ADME NTP Study S0084 4-Vinylcyclohexene

The contract laboratory used the abbreviation VCH for the test article.
4-Vinylcyclohexene diepoxide (CASRN 106-87-6), abbreviated VCD, was also studied.
Sex/Species: adult female F344 rats and B6C3F1 mice (for both studies).
Vehicles: oral, not specified; dermal, acetone.

VCH CASRN 100-40-3

Radiolabeled VCH with carbon-14 in the ethylene moiety; [^{14}C]4-Vinylcyclohexene
Radiolabeled VCD with carbon-14 in the ethylene moiety; [^{14}C]4-Vinylcyclohexene diepoxide

Studies Performed:

- Single oral gavage administration of 400 mg/kg 4-vinylcyclohexene (VCH) to fasted rats and mice with sacrifice 48 hours (hr) postdose.

- Single dermal administration of 50 mg/rat or 5 mg/mouse 4-vinylcyclohexene diepoxide (VCD) to rats and mice with covered dose site and sacrifice 24 hours (hr) postdose. Both these doses approximate 250 mg/kg.

These studies investigated species difference in the susceptibililty of ovarian tumors induced by VCH and its metabolite VCD.

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Table 1

Cumulative Percentage of Dose Excreted (as total ^{14}C) by

Mice at Various Time After Administration of VCH (400 mg/kg p.o.)[a]

Route	0.5 hr n = 6	1 hr n = 6	4 hr n = 4	8 hr n = 4	24 hr n = 6	48 hr n = 3
Urine			22.15 ± 5.57	27.78 ± 16.67	58.66 ± 4.45	60.63 ± 1.90
Expired Air	4.64 ± 1.21	12.53 ± 3.44	27.68 ± 7.01	32.03 ± 7.43	29.40 ± 4.54	28.06 ± 6.48
Feces[b]		1.91 ± 0.51	2.29 ± 0.22	2.68 ± 0.84	3.20 ± 2.80	1.92 ± 0.32
Recovery[c]					96.92 ± 3.80	90.81 ± 7.67

[a] Data presented as mean ± standard deviation.

[b] Includes intestinal contents.

[c] Recovery includes ^{14}C remaining in tissues.

Table 2

Cumulative Percentage of Dose Excreted (as total ^{14}C) by

Rats at Various Times after Administration of VCH (400 mg/kg p.o.)[a]

Route	0.5 hr	1 hr	4 hr	8 hr	24 hr	48 hr
		n = 3	n = 3	n = 3	n = 6	n = 3
Urine			4.16 ± 1.53	12.26 ± 3.39	28.38 ± 5.38	41.95 ± 9.22
Expired Air		0.76 ± 0.15	13.36 ± 1.00	28.91 ± 1.08	33.90 ± 4.71	34.61 ± 4.59
Feces[b]					5.61 ± 0.95	4.22 ± 1.81
Recovery[c]						79.12 ± 12.55

[a] Data presented as mean ± standard deviation.

[b] Includes intestinal contents.

[c] Expired air only collected only for the 48 hour animals. Recovery includes ^{14}C remaining in tissues.

Table 3

Effect of Time on the Percentage of Dose (as total ^{14}C) in Tissues of Mice Administered VCH (400 mg/kg p.o.)[a]

	1 hr	4 hr	8 hr	24 hr	48 hr
Blood	0.57 ± 0.09	0.45 ± 0.08	0.30 ± 0.10	0.04 ---[b]	0.03 ± 0.00
Brain	0.20 ± 0.10	0.14 ± 0.02	0.07 ± 0.04	0.01 ± 0.00	0.01 ± 0.00
Adipose	3.89 ± 1.77	2.52 ± 1.84	1.17 ± 0.73	0.06 ± 0.02	0.06 ± 0.01
Kidney	0.47 ± 0.07	0.35 ± 0.08	0.22 ± 0.07	0.02 ± 0.00	0.01 ± 0.00
Large Intestine	0.35 ± 0.05	0.52 ± 0.16	0.36 ± 0.17	0.03 ± 0.01	0.01 ± 0.01
Liver	1.57 ± 0.68	1.18 ± 0.33	0.74 ± 0.28	0.19 ± 0.05	0.09 ± 0.01
Lung	0.11 ± 0.01	0.07 ± 0.02	0.03 ± 0.01	0.01 ± 0.00	0.00 ± 0.00
Muscle	4.82 ± 1.44	3.12 ± 0.70	2.13 ± 0.75	0.30 ± 0.29	0.11 ± 0.01
Skin	2.79 ± 0.72	1.38 ± 0.59	1.06 ± 0.60	N.D.[c]	0.04 ± 0.01
Small Intestine	2.89 ± 1.11	1.59 ± 0.74	0.79 ± 0.29	0.07 ± 0.03	0.05 ± 0.01
Spleen	0.03 ± 0.00	0.03 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00
Stomach	6.03 ± 2.27	2.68 ± 1.32	0.45 ± 0.57	0.07 ± 0.03	0.05 ± 0.01
	n = 3	n = 4	n = 4	n = 3	n = 3

[a] Data presented as mean ± standard deviation

[b] n = 2

[c] Not determined

Table 4

Effect of Time on the Concentration (nmol ^{14}C VCH Equivalents per mg Tissue)

In Tissues of Mice Administered VCH (400 mg/kg p.o.)[a]

	1 hr	4 hr	8 hr	24 hr	48 hr
Blood	0.26 ± 0.04	0.22 ± 0.03	0.15 ± 0.05	0.02 ---[b]	0.02 ± 0.00
Brain	0.33 ± 0.15	0.25 ± 0.03	0.13 ± 0.06	0.03 ± 0.02	0.01 ± 0.00
Adipose	1.40 ± 0.77	1.01 ± 0.65	0.45 ± 0.29	0.02 ± 0.01	0.02 ± 0.00
Kidney	1.10 ± 0.11	0.93 ± 0.16	0.67 ± 0.23	0.05 ± 0.01	0.04 ± 0.00
Large Intestine	0.93 ± 0.22	1.38 ± 0.40	1.37 ± 0.63	0.08 ± 0.03	0.06 ± 0.02
Liver	1.37 ± 0.85	0.93 ± 0.20	0.67 ± 0.23	0.15 ± 0.02	0.10 ± 0.01
Lung	0.50 ± 0.08	0.29 ± 0.03	0.25 ± 0.08	0.04 ± 0.01	0.03 ± 0.00
Muscle	0.40 ± 0.12	0.29 ± 0.05	0.18 ± 0.06	0.03 ± 0.02	0.01 ± 0.00
Skin	0.73 ± 0.22	0.33 ± 0.16	0.28 ± 0.16	N.D.[c]	0.01 ± 0.00
Small Intestine	2.85 ± 1.21	1.74 ± 0.62	0.93 ± 0.27	0.10 ± 0.04	0.05 ± 0.01
Spleen	0.35 ± 0.05	0.29 ± 0.06	0.24 ± 0.03	0.04 ± 0.00	0.04 ± 0.00
Stomach	26.50 ± 9.43	15.38 ± 5.18	3.31 ± 2.96	0.06 ± 0.03	0.07 ± 0.03
	n = 3	n = 4	n = 4	n = 3	n = 3

[a] Data presented as mean ± standard deviation.

[b] n = 2

[c] Not determined

Table 5

Effect of Time on the Percentage of Dose (as total ^{14}C) in Tissues of Rats Administered VCH (400 mg/kg p.o.)

	1 hr	4 hr	8 hr	24 hr	48 hr
Blood	0.76 ± 0.08[a]	0.65 ± 0.14	0.63 ± 0.09	0.35 ± 0.15	0.17 ± 0.02
Brain	0.09 ± 0.02	0.09 ± 0.04	0.05 ± 0.01	0.02 ± 0.01	0.01 ± 0.00
Adipose	2.04 ± 0.17	9.27 ± 3.29	8.86 ± 3.09	3.43 ± 2.53	1.44 ± 0.70
Kidney	0.16 ± 0.03	0.21 ± 0.05	0.19 ± 0.03	0.07 ± 0.01	0.02 ± 0.00
Large Intestine	0.20 ± 0.20	0.51 ± 0.31	0.28 ± 0.09	0.09 ± 0.03	0.02 ± 0.01
Liver	0.98 ± 0.08	0.89 ± 0.25	0.70 ± 0.04	0.28 ± 0.00	0.09 ± 0.02
Lung	0.08 ± 0.02	0.08 ± 0.05	0.05 ± 0.01	0.02 ± 0.02	0.00 ± 0.00
Muscle	3.02 ± 0.55	3.44 ± 0.70	3.55 ± 0.59	1.05 ± 0.54	0.30 ± 0.04
Skin	2.31 ± 0.66	3.46 ± 0.86	6.27 ± 3.68	1.14 ± 0.47	0.17 ± 0.05
Small Intestine	2.31 ± 0.27	2.69 ± 1.51	1.32 ± 1.05	0.19 ± 0.13	0.04 ± 0.01
Spleen	0.03 ± 0.02	0.03 ± 0.00	0.01 ± 0.00	0.01 ± 0.00	0.00 ± 0.00
Stomach	2.89 ± 0.20	0.68 ± 0.32	0.12 ± 0.06	0.04 ± 0.00	0.01 ± 0.00
	n = 3	n = 3	n = 3	n = 3	n = 3

[a] Data presented as mean ± standard deviation.

Table 6

Effect of Time on the Concentration (nmole ^{14}C-VCH Equivalents per mg Tissue)

In Tissues of Rats Administered VCH (400 mg/kg p.o.)

	1 hr	4 hr	8 hr	24 hr	48 hr
Blood	0.31 ± 0.03[a]	0.27 ± 0.06	0.26 ± 0.04	0.14 ± 0.06	0.07 ± 0.01
Brain	0.40 ± 0.06	0.40 ± 0.12	0.21 ± 0.03	0.080 ± 0.04	0.02 ± 0.00
Adipose	1.08 ± 0.09	4.90 ± 1.74	4.68 ± 1.63	1.81 ± 1.34	0.76 ±0.37
Kidney	0.81 ± 0.14	1.08 ± 0.25	0.94 ± 0.10	0.36 ± 0.05	0.07 ± 0.01
Large Intestine	0.70 ± 0.60	2.08 ± 1.11	1.22 ± 0.53	0.39 ± 0.13	0.06 ± 0.02
Liver	1.18 ± 0.09	1.20 ± 0.41	0.82 ± 0.04	0.27 ± 0.00	0.09 ± 0.01
Lung	0.57 ± 0.15	0.49 ± 0.30	0.32 ± 0.08	0.12 ± 0.04	0.03 ± 0.00
Muscle	0.22 ± 0.04	0.25 ± 0.05	0.26 ± 0.04	0.08 ± 0.04	0.02 ± 0.00
Skin	0.53 ± 0.15	1.02 ± 0.20	1.18 ± 1.05	0.26 ± 0.11	0.04 ± 0.01
Small Intestine	4.18 ± 0.35	5.04 ± 2.63	2.41 ± 1.66	0.41 ± 0.28	0.12 ± 0.03
Spleen	0.49 ± 0.30	0.41 ± 0.05	0.24 ± 0.06	0.10 ± 0.03	0.04 ± 0.01
Stomach	14.66 ± 2.39	4.37 ± 2.22	1.50 ± 0.84	0.25 ± 0.08	0.06 ± 0.01
	n = 3	n = 3	n = 3	n = 3	n = 3

[a] Data presented as mean ± standard deviation.

Table 7

Effect of Time on the Percentage of Dose (as total ^{14}C) in the Ovaries of Rats and Mice Administered VCH (400 mg/kg p.o.)

	1 hr	4 hr	8 hr	24 hr	48 hr
Rat Ovary	0.0096 ± 0.0017a	0.0184 ± 0.0104	0.0145 ± 0.0028	0.0027 ± 0.0028	0.0009 ± 0.0002
	n = 3	n = 3	n = 3	n = 3	n = 3
Mouse Ovary	0.0304 ± 0.0044	0.0254 ± 0.0142	0.0081 ± 0.0040	0.0005 ± 0.0002	0.0008 ± 0.0001
	n = 3	n = 4	n = 4	n = 3	n = 3

[a] Data presented as mean ± standard deviation.

Table 8

Effect of Tome on the Concentration (nmol 14C-VCH Equivalents per mg Tissue) In the Ovaries of Rats and Mice Administered VCH (400 mg/kg p.o.)

	1 hr	4 hr	8 hr	24 hr	48 hr
Rat Ovary	0.72 ± 0.09a	1.28 ± 0.62	1.00 ± 0.12	0.21 ± 0.09	0.07 ± 0.03
	n = 3	n = 3	n = 3	n = 3	n = 3
Mouse Ovary	1.10 ± 0.35	1.18 ± 0.58	0.34 ± 0.22	0.08 ± 0.03	0.04 ± 0.01
	n = 3	n = 4	n = 4	n = 3	n = 3

[a] Data presented as mean ± standard deviation.

VCD Table 1

Elimination of Radioactivity in 24 hr Following Dermal Administration of ^{14}C-Vinylcyclohexene Diepoxide [a] to Female $B_6C_3F_1$ Mice

Sample Analyzed	Percentage of Applied Dose
Urine	19.82 +/- 3.43 [b]
Feces	1.62 +/- 0.83
Expired CO_2	1.81 +/- 0.28
Depot	67.03 +/- 3.96
Cage Wash	1.10 +/- 0.69
Tissues	5.54 +/- 2.12
Recovery	97.09 +/- 4.81

[a] Dose: 5 mg/mouse (approximately 250 mg/kg).
[b] Means +/- SD of five animals.

VCD Table 2

Elimination of Radioactivity in 24 hr Following Dermal Administration of ^{14}C-Vinylcyclohexene Diepoxide [a] to Female Fischer 344 Rats

Sample Analyzed	Percentage of Applied Dose
Urine	17.29 +/- 0.46 [b]
Feces	3.86 +/- 2.43
Expired CO_2	1.17 +/- 0.15
Depot	72.37 +/- 5.49
Cage Wash	0.71 +/- 0.28
Tissues	4.78 +/- 1.00
Recovery	100.23 +/- 5.86

[a] Dose: 50 mg/rat (approximately 250 mg/kg).
[b] Means +/- SD of four animals.

VCD Table 3

Distribution of Radioactivity in Female $B_6C_3F_1$ Mice at 24 hr Following Dermal Administration of ^{14}C-Vinylcyclohexene Diepoxide [a]

	% of Dose	nmol ^{14}C VCD-equivalents / gm Tissue	T/B [b]
Blood	0.34 +/- 0.09[c]	83.0 +/- 19.8	1.00
Brain	0.09 +/- 0.02	74.3 +/- 12.4	0.92 +/- 0.17
Fat	0.52 +/- 0.15	98.6 +/- 25.6	1.20 +/- 0.17
GI Contents	0.20 +/- 0.08	----------[f]	----------[f]
Heart	0.02 +/- 0.02	62.7 +/- 10.3	0.77 +/- 0.14
Kidney	0.06 +/- 0.01	62.5 +/- 7.2	0.77 +/- 0.14
Large Intestine	0.07 +/- 0.01	66.1 +/- 12.2	0.81 +/- 0.11
Liver	0.41 +/- 0.11	122.8 +/- 20.5	1.56 +/- 0.35
Lung	0.04 +/- 0.01	77.9 +/- 8.8	0.99 +/- 0.19
Muscle	0.95 +/- 0.09	39.8 +/- 3.7	0.51 +/- 0.13
Ovary	0.01 +/- 0.00	222.7 +/- 73.6	2.79 +/- 0.95
Skin	0.36 +/- 0.10	46.6 +/- 10.2	0.57 +/- 0.08
Skin Site[d]	1.39 +/- 1.31	----------[f]	----------[f]
Small Intestine	0.19 +/- 0.02	75.4 +/- 4.0	0.96 +/- 0.31
Spleen	0.02 +/- 0.01	94.2 +/- 19.1	1.16 +/- 0.40
Stomach	0.03 +/- 0.01	56.8 +/- 6.3	0.76 +/- 0.15
Thymus	0.01 +/- 0.01	130.4 +/- 37.0	1.61 +/- 0.40
Total	4.69 +/- 0.98		

[a] Dose: 5 mg/mouse (approximately 250 mg/kg).
[b] Ratio ^{14}C in tissue to ^{14}C in blood.
[c] Mean +/- SD of four animals.
[d] Percentage of dose remaining at the site of application 24 hr after administration.
[f] Not calculated.

VCD Table 4

Distribution of Radioactivity in Female Fischer 344 Rats at 24 hr Following Dermal Administration of ^{14}C-Vinylcyclohexene Diepoxide [a]

	% of Dose	nmol ^{14}C VCD-equivalents / gm Tissue	T/B [b]
Blood	0.27 +/- 0.05[c]	58.7 +/- 11.1	1.00
Brain	0.03 +/- 0.01	61.2 +/- 10.6	1.06 +/- 0.23
Fat	0.13 +/- 0.08	36.0 +/- 22.9	0.58 +/- 0.32
GI Contents	0.39 +/- 0.18	----------[f]	----------[f]
Heart	0.01 +/- 0.01	29.3 +/- 2.0	0.50 +/- 0.06
Kidney	0.03 +/- 0.01	83.3 +/- 14.0	1.46 +/- 0.40
Large Intestine	0.03 +/- 0.01	84.1 +/- 28.7	1.44 +/- 0.50
Liver	0.11 +/- 0.01	70.2 +/- 8.2	1.22 +/- 0.24
Lung	0.01 +/- 0.00	43.4 +/- 1.5	0.76 +/- 0.14
Muscle	0.44 +/- 0.03	17.2 +/- 1.6	0.30 +/- 0.06
Ovary	0.00 +/- 0.00	31.5 +/- 7.3	0.54 +/- 0.12
Skin	0.21 +/- 0.05	25.9 +/- 6.1	0.47 +/- 0.18
Skin Site[d]	3.06 +/- 1.10	----------[f]	----------[f]
Small Intestine	0.04 +/- 0.03	59.4 +/- 23.0	1.01 +/- 0.33
Spleen	0.00 +/- 0.01	40.4 +/- 4.7	0.70 +/- 0.12
Stomach	0.01 +/- 0.01	28.8 +/- 4.2	0.50 +/- 0.10
Thymus	0.00 +/- 0.00	34.5 +/- 1.6	0.60 +/- 0.12
Total	4.78 +/- 1.00		

[a] Dose: 50 mg/rat (approximately 250 mg/kg).
[b] Ratio ^{14}C in tissue to ^{14}C in blood.
[c] Mean +/- SD of four animals.
[d] Percentage of dose remaining at the site of application 24 hr after administration.
[f] Not calculated.