

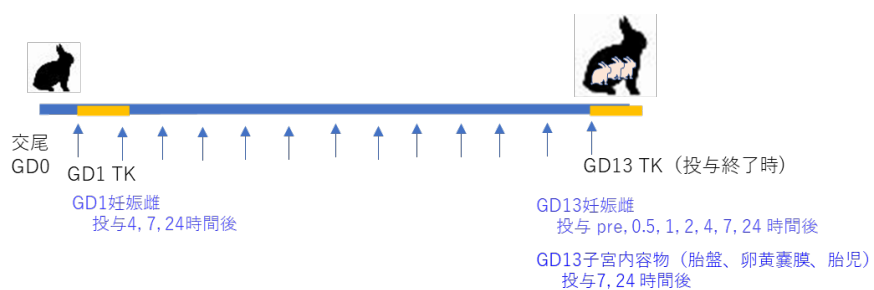
## IV.資料

# 1. 妊娠ウサギを用いたサリドマイド反復経口投与による胚・胎児移行への影響（TK試験、妊娠13-14日帝王切開）

群構成

試験群	投与量 (mg/kg体重/day)	容量/ mL/kg	動物数(妊娠雌)	全胚吸収 胚例	腹数	投与期間
1(TK)	12.5	5	8(6)	0	6	GDs1-13
1(TK)	25	5	10(9)	1	6	GDs1-13
2(TK)	250	5	12(11)	3	4	GDs1-13

動物数は先行試験及び追加試験の合計

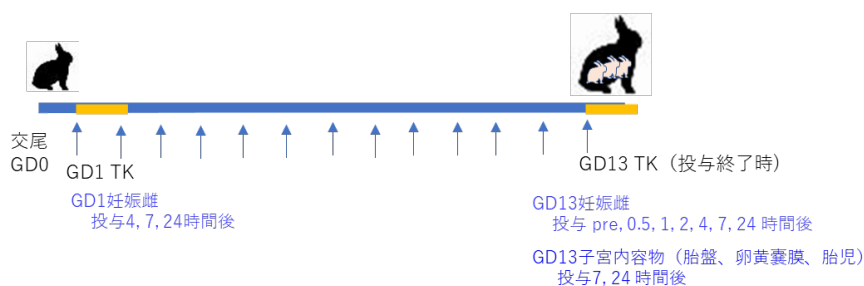


1. 妊娠ウサギを用いたサリドマイド反復経口投与による胚・胎児移行への影響（TK試験、妊娠13-14日帝王切開）

群構成

試験群	投与量 (mg/kg体重/day)	容量/ mL/kg	動物数(妊娠雌)	全胚吸収 胚例	腹数	投与期間
1(TK)	12.5	5	8(6)	0	6	GDs1-13
1(TK)	25	5	10(9)	1	6	GDs1-13
2(TK)	250	5	12(11)	3	4	GDs1-13

動物数は先行試験及び追加試験の合計



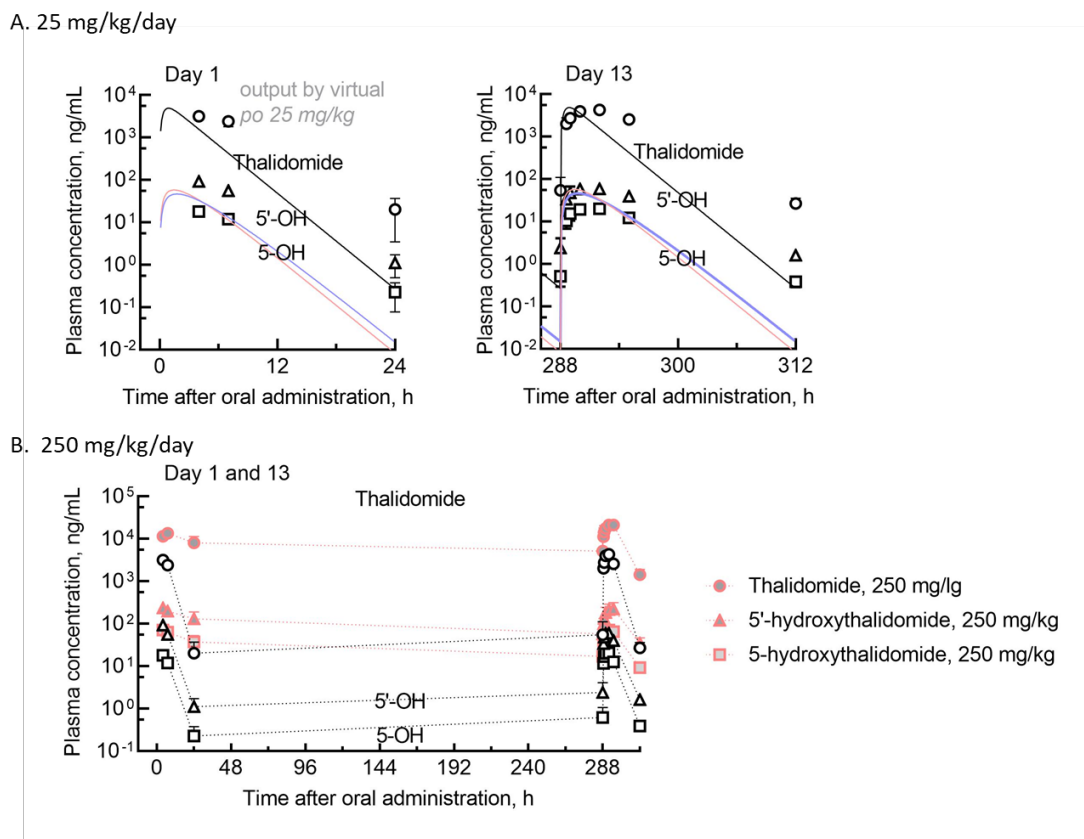


図1-1 生理学的薬物動態モデルによる出力結果と妊娠雌経口投与による実測値の比較(先行実験)

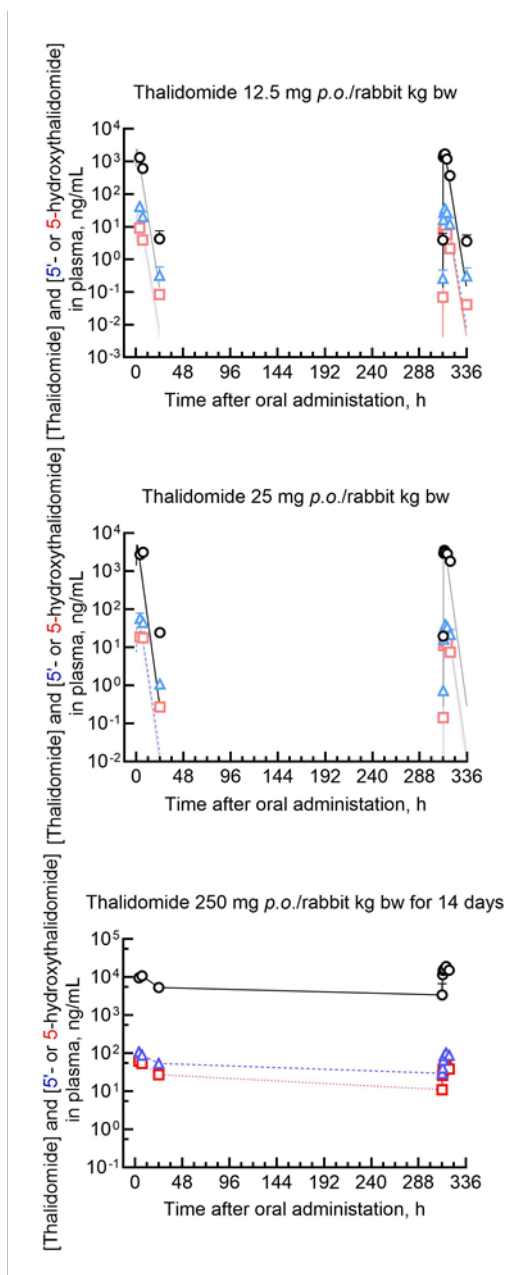


図1-2 生理学的薬物動態モデルによる出力結果と妊娠雌経口投与による実測値の比較 (追加実験)

表1 妊娠雌ウサギを用いたサリドマイド経口投与による母動物一般状態:胚・胎児への移行に関する検討

(1)先行実験

Dose (mg/kg)	Signs	Gestational day														
		1	3	6	8	10	12	13	14							
		Treatment period (GDs1-13)														
25	Number of dams	7	7	7	7	7	7	7	7	7	7	7	7	7	4	
	Abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
250	Number of dams	7	7	7	7	7	7	7	7	7	7	7	7	7	4	
	Number of dams with abnormal findings	0	0	4	4	2	1	0	1	1	0	0	0	1	1	0
	Decrease feces	0	0	3	4	2	1	0	1	1	0	0	0	1	1	0
	No feces	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0

(2)追加実験

Dose (mg/kg)	Signs	Gestational day														
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
		Treatment period (GDs1-13)														
12.5	Number of dams	6	6	6	6	6	6	6	6	6	6	6	6	6	6	3
	Abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
25	Number of dams	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0
	Abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
50	Number of dams	4	4	4	4	4	4	4	4	4	4	4	4	4	4	0
	Number of dams with abnormal findings	0	0	0	1	1	1	0	0	0	0	0	1	1	1	0
	Decrease feces	0	0	0	1	1	1	0	0	0	0	0	1	1	1	0

表2 妊娠雌ウサギを用いたサリドマイド経口投与による母動物体重推移:胚・胎児への移行に関する検討

(1)先行実験

Dose (mg/kg)		Gestational day									Body weight gain GDs1-13
		0	1	3	6	8	10	12	13	14	
		Treatment period (GDs1-13)									
25	No.dams	7	7	7	7	7	7	7	7	4	7
	Mean	3.10	3.19	3.17	3.20	3.26	3.30	3.34	3.36	3.50	0.17
	S.D.	0.28	0.31	0.29	0.30	0.30	0.29	0.30	0.31	0.34	0.05
250	No.dams	7	7	7	7	7	7	7	7	4	7
	Mean	3.01	3.06	3.01	3.06	3.12	3.15	3.17	3.17	3.19	0.11
	S.D.	0.12	0.14	0.12	0.12	0.14	0.16	0.18	0.20	0.08	0.18

(2)追加実験

Dose (mg/kg)		Gestational day								
		0	1	3	6	8	10	12	13	14
		Treatment period (GDs1-13)								
12.5	No.dams	6	6	6	6	6	6	6	6	3
	Mean	3.11	3.15	3.16	3.24	3.28	3.30	3.32	3.33	3.20
	S.D.	0.22	0.24	0.21	0.23	0.23	0.25	0.24	0.24	0.13
25	No.dams	2	2	2	2	2	2	2	2	0
	Mean	3.40	3.42	3.43	3.48	3.55	3.57	3.57	3.59	
	S.D.	0.11	0.15	0.11	0.08	0.08	0.08	0.11	0.15	
250	No.dams	4	4	4	4	4	4	4	4	0
	Mean	3.21	3.28	3.22	3.21	3.26	3.28	3.24	3.29	
	S.D.	0.17	0.20	0.14	0.19	0.19	0.21	0.21	0.24	

表3 妊娠雌ウサギを用いたサリドマイド経口投与による帝王切開所見(妊娠13-14日):胚・胎児への移行に関する検討

(1)先行実験

Test article		Number of corpora lutea	Number of implantations	Preimplantation loss (%) a	Implantation index (%) b	Number of resorptions Total	Postimplantation loss(%) Total c	Number of live fetuses Total
thalidomide	No.dams	7	7	7	7	7	7	7
25 mg/kg	Mean	7.9	7.6	3.3	96.7	1.6	27.7	6.0
	S.D.	3.4	3.3	5.9	5.9	2.6	40.0	3.1
thalidomide	No.dams	7	7	7	7	7	7	7
250 mg/kg	Mean	7.6	7.0	7.2	92.8	4.4	63.1	2.6
	S.D.	1.7	1.5	7.0	7.0	2.8	36.1	2.6

(2)追加実験

Test article		Number of corpora lutea	Number of implantations	Preimplantation loss (%) a	Implantation index (%) b	Number of resorptions Total	Postimplantation loss(%) Total d	Number of live fetuses Total
thalidomide	No.dams	6	6	6	6	6	6	6
12.5 mg/kg	Mean	8.3	7.2	10.7	89.4	0.5	7.9	6.7
	S.D.	2.1	0.8	17.6	17.6	0.8	13.7	1.5
thalidomide	n	2	2	2	2	2	2	2
25 mg/kg	Mean	11.0	10.0	9.4	90.6	1.0	12.5	9.0
	S.D.	2.8	2.8	2.4	2.4	1.4	17.7	4.2
thalidomide	No.dams	4	4	4	4	4	4	4
250 mg/kg	Mean	8.3	8.0	2.8	97.2	5.3	71.1	2.8
	S.D.	4.3	4.3	5.6	5.6	4.0	31.7	3.1

a): [(Number of corpora lutea - Number of implantations) / Number of corpora lutea] x 100

b): (Number of implantations / Number of corpora lutea) x 100

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



表4-1 妊娠雌ウサギを用いたサリドマイド経口投与による帝王切開所見個別表(妊娠13-14日): 胚・胎児への移行に関する検討  
 先行実験

(1) 25 mg/kg 群

Dam No.	Number of corpora lutea	Number of implantation	Preimplantation loss (%) a	Implantation index (%) b	Number of resorptions Total	Postimplantation loss(%) Total c)	Number of live fetuses Total
1101	Non-Pregnancy						
1102	1(0/1)	1(0/1)	0.0	100.0	1	100.0	0
1103	8(1/7)	8(1/7)	0.0	100.0	0	0.0	8
1104	8(3/5)	8(3/5)	0.0	100.0	0	0.0	8
1105	11(4/7)	10(3/7)	9.1	90.9	3	30.0	7
1106	11(9/2)	11(9/2)	0.0	100.0	7	63.6	4
1107	7(4/3)	6(4/2)	14.3	85.7	0	0.0	6
1108	9(4/5)	9(4/5)	0.0	100.0	0	0.0	9
Total	55	53			11		42
n	7	7	7	7	7	7	7
Mean	7.9	7.6	3.3	96.7	1.6	27.7	6.0
S.D.	3.4	3.3	5.9	5.9	2.6	40.0	3.1

(2) 250 mg/kg 群

Dam No.	Number of corpora lutea	Number of implantation	Preimplantation loss (%) a	Implantation index (%) b	Number of resorptions Total	Postimplantation loss(%) Total c)	Number of live fetuses Total
2101	Non-Pregnancy						
2102	5(4/1)	5(4/1)	0.0	100.0	5	100.0	0
2103	7(4/3)	7(4/3)	0.0	100.0	7	100.0	0
2104	9(4/5)	8(3/5)	11.1	88.9	4	50.0	4
2105	10(6/4)	9(6/3)	10.0	90.0	9	100.0	0
2106	8(8/0)	8(8/0)	0.0	100.0	3	37.5	5
2107	6(5/1)	5(4/1)	16.7	83.3	2	40.0	3
2108	8(2/6)	7(2/5)	12.5	87.5	1	14.3	6
Total	53	49			31		18
n	7	7	7	7	7	7	7
Mean	7.6	7.0	7.2	92.8	4.4	63.1	2.6
S.D.	1.7	1.5	7.0	7.0	2.8	36.1	2.6

( / ) : Right/Left

n: Number of dams

a): [(Number of corpora lutea - Number of implantations) / Number of corpora lutea] x 100

b): (Number of implantations / Number of corpora lutea) x 100

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

表4-2 妊娠雌ウサギを用いたサリドマイド経口投与による帝王切開所見個別表(妊娠13-14日): 胚・胎児への移行に関する検討  
追加実験

(1) 12.5 mg/kg

Dam No.	Number of corpora lutea	Number of implantation	Preimplantation loss (%) a)	Implantation index (%) b)	Number of resorptions Total	Postimplantation loss(%) Total c)	Number of live fetuses Total
2101	6(1/5)	6(1/5)	0.0	100.0	2	33.3	4
2102	Non-Pregnancy						
2103	12(7/5)	7(5/2)	41.7	58.3	0	0.0	7
2104	8(2/6)	8(2/6)	0.0	100.0	0	0.0	8
2105	Non-Pregnancy						
2106	9(5/4)	7(4/3)	22.2	77.8	1	14.3	6
2107	8(4/4)	8(4/4)	0.0	100.0	0	0.0	8
2108	7(2/5)	7(2/5)	0.0	100.0	0	0.0	7
Total	50	43			3		40
n	6	6	6	6	6	6	6
Mean	8.3	7.2	10.7	89.4	0.5	7.9	6.7
S.D.	2.1	0.8	17.6	17.6	0.8	13.7	1.5

(2) 25 mg/kg

Dam No.	Number of corpora lutea	Number of implantation	Preimplantation loss (%) a)	Implantation index (%) b)	Number of resorptions Total	Postimplantation loss(%) Total c)	Number of live fetuses Total
3101	9(6/3)	8(5/3)	11.1	88.9	2	25.0	6
3102	13(5/8)	12(5/7)	7.7	92.3	0	0.0	12
Total	22	20			2		18
n	2	2	2	2	2	2	2
Mean	11.0	10.0	9.4	90.6	1.0	12.5	9.0
S.D.	2.8	2.8	2.4	2.4	1.4	17.7	4.2

(3) 250 mg/kg

Dam No.	Number of corpora lutea	Number of implantation	Preimplantation loss (%) a)	Implantation index (%) b)	Number of resorptions Total	Postimplantation loss(%) Total c)	Number of live fetuses Total
4101	12(6/6)	12(6/6)	0.0	100.0	11	91.7	1
4102	9(5/4)	8(5/3)	11.1	88.9	5	62.5	3
4103	2(2/0)	2(2/0)	0.0	100.0	2	100.0	0
4104	10(4/6)	10(4/6)	0.0	100.0	3	30.0	7
Total	33	32			21		11
n	4	4	4	4	4	4	4
Mean	8.3	8.0	2.8	97.2	5.3	71.1	2.8
S.D.	4.3	4.3	5.6	5.6	4.0	31.7	3.1

(/): Right/Left

n: Number of dams

a): [(Number of corpora lutea - Number of implantations) / Number of corpora lutea] x 100

b): (Number of implantations / Number of corpora lutea) x 100

c): (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経口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1日):胚・胎児への移行に関する検討

(1)先行実験

Thalidomide (GD1)					TKパラメータ (Thalidomide; GD1)				
Dose level (mg/kg)	Animal No.	Concentration (ng/mL)			Dose level (mg/kg)	Animal No.	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	AUC <sub>0-t</sub> (h*ng/mL)
		4 h	7 h	24 h					
25	1102	2730	2000	6.86	25	1102	2730	4.00	29600
	1103	2670	2600	48.8		1103	2670	4.00	35800
	1104	2790	1560	5.64		1104	2790	4.00	25400
	1105	3140	3380	27.1		1105	3380	7.00	45000
	1106	3060	2590	7.83		1106	3060	4.00	36700
	1107	2920	2440	11.2		1107	2920	4.00	34700
	1108	4760	2050	32.4		1108	4760	4.00	37400
	Mean		3150	2370		20.0	Mean		3190
SD		729	580	16.5	SD		734	1.13	6200
250	2102	11000	14100	7140	250	2102	14100	7.00	240000
	2103	13400	17700	5790		2103	17700	7.00	273000
	2104	9870	11700	10300		2104	11700	7.00	239000
	2105	7330	7360	13300		2105	13300	24.0	212000
	2106	11500	16900	3700		2106	16900	7.00	241000
	2107	11900	9530	9730		2107	11900	4.00	220000
	2108	15100	16600	6170		2108	16600	7.00	271000
	Mean		11400	13400		8020	Mean		14600
SD		2480	4000	3260	SD		2470	6.71	23100

(2)追加実験

Thalidomide (GD1)					TKパラメータ (Thalidomide; GD1)						
Dose level (mg/kg)	Animal No.	Concentration (ng/mL)			Dose level (mg/kg)	Animal No.	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	AUC <sub>0-t</sub> (h*ng/mL)		
		4 h	7 h	24 h							
12.5	2101	1440	561	1.26	12.5	2101	1440	4.00	10700		
	2103	1590	947	8.75		2103	1590	4.00	15100		
	2104	1190	356	2.21		2104	1190	4.00	7740		
	2106	1170	725	2.95		2106	1170	4.00	11400		
	2107	1260	428	2.41		2107	1260	4.00	8710		
	2108	1260	686	8.11		2108	1260	4.00	11300		
	Mean		1320	617		4.28	Mean		1320	4.00	10800
	SD		164	216		3.27	SD		164	0.00	2560
25	3101	2200	3170	30.0	25	3101	3170	7.00	39700		
	3102	3250	3120	19.0		3102	3250	4.00	42700		
	Mean		2730	3150		24.5	Mean		3210	5.50	41200
250	4101	6850	7040	7430	250	4101	7430	24.0	158000		
	4102	8030	10900	5480		4102	10900	7.00	184000		
	4103	13600	13400	3990		4103	13600	4.00	216000		
	4104	9880	12000	4530		4104	12000	7.00	193000		
	Mean		9590	10800		5360	Mean		11000	10.5	188000
	SD		2950	2730		1510	SD		2610	9.11	24000

表6-1 妊娠雌ウサギを用いたサリドマイド経口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・胎児への移行に関する検討

先行実験

(1) Thalidomide (GD13)

Dose level (mg/kg)	Animal No.	Concentration (ng/mL)							
		Pre	0.5 h	1 h	2 h	4 h	7 h	24 h	
25	1102	12.2	1320	2260	3740	4840	2050	-	
	1103	60.7	1390	2030	3280	3740	3130	-	
	1104	25.5	2630	3180	4570	4490	2040	-	
	1105	48.4	1070	1940	3680	5140	3170	31.1	
	1106	25.0	2600	3150	2750	2820	3760	22.8	
	1107	38.4	3140	3680	4750	4200	1540	16.4	
	1108	174	1830	2940	5030	4760	2210	36.5	
	Mean	54.9	2000	2740	3970	4280	2560	26.7	
SD	54.9	794	666	836	791	799	8.88		
250	2102	1410	8730	14500	17600	22000	21800	-	
	2103	25300	25700	26700	24200	27500	29300	-	
	2104	2090	8730	12400	15300	20400	13800	-	
	2105	1650	11400	13100	17800	18300	26900	1570	
	2106	994	10500	15100	17900	21700	17200	730	
	2107	2210	7160	9980	12400	16000	21600	1720	
	2108	2220	5800	8530	17400	21200	16900	1680	
	Mean	5120	11100	14300	17500	21000	21100	1430	
SD	8910	6690	5940	3560	3570	5590	468		

(2) TKパラメータ (Thalidomide; GD13)

Dose level (mg/kg)	Animal No.	Cmax (ng/mL)	Tmax (h)	AUC <sub>0-t</sub> (h*ng/mL)
25	1102	4840	4.00	23100
	1103	3740	4.00	21200
	1104	4570	2.00	24800
	1105	5140	4.00	52300
	1106	3760	7.00	52600
	1107	4750	2.00	37500
	1108	5030	2.00	45000
	Mean	4550	3.57	36600
SD	575	1.81	13700	
250	2102	22000	4.00	130000
	2103	29300	7.00	188000
	2104	20400	4.00	109000
	2105	26900	7.00	371000
	2106	21700	4.00	276000
	2107	21600	7.00	301000
	2108	21200	4.00	272000
	Mean	23300	5.29	235000
SD	3390	1.60	95800	

表6-2 妊娠雌ウサギを用いたサリドマイド経口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・胎児への移行に関する検討

追加実験

(1) Thalidomide (GD13)

Dose level (mg/kg)	Animal No.	Concentration (ng/mL)							
		Pre	0.5 h	1 h	2 h	4 h	7 h	24 h	
12.5	2101	1.69	1240	1750	1590	992	197	-	
	2103	4.49	1290	2010	2220	1350	414	-	
	2104	2.00	1340	1580	1780	1410	479	-	
	2106	6.25	1770	1800	1950	1110	306	4.35	
	2107	2.13	941	1250	1260	986	312	1.24	
	2108	7.05	1640	1510	1450	1270	497	5.12	
	Mean	3.94	1370	1650	1710	1190	368	3.57	
	SD	2.34	297	263	348	183	116	2.05	
25	3101	23.5	3290	3820	3210	3220	1930	-	
	3102	15.5	2680	3210	3160	2500	1730	-	
	Mean	19.5	2990	3520	3190	2860	1830	-	
250	4101	977	10400	13100	12900	15400	13900	-	
	4102	1000	12700	14800	16300	21700	14200	-	
	4103	3590	12300	18900	21700	20200	16700	-	
	4104	8010	10800	13500	14900	18500	16400	-	
	Mean	3390	11600	15100	16500	19000	15300	-	
	SD	3310	1120	2650	3770	2700	1450	-	

(2) TKパラメータ (Thalidomide; GD13)

Dose level (mg/kg)	Animal No.	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	AUC <sub>0-t</sub> (h*ng/mL)
12.5	2101	1750	1.00	7090
	2103	2220	2.00	9480
	2104	1780	2.00	8770
	2106	1950	2.00	11000
	2107	1260	2.00	8890
	2108	1640	0.500	12300
	Mean	1770	1.58	9590
	SD	320	0.665	1830
25	3101	3820	1.00	20300
	3102	3210	1.00	17300
	Mean	3520	1.00	18800
250	4101	15400	4.00	94000
	4102	21700	4.00	118000
	4103	21700	2.00	129000
	4104	18500	4.00	111000
	Mean	19300	3.50	113000
	SD	3020	1.00	14700

表7 妊娠雌ウサギを用いたサリドマイド経口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1日):胚・胎児への移行に関する検討

(1)先行実験

(1) 5-Hydroxythalidomide (GD1)

Dose level (mg/kg)	Animal No.	Concentration (ng/mL)		
		4 h	7 h	24 h
25	1102	15.7	12.0	0.145
	1103	14.5	12.5	0.432
	1104	14.6	7.31	0.0598
	1105	17.6	15.2	0.305
	1106	20.8	13.1	0.113
	1107	18.1	12.8	0.131
	1108	24.4	9.60	0.389
	Mean		18.0	11.8
SD		3.61	2.57	0.148
250	2102	72.4	58.7	32.3
	2103	70.9	73.0	29.3
	2104	75.4	75.9	56.3
	2105	53.3	49.1	56.8
	2106	72.9	69.7	17.0
	2107	72.5	47.4	41.6
	2108	73.6	63.8	24.3
	Mean		70.1	62.5
SD		7.55	11.3	15.4

(2) TKパラメータ (5-Hydroxythalidomide; GD1)

Dose level (mg/kg)	Animal No.	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	AUC <sub>0-4</sub> (h*ng/mL)
25	1102	15.7	4.00	176
	1103	14.5	4.00	179
	1104	14.6	4.00	125
	1105	17.6	4.00	216
	1106	20.8	4.00	205
	1107	18.1	4.00	192
	1108	24.4	4.00	185
	Mean		18.0	4.00
SD		3.61	0.00	29.1
250	2102	72.4	4.00	1110
	2103	73.0	7.00	1230
	2104	75.9	7.00	1500
	2105	56.8	24.0	1160
	2106	72.9	4.00	1100
	2107	72.5	4.00	1080
	2108	73.6	4.00	1100
	Mean		71.0	7.71
SD		6.38	7.32	149

(2)追加実験

(1) 5-Hydroxythalidomide (GD1)

Dose level (mg/kg)	Animal No.	Concentration (ng/mL)			
		4 h	7 h	24 h	
12.5	2101	12.2	4.71	BLQ	
	2103	9.25	4.27	0.0623	
	2104	8.41	2.27	BLQ	
	2106	7.72	5.14	BLQ	
	2107	8.89	3.03	BLQ	
	2108	8.78	4.42	0.104	
	Mean		9.21	3.97	0.0277
	SD		1.55	1.09	0.0449
25	3101	14.9	15.7	0.317	
	3102	22.5	19.6	0.224	
	Mean		18.7	17.7	0.271
250	4101	42.6	30.9	26.7	
	4102	70.1	63.9	40.6	
	4103	79.1	69.1	22.9	
	4104	55.7	52.3	19.1	
	Mean		61.9	54.1	27.3
	SD		16.1	17.0	9.38

(2) TKパラメータ (5-Hydroxythalidomide; GD1)

Dose level (mg/kg)	Animal No.	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	AUC <sub>0-4</sub> (h*ng/mL)	
12.5	2101	12.2	4.00	89.8	
	2103	9.25	4.00	75.6	
	2104	8.41	4.00	52.1	
	2106	7.72	4.00	78.4	
	2107	8.89	4.00	61.4	
	2108	8.78	4.00	75.8	
	Mean		9.21	4.00	72.2
	SD		1.55	0.00	13.4
25	3101	15.7	7.00	212	
	3102	22.5	4.00	277	
	Mean		19.1	5.50	245
250	4101	42.6	4.00	685	
	4102	70.1	4.00	1230	
	4103	79.1	4.00	1160	
	4104	55.7	4.00	880	
	Mean		61.9	4.00	989
	SD		16.1	0.00	253

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

表8-1 妊娠雌ウサギを用いたサリドマイド経口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・胎児への移行に関する検討

(1) 先行実験

(1) 5-Hydroxythalidomide (GD13)

Dose level (mg/kg)	Animal No.	Concentration (ng/mL)						
		Pre	0.5 h	1 h	2 h	4 h	7 h	24 h
25	1102	0.268	12.1	17.4	25.9	26.1	11.7	-
	1103	0.620	6.21	9.36	14.2	17.9	14.2	-
	1104	0.259	12.1	17.6	19.6	17.7	10.6	-
	1105	0.646	6.82	10.8	15.3	23.7	15.2	0.475
	1106	0.385	11.8	15.7	16.9	17.4	17.4	0.349
	1107	0.597	23.9	33.1	27.0	21.4	9.20	0.313
	1108	1.53	7.74	12.6	20.3	18.0	9.45	0.415
	Mean	0.615	11.5	16.7	19.9	20.3	12.5	0.388
SD	0.436	6.04	7.92	4.99	3.48	3.13	0.0717	
250	2102	9.40	33.4	53.4	78.5	92.4	98.8	-
	2103	57.6	60.6	56.9	57.0	57.2	65.1	-
	2104	12.7	32.5	45.5	63.4	71.6	48.1	-
	2105	8.81	39.0	50.1	67.2	67.2	68.5	11.1
	2106	7.44	43.1	61.7	73.9	85.0	55.6	6.33
	2107	9.09	24.3	34.9	48.6	55.7	70.4	8.12
	2108	13.2	25.9	34.2	53.8	63.1	40.6	11.1
	Mean	16.9	37.0	48.1	63.2	70.3	63.9	9.16
SD	18.1	12.4	10.6	10.8	13.9	18.9	2.35	

(2) TKパラメータ (5-Hydroxythalidomide; GD13)

Dose level (mg/kg)	Animal No.	Cmax (ng/mL)	Tmax (h)	AUC <sub>0-t</sub> (h*ng/mL)
25	1102	26.1	4.00	141
	1103	17.9	4.00	97.6
	1104	19.6	2.00	109
	1105	23.7	4.00	250
	1106	17.4	4.00	264
	1107	33.1	1.00	226
	1108	20.3	2.00	187
	Mean	22.6	3.00	182
SD	5.58	1.29	67.6	
250	2102	98.8	7.00	556
	2103	65.1	7.00	414
	2104	71.6	4.00	400
	2105	68.5	7.00	1110
	2106	85.0	4.00	1000
	2107	70.4	7.00	1030
	2108	63.1	4.00	781
	Mean	74.6	5.71	756
SD	12.8	1.60	301	

表8-2 妊娠雌ウサギを用いたサリドマイド経口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・胎児への移行に関する検討

(2)追加実験

(1) 5-Hydroxythalidomide (GD13)

Dose level (mg/kg)	Animal No.	Concentration (ng/mL)							
		Pre	0.5 h	1 h	2 h	4 h	7 h	24 h	
12.5	2101	BLQ	7.39	9.38	10.3	6.36	1.61	-	
	2103	BLQ	6.11	8.95	11.8	6.34	2.17	-	
	2104	BLQ	6.34	7.53	9.63	6.84	2.76	-	
	2106	BLQ	6.58	6.48	8.58	4.88	1.99	BLQ	
	2107	BLQ	4.09	5.25	6.02	5.05	1.78	BLQ	
	2108	0.0689	8.20	7.78	8.01	6.16	2.66	0.0410	
	Mean	NC	6.45	7.56	9.06	5.94	2.16	NC	
SD	NC	1.39	1.54	2.00	0.789	0.466	NC		
25	3101	0.128	9.63	12.8	14.2	11.4	6.01	-	
	3102	0.155	12.3	15.7	18.9	13.7	8.87	-	
	Mean	0.142	11.0	14.3	16.6	12.6	7.44	-	
250	4101	3.69	19.5	22.5	28.3	28.3	28.7	-	
	4102	4.76	31.9	42.5	53.3	64.9	49.9	-	
	4103	11.8	24.9	38.5	43.9	44.3	34.8	-	
	4104	24.0	28.8	33.8	40.7	41.7	41.9	-	
	Mean	11.1	26.3	34.3	41.6	44.8	38.8	-	
	SD	9.35	5.35	8.65	10.3	15.1	9.14	-	

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

(2) TKパラメータ (5-Hydroxythalidomide; GD13)

Dose level (mg/kg)	Animal No.	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	AUC <sub>0-t</sub> (h*ng/mL)
12.5	2101	10.3	2.00	44.5
	2103	11.8	2.00	46.6
	2104	9.63	2.00	44.5
	2106	8.58	2.00	53.1
	2107	6.02	2.00	45.4
	2108	8.20	0.500	64.3
	Mean	9.09	1.75	49.7
SD	1.98	0.612	7.83	
25	3101	14.2	2.00	73.3
	3102	18.9	2.00	93.9
	Mean	16.6	2.00	83.6
250	4101	28.7	7.00	184
	4102	64.9	4.00	366
	4103	44.3	4.00	273
	4104	41.9	7.00	274
	Mean	45.0	5.50	274
	SD	15.0	1.73	74.3



表9 妊娠雌ウサギを用いたサリドマイド経口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1日):胚・胎児への移行に関する検討

(1)先行実験

(1) 5'-Hydroxythalidomide (GD1)

Dose level (mg/kg)	Animal No.	Concentration (ng/mL)		
		4 h	7 h	24 h
25	1102	96.5	56.0	0.493
	1103	61.1	43.3	1.76
	1104	82.0	43.0	0.451
	1105	113	73.2	1.59
	1106	91.3	61.7	0.571
	1107	100	62.5	1.05
	1108	96.4	46.2	1.81
	Mean		91.5	55.1
SD		16.3	11.5	0.613
250	2102	365	298	179
	2103	217	197	88.1
	2104	146	131	116
	2105	258	199	238
	2106	249	231	76.7
	2107	163	114	115
	2108	229	210	96.5
	Mean		232	197
SD		71.9	61.6	58.0

(2) TKパラメータ (5'-Hydroxythalidomide; GD1)

Dose level (mg/kg)	Animal No.	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	AUC <sub>0-t</sub> (h*ng/mL)
25	1102	96.5	4.00	902
	1103	61.1	4.00	662
	1104	82.0	4.00	721
	1105	113	4.00	1140
	1106	91.3	4.00	941
	1107	100	4.00	984
	1108	96.4	4.00	815
	Mean		91.5	4.00
SD		16.3	0.00	163
250	2102	365	4.00	5780
	2103	217	4.00	3480
	2104	146	4.00	2810
	2105	258	4.00	4920
	2106	249	4.00	3830
	2107	163	4.00	2690
	2108	229	4.00	3720
	Mean		232	4.00
SD		71.9	0.00	1110

(2)追加実験

(1) 5'-Hydroxythalidomide (GD1)

Dose level (mg/kg)	Animal No.	Concentration (ng/mL)			
		4 h	7 h	24 h	
12.5	2101	66.5	31.5	0.159	
	2103	58.7	29.2	0.749	
	2104	51.0	20.7	0.232	
	2106	51.7	31.2	0.339	
	2107	64.3	26.9	0.431	
	2108	118	59.8	1.37	
	Mean		68.4	33.2	0.547
	SD		25.1	13.6	0.453
25	3101	74.3	68.8	1.59	
	3102	115	80.6	1.89	
	Mean		94.7	74.7	1.74
250	4101	156	122	99.4	
	4102	163	153	98.9	
	4103	204	175	68.8	
	4104	168	157	74.0	
	Mean		173	152	85.3
	SD		21.4	22.0	16.2

(2) TKパラメータ (5'-Hydroxythalidomide; GD1)

Dose level (mg/kg)	Animal No.	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	AUC <sub>0-t</sub> (h*ng/mL)	
12.5	2101	66.5	4.00	549	
	2103	58.7	4.00	504	
	2104	51.0	4.00	387	
	2106	51.7	4.00	496	
	2107	64.3	4.00	498	
	2108	118	4.00	1020	
	Mean		68.4	4.00	576
	SD		25.1	0.00	224
25	3101	74.3	4.00	962	
	3102	115	4.00	1220	
	Mean		94.7	4.00	1090
250	4101	156	4.00	2610	
	4102	163	4.00	2940	
	4103	204	4.00	3050	
	4104	168	4.00	2790	
	Mean		173	4.00	2850
SD		21.4	0.00	191	

表10-1 妊娠雌ウサギを用いたサリドマイド経口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・胎児への移行に関する検討

(1) 先行実験

(1) 5'-Hydroxythalidomide (GD13)

Dose level (mg/kg)	Animal No.	Concentration (ng/mL)							
		Pre	0.5 h	1 h	2 h	4 h	7 h	24 h	
25	1102	1.06	38.7	56.1	75.7	80.4	39.8	-	
	1103	1.95	18.6	26.3	38.3	39.0	35.4	-	
	1104	1.30	40.8	56.7	66.9	58.1	34.9	-	
	1105	2.57	22.8	36.1	56.0	71.9	53.7	1.84	
	1106	1.32	32.7	42.2	47.4	43.4	43.4	1.12	
	1107	2.78	57.8	82.9	74.3	65.9	36.6	1.34	
	1108	5.80	24.0	34.1	53.2	54.0	31.9	2.16	
	Mean	2.40	33.6	47.8	58.8	59.0	39.4	1.62	
	SD	1.64	13.5	19.1	14.0	15.0	7.31	0.472	
250	2102	58.7	115	179	271	326	341	-	
	2103	157	142	143	146	147	177	-	
	2104	36.1	75.5	102	137	176	137	-	
	2105	46.9	124	167	247	278	353	51.0	
	2106	32.8	113	149	206	245	215	27.5	
	2107	31.1	60.7	88.5	113	131	161	26.6	
	2108	38.7	61.4	84.4	144	193	165	32.5	
	Mean	57.3	98.8	130	181	214	221	34.4	
	SD	45.0	32.6	38.5	60.9	71.7	89.1	11.4	

(2) TKパラメータ (5'-Hydroxythalidomide; GD13)

Dose level (mg/kg)	Animal No.	Cmax (ng/mL)	Tmax (h)	AUC <sub>0-t</sub> (h*ng/mL)
25	1102	80.4	4.00	436
	1103	39.0	4.00	238
	1104	66.9	2.00	361
	1105	71.9	4.00	856
	1106	47.4	2.00	671
	1107	82.9	1.00	745
	1108	54.0	4.00	591
	Mean	63.2	3.00	557
	SD	16.8	1.29	221
250	2102	341	7.00	1940
	2103	177	7.00	1070
	2104	176	4.00	974
	2105	353	7.00	5230
	2106	245	4.00	3480
	2107	161	7.00	2440
	2108	193	4.00	2730
	Mean	235	5.71	2550
	SD	81.0	1.60	1480

表10-2 妊娠雌ウサギを用いたサリドマイド経口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・胎児への移行に関する検討

(2)追加実験

(1) 5'-Hydroxythalidomide (GD13)

Dose level (mg/kg)	Animal No.	Concentration (ng/mL)						
		Pre	0.5 h	1 h	2 h	4 h	7 h	24 h
12.5	2101	0.207	57.3	63.8	69.0	42.8	12.5	-
	2103	0.410	38.6	53.0	59.1	40.0	16.3	-
	2104	0.173	41.3	49.1	52.0	39.0	18.9	-
	2106	0.540	41.9	50.3	57.1	38.1	14.6	0.457
	2107	0.297	40.4	49.0	51.4	37.7	15.4	0.187
	2108	1.20	67.9	85.3	98.8	87.8	40.6	1.06
	Mean	0.471	47.9	58.4	64.6	47.6	19.7	0.568
	SD	0.382	11.9	14.3	17.9	19.8	10.4	0.447
25	3101	1.22	44.0	58.3	56.4	51.6	29.4	-
	3102	1.29	55.2	77.6	85.3	67.3	44.6	-
	Mean	1.26	49.6	68.0	70.9	59.5	37.0	-
250	4101	21.4	89.9	126	138	159	150	-
	4102	23.0	96.2	123	149	194	139	-
	4103	58.2	103	153	201	208	172	-
	4104	87.1	89.0	113	124	157	154	-
	Mean	47.4	94.5	129	153	180	154	-
	SD	31.4	6.49	17.1	33.6	25.5	13.7	-

(2) TKパラメータ (5'-Hydroxythalidomide; GD13)

Dose level (mg/kg)	Animal No.	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	AUC <sub>0-t</sub> (h*ng/mL)
12.5	2101	69.0	2.00	306
	2103	59.1	2.00	272
	2104	52.0	2.00	261
	2106	57.1	2.00	390
	2107	51.4	2.00	384
	2108	98.8	2.00	881
	Mean	64.6	2.00	416
	SD	17.9	0.00	234
25	3101	58.3	1.00	324
	3102	85.3	2.00	449
	Mean	71.8	1.50	387
250	4101	159	4.00	974
	4102	194	4.00	1060
	4103	208	4.00	1260
	4104	157	4.00	961
	Mean	180	4.00	1060
	SD	25.5	0.00	138

表11-1 妊娠雌ウサギを用いたサリドマイド経口投与による胎盤、卵黄嚢、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検討

追加実験

12.5 mg/kg 群

Dose level (mg/kg)	Sampling time (h)	Animal No.	Fetus No.	Concentration (ng/g)		
				Yolk sac membrane	Embryo	Placenta
12.5	7	2101	R-1	81.7	60.1	93.6
			L-2	64.1	55.7	89.4
			L-3	62.3	67.1	81.9
			L-4	117	62.0	88.1
		Mean		81.3	61.2	88.3
		SD		25.4	4.72	4.84
		2103	R-1	122	123	178
			R-2	118	126	189
			R-3	172	135	153
			R-4	108	130	187
			R-5	184	122	164
			L-1	86.3	134	206
	Mean		127	129	178	
	SD		36.8	5.24	17.6	
	2104	R-1	161	396	203	
		R-2	167	151	240	
		L-1	184	148	205	
		L-2	186	159	227	
		L-3	143	159	190	
		L-4	138	170	203	
L-5		221	148	221		
L-6		221	175	214		
Mean		178	188	213		
SD		31.7	84.5	16.0		
Mean		129	126	160		
SD		48.2	63.6	64.3		
12.5	24	2106	R-1	1.03	1.37	2.77
			R-2	2.26	5.02	2.36
			R-4	1.52	2.13	2.58
			L-1	1.20	2.46	2.83
			L-2	1.60	1.55	2.43
			L-3	1.93	7.01	1.87
	Mean		1.59	3.26	2.47	
	SD		0.455	2.26	0.348	
	2107	R-1	0.753	0.707	1.56	
		R-2	0.735	0.854	1.42	
		R-3	1.10	0.584	1.43	
		R-4	1.19	0.755	1.52	
		L-1	0.916	0.881	1.25	
		L-2	1.31	0.713	1.27	
		L-3	0.655	0.532	1.35	
		L-4	1.14	0.604	1.51	
	Mean		0.975	0.704	1.41	
	SD		0.243	0.126	0.116	
2108	R-1	2.45	1.42	2.42		
	R-2	2.36	6.30	2.76		
	L-1	1.39	1.28	2.36		
	L-2	2.25	3.65	2.43		
	L-3	1.50	1.69	2.61		
	L-4	1.22	8.75	2.69		
	L-5	1.37	2.08	2.65		
	Mean		1.79	3.60	2.56	
	SD		0.535	2.88	0.155	
	Mean		1.45	2.52	2.15	
SD		0.425	1.58	0.638		

表11-2 妊娠雌ウサギを用いたサリドマイド経口投与による胎盤、卵黄嚢、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検討

(1)先行実験

25 mg/kg 群

Dose level (mg/kg)	Sampling time (h)	Animal No.	Fetus No.	Concentration (ng/g)		
				Placenta	Yolk sac membrane	Embryo
25	7	1103	R-1	1370	997	881
			L-1	1490	702	826
			L-2	1130	1320	792
			L-3	1340	1050	836
			L-4	1220	1180	909
			L-5	1320	675	744
			L-6	1370	736	868
		L-7	1240	1090	992	
		Mean	1310	969	856	
		SD	111	240	75.6	
		1104	L-1	851	485	555
			L-5	981	784	602
			Mean	916	635	579
		Mean	1110	802	717	
	SD	279	236	196		
	24	1105	R-3	17.8	23.9	10.5
			L-1	16.6	15.4	10.7
			L-2	18.6	15.0	11.4
			L-3	17.9	41.5	12.5
			L-5	18.8	15.6	10.8
			L-6	19.9	17.6	11.8
			L-7	21.4	11.8	13.2
		Mean	18.7	20.1	11.6	
		SD	1.56	10.1	1.01	
		1106	R-8	17.0	12.5	8.66
R-9			16.1	14.3	9.42	
Mean		16.6	13.4	9.04		
1107		R-1	8.38	5.47	4.75	
		R-2	8.58	4.40	4.63	
	R-3	9.30	12.7	4.60		
	R-4	8.18	2.93	4.92		
	L-1	8.81	5.89	4.84		
	L-2	8.20	5.95	5.11		
	Mean	8.58	6.22	4.81		
SD	0.428	3.37	0.191			
1108	L-1	24.7	15.2	14.9		
	L-5	21.3	20.4	13.1		
Mean	23.0	17.8	14.0			
Mean	16.7	14.4	9.85			
SD	6.05	6.11	3.92			

(2)追加実験

Dose level (mg/kg)	Sampling time (h)	Animal No.	Fetus No.	Concentration (ng/g)		
				Placenta	Yolk sac membrane	Embryo
25	7	3101	R-1	522	536	1020
			R-2	892	636	1010
			R-3	809	626	941
			R-4	671	622	900
			R-5	415	696	955
			L-1	380	579	889
			Mean	615	616	953
		SD	210	54.2	54.4	
		3102	R-1	369	405	656
			R-2	740	492	639
			R-3	425	526	611
			R-4	512	491	632
			R-5	902	562	711
			L-1	621	476	621
	L-2		601	494	696	
	L-3	641	488	643		
	L-4	494	445	674		
	L-5	413	527	697		
	L-6	491	419	595		
	L-7	698	470	831		
	Mean	576	483	667		
	SD	155	44.9	63.1		
	Mean	595	549	810		
	SD	27.8	94.0	202		

表11-3 妊娠雌ウサギを用いたサリドマイド経口投与による胎盤、卵黄嚢、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検討

(1) 先行実験

250 mg/kg 群

Dose level (mg/kg)	Sampling time (h)	Animal No.	Fetus No.	Concentration (ng/g)		
				Placenta	Yolk sac membrane	Embryo
250	7	2104	R-1	6930	3850	5130
			R-2	7530	4780	4380
			L-1	7040	2980	4160
			L-2	6240	3780	4260
		Mean	6940	3850	4480	
		SD	532	736	441	
		2106	R-3	310	190	68.8
			R-5	267	163	87.4
	R-6		262	249	183	
	R-7		265	141	155	
	Mean	282	190	131		
	SD	24.4	41.5	49.9		
	24	2107	R-1	722	503	464
			R-2	712	616	345
			R-4	743	914	464
			Mean	726	678	424
SD		15.8	212	68.7		
2108		R-1	613	499	409	
		R-2	665	594	415	
		L-1	700	412	412	
	L-2	640	660	381		
Mean	629	459	433			
SD	49.7	178	80.9			
Mean	546	442	330			
SD	233	244	172			

(2) 追加実験

250 mg/kg 群

Dose level (mg/kg)	Sampling time (h)	Animal No.	Fetus No.	Concentration (ng/g)		
				Placenta	Yolk sac membrane	Embryo
250	7	4101	L-2	6620	6790	8960
			R-1	5490	5260	6620
		4102	R-4	4700	5280	7540
			R-5	3710	5250	7650
		Mean	4630	5260	7270	
		SD	892	15.3	566	
		4104	R-1	10700	7540	13700
			R-3	5860	7560	11900
			L-1	15000	9060	15400
			L-2	15400	8610	12900
	L-3	11500	7810	12700		
	L-4	17600	8630	12700		
	L-6	14700	9290	13700		
	Mean	13000	8360	13300		
	SD	3920	719	1120		
	Mean	9050	7000	10500		
SD	5540	1920	3950			

表12-1 妊娠雌ウサギを用いたサリドマイド経口投与による胎盤、卵黄嚢、胚中の5-hydroxythalidomide 濃度(妊娠13日)  
:胚・胎児への移行に関する検討

(2)追加実験

12.5 mg/kg 群

Dose level (mg/kg)	Sampling time (h)	Animal No.	Fetus No.	Concentration (ng/g)		
				Yolk sac membrane	Embryo	Placenta
12.5	7	2101	R-1	0.605	0.300	1.24
			L-2	0.567	0.299	1.06
			L-3	0.595	0.363	0.849
			L-4	1.83	0.317	1.00
		Mean		0.899	0.320	1.04
		SD		0.621	0.0300	0.162
		2103	R-1	0.645	0.316	1.72
			R-2	0.707	0.326	1.76
			R-3	0.931	0.332	1.24
			R-4	2.86	0.409	1.89
			R-5	1.75	0.296	1.68
			L-1	0.454	0.390	1.93
	L-2	0.509	0.361	1.53		
	Mean		1.12	0.347	1.68	
	SD		0.883	0.0411	0.235	
	2104	R-1	1.14	1.11	2.45	
		R-2	0.962	0.389	2.22	
		L-1	1.39	0.431	2.33	
		L-2	0.910	0.412	1.90	
		L-3	0.641	0.312	2.07	
L-4		0.685	0.526	1.94		
L-5	1.39	0.441	2.04			
L-6	1.24	0.515	2.61			
Mean		1.04	0.517	2.20		
SD		0.294	0.249	0.253		
Mean		1.02	0.395	1.64		
SD		0.113	0.107	0.580		
12.5	24	2106	R-1	BLQ	BLQ	BLQ
			R-2	BLQ	BLQ	BLQ
			R-4	BLQ	BLQ	BLQ
			L-1	BLQ	BLQ	BLQ
			L-2	BLQ	BLQ	BLQ
			L-3	BLQ	BLQ	BLQ
		Mean		NC	NC	NC
		SD		NC	NC	NC
		2107	R-1	BLQ	BLQ	BLQ
			R-2	BLQ	BLQ	BLQ
			R-3	BLQ	BLQ	BLQ
			R-4	BLQ	BLQ	BLQ
	L-1		BLQ	BLQ	BLQ	
	L-2		BLQ	BLQ	BLQ	
	L-3	BLQ	BLQ	BLQ		
	L-4	BLQ	BLQ	BLQ		
	Mean		NC	NC	NC	
	SD		NC	NC	NC	
2108	R-1	BLQ	BLQ	BLQ		
	R-2	BLQ	BLQ	BLQ		
	L-1	BLQ	BLQ	BLQ		
	L-2	BLQ	BLQ	BLQ		
	L-3	BLQ	BLQ	BLQ		
	L-4	BLQ	BLQ	BLQ		
L-5	BLQ	BLQ	BLQ			
Mean		NC	NC	NC		
SD		NC	NC	NC		
Mean		NC	NC	NC		
SD		NC	NC	NC		

表12-2 妊娠雌ウサギを用いたサリドマイド経口投与による胎盤、卵黄嚢、胚中の5-hydroxythalidomide 濃度 (妊娠13日)  
:胚・胎児への移行に関する検討

(1)先行実験

Dose level (mg/kg)	Sampling time (h)	Animal No.	Fetus No.	Concentration (ng/g)			
				Placenta	Yolk sac membrane	Embryo	
25	7	1103	R-1	7.38	7.01	1.39	
			L-1	6.40	3.11	1.95	
			L-2	7.51	6.56	1.30	
			L-3	8.22	6.12	1.64	
			L-4	7.25	9.87	1.58	
			L-5	6.29	3.92	1.24	
			L-6	6.75	5.18	1.75	
	Mean			7.04	6.06	1.53	
		SD		0.664	2.08	0.243	
	1104	L-1	5.98	4.22	1.11		
		L-5	7.46	4.99	0.966		
	Mean			6.72	4.61	1.04	
		SD		0.227	1.03	0.349	
	25	7	1105	R-3	0.198	0.242	BLQ
				L-1	0.177	0.344	BLQ
				L-2	0.166	0.187	BLQ
				L-3	0.175	0.764	BLQ
				L-5	0.179	0.299	BLQ
				L-6	0.163 <sup>1)</sup>	0.427	BLQ
				L-7	0.255	0.216	BLQ
		Mean			0.188	0.354	NC
			SD		0.0318	0.198	NC
		1106	R-8	0.164	0.438	BLQ	
			R-9	0.162	0.365	BLQ	
		Mean			0.163	0.402	NC
SD							
24		1107	R-1	0.149	BLQ	BLQ	
	R-2		0.143	BLQ	BLQ		
	R-3		0.148	0.186	BLQ		
	R-4		0.147	BLQ	BLQ		
	L-1		0.133	0.123	BLQ		
	L-2		0.119	0.262	BLQ		
	Mean				0.140	0.0952	NC
SD			0.0118	0.113	NC		
1108	L-1	0.378	0.174	BLQ			
	L-5	0.331	0.464	BLQ			
Mean			0.355	0.319	NC		
	SD						
Mean			0.211	0.292	NC		
	SD		0.0975	0.136	NC		

(2)追加実験

Dose level (mg/kg)	Sampling time (h)	Animal No.	Fetus No.	Concentration (ng/g)			
				Placenta	Yolk sac membrane	Embryo	
25	7	3101	R-1	15.1	2.43	5.89	
			R-2	3.40	1.02	5.37	
			R-3	2.45	0.990	4.73	
			R-4	1.45	1.40	4.88	
			R-5	1.54	1.66	5.27	
			L-1	1.17	1.82	4.82	
			Mean			4.19	1.55
	SD			5.41	0.543	0.440	
	25	7	3102	R-1	1.39	0.905	5.25
				R-2	4.19	1.20	5.52
				R-3	1.37	0.963	4.77
				R-4	1.68	0.855	5.31
				R-5	4.32	1.18	5.30
				L-1	3.37	0.866	4.51
				L-2	2.47	1.09	5.99
		L-3	2.90	1.07	5.41		
		L-4	1.87	0.910	5.70		
		L-5	1.25	1.41	5.55		
		L-6	2.50	0.852	4.57		
		L-7	4.32	0.956	5.88		
		Mean			2.64	1.02	5.31
			SD		1.18	0.173	0.480
	Mean			3.41	1.29	5.24	
		SD		1.10	0.376	0.108	



表12-3 妊娠雌ウサギを用いたサリドマイド経口投与による胎盤、卵黄嚢、胚中の5-hydroxythalidomide 濃度 (妊娠13日): 胚・胎児への移行に関する検討

(1)先行実験

250 mg/kg 群						
Dose level (mg/kg)	Sampling time (h)	Animal No.	Fetus No.	Concentration (ng/g)		
				Yolk sac membrane	Embryo	Placenta
250	7	2104	R-1	21.2	14.9	28.3
			R-2	23.5	8.56	37.2
			L-1	21.0	6.68	40.0
			L-2	16.5	8.90	30.6
		Mean	20.6	9.76	34.0	
		SD	2.93	3.56	5.49	
	24	2106	R-3	9.65	0.951	3.30
			R-5	1.65	1.00	2.79
			R-6	7.50	18.0	3.10
			R-7	3.24	1.72	3.10
		R-8	3.30	5.68	3.32	
		Mean	5.07	5.47	3.12	
	SD	3.36	7.27	0.213		
	24	2107	R-1	2.50	0.889	5.86
R-2			15.6	1.27	5.06	
R-4			70.7	6.90	4.88	
Mean			29.6	3.02	5.27	
SD		36.2	3.37	0.522		
24		2108	R-1	3.83	0.663	5.03
	R-2		4.58	0.698	5.63	
	L-1		4.23	2.62	6.18	
	L-2		11.7	2.29	5.80	
	L-3	2.16	37.1	5.14		
	L-4	4.65	0.945	4.60		
Mean	5.19	7.39	5.40			
SD	3.32	14.6	0.577			
Mean		13.3	5.29	4.60		
SD		14.1	2.19	1.28		

(2)追加実験

250 mg/kg 群						
Dose level (mg/kg)	Sampling time (h)	Animal No.	Fetus No.	Concentration (ng/g)		
				Yolk sac membrane	Embryo	Placenta
250	7	4101	L-2	12.4	9.81	42.6
			R-1	12.4	14.0	40.8
		4102	R-4	10.5	9.69	39.4
			R-5	8.92	8.54	41.6
		Mean	10.6	10.7	40.6	
		SD	1.74	2.88	1.11	
	7	4104	R-1	11.7	15.0	59.8
			R-3	19.9	10.2	55.8
			L-1	35.1	12.8	54.9
			L-2	278	12.8	50.6
		L-3	21.8	8.87	49.0	
		L-4	132	12.0	53.2	
	L-6	84.4	13.8	53.3		
	Mean	83.3	12.2	53.8		
SD	96.2	2.09	3.54			
Mean		47.2	11.4	47.5		
SD		51.1	1.20	8.98		

表13-1 妊娠雌ウサギを用いたサリドマイド経口投与による胎盤、卵黄嚢、胚中の5'-hydroxythalidomide 濃度（妊娠13日）  
:胚・胎児への移行に関する検討

(2)追加実験

12.5 mg/kg 群

Dose level (mg/kg)	Sampling time (h)	Animal No.	Fetus No.	Concentration (ng/g)		
				Yolk sac membrane	Embryo	Placenta
12.5	7	2101	R-1	3.91	2.26	5.55
			L-2	2.88	1.73	5.33
			L-3	3.07	3.17	5.02
			L-4	6.04	2.93	4.86
		Mean		3.98	2.52	5.19
		SD		1.45	0.654	0.309
		2103	R-1	3.63	3.24	6.68
			R-2	3.55	3.70	6.59
			R-3	5.01	3.81	5.38
			R-4	2.94	4.15	6.65
			R-5	4.95	2.71	5.73
			L-1	2.94	3.34	7.41
	L-2	3.32	3.94	5.74		
	Mean		3.76	3.56	6.31	
	SD		0.873	0.491	0.715	
	2104	R-1	4.26	10.4	6.16	
		R-2	5.63	3.54	7.20	
		L-1	6.08	3.46	7.28	
		L-2	5.29	3.45	6.65	
		L-3	4.47	3.81	5.66	
L-4		4.30	3.38	6.60		
L-5		6.20	3.71	7.22		
L-6		6.00	4.19	7.65		
Mean		5.28	4.49	6.80		
SD		0.827	2.40	0.661		
Mean		4.34	3.52	6.10		
SD		0.821	0.985	0.827		
12.5	24	2106	R-1	BLQ	0.0833	BLQ
			R-2	BLQ	0.106	0.105
			R-4	BLQ	BLQ	0.0803
			L-1	BLQ	0.0996	0.0950
			L-2	0.0817	BLQ	0.0986
			L-3	0.0934	0.103	0.0898
		Mean		0.0292	0.0653	0.0781
		SD		0.0454	0.0512	0.0392
		2107	R-1	BLQ	BLQ	BLQ
			R-2	BLQ	BLQ	BLQ
			R-3	BLQ	BLQ	BLQ
			R-4	BLQ	BLQ	BLQ
	L-1		0.143	BLQ	BLQ	
	L-2		BLQ	BLQ	BLQ	
	L-3	BLQ	BLQ	BLQ		
	L-4	BLQ	BLQ	BLQ		
	Mean		NC	NC	NC	
	SD		NC	NC	NC	
2108	R-1	0.252	0.149	0.212		
	R-2	0.228	0.187	0.221		
	L-1	0.138	0.146	0.221		
	L-2	0.192	0.118	0.212		
	L-3	0.128	0.142	0.226		
	L-4	0.125	0.178	0.270		
L-5	0.149	0.154	0.270			
Mean		0.173	0.153	0.233		
SD		0.0512	0.0231	0.0257		
Mean		0.0734	0.0729	0.104		
SD		0.0866	0.0770	0.119		

表13-2 妊娠雌ウサギを用いたサリドマイド経口投与による胎盤、卵黄嚢、胚中の5'-hydroxythalidomide 濃度（妊娠13日）：胚・胎児への移行に関する検討

(1)先行実験

25 mg/kg 群

Dose level (mg/kg)	Sampling time (h)	Animal No.	Fetus No.	Concentration (ng/g)		
				Yolk sac membrane	Embryo	Placenta
25	7	1103	R-1	12.8	8.49	16.3
			L-1	5.63	9.98	15.3
			L-2	18.6	7.18	15.2
			L-3	14.9	8.20	16.2
			L-4	13.6	8.91	15.3
			L-5	6.89	7.29	15.4
			L-6	8.83	8.35	16.2
	L-7	14.0	9.74	15.4		
	Mean			11.9	8.52	15.7
	SD			4.41	1.02	0.478
	1104	L-1	7.58	8.69	15.8	
		L-5	13.9	6.38	18.3	
	Mean			10.7	7.54	17.1
	SD			11.3	8.03	16.4
24	7	1105	R-3	0.943	0.390	0.898
			L-1	0.475	0.404	0.881
			L-2	0.630	0.444	0.933
			L-3	1.71	0.440	0.990
			L-5	0.623	0.432	0.980
			L-6	0.757	0.455	0.910
			L-7	0.335	0.498	1.01
	Mean			0.782	0.438	0.943
	SD			0.453	0.0352	0.0502
	1106	R-8	0.342	0.279	0.604	
		R-9	0.383	0.282	0.615	
	Mean			0.363	0.281	0.610
	1107	R-1	0.199	0.240	0.551	
		R-2	0.218	0.214	0.546	
R-3		0.658	0.241	0.567		
R-4		0.129	0.280	0.527		
L-1		0.246	0.260	0.591		
L-2		0.263	0.270	0.418		
Mean				0.286	0.251	0.533
SD			0.188	0.0240	0.0605	
1108	L-1	0.457	0.546	1.06		
	L-5	0.964	0.504	1.05		
Mean			0.711	0.525	1.06	
Mean			0.535	0.373	0.785	
SD			0.247	0.130	0.253	

(2)追加実験

25 mg/kg 群

Dose level (mg/kg)	Sampling time (h)	Animal No.	Fetus No.	Concentration (ng/g)		
				Placenta	Yolk sac membrane	Embryo
25	7	3101	R-1	7.06	6.49	15.3
			R-2	10.7	6.81	14.0
			R-3	10.5	7.20	12.8
			R-4	8.64	7.33	13.4
			R-5	4.30	7.74	13.8
			L-1	4.48	6.01	12.9
			Mean			7.61
	SD			2.83	0.623	0.917
	7	R-1	7.73	8.42	18.0	
		R-2	16.0	9.76	16.4	
		R-3	9.76	10.2	16.2	
		R-4	9.22	8.40	15.6	
		R-5	18.9	10.9	17.6	
		L-1	13.0	8.95	15.0	
L-2		12.0	8.62	17.2		
3102	L-3	13.9	9.21	15.7		
	L-4	9.71	8.17	16.3		
	L-5	8.31	8.49	17.6		
	L-6	10.9	7.15	13.8		
	L-7	15.1	7.94	17.2		
	Mean			12.0	8.85	16.4
	SD			3.42	1.03	1.23
Mean			9.83	7.89	15.0	
SD			3.13	1.36	1.90	

表13-3 妊娠雌ウサギを用いたサリドマイド経口投与による胎盤、卵黄嚢、胚中の5'-hydroxythalidomide 濃度（妊娠13日）：胚・胎児への移行に関する検討

(1)先行実験

Dose level (mg/kg)	Sampling time (h)	Animal No.	Fetus No.	Concentration (ng/g)		
				Yolk sac membrane	Embryo	Placenta
250	7	2104	R-1	29.6	36.3	53.6
			R-2	43.4	31.0	61.2
			L-1	23.7	29.1	58.2
			L-2	29.5	29.0	51.3
			Mean	31.6	31.4	56.1
			SD	8.37	3.43	4.46
	24	2106	R-3	4.92	1.39	9.06
			R-5	4.77	1.53	8.32
			R-6	7.25	4.90	8.75
			R-7	4.30	4.46	9.26
			R-8	5.52	2.53	9.83
			Mean	5.35	2.96	9.04
	24	2107	R-1	5.94	5.28	9.99
			R-2	6.31	3.36	10.2
			R-4	11.7	5.50	10.1
			Mean	7.98	4.71	10.1
			SD	3.22	1.18	0.105
			24	2108	R-1	7.88
R-2	8.52	6.67			11.2	
L-1	6.80	5.62			12.2	
L-2	8.90	4.63			11.4	
L-3	2.41	10.8			10.7	
L-4	6.36	6.06			9.64	
Mean	6.81	6.66	11.0			
SD	2.37	2.14	0.847			
Mean	6.72	4.78	10.0			
SD	1.32	1.85	0.982			

(2)追加実験

Dose level (mg/kg)	Sampling time (h)	Animal No.	Fetus No.	Concentration (ng/g)		
				Yolk sac membrane	Embryo	Placenta
250	7	4101	L-2	47.3	36.9	77.0
			R-1	28.2	26.5	60.2
		4102	R-4	29.6	31.9	62.0
			R-5	30.5	37.2	65.5
		Mean	29.4	31.9	62.6	
		SD	1.16	5.35	2.70	
	7	4104	R-1	56.0	36.9	99.0
			R-3	32.6	38.8	87.6
			L-1	76.9	48.6	107
			L-2	105	45.8	83.4
			L-3	65.2	39.4	84.8
			L-4	125	44.5	85.0
	7	4104	L-6	88.6	46.4	86.3
			Mean	78.5	42.9	90.4
	SD	31.0	4.49	8.98		
	Mean	56.2	38.0	78.3		
	SD	31.5	6.92	17.2		

表14 妊娠雌ウサギを用いたサリドマイド経口投与による母動物一般状態観察:胚・胎児発生に関する検討(妊娠28日帝王切開)

(1) 先行試験

Dose (mg/kg)	Signs	Gestational day													
		Treatment period (GDs1-13)													
		0	1	2	3	4	5	6	7	8	9	10	11	12	13
0	Number of dams	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	Number of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Decrease feces	0	0	0	0	0	0	0	0	0	0	0	0	0	1
25	Number of dams	8	8	8	8	8	8	8	8	8	8	8	8	8	8
	Number of dams with abnormal findings	0	0	0	1	0	0	0	0	0	0	0	0	0	0
	Decrease feces	0	0	0	1	0	0	0	0	0	0	0	0	0	0
250	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Number of dams with abnormal findings	0	0	8	4	0	0	0	0	0	0	0	0	0	1
	Decrease feces	0	0	8	4	0	0	0	0	0	0	0	0	0	1
	No feces	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Abortion	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Dose (mg/kg)	Signs	Gestational day													
		15	16	17	18	19	20	21	22	23	24	25	26	27	28
0	Number of dams	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	Number of dams with abnormal findings	1	1	0	0	0	0	0	0	1	0	0	0	0	0
	Decrease feces	1	1	0	0	0	0	0	0	1	0	0	0	0	0
25	Number of dams	8	8	8	8	8	8	8	8	8	8	8	8	8	8
	Number of dams with abnormal findings	0	0	4	3	3	2	0	0	0	0	0	0	0	1
	Decrease feces	0	0	4	3	3	2	0	0	0	0	0	0	0	1
250	Number of dams	12	12	12	12	12	12	12	12	12	11	11	11	11	11
	Number of dams with abnormal findings	1	4	3	2	5	5	5	3	2	0	0	0	0	0
	Decrease feces	1	4	3	2	5	4	5	3	1	0	0	0	0	0
	No feces	0	0	0	0	0	1	0	0	0	0	0	0	0	0
	Abortion	0	0	0	0	0	0	0	0	1	0	0	0	0	0

(2) 追加試験

Dose (mg/kg)	Signs	Gestational day													
		0	1	2	3	4	5	6	7	8	9	10	11	12	13
0	Number of dams	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	Number of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Decrease feces	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12.5	Number of dams	8	8	8	8	8	8	8	8	8	8	8	8	8	8
	Number of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Decrease feces	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Dose (mg/kg)	Signs	Gestational day													
		15	16	17	18	19	20	21	22	23	24	25	26	27	28
0	Number of dams	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	Number of dams with abnormal findings	0	0	1	1	1	0	0	0	0	0	0	0	0	0
	Decrease feces	0	0	1	1	1	0	0	0	0	0	0	0	0	0
12.5	Number of dams	8	8	8	8	8	8	8	8	8	8	8	8	8	8
	Number of dams with abnormal findings	1	1	1	2	1	0	0	0	0	0	0	0	0	0
	Decrease feces	1	1	1	2	1	0	0	0	0	0	0	0	0	0

表15 妊娠雌ウサギを用いたサリドマイド経口投与による母動物体重推移・胚・胎児発生に関する検討(妊娠28日帝王切開)

(1) 先行試験

Dose (mg/kg)		Gestational day								
		0	1	3	6	8	10	12	13	14
		Treatment period (GDs1-13)								
0	No. dams	7	7	7	7	7	7	7	7	7
	Mean	3.26	3.30	3.32	3.39	3.42	3.47	3.50	3.53	3.56
	S.D.	0.18	0.19	0.20	0.19	0.19	0.20	0.20	0.21	0.22
25	n	8	8	8	8	8	8	8	8	8
	Mean	3.32	3.37	3.35	3.38	3.41	3.44	3.46	3.48	3.49
	S.D.	0.22	0.21	0.20	0.22	0.23	0.25	0.24	0.24	0.24
250	n	12	12	12	12	12	12	12	12	12
	Mean	3.11	3.16	3.15	3.19	3.22	3.25	3.27 *	3.28 *	3.29 *
	S.D.	0.14	0.14	0.15	0.17	0.17	0.17	0.16	0.17	0.16

Dose (mg/kg)		Gestational day						Body weight		
		16	19	22	24	26	28	GD0-28	GD1-14	GD14-28
0	n	7	7	7	7	7	7	7	7	7
	Mean	3.63	3.67	3.70	3.73	3.76	3.80	0.54	0.26	0.24
	S.D.	0.22	0.21	0.23	0.21	0.21	0.20	0.10	0.08	0.07
25	n	8	8	8	8	8	8	8	8	8
	Mean	3.48	3.46	3.53	3.58	3.62	3.65	0.33 **	0.12 *	0.16
	S.D.	0.25	0.22	0.23	0.24	0.23	0.20	0.14	0.14	0.10
250	n	12	12	12	11	11	11	11	12	11
	Mean	3.19 **	3.09 **	3.09 **	3.18 **	3.24 **	3.28 **	0.16 **	0.14 **	-0.01 **
	S.D.	0.16	0.20	0.20	0.19	0.15	0.18	0.10	0.05	0.09

Significantly different from the control : \* P<0.05, \*\* P<0.01

(2) 追加試験

Dose (mg/kg)		Gestational day								
		0	1	3	6	8	10	12	13	14
		Treatment period (GDs1-13)								
thalidomi 0 mg/kg	n	4	4	4	4	4	4	4	4	4
	Mean	3.53	3.54	3.56	3.60	3.64	3.64	3.66	3.68	3.67
	S.D.	0.30	0.28	0.28	0.25	0.26	0.25	0.25	0.29	0.28
thalidomi 12.5 mg/l	n	8	8	8	8	8	8	8	8	8
	Mean	3.28	3.34	3.36	3.43	3.48	3.51	3.54	3.56	3.57
	S.D.	0.37	0.39	0.38	0.37	0.36	0.37	0.38	0.37	0.39

Dose (mg/kg)		Gestational day						Body weight		
		16	19	22	24	26	28	GD0-28	GD1-14	GD14-28
thalidomi 0 mg/kg	n	4	4	4	4	4	4	4	4	4
	Mean	3.70	3.69	3.71	3.73	3.72	3.70	0.17	0.12	0.04
	S.D.	0.26	0.21	0.23	0.22	0.21	0.21	0.10	0.03	0.08
thalidomi 12.5 mg/l	n	8	8	8	8	8	8	8	8	8
	Mean	3.57	3.59	3.61	3.63	3.66	3.70	0.42 **	0.23 *	0.13
	S.D.	0.40	0.39	0.38	0.36	0.37	0.38	0.09	0.08	0.11

Significantly different from thalidomide 0 mg/kg : \*\* P<0.01

表16 妊娠雌ウサギを用いたサリドマイド経口投与による帝王切開所見(妊娠28日):胚・胎児発生に関する検討

(1) 先行試験

Dose (mg/kg)	Number of corpora lutea	Number of implan- tation	Preimplan- tation loss (%) a)	Implantation index (%) b)	Number of resorptions Total c)	Postimplan- tation 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	
	n	7	7	7	7	7	7	7	7	7	25/63	7	7	7	7	7	7
0	Mean	10.1	9.4	6.4	93.6	0.4	4.5	3.6	5.4	9.0	39.7	33.66	33.76	33.83	3.34	3.14	3.22
	S.D.	2.0	1.7	8.6	8.6	0.5	5.6	1.6	1.0	1.7		3.53	3.10	3.14	0.71	0.70	0.70
	n	8	8	8	8	8	8	8	8	8	30/59	8	8	8	8	8	8
25	Mean	10.0	8.6	13.1	86.9	1.3	13.4	3.8	3.6	7.4	50.8	31.56	29.77	30.70	3.28	3.03	3.17
	S.D.	1.2	0.9	9.5	9.5	2.4	24.6	1.2	1.3	2.1		2.29	3.22	2.56	0.46	0.45	0.39
											DT *						
	n	11	11	11	11	11	11	11	11	11	7/14	5	3	5	5	3	5
250	Mean	7.5 **	6.6 **	10.3	89.7	5.4 **	83.2 **	0.6 **	0.6 **	1.3 **	50.0	29.99	30.81	29.60 *	4.19	3.02	3.79
	S.D.	1.6	1.4	11.2	11.2	1.4	22.4	0.8	1.1	1.7		3.14	3.87	2.72	0.67	0.39	0.74

(2) 追加試験

Dose (mg/kg)	Number of corpora lutea	Number of implan- tation	Preimplan- tation loss (%) a)	Implantation index (%) b)	Number of resorptions Total c)	Postimplan- tation 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 0 mg/kg	n	4	4	4	4	4	4	4	4	4	15/20	4	4	4	4	4	4
	Mean	8.3	5.3	34.8	65.2	0.3	2.8	3.8	1.3	5.0	75.0	35.47	37.72	36.01	3.91	4.27	3.96
	S.D.	3.3	3.0	30.8	30.8	0.5	5.6	2.8	0.5	2.6		6.08	5.03	6.20	0.86	1.03	0.88
thalidomide 12.5 mg/kg	n	8	8	8	8	8	8	8	8	8	30/61	8	7	8	8	7	8
	Mean	9.1	8.1	10.9	89.1	0.5	6.9	3.8	3.9 *	7.6	49.2	30.99	30.04 *	31.07	3.30	2.97 *	3.18
	S.D.	1.9	1.9	12.5	12.5	0.5	8.0	1.4	2.2	2.1		3.64	4.00	3.92	0.59	0.48	0.51

Significantly different from the control : \* P<0.05, \*\* P<0.01

n: Number of dams

a): [(Number of corpora lutea - Number of implantations) / Number of corpora lutea] x 100

b): (Number of implantations / Number of corpora lutea) x 100

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

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

e): (Number of live male fetuses / Number of live fetuses) x 100

表17 妊娠雌ウサギを用いたサリドマイド経口投与による胚・胎児死亡数(妊娠28日) :胚・胎児発生に関する検討

(1) 先行試験

Dose (mg/kg)	Number of implan- tation	Number of resorptions								Postimplantation loss(%) a)						
		i	r	p	e	l	d	Total	i	r	p	e	l	d	Total	
	n	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
0	Mean	9.4	0.0	0.1	0.3	0.0	0.0	0.0	0.4	0.0	1.6	2.9	0.0	0.0	0.0	4.5
	S.D.	1.7	0.0	0.4	0.5	0.0	0.0	0.0	0.5	0.0	4.2	5.0	0.0	0.0	0.0	5.6
	n	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
25	Mean	8.6	0.0	0.3	1.0	0.0	0.0	0.0	1.3	0.0	2.5	10.9	0.0	0.0	0.0	13.4
	S.D.	0.9	0.0	0.7	1.8	0.0	0.0	0.0	2.4	0.0	7.1	18.2	0.0	0.0	0.0	24.6
	n	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
250	Mean	6.6 **	3.2 *	0.4	1.5	0.3	0.0	0.0	5.4 **	54.5 *	4.4	20.4	3.9	0.0	0.0	83.2 **
	S.D.	1.4	3.2	0.7	2.3	0.9	0.0	0.0	1.4	52.2	8.3	29.9	12.9	0.0	0.0	22.4

(2) 追加試験

Dose (mg/kg)	Number of implan- tation	Number of resorptions								Postimplantation loss(%) a)						
		i	r	p	e	l	d	Total	i	r	p	e	l	d	Total	
	n	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
0	Mean	5.3	0.0	0.0	0.0	0.3	0.0	0.0	0.3	0.0	0.0	0.0	2.8	0.0	0.0	2.8
	S.D.	3.0	0.0	0.0	0.0	0.5	0.0	0.0	0.5	0.0	0.0	0.0	5.6	0.0	0.0	5.6
	n	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
12.5	Mean	8.1	0.0	0.3	0.1	0.1	0.0	0.0	0.5	0.0	3.0	2.5	1.4	0.0	0.0	6.9
	S.D.	1.9	0.0	0.5	0.4	0.4	0.0	0.0	0.5	0.0	5.7	7.1	3.9	0.0	0.0	8.0

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

Significantly different from the control : \* P<0.05, \*\* P<0.01

DT : Dunnett test (two-side), ST : Steel test (two-side), W2 : Wilcoxon rank sum test (two-side)

n: Number of dams

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



表18 妊娠雌ウサギを用いたサリドマイド経口投与による胎児外表観察:胚・胎児発生に関する検討

(1) 先行試験

Test article	Thalidomide		
	0	25	250
Dose (mg/kg)	0	25	250
Number of dams	7	8	5
Number of fetuses	63	59	14
Number of dams with anomalous fetuses (%) a)	0 (0.0)	1 (12.5)	5 (100.0) **
Number of fetuses with any anomaly (%) b)	0 (0.0)	1 (2.1)	11 (82.0) **
Types of abnormality			
Domed head	n	0 (0)	1 (1)
	Mean		2.1
	S.D.		5.9
Hyperflexion of limb	n	0 (0)	1 (1)
	Mean		20.0
	S.D.		44.7
Malrotated limb	n	0 (0)	6 (3)
	Mean		34.7 *
	S.D.		33.5
Micromelia	n	0 (0)	1 (1)
	Mean		6.7
	S.D.		14.9
Ectrodactyly	n	0 (0)	5 (3)
	Mean		50.0 *
	S.D.		50.0
Hyperflexion of paw	n	0(0)	7(4)
	Mean		57.3 **
	S.D.		45.9
Polydactyly	n	0 (0)	1 (1)
	Mean		20.0
	S.D.		44.7
Hooked tail	n	0 (0)	1 (1)
	Mean		4.0
	S.D.		8.9
Short tail	n	0 (0)	1 (1)
	Mean		6.7
	S.D.		14.9
Pendulous digit	n	0 (0)	3 (2)
	Mean		28.0
	S.D.		43.8

(2) 追加試験

Test article	Thalidomide	
	0	12.5
Dose (mg/kg)	0	12.5
Number of dams	4	8
Number of fetuses	20	61
Number of dams with anomalous fetuses (%) a)	0 (0.0)	0 (0.0)
Number of fetuses with any anomaly (%) b)	0 (0.0)	0 (0.0)

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

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

Significantly different from the control : \*P<0.05, \*\* P<0.01

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19-1 妊娠雌ウサギを用いたサリドマイド経口投与による胎児内臓観察:胚・胎児発生に関する検討

(1) 先行試験

Test article		thalidomide 0	thalidomide 25	thalidomide 250
Dose (mg/kg)		0	25	250
Number of dams (Number of fetuses)		7 (63)	8 (59)	5 (14)
Number of dams with anomalous fetuses (incidence %) a)		0 (0.0)	7 (87.5) **	5 (100.0) **
Number of fetuses with any anomaly (incidence %) b)		0 (0.0)	10 (19.5) **	9 (72.0) **
Number of dams with variant fetuses (incidence %) a)		6 (85.7)	6 (75.0)	4 (80.0)
Number of fetuses with any variation (incidence %) b)		7 (11.7)	12 (21.5)	8 (48.7)
Types of abnormality				
Fluid-filled abdomen	n	0 (0)	1 (1)	0 (0)
	Mean		1.6	
	S.D.		4.4	
Dilated cerebral ventricle	n	0 (0)	3(3)	1(1)
	Mean		5.0	6.7
	S.D.		7.1	14.9
Muscular ventricular septal defect	n	0 (0)	3(3)	3(3)
	Mean		7.5	30.7 *
	S.D.		12.1	41.3
Persistent atrioventricular canal	n	0 (0)	1(1)	0 (0)
	Mean		1.6	
	S.D.		4.4	
Overriding aorta	n	0 (0)	0 (0)	3(2)
	Mean			18.0
	S.D.			24.9
Dilated aortic arch	n	0 (0)	3(2)	3(3)
	Mean		4.9	36.7 *
	S.D.		9.5	41.5
Interrupted aortic arch	n	0 (0)	1(1)	0(0)
	Mean		1.8	
	S.D.		5.1	
Retrosophageal aortic arch	n	0 (0)	0 (0)	1(1)
	Mean			6.7
	S.D.			14.9
Right-sided aortic arch	n	0 (0)	0 (0)	1(1)
	Mean			10.0
	S.D.			22.4
Diaphragmatic hernia	n	0 (0)	0 (0)	1(1)
	Mean			10.0
	S.D.			22.4
Distended bladder	n	0 (0)	1(1)	0 (0)
	Mean		2.1	
	S.D.		5.9	
Types of variation				
Malpositioned subclavian artery origin	n	1 (1)	7 (3)	3 (2)
	Mean	1.4	10.1	23.3
	S.D.	3.8	15.8	32.5
Absent accessory lung lobe	n	4 (4)	4 (3)	3 (2)
	Mean	7.0	9.8	14.7
	S.D.	6.7	14.3	20.2
Small gallbladder	n	0 (0)	4 (2)	2 (1)
	Mean		6.9	8.0
	S.D.		15.2	17.9
Retrocaval ureter	n	3 (3)	1 (1)	3 (2)
	Mean	5.0	4.2	20.0
	S.D.	6.3	11.8	29.8

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

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

Significantly different from the control : \*P<0.05, \*\* P<0.01

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

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

表19-2 妊娠雌ウサギを用いたサリドマイド経口投与による胎児内臓観察: 胎・胎児発生に関する検討

(2) 追加試験

Test article		thalidomide	thalidomide
Dose (mg/kg)		0	12.5
Number of dams (Number of fetuses)		4(20)	8(61)
Number of dams with anomalous fetuses (incidence %) a)		0 (0.0)	4(50.0)
Number of fetuses with any anomaly (incidence %) b)		0 (0.0)	6(13.5)
Number of dams with variant fetuses (incidence %) a)		2(50.0)	6(75.0)
Number of fetuses with any variation (incidence %) b)		2(10.4)	9(15.1)
Types of anomaly			
Muscular ventricular septal defect	n	0(0)	3(2)
	Mean		5.7
	S.D.		12.0
Dilated aortic arch	n	0(0)	3(2)
	Mean		8.3
	S.D.		17.8
Absent kidney	n	0(0)	1(1)
	Mean		1.6
	S.D.		4.4
Absent ureter	n	0(0)	1(1)
	Mean		1.6
	S.D.		4.4
Misshapen heart	n	0(0)	1(1)
	Mean		3.1
	S.D.		8.8
Types of variation			
Malpositioned subclavian artery origin	n	0(0)	2(2)
	Mean		4.7
	S.D.		9.3
Absent accessory lung lobe	n	1(1)	5(4)
	Mean	6.3	8.6
	S.D.	12.5	10.5
Retrocaval ureter	n	1(1)	3(2)
	Mean	4.2	4.9
	S.D.	8.4	9.5

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 variations / Number of dams) x 100

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

表20-1 妊娠雌ウサギを用いたサリドマイド経口投与による胎児骨格観察:胚・胎児発生に関する検討

(1) 先行試験

Test article		thalidomid 0	thalidomid 25	thalidomid 250
Dose (mg/kg)				
Number of dams (Number of fetuses)		7(63)	8(59)	5(14)
Number of dams with anomalous fetuses (incidence %)		2(28.6)	3(37.5)	5(100.0) *
Number of fetuses with any anomaly (incidence %)		2(3.2)	3(5.4)	10(75.3) **
Number of dams with variant fetuses (incidence %) a)		5(71.4)	5(62.5)	3(60.0)
Number of fetuses with any variation (incidence %) b)		9(15.9)	8(12.2)	9(52.0)
Types of anomalies				
Misaligned sacral and caudal vertebra	n	0(0)	0(0)	1(1)
	Mean			4.0
	S.D.			8.9
11 ribs	n	1(1)	0(0)	0(0)
	Mean	1.8		
	S.D.	4.7		
Incomplete ossified parietal	n	0(0)	1(1)	0(0)
	Mean		2.1	
	S.D.		5.9	
Short humerus	n	0(0)	0(0)	1(1)
	Mean			6.7
	S.D.			14.9
Absent radius	n	0(0)	0(0)	2(1)
	Mean			13.3
	S.D.			29.8
Absent metacarpal	n	0(0)	1(1)	6(4)
	Mean		1.6	54.0 **
	S.D.		4.4	45.6
Absent forepaw phalanx	n	0(0)	1(1)	6(4)
	Mean		1.6	54.0 **
	S.D.		4.4	45.6
Fused sternebra	n	0(0)	1(1)	0(0)
	Mean		1.8	
	S.D.		5.1	
Branched rib	n	1(1)	0(0)	0(0)
	Mean	1.8		
	S.D.	4.7		
Hemicentric lumbar centrum	n	1(1)	0(0)	0(0)
	Mean	1.4		
	S.D.	3.8		
Bent fibula	n	0(0)	0(0)	2(2)
	Mean			13.3
	S.D.			18.2
Absent tibia	n	0(0)	0(0)	5(3)
	Mean			30.7 *
	S.D.			33.9
Misshapen tibia	n	0(0)	0(0)	1(1)
	Mean			4.0
	S.D.			8.9

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

Significantly different from thalidomide 0 mg/kg : \* P<0.05, \*\* P<0.01

表20-2 妊娠雌ウサギを用いたサリドマイド経口投与による胎児骨格観察:胚・胎児発生に関する検討

(1) 先行試験

Test article		thalidomid	thalidomid	thalidomid
Dose (mg/kg)		0	25	250
Number of dams (Number of fetuses)		7(63)	8(59)	5(14)
Number of dams with anomalous fetuses (incidence %)		2(28.6)	3(37.5)	5(100.0) *
Number of fetuses with any anomaly (incidence %)		2(3.2)	3(5.4)	10(75.3) **
Number of dams with variant fetuses (incidence % a)		5(71.4)	5(62.5)	3(60.0)
Number of fetuses with any variation (incidence % b)		9(15.9)	8(12.2)	9(52.0)
Types of variation				
Split sternbra	n	2(1)	3(2)	1(1)
	Mean	3.6	4.0	6.7
	S.D.	9.4	8.1	14.9
27 presacral vertebrae	n	5(3)	5(3)	0(0)
	Mean	9.1	7.8	
	S.D.	12.7	12.3	
25 presacral vertebrae	n	2(2)	0(0)	0(0)
	Mean	3.2		
	S.D.	5.5		
Unossified talus	n	0(0)	1(1)	9(3)
	Mean		1.8	52.0 *
	S.D.		5.1	50.2
Asymmetric sternbra	n	0(0)	0(0)	1(1)
	Mean			6.7
	S.D.			14.9

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

Significantly different from thalidomide 0 mg/kg : \* P<0.05, \*\* P<0.01

表20-3 妊娠雌ウサギを用いたサリドマイド経口投与による胎児骨格観察: 胎・胎児発生に関する検討

(2) 追加試験

Test article		thalidomid	thalidomid
Dose (mg/kg)		0	12.5
Number of dams (Number of fetuses)		4(20)	8(61)
Number of dams with anomalous fetuses (incidence %)		0(0.0)	0(0.0)
Number of fetuses with any anomaly (incidence %)		0(0.0)	0(0.0)
Number of dams with variant fetuses (incidence % a)		2(50.0)	2(25.0)
Number of fetuses with any variation (incidence % b)		8(26.1)	4(6.3)
Types of variation			
Split sternebra	n	1(1)	1(1)
	Mean	4.2	1.6
	S.D.	8.4	4.4
27 presacral vertebrae	n	6(1)	2(1)
	Mean	18.8	3.1
	S.D.	37.5	8.8
Unossified talus	n	1(1)	1(1)
	Mean	3.1	1.6
	S.D.	6.3	4.4

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 variations / Number of dams) x 100

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

表21-1 妊娠雌ウサギを用いたサリドマイド経口投与による胎児主要部位骨化数観察: 胎・胎児発生に関する検討

(1) 先行試験

(a) 胸骨、仙尾椎骨、手骨

Test article		thalidomid	thalidomid	thalidomid
Dose		0	25	250
Dose unit		mg/kg	mg/kg	mg/kg
Number of dams		7	8	5
Number of fetuses		63	59	14
Sternebra	Mean	5.41	5.45	5.47
	S.D.	0.52	0.44	0.60
Sac.&caud. Vertebra	Mean	19.15	18.67	17.91 **
	S.D.	0.34	0.60	0.48
Metacarpal phalanges of forelimbs R	Mean	4.66	4.29 *	4.15 *
	S.D.	0.27	0.22	0.39
Metacarpal phalanges of forelimbs L	Mean	4.67	4.30	4.08
	S.D.	0.32	0.25	0.51
Proximal phalanges of forelimbs R	Mean	5.00	4.95	4.46 *
	S.D.	0.00	0.15	0.46
Proximal phalanges of forelimbs L	Mean	5.00	4.96	4.22 **
	S.D.	0.00	0.06	0.56
Middle phalanges of forelimbs R	Mean	3.89	3.25 *	2.97 **
	S.D.	0.20	0.40	0.61
Middle phalanges of forelimbs L	Mean	3.83	3.30 **	3.04 **
	S.D.	0.29	0.35	0.09
Distal phalanges of forelimbs R	Mean	5.00	5.00	4.76
	S.D.	0.00	0.00	0.43
Distal phalanges of forelimbs L	Mean	5.00	4.99	4.37 *
	S.D.	0.00	0.04	0.71

Significantly different from thalidomide 0 mg/kg : \* P<0.05, \*\* P<0.01

表21-2 妊娠雌ウサギを用いたサリドマイド経口投与による胎児主要部位骨化数観察: 胚・胎児発生に関する検討

(1) 先行試験

(b) 足骨

Test article		thalidomid	thalidomid	thalidomid
Dose		0	25	250
Dose unit		mg/kg	mg/kg	mg/kg
Number of dams		7	8	5
Number of fetuses		63	59	14
Metatarsal phalanges of hindlimbs R	Mean	4.00	4.00	4.00
	S.D.	0.00	0.00	0.00
Metatarsal phalanges of hindlimbs L	Mean	4.00	4.00	4.00
	S.D.	0.00	0.00	0.00
Proximal phalanges of hindlimbs R	Mean	4.00	4.00	4.00
	S.D.	0.00	0.00	0.00
Proximal phalanges of hindlimbs L	Mean	4.00	4.00	4.00
	S.D.	0.00	0.00	0.00
Middle phalanges of hindlimbs R	Mean	3.98	3.77	3.35 *
	S.D.	0.06	0.32	0.60
Middle phalanges of hindlimbs L	Mean	3.98	3.73	3.35 *
	S.D.	0.06	0.43	0.60
Distal phalanges of hindlimbs R	Mean	4.00	4.00	4.00
	S.D.	0.00	0.00	0.00
Distal phalanges of hindlimbs L	Mean	4.00	4.00	4.00
	S.D.	0.00	0.00	0.00

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

ST : Steel test (two-side)

EF : The group mean is the same and unbiased variance 0 for all groups. All data of all groups are same.

n: Number of dams



表21-3 妊娠雌ウサギを用いたサリドマイド経口投与による胎児主要部位骨化数観察: 胚・胎児発生に関する検査

(2) 追加試験

(a) 胸骨、仙尾椎骨、手骨

Test article		thalidomide	thalidomide
Dose		0	12.5
Dose unit		mg/kg	mg/kg
Number of dams		4	8
Number of fetuses		20	61
Sternebra	Mean	5.62	5.22 *
	S.D.	0.16	0.27
Sac.&caud. Vertebra	Mean	19.00	18.95
	S.D.	0.35	0.32
Metacarpal phalanges of forelimbs R	Mean	4.91	4.51
	S.D.	0.19	0.36
Metacarpal phalanges of forelimbs L	Mean	4.88	4.50
	S.D.	0.25	0.36
Proximal phalanges of forelimbs R	Mean	5.00	5.00
	S.D.	0.00	0.00
Proximal phalanges of forelimbs L	Mean	5.00	4.99
	S.D.	0.00	0.04
Middle phalanges of forelimbs R	Mean	3.85	3.69
	S.D.	0.31	0.38
Middle phalanges of forelimbs L	Mean	3.85	3.69
	S.D.	0.31	0.35
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

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

表21-4 妊娠雌ウサギを用いたサリドマイド経口投与による胎児主要部位骨化数観察:胚・胎児発生に関する検討

(2) 追加試験

(b)足骨

Test article		thalidomide	thalidomide
Dose		0	12.5
Dose unit		mg/kg	mg/kg
Number of dams		4	8
Number of fetuses		20	61
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	3.97	3.91
	S.D.	0.06	0.19
Middle phalanges of hindlimbs L	Mean	3.97	3.91
	S.D.	0.07	0.19
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