ADME NTP Study S0876 Ethanone, 1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-Tetramethyl-2-Naphthalenyl)- (Iso-E Super [reg]; OTNE) Toxicokinetics

The contractor used the commercial name Iso E Super® and the abbreviation IES for the test article. This test article mixture is > 95% 1a-beta isomer.
Sex/Species: male F344 rats.
Vehicle: oral, 0.9% saline:Alkamuls (9:1); dermal, 100% ethanol.

CASRN 54464-57-2

Radiolabeled with carbon-14 in the C-8 position; [8-^{14}C]Iso E Super

Studies Performed:

Oral

1. Single 20 mg/kg oral gavage dose with sacrifice at 4, 8, 24, and 48 hours postdose. (tissue distribution of [^{14}C]IES-derived radioactivity as a function of time data; n=4 per time point)

Dermal 55 mg/kg Dose

2. Single 55 mg/kg dermal dose with covered dose site and blood collected at 0, 6, 12, and 24 hours postdose with sacrifice at 24 hours. (n=4)

3. Single 55 mg/kg dermal dose with covered dose site and blood collected at 0, 6, 12, 24, 36, and 48 hours postdose with sacrifice at 48 hours. (n=4)

4. Single 55 mg/kg dermal dose with covered dose site and blood collected at 0, 6, 12, 24, 36, 48, 72, and 96 hours postdose with sacrifice at 96 hours. (n=4)

5. Single 55 mg/kg dermal dose with uncovered dose site and blood collected at 0, 6, 12, and 24 hours postdose with sacrifice at 24 hours. (n=4)

6. Single 55 mg/kg dermal dose with uncovered dose site and blood collected at 0, 6, 12, 24, 36, and 48 hours postdose with sacrifice at 48 hours. (n=4)

7. Single 55 mg/kg dermal dose with uncovered dose site and blood collected at 0, 6, 12, 24, 36, 48, 72, and 96 hours postdose with sacrifice at 96 hours. (n=4)

Dermal 550 mg/kg Dose

8. Single 550 mg/kg dermal dose with covered dose site and blood collected at 0, 6, 12, and 24 hours postdose with sacrifice at 24 hours. (n=4)

9. Single 550 mg/kg dermal dose with covered dose site and blood collected at 0, 6, 12, 24, 36, and 48 hours postdose with sacrifice at 48 hours. (n=4)

10. Single 550 mg/kg dermal dose with covered dose site and blood collected at 0, 6, 12, 24, 36, 48, 72, and 96 hours postdose with sacrifice at 96 hours. (n=4)

11. Single 550 mg/kg dermal dose with uncovered dose site and blood collected at 0, 6, 12, and 24 hours postdose with sacrifice at 24 hours. (n=4)

12. Single 550 mg/kg dermal dose with uncovered dose site and blood collected at 0, 6, 12, 24, 36, and 48 hours postdose with sacrifice at 48 hours. (n=4)

13. Single 550 mg/kg dermal dose with uncovered dose site and blood collected at 0, 6, 12, 24, 36, 48, 72, and 96 hours postdose with sacrifice at 96 hours. (n=4)

Toxicokinetics:

For tissues, the distribution concentration data from the groups of 4 rats sacrificed at 4, 8, 24, and 48 hours postdose of a single 20 mg/kg oral gavage dose were used to determine the tissue pharmacokinetic parameters t1/2 (h), MRT (h), and $AUC_{0\text{-}48}$ (µg-eq*h/g).

Dermally dosed rats were first surgically fitted with indwelling jugular vein cannulae. Blood toxicokinetic parameters were calculated from the mean of all concentration collected for each treatment group per time point for the 6, 12, 24, 36, 48, 72, and 98 hour time points. For calculation for other tissues following dermal administration, mean data from each of the three terminal time points (24, 48, and 96 hours) were included. Phoenix WinNonlin 6.3 (Pharsight, Cary, NC) was used for modeling. Noncompartmental analysis with extravascular dosing (Model 200) with no weighting was used for all analyses. For datasets where no Lambda_z was estimable, no t1/2 or $AUC_{0 \text{ to infinity}}$ were calculable. WinNonlin used the linear trapezoidal method to calculate $AUC_{0\text{-}96\ h}$.

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Table 1

Pharmacokinetic Parameters for [^{14}C]Iso E Super-Derived Compounds in Tissues Following Single Oral Administration of [^{14}C]Iso E Super to Male Rats (20 mg/kg)

Tissue	T1/2 (h)	MRT (h)	AUC_{0-48} (µg-eq*h/g)
Blood	34.3	20.3	25.7
Adipose	30.1	12.7	70.7
Bladder	8.7	13.8	521.0
Brain	24.7	18.5	3.8
Heart	24.4	17.2	18.6
Kidney	24.9	17.3	181.5
Liver	35.2	19.4	216.7
Lung	26.7	18.7	24.9
Muscle	26.5	15.1	34.1
Pancreas	19.0	16.2	194.2
Skin	22.1	16.3	17.1
Spleen	17.2	14.3	45.0
Testes	19.9	17.4	10.7
Thymus	24.4	17.3	12.5

1. Total [^{14}C]IES-derived radioactivity in ng-eq IES per g tissue was measured for the distribution versus time curves.
2. N=4 at each of the timepoints (4, 8, 24, and 48 h postdose) per tissue.
3. Whole body elimination half-life was estimated to be circa 27 h.

Table 2
Toxicokinetic Parameters Defined

WinNonlin Output	Table/Report	Definition
Cmax	C_{max}	Maximum observed concentration, occurring at T_{max}
Tmax	T_{max}	Time at which C_{max} occurs
Lambda_z	λz	Terminal elimination rate constant
t1/2_Lamda_z	$t1/2$	Terminal elimination half-life
AUClast	$AUC_{0-96\,h}$	Area under the concentration-time curve
AUCINF-obs	$AUC_{0-\infty}$	Area under the concentration-time curve extrapolated to infinity

Noncompartmental analysis with extravascular dosing (Model 200) Phoenix WinNonlin 6.3 (Pharsight, Cary, NC) with no weighting was used for modeling.

Table 3

Concentration of [^{14}C]Iso E Super-Derived Compounds in Blood Following Dermal Administration of [^{14}C]Iso E Super to F-344 Rats

Units are (ng-eq / g).

Dose Site/ Dose	Covered[a] 55 mg/kg	Covered[a] 55 mg/kg	Uncovered[b] 55 mg/kg	Uncovered[b] 55 mg/kg	Covered[c] 550 mg/kg	Covered[c] 550 mg/kg	Uncovered[d] 550 mg/kg	Uncovered[d] 550 mg/kg
Time (h)	Mean	SD	Mean	SD	Mean	SD	Mean	SD
6	83	30	436	195	770	1098	3315	2967
12	87	59	603	311	1019	1305	8163	7198
24	152	106	860	287	3049	2216	15393	6410
36	139	83	815	152	3257	2640	20423	7755
48	224	81	694	113	3806	2333	15516	5974
72	164	56	596	154	3434	786	14288	2542
96	197	25	425	58	2349	1618	7483	1009

[a] For 6, 12 and 24 h, N=11; for 36 h N=7; for 48 h, N=6; for 72 and 96 h, N=3.
[b] For 6, 12 and 24 h, N=12; for 36 and 48 h N=8; for 72 and 96 h, N=4.
[c] For 6, 12 and 24 h, N=11; for 36 and 48 h N=7; for 72 and 96 h, N=3.
[d] For 6, 12 and 24 h, N=11; for 36 and 48 h N=8; for 72 and 96 h, N=4.

Table 4

Pharmacokinetic Parameters Derived from Total Radioactivity in Blood Following Dermal Administration of [^{14}C]Iso E Super to F-344 Rats

Parameter	55 mg/kg Covered	55 mg/kg Uncovered	550 mg/kg Covered	550 mg/kg Uncovered
λz (h^{-1})	NC	0.0103	NC	0.0152
$t_{1/2}$ (h)	NC	67.1	NC	45.6
Tmax (h)	48	24	48	36
Cmax (μg-eq/mL)	0.22	0.86	3.8	20.4
$AUC_{0\text{-}96\ h}$ (μg-eq*h/mL)	15.1	60.0	269	124
$AUC_{0\text{-}\infty}$ (μg-eq*h/mL)	NC	101	NC	1727

NC = not calculable

Table 5

AUC_{0-96} Parameters for [^{14}C]Iso E Super-derived Compounds in Tissues Following a Dermal Exposure of Male Rats to either 55 or 550 mg/kg of [^{14}C]Iso E Super

a. Values expressed for entire dose. Units are μg-eq*h/g/(mg/kg dose).

Tissue	55 mg/kg Covered	55 mg/kg Uncovered	550 mg/kg Covered	550 mg/kg Uncovered
Blood	15.1	60.0[a]	269	1235
Adipose	120	175	1904	3684
Bladder	216	325	1310	3962
Brain	7.6	14.3	134	269
Heart	25.1	51	313	1666
Kidney	149	302	2257	5590
Liver	155	361	1409	3691
Lung	41.2	81.8	502	1246
Muscle	37.8	39.4	280	617
Pancreas	162	214	1595	2334
Spleen	39.0	68.1	328	2093
Testes	12.0	23.4	158	446
Thymus	23.8	46.9	684	1484

b. Values normalized to a 1 mg/kg dose. Units are μg-eq*h/g/(mg/kg dose).

Tissue	55 mg/kg Covered	55 mg/kg Uncovered	550 mg/kg Covered	550 mg/kg Uncovered
Blood	0.27	1.09	0.49	2.25
Adipose	2.18	3.17	3.46	6.70
Bladder	3.93	5.92	2.38	7.20
Brain	0.14	0.26	0.24	0.49
Heart	0.46	0.93	0.57	3.03
Kidney	2.71	5.49	4.10	10.16
Liver	2.81	6.57	2.56	6.71
Lung	0.75	1.49	0.91	2.26
Muscle	0.69	0.72	0.51	1.12
Pancreas	2.94	3.89	2.90	4.24
Spleen	0.71	1.24	0.60	3.81
Testes	0.22	0.43	0.29	0.81
Thymus	0.43	0.85	1.24	2.70