考え方により、毒性影響と評価した。ただし、イヌ 13 週間混餌投与試験では、200 mg/kg 体重/日以上の投与群でみられた ALP の上昇を根拠に NOAEL 59.7 mg/kg 体重/日が得られたが、同様の方法でさらに長期間投与したイヌ 52 週間混餌投与試験では、200 mg/kg 体重/日投与群で ALP の上昇は認められなかったこと及び本物質には蓄積性がないことから、イヌ 13 週間混餌投与試験の 200 mg/kg 体重/日投与群でみられた ALP の上昇は一過性のものであり、ADI 設定にあたっては本試験の NOAEL は考慮しないと評価した。

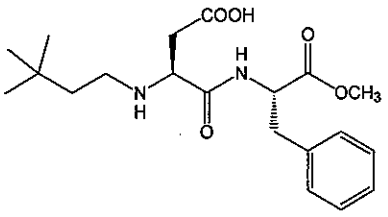
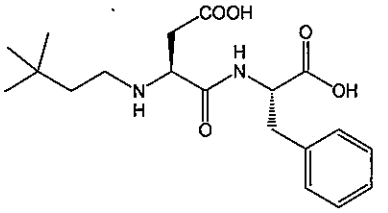
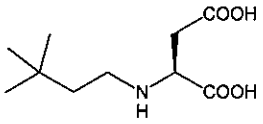
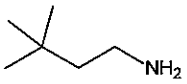
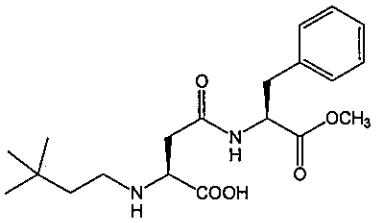
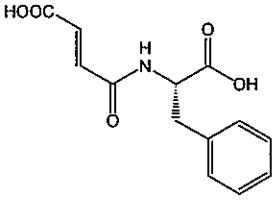
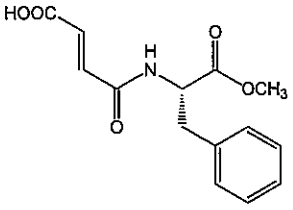
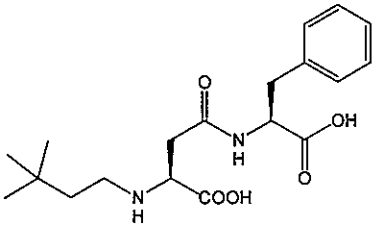
一方、体重増加抑制については、本物質を高濃度に飼料へ添加したことによる実験動物の嗜好性の低下に起因した摂餌量の減少によるものと判断し、毒性影響とは評価しなかった。ただし、ラットを用いた二世代繁殖試験でみられた授乳初期の F_1 児動物における低体重については、親動物に嗜好性の低下はみられず、新生児の成長は母乳に依存していることから、本試験の児の低体重を毒性影響と評価した。

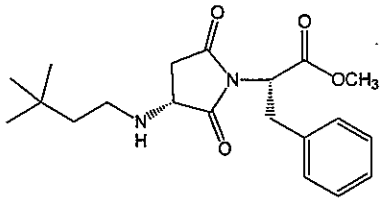
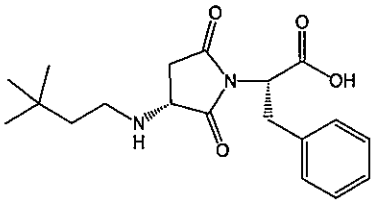
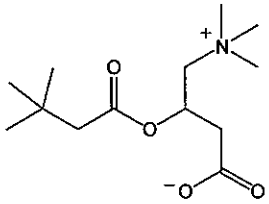
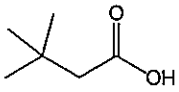
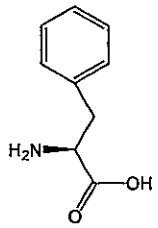
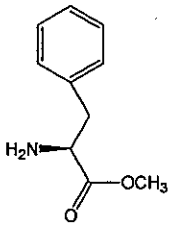
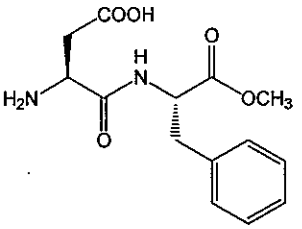
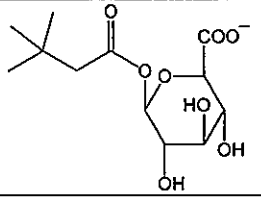
以上のことから、ネオテームの NOAEL は、ラットを用いた二世代繁殖試験における F_1 児動物の低体重を根拠に NOAEL 96.5 mg/kg 体重/日と考えられることから、本物質の ADI は、安全係数を 100 として 1.0 mg/kg 体重/日と評価した。

なお、限られたデータではあるが、本物質の分解物においても、生体にとって特段問題となるような影響は認められていない。

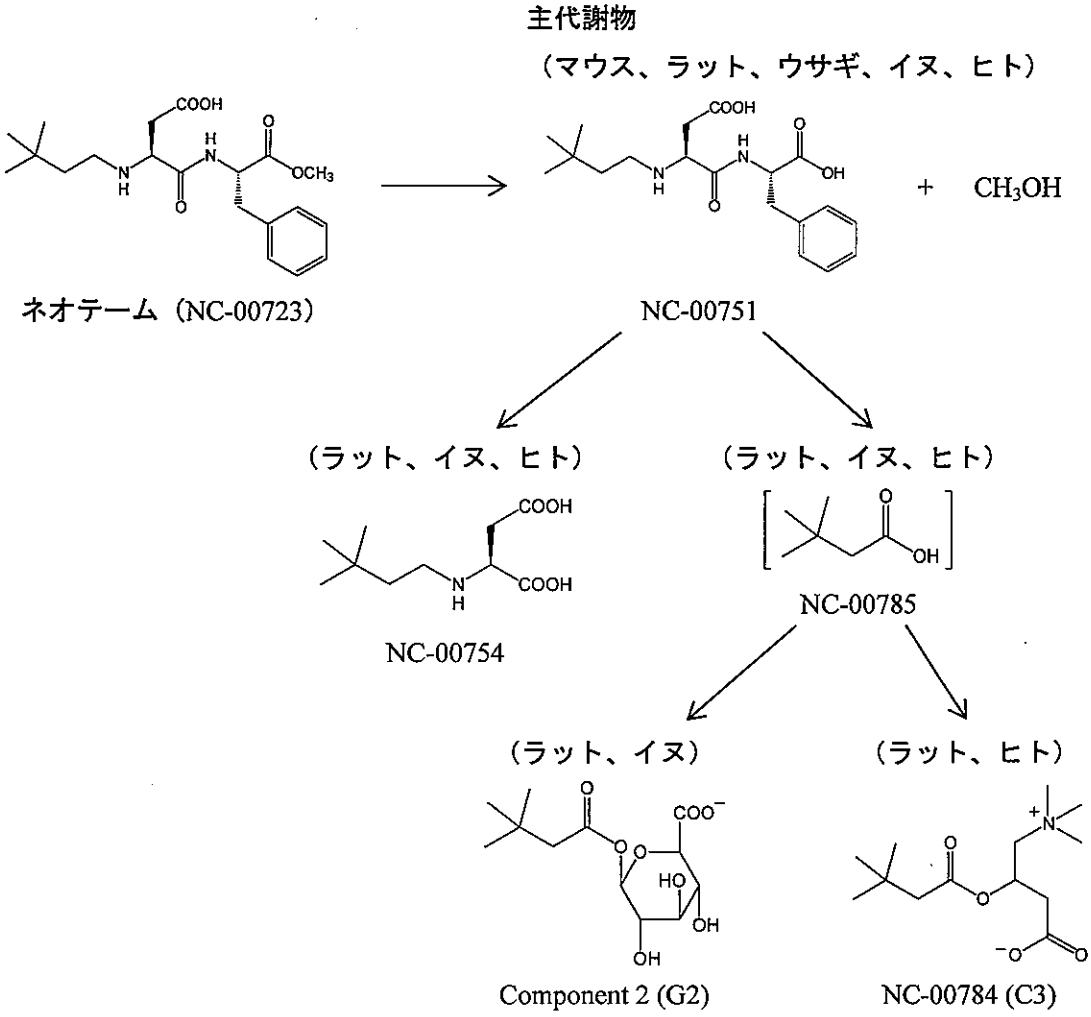
ADI	1.0 mg/kg 体重/日
(ADI 設定根拠資料)	二世代繁殖試験
(動物種)	ラット
(投与方法)	混餌投与
(NOAEL 設定根拠所見)	F_1 児動物の低体重
(NOAEL)	96.5 mg/kg 体重/日
(安全係数)	100

【表　ネオテーム関連化合物一覧】

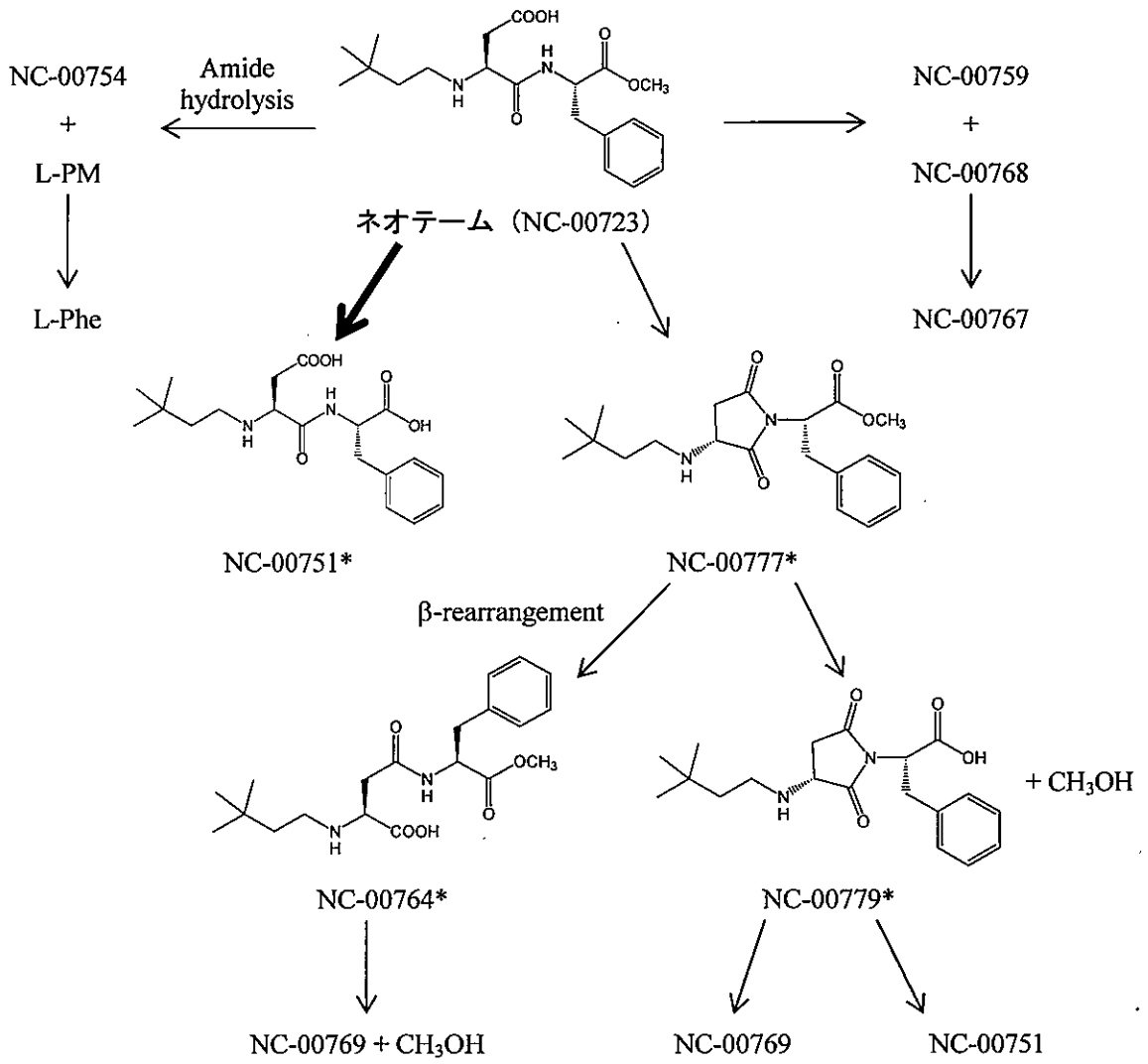
名　称	化学名（一般名）	構　造　式
ネオテーム (NC-00723)	Neoteme N-[N-(3,3,-dimethylbutyl)-L-α-aspartyl]- L-phenylalanine 1-methyl ester N-[N-(3,3-ジメチルブチル)-L-α-アスパルチル]- L-フェニルアラニン　1-メチルエステル	
NC-00751	N-[N-(3,3,-dimethylbutyl)-L-α-aspartyl]- L-phenylalanine N-[N-(3,3-ジメチルブチル)-L-α-アスパルチル]- L-フェニルアラニン	
NC-00754	N-(3,3,-dimethylbutyl)-L-α-aspartic acid N-(3,3-ジメチルブチル)-L-アスパラギン酸	
NC-00759	3,3,-dimethylbutylamine 3,3-ジメチルブチルアミン	
NC-00764	N-[N-(3,3,-dimethylbutyl)-L-β-aspartyl]- L-phenylalanine 1-methyl ester N-[N-(3,3-ジメチルブチル)-L-β-アスパルチル]- L-フェニルアラニン　1-メチルエステル	
NC-00767	N-fumaryl-L-phenylalanine N-フマリル-L-フェニルアラニン	
NC-00768	N-fumaryl-L-phenylalanine 1-methyl ester N-フマリル-L-フェニルアラニン　1-メチルエステル	
NC-00769	N-[N-(3,3,-dimethylbutyl)-L-β-aspartyl]- L-phenylalanine N-[N-(3,3-ジメチルブチル)-L-β-アスパルチル]- L-フェニルアラニン	

名　称	化学名（一般名）	構　造　式
NC-00777	N-[N-(3,3,-dimethylbutyl)-L-aspartimide]-L-phenylalanine 1-methyl ester N-[N-(3,3-ジメチルブチル)-L-アスパルチミド-L-フェニルアラニン　1-メチルエステル	
NC-00779	N-[N-(3,3,-dimethylbutyl)-L-aspartimide]-L-phenylalanine N-[N-(3,3-ジメチルブチル)-L-アスパルチミド-L-フェニルアラニン	
NC-00784 (C3)	3,3-dimethylbutanoyl-L-carnitine 3,3-ジメチルブタノイル-L-カルニチン	
NC-00785	3,3-dimethylbutanoic acid 3,3-ジメチルブタン酸	
L-Phe	L-phenylalanine L-フェニルアラニン	
L-PM	L-phenylalanine methyl ester L-フェニルアラニンメチルエステル	
アスパルテーム (APM)	Aspartame α-L-aspartyl-L-phenylalanine methyl ester α-L-アスパルチル-L-フェニルアラニンメチルエステル	
Component 2 (G2)	β-glucuronide 3,3-dimethylbutanoic acid （グルクロン酸抱合体）	

【図 1　ネオテームの推定代謝経路】[10), 11), 15), 20), 24), 33), 34)]



【図２　ネオテームの分解経路（苛酷条件下）】[7)]



＊ 現実的な保存条件下（pH3.2, 20℃, 8 w）における分解物

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※ 本評価書における Unpublished report とは、未発表資料をいう。

ネオテーム及び関連化合物の安全性試験結果

試験種類	動物種	試験	投与方法	動物数/群	被験物質	投与量	試験結果〈NOAEL〉	文献
反復投与毒性	マウス	13 週間混餌投与試験	混餌	雌雄各 20 匹	ネオテーム	0、100、1,000、4,000、8,000 (mg/kg 体重/日)	4,000 mg/kg 体重/日以上の投与群で肝比重量増加。8,000 mg/kg 体重/日投与群で肝重量増加。〈1,003 mg/kg 体重/日〉	26
	ラット	13 週間混餌投与及び 4 週間回復試験	混餌	雌雄各 20or25 匹	ネオテーム	0、100、300、1,000、3,000 (mg/kg 体重/日)	1,000 mg/kg 体重/日投与群雄、3,000 mg/kg 体重/日投与群においてALP 上昇。〈293 mg/kg 体重/日〉	27
	イヌ	13 週間混餌投与及び 4 週間回復試験	混餌	雌雄各 4 or 6 匹	ネオテーム	0、60、200、600、2,000/1,200 (mg/kg 体重/日)	200、600 mg/kg 体重/日投与群の雌 及び 2,000/1,200 mg/kg 体重/日投与群で ALP 上昇。2,000/1,200 mg/kg 体重/日投与群で RBC、Hb、Hct の低下。〈59.7 mg/kg 体重/日〉	28
	ラット	*in utero* 暴露/52 週間混餌投与及び 4 週間回復試験	*in utero*/混餌	親:雌雄各 25 匹 F_1:雌雄各 20 匹	ネオテーム	0、10、30、100、300、1,000 (mg/kg 体重/日)	影響なし。〈1,006 mg/kg 体重/日以上〉	29
	イヌ	52 週間混餌投与及び 4 週間回復試験	混餌	雌雄各 4 or 6 匹	ネオテーム	0、20、60、200、800 (mg/kg 体重/日)	800 mg/kg 体重/日投与群で ALP 上昇。〈197 mg/kg 体重/日〉	30
繁殖	ラット	繁殖試験(注1)	混餌	雌雄各 28 匹	ネオテーム	0、100、300、1,000 (mg/kg 体重/日)	親動物 (F_0、F_1):1,000 mg/kg 体重/日投与群で摂餌効率の低下が交配前期間に認められた。児動物 (F_1、F_2):F_1 の 300 mg/kg 体重/日投与群の雄及び 1,000 mg/kg 体重/日投与群の生後 1 日の低体重、並びに F_1 の 300 mg/kg 体重/日以上の投与群及び F_2 の 1,000 mg/kg 体重/日投与群の生後 21 日の低体重がみられた。〈親動物の一般毒性に対して 299 mg/kg 体重/日、生殖発生毒性に対して 96.5 mg/kg 体重/日〉	31

(注1) F_0:雄;交配前～F_1 出生まで 14 週間、雌;交配前～F_1 離乳まで 10～11 週間
F_1:雄;離乳～F_2 出生まで 15～16 週間、雌;離乳～F_2 離乳まで 17～20 週間

試験種類	動物種	試験	投与方法	動物数/群	被験物質	投与量	試験結果〈NOAEL〉	文献
催奇形性	ラット	催奇形性試験(注2)	混餌	雌24匹	ネオテーム	0、100、300、1,000 (mg/kg体重/日)	催奇形性は認められない。〈964 mg/kg体重/日以上〉	32
	ウサギ(妊娠)	催奇形性試験(注3)	強制経口	20～25匹	ネオテーム	0、50、150、500 (mg/kg体重/日)	催奇形性は認められない。母動物：対照群及び500 mg/kg体重/日投与群の各1母体で全胚／胎児死亡。500 mg/kg体重/日投与群で死亡1例、流産2例。〈母動物150 mg/kg体重/日、胎児500 mg/kg体重/日以上〉	33
発がん性	マウス	104週間発がん性試験	混餌	対照群:雌雄各140匹 投与群:雌雄各70匹	ネオテーム	0、50、400、2,000、4,000 (mg/kg体重/日)	発がん性は認められない。	34
	ラット	*in utero*暴露/104週間発がん性試験	*In utero*/混餌	(F_0) 対照群:雌雄各170匹、投与群:雌雄各85匹 (F_1) 対照群:雌雄各147匹、投与群:雌雄各73～75匹	ネオテーム	0、50、500、1,000 (mg/kg体重/日)	発がん性は認められない。	35
抗原性	モルモット	皮膚感作性試験	閉塞貼付	対照群:雌雄各5匹 投与群:雌雄各10匹	ネオテーム	0、0.4 (g/匹)	皮膚反応は認められなかった。	36
遺伝毒性	*in vitro*	復帰突然変異試験(+/－S9mix)	TA98、TA100、TA1535、TA1537、TA1538、WP2*uvrA*		ネオテーム	312～10,000 (μg/プレート)	陰性	37
		遺伝子突然変異試験(+/－S9mix)	L5178Yマウスリンパ腫細胞		ネオテーム	100～1,000 (μg/mL)	陰性	38
		染色体異常試験(+/－S9mix)	チャイニーズハムスター卵巣(CHO)由来細胞		ネオテーム	S9mix存在下:250～1,000(μg/mL) S9mix非存在下:62.5～500(μg/mL)	陰性	39
	in vivo	マウス小核試験	強制経口	雌雄各10匹	ネオテーム	500、1,000、2,000 (mg/kg体重)	陰性	40
一般薬理	ラット	一般症状及び行動中枢神経系	混餌	雌雄各20or25匹	ネオテーム	0、100、300、1,000、3,000 (mg/kg体重/日)	影響なし。	27
	イヌ	一般症状及び行動中枢神経系	混餌	雌雄各4or6匹	ネオテーム	0、60、200、600、2,000/1,200 (mg/kg体重/日)	影響なし。	28
	ラット	中枢神経系(自発運動量)	混餌	雌雄各28匹	ネオテーム	0、100、300、1,000 (mg/kg体重/日)	影響なし。	31
	ラット	中枢神経系(麻酔作用)	経口	雌雄各5匹	ネオテーム	5、15 (mg/kg体重)	影響なし。	41

(注2) 交配前28日～交配後20日
(注3) 妊娠6～19日の14日間