

IV.資料

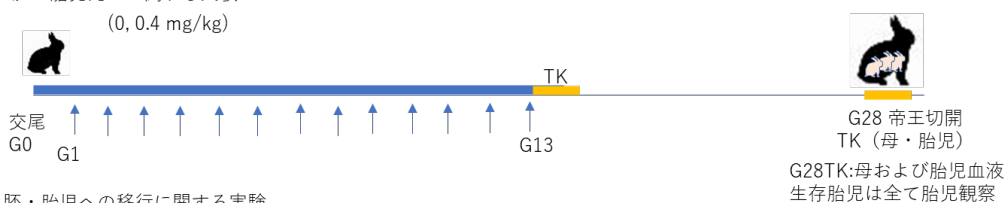
1. 妊娠雌ウサギを用いた腔内投与発生毒性試験(令和3年度実施)

目的：精漿を介した母体および胎児への影響を確認

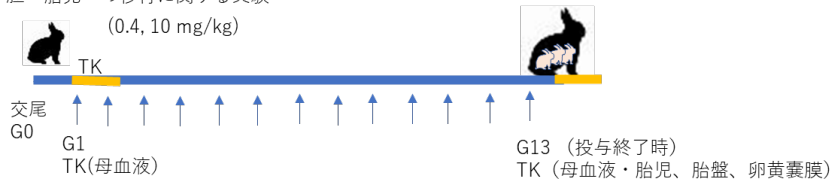
1. 群構成

試験群	投与量 (mg/kg体重/day)	容量/腔 mL/kg*	投与期間	解剖時期	動物数(妊娠雌)
1	0	0.05	G1-G13	G28	8
2 (TK)	0.4	0.05	G1-G13	G28	16(14)
3 (TK)	10	0.05	G1-G13	G13	8(7)

試験1 胚・胎児発生に関する実験



試験2 胚・胎児への移行に関する実験

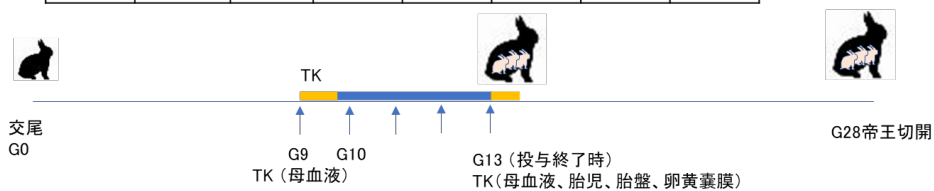


2. 奇形発現量における妊娠雌ウサギを用いた経口投与毒性試験(R4年度実施)

目的: 催奇形性が発現する用量での母体および胎児血中濃度を確認

1. 群構成

試験群	投与量 (mg/kg体重/day)	容量/ mL/kg	動物数 (妊娠雌)	投与期 間	G9採血	G13採血	G28 帝王切開
1	0	10	4	G9-G13		-	○
2(TK)	25	10	8	G9-G13	○	○	○
3(TK)	250	10	8	G9-G10	○	-	○



膣内投与結果と比較し、膣内投与では奇形発現濃度に達していないことを確認

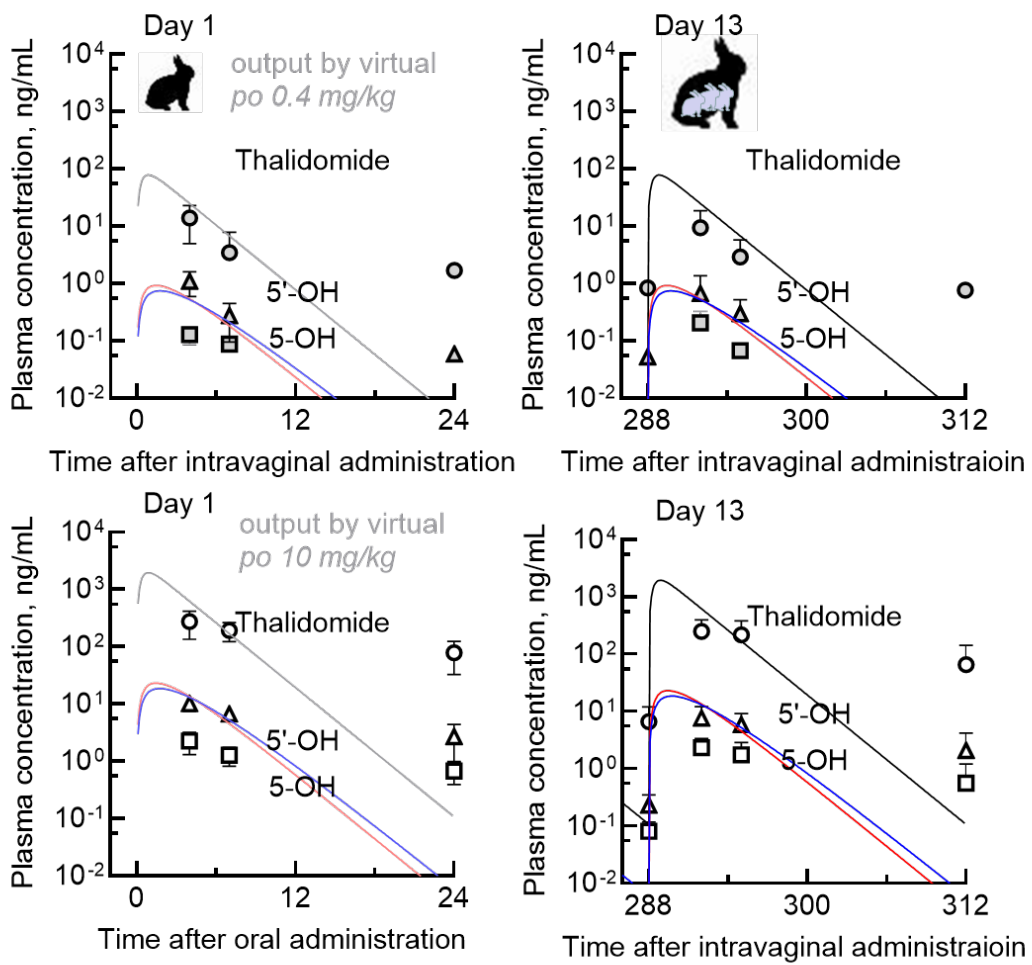


図1 生理学的薬物動態モデルによる出力結果値と腔内投与による実測値との比較

表 1 妊娠雌ウサギを用いたサリドマイド臍内投与による母動物体重推移・胎・胎児発生に関する実験

Test article		Gestational day										
Dose		0	3	6	8	10	12	13	14	16	19	22
		Treatment period (GD1-GD13)										
thalidomide	n	7	7	7	7	7	7	7	7	7	7	7
0 mg/kg	Mean	3.09	3.18	3.25	3.28	3.33	3.35	3.35	3.38	3.43	3.48	3.51
	S.D.	0.17	0.20	0.20	0.21	0.20	0.22	0.21	0.22	0.23	0.22	0.23
thalidomide	n	8	8	8	8	8	8	8	8	8	8	8
0.4 mg/kg	Mean	3.08	3.20	3.26	3.28	3.30	3.32	3.31	3.29	3.40	3.48	3.49
	S.D.	0.14	0.17	0.14	0.15	0.17	0.21	0.18	0.15	0.16	0.17	0.17

Test article		Gestational day		
Dose		24	26	28
thalidomide	n	7	7	7
0 mg/kg	Mean	3.53	3.58	3.62
	S.D.	0.22	0.22	0.22
thalidomide	n	8	8	8
0.4 mg/kg	Mean	3.53	3.60	3.65
	S.D.	0.16	0.15	0.15

Not significantly different from thalidomide 0 mg/kg

n: Number of dams

表 2 妊娠雌ウサギを用いたサリドマイド臍内投与による母動物体重増加量: 胚・胎児発生に関する実験

Test article	Dose	Body weight gain			
		GDs1-14	GDs14-28	GDs0-28	
thalidomide	n	7	7	7	
	0 mg/kg	Mean	0.20	0.24	0.53
		S.D.	0.04	0.08	0.09
thalidomide	n	8	8	8	
	0.4 mg/kg	Mean	0.10	0.35	0.57
		S.D.	0.10	0.08	0.04
		A2 *	T2 *	NS	

NS; Not significantly different from thalidomide 0 mg/kg

Significantly different from thalidomide 0 mg/kg : * P<0.05

A2 : Welch test (two-side)

T2 : Student t-test (two-side)

n: Number of dams

表3 妊娠雌ウサギを用いたサリドマイド臍内投与後の帝王切開所見: 胚・胎児発生に関する実験

Test article	Dose	Number of corpora lutea	Number of implantation	Preimplantation loss (%) a)	Implantation index (%) b)	Number of resorptions Total c)	Postimplantation loss (%) Total d)	Number of live fetuses			Sex rate (fetuses) (%) e)	Fetal weight (g)			Placental weight (g)		
								Male	Female	Total		Male	Female	Total	Male	Female	Total
thalidomide	n	7	7	7	7	7	7	7	7	7	26/54	7	7	7	7	7	7
0 mg/kg	Mean	8.7	8.1	5.2	94.8	0.4	6.0	3.7	4.0	7.7	48.1	35.12	35.55	35.26	5.07	5.14	5.10
	S.D.	1.6	1.3	13.8	13.8	0.8	10.5	1.5	1.0	1.8		2.80	2.76	2.70	0.64	0.63	0.63
thalidomide	n	8	8	8	8	8	8	8	8	8	25/64	8	8	8	8	8	8
0.4 mg/kg	Mean	9.3	8.3	10.9	89.1	0.3	2.7	3.1	4.9	8.0	39.1	35.86	33.71	34.60	5.33	5.21	5.30
	S.D.	1.2	2.0	17.5	17.5	0.5	5.1	1.4	2.0	1.9		2.67	3.99	3.38	0.52	0.77	0.59

Not significantly different from thalidomide 0 mg/kg

n: Number of dams

a): $[(\text{Number of corpora lutea} - \text{Number of implantations}) / \text{Number of corpora lutea}] \times 100$

b): $(\text{Number of implantations} / \text{Number of corpora lutea}) \times 100$

c): Resorptions: Implantation site, resorbed embryo, placental remnant, early macerated fetus, late macerated fetus and dead fetus

d): $(\text{Number of resorptions} / \text{Number of implantations}) \times 100$

e): $(\text{Number of live male fetuses} / \text{Number of live fetuses}) \times 100$

表 4 妊娠雌ウサギを用いたサリドマイド膈内投与による胚・胎児死亡数：胚・胎児発生に関する実験

Test article	Number of implan- tation	Number of resorptions								Postimplantation loss(%) a)						
		i	r	p	e	l	d	Total	i	r	p	e	l	d	Total	
thalidomide	n	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
0 mg/kg	Mean	8.1	0.0	0.3	0.0	0.1	0.0	0.0	0.4	0.0	4.2	0.0	1.8	0.0	0.0	6.0
	S.D.	1.3	0.0	0.5	0.0	0.4	0.0	0.0	0.8	0.0	7.2	0.0	4.7	0.0	0.0	10.5
thalidomide	n	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
0.4 mg/kg	Mean	8.3	0.0	0.3	0.0	0.0	0.0	0.0	0.3	0.0	2.7	0.0	0.0	0.0	0.0	2.7
	S.D.	2.0	0.0	0.5	0.0	0.0	0.0	0.0	0.5	0.0	5.1	0.0	0.0	0.0	0.0	5.1

i : Implantation site, r : Resorbed embryo, p : Placental remnant, e : Early macerated fetus, l : Late macerated fetus, d : Dead fetus

Not significantly different from thalidomide 0 mg/kg

n: Number of dams

a): (Number of resorptions / Number of implantations) x 100

表 5 妊娠雌ウサギを用いたサリドマイド膈内投与による胎児外表観察：胚・胎児発生に関する実験

Test article	thalidomide	thalidomide
Dose	0	0.4
Dose unit	mg/kg	mg/kg
Number of dams	7	8
Number of fetuses	54	64
Number of dams with anomalous fetuses (incidence %) a)	0 (0.0)	0 (0.0)
Number of fetuses with any anomaly (incidence %) b)	0 (0.0)	0 (0.0)

Not significantly different from thalidomide 0 mg/kg

n: Number of dams

a): (Number of dams bearing live fetuses with external anomalies / Number of dams) x 100

b): (Number of fetuses with external anomalies / Number of live fetuses examined) x 100

表 6 妊娠雌ウサギを用いたサリドマイド臍内投与による胎児内臓観察：胚・胎児発生に関する実験

Test article		thalidomide	thalidomide
Dose		0	0.4
Dose unit		mg/kg	mg/kg
Number of dams		7	8
Number of fetuses		54	64
<hr/>			
Number of dams with anomalous fetuses (incidence %)	a)	1(14.3)	0(0.0)
Number of fetuses with any anomaly (incidence %)	b)	1(1.4)	0(0.0)
<hr/>			
Number of dams with variant fetuses (incidence %)	a)	3 (42.9)	2 (25.0)
Number of fetuses with any variation (incidence %)	b)	6 (9.5)	2 (3.5)
<hr/>			
Abnormality			
Diaphragmatic hernia	n	1(1)	0(0)
	Mean	1.4	
	S.D.	3.8	
<hr/>			
Variation			
Absent accessory lung lobe	n	5 (2)	0 (0)
	Mean	7.5	
	S.D.	12.9	
Retrocaval ureter	n	1 (1)	2 (2)
	Mean	2.0	3.5
	S.D.	5.4	6.6

n : Number of variant fetuses (number of dams with variant fetuses)

Mean : Number of variant fetuses / Number of fetuses examined x 100(%), on litter basis

Not significantly different from thalidomide 0 mg/kg

a): (Number of dams bearing live fetuses with visceral abnormalities or variations / Number of dams) x 100

b): (Number of fetuses with visceral abnormalities or variations / Number of fetuses examined) x 100

表 7 妊娠雌ウサギを用いたサリドマイド臍内投与による胎児骨格観察：胚・胎児発生に関する実験

Test article		thalidomide	thalidomide
Dose		0	0.4
Dose unit		mg/kg	mg/kg
Number of dams		7	8
Number of fetuses		54	64
<hr/>			
Number of dams with anomalous fetuses (incidence %) a)		1(14.3)	2(25.0)
Number of fetuses with any anomaly (incidence %) b)		1(1.4)	2(3.5)
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Number of dams with variant fetuses (incidence %) a)		6 (85.7)	7 (87.5)
Number of fetuses with any variation (incidence %) b)		17 (34.1)	29 (44.9)
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Abnormality			
Fused sternebra	n	1(1)	1(1)
	Mean	1.4	1.4
	S.D.	3.8	3.9
Fused rib	n	0(0)	1(1)
	Mean		2.1
	S.D.		5.9
Fused thoracic arch	n	0(0)	1(1)
	Mean		2.1
	S.D.		5.9
Hemicentric thoracic centrum	n	0(0)	1(1)
	Mean		2.1
	S.D.		5.9
<hr/>			
Variation			
Split sternebra	n	2 (2)	2 (1)
	Mean	5.2	4.2
	S.D.	9.0	11.8
Split thoracic centrum	n	0 (0)	1 (1)
	Mean		2.1
	S.D.		5.9
27 presacral vertebrae	n	15 (5)	24 (5)
	Mean	28.8	35.9
	S.D.	24.2	31.4
25 presacral vertebrae	n	0 (0)	1 (1)
	Mean		2.1
	S.D.		5.9
Unossified talus	n	0 (0)	2 (2)
	Mean		2.8
	S.D.		5.3

n : Number of variant fetuses (number of dams with variant fetuses)

Mean : Number of variant fetuses / Number of fetuses examined x 100(%) , on litter basis

Not significantly different from thalidomide 0 mg/kg

a): (Number of dams bearing live fetuses with skeletal abnormalities or variations / Number of dams) x 100

b): (Number of fetuses with skeletal abnormalities or variations / Number of fetuses examined) x 100

表 8-1 妊娠雌ウサギを用いたサリドマイド臍内投与による胎児主要部位骨化数観察：胚・胎児発生に関する実験

(1) 胸骨、仙尾椎骨、手骨

Test article		thalidomide	thalidomide
Dose		0	0.4
Dose unit		mg/kg	mg/kg
Number of dams		7	8
Number of fetuses		54	64
Sternebra	Mean	5.43	5.50
	S.D.	0.56	0.52
Sac.&caud. Vertebra	Mean	19.01	19.24
	S.D.	0.48	0.36
Metacarpal phalanges of forelimbs R	Mean	4.68	4.61
	S.D.	0.30	0.22
Metacarpal phalanges of forelimbs L	Mean	4.68	4.66
	S.D.	0.27	0.20
Proximal phalanges of forelimbs R	Mean	5.00	5.00
	S.D.	0.00	0.00
Proximal phalanges of forelimbs L	Mean	5.00	5.00
	S.D.	0.00	0.00
Middle phalanges of forelimbs R	Mean	3.88	3.74
	S.D.	0.11	0.43
Middle phalanges of forelimbs L	Mean	3.90	3.73
	S.D.	0.08	0.43
Distal phalanges of forelimbs R	Mean	5.00	5.00
	S.D.	0.00	0.00
Distal phalanges of forelimbs L	Mean	5.00	5.00
	S.D.	0.00	0.00

Not significantly different from thalidomide 0 mg/kg

Sac.&caud.: sacral and caudal

表 8-2 妊娠雌ウサギを用いたサリドマイド臍内投与による胎児主要部位骨化数観察：胚・胎児発生に関する実験

(2) 足骨

Test article		thalidomide	thalidomide
Dose		0	0.4
Dose unit		mg/kg	mg/kg
Number of dams		7	8
Number of fetuses		54	64
Metatarsal phalanges of hindlimbs R	Mean	4.00	4.00
	S.D.	0.00	0.00
Metatarsal phalanges of hindlimbs L	Mean	4.00	4.00
	S.D.	0.00	0.00
Proximal phalanges of hindlimbs R	Mean	4.00	4.00
	S.D.	0.00	0.00
Proximal phalanges of hindlimbs L	Mean	4.00	4.00
	S.D.	0.00	0.00
Middle phalanges of hindlimbs R	Mean	3.98	3.95
	S.D.	0.05	0.13
Middle phalanges of hindlimbs L	Mean	3.98	3.95
	S.D.	0.06	0.13
Distal phalanges of hindlimbs R	Mean	4.00	4.00
	S.D.	0.00	0.00
Distal phalanges of hindlimbs L	Mean	4.00	4.00
	S.D.	0.00	0.00

Not significantly different from thalidomide 0 mg/kg

表 9 妊娠雌ウサギを用いたサリドマイド膣内投与による母動物体重推移: 胚・胎児への移行に関する実験

Test article	Dose	Gestational day (GD)								Body weight gain (GDs 0-13)
		0	3	6	8	10	12	13	14	
		Intravaginal treatment days (GDs 1-13)								
thalidomide	n	6	6	6	6	6	6	6	3	6
0.4 mg/kg	Mean	3.15	3.21	3.27	3.32	3.34	3.38	3.39	3.31	0.18
	S.D.	0.13	0.14	0.14	0.14	0.14	0.13	0.14	0.05	0.03
thalidomide	n	7	7	7	7	7	7	7	3	7
10 mg/kg	Mean	3.17	3.26	3.37	3.39	3.43	3.44	3.45	3.35	0.19
	S.D.	0.12	0.09	0.10	0.09	0.09	0.10	0.10	0.05	0.05

n: Number of dams

表 10 妊娠雌ウサギを用いたサリドマイド臍内投与後の帝王切開所見: 胚・胎児への移行に関する実験

Test article	Dose	n	Number of corpora lutea	Number of implantation	Preimplantation loss (%) a)	Implantation index (%) b)	Number of resorptions Total	Postimplantation loss(%) Total c)	Number of live embryos Total	Placental weight(g)	
										GD13	GD14
thalidomide	0.4 mg/kg	6	6	6	6	6	6	6	6	3	3
	Mean	8.7	8.3	3.9	96.1	0.0	0.0	8.3	1.79	2.06	
	S.D.	1.2	1.4	6.1	6.1	0.0	0.0	1.4	0.15	0.02	
thalidomide	10 mg/kg	7	7	7	7	7	7	7	7	4	3
	Mean	8.7	6.6	26.2	73.8	0.4	8.3	6.1	1.52	2.12	
	S.D.	1.6	3.3	33.4	33.4	0.8	14.4	3.4	0.28	0.30	

n: Number of dams

GD: Gestation Day

a): $[(\text{Number of corpora lutea} - \text{Number of implantations}) / \text{Number of corpora lutea}] \times 100$

b): $(\text{Number of implantations} / \text{Number of corpora lutea}) \times 100$

c): $(\text{Number of resorptions} / \text{Number of implantations}) \times 100$

表11 妊娠雌ウサギを用いたサリドマイド膣内投与による母動物血漿中サリドマイド濃度及びTKパラメータ（妊娠13日）：胚・胎児発生に関する実験

(1) Thalidomide

Dose level (mg/kg)	Animal No.	Concentration (ng/mL)						
		Pre	0.5 h	1 h	2 h	4 h	7 h	
0.4	2101	BLQ	1.25	2.67	2.53	2.17	BLQ	
	2102	BLQ	6.04	7.45	7.08	3.10	1.21	
	2103	0.472	4.85	4.46	2.52	1.10	0.492	
	2104	BLQ	46.2	35.1	13.5	2.02	0.606	
	2105	BLQ	15.1	24.9	15.0	5.42	1.90	
	2106	BLQ	5.80	6.61	4.64	0.966	BLQ	
	2107	BLQ	4.64	5.98	4.88	2.17	0.826	
	2108	BLQ	8.91	6.05	2.77	0.520	BLQ	
	Mean	NC	11.6	11.7	6.62	2.18	0.629	
SD	NC	14.6	11.7	4.97	1.55	0.676		

BLQ: Below the lower limit of quantification (0.400 ng/mL)

NC: Not calculated

(2) TKパラメータ (thalidomide)

Dose level (mg/kg)	Animal No.	TK parameter		
		C _{max} (ng/mL)	T _{max} (h)	AUC _{0-t} (h*ng/mL)
0.4	2101	2.67	1.00	11.8
	2102	7.45	1.00	28.8
	2103	4.85	0.500	13.2
	2104	46.2	0.500	75.6
	2105	24.9	1.00	65.1
	2106	6.61	1.00	17.2
	2107	5.98	1.00	20.8
	2108	8.91	0.500	14.4
	Mean	13.4	0.813	30.9
SD	14.9	0.259	25.1	

表12 妊娠雌ウサギを用いたサリドマイド膈内投与による母動物血漿中5-hydroxythalidomide濃度及びTKパラメータ（妊娠13日）：胚・胎児発生に関する実験

(1) 5-hydroxythalidomide

Dose level (mg/kg)	Animal No.	Concentration (ng/mL)					
		Pre	0.5 h	1 h	2 h	4 h	7 h
0.4	2101	BLQ	BLQ	BLQ	0.0448	BLQ	BLQ
	2102	BLQ	0.0944	0.172	0.141	0.0551	BLQ
	2103	BLQ	BLQ	0.0417	BLQ	BLQ	BLQ
	2104	BLQ	0.222	0.269	0.144	BLQ	BLQ
	2105	BLQ	0.227	0.347	0.234	0.0831	BLQ
	2106	BLQ	0.0704	0.0816	0.0556	BLQ	BLQ
	2107	BLQ	0.0557	0.0809	0.0697	BLQ	BLQ
	2108	BLQ	0.201	0.142	0.0615	BLQ	BLQ
	Mean	NC	0.109	0.142	0.0938	0.0173	NC
	SD	NC	0.0952	0.118	0.0743	0.0329	NC

BLQ: Below the lower limit of quantification (0.0400 ng/mL)

NC: Not calculated

(2) TKパラメータ (5-hydroxythalidomide)

Dose level (mg/kg)	Animal No.	TK parameter		
		C _{max} (ng/mL)	T _{max} (h)	AUC _{0-t} (h*ng/mL)
0.4	2101	0.0448	2.00	0.0672
	2102	0.172	1.00	0.525
	2103	0.0417	1.00	0.0313
	2104	0.269	1.00	0.529
	2105	0.347	1.00	0.933
	2106	0.0816	1.00	0.180
	2107	0.0809	1.00	0.193
	2108	0.201	0.500	0.299
	Mean	0.155	1.06	0.345
	SD	0.112	0.417	0.302

表13 妊娠雌ウサギを用いたサリドマイド膈内投与による母動物血漿中5'-hydroxythalidomide濃度及びTKパラメータ（妊娠13日）：胚・胎児発生に関する実験

(1) 5'-hydroxythalidomide

Dose level (mg/kg)	Animal No.	Concentration (ng/mL)					
		Pre	0.5 h	1 h	2 h	4 h	7 h
0.4	2101	BLQ	BLQ	0.0721	0.160	0.213	BLQ
	2102	BLQ	0.0537	0.171	0.291	0.200	0.0595
	2103	BLQ	0.0681	0.110	0.126	0.0904	BLQ
	2104	BLQ	0.481	0.843	0.806	0.234	BLQ
	2105	BLQ	0.173	0.482	0.694	0.382	0.140
	2106	BLQ	0.0848	0.240	0.283	0.119	BLQ
	2107	BLQ	0.0451	0.152	0.258	0.148	0.0743
	2108	BLQ	0.143	0.253	0.231	0.0445	BLQ
	Mean	NC	0.131	0.290	0.356	0.179	0.0342
SD	NC	0.152	0.256	0.252	0.104	0.0525	

BLQ: Below the lower limit of quantification (0.0400 ng/mL)

NC: Not calculated

(2) TKパラメータ (5'-hydroxythalidomide)

Dose level (mg/kg)	Animal No.	TK parameter		
		C _{max} (ng/mL)	T _{max} (h)	AUC _{0-t} (h*ng/mL)
0.4	2101	0.213	4.00	0.827
	2102	0.291	2.00	1.18
	2103	0.126	2.00	0.532
	2104	0.843	1.00	2.67
	2105	0.694	2.00	2.65
	2106	0.283	2.00	0.944
	2107	0.258	2.00	1.01
	2108	0.253	1.00	0.719
	Mean	0.370	2.00	1.32
SD	0.254	0.926	0.851	

表14 妊娠雌ウサギを用いたサリドマイド臍内投与後の母動物血漿中サリドマイド及び代謝物濃度(妊娠28日)：胚・胎児発生に関する実験

Dose level (mg/kg)	Animal No.	Concentration (ng/mL)		
		Thalidomide	5-hydroxythalidomide	5'-hydroxythalidomide
0.4	2101	BLQ	BLQ	BLQ
	2102	BLQ	BLQ	BLQ
	2103	BLQ	BLQ	BLQ
	2104	BLQ	BLQ	BLQ
	2105	BLQ	BLQ	BLQ
	2106	BLQ	BLQ	BLQ
	2107	BLQ	BLQ	BLQ
	2108	BLQ	BLQ	BLQ
	Mean	NC	NC	NC
	SD	NC	NC	NC

BLQ: Below the lower limit of quantification (0.400 ng/mL for thalidomide; 0.0400 ng/mL for 5-hydroxy/5'-hydroxy-thalidomide)

NC: Not calculated

表15-1 妊娠雌ウサギを用いたサリドマイド臍内投与による胎児血漿中サリドマイド濃度(妊娠28日): 胚・胎児発生に関する実験

(1) thalidomide

Dose level (mg/kg)	fetus No.	Concentration (ng/mL)							
		2101	2102	2103	2104	2105	2106	2107	2108
0.4	R-1	BLQ	BLQ	BLQ	BLQ	BLQ	-	BLQ	BLQ
	R-2	BLQ	BLQ	BLQ	-	BLQ	BLQ	BLQ	BLQ
	R-3	-	-	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	R-4	-	-	BLQ	BLQ	BLQ	-	BLQ	-
	R-5	-	-	-	BLQ	-	-	BLQ	-
	R-6	-	-	-	BLQ	-	-	BLQ	-
	R-7	-	-	-	-	-	-	BLQ	-
	L-1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	L-2	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	-	BLQ
	L-3	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	-
	L-4	BLQ	BLQ	BLQ	-	BLQ	BLQ	BLQ	-
	L-5	-	BLQ	BLQ	-	-	BLQ	-	-
	L-6	-	BLQ	BLQ	-	-	-	-	-
	L-7	-	BLQ	-	-	-	-	-	-
Mean		NC	NC	NC	NC	NC	NC	NC	NC
SD		NC	NC	NC	NC	NC	NC	NC	NC

BLQ: Below the lower limit of quantification (0.400 ng/mL)

NC: Not calculated

表15-2 妊娠雌ウサギを用いたサリドマイド臍内投与による胎児血漿中5-hydroxythalidomide濃度(妊娠28日)：胚・胎児発生に関する実験

(2) 5-hydroxythalidomide

Dose level (mg/kg)	fetus No.	Concentration (ng/mL)							
		2101	2102	2103	2104	2105	2106	2107	2108
0.4	R-1	BLQ	BLQ	BLQ	BLQ	BLQ	-	BLQ	BLQ
	R-2	BLQ	BLQ	BLQ	-	BLQ	BLQ	BLQ	BLQ
	R-3	-	-	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	R-4	-	-	BLQ	BLQ	BLQ	-	BLQ	-
	R-5	-	-	-	BLQ	-	-	BLQ	-
	R-6	-	-	-	BLQ	-	-	BLQ	-
	R-7	-	-	-	-	-	-	BLQ	-
	L-1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	L-2	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	-	BLQ
	L-3	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	-
	L-4	BLQ	BLQ	BLQ	-	BLQ	BLQ	BLQ	-
	L-5	-	BLQ	BLQ	-	-	BLQ	-	-
	L-6	-	BLQ	BLQ	-	-	-	-	-
	L-7	-	BLQ	-	-	-	-	-	-
Mean		NC	NC	NC	NC	NC	NC	NC	NC
SD		NC	NC	NC	NC	NC	NC	NC	NC

BLQ: Below the lower limit of quantification (0.0400 ng/mL)

NC: Not calculated

表15-3 妊娠雌ウサギを用いたサリドマイド臍内投与による胎児血漿中5'-hydroxythalidomide濃度(妊娠28日)：胚・胎児発生に関する実験

(3) 5'-hydroxythalidomide

Dose level (mg/kg)	fetus No.	Concentration (ng/mL)							
		2101	2102	2103	2104	2105	2106	2107	2108
0.4	R-1	BLQ	BLQ	BLQ	BLQ	BLQ	-	BLQ	BLQ
	R-2	BLQ	BLQ	BLQ	-	BLQ	BLQ	BLQ	BLQ
	R-3	-	-	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	R-4	-	-	BLQ	BLQ	BLQ	-	BLQ	-
	R-5	-	-	-	BLQ	-	-	BLQ	-
	R-6	-	-	-	BLQ	-	-	BLQ	-
	R-7	-	-	-	-	-	-	BLQ	-
	L-1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	L-2	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	-	BLQ
	L-3	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	-
	L-4	BLQ	BLQ	BLQ	-	BLQ	BLQ	BLQ	-
	L-5	-	BLQ	BLQ	-	-	BLQ	-	-
	L-6	-	BLQ	BLQ	-	-	-	-	-
	L-7	-	BLQ	-	-	-	-	-	-
Mean		NC	NC	NC	NC	NC	NC	NC	NC
SD		NC	NC	NC	NC	NC	NC	NC	NC

BLQ: Below the lower limit of quantification (0.0400 ng/mL)

NC: Not calculated

表16-1 妊娠雌ウサギを用いたサリドマイド臍内投与による母動物血漿中サリドマイド濃度
: 胚・胎児への移行に関する実験

投与初日; 妊娠1日

(1) Thalidomide

Dose level (mg/kg)	Animal No.	Concentration (ng/mL)		
		4 h	7 h	24 h
0.4	1101	9.55	1.06	BLQ
	1102 ^{a)}	8.46	0.957	BLQ
	1103	30.1	5.03	BLQ
	1104	7.36	0.690	BLQ
	1105 ^{a)}	15.9	2.05	BLQ
	1106	23.6	13.8	1.69
	1107	3.42	1.64	BLQ
	1108	12.6	2.35	BLQ
	Mean	13.9	3.45	NC
	SD	8.97	4.40	NC
10	2101	603 ¹⁾	307	22.1
	2102	277	261	97.8
	2103	236	182	106
	2104	210	155	58.7
	2105	191	140	99.1
	2106 ^{a)}	157	124	110
	2107	283	246	127
	2108	235	123	1.90
	Mean	274	192	77.8
	SD	139	70.2	45.3

BLQ: Below the lower limit of quantification (0.400 ng/mL), a) not pregnant

1) Reanalysis value

(2) TK パラメータ (thalidomide)

Dose level (mg/kg)	Animal No.	Cmax (ng/mL)	Tmax (h)	AUC _{0-t} (h*ng/mL)
0.4	1101	9.55	4.00	44.0
	1102 ^{a)}	8.46	4.00	39.2
	1103	30.1	4.00	156
	1104	7.36	4.00	32.7
	1105 ^{a)}	15.9	4.00	76.2
	1106	23.6	4.00	235
	1107	3.42	4.00	28.4
	1108	12.6	4.00	67.6
	Mean	13.9	4.00	84.9
	SD	8.97	0.00	73.3
10	2101	603	4.00	5370
	2102	277	4.00	4410
	2103	236	4.00	3550
	2104	210	4.00	2780
	2105	191	4.00	2910
	2106 ^{a)}	157	4.00	2720
	2107	283	4.00	4530
	2108	235	4.00	2070
	Mean	274	4.00	3540
	SD	139	0.00	1130

a) not pregnant

表16-2 妊娠雌ウサギを用いたサリドマイド臍内投与による母動物血漿中サリドマイド濃度
: 胚・胎児への移行に関する実験

投与最終日; 妊娠13日

(1) Thalidomide

Dose level (mg/kg)	Animal No.	Concentration (ng/mL)			
		Pre	4 h	7 h	24 h
0.4	1101	0.919	1.73	0.967	-
	1102 ^{a)}	1.14	11.4	2.38	-
	1103	0.934	18.4	8.68	-
	1104	0.688	26.0	5.62	-
	1105 ^{a)}	0.593	11.7	1.70	0.694
	1106	1.06	3.52	2.16	1.02
	1107	0.782	1.24	0.875	0.873
	1108	0.560	1.30	0.752	0.481
	Mean	0.835	9.41	2.89	0.767
	SD	0.214	9.19	2.82	0.233
10	2101	4.13	466 ¹⁾	339	-
	2102	6.55	96.4	31.3	-
	2103	1.81	87.8	62.9	-
	2104	17.5	329	507 ¹⁾	-
	2105	4.64	358	251	74.4
	2106 ^{a)}	5.04	349	270	170
	2107	11.3	107	37.4	13.0
	2108	2.25	196	244	4.38
	Mean	6.65	249	218	65.4
	SD	5.28	145	167	76.4

1) Reanalysis value, a) not pregnant

(2) TKパラメータ (thalidomide)

Dose level (mg/kg)	Animal No.	Cmax (ng/mL)	Tmax (h)	AUC _{0-t} (h*ng/mL)
0.4	1101	1.73	4.00	9.34
	1102 ^{a)}	11.4	4.00	45.8
	1103	18.4	4.00	79.3
	1104	26.0	4.00	101
	1105 ^{a)}	11.7	4.00	65.0
	1106	3.52	4.00	44.7
	1107	1.24	4.00	22.1
	1108	1.30	4.00	17.3
	Mean	9.41	4.00	48.1
	SD	9.19	0.00	32.1
10	2101	466	4.00	2150
	2102	96.4	4.00	397
	2103	87.8	4.00	405
	2104	507	7.00	1950
	2105	358	4.00	4400
	2106 ^{a)}	349	4.00	5380
	2107	107	4.00	882
	2108	244	7.00	3170
	Mean	277	4.75	2340
	SD	169	1.39	1850

a) not pregnant

表17-1 妊娠雌ウサギを用いたサリドマイド膈内投与による母動物血漿中5-hydroxythalidomide濃度
: 胚・胎児への移行に関する実験

投与初日; 妊娠1日

(1) 5-hydroxythalidomide

Dose level (mg/kg)	Animal No.	Concentration (ng/mL)		
		4 h	7 h	24 h
0.4	1101	0.152	BLQ	BLQ
	1102 ^{a)}	0.100	BLQ	BLQ
	1103	0.175	BLQ	BLQ
	1104	0.122	BLQ	BLQ
	1105 ^{a)}	0.135	BLQ	BLQ
	1106	0.156	0.0873	BLQ
	1107	0.038	BLQ	BLQ
	1108	0.147	BLQ	BLQ
	Mean	0.128	NC	NC
	SD	0.0429	NC	NC
10	2101	4.39	2.08	0.151
	2102	2.24	1.76	0.912
	2103	2.24	1.11	0.964
	2104	2.10	1.24	0.493
	2105	1.85	1.04	0.638
	2106 ^{a)}	1.20	0.755	0.756
	2107	2.26	1.39	0.798
	2108	1.63	0.813	BLQ
	Mean	2.24	1.27	0.589
	SD	0.945	0.457	0.352

BLQ: Below the lower limit of quantification (0.0400 ng/mL), a) not pregnant

(2) TKパラメータ (5-hydroxythalidomide)

Dose level (mg/kg)	Animal No.	Cmax (ng/mL)	Tmax (h)	AUC _{0-t} (h*ng/mL)
0.4	1101	0.152	4.00	0.532
	1102 ^{a)}	0.100	4.00	0.350
	1103	0.175	4.00	0.613
	1104	0.122	4.00	0.427
	1105 ^{a)}	0.135	4.00	0.473
	1106	0.156	4.00	1.42
	1107	NC	NC	NC
	1108	0.147	4.00	0.515
	Mean	0.141	4.00	0.619
	SD	0.0245	0.00	0.363
10	2101	4.39	4.00	37.4
	2102	2.24	4.00	33.2
	2103	2.24	4.00	27.1
	2104	2.10	4.00	23.9
	2105	1.85	4.00	22.3
	2106 ^{a)}	1.20	4.00	18.2
	2107	2.26	4.00	28.6
	2108	1.63	4.00	13.8
	Mean	2.24	4.00	25.6
	SD	0.945	0.00	7.71

NC: Not calculated, a) not pregnant

表17-2 妊娠雌ウサギを用いたサリドマイド膈内投与による母動物血漿中5-hydroxythalidomide濃度
: 胚・胎児への移行に関する実験

投与最終日; 妊娠13日

(1) 5-hydroxythalidomide

Dose level (mg/kg)	Animal No.	Concentration (ng/mL)			
		Pre	4 h	7 h	24 h
0.4	1101	BLQ	BLQ	BLQ	-
	1102 ^{a)}	BLQ	0.164	BLQ	-
	1103	BLQ	0.154	0.0647	-
	1104	BLQ	0.403	0.0697	-
	1105 ^{a)}	BLQ	0.0815	BLQ	BLQ
	1106	BLQ	BLQ	BLQ	BLQ
	1107	BLQ	0.226	BLQ	BLQ
	1108	BLQ	BLQ	BLQ	BLQ
	Mean	NC	0.129	0.0168	NC
SD	NC	0.141	0.0311	NC	
10	2101	0.0553	3.90	3.35	-
	2102	0.107	1.30	0.532	-
	2103	0.0434	1.96	1.19	-
	2104	0.148	2.08	3.20	-
	2105	0.0791	3.26	1.87	0.664
	2106 ^{a)}	0.0726	3.20	1.74	1.44
	2107	0.0961	0.829	0.287	0.0709
	2108	0.0429	2.13	1.77	0.0630
	Mean	0.0806	2.33	1.74	0.559
SD	0.0358	1.04	1.11	0.651	

BLQ: Below the lower limit of quantification (0.0400 ng/mL), a) not pregnant

(2) TKパラメータ (5-hydroxythalidomide)

Dose level (mg/kg)	Animal No.	Cmax (ng/mL)	Tmax (h)	AUC _{0-t} (h*ng/mL)
0.4	1101	NC	NC	NC
	1102 ^{a)}	0.164	4.00	0.574
	1103	0.154	4.00	0.636
	1104	0.403	4.00	1.52
	1105 ^{a)}	0.0815	4.00	0.285
	1106	NC	NC	NC
	1107	0.226	4.00	0.791
	1108	NC	NC	NC
	Mean	0.206	4.00	0.761
SD	0.122	0.00	0.462	
10	2101	3.90	4.00	18.8
	2102	1.30	4.00	5.56
	2103	1.96	4.00	8.73
	2104	3.20	7.00	12.4
	2105	3.26	4.00	35.9
	2106 ^{a)}	3.20	4.00	41.0
	2107	0.829	4.00	6.57
	2108	2.13	4.00	25.8
	Mean	2.47	4.38	19.3
SD	1.08	1.06	13.6	

NC: Not calculated, a) not pregnant

表18-1 妊娠雌ウサギを用いたサリドマイド臍内投与による母動物血漿中5'-hydroxythalidomide濃度
: 胚・胎児への移行に関する実験

投与初日; 妊娠1日

(1) 5'-hydroxythalidomide

Dose level (mg/kg)	Animal No.	Concentration (ng/mL)		
		4 h	7 h	24 h
0.4	1101	1.09	0.146	BLQ
	1102 ^{a)}	0.616	0.129	BLQ
	1103	1.95	0.583	BLQ
	1104	1.47	0.196	BLQ
	1105 ^{a)}	1.30	0.240	BLQ
	1106	1.15	0.527	0.0587
	1107	0.396	0.172	BLQ
	1108	0.758	0.190	BLQ
	Mean	1.09	0.273	NC
SD	0.500	0.178	NC	
10	2101	13.4	8.24	0.776
	2102	8.69	8.17	3.45
	2103	12.1	7.47	4.12
	2104	7.67	5.12	1.84
	2105	13.4	8.49	5.01
	2106 ^{a)}	6.57	4.92	3.68
	2107	8.20	5.50	2.42
	2108	10.0	5.16	0.124
	Mean	10.0	6.63	2.68
SD	2.66	1.59	1.69	

BLQ: Below the lower limit of quantification (0.0400 ng/mL), a) not pregnant

(2) TKパラメータ (5'-hydroxythalidomide)

Dose level (mg/kg)	Animal No.	Cmax (ng/mL)	Tmax (h)	AUC _{0-t} (h*ng/mL)
0.4	1101	1.09	4.00	5.28
	1102 ^{a)}	0.616	4.00	3.45
	1103	1.95	4.00	12.7
	1104	1.47	4.00	7.11
	1105 ^{a)}	1.30	4.00	6.95
	1106	1.15	4.00	9.79
	1107	0.396	4.00	3.11
	1108	0.758	4.00	4.55
	Mean	1.09	4.00	6.62
SD	0.500	0.00	3.29	
10	2101	13.4	4.00	136
	2102	8.69	4.00	141
	2103	12.1	4.00	152
	2104	7.67	4.00	93.7
	2105	13.4	4.00	174
	2106 ^{a)}	6.57	4.00	103
	2107	8.20	4.00	104
	2108	10.0	4.00	87.7
	Mean	10.0	4.00	124
SD	2.66	0.00	31.2	

a) not pregnant

表18-2 妊娠雌ウサギを用いたサリドマイド膈内投与による母動物血漿中5'-hydroxythalidomide濃度
: 胚・胎児への移行に関する実験

投与最終日; 妊娠13日

(1) 5'-hydroxythalidomide

Dose level (mg/kg)	Animal No.	Concentration (ng/mL)			
		Pre	4 h	7 h	24 h
0.4	1101	BLQ	0.133	BLQ	-
	1102 ^{a)}	0.0522	0.846	0.168	-
	1103	BLQ	1.06	0.472	-
	1104	BLQ	2.08	0.607	-
	1105 ^{a)}	BLQ	0.846	0.130	BLQ
	1106	BLQ	0.210	0.107	BLQ
	1107	BLQ	0.0978	BLQ	BLQ
	1108	BLQ	0.0694	BLQ	BLQ
	Mean	NC	0.668	0.186	NC
	SD	NC	0.696	0.231	NC
10	2101	0.0787	7.42	6.89	-
	2102	0.255	4.83	1.95	-
	2103	0.0774	5.44	4.58	-
	2104	0.381	5.86	7.57	-
	2105	0.328	17.3	11.8	3.55
	2106 ^{a)}	0.294	10.2	6.80	4.22
	2107	0.301	2.74	1.22	0.410
	2108	0.125	7.30	6.17	0.125
	Mean	0.230	7.64	5.87	2.08
	SD	0.119	4.47	3.35	2.11

BLQ: Below the lower limit of quantification (0.0400 ng/mL), a) not pregnant

(2) TKパラメータ (5'-hydroxythalidomide)

Dose level (mg/kg)	Animal No.	C _{max} (ng/mL)	T _{max} (h)	AUC _{0-t} (h*ng/mL)
0.4	1101	0.133	4.00	0.466
	1102 ^{a)}	0.846	4.00	3.32
	1103	1.06	4.00	4.42
	1104	2.08	4.00	8.19
	1105 ^{a)}	0.846	4.00	4.26
	1106	0.210	4.00	1.81
	1107	0.0978	4.00	0.342
	1108	0.0694	4.00	0.243
	Mean	0.668	4.00	2.88
	SD	0.696	0.00	2.75
10	2101	7.42	4.00	36.5
	2102	4.83	4.00	20.3
	2103	5.44	4.00	26.1
	2104	7.57	7.00	32.6
	2105	17.3	4.00	209
	2106 ^{a)}	10.2	4.00	140
	2107	2.74	4.00	25.9
	2108	7.30	4.00	88.6
	Mean	7.85	4.38	72.4
	SD	4.41	1.06	69.1

a) not pregnant

表19-1 妊娠雌ウサギを用いたサリドマイド臍内投与による胎盤、卵黄囊膜、胚中のサリドマイド濃度(妊娠13日)
: 胎・胎児への移行に関する実験

0.4 mg/kg投与群

Dose level (mg/kg)	Sampling time (h)	Animal No.	Fetus No.	Concentration (ng/g)			
				Placenta	Yolk sac membrane	Embryo	
0.4	7 h	1101	L-1	BLQ	BLQ	BLQ	
		1101	L-6	BLQ	BLQ	BLQ	
		Mean			NC	NC	NC
		1103	L-1	4.46	3.82	5.53	
		1103	L-2	4.19	2.52	5.64	
		Mean			4.33	3.17	5.59
		1104	R-1	1.87	2.21	0.757	
		1104	R-6	1.74	1.83	0.911	
		Mean			1.81	2.02	0.834
	Mean			2.04	1.73	2.14	
	SD			2.17	1.60	3.01	
	24 h	1106	R-1	0.837	1.66	BLQ	
		1106	R-2	1.17	BLQ	BLQ	
		Mean			1.00	NC	NC
		1107	L-1	BLQ	0.977	BLQ	
		1107	L-3	BLQ	BLQ	BLQ	
		Mean			NC	NC	NC
		1108	R-1	BLQ	BLQ	BLQ	
		1108	R-5	BLQ	BLQ	BLQ	
		Mean			NC	NC	NC
Mean			0.335	0.440	NC		
SD			0.579	0.417	NC		

BLQ: Below the lower limit of quantification (0.800 ng/g)

表19-2 妊娠雌ウサギを用いたサリドマイド臍内投与による胎盤、卵黄囊膜、胚中のサリドマイド濃度(妊娠13日)
: 胚・胎児への移行に関する実験

10 mg/kg投与群

Dose level (mg/kg)	Sampling time (h)	Animal No.	Fetus No.	Concentration (ng/g)			
				Placenta	Yolk sac membrane	Embryo	
10	7 h	2101	R-1	260	91.2	159	
		2101	R-2	221	267	186	
		Mean			241	179	173
		2102	L-1	27.8	24.7	22.1	
		Mean			NC	NC	NC
		2103	R-1	15.2	11.9	8.01	
		2103	R-2	15.2	15.4	10.9	
		2103	R-3	17.0	16.6	10.5	
		2103	R-4	13.2	15.1	10.1	
		2103	L-1	16.0	16.5	13.5	
		2103	L-2	12.3	11.9	8.32	
		2103	L-3	16.1	10.8	11.0	
	2103	L-4	17.8	15.6	11.6		
	2103	L-5	17.2	17.6	13.3		
	2103	L-6	14.4	16.5	12.3		
	Mean			15.4	14.8	11.0	
	SD			1.76	2.38	1.85	
	Mean			156	120	115	
	SD			160	121	118	
	2104			367	230	238	
2104			303	365	255		
2104			315	276	265		
2104			299	222	260		
2104			352	288	251		
2104			313	259	245		
2104			428	201	265		
Mean			340	263	254		
SD			46.6	54.5	10.2		
2105			50.1	43.0	38.2		
2105			49.1	36.5	33.1		
Mean			49.6	39.8	35.7		
2107			3.02	3.03	2.58		
2107			5.13	3.44	2.22		
Mean			4.08	3.24	2.40		
2108			5.01	4.13	2.93		
2108			6.73	3.43	3.67		
Mean			5.87	3.78	3.30		
Mean			19.8	15.6	13.8		
SD			25.8	20.9	18.9		

表20-1 妊娠雌ウサギを用いたサリドマイド膈内投与による胎盤、卵黄囊膜、胚中の5-hydroxythalidomide 濃度(妊娠13日)
:胚・胎児への移行に関する実験

0.4 mg/kg投与群

Dose level (mg/kg)	Sampling time (h)	Animal No.	Fetus No.	Concentration (ng/g)			
				Placenta	Yolk sac membrane	Embryo	
0.4	7 h	1101	L-1	BLQ	BLQ	BLQ	
		1101	L-6	BLQ	BLQ	BLQ	
		Mean		NC	NC	NC	
		1103	L-1	BLQ	BLQ	BLQ	
		1103	L-2	BLQ	BLQ	BLQ	
		Mean		NC	NC	NC	
		1104	R-1	BLQ	BLQ	BLQ	
		1104	R-6	BLQ	BLQ	BLQ	
		Mean		NC	NC	NC	
	Mean				NC	NC	NC
	SD				NC	NC	NC
	24 h	1106	R-1	BLQ	BLQ	BLQ	
		1106	R-2	BLQ	BLQ	BLQ	
		Mean		NC	NC	NC	
		1107	L-1	BLQ	BLQ	BLQ	
		1107	L-3	BLQ	BLQ	BLQ	
		Mean		NC	NC	NC	
		1108	R-1	BLQ	BLQ	BLQ	
1108		R-5	BLQ	BLQ	BLQ		
Mean			NC	NC	NC		
Mean				NC	NC	NC	
SD				NC	NC	NC	

BLQ: Below the lower limit of quantification (0.0800 ng/g)

表20-2 妊娠雌ウサギを用いたサリドマイド膈内投与による胎盤、卵黄囊膜、胚中の5-hydroxythalidomide 濃度(妊娠13日)
:胚・胎児への移行に関する実験

10 mg/kg投与群

Dose level (mg/kg)	Sampling time (h)	Animal No.	Fetus No.	Concentration (ng/g)			
				Placenta	Yolk sac membrane	Embryo	
10	7 h	2101	R-1	1.94	0.659	0.421	
		2101	R-2	1.73	1.76	0.392	
		Mean		1.84	1.21	0.407	
		2102	L-1	0.130	0.128	BLQ	
		Mean		NC	NC	NC	
		2103	R-1	0.455	0.263	BLQ	
		2103	R-2	0.471	0.889	BLQ	
		2103	R-3	0.567	0.785	BLQ	
		2103	R-4	0.285	0.340	BLQ	
		2103	L-1	0.247	0.975	BLQ	
		2103	L-2	0.193	0.456	BLQ	
		2103	L-3	0.337	0.333	BLQ	
		2103	L-4	0.276	0.202	BLQ	
		2103	L-5	0.646	2.29	BLQ	
	2103	L-6	0.186	1.01	BLQ		
	Mean		0.366	0.754	NC		
	SD		0.160	0.621	NC		
		24 h	2104	R-1	3.30	1.33	0.524
			2104	R-2	2.91	2.03	0.297
			2104	R-3	2.73	1.58	0.460
			2104	R-4	2.68	1.23	0.418
			2104	R-5	3.22	1.25	0.394
			2104	L-1	2.80	1.02	0.273
			2104	L-2	2.47	0.552	0.263
			Mean		2.87	1.28	0.376
			SD		0.297	0.458	0.101
			Mean		1.30	0.844	0.196
			SD		1.29	0.532	0.226
			2105	L-1	0.568	0.260	BLQ
			2105	L-3	0.618	0.199	BLQ
			Mean		0.593	0.230	NC
		2107	L-1	BLQ	BLQ	BLQ	
		2107	L-4	BLQ	BLQ	BLQ	
		Mean		NC	NC	NC	
		2108	R-1	BLQ	BLQ	BLQ	
		2108	R-4	BLQ	BLQ	BLQ	
		Mean		NC	NC	NC	
	Mean		0.198	0.0765	NC		
	SD		0.342	0.133	NC		

BLQ: Below the lower limit of quantification (0.0800 ng/g)

表21-1 妊娠雌ウサギを用いたサリドマイド臍内投与による胎盤、卵黄囊膜、胚中の5'-hydroxythalidomide 濃度(妊娠13日)
: 胚・胎児への移行に関する実験

0.4 mg/kg投与群

Dose level (mg/kg)	Sampling time (h)	Animal No.	Fetus No.	Concentration (ng/g)			
				Placenta	Yolk sac membrane	Embryo	
0.4	7 h	1101	L-1	BLQ	BLQ	BLQ	
		1101	L-6	BLQ	BLQ	BLQ	
		Mean		NC	NC	NC	
		1103	L-1	0.294	0.155	0.302	
		1103	L-2	0.315	0.102	0.305	
		Mean		0.305	0.129	0.304	
		1104	R-1	0.234	0.165	0.152	
		1104	R-6	0.239	0.104	0.130	
		Mean		0.237	0.135	0.141	
		Mean			0.180	0.0877	0.148
		SD			0.160	0.0760	0.152
		24 h	1106	R-1	BLQ	BLQ	BLQ
	1106		R-2	BLQ	BLQ	BLQ	
	Mean			NC	NC	NC	
	1107		L-1	BLQ	BLQ	BLQ	
	1107		L-3	BLQ	BLQ	BLQ	
	Mean			NC	NC	NC	
	Mean	1108	R-1	BLQ	BLQ	BLQ	
1108		R-5	BLQ	BLQ	BLQ		
Mean			NC	NC	NC		
SD			NC	NC	NC		

BLQ: Below the lower limit of quantification (0.0800 ng/g)

表21-2 妊娠雌ウサギを用いたサリドマイド臍内投与による胎盤、卵黄囊膜、胚中の5'-hydroxythalidomide 濃度(妊娠13日)
:胚・胎児への移行に関する実験

10 mg/kg投与群

Dose level (mg/kg)	Sampling time (h)	Animal No.	Fetus No.	Concentration (ng/g)			
				Placenta	Yolk sac membrane	Embryo	
10	7 h	2101	R-1	5.69	1.73	2.97	
		2101	R-2	5.40	4.12	3.32	
		Mean			5.55	2.93	3.15
		2102	L-1	1.50	0.964	0.883	
		Mean			NC	NC	NC
		2103	R-1	1.50	1.14	0.647	
		2103	R-2	1.46	1.11	0.898	
		2103	R-3	1.53	1.48	0.916	
		2103	R-4	1.42	1.33	0.893	
		2103	L-1	1.60	1.34	1.17	
		2103	L-2	1.27	1.13	0.690	
		2103	L-3	1.64	0.987	0.922	
		2103	L-4	1.69	1.58	1.11	
		2103	L-5	1.58	1.24	1.06	
	2103	L-6	1.38	1.26	0.958		
	Mean			1.51	1.26	0.926	
	SD			0.128	0.180	0.166	
	2104	R-1	9.15	5.56	5.05		
	2104	R-2	8.51	8.88	5.03		
	2104	R-3	8.26	6.38	5.06		
	2104	R-4	7.47	5.08	5.20		
	2104	R-5	8.53	6.22	4.77		
	2104	L-1	8.59	5.40	4.30		
	2104	L-2	9.89	4.32	5.35		
	Mean			8.63	5.98	4.97	
	SD			0.749	1.46	0.343	
	Mean			4.30	2.78	2.48	
	SD			3.46	2.30	1.97	
2105	L-1	3.53	2.71	2.14			
2105	L-3	3.24	2.02	1.66			
Mean			3.39	2.37	1.90		
24 h	2107	L-1	0.243	0.151	0.136		
	2107	L-4	0.230	0.0903	0.143		
	Mean			0.237	0.121	0.140	
	2108	R-1	0.299	0.159	0.177		
	2108	R-4	0.286	BLQ	0.197		
	Mean			0.293	NC	0.187	
Mean			1.30	0.855	0.742		
SD			1.80	1.31	1.00		

BLQ: Below the lower limit of quantification (0.0800 ng/g)