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# Hoechst

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KINETICS OF OCTOPIROX<sup>R</sup>

AFTER ORAL ADMINISTRATION TO DOGS AND RATS

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Kinetics of Octopirox<sup>R</sup> after Oral Administration to Dogs and Rats

SUMMARY

The present report describes the kinetics of the substance in serum, using fluorometric determination (limit of detection: 0.06  $\mu\text{g/ml}$ ).

Dogs received the drug orally per stomach tube as a suspension in sesame oil (dosages: 50 and 100 mg/kg). Depending on the absorption delay, maximal blood levels were reached after 1.25 - 3.2 hours and amounted to  $22.9 \pm 3.0 \mu\text{g/ml}$  after 50 mg/kg and  $33.0 \mu\text{g/ml}$  after 100 mg/kg. The elimination occurred with a half-life of  $2.7 \pm 0.7$  hours. The areas under the serum level curves were compared and proved to be dose-dependent (279 vs.  $122 \pm 23 \mu\text{g}\cdot\text{hr}\cdot\text{ml}^{-1}$ ).

Rats received 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2(1H)-pyridone (= H 72 6146 B) orally per stomach tube not only as monoethanolamine salt (dosage: 100 mg/kg), but also as sodium salt (dosage: 87.2 mg/kg) and as free acid (dosage: 79.9 mg/kg), all three suspended in starch mucilage; in another study, rats received by the same route Octopirox<sup>R</sup> 100 mg/kg as a suspension in sesame oil. Five animals were killed at each sampling time. The individual measuring values showed a considerable range of variation. Apart from the absorption delay, no difference was found among the various salts and vehicles. Maximal serum levels of  $12.3 \pm 3.0 \mu\text{g/ml}$  were reached after  $1.2 \pm 0.3$  hours. The elimination occurred in two phases with half-lives of 0.5 hour ( $\alpha$  slope) and 4.5 hours ( $\beta$  slope).

PURPOSE OF THE STUDY

The pharmacokinetic data of Octopirox<sup>R</sup> (= H 72 6146 A) were to be determined in animals.

STUDIES IN DOGS

Study conduct:

The test animals were fasted for 12 hours before beginning of study, but had free access to water. In a preliminary study, one dog received Octopirox<sup>R</sup> (batch E 001) 50 mg/kg orally per stomach tube as a 2 percent suspension in sesame oil. In the actual study, two further dogs received Octopirox<sup>R</sup> in dosages of 50 and 100 mg/kg, respectively. Blood samples were taken from the jugular veins of the animals at definite times, and the drug content was determined by fluorometry in the serum obtained (1).

The serum levels are shown in Table 1.

Kinetics:

The calculations performed for each animal are enclosed as Appendix 1 - 3. The open one-compartment model was selected (model 1, Bateman function):

$$y = A_0 \cdot (e^{-k_1(t-t_0)} - e^{-k_2(t-t_0)})$$

The coefficient of determination is good ( $r^2 = 0.986 \pm 0.008$ ).

The dose-independent parameters coincided well in all three animals; the dog of the preliminary study showed only a difference concerning the absorption ( $K_1 = 16.9/\text{hr}$ .  $T_{\max} = 1.25$  hrs. vs.  $K_1 = 0.70$  or  $0.46/\text{hr}$ . and  $T_{\max} = 2.8$  or  $3.2$  hrs. in both remaining animals).

The maximal serum level was only about 50 percent higher after the double dosage ( $33.0 \mu\text{g/ml}$  vs.  $20.7$  and  $25.0 \mu\text{g/ml}$ ), but the areas under curves

were dose-dependent in the ratio 2 : 1 (279  $\mu\text{g}\cdot\text{hr}\cdot\text{ml}^{-1}$  vs. 105 and 138  $\text{g}\cdot\text{hr}\cdot\text{ml}^{-1}$ ).

Constants of the Bateman function

	Prelim. study 50 mg/kg	Animal 1 50 mg/kg	Animal 2 100 mg/kg	
$A_0$	21.9	51.0	67.0	$\mu\text{g/ml}$
$K_1$	16.894	0.701	0.463	1/Std.
$K_2$	0.209	0.369	0.240	1/Std.
Elimination half-life	3.31	1.88	2.88	Std.
$T_0$	0.98	0.84	0.21	Std.
Position of curve maximum				
Time	1.25	2.8	3.2	Std.
Height	20.7	25.0	33.0	$\mu\text{g/ml}$
Area under curve	105	138	279	$\mu\text{g}\cdot\text{Std}\cdot\text{ml}^{-1}$

#### STUDIES IN RATS

##### Study conduct:

The test animals were fasted for at least 12 hours before beginning of study, but had free access to water. Groups of 50 female Wistar rats of the strain Hoe: WISKf(SPF71) with a mean body weight of  $213 \pm 11$  g received the compound 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2(1H)-pyridone (= H 72 6146 B) in a dosage of 79.9 mg/kg, its sodium salt (=H 72 6146 C, batch 5816 C) in a dosage of 87.2 mg/kg, or its monoethanolamine salt (= Octopirox<sup>R</sup> = H 72 6146 A, batch N003) in a dosage of 100 mg/kg; all three compounds were given as a one percent suspension in two percent starch mucilage and administered orally by stomach tube in a volume of 1 ml per 100 g body weight.

In a further study, 22 rats received orally Octopirox<sup>R</sup> (= H 72 6146 A, batch N003) in a dosage of 100 mg/kg as a one percent suspension in sesame oil.

Blood sampling took place at definite times, the animals having been killed by a blow on the neck, opening the thorax and severing the cranial vena cava. Five animals were killed at each sampling time. Serum was prepared for drug determination. If the amount of serum obtained from one animal was insufficient, the samples of two animals were pooled. The drug content was determined by fluorometry (1).

The serum levels are shown in Table 2.

Kinetics:

Model 16 (central + peripheral compartment) was selected for the calculation:

$$y = A \cdot e^{-\alpha(t-t_0)} + B \cdot e^{-\beta(t-t_0)} - (A+B) \cdot e^{-\gamma(t-t_0)}$$

The calculations for all four groups are enclosed as Appendix 4 - 7.

The coefficient of determination is fairly good ( $r^2 = 0.783 \pm 0.041$ ), considering the considerable variation range of values at the individual measuring times.

Apart from the absorption delay, no difference was found between the various salts and vehicles (variation range of the means: about 30 percent).

The pharmacokinetic data are summarized in Table 3. A serum level curve is enclosed as Figure 1.

LITERATURE

(1) D. Damm and P. Hajdú

Fluorometric determination of Octopirox<sup>R</sup> in serum

September 21, 1978

APPENDIX 1

OCTOPIROX, STUDY IN DOGS, ORALLY

	I	1	2
	50 MG/KG	50 MG/KG	100 MG/KG
TIME	OBSERVED LEVELS IN $\mu$ g/ml		
0.5	-	0.7*	7.7
1	5.7	4.6	20.2
1.5	-	18.9	23.9
2	18.0	20.0	-
4	11.5	23.3	33.1
6	8.4	12.1	23.4
8	4.3	6.8	19.1
12	-	2.5	6.7
24	0.7	1.0	1.7
30	-	0.4	1.0
48	-	-	0.1

THE VALUE MARKED WITH "\*" HAVE NOT BEEN CONSIDERED FOR THE COMPUTATION OF KINETICS.

SUMMARY OF OBSERVATIONS

APPENDIX 2

SUB. NO.	MONOETHANOLAMINE		SODIUM μg/ml	FREE ACID μg/ml	MEAN ± S.D.
	SESAME μg/ml	STARCH μg/ml			
0.5	∅	5.2	6.9	6.5	
0.5	∅		11.7		
0.5			12.1		
0.5			14.5		
0.5		9.2		7.1	
0.5		11.7		8.7	
0.5		13.0		8.9	0.3 ± 4.5
1.0	2.0	4.7*	7.3*	3.1*	
1.0	7.4	6.4*	9.1	3.5*	
1.0		16.2	13.3	4.3	
1.0				4.7*	6.8 ± 4.3
2.0	7.1	4.6	2.9*	7.2	
2.0	8.9	8.0	6.9	8.0	
2.0		9.9	11.4	8.4	
2.0		11.6	17.8	9.3	
2.0		11.6	17.8	9.3	
2.0				13.3	9.7 ± 3.9
3.0	1.4	0.9	7.2	1.4	
3.0	7.3	1.1	1.2*	2.2	
3.0		1.2	4.2	4.2	
3.0		5.9	5.8	4.6	
3.0		6.9	5.7		3.8 ± 2.5
4.0	1.1	0.8	7.0		
4.0	1.6	1.0	1.8		
4.0		4.5	3.4		2.7 ± 2.2
5.0	0.3	1.5	3.2	1.4	
5.0	1.3	2.9	4.5	1.7	
5.0		3.4	1.8	1.8	
5.0		4.5	4.9	2.2	
5.0			1.8		2.5 ± 1.4
6.0	∅	1.2	3.1	0.8	
6.0	3.1	2.2	1.3	1.1	
6.0		4.7	6.6	1.5	
6.0			1.7	2.8	
6.0			1.6	3.6	2.4 ± 1.7
8.0	0.1	2.4*	2.3	0.6	
8.0	2.1	5.9*	8.5*	0.9	
8.0			2.6	1.0	
8.0			1.0		
8.0			5.3*		2.7 ± 2.6
24.0	0.3	0.1	0.9	0.1	
24.0	∅	0.2	0.5	0.1	
24.0		0.3	0.3	0.3	
24.0		0.3	0.3	0.4	
24.0		0.6	0.2	0.4	0.3 ± 0.2
48.0		∅	∅	∅	
48.0	∅	∅	∅	∅	
48.0	∅	∅	∅	0.1	
48.0		∅		0.2	
48.0		∅		0.2	∅ ± 0.1

THE VALUES MARKED WITH "\*" HAVE NOT BEEN CONSIDERED FOR THE COMPUTATION OF KINETICS.

APPENDIX 3

	Monoethanolamine-salt sesame oil/starch mucilage	Na-salt	Acid	$\bar{x}$	$\pm$		Standard error (%)
A	116.7	257.6	329.8	48.2	188.1	128.5	g/ml 68.34
$\alpha$	1.550	1.923	0.926	0.863	1.316	0.510	l/Std. 38.75
B	4.243	7.253	4.585	3.270	4.838	1.704	g/ml 35.22
R	0.172	0.206	0.100	0.112	0.148	0.050	l/Std. 33.99
T-50	4.03	3.369	6.948	6.185	5.133	1.706	Std. 33.23
$\gamma$	1.83	2.176	1.012	1.368	1.597	0.511	l/Std. 32.02
T 0	0.852	0.325	0.003	0.048	0.307	0.390	Std. 127.11
curve maximum							
time	1.54	0.89	1.15	1.05	1.157	0.277	Std. 23.89
height	9.61	15.94	13.39	10.16	12.275	2.958	g/ml 24.10
AHC	33.87	47.53	71.77	47.41	50.147	15.778	g*Std./ml 31.46
R2	0.745	0.783	0.763	0.840	0.783	0.041	5.26

ZENTR. + PER. KOMP.

RAT

DRUG: OCTOPIROX MONOETHYNOLAMINE

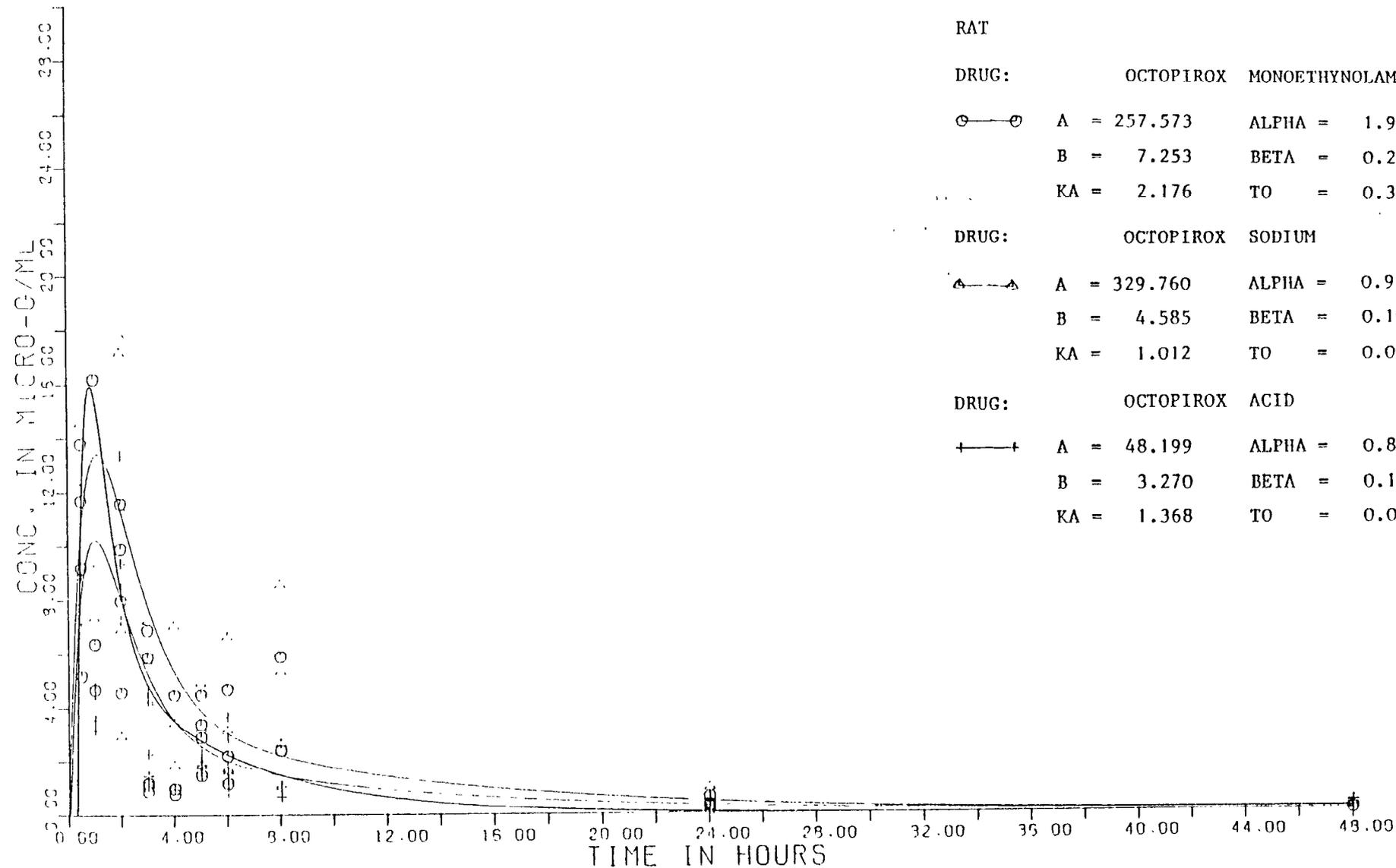
○—○ A = 257.573 ALPHA = 1.923  
 B = 7.253 BETA = 0.206  
 KA = 2.176 TO = 0.325

DRUG: OCTOPIROX SODIUM

△—△ A = 329.760 ALPHA = 0.926  
 B = 4.585 BETA = 0.100  
 KA = 1.012 TO = 0.003

DRUG: OCTOPIROX ACID

+—+ A = 48.199 ALPHA = 0.863  
 B = 3.270 BETA = 0.112  
 KA = 1.368 TO = 0.048



A P P E N D I X

APPENDIX 1

RESULTS OF KINETICS

MODEL USED: BATEMAN-FUNCTION  
(KZ = 1)  
DATE OF TRIAL: JUNE 78  
IDENTIFICATION OF TRIAL: ◆◆◆  
SUBJECT NUMBER: I  
PREPARATION: OCTOPIROX  
DOSE: 50.00 MG/KG  
TOTAL DOSE: 880.00 MG  
WAY OF APPLICATION:  
  
SPECIES: DOG  
BODY WEIGHT: 17.60 KG  
SUBSTANCE: SERUM  
  
ANNOTATIONS: PILOT TEST

TIME	OBS. CONC.	CALC. CONC.	WEIGHTS
H	MICRO-G/ML	MICRO-G/ML	
1.000	5.700	5.700	1.000
2.000	18.000	17.909	1.000
4.000	11.500	11.784	1.000
6.000	8.400	7.754	1.000
8.000	4.300	5.102	1.000
24.000	0.700	0.179	1.000

PHARMACOKINETICAL CONSTANTS

INITIAL CONCENTR. 21.886 MICRO-G/ML  
RATE OF ADSORPTION 16.894 1/H  
CORRESPONDING T-50% 0.041 H  
RATE OF ELIMINATION 0.209E 00 1/H  
CORRESPONDING T-50% 3.312 H  
LAG-TIME 0.982 H  
REAL HALF-LIFE-TIME 3.635 H  
  
POS. OF CURVE MAXIMUM  
AT SINGLE DOSAGE  
TIME: 1.245 H  
HEIGHT: 20.714 MICRO-G/ML  
  
AREA UNDER CURVE 104.576 MICRO-G•H/ML  
R-SQUARED 0.992

RESULTS OF KINETICS

MODEL USED: BATEMAN-FUNCTION  
(KZ = 1)

DATE OF TRIAL: JULY 78  
IDENTIFICATION OF TRIAL: ◆◆◆  
SUBJECT NUMBER: 1  
PREPARATION: OCTOPIROX  
DOSE: 50.00 MG/KG  
TOTAL DOSE: 745.00 MG  
WAY OF APPLICATION:

SPECIES: DOG  
BODY WEIGHT: 14.90 KG  
SUBSTANCE: SERUM

ANNOTATIONS: -

TIME H	OBS. CONC. MICRO-G/ML	CALC. CONC. MICRO-G/ML	WEIGHTS
0.500	0.700	0.000	0.000
1.000	4.600	5.189	1.000
1.500	18.900	16.576	1.000
2.000	20.000	22.419	1.000
4.000	23.300	21.814	1.000
6.000	12.100	13.160	1.000
8.000	6.800	6.964	1.000
12.000	2.500	1.712	1.000
24.000	1.000	0.021	1.000
30.000	0.400	0.002	1.000
48.000	0.000	0.000	1.000

PHARMACOKINETICAL CONSTANTS

INITIAL CONCENTR.	51.003	MICRO-G/ML
RATE OF ADSORPTION	0.701	1/H
CORRESPONDING T-50%	0.989	H
RATE OF ELIMINATION	0.369E 00	1/H
CORRESPONDING T-50%	1.879	H
LAG-TIME	0.842	H
REAL HALF-LIFE-TIME	5.331	H
POS. OF CURVE MAXIMUM AT SINGLE DOSAGE		
TIME:	2.775	H
HEIGHT:	24.995	MICRO-G/ML
AREA UNDER CURVE	138.236	MICRO-G•H/ML
R. SQUARED	0.977	

RESULTS OF KINETICS

MODEL USED: BATEMAN-FUNCTION  
(KZ = 1)  
DATE OF TRIAL: JULY 78  
IDENTIFICATION OF TRIAL: ♦♦♦  
SUBJECT NUMBER: 2  
PREPARATION: OCTOPIROX  
DOSE: 100.00 MG/KG  
TOTAL DOSE: 1270.00 MG  
WAY OF APPLICATION:  
  
SPECIES: DOG  
BODY WEIGHT: 12.70 KG  
SUBSTANCE: SERUM  
  
ANNOTATIONS: -

TIME H	OBS. CONC. MICRO-G/ML	CALC. CONC. MICRO-G/ML	WEIGHTS
0.500	7.700	8.116	1.000
1.000	20.200	18.576	1.000
1.500	23.900	25.501	1.000
4.000	33.100	31.931	1.000
6.000	23.400	25.102	1.000
8.000	19.100	17.645	1.000
12.000	6.700	7.601	1.000
24.000	1.700	0.456	1.000
30.000	1.000	0.108	1.000
48.000	0.100	0.001	1.000

PHARMACOKINETIC CONSTANTS

INITIAL CONCENTR. 66.988 MICRO-G/ML  
RATE OF ADSORPTION 0.463 1/H  
CORRESPONDING T-50% 1.497 H  
RATE OF ELIMINATION 0.240E 00 1/H  
CORRESPONDING T-50% 2.884 H  
LAG-TIME 0.210 F  
REAL HALF-LIFE-TIME 8.133 h  
  
POS. OF CURVE MAXIMUM  
AT SINGLE DOSAGE  
TIME: 3.155 H  
HEIGHT: 33.009 MICRO-G/ML  
  
AREA UNDER CURVE 278.762 MICRO-G•H/ML  
R-SQUARED 0.988







RESULTS OF KINETIC

APPENDIX 7

MODEL USED: CENTE.+REF. (D.F. 1)  
 DATE OF TRIAL: 29.08.81  
 IDENTIFICATION OF TRIAL: \*\*\*  
 SUBJECT NUMBER: -  
 REPERATION: OCTOBER  
 DATE: 29.08 08.45  
 TOTAL DOSE: 15.00 MG  
 NBR. OF APPLICATION: 0FRL  
 SPECIES: RAT  
 EST. WEIGHT: 0.200 KG  
 DISTANCE: 15.000  
 ANNOTATION: FREE HOLD

TIME (H)	DETERMINED (MICRO-G ML)	CALC. CONC. (MICRO-G ML)	WEIGHT (G)
0.500	6.500	6.015	1.000
0.500	7.100	6.014	1.000
0.500	6.700	6.015	1.000
0.500	8.400	6.015	1.000
1.000	6.100	10.144	0.000
1.000	6.500	10.144	0.000
1.000	4.500	10.144	0.000
1.000	4.700	10.144	0.000
2.000	7.200	6.007	1.000
2.000	6.000	6.006	1.000
2.000	6.400	6.006	1.000
2.000	6.500	6.006	1.000
2.000	13.500	6.005	1.000
3.000	1.400	5.213	1.000
3.000	2.200	5.213	1.000
3.000	4.200	5.213	1.000
3.000	4.600	5.213	1.000
3.000	1.400	2.489	1.000
3.000	1.700	2.489	1.000
3.000	1.800	2.489	1.000
3.000	2.200	2.489	1.000
4.000	0.600	1.345	1.000
4.000	1.100	1.345	1.000
4.000	1.500	1.345	1.000
4.000	2.500	1.345	1.000
4.000	3.500	1.345	1.000
4.000	0.600	1.330	1.000
4.000	0.900	1.330	1.000
4.000	1.000	1.330	1.000
24.000	0.100	0.223	1.000
24.000	0.100	0.223	1.000
24.000	0.300	0.223	1.000
24.000	0.400	0.223	1.000
24.000	0.400	0.223	1.000
48.000	0.000	0.015	1.000
48.000	0.000	0.015	1.000
48.000	0.100	0.015	1.000
48.000	0.200	0.015	1.000
48.000	0.200	0.015	1.000

PARAMETRIC KINETICAL CONSTANTS

PARAMETERS OF FORMULA

A	48.199	(MICRO-G/ML)
ALPHA	0.893E 00	(1/H)
CORRESPONDING T1/2	0.203	(H)
B	3.270	(MICRO-G/ML)
BETA	0.112E 00	(1/H)
CORRESPONDING T1/2	6.185	(H)
C	-51.469	(MICRO-G/ML)
LR	0.137E 01	(1/H)
TD	0.046	(H)
POS. OF CURVE MAXIMUM TIME	1.053	(H)
HEIGHT	10.197	(MICRO-G/ML)
RUC	47.407	(MICRO-G+H/ML)
R-SQUARED	0.840	