

ADME NTP Study S0662 Diisopropylcarbodiimide

The contract laboratory abbreviation for the test article is DIPC.

Species: young adult male F344 rats and B6C3F1 mice.

Vehicles: intravenous, propylene glycol; dermal, hexane.

CASRN 693-13-0

Radiolabeled with carbon-14 in the 2-propyl position; Diisopropylcarbodiimide, [propyl-2-¹⁴C]-

Studies Performed:

- Study A – Single dose 4.1 mg/kg dermal exposure study in rats with covered dose site and sacrifice at 72 hours.
- Study A' – Single dose 3.9 mg/kg dermal exposure study in rats with covered dose site (charcoal filter) and sacrifice at 72 hours.
- Study B – Single dose 40.9 mg/kg dermal exposure study in rats with covered dose site (charcoal filter) and sacrifice at 72 hours.
- Study E – Single dose 6.9 mg/kg dermal exposure study in mice with covered dose site (charcoal filter) and sacrifice at 72 hours.
- Study G – Single 7.6 mg/kg intravenous administration in mice with sacrifice at 48 hours.
- Study H – Single 7.8 mg/kg intravenous administration in mice with sacrifice at 48 hours (a blood concentration time course with an n of 3 to 4 animals per time point).

Study A was repeated with a different dermal appliance (Study A'). For Studies A' and B, the tissue:blood ratio could not be determined since the measured radioactivity in the blood was not significantly different than background.

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Table 1

**Cumulative Excretion of Radioactivity by Male Fischer 344 Rats following
Dermal Exposure to [¹⁴C]DIPC^a**

4.1 mg/kg Study A

End of Collection Period (h)	Cumulative Percent of Dose Recovered in:					
	Urine	Feces	Volatile Organics Trapped by EtOH	Volatile Organics Trapped by Charcoal	CO ₂	Total
4	NC	NC	1.2 ± 0.5	0.004 ± 0.003	0.24 ± 0.01	1.4 ± 0.5
8	0.31 ± 0.07	NC	1.3 ± 0.5	0.006 ± 0.004	0.45 ± 0.03	2.0 ± 0.6
24	0.8 ± 0.1	0.11 ± 0.03	1.5 ± 0.5	0.006 ± 0.004	1.0 ± 0.1	3.3 ± 0.8
48	1.1 ± 0.1	0.16 ± 0.04	1.5 ± 0.5	0.006 ± 0.004	1.5 ± 0.2	4.3 ± 0.8
72	1.4 ^b ± 0.2	0.19 ± 0.04	1.6 ± 0.5	0.006 ± 0.004	1.9 ± 0.3	5.1 ± 0.9

3.9 mg/kg Study A'

End of Collection Period (h)	Cumulative Percent of Dose Recovered in:			
	Urine	Feces	Volatile Organics	Total
8	0.11 ± 0.02	NC	0.4 ± 0.2	0.5 ± 0.2
24	0.31 ± 0.06	0.037 ± 0.009	0.5 ± 0.2	0.8 ± 0.2
48	0.40 ± 0.07	0.08 ± 0.01	0.5 ± 0.2	1.0 ± 0.3
72	0.46 ^b ± 0.07	0.09 ± 0.02	0.5 ± 0.2	1.0 ± 0.3

^a Values are mean ± SD for four rats.

^b Included the cage rinse result.

NC No collection was scheduled for this time interval.

Table 2

**Cumulative Excretion of Radioactivity by Male Fischer 344 Rats following
Dermal Exposure to [¹⁴C]DIPC^a**

40.9 mg/kg Study B

End of Collection Period (h)	Cumulative Percent of Dose Recovered in:				
	Urine ^b	Feces ^c	Volatile Organics	CO ₂ ^d	Total
8	0.03 ± 0.03	NC	0.7 ± 0.2	0.15	0.8 ± 0.3
24	0.07 ± 0.08	0.010	0.7 ± 0.2	0.15	0.9 ± 0.3
48	0.10 ± 0.11	0.010	0.8 ± 0.2	0.15	0.9 ± 0.4
72	0.11 ± 0.12	0.010	0.8 ± 0.2	0.15	1.0 ± 0.4

^a Values are mean ± SD for four rats unless stated otherwise.

^b Urine at 8, 24 and 48 h included the methanol rinse for that time interval. The cage rinse was not included in the 72 h urine since the value was not significantly different from background.

^c Values are mean for one rat.

^d Values are mean for two rats.

NC No collection was scheduled for this time interval.

Table 3

**Distribution of Radioactivity in Male Fischer 344 Rats
after Dermal Exposure to [¹⁴C]DIPC^a**

Route	4.1 mg/kg - Study A	3.9 mg/kg - Study A'	40.9 mg/kg - Study B
% Dose Absorbed			
Urine	1.4 ^b ± 0.2	0.5 ^c ± 0.1	0.1 ^d ± 0.1
Feces	0.19 ± 0.04	0.09 ± 0.02	0.01 ^e
Exhaled CO ₂	1.9 ± 0.3	NA	0.2 ^f
Volatile Organics by EtOH	1.6 ± 0.5	0.5 ± 0.2	0.8 ± 0.2
Volatile Organics by Charcoal	0.006 ± 0.004	NA	NA
Dose Site Tissue	1.2 ± 0.2	0.6 ± 0.3	0.1 ± 0.1
Residual Carcass ^g	0.3 ± 0.2	0.2 ± 0.1	0.1
Collected Tissues	0.068 ± 0.007	0.022 ± 0.001	0.001 ± 0.002
Total % Dose Absorbed	6.6 ± 0.8	1.9 ± 0.6	1.1 ± 0.5
Total % Dose Unabsorbed (appliance, skinwash, etc.)	65.4 ± 3.0	84.1^h ± 0.9	95.5^h ± 3.2
Total Recovery of Administered Radiolabel (%)	72.0 ± 3.8	86.0 ± 0.7	96.6 ± 2.7

^a Values are mean ± SD for four rats unless stated otherwise. Study duration of 72 h.

^b Urine included the cage and methanol rinse.

^c Urine included the cage rinse.

^d Urine included hexane cage and methanol rinse. The cage rinse was not included since the value was not significantly different from background.

^e Value is mean for one rat.

^f Value is mean for two rats.

^g % dose recovered in the residual carcass less the % dose measured as individual tissues: skin, muscle, adipose, and blood. For Study B, value is mean for two rats.

^h Oxidized charcoal cover within the unabsorbed analysis was corrected for the oxidizer efficiency.

NA Not Applicable

Table 4

Concentration of Radiolabel in Tissues of Male Fischer 344 Rats following Dermal Exposure to [¹⁴C]DIPC

Dose	4.1 mg/kg — Study A ^a (72 h)		
Tissue Name	ng-eq DIPC per g Tissue	Tissue Blood Ratio	Percent Dose in Total Tissue ^c
Adipose	20.3 ± 2.2	1.40 ± 0.16	0.031 ± 0.004
Bladder	34.8 ± 7.2	2.40 ± 0.51	0.00029 ± 0.00006
Blood	14.5 ± 0.9	unity	0.0164 ± 0.0007
Brain	16.3 ± 1.1	1.12 ± 0.04	0.0030 ± 0.0002
Heart	24.7 ± 2.9	1.70 ± 0.18	0.0019 ± 0.0001
Kidney	61.1 ± 7.6	4.20 ± 0.41	0.011 ± 0.001
Liver	48.7 ± 9.1	3.33 ± 0.50	0.045 ± 0.006
Lung	27.2 ± 4.2	1.88 ± 0.34	0.0025 ± 0.0005
Muscle	13.4 ± 0.7	0.92 ± 0.09	0.14 ± 0.01
Skin ^d	65.4 ± 17.3	4.48 ± 1.00	0.24 ± 0.06
Spleen	26.3 ± 2.9	1.81 ± 0.18	0.0013 ± 0.0001
Testes	13.1 ± 0.7	0.90 ± 0.03	0.0037 ± 0.0002
Dose	3.9 mg/kg — Study A' ^a (72 h)		
Tissue Name	ng-eq DIPC per g Tissue	Tissue Blood Ratio	Percent Dose in Total Tissue ^c
Adipose	11.1 ± 3.2	NA	0.019 ± 0.005
Bladder	NA	NA	NA
Blood	NA	NA	NA
Brain	3.8 ± 0.4	NA	0.00077 ± 0.00006
Heart	6.3 ± 2.2	NA	0.0005 ± 0.0001
Kidney	17.7 ± 1.7	NA	0.0038 ± 0.0003
Liver	16.1 ± 0.6	NA	0.0156 ± 0.0008
Lung	5.7 ± 1.4	NA	0.0006 ± 0.0002
Muscle ^e	3.9	NA	0.05
Skin ^d	25.9 ± 18.5	NA	0.11 ± 0.07
Spleen ^f	8.0	NA	0.0004
Testes	2.6 ± 0.8	NA	0.0008 ± 0.0002
Dose	40.9 mg/kg — Study B ^b (72 h)		
Tissue Name	ng-eq DIPC per g Tissue	Tissue Blood Ratio	Percent Dose in Total Tissue ^c
Adipose	88	NA	0.014
Bladder	NA	NA	NA
Blood	NA	NA	NA
Brain	24.7	NA	0.0005
Heart	42.9	NA	0.0004
Kidney	154.2	NA	0.003
Liver	NA	NA	NA
Lung	47.9	NA	0.0004
Muscle	NA	NA	NA
Skin ^{d,e}	86.6	NA	0.03
Spleen	NA	NA	NA
Testes	22.2	NA	0.0006

^a Values are mean ± SD for four rats unless stated otherwise. See Table 1 for actual delivered dose.

^b Values are mean for one rat unless stated otherwise. See Table 1 for actual delivered dose.

^c Percent dose was calculated using the following values for the mass of total tissue, expressed as percent of body weight: adipose, 7.0%; blood, 5.2%; muscle, 48.0%; and skin, 17.0%.

^d Excludes dose site skin.

^e Values are mean for two rats.

^f Values are mean for three rats.

NA Not Applicable. DPM values for aliquots were not significantly different from background. (note: TBR cannot be calculated when concentrations in blood were not above background levels.)

Table 5

**Distribution of Radioactivity in Male B6C3F₁ Mice
after Dermal Exposure to [¹⁴C]DIPC**

Route	6.9 mg/kg - Study E ^a	80.6 mg/kg - Pilot 3 ^c	82.2 mg/kg - Pilot 4 ^d
% Dose Absorbed			
Urine ^e	0.7 ± 0.4	0.02	0.01 ± 0.01
Feces	0.4 ± 0.2	NA	NA
Exhaled CO ₂	0.8 ± 0.1	NC	NC
Volatile Organics by EtOH	0.3 ± 0.1	NC	NC
Volatile Organics by Charcoal	0.005 ± 0.001	NC	NC
Dose Site Tissue	0.13 ± 0.03	NC	NC
Residual Carcass ^b	0.01 ± 0.01	0.04	0.44 ± 0.65
Collected Tissues	0.014 ± 0.001	NC	NC
Total % Dose Absorbed	2.3 ± 0.4	0.1	0.5 ± 0.6
% Dose Unabsorbed			
Charcoal Cover	1.7 ± 0.5	82.4	90.5 ± 0.2
Skin Wash	0.8 ± 0.5	0.0	0.1 ± 0.2
Appl./Elastoplast Extract	1.6 ± 0.3	0.0	0.1 ± 0.1
Instrument Swipe	0.01 ± 0.01	0.01	0.01 ± 0.01
Hexane Cage Rinse	0.01 ± 0.00	NC	NC
Total % Dose Unabsorbed	4.1 ± 0.6	82.4	90.7 ± 0.2
Total Recovery of Administered Radiolabel (%)	6.5 ± 0.6	82.5	91.2 ± 0.8

^a Values are mean ± SD for four mice. Study duration of 72 h.

^b % dose recovered in the residual carcass less the % dose measured as individual tissues: skin, muscle, adipose, and blood. For Pilots 3 and 4, no tissues were collected.

^c Values are mean for two mice. Study duration of 6 h.

^d Values are mean ± SD for three mice. Study duration of 6 h.

^e Pilots 3 and 4 urine included cage rinse. Study E urine included cage rinse as well as methanol rinse.

NA Not Applicable. Value was not significantly different from background. Therefore % dose absorbed could not be calculated.

NC Not Collected.

Table 6
Cumulative Excretion of Radioactivity by Male B6C3F₁ Mice following
Dermal Exposure to [¹⁴C]DIPC

6.9 mg/kg Study E^a

End of Collection Period (h)	Cumulative Percent of Dose Recovered in:					
	Urine ^b	Feces	Volatile Organics Trapped by EtOH	Volatile Organics Trapped by Charcoal	CO ₂	Total
4	NC	NC	0.16 ± 0.10	0.004 ± 0.002	0.7 ± 0.1	0.9 ± 0.2
8	0.3 ± 0.3	NC	0.2 ± 0.1	0.005 ± 0.001	0.7 ± 0.1	1.2 ± 0.3
24	0.5 ± 0.3	0.2 ± 0.2	0.3 ± 0.1	0.005 ± 0.001	0.8 ± 0.1	1.8 ± 0.3
48	0.6 ± 0.3	0.3 ± 0.2	0.3 ± 0.1	0.005 ± 0.001	0.8 ± 0.1	2.0 ± 0.3
72	0.7 ± 0.4	0.4 ± 0.2	0.3 ± 0.1	0.005 ± 0.001	0.8 ± 0.1	2.2 ± 0.3

^a Values are mean ± SD for four mice. See Table 1 for actual delivered dose.

^b Urine at 8, 24, and 48 h included the methanol rinse for that time interval. 72 h urine included the cage rinse.

NC No collection was scheduled for this time interval.

Table 7

**Concentration of Radiolabel in Tissues of Male B6C3F₁ Mice
following Dermal Exposure to [¹⁴C]DIPC**

Dose	6.9 mg/kg — Study E ^a (72 h)		
Tissue Name	ng-eq DIPC per g Tissue	Tissue Blood Ratio	Percent Dose in Total Tissue ^b
Adipose	21.0 ± 17.1	7.76 ± 7.01	0.03 ± 0.02
Bladder	11.8 ± 3.6	4.19 ± 1.65	0.00020 ± 0.00007
Blood	2.91 ± 0.62	Unity	0.0031 ± 0.0006
Brain	5.63 ± 0.40	1.98 ± 0.30	0.0014 ± 0.0001
Heart	7.52 ± 0.73	2.63 ± 0.28	0.00060 ± 0.00009
Kidney	13.3 ± 2.0	4.64 ± 0.55	0.0033 ± 0.0005
Liver	9.63 ± 1.48	3.37 ± 0.61	0.0071 ± 0.0007
Lung	5.49 ± 0.21	1.94 ± 0.31	0.00051 ± 0.00004
Muscle	4.46 ± 0.59	1.56 ± 0.27	0.028 ± 0.003
Skin ^c	31.4 ± 13.7	11.6 ± 6.0	0.06 ± 0.03
Spleen	4.67 ± 0.32	1.66 ± 0.37	0.00018 ± 0.00001
Testes	3.49 ± 0.59	1.23 ± 0.29	0.00040 ± 0.00005

^a Values are mean ± SD for four mice. See Table 1 for actual delivered dose.

^b Percent dose was calculated using the following values for the mass of total tissue, expressed as percent of body weight: adipose, 9.6%; blood, 7.6%; muscle, 45.2%; and skin, 14.4%.

^c Excludes dose site skin

Table 8

Cumulative Excretion of Radioactivity by Male B6C3F₁ Mice following
 iv Exposure to [¹⁴C]DIPC
 7.6 mg/kg Study G^a

End of Collection Period (h)	Cumulative Percent of Dose Recovered in:				
	Urine	Feces	Volatile Organics	CO ₂	Total
4	NC	NC	6.68 ± 1.66	7.87 ± 2.63	14.6 ± 4.10
8	3.09 ^b ± 6.89	NC	7.50 ± 1.59	24.9 ± 1.76	35.0 ± 7.71
24	26.1 ± 7.79	6.26 ± 3.55	7.78 ± 1.63	28.0 ± 1.43	69.0 ± 6.20
48	36.8 ^c ± 8.05	10.6 ± 5.59	7.92 ± 1.62	29.2 ± 1.44	84.4 ± 3.58

^a Values are mean ± SD for six mice unless stated otherwise. See Table 1 for actual delivered dose.

^b Values are mean ± SD for five mice.

^c Included the cage rinse result.

NC No collection was scheduled for this time interval.

Table 9

**Concentration of Radiolabel in Tissues of Male B6C3F₁ Mice
following iv Exposure to [¹⁴C]DIPC**

Dose	7.6 mg/kg — Study G ^a (48 h)		
Tissue Name	ng-eq DIPC per g Tissue	Tissue Blood Ratio	Percent Dose in Total Tissue ^b
Adipose	1770 ± 692	8.18 ± 3.73	2.36 ± 0.895
Bladder	486 ± 60.5	2.21 ± 0.378	0.00810 ± 0.00165
Blood	222 ± 19.9	Unity	0.235 ± 0.0264
Brain	581 ± 221	2.60 ± 0.868	0.142 ± 0.0484
Heart	1140 ± 536	5.10 ± 2.18	0.0965 ± 0.0758
Kidney	2040 ± 280	9.28 ± 1.85	0.458 ± 0.0718
Liver	508 ± 46.9	2.28 ± 0.0691	0.411 ± 0.0581
Lung	456 ± 86.9	2.05 ± 0.309	0.0445 ± 0.0187
Muscle	415 ± 125	1.87 ± 0.577	2.62 ± 0.849
Skin	448 ± 122	2.04 ± 0.635	0.899 ± 0.262
Spleen	371 ± 19.7	1.68 ± 0.158	0.0160 ± 0.00315
Testes	223 ± 30.7	1.00 ± 0.149	0.0245 ± 0.00425

^a Values are mean ± SD for six mice. See Table 1 for actual delivered dose.

^b Percent dose was calculated using the following values for the mass of total tissue, expressed as percent of body weight: adipose, 9.6%; blood, 7.6%; muscle, 45.2%; and skin, 14.4%.

Table 10

Concentrations of Radiolabel in Mouse Blood following Intravenous Administration of [¹⁴C]DIPC at 7.8 mg/kg (Study H)^a

Timepoint	ng-eq/g in Blood					Mean ± SD
	Set-1	Set-2	Set-3	Set-4		
1 min	6920	8710	8060	_b	7900 ^c ± 906	
4 min	2850	601	140	823	1100 ± 1200	
8 min	3780	5110	_b	4590	4490 ^c ± 672	
20 min	3900	1230	4430	3580	3290 ± 1410	
1 hr	10300	5640	2000	NA	5970 ^c ± 4150	
2 hr	4230	4610	4780	4820	4610 ± 265	
8 hr	638	615	523	755	633 ± 95.4	
24 hr	418	314	314	302	337 ± 54.3	
48 hr	198	203	230	_b	210 ^c ± 17.0	

Timepoint	% Dose in Blood					Mean ± SD
	M-1	M-2	M-3	M-4		
1 min	6.64	8.35	7.87	_b	7.62 ^c ± 0.883	
4 min	2.84	0.617	0.131	0.820	1.10 ± 1.19	
8 min	3.69	5.00	_b	4.48	4.39 ^c ± 0.657	
20 min	3.74	1.20	4.03	3.63	3.15 ± 1.31	
1 hr	10.0	4.97	1.95	NA	5.65 ^c ± 4.08	
2 hr	4.05	4.55	4.67	4.56	4.46 ± 0.275	
8 hr	0.611	0.624	0.501	0.762	0.624 ± 0.107	
24 hr	0.404	0.310	0.313	0.268	0.324 ± 0.0575	
48 hr	0.192	0.194	0.226	_b	0.204 ^c ± 0.0194	

^a Values are mean ± SD for four mice unless stated otherwise. (Note: Subsequent timepoints involved different mice as serial sacrifice was necessary for blood collection). See Table 1 for actual delivered dose.

^b Animal did not get an iv dose due to dosing error.

^c Values are mean ± SD for three mice.

NA Not Applicable. Value was not significantly different from background. Therefore ng-eq/g in blood and % dose in blood could not be calculated.