3.54				9:36		2/3	0.0
Inactive.	-0.58				5 34		2/3	3.0
				3.91	5&ଇ ଅନ	5/5	8/8	Ø
WO0	Prophylectic Activity	kesi-jual Áctivity	$(h - f) = \left[\frac{(b - a)(e - a)}{(c - a)} - (b - a)\right]$, c	f. Jh		C [°] / _T [°] X [°]	mg/kg
		VALUES	(a = 2) ACTIVITY	2%P	GMP	Y RATE	PATENC	DOSE
Sikaiti, Nic	iensis	rs. <u>P. v. nigre</u>	PARASHE (SUM) SPECH	ų	O TEW MIG	13011	V IR 11-8KAT	
TIME AL (P. 1147 F. 110)	£	PATIONS #1/45	ROUP OF JOANSHING	0	eer. 80, H ₂ C		PRLPARA H	
CC642.00 11100			WK 81844 AD	LISI /	·		DRUG:	
8E/C/SI 'JIVA			δ	BRGG	is lest NO	ОРНАХ	C/USAL IR	

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		Comments and a second second static static second									
	CAUSAL	ALL RUCH	It six	ES L NO	ð Ö	R663					84 CISI .11V0
	DRUG.				.	Fig		WK 81844 AD			BOTH F NO. ZFS22
	PRLFARA		I veer.	80, H ₂ (0			ROUTE OF JOMINIST	PARONI: HVAY	. sd	TIME AFTER THIFT TO
	v 18.11-862	ATL (1021;	0	TEW MI	Ĵ.)			PARASITE (SUR) SPECI	FS: P. v. nigeri	eusis	SikAthi: Nic
DOSE	PÀTEN	JCY RATE		GMP	2% p			(a = 2) ACTIVIT	/ VALUES	- A MARKAN AND A REAL AND A MARKAN	
mg/kg	C°/To	XC CX	· · · · · · · · · · · · · · · · · · ·		ع	;/e	(h - f) -	$\frac{(b-\alpha)(e-\alpha)}{(c-\alpha)} - (b-\alpha)$	Resi-jual Áctivity	Prophylactic Activity	CON
Ø	8/8	5	i S	8		3.91					
3.0	3/3		و.	ŧ						0.45	Inactive.
0.0	3/3		Ś	S4						-0.28	Inachive.
30 0	3/3	3/5	s S	-66		8£:8			Nil	Г ò	Inactive.
			••••••••							e n al status eg enetis	
								-			
	1										
	MINIMU	м ғылұ а	CTIVE	DOSE	∧ <u>.</u> ∶	8	/õm	ľ.g			-
	RFSIDIJAI	η Αςτινηγ	_ 	Nil	ちょ) 6200	فم)		1:34	ICIPAL INVEST	IGATOR: PROFESSOR W
											TABLE 45
うとうというなかくなったことのなるのとい	AND PROVING A DATABASED OF A DATABAS	「日本にしたのできたとうない」というないのないです。「たんな」	AND PROPERTY AND	APROXIMATION AND A DESCRIPTION OF A DESC	TOTAL CONTRACTOR OF THE OWNER OF	The second second second second	The POINT N THE PARTY IS NOT THE PARTY I				

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. Auto 142

CAUSAL PROPERTAXIS TEST NO: BR682	DRUG: L-V/ 1518 WR 87781 AB BOTTLE NO. AB 34313	PREPARATION: Liveer 80/H ₂ O ROUTE OF ADMINISTRATION: 14/4/10 11 ME AFFTP INFECTION	VIRTEBRATE (1051) O'TEW MICE PARASITE (104) SPECIES: P. Y. nigeriersa StkAtsis Nig	PATENCY RATE GMP 2% P (a = 2) ACTIVITY VALUES	$\frac{1}{C^{2}/T^{0}} \times C = \frac{C^{2}/T^{2}}{C} + \frac{f}{h} = \frac{c}{h} = \frac{(h - f)}{(c - a)} - \frac{(b - a)(e - a)}{(c - a)} - \frac{(b - a)}{b} + (b - a)$	5/s 6.41	3/3 6.39 Inachive	0/3 >14 Fully active	0/3 Fully active		MINIMUM FULLY ACTIVE DOSE	RESIDUAL ACTIVITY:	TABLE 46	
CAUSAI	DRUG	PR LPAN/	VIRUB	SE PATE	'kg c°∕ _T o	5 5/S	0 3/3	o 0/3	0 0/3		WINIW	RESIDUA		: .: .: .:

			مد معرفین درمان است. مرد معرفین زنده کار مترور مو	the states of the states			na shekara na shekara s			
	CAUSAL PR	XA IYHIO	IS TEST N	<u>ç</u> Ö	8983					DATF: 8/5/78
7	DRUG:			[/\/]	Sig	WR	8A 13FF8			BOTHE NO. AB 34 3
	PR EPARA 1 10		eer. 80,′H	04		ROU	IF OF ADMINISTRA	VION: 4/	(po	TIME AFTER I NEFCHON
	VTR 1 F.BKAT	FHOST:	Ó TFW I	MIC.E		PARA	ASITE (SUB) SPECIES	: P. y. nigar i	ensis	Sikaid: Nic
DOSE	PATENC	Y RATE	<u>Ģ</u>	MP 2%	4		(a = 2) ACTIVITY \	/AI.UES		
mg/kg	c°/To X	c cx/tx		م	c/e	$(h - f) - \int \frac{(b - a)(e}{(a - b)}$	$\frac{1}{a} = \frac{1}{a} - (b \cdot a) = \frac{1}{a}$	Residual Áctivity	Prophylectic Activity	COM
Ø	5/S		6.41						2	
ы 0	1/3		>11.4S							Achive
0.0	o/₃		4<							Fully active
S S S	٤/٥		>14.							Fullyactive
										ייי איז איז איז איז איז איז איז איז איז
	WIWIWIW	FULLY AC	TIVE DOS	SE	3-10	6X/6m				
	RESIDUAL, A	CTIVITY:						4:89	ICIPAL INVEST	IGATOR: PROFESSOR W
										TABLE 47
	View Contraction									

	CALCULAR STATE		Statute of Source of	Wax death and and and and and and and and and and								
	CAUSA		нидхі	S IEST P	Ö.	RLES						DATT: 16/3/78
	URHG.				L·V/ 16	0000		WR 2310	93 AA			80111 F NO. 848908
	PREFAR	A BON	: 1*6	eer. 80,1				s to Hinor	SUME US IN	A RON: #///	Ł	TIME AF I'P ANER TON
	V FR 1F8	kATI +4	051:	Ó TFW	MICE			PARASITE (S	tia) specif	S: F. <u>v. niger</u> i	ieussa 	SikAit4: NiG
DOSE	PÁTI		ATE	5	MP 2% F			(a = 2)	ACTIVITY	VALUES		
mg/kg	c°/ _T 0		ت ۲⁄۲×	, h	ىد	°/e	(h - f)	$-\left[\frac{(b-\alpha)(e-\alpha)}{(c-\alpha)}-\right]$	(p ·· q)	Residual Áctivity	Prophylectic Activity	COM
a	5/2	3/3	5/5	5.51	3.54	3.S4						
3.0	3/3		3/3	6.49		4.26]-860	1.54 × 2.24 -1.	54]	GE-0	0.26	Inachue
0.0	٤/۱ ا		3/3	211.62		28.F	>S·SI- [1.54 × 5.82	54	4.28	62.1	Active - mainly residue
30.0	o/3		e/9	× 4		4 ×	- 64-8 <	1.54 × 12.00	[+s.	> 10:46	+6·1 -	Fully Active. Residual activity only
											- 00- 1000 - 10-10-10-10-10-10-10-10-10-10-10-10-10-1	
								-				1949 - 1949 - 1949 - 1949 - 1949 - 1949 - 1949 - 1949 - 1949 - 1949 - 1949 - 1949 - 1949 - 1949 - 1949 - 1949 -
	WINIW	UM FUL	LY ACT	IVE DO	SE . ĮO	0.	Ĕ	6%/E				
	RESIDU	AL ACT	IVITY:	Mauk	to par	0	5-1/5-			PK:	ACIPAL INVEST	IGATOR: PROFESSOR W
									•	, ,		TABLE 48
										·		
		La Strategia	NO NAMES									

) : !/		
TABLE 49				•						
TIGATOR: PROFESSOR W	VCIPAL INVES	PR:N	mg/kg, marked at 30 mg/kg.	ar 10	twas	Å	:YuY:	AL. ACT	RESIDU	
			mg/kg	10-30	DSE	IIVE DO	TY ACI	UM FUI	WINIW	
										Source provide a second se
Fully active. Residual activity only	t6:1 -	9 4 -C.<	> 849 - [1.54 42.00 + 154]	4		¥.	0/3		o/3	0 0 0
Slight residual activit	0.25	90.1	1.31- [1.54.x 2.60 . 1.54]	4.60		6.8			3/3	0.0
Inactive	- בניס	69.0	0.35 - [1:54 × 2.16 -1.54]	4.16		5.86			3/3	3.0
				2.S4	3.54	N N	s/s	3/3	5/5	Ø
CON	Prophylaciu Aati iy	kesi-jud Áchvity	$(h-f) = \left[\frac{(b-a)(e-a)}{(c-a)} - (b-a)\right]$	Ś	ع	ب ٹر	CX/TX	С Х	c°/ _T °	mg/kg
	~	VALUES	(a = 2) ACTIVITY	٩	3MP 2%		ATE	NCY R	PATI	DOSE
Sikaliye Njo	iensis,	S: F. v. nigni	PARASITE (SUB) SPFCH		/ Mic.E	Ó TFW	:150	kati; h	∨ FR I E8	
TIME AF THE INFECTION	ody	AIION: Hyte	ROUTE OF ADMINIST		0 ^Z H ² O	eer, 80,	: .	NOILA	PREPAR	*~~ * * *
BOTHLE NO. BG 890			W SBIOBS AA	1530	ト・ノ /				DRUG:	•
DATE. 16/3/78			Ő,	BR 66	NO:	IS IEST	HAAN	JC ái l	CAUSA	
					STATISTICS STATES	nalitatikatika La	ell tonit solatio	iocraatin (A)		

TABLE 50
PRINCIPAL INVESTIGATOR: PROFESSOR
NIL > 2.94 Active.
0.37 Inactive.
0.10 Inuchise.
$\frac{-\alpha}{1} - (b - \alpha) = \frac{\text{Residual}}{Activity} + \frac{1}{Activity} + \frac{1}{Ac$
a - 2) ACTIVITY VALUES
OFF (Sta) SPECIFS: P. V. aigrieusis StkAid, NG
CI ADMITISTRATIONI: The way the state of the
31138 AA BOTHE NO. BCS
DATE. 16/3178

	IANUM.	V DO AL	XIS IEST	NO.	BRE	0	THE A PERSON AND A P			AIT. 16/3/78
•	orne.			Ŀ.<``	ISAI	·	WR ABIIBBAA		\$	1010 F NO. BG 8556
	FR EFAXA	1 Oite	Aect. 60.	ы, С			ROUTE OF LOWING IST	ALIONIS 4	sd,	NOUS ALTER THE EVEN
	v f.R i F8k	ATF +POST:	о њw	Mic.E			PARASHE (SUR) SPECH	5. F. V. alin		SikArd NiG
DOSE	PATE	NCYRATE		3 MP 2%	d		<u>(a = 2) AC ItVITY</u>	VAI UES		
mg/kg	c°/ _T u	XU UX	T× F/h	ىد	:/e.	(h - f) <u>-</u>	$\frac{-\alpha)(e - \alpha)}{(c - \alpha)} - (p - \alpha)$	kesi-jual Activity	Prophylecius Activity	COMA
8	5/5	5/\$	S SSI		3.54					
ы О	3/3		6.38					•	EF:0	Inactive
0 0	3/3		6.02						15.0	Inactive
0.0	2/3	3/2	>8.4C		4-17			NIL	52.89	Active
-	NINIM	M FULLY A	CTIVE DO	DSE	v 30	6y/õu				
	kf SilDUA	A ACTIVITY	IIN .	ц т	30 mg	الجع .		PR.1	ACIFAL INVENT	GATOR: PROFESSOR W.
										TABLE 51
:	:				٤		•			
		· · · · · ·								

	ASUND	Юåн I	1× 5171.	IS TEST ?	ÜZ	3R ୧୫୯			DATE, 5 6 78
	ORNO.				1.//1	1522	AN 199507 AN		POLITING, BD 240
	PRLFAK	AliOn	4: 1 w	eer. 80,4	H ₂ O		ROUTE OF SOMETISTRAL	iONs the support	TAME ALL TRE INFECTION
	v fR 11:8	kATF' -	1021:	Ó TrW	Μις.Ε		PARAUNE (NIM) SPECIES	P. v. akçırletise	SikAria Nic
DOSE	PAT	ENCY I	KATE	3	MP 2%	٩	<u>(a - 2) ACTIVITY VI</u>	<u>NI UES</u>	
mg/kg	c ^c / _T u	С Х	c*/T×	F.h	ك	.'e.	$(h - f) - \frac{(b - a)(b - a)}{(c - a)} - (b - a)$	kesidual Frephyled Activity Activity	йњ. (COM
a	s/s		s/s	5.40		3.82			
a.o	3/3			5.24				91.0 -	Inactive
0.0	3/3			6.05				0.65	Inactive
30.0	2/3 *	 	3/3	£8.2		3.58		Nil 0.47	Inactive
	MINIM	UM FU	יניא אכו	TIVE DO	SE	I	6:1/bm		
	kFSIDU * / 3	AI AC DIED	1:VBY:	N N	4	ရှိ ရှိ	. و <i>حا</i> /ر	PRINCIPAL IN	ZESTIGATOR: PROFESSOR W. TABLE 62
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March Live Low 1322 M 1939 5537 AB 60111 E VIC - BD 24g FELTANULON Leven a0 H ₂ O 20111 F ULS : CLASS 10011 F ULS : CLASS 10011 F ULS : ULS : CLASS 10011 F ULS : ULS : CLASS FELTANULON Leven a0 H ₂ O 20111 F ULS : CLASS 20111 F ULS : CLASS 20111 F ULS : ULS : CLASS 10011 F ULS : ULS		- AUSAI	ワールしょう	λXiS	TEST NC		5690					0415. 5/6/78
Field Advaltional Reduited frame Routh Cit commission (1) Transfer (10) Transfer (10) Transfer (10) Constraint of Sign Constraint of Sign Constraint of Sign Parative (1) Parative (1) Constraint of Sign	•	.ખ્યાપુર્વે.				·// 15	322	WR.	SA Fos 661 AB		Ŧ	0111 E NO. BD 240
VIETERATT 40591. OTAW MICE PARATIFF (suit), STPC/TE: P. s. congression. Classical frequence. Classical freq		PREFARA I	-tuOit	1 460	n. 80, H	0		0"	UTE OF SOME BAR	ALION: 471-	bo	I WE ALL FR. AMERICAN
FOSE Faith of Value CAP Faith of Value Construction Faith of Value Construction		∵ {R I FBK 2	4TF +1035	:	j tew M	I.C.E		PA	RASITE (N.B.) SPECIE	S: <u>Y. y. aigra</u> i		SikAri-U NiG
marking Column (c/1/m) Kr Fr. (n - n) Restand Restand Resplayment CO Ø 5/5 3/3 5:40 3:83 -0.01 Activity Activit	DOSE	PATE	ICY RATE		1W S	P 2% P			(a - 2) ACTIVITY	VALUES		
Ø 5/5 3/3 5:40 3.83 3:0 3/3 5:35 3.93 1000 10:0 3/3 5:35 3.73 1000 30:0 3/3 5:55 3.73 1000 30:0 3/3 5:55 3.73 1000 30:0 3/3 5:55 3.73 1000 30:0 3/3 5:55 3.73 1000 30:0 3/3 5:55 3.73 1000 30:0 3/3 5:55 3.73 1000 30:0 3/3 5:55 3.73 1000 30:0 3/3 5:55 3.73 1000 30:0 10 0:25 1000 1000 30:0 10 0:25 1000 1000 MINUM HULLY ACTIVE DOSE	mg/kg	c°/ _T °	<u>い</u> し×	× + ×	7.	ع	,e ,	$(y - t) = \frac{1}{(t)} \frac{1}{(t)} - \frac{1}{(t)} \frac{1}{(t)}$	$\frac{1}{(\alpha - \alpha)} - (b - \alpha)$	Reși-Jual Áchivity	Frophylecies Activity	00
3:0 3/3 5:33 5:33 10:0:0 3/3 5:35 10:05 30:0 3/3 5:55 3:73 30:0 3/3 5:55 3:73 30:0 3/3 5:55 3:73 30:0 3/3 5:55 3:73 30:0 3/3 5:55 3:73 30:0 3/3 5:55 3:73 30:0 3/3 5:55 3:73 30:0 3/3 5:55 3:73 30:0 3/3 5:55 3:73 MINIMUM HULLY ACTIVE DOSE mg/Mg Mini or 25 MINIMUM HULLY ACTIVE DOSE mg/Mg Mini or 255	Ø	5/s	<u>ñ</u>	e,	6 6		3.82					
IO-0 3/3 5:35 Imachine 30-0 3/3 5:65 3-73 Imachine MINIMUM FULLY ACTIVE DOSE Imachine Imachine Imachine MINIMUM FULLY ACTIVE DOSE Imachine Imachine Imachine RESIDIAL ACTIVE DOSE Imachine Imachine Imachine	3.0	3/3			freis	 					-0-13	Inachue
Bool 3/3 Stes 3-73 Bool 3/3 Stes 3-73 Minimum Hult VacTive DOSE Minimum Hult VacTive DOSE Minimum Hult VacTive DOSE Minimum Hult VacTive DOSE Minimum Hult VacTive DOSE Minimum Hult VacTive DOSE Restocial Activity Nil at 30 mg/kg Restocial Notestication Hult Notestication Hult State State	0.01	3/3			5:35						20.05	Inachive
MINIMUM FULLY ACTIVE DOSE	30.0	3/3	რ 	(3 (3	3.65		EF.E			Ni	0.25	Inactive
MINIMUM FULLY ACTIVE DOSE mg/kg KFSIDUAL ACTIVE DOSE mg/kg RFSIDUAL ACTIVE DOSE mg/kg												
MINIMUM FUELY ACTIVE DOSE												
MINIMUM FULLY ACTIVE DOSE The market investigation were seen as the second verse of the second version of												
RESUDIAL ACTIVITY: Nil at 30 mg/kg RESUDIAL INVESTIGATOR: MOTESCORV TABLE 53		WI WI WW	ላ የብደረ	ACTN	/E DOSE	• • •	1	ნა//ճա				
TABLE 53		RESIDUAL	RCIVE	: , ;	Nil	ar 3	e E	الاق ا			ICITAL INVEST	GATOR: PROFESSOR V
							L			•		TABLE 53
		• • • • • • • • • • • • • • • • • • • •										

.	C/AUSAI		AIS TEST I	Ö Ö	R686	•				DATF. 26/5/78
•	DINIG.			1.1.1	524	WR 2308	BA FE			BOTHENO. BG854
	P RLPARA	10%	vecr. 80, 1	0 H		ROUTE OF A	ADMI-1151PA	130N: ++ '**/	\$	1;MF AI FR. INFECTO
	V IR (F.BK)	ATF HOST:	Ó TFW	Mic.E		PARASITE (5	(B) SPECIES:	P. V. aigrei	¥:stia	SikAiji. Nic
DOSE	PATE	ICY RATE	5	MP 2% F		(a = 2)) ΑςτινίτΥ Ν	ALUES		
mg/kg	c°/ _T o	xc cx/1	r× f,h	٩	ر'. ثر	$(h - f) - \left \frac{(b - g)(e - a)}{(c - a)} - \right $	(p - a)	Resi-Jual Áctivity	Prophylecite Activity	CON
Ø	5/S	3/2	5.99		3.85					
9 0	3/3		5.51						-0.4	Inachive .
0.01	3/3		98.9					9	0.94	Inactive.
30.0	3/3	3/3	£8.84		4.03			Nil	16.2 <	Active
	IOWINIW	M FULLY AG	CTIVE DO	SE	30	6%/gm				
	RESIDUAL	L ACITVITY	IJŻ.	at 3) em o	رق م		FR.17	ICIPAL INVEST	GATOR: PROFESSOR V
									-	ABLE 54
3										
TABLE 55				۲						
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IGATOR: PROFESSOR W.	ICIPAL INVEST	PRIN	бу/бш	.060	VE DOSE I Nil at	Γυι LY ACTI (CTΙΝΠΥ:	MINIMUM I RESIDUAL A	_		
	ž									
-										
Fully active	>8.O8	N:L		3.95	4.	3/3	%	30.0		
Active	>S.88				>11.80		1/3	0.0		
Active	>2.85				£F-8<		2/3	3 0		
				3.85	5.92	3/3	5/5	Ø		
COM	Prophylactic Activity	Kesidual - Áctivity	$(h - f) - \int \frac{(b - a)(e - a)}{(c - a)} - (b - a) \int \frac{1}{2}$	é Cé	f/h b	$c \frac{c^{X}}{c^{X}}$	C ⁰ /T ⁰ X0	ng/kg		
	ensia	2: F. V. Augur				: 16(0)1 : 5 6 A Fe	VIKHBKAH			
TIME AFTER INFECTION	sd,	AllON: 49/11	ROUTE OF ADMINIST		er. 80, H ₂ O):1: 1we	PRLFARA11C			
BOTHE NO. BCB54C			AA FEBOEL M	1524	ריע/		DRUG:	•		
DATE. 26/5/78		to Vine devices the device " a second se		BR686	IEST NO:	OPPEN AXIS	CAUSAL PP			
				in an						

	そうろう しょう こちちろん	S. D. S. A. S.					ない。これには、こので、こので、こので、こので、こので、こので、こので、こので、こので、こので	
	CAUSAL PRO	IX V'IV.Ed	S TEST NO.	59550				DATE. 5/6/78
	SKUG.		[/	1525	WR 27653 AD			BOTHE NO. AHON
	PREPARA 1101		0 H. 00 H.O		ROUTE OF ADMINISH	ALON: #/ac/	ţ.	TAF AFTER UNFECT
	V FR I FBEATE	+{O51:	O TEW MICE		PARASUTE (SUB) SPECH	S: <u>P. Z. aigri</u>		Sikard NG
DOSE	PATENCY	KATE	GMP 2	% P	(a = 2) ACTIVITY	VALUES		
mg/kg	c°∕ _T v xc	CX/TX	f Ji	, , ,	$(h - f) = \int \frac{(b - a)(e - a)}{(e - a)} - (b - a)$	Residual Áctivity	Frophylecie Activity	
Ø	5/S	5/5	5.40	3-82				
ы О	3/3		5.24	 			-0.16	Inachive
0.0	3/3		16.9				15.0	Inactive
0.08	3/3	3/3	S.60	3.83		Nil	0.20	Inachive
	MINIMUM FL	<u>н</u> гу аст	IVE DOSE	1	mg/kg			
	RFSIDUAL AC	i Yulyi	Nil at	Jem OE	Ð	N:34	ICIPAL INVEST	TABLE 56
 	• .			•	·			

					A CONTRACTOR			na se anno 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 19 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 -			
- 	CAUSAL P	⊄17411⊖ á	l SIXA	EST NC	0 č	R656	۵				8E/1/EC JIVO
•	SRUG:			ت	×/	541	, AN	R 333584 AA			BOTH F NO. BHOS
	PREPARAL	NON:	i veer	80/H ₂ (0		RC	DUTE OF ADMINISTR.	A110N: +*/'sc/	8	TIME AFTER I NFECHO
	∨ FR 1E8kA	IF HOST:	C ²	TFW MI	ICE		PA	RASITE (SUB) SPECIE	S: <u>P. y. nigeri</u> i	s is a	Sikain: Nic
DOSE	PATEN	CYRATE		GMP	2% P			(a = 2) ACTIVITY	VALUES		
mg/kg	c^{0}/r^{0}	xu Cx	1 × 1	્ષ	q	^c /e .	$(h - f) = \int_{-\infty}^{\infty} \frac{(b - a)}{(c)}$	$\frac{1}{\alpha-\alpha} - (b - \alpha) + \frac{1}{\alpha}$	Kesidual Áctivity	Prophylectic Activity	CON
Ø	4/4	3/:	ა ა	Řt:		3.62					
3.0	3/3		S	SS					Ŧ	-0.38	Inactive.
0.0	2/3		~	Sist						> 2.82	Active .
30.0	o/3	3/	_W	 4.		3.80			NIL	F6.8 <	Fully Active
	•										
	MUMINIM	ΓυιτΥΑ	CTIVI	E DOSE	<u>v</u>		6√/6m				
· * * * *	RESIDUAL	ACTIVITY	ž	INN.	ち	e S	- G-1/		PRIN	ICIPAL INVEST	IGATOR: PROFESSOR W
2. X. 1 10						۰					TABLE 57
	indition in the distance of the	a a transformed and the second se	And Street Store								

ĸ	CAUSAI	PR OPH	NLAXIS	S TEST N	B Ö	Resi	٩	•				BE I LE JIVO
•	DRUG:			اس	H /N.	541		WR 2325	584 A	_		BOTHE NO. BHO
	PR EPAR ≠	NION:	i we	er 80/H,	್ನ			ROUTE OF #	ADMINISTR	AlloN: Lip/	6,bo	TIME AF FER I NFECT
	V FR TEBR	ATF HC	51:	ď tfw a	AICE			PARASITE (5	UB) SPECIE	S: P. y. niger	iensis	Sikain: Nig
DOSE	PATE	NCYRA	TE	GM	IP 2% F			(a = 2)	ΑCTIVITY	VALUES		
mg/kg	c°/ _T o	XC	c ^x / _T x	f_h	٩	c_e	(h - f)	$-\left \frac{(b-a)(e-a)}{(c-a)}\right $	(p q)	Residual ⁻ Áctivity	Prophylectic Activity	0
Ð	4/4		3/3	EF.S		3.62						
ю Ю	3/3			Sile							- 0.57	I nachive.
0,0	2/3			>8. 48							5E.c <	Active
30.0	£/0		3/3	¥. 4.		14.5				N IL	とている く	Fully active

	MINIM	IM FULL	Y ACTI	IVE DOSI	ب لا	03	E O	6¥∕¢				
	RESIDUA	N. ACTN	γnΥ:	Z in	で、	Su Q	5-1			PRII	NCIPAL INVEST	IGATOR: PROFESSOR
												TABLE 58
			400 500 400 400 400			•						

			LIV/1342	2 (WR 158,1	22)		~~. Qu
1 4		Ø	0.03	0.1	0.3	1.0	ED ₉₀
	Ø		100 + 2.3	95.7+3.2	68.5 <u>+</u> 5.9	30.9 <u>+</u> 9.8	1.6
	0.03	77.5 +7.4	73.7 <u>+</u> 6.9	17.6 <u>+</u> 5.4	1.3 <u>+</u> 0.7	0	0.14
	0.1	63.6 <u>+</u> 8.2	49.6 <u>+</u> 11.4	6.7 <u>+</u> 2.7	0.4 +0.3	0	0.09
500	0.3	59.4 <u>+</u> 16.2	14.5+6.7	5.3 <u>+</u> 3.8	0.3 <u>+</u> 0.2	0	0.08
	1.0	23.7 <u>+</u> 8.5	0.7 <u>+</u> 0.4	0.1 <u>+</u> 0.1	0	0	0.004
	ED ₉₀	4.0	0.32	0,12	0.009	-	

TABLE 59

CONTRACTOR NO.

CUMPERIN

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City.

			LIV/134	2 (WR 158,	122)		
		Ø	0.03	0.1	0.3	1.0	ED ₉₀
	Ø		100 +3.2	95.8 <u>+</u> 2.1	71.9+8.2	31.1 <u>+</u> 8.2	1.6
	0.003	95. <u>7</u> +3.3	69.3 <u>+</u> 3.1	50.4+11.1	6.1 <u>+</u> 3.4	0	C.18
XI NE	0.01	78.5 <u>+</u> 4.8	53.8 <u>+</u> 5.2	57.2 <u>+</u> 5.0	5.5 <u>+</u> 4.3	c	0.15
Odv	C.C3	5.: <u>+</u> 2.3	59.045.7	24.9+5.?	0.2 <u>+</u> 0.2	0	0.12
Hann	0.1	52.5+4.5	41.9+2.4	2.8 <u>+</u> 1.5	C	C	0.05
		C.6	C.4	0.05	0.005	-	

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TABLE 60

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A comparison of the response of Plasmodium berghei to primaquine phosphate following drug administration by repeated daily injections via mini osmotic pumps (at 4.125 µg/µl/hr. v. 5 mg/kg/day).



A comparison of the response of Plasmodium berghei to primaquine phosphate following drug administration by repeated daily injections via osmotic minipumps (at 8.25 µg/µl/hr. v. 10 mg/kg/day).



A comparison of the response of Plasmodium berghei to primaquine phosphate following drug administration by repeated daily injections via osmotic minipumps (at 16.5 µg/µl/hr. v. 20 mg/kg/day).



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WR 158,122 and DDS - ED₉₀ values when compounds are used alone or in combination in varying proportions. (See data in Table 59). The graph shows a very strong potentiation between two compounds.



WR 158,122 and sulphadoxine – ED_{90} values when compounds are used alone or in combination in varying proportions. (See data in Table 60). The graph shows a very strong potentiation between the two compounds.

ADDENDUM

A technique for screening of drugs with residual antimalarial action

P. Schofield, R. E. Howells and W. Peters

The method described here for the screening of long-acting antimalarial agents in a podent malaria system represents a primary screening system with limited objectives. The screen is designed to detect compounds which may possess either residual causal prophylactic or residual blood schizontocidal activity or both and which may act following administration either orally (po) or subcutaneously (sr.). The technique employs a single dosage level of test compounds and this dosage is that which, in a series of preliminary experiments using selected candidate compounds, has proven optimal in terms of demonstrable residual activity and minimal local tissue reaction at the site of administration. The test is limited to a 35 day period of observation.

Materials and methods

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<u>Plasmodium y. yoelii</u> (17X) is employed in this screen. The parasite is maintained by cyclical passage through <u>Anopheles stephensi</u> and albino mice. Mice are maintained at $22^{\circ}C + 2^{\circ}C$ and supplied with Dixon's 41B diet and water ad libitum. Mosquitoes are maintained at $26^{\circ}C + 2^{\circ}C$ and at 75%-85% R.H. All experimental procedures are performed in random-bred male albino mice (Tuck, TFW) which are of 20 g body weight on the first day of an experiment. The mice are employed in groups of five. Sporozoites are obtained from mosquitoes iwelve days after the infective blood meal. Whole mosquitoes are homogenised in tissue culture medium 199 containing 1% bovine serum albumin (BSA) and the crude homogenate is centrifuged at 500 rpm for 1 minute to sediment the mosquito tissue. The supernatant, containing sporozoites, is removed and stored on ice until required. Sporozoite numbers are determined in a haemocytometer and the sporozoite suspension is diluted with TC 199 and 1% BSA to give a final count of 40,000 sporozoites/0.2 ml. Mice are infected by the intravenous (iv) injection of 0.2 ml of the sporozoite suspension. All experimental compounds are prepared in suspension or solution with 0.2% Tween 80. Ager (personal communication) has observed that Tween 80 and hydroxyethyl cellulose are equally effective, and superior to arachis oil, as vehicles for experimental agents in the screening of residual antimalarial activity. The screen has been developed with a series of compounds provided by WRAIR. Table 1).

Experimental procedure

The screening method involves a preliminary stage designed to eliminate from the screen those compounds which possess no appreciable residual activity and a second stage, performed on selected compounds, which is designed to detect compounds which have a residual action of <7 days, >7 days and <14 days, >14 <21 days, and of greater than 21 days. The observation period is limited to 35 days.

The preliminary stage

In this stage, mice are treated po and sc with 80 mg/kg body weight of the test compound on Day 0 (D0). Thus the total dosage per mouse is 160 mg/kg Three days later (D+3) the mice are infected by iv inoculation of 40,000 sporozoites of <u>P. y. yoelii</u> 17X. Blood films are prepared from the mice on D+10 and the parasitaemia determined. On D+17 the number of surviving mice are recorded.

All experiments include groups of control animals which receive 0.2 ml of 0.2% Tween 80 po and sc and groups which receive a standard, long-acting antimalarial compound. Diformyl dapsone (DFD) is an appropriate standard compound for inclusion in this screen. DFD has no demonstrable residual activity following administration po but has a marked residual effect sc, even at 20 mg /kg. To ensure uniformity in the test, however, DFD is employed po and sc at 80 mg /kr.

The parasitaemia of mice on D+10 is determined from Giemsa-stained blood films and scored 0 through +++++. The following system is used in scoring parasitaemia (using a microscope fitted with x 100 objective and x 10 eyepiece).

0	= negative	(no parasites in 10 fields)
+	= very scanty	(5 infected cells in 10 fields)
++	= scanty	(\$ 5 infected cells per field)
+++	= moderate	(\leq 20 per cent of erythrocytes infected)
++++	= heavy	(\leq 50 per cent of erythrocytes infected)
++++++	= very heavy	($>$ 50 per cent of erythrocytes infected)

Examples of the results obtained in this preliminary test are appended (Table III). Compounds which possess some demonstrable antimalarial activity in this screen are selected for further evaluation.

The secondary stage

A further evaluation of the residual antimalarial activity $\sim f$ selected compounds is performed in a secondary stage. In this stage of the procedure three groups of mice receive po and sc 80 mg/kg body weight (total 160 mg/kg) of the test compounds on D0, +7 and +14 respectively. Groups of control animals are also treated on these days, one with 0.2% Tween 80 alone (untreated control) and a second with DFD at 90 mg/kg; po and sc. All mice are infected on D+21 by the inoculation iv of 40,000 sporozoites of <u>P. y. yoelii</u> 17X. Blood films are prepared from mice on D+28 and D+35, parasitaemia being scored 0 through +++++, as described in the preliminary stage. Mortalities on D+28 and D+35 are recorded.

The results obtained with a series of selected antimalarial compounds are presented in Tables IV and V. These results demonstrate that DFD is an ideal standard compound for inclusion in this test, giving at the dosage employed a marked residual effect, but one that is a shorter duration than the observation period. It is therefore convenient to express the residual effect observed with other compounds relative to that of DFJ. In this DFD Index (DFDI) the residual effect of DFD is considered as 1. Candidate compounds in the secondary screening stage may be expected to vary from those with no demonstrable residual activity to those which totally suppress, for a period of 14 days (to D+35), the parasitaemia of mice challenged 21 days posttreatment. The performance of such compounds and those with intermediate residual activities has been scored from 0 through 4 on the basis of comparison with the residual activity of DFD, as illustrated in Table II.

Examples of the interpretation of results in DFD1 terms are presented in Table IV. A simplified system for the presentation of results in terms of DFD1 is represented in Table V.

It should be noted that in our laboratory, few untreated mice die within 14 days of infection with 40,000 sporozoites of <u>P. y. yoelii</u> 17X. The DFDI presented here is consequently based on parasitaemia scores. In other laboratories where the strain of parasite may be of greater virulence, or the mice of greater susceptibility to infection than those presently employed, significant mortality rates may be expected within this period. It is considered highly improbable however, that the death of mice will occur by seven days post infection (D+28). Under these circumstances both mouse survival and parasitaemia scores will be considered in the interpretation of results, but should not influence the applicability of the index and the scoring of individual compounds.

Observations

- ----

The methods which are described in this document are designed for the primary screening of compounds for long-acting antimalarial activity and enable compounds with varying degrees of residual activity to be selected. The tests are limited in that they employ a single dosage level of the test compound, do not differentiate between compounds which are active po or sc or both, and will select compounds with both causal prophylactic and blood schizontocidal activity. A flow-chart outlining the sequential stages for the further evaluation of long-acting antimalarial compounds is appended (Figure A).

The results obtained with cycloguanil pamoate in the secondary screening stage, at first sight appear enigmatic and might be considered to cast doubt upon the validity of the test. As indicated in Table IV 3/5, 1/5 and 4/5 mice were negative 7 and 14 days post-challenge (on D+21), following treatment on days 0, 7 and 14

iii

respectively. The compound does therefore demonstrate a marked residual effect and would therefore be selected for further study, particularly since no sign of induration or ulceration was observed at the injection site at the dosage level of 80 mg/kg. The results furthermore are consistent with those reported by Thompson et al. (Am. J. trop. Med. Hyg., 1963, 12, 481-493) who described the repository action of cycloguanil pamoate in mice, following injection sc at dosages from 24 mg/kg to 1317 mg/kg. In that study 2/3, 3/5 and 3/3 mice exhibited patent parasitaemias seven days after challenge at 3, 4 and 5 weeks respectively post-treatment with 189 mg/kg sc in lipid and aqueous suspensions. We conclude that even were the secondary screening stage to employ cycloguanil pamoate at a dosage level of approximately 200 mg/kg, essentially similar results would be obtained to those at 80 mg/kg.

NV CURTUM CONSTRA

EXPERIMENTAL AGENTS EMPLOYED IN THE DEVELOPMENT OF THE SCREENING TECHNIQUE

Standard	Agents (11)				
WR 1544	Chlor	roquine	AR 20613	LIV 1488	
WR 5473	Cyclo	oguanil (Pamoate)	AU 76138	LIV 1489	
WR 2978	Pyrin	nethamine	AG 65046.	LIV 1490	
WR 7557	Su1pt	ladiazine	ZN 32629	LIV 1491	
WR 4629	Sulph	alene	AU 72569	LIV 1492	
WR 5949	Trime	thoprim	AF 87341	LIV 1493	
WR 2977	Amodi	aquine	AG 64870	LIV 1494	
WR 1543	Atebr	in	AR 78360	LIV 1495	
WR 2975	Prima	quine	AH 24988	LIV 1496	,
WR 2976	Quini	ne	AW 23860	LIV 1497	
WR 25979	Nitro	guanil	AH 78744	LIV 1498	
Experiment	al Agents (20)			
Quinoline	<u>Methanols</u>		Naphthogu	inones	
WR 30090	AV 07996	LIV 1499	WF 49808	AJ 32298	LIV 1509
WR 134806	ZN 37115	LIV 1500			
Phenanthre	ne Methanol	<u>s</u>	Triazines		
WR 33063	AW 43746	LIV 1501	WR 38839	AM 33272	LIV 1510
WR 171669	BB 43914	LIV 1502	WR 99210	AW 23628	LIV 1511
Pyridine M	ethanols		Quinazolir	les	
WR 172435	AY 98670	LIV 1503	WR 141871	AX 26848	LIV 1512
WR 180409	BE 99420	LIV 1504	WR 159412	BB 59823	LIV 1513
			WR 180872	BD 09556	LIV 1514
Sulphones			Mannich Ba	ses	
WR 448	AG 28874	LIV 1505	WR 194965	BG 56327	LIV 1515
WR 6798	AF 50013	LIV 1506	WR 228258	BG 85640	LIV 1516
Furans			Miscellane	ous	
WR 93133	BB 59627	LIV 1507	WR 81844	ZF 92291	LIV 1517
WR 179305	BB 47734	LIV 1508	WR 87781	AB 34313	LIV 1518

			IVI	
	THE P	ARAMETERS EMPL	OYED IN THE	CONSTRUCTION OF THE DFD INDEX (DFDI)
TREAFMENT DAY	PARASIT, +28	AEMIA ON DAY +35	DFDI	COMMENTS
0 7 14	+++ 0 0	++++	-	Residual activity (RA) of DFD standard. RA $<$? days Animals challenged 14 days post treatment pt) negative at 7 davs but positive at 14 days post challenge (pi).
0 7 14	000	000	4	RA > 21 days Total suppression of parasitaemia for duration of test.
0 7 14	000	+ 0 0	< 4	RA intermediate between 3.0 and 4.0
0 7 14	0 0 0	* о о	m	RA > 21 days Animals challenged 21 days pt negative at 7 days but positive at 14 days pi.
0 7 14	+ 0 0	+++ 0	۳ ۲	RA intermediate between 2.0 and 3.0
0 7 14	** 0 0	++++ 0	2	RA < 21 days Animals challenged 14 days pt negative at 7 and 14 days pi.
0 7 14	++ 0 0	+++++ 0	∢ 2	RA intermediate between 1.0 and 2.0

• " Footnote Parasitaemia scores refer to mean parasitaemia obtained in a group of 5 mice and not number of mice positive Animals challenged 7 days pt negative at 7 days but positive at 14 days pi RA < 14 days Animals challenged 7 days pt negative at 7 and 14 days pi RA intermediate between 0.5 and 1.0 RA intermediate between 0.2 and 0.5 RA intermediate between 0 and 0.2 No residual activity observed THE PARAMETERS EMPLOYED IN THE CONSTRUCTION OF THE DI'D INDEX RA as DFD standard above COMMENTS RA < 14 days < 7 days (ctd.) RA TABLE II DFDI 1.0 0. -V < 0.2 0.5 0.2 < 0.5 0 PARASITAEMIA ON DAY +28 +35 ++++ ++++ +++ ++++ ++++ ++++ ++++ ++++ ++++ ++++ ++++ ‡ ***+++** ++++ ++++ ++++ ++++ 0 0 0 + +++ ++++ +++ +++ ‡ +++ +++ ++++ ++++ +++ +++ +++ ++++ 0 0 0 0 0 + 0 + TREAIMENT DAY 17 0 14 0 14 14 0 0 ~ ~ \sim 14 0 0 Ϋ́ 2 2 ~ 0 ž ~

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ILSI)	on Day +3	version and the second s		Pass	Pass	Reject	Pass	Pass	P	r dss Pres	Reiert	Reject	Pass	Reject	Pass	Pass	Pass	Repeat	Pass	Pass	· Pass	Fass		Reject	Repeat	Pass	Pass	keject	Reject	Reject	Reject	Reject
IMALARIAL ACTIVITY (3 DAY	Comment	Control 0.2% Tween 80	Standard	Quinoline methanol	Quinoline methanol	Phenanthrene methanol	Puriding mothered	Pvridine methanol	Sulphone	Sulphone	Furan	Furan	Naphthoguinone	Triazine	Triazine	Quinazoline	Quinazoline	Quinazoline	Mannich base	Mannich base	Miscellaneous Miscellaneous	Control 0.2% Tween 80	Standard	Chloroquine	Cycloguanil pamoate	Pyr i methami ne	Sulphadiazine	Sulphalene	Irimethoprim	Amodiaquine	Areorine .	Primaguine
GE FOR RESIDUAL ANT	Survival on D+17 following treatment	5/5	5/5	5/5	5/5	2/3 2/3	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5	3/5	2/2	5/S	5/2	5/5	4/5	5/5	3/5	2/5	3/5	3/3	2/2	c/c	2/3	3/5	- ^ ^
INARY SCREENING STA 80 ma/ka ROUTE sc	Parasitaenia on D+10 following treatment	++++	0	++	0		, o	0	++	0	++++	+++	0	++	0					- +	+	++	0	++++	0						+++	
PRELIM DOSE:	5M N.o.		AV/07004	AV U/ 740	CITICNIZ	BB43914	AY98670	BE99420	AG28874	AF50013	BB59627	BB47734	AJ32298	AM332/2	AW23628	AA20040 BB50073	BDD0554	RC-54377	RG85640	ZF92291	AB34313			AK20613	AU/61.38	71137630	A1177540	AF87341	AG64870	AR78360	AH24988	0,000,11
	Compound . WR No.				33063	171669	172435	180409	448	6798	93133	c054/1	49808	- 38839	74210	150412	180872	194965	228258	81844	87781		Control	1544	04/3	7557	4679	5949		1543	2975	1-00
1		DED	1400	1500	1501	1502	1503	1504	1505	1506	/001	8001	6001	1010	1101	1513	1514	1515	1516	1517	1518		<u>1,000</u>	1488	1400	1491	1492	1493	1494	1495	1496	

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a cabing to get a cabing the second					TABLE IV				are deele statue e east a base of the same of the same statue is a same to be the same of the same statue of th
		s c	ECONDARY SCREENIA 10SE: ROma/ka ROM	NG STAG TTE: SC	L FOR RES	IDUAL A	NTIMALARIA NGF : Shoro	NL ACTIVI	TY 'P.v.voclii 12X on dav 121
1	COMPOUND		TREATMENT	PAR	VSITACMIA	(AND S	URVIVAL)	0.01	COMMENTS.
1.1V N0	MS NO	BN NO	HKEAIMENI UAT		+28 UN	•	35		CUPPTENIS
			0	+++	(5/5)	+++++	(5/5)		
			2	+++	(2/2)	++++	(5/2)	0	Control (0.2% Tween 80)
			14	+++	(2/2)	++++	(2/2)		
			0	‡	(5/5)	+++	(5/5)		
DFD	CONTROL		7	0	(2/2)	+	(5/5)	~	Standard
			14	0	(2/2)	0	(5/5)		
1503	172435	AY98670	0	0	(5/5)	0	(5/5)		
**********			7	0	(2/2)	0	(5/5)	4	Pvridine methanol
			14	0	(2/2)	0	(2/2)		
1502	171669	BB43914	0	0	(5/5)	‡ +	(5/5)		
			7	0	(2/2)	+	(5/2)	е К Х	Phenanthrene methanol
			14	0	(2/2)	0	(5/5)		
1514	180872	8009556	0	++	(5/5)	+	(5/5)		
			7	0	(2/2)	0	(5/2)	2	Outnazoline
			14	0	(2/2)	<u> </u>	(5/2)		
1516	228258	8685640	0	‡	(5/5)	++++	(5/5)		
			7	0	(2/2)	+	(2/2)	,	Mannich base
			14	0	(2/2)	0	(5/2)		
1506	6798	AF50013	0	‡	(5/5)	+	(5/5)		
			7	0	(2/2)		(5/2)		Sulphone
			14	0	(2/2)	0	(5/2)		
									(ctd
		·	おんてんない ちょうちょう ちょうち かくまちょう だっしん アノー・・・・・・・・・・・・・・・・・・・・・・・・・・・・・・・・・・・・	Specifical Address					
katan katan kutan s	and the second second second second second	ر این میکورد این این میکرد. میکرد میکورد که مالند از مرابع	ى بىرىمىيەتى بۇلار - مىغىلەر . يېلىغىرىكى كىيىرىمىيە بىر	1	-	ł			
AND DESCRIPTION OF THE PARTY OF T									

:TY of <u>P.y.yoelii</u> 17X on day 421		COMMENTS		Quinazoline			Naph thoqui none			Mannich base			Quinazoline			Pyridine methanol		Cvc]onuanil namosto	Parasitaemia in individual mice	variable - REPEAT		Pyrimethamine - REPEAT		
AL ACTIV rozoites		DFDI		0.5			0.5			0.2			0.2			< 0.2			0			0		
. ANTIMALARI. LENGE: Spor	SURVIVAL)	+35	(4/5)	(2/2)	(2/2)	(5/5)	(2/2)	(2/2)	(2/2)	(5/2)	(2/2)	(5/5)	(2/2)	(5/2)	(5/5)	(4/5)	(2/2)	(5/5)	(5/2)	(5/5)	(1/5)	(3/2)	(2/5)	
CHAL	(AND	DAY	+++	+++	<u> </u>		++++	0		++++	+		++++	+	<u></u>	++++	+++	‡	+++	+	+++++++++++++++++++++++++++++++++++++++	++++	‡	
AGE FOR RES sc and po	RASITAEMIA	+28 +28	(4/5)	(5/2)	(2/2)	(2/2)	(2/2)	(2/2)	(5/5)	(2/2)	(2/2)	(5/2)	(2/2)	(2/2)	(5/5)	(4/5)	(2/2)	(5/5)	(2/2)	(2/2)	(1/5)	(3/5)	(2/5)	
NG ST UTE: 3	Vd		+	++++	0	+++	+++	0	+	+++	0	+++	+++	0	‡	++	<u>+</u>	+++++	+++	+	‡ ‡	+++	++	
ECONDARY SCREENI OSE: 80mg/kg R0	Thraturn's Dav	IKEAIMENI UAY	0	7	14	0	7	14	0	7	14	0	7	14	ΰ	7	14	0	7	14	0	7	14	
SO		BN NO	AX26848			AJ32298				BG56327		BB59823			BE39420			AU76138			AG65046			
	COMPOUND	ON XM	1418/1			49808				194965		159412			180409			5473			2978			
		LIV NO	1512			1509				1515		1513			1504			1489			1490			

:

TABLE IV (ctd.)

LARIAL ACTIVITY Porozoites of P.v.voelii 17X on dav 121	1	COMMENTS		Sulphadiazine		& Quinoline methanol			Quinoline methanol			Sulphone			Triazine			Miscellaneous ·			Miscellaneous		254 1	
		DFDI		0			0			0			0			0			0			0		
IL ANTIMALARI	D SURVIVAL)	/ +35	+ (5/5)	++ (5/5)	+ (5/5)	+ (4/5)	+ (5/5)	+ (5/5)	++ (5/5)	+ (5/5)	+ (5/5)	+ (5/5)	++ (4/5)	+ (5/5)	+ (5/5)	+ (4/5)	+ (5/5)	. (5/5)	. (5/5)	(2/2)	(5/5)	(5/2)	(2/2)	
SIDUA	A (AN	N DAY	ļ‡	+++	+++++	‡	++++	+++++++++++++++++++++++++++++++++++++++		‡ +	+					+++	+++++		++++	+++++++++++++++++++++++++++++++++++++++		+++++	++	
AGE FOR RE	RASITAEMI	+28	(5/5)	(2/2)	(2/2)	- (5/5)	(2/2)	(2/2)	(5/5)	(2/2)	(2/2)	(2/2)	(2/2)	(2/2)	(5/5)	(4/2)	(2/2)	(2/2)	(2/2)	(2/2)	(2/2)	(2/2)	(2/2)	
ING STU	M	•	‡	+++	+ + +	+++++	‡	+	‡	+++	‡	ŧ	+++	+++++++++++++++++++++++++++++++++++++++	ŧ	+++	++++	+++++	+++++	+ + +	‡ ‡	++ ++	++++	
ECONDARY SCREEN 05E: 80mg /kg R0		TREATMENT DAY		7	14	0	7	14	0	7	14	0	r.	14	0	7	14	0	7	14	0	7	14	
		ON NO	ZN32629			AV07996			ZN37115			AG28874			AW2 3628			ZF92291			AB34313			
	COMPOUND	UR NO	7557			0600E			184806			448			99210	-		81814			87781			
		LIV NO	1691			1499			1500			1505			1511			1517			1518			•

TABLE IV (ctd.)

TABLE V

RESULTS OF SECONDARY SCREENING STAGE FOR RESIDUAL ANTIMALARIAL ACTIVITY	Comments	Control 0.2% Tween 80	Standard	Pyridine methonol	Phenanthrene methonol	Quindzoline	Mennich here	Culaboro			INAphthoquinone	Mannich base	Quinazoline	Pyridine methanol	Cycloquanil pamoate	Pyr imethamine	Sulahadiazine	Quincline mothered						Miscellaneous
	DFDI	0		4	3	2			0.5	0.5		7.0	0.2	0.2	0	0	0	C	0					- >
	mg/kg sc		80	80	80	80	80	80	80	80 Ng			80 R	80	80	80	80	80	80	80	80	808	No o	2
	Dosage		80	80	80	80	80	80	80	80	C C C C C C C C C C C C C C C C C C C		00	0R	80	80	80	80	80	80	80	80	80 B	3
	BN No.			AY98670	B B43914	BD09556	BG85640	AF50013	AX26848	AJ32298	BG:56327	BB 50077	0070070	DCY74ZU	AU/6138	AG65046	ZN32629	AV07996	ZN37115	AG28874	AW23628	ZF92291	AB34313	
RESUME OF	Compound WR No.		Control	172435	171669	180872	228258	6,798	141871	49808	194565	1 5041 2		10000	54/3	2978	7557	30090	134806	448	99210	81844	87781	
	LIV No.			- 1503	-1502	1514	1516	1506	1512	1509	1515	[1513 - 1	- 1504 - +			1490	1491	1499	1500	1505	1511	1517	1518	

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