

## ADME NTP Study S0768 Urethane

The contract laboratory used the synonym ethyl carbamate and EC as the abbreviation for the test article.

Animals used were adult male Fischer 344 (F-344) rats and B6C3F<sub>1</sub> mice.

CASRN 51-79-6

Start date: possibly 10/00/1989

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Studies Performed:

### First study:

- 4.75 mg/kg [<sup>14</sup>C]urethane intravenous dose in rats and mice with CO<sub>2</sub>, volatile breath, urine, and feces collected up to 24 or 48 hours post dosing and analyzed for <sup>14</sup>C radioactivity. Animals were pretreated with 5% ethanol in their drinking water for 0, 1, 3, 10, and 30 days and allowed access to 5% ethanol drinking water until sacrifice.
- 119 mg/kg [<sup>14</sup>C]urethane intravenous dose in rats and mice with CO<sub>2</sub>, volatile breath, urine, and feces collected up to 24 or 48 hours post dosing and analyzed for <sup>14</sup>C radioactivity. Animals were pretreated with 5% ethanol in their drinking water for 0, 1, 3, 10, and 30 days and allowed access to 5% ethanol drinking water until sacrifice.

### Second study:

- Single oral gavage administration of 3,000 mg/kg ethanol with percent ethanol concentrations determined in blood and plasma of rats and mice.
- Oral administration of initial dose of 3,000 mg/kg ethanol to rats followed by a second dose of 2,000 mg/kg 7.45 hours after the first dose. Percent ethanol concentrations determined in blood and plasma of rats.
- Oral administration of initial dose of 3,000 mg/kg ethanol to mice followed by a second dose of 3,000 mg/kg 4.45 hours after the first dose. Percent ethanol concentrations determined in blood and plasma of mice.

### Third study:

- Oral administration of initial dose of 3,000 mg/kg ethanol to rats followed by a second dose of 2,000 mg/kg ethanol 7.45 hours after the first dose and 15 minutes after the first dose by a 4.75 mg/kg intravenous dose of [<sup>14</sup>C]urethane. <sup>14</sup>C radioactivity as CO<sub>2</sub> and volatile organic levels in breath and in urine and feces was determined.

- Oral administration of initial dose of 3,000 mg/kg ethanol to rats followed by a second dose of 2,000 mg/kg ethanol 7.45 hours after the first dose and 15 minutes after the first dose by a 119 mg/kg intravenous dose of [<sup>14</sup>C]urethane. <sup>14</sup>C radioactivity as CO<sub>2</sub> and volatile organic levels in breath and in urine and feces was determined.
- Oral administration of initial oral gavage dose of 3,000 mg/kg ethanol to mice followed 15 minutes later by an 4.75 mg/kg [<sup>14</sup>C]urethane intravenous dose and 4.45 hours later by a second oral dose of 3,000 mg/kg. <sup>14</sup>C radioactivity as CO<sub>2</sub> and volatile organic levels in breath was determined.
- Oral administration of initial oral gavage dose of 3,000 mg/kg ethanol to mice followed 15 minutes later by an 119 mg/kg [<sup>14</sup>C]urethane intravenous dose and 4.45 hours later by a second oral dose of 3,000 mg/kg. <sup>14</sup>C radioactivity as CO<sub>2</sub> and volatile organic levels in breath determined.

#### **Fourth study:**

- Oral gavage administration of 3,000 mg/kg/day ethanol to rats and mice for 10 days, followed by a 24 hour washout period, then dosing with 4.75 mg/kg [<sup>14</sup>C]urethane. <sup>14</sup>C radioactivity as CO<sub>2</sub> and volatile organic levels in breath and in urine and feces was determined.
- Oral gavage administration of 3,000 mg/kg/day ethanol to rats and mice for 10 days, followed by a 24 hour washout period, then dosing with 119 mg/kg [<sup>14</sup>C]urethane. <sup>14</sup>C radioactivity as CO<sub>2</sub> and volatile organic levels in breath and in urine and feces was determined.

Four studies were carried out. Three were designed to investigate the metabolism of urethane after pretreatment with ethanol using an unsaturating dose (4.75 mg/kg) or a saturating dose (119 mg/kg) of urethane. The other study was designed to investigate the pharmacokinetics of ethanol after oral dosing.

In the first study, animals of both species were pretreated with ethanol in drinking water at a 5% concentration (v/v). Of the two control groups, one group was treated with [<sup>14</sup>C]urethane at the beginning of the study (Day 0) and the other control animals were kept for 30 days under similar conditions but without ethanol pretreatment and then treated with [<sup>14</sup>C]urethane intravenously. The other groups were dosed with [<sup>14</sup>C]urethane intravenously following consumption of 5% ethanol drinking water for 1, 3, 10, or 30 days.

The second study was a preliminary study to investigate the pharmacokinetics of ethanol in plasma and blood cells of rats and mice following a single and double dose

administration of ethanol by gavage (30% w/v in water). Animals were not treated with urethane in the pharmacokinetic study. The single dose study allowed selection of the level and time of administration of the second dose to achieve and maintain alcohol concentration levels in plasma and blood cells for 10-12 hours at at least 50% of the maximum value after the initial dose in order to ensure that after dosing with [<sup>14</sup>C]urethane, the ethanol level in the plasma was high enough to affect the metabolism of urethane (if any).

The third study was a co-administration study to investigate the effect of ethanol present in plasma and blood cells at a relatively high concentration on the metabolism of urethane in rats and mice.

The fourth study was to determine the effect on the metabolism of urethane after pretreatment with ethanol by gavage at 3,000 mg/kg/day for 10 days, followed by a 24 hour washout period, in rats and mice. At 24 hours after the last ethanol dose, [<sup>14</sup>C]urethane was intravenously administered. The major objective was to determine if ethanol pretreatment induced the metabolism of [<sup>14</sup>C]urethane without the presence of ethanol in plasma at the time of urethane administration.

The total recovery of [<sup>14</sup>C]urethane following intravenous administration (Table 35) shows a high recovery value obtained in the low dose rats of the third study which is probably due to cross-contamination.

Note that in the figure captions for Tables 7, 8, 15, 16, 23, 24, 31, and 32, the second dose in rats was administered 7.45 min [sic] after the first dose. However, the text in the report has the time as 7.45 hours after the first dose with the [<sup>14</sup>C]urethane dose given 15 minutes after the first dose in both the compound administration and the results section.

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**Table 1: Concentration of ethanol (as %) in plasma and blood cells of rats and mice following a single oral administration of ethanol at 3000 mg/kg**

Time (hr)	Concentration of ethanol <sup>a</sup>			
	Plasma	Blood cells	Plasma	Blood cells
	<i>Rats</i>		<i>Mice</i>	
0.25	0.131 ± 0.025	0.092 ± 0.017	0.222 ± 0.055	0.131 ± 0.019
0.5	0.161 ± 0.054	0.101 ± 0.029	0.261 ± 0.018	0.158 ± 0.010
1	0.167 ± 0.042	0.096 ± 0.028	0.284 ± 0.028	0.157 ± 0.017
2	0.181 ± 0.087	0.103 ± 0.042	0.254 ± 0.025	0.150 ± 0.010
3	0.188 ± 0.091	0.113 ± 0.060	0.194 ± 0.100 <sup>b</sup>	0.122 ± 0.012
4	0.179 ± 0.103	0.105 ± 0.067	0.137 ± 0.027	0.080 ± 0.012
5	0.153 ± 0.098	0.088 ± 0.064	0.116 ± 0.09 <sup>b</sup>	0.030 ± 0.018
6	0.121 ± 0.093	0.073 ± 0.059	0.006 ± 0.007	0.002 ± 0.003
7	0.099 ± 0.086	0.060 ± 0.055	0.00 ± 0.00 <sup>b</sup>	0.0 ± 0.0
8	0.072 ± 0.069	0.045 ± 0.045	0.001 ± 0.001	0.0 ± 0.0

<sup>a</sup>Mean ± SD of data from four animals, unless otherwise indicated.

<sup>b</sup>Mean of data from three animals.

**Table 2: Concentration of ethanol (as %) in plasma and blood cells of rats and mice following p.o. administration of two doses of ethanol**

Time (hr)	Concentration of ethanol <sup>a</sup>			
	Plasma	Blood cells	Plasma	Blood cells
	<i>Rats</i> <sup>b</sup>		<i>Mice</i> <sup>c</sup>	
0.25	0.138 ± 0.043	0.095 ± 0.016 <sup>d</sup>	0.314 ± 0.148 <sup>d</sup>	0.128 ± 0.012
1	0.146 ± 0.041	0.097 ± 0.027	0.220 ± 0.046	0.160 ± 0.028
2	0.150 ± 0.064	0.108 ± 0.052	0.210 ± 0.060	0.136 ± 0.036
4	0.135 ± 0.059	0.081 ± 0.040	0.102 ± 0.017	0.062 ± 0.010
6	0.096 ± 0.063	0.065 ± 0.054 <sup>d</sup>	0.319 ± 0.043	0.169 ± 0.116
8	0.186 ± 0.087	0.099 ± 0.061	0.384 ± 0.032	0.283 ± 0.032
9	0.329 ± 0.062 <sup>d</sup>	0.194 ± 0.054	0.307 ± 0.035	0.211 ± 0.028
10	0.231 ± 0.111	0.163 ± 0.082	0.338 ± 0.124	0.176 ± 0.032
11	0.246 ± 0.119	0.150 ± 0.074	0.177 ± 0.060	0.121 ± 0.034
12	0.210 ± 0.101	0.157 ± 0.071	0.029 ± 0.055	0.025 ± 0.032

<sup>a</sup>Mean ± SD of data from four animals, unless otherwise indicated.

<sup>b</sup>Rats received an initial dose of 3000 mg/kg. At 7.45 after the first dose, they received a second dose of 2000 mg/kg.

<sup>c</sup>Mice received two 3000 mg/kg doses, 4.45 hr apart.

<sup>d</sup>Mean of data from three animals.

**Table 3: Exhalation of  $^{14}\text{CO}_2$  following administration of [ $^{14}\text{C}$ ]EC at 4.75 mg/kg i.v. to rats pretreated with 5% ethanol in drinking water for 0-30 days**

Time (hr)	Ethanol pretreatment (days)					Control <sup>a</sup>
	0	1	3	10	30	
	<i>Dose excreted (%)<sup>b</sup></i>					
0-2	19.7 ± 2.1	37.3 ± 4.0	28.8 ± 3.1	42.9 ± 8.4	29.3 ± 19.0	14.5 ± 4.6
2-4	22.2 ± 1.2	22.5 ± 6.3	25.5 ± 2.3	17.4 ± 3.7	18.5 ± 5.6	17.3 ± 3.6
4-6	19.5 ± 2.9	11.1 ± 1.6	14.4 ± 2.7	11.7 ± 3.4	13.7 ± 1.6	17.2 ± 7.5
6-8	12.6 ± 3.5	5.2 ± 1.3	5.2 ± 0.8	6.9 ± 2.3	5.5 ± 1.9	9.6 ± 0.7
8-10	8.3 ± 2.8	3.1 ± 0.9	3.4 ± 0.8	3.6 ± 1.1	2.7 ± 1.2	5.6 ± 1.2
10-12	5.4 ± 1.9	1.3 ± 0.8	1.8 ± 0.4	1.0 ± 0.4	1.6 ± 0.6	3.5 ± 0.3
12-24	4.1 ± 1.7	1.9 ± 0.7	1.9 ± 0.5	2.2 ± 0.8	1.9 ± 0.7	4.2 ± 0.7
	<i>Dose excreted (cumulative %)</i>					
0-2	19.7 ± 2.1	37.3 ± 4.0	28.8 ± 3.1	42.9 ± 8.4	29.3 ± 19.0	14.5 ± 4.6
0-4	41.9 ± 1.9	59.9 ± 8.7	54.2 ± 1.6	60.2 ± 11.0	47.8 ± 24.4	31.9 ± 7.7
0-6	61.4 ± 3.3	71.0 ± 7.8	68.6 ± 1.4	71.9 ± 12.6	61.4 ± 25.4	49.0 ± 5.3
0-8	74.0 ± 5.7	76.2 ± 6.8	73.8 ± 1.8	78.8 ± 14.0	66.9 ± 27.1	58.6 ± 4.7
0-10	82.3 ± 8.2	79.3 ± 6.0	77.2 ± 2.2	82.4 ± 14.7	69.5 ± 28.1	64.2 ± 3.7
0-12	87.7 ± 9.8	80.5 ± 5.3	79.0 ± 2.5	83.4 ± 14.8	71.1 ± 28.6	67.8 ± 3.6
0-24	91.8 ± 11.3	82.4 ± 4.6	80.9 ± 2.6	85.6 ± 15.4	73.1 ± 29.2	72.0 ± 3.2

<sup>a</sup>These animals were kept for 30 days without ethanol pretreatment, then dosed with EC.

<sup>b</sup>Mean ± SD of data from four animals.

**Table 4: Exhalation of  $^{14}\text{CO}_2$  following administration of [ $^{14}\text{C}$ ]EC at 119 mg/kg i.v. to rats pretreated with 5% ethanol in drinking water for 0-30 days**

Time (hr)	Ethanol pretreatment (days)					Control <sup>a</sup>
	0	1	3	10	30	
	<i>Dose excreted (%)<sup>b</sup></i>					
0-2	6.4 ± 1.0	6.6 ± 1.1	6.1 ± 1.2	10.2 ± 2.2	8.1 ± 1.2	4.3 ± 0.3
2-4	7.5 ± 1.1	12.1 ± 0.4	11.7 ± 1.2	11.9 ± 2.0	9.6 ± 0.7	7.2 ± 2.0
4-6	8.3 ± 5.1	13.5 ± 0.6	15.4 ± 2.6	13.7 ± 3.0	12.6 ± 1.7	7.8 ± 1.3
6-8	10.9 ± 3.7	13.1 ± 1.4	10.5 ± 0.8	12.3 ± 2.3	11.1 ± 0.7	9.6 ± 2.0
8-10	11.0 ± 2.4	12.4 ± 0.9	13.4 ± 1.5	15.0 ± 2.2	9.5 ± 0.6	7.8 ± 0.9
10-12	9.7 ± 2.2	6.7 ± 2.9	9.8 ± 1.1	6.5 ± 1.8	9.1 ± 0.7	8.9 ± 1.3
12-24	27.9 ± 8.5	10.7 ± 4.9	12.7 ± 6.5	13.0 ± 5.6	16.3 ± 5.1	15.8 ± 12.0
	<i>Dose excreted (cumulative %)</i>					
0-2	6.4 ± 1.0	6.6 ± 1.1	6.1 ± 1.2	10.2 ± 2.2	8.1 ± 1.2	4.3 ± 0.3
0-4	13.9 ± 1.0	18.7 ± 1.2	17.8 ± 2.0	22.1 ± 3.3	17.6 ± 1.5	11.4 ± 2.2
0-6	22.1 ± 4.5	32.2 ± 1.2	33.2 ± 4.4	35.8 ± 3.8	30.2 ± 3.0	19.2 ± 3.4
0-8	33.1 ± 4.9	45.3 ± 2.5	43.8 ± 5.1	48.1 ± 5.3	41.2 ± 3.6	28.7 ± 5.3
0-10	44.0 ± 7.0	57.7 ± 3.0	57.1 ± 6.6	63.1 ± 7.1	50.8 ± 4.1	36.5 ± 6.2
0-12	53.7 ± 9.1	64.4 ± 1.4	66.9 ± 6.5	69.6 ± 7.7	59.9 ± 4.6	45.3 ± 7.5
0-24	81.6 ± 8.6	75.1 ± 5.6	79.5 ± 2.4	82.6 ± 12.0	76.1 ± 5.3	61.2 ± 17.8

<sup>a</sup>These animals were kept for 30 days without ethanol pretreatment, then dosed with EC.

<sup>b</sup>Mean ± SD of data from four animals.

**Table 5: Exhalation of  $^{14}\text{CO}_2$  following administration of [ $^{14}\text{C}$ ]EC at 4.75 mg/kg i.v. to mice pretreated with 5% ethanol in drinking water for 0-30 days**

Time (hr)	Ethanol pretreatment (days)					Control <sup>a</sup>
	0	1	3	10	30	
	<i>Dose excreted (%)<sup>b</sup></i>					
0-2	82.2 ± 4.1	71.2 ± 8.9	75.2 ± 1.4	68.9 ± 4.7	68.0 ± 9.3	75.0 ± 3.1
2-4	10.0 ± 0.1	9.4 ± 8.5	6.3 ± 1.1	13.0 ± 3.0	6.8 ± 0.7	7.1 ± 0.6
4-6	2.7 ± 0.2	1.0 ± 0.4	1.0 ± 0.5	1.5 ± 0.2	0.9 ± 0.2	1.1 ± 0.1
6-8	2.1 ± 0.1	0.4 ± 0.1	0.0 ± 0.0 <sup>c</sup>	0.7 ± 0.1	0.3 ± 0.2	0.0 ± 0.0
8-10	2.0 ± 0.1	0.3 ± 0.2	0.0 ± 0.0	0.6 ± 0.2	0.2 ± 0.3	0.0 ± 0.0
10-12	1.9 ± 0.1	0.1 ± 0.2	0.0 ± 0.0	0.6 ± 0.1	0.3 ± 0.3	0.0 ± 0.0
12-24	2.3 ± 0.1	0.5 ± 0.1	0.4 ± 0.5	0.7 ± 0.1	0.4 ± 0.5	0.0 ± 0.0
	<i>Dose excreted (cumulative %)</i>					
0-2	82.2 ± 4.1	71.2 ± 8.9	75.2 ± 1.4	68.9 ± 4.7	68.0 ± 9.3	75.0 ± 3.1
0-4	92.2 ± 4.0	80.6 ± 2.8	81.5 ± 1.0	81.9 ± 2.7	74.8 ± 9.5	82.1 ± 3.6
0-6	94.9 ± 4.3	81.5 ± 2.9	82.5 ± 0.9	84.0 ± 3.0	75.6 ± 9.5	83.2 ± 3.7
0-8	97.0 ± 4.2	81.9 ± 3.0	82.5 ± 0.9	84.0 ± 3.0	76.0 ± 9.5	83.2 ± 3.7
0-10	99.0 ± 4.2	82.2 ± 3.1	82.5 ± 0.9	84.6 ± 3.1	76.2 ± 9.7	83.2 ± 3.7
0-12	100.9 ± 4.2	82.3 ± 3.2	82.5 ± 0.9	85.1 ± 3.1	76.4 ± 9.9	83.2 ± 3.7
0-24	103.1 ± 4.2	82.8 ± 3.2	82.9 ± 1.1	85.8 ± 3.2	76.8 ± 10.3	83.2 ± 3.7

<sup>a</sup>These animals were kept for 30 days without ethanol pretreatment, then dosed with EC.

<sup>b</sup>Mean ± SD of data from four animals.

<sup>c</sup>Samples in which radioactivity was less than twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.



**Table 6: Exhalation of  $^{14}\text{CO}_2$  following administration of [ $^{14}\text{C}$ ]EC at 119 mg/kg i.v. to mice pretreated with 5% ethanol in drinking water for 0-30 days**

Time (hr)	Ethanol pretreatment (days)					Control <sup>a</sup>
	0	1	3	10	30	
	<i>Dose excreted (%)<sup>b</sup></i>					
0-2	29.0 ± 1.4	46.0 ± 2.5	38.3 ± 2.8	64.9 ± 5.2	54.1 ± 3.4	31.9 ± 1.4
2-4	46.1 ± 4.0	23.8 ± 4.2	23.5 ± 3.1	8.3 ± 2.6	20.8 ± 2.5	32.9 ± 2.5
4-6	15.3 ± 2.0	2.7 ± 0.8	4.5 ± 1.9	0.9 ± 0.2	1.6 ± 0.4	13.3 ± 1.6
6-8	2.2 ± 0.7	0.6 ± 0.1	1.3 ± 0.3	0.5 ± 0.1	0.5 ± 0.0	1.6 ± 0.4
8-10	1.0 ± 0.6	0.0 ± 0.0 <sup>c</sup>	0.9 ± 0.1	0.3 ± 0.2	0.1 ± 0.2	0.6 ± 0.4
10-12	1.0 ± 0.8	0.0 ± 0.0	0.7 ± 0.2	0.3 ± 0.2	0.1 ± 0.2	0.2 ± 0.4
12-24	1.9 ± 1.5	0.3 ± 0.3	1.2 ± 0.2	0.2 ± 0.3	0.2 ± 0.3	0.2 ± 0.4
	<i>Dose excreted (cumulative %)</i>					
0-2	29.0 ± 1.4	46.0 ± 2.5	38.3 ± 2.8	64.9 ± 5.2	54.1 ± 3.4	31.9 ± 1.4
0-4	75.1 ± 2.7	69.8 ± 2.0	61.7 ± 3.2	73.3 ± 7.7	74.9 ± 2.6	64.8 ± 3.9
0-6	90.4 ± 0.8	72.5 ± 2.7	66.3 ± 3.2	74.2 ± 7.9	76.5 ± 2.5	78.1 ± 5.0
0-8	92.6 ± 1.0	73.1 ± 2.8	67.6 ± 2.9	74.7 ± 7.9	76.9 ± 2.6	79.7 ± 5.1
0-10	93.6 ± 0.9	73.1 ± 2.8	68.4 ± 2.9	75.0 ± 8.1	77.0 ± 2.4	80.3 ± 5.2
0-12	94.6 ± 1.4	73.1 ± 2.8	69.1 ± 3.0	75.3 ± 8.3	77.1 ± 2.4	80.5 ± 5.1
0-24	96.5 ± 2.3	73.3 ± 2.9	70.3 ± 3.0	75.5 ± 8.1	77.3 ± 2.2	80.6 ± 5.1

<sup>a</sup>These animals were kept for 30 days without ethanol pretreatment, then dosed with EC.

<sup>b</sup>Mean ± SD of data from four animals.

<sup>c</sup>Samples in which radioactivity was less than twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.

**Table 7: Exhalation of  $^{14}\text{CO}_2$  by rats after ethanol treatment at a dose level of 3000 mg/kg p.o. for 0, 1 and 10 days and administration of [ $^{14}\text{C}$ ]EC at 4.75 mg/kg i.v.<sup>a</sup>**

Time (hr)	Day		
	1 <sup>b</sup>	10 <sup>c</sup>	Control
	<i>Dose excreted (%)</i>		
0-2	2.0 ± 0.1	24.4 ± 2.1	19.7 ± 2.1
2-4	2.2 ± 0.5	19.8 ± 1.4	22.2 ± 1.2
4-6	8.3 ± 5.5	12.4 ± 1.1	19.5 ± 2.9
6-8	17.6 ± 1.5	9.3 ± 0.4	12.6 ± 3.5
8-10	2.8 ± 0.3	3.6 ± 0.5	8.3 ± 2.8
10-12	1.7 ± 0.2	2.5 ± 0.7	5.4 ± 1.9
12-24	43.5 ± 6.3	2.9 ± 1.0	4.1 ± 1.7
24-32 <sup>d</sup>	1.0 ± 0.2	0.0 ± 0.0 <sup>e</sup>	f
32-48 <sup>d</sup>	0.8 ± 0.7	0.0 ± 0.0	f
	<i>Dose excreted (cumulative %)</i>		
0-2	2.0 ± 0.1	24.4 ± 2.1	19.7 ± 2.1
0-4	4.2 ± 0.6	44.2 ± 3.6	41.9 ± 1.9
0-6	12.4 ± 6.0	56.6 ± 3.2	61.4 ± 3.3
0-8	30.0 ± 6.3	65.8 ± 3.5	74.0 ± 5.7
0-10	32.7 ± 6.2	69.4 ± 3.1	82.3 ± 8.2
0-12	34.4 ± 6.3	71.9 ± 2.9	87.7 ± 9.8
0-24	77.9 ± 1.6	74.8 ± 2.6	91.8 ± 11.3
0-32 <sup>d</sup>	79.6 ± 1.1	73.9 ± 2.4	f
0-48 <sup>d</sup>	80.4 ± 1.6	73.9 ± 2.4	f

<sup>a</sup>Mean ± SD of data from four rats, unless otherwise indicated.

<sup>b</sup>Rats were given two doses of ethanol, the first 3000 mg/kg, the second 2000 mg/kg, administered at 7.45 min after the first dose. [ $^{14}\text{C}$ ]EC was administered at 15 min following the first ethanol dose.

<sup>c</sup>Rats were dosed with ethanol by gavage at 3000 mg/kg/day for 10 days, followed by a 24 hr washout period, then dosed with [ $^{14}\text{C}$ ]EC.

<sup>d</sup>Mean of data from three rats.

<sup>e</sup>Samples in which radioactivity was below twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.

<sup>f</sup>Control rats were sacrificed at 24 hr.

**Table 8: Exhalation of  $^{14}\text{CO}_2$  by rats after ethanol treatment at a dose level of 3000 mg/kg p.o. for 0, 1 and 10 days and administration of [ $^{14}\text{C}$ ]EC at 119 mg/kg i.v.<sup>a</sup>**

Time (hr)	Day		
	1 <sup>b</sup>	10 <sup>c</sup>	Control
	<i>Dose excreted (%)</i>		
0-2	1.6 ± 0.1	7.0 ± 0.6	6.4 ± 1.0
2-4	1.4 ± 0.2	9.5 ± 0.5	7.5 ± 1.1
4-6	1.4 ± 0.1	8.2 ± 0.9	8.3 ± 5.1
6-8	1.7 ± 0.3	12.5 ± 1.1	10.9 ± 3.7
8-10	1.0 ± 0.1	9.3 ± 0.4	11.0 ± 2.4
10-12	1.3 ± 0.1	11.8 ± 0.9	9.7 ± 2.2
12-24	61.2 ± 3.3	11.8 ± 8.1	27.9 ± 8.5
24-32 <sup>d</sup>	2.9 ± 2.1	0.2 ± 0.3	f
32-48 <sup>d</sup>	0.4 ± 0.9	0.0 ± 0.0 <sup>e</sup>	f
	<i>Dose excreted (cumulative %)</i>		
0-2	1.6 ± 0.1	7.0 ± 0.6	6.4 ± 1.0
0-4	3.0 ± 0.3	16.6 ± 0.8	13.9 ± 1.0
0-6	4.4 ± 0.4	24.7 ± 1.7	22.1 ± 4.5
0-8	6.0 ± 0.6	37.2 ± 2.6	33.1 ± 4.9
0-10	7.0 ± 0.8	46.5 ± 2.8	44.0 ± 7.0
0-12	8.4 ± 0.8	58.3 ± 2.7	53.7 ± 9.1
0-24	69.6 ± 4.0	70.1 ± 7.9	81.6 ± 8.6
0-32 <sup>d</sup>	72.4 ± 3.8	74.1 ± 2.2	f
0-48 <sup>d</sup>	72.8 ± 4.2	74.1 ± 2.2	f

<sup>a</sup>Mean ± SD of data from four rats, unless otherwise indicated.

<sup>b</sup>Rats were given two doses of ethanol, the first 3000 mg/kg, the second 2000 mg/kg, administered at 7.45 min after the first dose. [ $^{14}\text{C}$ ]EC was administered at 15 min following the first ethanol dose.

<sup>c</sup>Rats were dosed with ethanol by gavage at 3000 mg/kg/day for 10 days, followed by a 24 hr washout period, then dosed with [ $^{14}\text{C}$ ]EC.

<sup>d</sup>Mean of data from three rats.

<sup>e</sup>Samples in which radioactivity was below twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.

<sup>f</sup>Control rats were sacrificed at 24 hr.

**Table 9: Exhalation of  $^{14}\text{CO}_2$  by mice after ethanol treatment at a dose level of 3000 mg/kg p.o. for 0, 1 and 10 days and administration of [ $^{14}\text{C}$ ]EC at 4.75 mg/kg i.v.<sup>a</sup>**

Time (hr)	Day		
	1 <sup>b</sup>	10 <sup>c</sup>	Control
	<i>Dose excreted (%)</i>		
0-2	1.8 ± 0.2	61.8 ± 3.3	72.6 ± 3.8
2-4	2.0 ± 0.6	8.3 ± 0.8	8.8 ± 4.8
4-6	5.3 ± 7.2	1.1 ± 0.2	1.2 ± 0.4
6-8	1.1 ± 0.3	0.0 ± 0.0 <sup>d</sup>	0.3 ± 0.3
8-10	1.5 ± 0.5	0.0 ± 0.0	0.0 ± 0.0
10-12	40.4 ± 27.9	0.0 ± 0.0	0.0 ± 0.0
12-24	19.6 ± 24.0	0.0 ± 0.0	0.2 ± 0.0
24-32	0.6 ± 0.5	0.0 ± 0.0	0.0 ± 0.0
32-48	0.1 ± 0.2	0.0 ± 0.0	0.0 ± 0.0
	<i>Dose excreted (cumulative %)</i>		
0-2	1.8 ± 0.2	61.8 ± 3.3	72.6 ± 3.8
0-4	3.8 ± 0.8	70.1 ± 3.4	81.4 ± 1.2
0-6	9.0 ± 8.0	71.2 ± 3.2	82.5 ± 1.5
0-8	10.1 ± 8.2	71.2 ± 3.2	82.8 ± 1.8
0-10	11.6 ± 8.0	71.2 ± 3.2	82.8 ± 1.8
0-12	52.0 ± 29.5	71.2 ± 3.2	82.8 ± 1.8
0-24	71.5 ± 5.9	71.2 ± 3.2	82.8 ± 1.8
0-32	72.1 ± 5.5	71.2 ± 3.2	82.8 ± 1.8
0-48	72.2 ± 5.6	71.2 ± 3.2	82.8 ± 1.8

<sup>a</sup>Mean ± SD of data from four mice.

<sup>b</sup>Mice were given two 3000 mg/kg doses of ethanol by gavage, separated by 4.45 hr. [ $^{14}\text{C}$ ]EC was administered at 15 min following the first ethanol dose.

<sup>c</sup>Mice were treated with ethanol by gavage at 3000 mg/kg/day for 10 days, followed by a 24 hr washout period, then dosed with [ $^{14}\text{C}$ ]EC.

<sup>d</sup>Samples in which radioactivity was less than twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.

**Table 10: Exhalation of  $^{14}\text{CO}_2$  by mice after ethanol treatment at a dose level of 3000 mg/kg p.o. for 0, 1 and 10 days and administration of [ $^{14}\text{C}$ ]EC at 119 mg/kg i.v.<sup>a</sup>**

Time (hr)	Day		
	1 <sup>b</sup>	10 <sup>c</sup>	Control
	<i>Dose excreted (%)</i>		
0-2	2.4 ± 0.1	25.5 ± 11.7	41.6 ± 1.9
2-4	2.2 ± 0.4	34.9 ± 11.0	31.7 ± 1.0
4-8	4.8 ± 4.1	4.3 ± 1.4	10.7 ± 1.4
6-8	1.1 ± 0.3	0.0 ± 0.0 <sup>d</sup>	2.0 ± 0.5
8-10	1.2 ± 0.2	0.0 ± 0.0	0.7 ± 0.1
10-12	11.1 ± 14.2	0.0 ± 0.0	0.2 ± 0.3
12-24	48.0 ± 17.8	0.0 ± 0.0	0.2 ± 0.4
24-32	1.2 ± 0.5	0.0 ± 0.0	0.0 ± 0.0
32-48	0.2 ± 0.5	0.0 ± 0.0	0.0 ± 0.0
	<i>Dose excreted (cumulative %)</i>		
0-2	2.4 ± 0.1	25.5 ± 11.7	41.6 ± 1.9
0-4	4.6 ± 0.4	60.3 ± 3.6	73.3 ± 2.6
0-6	9.4 ± 4.4	64.7 ± 2.4	64.0 ± 1.6
0-8	10.5 ± 4.6	64.7 ± 2.4	86.0 ± 1.4
0-10	11.7 ± 4.9	64.7 ± 2.4	86.6 ± 1.4
0-12	22.8 ± 18.9	64.7 ± 2.4	86.8 ± 1.4
0-24	70.8 ± 4.4	64.7 ± 2.4	87.0 ± 1.1
0-32	71.9 ± 4.4	64.7 ± 2.4	87.0 ± 1.1
0-48	72.2 ± 4.7	64.7 ± 2.4	87.0 ± 1.1

<sup>a</sup>Mean ± SD of data from four mice.

<sup>b</sup>Mice were given two 3000 mg/kg doses of ethanol by gavage, separated by 4.45 hr. [ $^{14}\text{C}$ ]EC was administered at 15 min following the first ethanol dose.

<sup>c</sup>Mice were treated with ethanol by gavage at 3000 mg/kg/day for 10 days, followed by a 24 hr washout period, then dosed with [ $^{14}\text{C}$ ]EC.

<sup>d</sup>Samples in which radioactivity was less than twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.

**Table 11: Exhalation of <sup>14</sup>C radioactivity as volatile organics following administration of [<sup>14</sup>C]EC at 4.75 mg/kg i.v. to rats pretreated with 5% ethanol in drinking water for 0-30 days**

Time (hr)	Ethanol pretreatment (days)					Control <sup>a</sup>
	0	1	3	10	30	
	<i>Dose excreted (%)<sup>b</sup></i>					
0-2	0.3 ± 0.2	0.3 ± 0.1	0.1 ± 0.0	0.2 ± 0.1	0.1 ± 0.0	0.0 ± 0.1
2-4	0.4 ± 0.2	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.0 ± 0.1
4-6	0.5 ± 0.3	0.1 ± 0.1	0.1 ± 0.1	0.0 ± 0.0 <sup>c</sup>	0.1 ± 0.1	0.0 ± 0.1
6-8	0.5 ± 0.3	0.0 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
8-10	0.4 ± 0.3	0.0 ± 0.1	0.0 ± 0.0	0.0 ± 0.1	0.0 ± 0.1	0.0 ± 0.0
10-12	0.4 ± 0.3	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
12-24	1.1 ± 0.6	0.1 ± 0.1	0.0 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.0
	<i>Dose excreted (cumulative %)</i>					
0-2	0.3 ± 0.2	0.3 ± 0.1	0.1 ± 0.0	0.2 ± 0.1	0.1 ± 0.0	0.0 ± 0.1
0-4	0.7 ± 0.4	0.4 ± 0.1	0.2 ± 0.0	0.2 ± 0.2	0.2 ± 0.1	0.1 ± 0.1
0-6	1.1 ± 0.6	0.4 ± 0.2	0.2 ± 0.1	0.2 ± 0.2	0.2 ± 0.1	0.1 ± 0.2
0-8	1.6 ± 0.9	0.5 ± 0.2	0.2 ± 0.1	0.2 ± 0.2	0.2 ± 0.1	0.1 ± 0.2
0-10	2.0 ± 1.2	0.5 ± 0.2	0.2 ± 0.1	0.3 ± 0.2	0.3 ± 0.1	0.1 ± 0.2
0-12	2.4 ± 1.5	0.5 ± 0.2	0.2 ± 0.1	0.3 ± 0.2	0.3 ± 0.1	0.1 ± 0.2
0-24	3.5 ± 2.1	0.5 ± 0.3	0.3 ± 0.1	0.3 ± 0.2	0.4 ± 0.2	0.2 ± 0.2

<sup>a</sup>These animals were kept for 30 days without ethanol pretreatment, then dosed with EC.

<sup>b</sup>Mean ± SD of data from four rats.

<sup>c</sup>Samples in which radioactivity was below twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.

**Table 12: Exhalation of <sup>14</sup>C radioactivity as volatile organics following administration of [<sup>14</sup>C]EC at 119 mg/kg i.v. to rats pretreated with 5% ethanol in drinking water for 0-30 days**

Time (hr)	Ethanol pretreatment (days)					Control <sup>a</sup>
	0	1	3	10	30	
	<i>Dose excreted (%)<sup>b</sup></i>					
0-2	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.1 ± 0.0	0.0 ± 0.1 <sup>c</sup>	0.1 ± 0.1
2-4	0.2 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.0 ± 0.1	0.0 ± 0.1	0.1 ± 0.1
4-6	0.2 ± 0.1	0.1 ± 0.1	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.1
6-8	0.3 ± 0.1	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1
8-10	0.3 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1
10-12	0.3 ± 0.0	0.1 ± 0.1	0.0 ± 0.1	0.0 ± 0.0	0.1 ± 0.1	0.1 ± 0.1
12-24	0.7 ± 0.3	0.2 ± 0.1	0.0 ± 0.1	0.1 ± 0.1	0.2 ± 0.1	0.1 ± 0.1
	<i>Dose excreted (cumulative %)</i>					
0-2	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.1 ± 0.0	0.0 ± 0.1	0.1 ± 0.1
0-4	0.4 ± 0.2	0.3 ± 0.2	0.3 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1
0-6	0.6 ± 0.2	0.4 ± 0.2	0.4 ± 0.1	0.2 ± 0.0	0.2 ± 0.1	0.2 ± 0.2
0-8	0.8 ± 0.1	0.5 ± 0.2	0.5 ± 0.1	0.3 ± 0.1	0.2 ± 0.1	0.3 ± 0.2
0-10	1.1 ± 0.2	0.6 ± 0.2	0.5 ± 0.2	0.4 ± 0.1	0.3 ± 0.2	0.4 ± 0.3
0-12	1.3 ± 0.3	0.7 ± 0.2	0.6 ± 0.2	0.4 ± 0.1	0.4 ± 0.2	0.4 ± 0.3
0-24	2.0 ± 0.6	0.9 ± 0.3	0.6 ± 0.1	0.6 ± 0.1	0.5 ± 0.2	0.6 ± 0.3

<sup>a</sup>These animals were kept for 30 days without ethanol pretreatment, then dosed with EC.

<sup>b</sup>Mean of data from four rats.

<sup>c</sup>Samples in which radioactivity was below twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.

**Table 13: Exhalation of <sup>14</sup>C radioactivity as volatile organics following administration of [<sup>14</sup>C]EC at 4.75 mg/kg i.v. to mice pretreated with 5% ethanol in drinking water for 0-30 days**

Time (hr)	Ethanol pretreatment (days)					Control <sup>a</sup>
	0	1	3	10	30	
	<i>Dose excreted (%)<sup>b</sup></i>					
0-2	0.5 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.0 ± 0.0 <sup>c</sup>	0.2 ± 0.0
2-4	0.1 ± 0.1	0.0 ± 0.1	0.0 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1
4-6	0.1 ± 0.1	0.1 ± 0.1	0.0 ± 0.1	0.0 ± 0.1	0.0 ± 0.1	0.0 ± 0.0
6-8	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.1	0.0 ± 0.0
8-10	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.1	0.0 ± 0.0	0.0 ± 0.0
10-12	0.0 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
12-24	0.0 ± 0.0	0.0 ± 0.1	0.0 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	<i>Dose excreted (cumulative %)</i>					
0-2	0.5 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.0 ± 0.0	0.2 ± 0.0
0-4	0.5 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.0	0.1 ± 0.1	0.3 ± 0.1
0-6	0.6 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.1 ± 0.1	0.3 ± 0.1
0-8	0.6 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.1 ± 0.0	0.3 ± 0.1
0-10	0.6 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.0	0.1 ± 0.0	0.3 ± 0.1
0-12	0.6 ± 0.2	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.0	0.1 ± 0.0	0.3 ± 0.1
0-24	0.6 ± 0.2	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.0	0.1 ± 0.0	0.3 ± 0.1

<sup>a</sup>These animals were kept for 30 days without ethanol pretreatment, then dosed with EC.

<sup>b</sup>Mean of data from four mice.

<sup>c</sup>Samples in which radioactivity was below twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.



**Table 14: Exhalation of <sup>14</sup>C radioactivity as volatile organics following administration of [<sup>14</sup>C]EC at 119 mg/kg i.v. to mice pretreated with 5% ethanol in drinking water for 0-30 days**

Time (hr)	Ethanol pretreatment (days)					Control <sup>a</sup>
	0	1	3	10	30	
	<i>Dose excreted (%)<sup>b</sup></i>					
0-2	0.3 ± 0.2	0.2 ± 0.1	0.2 ± 0.1	0.1 ± 0.1	0.1 ± 0.2	0.2 ± 0.2
2-4	0.2 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.2 ± 0.0	0.3 ± 0.1
4-6	0.1 ± 0.1	0.0 ± 0.1 <sup>c</sup>	0.0 ± 0.1	0.0 ± 0.0	0.1 ± 0.1	0.1 ± 0.1
6-8	0.0 ± 0.1	0.0 ± 0.0	0.0 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.1
8-10	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
10-12	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
12-24	0.1 ± 0.1	0.0 ± 0.0	0.0 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.1
	<i>Dose excreted (cumulative %)</i>					
0-2	0.3 ± 0.2	0.2 ± 0.1	0.2 ± 0.1	0.1 ± 0.1	0.1 ± 0.2	0.2 ± 0.2
0-4	0.5 ± 0.2	0.3 ± 0.1	0.3 ± 0.1	0.2 ± 0.1	0.3 ± 0.2	0.5 ± 0.2
0-6	0.5 ± 0.2	0.3 ± 0.1	0.3 ± 0.1	0.2 ± 0.1	0.4 ± 0.2	0.6 ± 0.2
0-8	0.6 ± 0.2	0.3 ± 0.1	0.3 ± 0.1	0.2 ± 0.1	0.4 ± 0.2	0.7 ± 0.3
0-10	0.6 ± 0.2	0.3 ± 0.1	0.3 ± 0.1	0.2 ± 0.1	0.4 ± 0.2	0.7 ± 0.3
0-12	0.6 ± 0.2	0.3 ± 0.1	0.4 ± 0.1	0.2 ± 0.1	0.4 ± 0.2	0.7 ± 0.3
0-24	0.6 ± 0.2	0.3 ± 0.1	0.4 ± 0.2	0.2 ± 0.1	0.4 ± 0.2	0.7 ± 0.3

<sup>a</sup>These animals were kept for 30 days without ethanol pretreatment, then dosed with EC.

<sup>b</sup>Mean of data from four animals.

<sup>c</sup>Samples in which radioactivity was below twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.

**Table 15: Exhalation of  $^{14}\text{C}$  radioactivity as volatile organics by rats after ethanol treatment at a dose level of 3000 mg/kg p.o. for 0, 1 and 10 days and administration of [ $^{14}\text{C}$ ]EC at 4.75 mg/kg I.v.<sup>a</sup>**

Time (hr)	Day		
	1 <sup>b</sup>	10 <sup>c</sup>	Control
	<i>Dose excreted (%)</i>		
0-2	0.1 ± 0.1	0.2 ± 0.1	0.3 ± 0.2
2-4	0.1 ± 0.1	0.1 ± 0.1	0.4 ± 0.2
4-6	0.1 ± 0.1	0.0 ± 0.0 <sup>d</sup>	0.5 ± 0.3
8-8	0.1 ± 0.0	0.0 ± 0.0	0.5 ± 0.3
8-10	0.1 ± 0.1	0.0 ± 0.0	0.4 ± 0.3
10-12	0.2 ± 0.1	0.0 ± 0.0	0.4 ± 0.3
12-24	0.3 ± 0.1	0.0 ± 0.0	1.1 ± 0.6
24-32 <sup>e</sup>	0.1 ± 0.0	0.0 ± 0.0	f
32-48 <sup>e</sup>	0.1 ± 0.1	0.1 ± 0.1	f
	<i>Dose excreted (cumulative %)</i>		
0-2	0.1 ± 0.1	0.2 ± 0.1	0.3 ± 0.2
0-4	0.2 ± 0.1	0.2 ± 0.1	0.7 ± 0.4
0-6	0.3 ± 0.1	0.2 ± 0.1	1.1 ± 0.6
0-8	0.4 ± 0.1	0.2 ± 0.1	1.6 ± 0.9
0-10	0.6 ± 0.1	0.2 ± 0.1	2.0 ± 1.2
0-12	0.7 ± 0.1	0.2 ± 0.1	2.4 ± 1.5
0-24	1.0 ± 0.1	0.2 ± 0.1	3.5 ± 2.1
0-32 <sup>e</sup>	1.0 ± 0.1	0.2 ± 0.1	f
0-48 <sup>e</sup>	1.2 ± 0.1	0.3 ± 0.1	f

<sup>a</sup>Mean ± SD of data from four rats, unless otherwise indicated.

<sup>b</sup>Rats were given two doses of ethanol, the first 3000 mg/kg, the second 2000 mg/kg, administered at 7.45 min after the first dose. [ $^{14}\text{C}$ ]EC was administered at 15 min following the first ethanol dose.

<sup>c</sup>Rats were dosed with ethanol by gavage at 3000 mg/kg/day for 10 days, followed by a 24 hr washout period, then dosed with [ $^{14}\text{C}$ ]EC.

<sup>d</sup>Samples in which radioactivity was less than twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.

<sup>e</sup>Mean of data from three rats.

<sup>f</sup>Control rats were sacrificed at 24 hr.

**Table 16: Exhalation of  $^{14}\text{C}$  radioactivity as volatile organics by rats after ethanol treatment at a dose level of 3000 mg/kg p.o. for 0, 1 and 10 days and administration of [ $^{14}\text{C}$ ]EC at 119 mg/kg i.v.<sup>g</sup>**

Time (hr)	Day		
	1 <sup>b</sup>	10 <sup>e</sup>	Control
	<i>Dose excreted (%)</i>		
0-2	0.0 ± 0.1 <sup>d</sup>	0.0 ± 0.1	0.2 ± 0.1
2-40	0.1 ± 0.1	0.1 ± 0.1	0.2 ± 0.1
4-60	0.1 ± 0.1	0.1 ± 0.1	0.2 ± 0.1
6-80	0.1 ± 0.0	0.1 ± 0.1	0.3 ± 0.1
6-100	0.2 ± 0.1	0.0 ± 0.1	0.3 ± 0.1
10-120	0.2 ± 0.1	0.1 ± 0.0	0.3 ± 0.0
12-240	0.7 ± 0.2	0.1 ± 0.0	0.7 ± 0.30
24-32 <sup>g</sup>	0.1 ± 0.1	0.0 ± 0.0	f
32-48 <sup>g</sup>	0.1 ± 0.1	0.0 ± 0.0	f
	<i>Dose excreted (cumulative %)</i>		
0-20	0.0 ± 0.1	0.0 ± 0.1	0.2 ± 0.1
0-40	0.1 ± 0.1	0.1 ± 0.1	0.4 ± 0.2
0-60	0.2 ± 0.1	0.2 ± 0.1	0.6 ± 0.2
0-60	0.3 ± 0.1	0.3 ± 0.2	0.8 ± 0.1
0-100	0.5 ± 0.2	0.3 ± 0.2	1.1 ± 0.2
0-120	0.6 ± 0.2	0.4 ± 0.2	1.3 ± 0.3
0-240	1.3 ± 0.3	0.5 ± 0.2	2.0 ± 0.6
0-32 <sup>g</sup>	1.4 ± 0.3	0.5 ± 0.3	f
0-48 <sup>g</sup>	1.5 ± 0.3	0.5 ± 0.3	f

<sup>a</sup>Mean ± SD of data from four rats, unless otherwise indicated.

<sup>b</sup>Rats were given two doses of ethanol, the first 3000 mg/kg, the second 2000 mg/kg, administered at 7.45 min after the first dose. [ $^{14}\text{C}$ ]EC was administered at 15 min following the first ethanol dose.

<sup>c</sup>Rats were dosed with ethanol by gavage at 3000 mg/kg/day for 10 days, followed by a 24 hr washout period, then dosed with [ $^{14}\text{C}$ ]EC.

<sup>d</sup>Samples in which radioactivity was less than twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.

<sup>e</sup>Mean of data from three rats.

<sup>f</sup>Control rats were sacrificed at 24 hr.

**Table 17: Exhalation of  $^{14}\text{C}$  radioactivity as volatile organics by mice after ethanol treatment at a dose level of 3000 mg/kg p.o. for 0, 1 and 10 days and administration of [ $^{14}\text{C}$ ]EC at 4.75 mg/kg i.v.<sup>a</sup>**

Time (hr)	Day		
	1 <sup>b</sup>	10 <sup>c</sup>	Control
	<i>Dose excreted (%)</i>		
0-2	0.4 ± 0.2	0.2 ± 0.1	0.5 ± 0.4
2-4	0.6 ± 0.3	0.1 ± 0.1	0.1 ± 0.1
4-6	0.7 ± 0.4	0.0 ± 0.0 <sup>d</sup>	0.1 ± 0.1
6-8	0.4 ± 0.1	0.0 ± 0.0	0.0 ± 0.1
8-10	0.3 ± 0.1	0.0 ± 0.0	0.0 ± 0.1
10-12	0.2 ± 0.1	0.0 ± 0.0	0.0 ± 0.0
12-24	0.4 ± 0.1	0.0 ± 0.0	0.0 ± 0.1
24-32	0.1 ± 0.1	0.0 ± 0.0	0.0 ± 0.0
32-48	0.2 ± 0.1	0.1 ± 0.1	0.0 ± 0.0
	<i>Dose excreted (cumulative %)</i>		
0-2	0.4 ± 0.2	0.2 ± 0.1	0.5 ± 0.4
0-4	0.9 ± 0.3	0.2 ± 0.1	0.6 ± 0.4
0-6	1.7 ± 0.6	0.2 ± 0.1	0.6 ± 0.3
0-8	2.0 ± 0.7	0.2 ± 0.1	0.7 ± 0.3
0-10	2.3 ± 0.7	0.2 ± 0.1	0.7 ± 0.4
0-12	2.5 ± 0.8	0.2 ± 0.1	0.7 ± 0.4
0-24	2.9 ± 0.8	0.2 ± 0.1	0.7 ± 0.4
0-32	2.9 ± 0.8	0.2 ± 0.1	0.7 ± 0.4
0-48	3.1 ± 0.9	0.3 ± 0.1	0.7 ± 0.4

<sup>a</sup>Mean ± SD of data from four mice.

<sup>b</sup>Mice were given two 3000 mg/kg doses of ethanol by gavage, separated by 4.45 hr. [ $^{14}\text{C}$ ]EC was administered at 15 min following the first ethanol dose.

<sup>c</sup>Mice were treated with ethanol by gavage at 3000 mg/kg/day for 10 days, followed by a 24 hr washout period, then dosed with [ $^{14}\text{C}$ ]EC.

<sup>d</sup>Samples in which radioactivity was less than twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.

**Table 18: Exhalation of <sup>14</sup>C radioactivity as volatile organics by mice after ethanol treatment at a dose level of 3000 mg/kg p.o. for 0, 1 and 10 days and administration of [<sup>14</sup>C]EC at 119 mg/kg i.v.<sup>a</sup>**

Time (hr)	Day		
	1 <sup>b</sup>	10 <sup>c</sup>	Control
	<i>Dose excreted (%)</i>		
0-2	0.6 ± 0.1	0.0 ± 0.1 <sup>d</sup>	0.3 ± 0.1
2-4	0.5 ± 0.2	0.3 ± 0.2	0.1 ± 0.1
4-6	0.8 ± 0.1	0.3 ± 0.0	0.0 ± 0.1
6-8	0.4 ± 0.1	0.1 ± 0.1	0.0 ± 0.0
8-10	0.3 ± 0.1	0.1 ± 0.1	0.0 ± 0.0
10-12	0.2 ± 0.0	0.0 ± 0.1	0.0 ± 0.0
12-24	0.5 ± 0.2	0.1 ± 0.1	0.0 ± 0.0
24-32	0.1 ± 0.1	0.1 ± 0.1	0.0 ± 0.0
32-48	0.2 ± 0.1	0.1 ± 0.1	0.0 ± 0.0
	<i>Dose excreted (cumulative %)</i>		
0-2	0.6 ± 0.1	0.0 ± 0.1	0.3 ± 0.1
0-4	1.0 ± 0.1	0.3 ± 0.2	0.4 ± 0.2
0-6	1.8 ± 0.1	0.6 ± 0.2	0.5 ± 0.2
0-8	2.2 ± 0.2	0.7 ± 0.1	0.5 ± 0.2
0-10	2.5 ± 0.3	0.8 ± 0.2	0.5 ± 0.2
0-12	2.7 ± 0.3	0.8 ± 0.2	0.5 ± 0.2
0-24	3.1 ± 0.4	0.9 ± 0.2	0.5 ± 0.2
0-32	3.3 ± 0.5	0.9 ± 0.3	0.5 ± 0.2
0-48	3.4 ± 0.5	1.0 ± 0.3	0.5 ± 0.2

<sup>a</sup>Mean ± SD of data from four mice.

<sup>b</sup>Mice were given two 3000 mg/kg doses of ethanol by gavage, separated by 4.45 hr. [<sup>14</sup>C]EC was administered at 15 min following the first ethanol dose.

<sup>c</sup>Mice were treated with ethanol by gavage at 3000 mg/kg/day for 10 days, followed by a 24 hr washout period, then dosed with [<sup>14</sup>C]EC.

<sup>d</sup>Samples in which radioactivity was less than twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.

**Table 19: Urinary excretion of <sup>14</sup>C radioactivity following administration of [<sup>14</sup>C]EC at 4.75 mg/kg i.v. to rats pretreated with 5% ethanol in drinking water for 0-30 days**

Time (hr)	Ethanol pretreatment (days)					Control <sup>a</sup>
	0	1	3	10	30	
	<i>Dose excreted (%)<sup>b</sup></i>					
0-4	0.8 ± 1.6	3.0 ± 1.5	3.2 ± 1.3	1.5 ± 1.7	4.8 ± 2.4	1.3 ± 2.7
4-8	4.1 ± 2.5	3.0 ± 1.7	3.4 ± 1.0	3.9 ± 2.0	4.0 ± 0.9	5.5 ± 1.8
8-12	3.0 ± 1.7	1.4 ± 0.7	1.8 ± 0.6	1.8 ± 0.9	1.5 ± 0.7	2.1 ± 0.9
12-24	1.5 ± 0.5	1.2 ± 0.2	1.4 ± 0.4	0.9 ± 0.3	1.6 ± 0.4	1.7 ± 0.6
	<i>Dose excreted (cumulative %)</i>					
0-4	0.8 ± 1.6	3.0 ± 1.5	3.2 ± 1.3	1.5 ± 1.7	4.8 ± 2.4	1.3 ± 2.7
0-8	4.9 ± 1.2	6.0 ± 1.1	6.7 ± 1.4	5.4 ± 1.2	8.8 ± 1.7	6.9 ± 1.4
0-12	7.9 ± 1.1	7.4 ± 0.4	8.4 ± 1.0	7.1 ± 1.6	10.2 ± 1.3	8.9 ± 1.0
0-24	9.4 ± 1.3	8.6 ± 0.6	9.8 ± 0.7	8.0 ± 1.7	11.9 ± 1.8	10.7 ± 1.0

<sup>a</sup>These animals were kept for 30 days without ethanol pretreatment, then dosed with EC.

<sup>b</sup>Mean ± SD of data from four animals.

**Table 20: Urinary excretion of  $^{14}\text{C}$  radioactivity following administration of [ $^{14}\text{C}$ ]EC at 119 mg/kg i.v. to rats pretreated with 5% ethanol in drinking water for 0-30 days**

Time (hr)	Ethanol pretreatment (days)					Control <sup>a</sup>
	0	1	3	10	30	
	<i>Dose excreted (%)<sup>b</sup></i>					
0-4	1.5 ± 1.0	0.3 ± 0.6	0.0 ± 0.0 <sup>c</sup>	0.2 ± 0.5	3.8 ± 2.8	0.4 ± 0.8
4-8	3.0 ± 1.5	4.0 ± 2.3	4.7 ± 3.3	3.9 ± 0.8	5.1 ± 4.0	4.6 ± 3.2
8-12	1.7 ± 1.4	2.0 ± 1.3	3.7 ± 2.8	3.4 ± 3.1	2.6 ± 0.6	2.9 ± 1.6
12-24	3.1 ± 0.4	1.8 ± 0.5	3.1 ± 0.4	1.6 ± 0.3	2.1 ± 0.4	3.5 ± 1.1
	<i>Dose excreted (cumulative %)</i>					
0-4	1.5 ± 1.0	0.3 ± 0.6	0.0 ± 0.0	0.2 ± 0.5	3.8 ± 2.8	0.4 ± 0.8
0-8	4.5 ± 1.4	4.3 ± 2.1	4.7 ± 3.3	4.2 ± 0.6	8.9 ± 1.5	5.0 ± 3.4
0-12	6.2 ± 1.7	6.2 ± 1.1	8.5 ± 0.8	7.6 ± 3.2	11.5 ± 1.4	7.8 ± 2.2
0-24	9.3 ± 1.8	8.1 ± 1.2	11.5 ± 0.7	9.1 ± 3.5	13.6 ± 1.8	11.3 ± 2.0

<sup>a</sup>These animals were kept for 30 days without ethanol pretreatment, then dosed with EC.

<sup>b</sup>Mean ± SD of data from four animals.

<sup>c</sup>Samples in which radioactivity was below twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.

**Table 21: Urinary excretion of  $^{14}\text{C}$  radioactivity following administration of [ $^{14}\text{C}$ ]EC at 4.75 mg/kg i.v. to mice pretreated with 5% ethanol in drinking water for 0-30 days**

Time (hr)	Ethanol pretreatment (days)					
	0	1	3	10	30	Control <sup>a</sup>
<i>Dose excreted (%)<sup>b</sup></i>						
0-4	1.1 ± 2.1	2.3 ± 1.9	2.0 ± 2.4	2.0 ± 4.1	3.5 ± 3.7	2.7 ± 3.4
4-8	0.8 ± 1.0	1.2 ± 1.5	0.3 ± 0.5	0.0 ± 0.0 <sup>c</sup>	0.0 ± 0.1	0.1 ± 0.2
8-12	4.8 ± 3.1	4.5 ± 4.5	1.2 ± 2.3	7.0 ± 2.8	2.2 ± 1.1	4.3 ± 3.1
12-24	0.8 ± 0.4	0.3 ± 0.2	0.0 ± 0.1	0.9 ± 0.8	0.4 ± 0.1	2.3 ± 1.7
<i>Dose excreted (cumulative %)</i>						
0-4	1.1 ± 2.1	2.3 ± 1.9	2.0 ± 2.4	2.0 ± 4.1	3.5 ± 3.7	2.7 ± 3.4
0-8	1.9 ± 2.4	3.5 ± 2.9	2.3 ± 2.1	2.0 ± 4.1	3.5 ± 3.7	2.8 ± 3.5
0-12	6.6 ± 1.1	8.0 ± 1.8	3.4 ± 3.7	9.0 ± 1.3	5.7 ± 4.2	7.0 ± 1.4
0-24	7.5 ± 0.8	8.2 ± 1.7	3.4 ± 3.7	9.9 ± 1.2	6.1 ± 4.2	9.3 ± 1.0

<sup>a</sup>These animals were kept for 30 days without ethanol pretreatment, then dosed with EC.

<sup>b</sup>Mean ± SD of data from four animals.

<sup>c</sup>Samples in which radioactivity was below twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.



**Table 22: Urinary excretion of  $^{14}\text{C}$  radioactivity following administration of [ $^{14}\text{C}$ ]EC at 119 mg/kg i.v. to mice pretreated with 5% ethanol in drinking water for 0-30 days**

Time (hr)	Ethanol pretreatment (days)					
	0	1	3	10	30	Control <sup>a</sup>
	<i>Dose excreted (%)<sup>b</sup></i>					
0-4	0.5 ± 1.0	2.3 ± 4.6	4.0 ± 4.0	2.2 ± 2.6	4.3 ± 3.0	2.9 ± 3.4
4-8	0.0 ± 0.0 <sup>c</sup>	0.0 ± 0.0	0.0 ± 0.1	0.8 ± 1.2	0.2 ± 0.5	1.3 ± 2.6
8-12	4.0 ± 3.4	3.6 ± 4.1	8.0 ± 6.1	6.8 ± 6.2	4.3 ± 4.2	3.5 ± 2.4
12-24	4.5 ± 3.5	2.0 ± 2.0	0.7 ± 0.9	0.5 ± 0.4	0.7 ± 0.4	0.9 ± 1.0
	<i>Dose excreted (cumulative %)</i>					
0-4	0.5 ± 1.0	2.3 ± 4.6	4.0 ± 4.0	2.2 ± 2.6	4.3 ± 3.0	2.9 ± 3.4
0-8	0.5 ± 1.0	2.3 ± 4.6	4.1 ± 4.0	3.0 ± 3.7	4.5 ± 3.2	4.2 ± 2.8
0-12	4.5 ± 3.2	5.9 ± 4.0	12.0 ± 6.5	9.7 ± 3.5	8.8 ± 1.5	7.7 ± 1.2
0-24	8.9 ± 0.8	7.8 ± 2.1	12.7 ± 7.0	10.3 ± 3.2	9.5 ± 1.4	8.6 ± 1.3

<sup>a</sup>These animals were kept for 30 days without ethanol pretreatment, then dosed with EC.

<sup>b</sup>Mean ± SD of data from four animals.

<sup>c</sup>Samples in which radioactivity was below twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.

**Table 23: Urinary excretion of <sup>14</sup>C radioactivity by rats after ethanol treatment at a dose level of 3000 mg/kg p.o. for 0, 1 and 10 days and administration of [<sup>14</sup>C]EC at 4.75 mg/kg i.v.<sup>a</sup>**

Time (hr)	Day		
	1 <sup>b,c</sup>	10 <sup>d</sup>	Control
	<i>Dose excreted (%)</i>		
0-4	12.5 ± 5.0	8.2 ± 2.5	0.8 ± 1.6
4-8	8.2 ± 1.5	3.4 ± 2.6	4.1 ± 2.5
8-12	4.6 ± 1.3	2.5 ± 2.2	3.0 ± 1.7
12-24	10.9 ± 3.4	1.6 ± 0.0	1.5 ± 0.5
24-32 <sup>e</sup>	3.7 ± 1.2	0.1 ± 0.1	f
32-48 <sup>e</sup>	4.9 ± 3.2	0.3 ± 0.1	f
	<i>Dose excreted (cumulative %)</i>		
0-4	12.5 ± 5.0	8.2 ± 2.5	0.8 ± 1.6
0-8	20.7 ± 4.8	11.6 ± 0.3	4.9 ± 1.2
0-12	25.3 ± 5.6	14.0 ± 2.2	7.9 ± 1.1
0-24	36.2 ± 7.9	15.6 ± 2.2	9.4 ± 1.3
0-32 <sup>e</sup>	39.3 ± 9.8	15.7 ± 0.3	f
0-48 <sup>e</sup>	44.2 ± 12.9	16.0 ± 0.2	f

<sup>a</sup>Mean ± SD of data from four rats, unless otherwise indicated.

<sup>b</sup>Rats were given two doses of ethanol, the first 3000 mg/kg, the second 2000 mg/kg, administered at 7.45 min after the first dose. [<sup>14</sup>C]EC was administered at 15 min following the first ethanol dose.

<sup>c</sup>Urinary radioactivity collected from this group was unusually high. We suspect cross-contamination of the metabolism cages.

<sup>d</sup>Rats were dosed with ethanol by gavage at 3000 mg/kg/day for 10 days, followed by a 24 hr washout period, then dosed with [<sup>14</sup>C]EC.

<sup>e</sup>Mean of data from three rats.

<sup>f</sup>Control rats were sacrificed at 24 hr.

**Table 24: Urinary excretion of <sup>14</sup>C radioactivity by rats after ethanol treatment p.o. for 0, 1 and 10 days and administration of [<sup>14</sup>C]EC at 119 mg/kg i.v.<sup>a</sup>**

Time (hr)	Day		
	1 <sup>b</sup>	10 <sup>b</sup>	Control
	<i>Dose excreted (%)</i>		
0-4	3.8 ± 2.6	5.6 ± 4.0	1.5 ± 1.0
4-8	8.0 ± 3.6	5.7 ± 2.7	3.0 ± 1.5
8-12	2.9 ± 0.7	4.1 ± 0.9	1.7 ± 1.4
12-24	6.9 ± 4.1	2.5 ± 0.8	3.1 ± 0.4
24-32 <sup>c</sup>	1.0 ± 0.4	0.2 ± 0.1 <sup>d</sup>	●
32-48 <sup>c</sup>	0.8 ± 0.3	0.4 ± 0.2 <sup>d</sup>	●
	<i>Dose excreted (cumulative %)</i>		
0-4	3.8 ± 2.6	5.6 ± 4.0	1.5 ± 1.0
0-8	11.8 ± 2.1	11.2 ± 1.8	4.5 ± 1.4
0-12	14.6 ± 1.6	15.3 ± 1.9	6.2 ± 1.7
0-24	21.5 ± 3.8	17.8 ± 1.3	9.3 ± 1.8
0-32 <sup>c</sup>	22.5 ± 3.7	17.9 ± 1.6 <sup>d</sup>	●
0-48 <sup>c</sup>	23.3 ± 3.4	18.3 ± 1.7 <sup>d</sup>	●

<sup>a</sup>Mean ± SD of data from four rats, unless otherwise indicated.

<sup>b</sup>Rats were given two doses of ethanol, the first 3000 mg/kg, the second 2000 mg/kg, administered at 7.45 min after the first dose. [<sup>14</sup>C]EC was administered at 15 min following the first ethanol dose.

<sup>c</sup>Rats were dosed with ethanol by gavage at 3000 mg/kg/day for 10 days, followed by a 24 hr washout period, then dosed with [<sup>14</sup>C]EC.

<sup>d</sup>Mean of data from three rats.

<sup>e</sup>Control rats were sacrificed at 24 hr.

**Table 25: Urinary excretion of  $^{14}\text{C}$  radioactivity by mice after ethanol treatment at a dose level of 3000 mg/kg p.o. for 0, 1 and 10 days and administration of [ $^{14}\text{C}$ ]EC at 4.75 mg/kg i.v.<sup>a</sup>**

Time (hr)	Day		
	1 <sup>b</sup>	10 <sup>c</sup>	Control
	<i>Dose excreted (%)</i>		
0-4	1.2 ± 2.4	1.4 ± 2.9	0.9 ± 1.1
4-8	3.3 ± 3.1	2.6 ± 5.2	1.6 ± 3.2
8-12	0.3 ± 0.4	6.3 ± 3.9	6.0 ± 2.2
12-24	5.4 ± 1.8	0.2 ± 0.2	0.8 ± 0.5
24-32	0.5 ± 0.5	0.7 ± 1.0	0.2 ± 0.3
32-48	0.7 ± 0.7	0.0 ± 0.1 <sup>d</sup>	0.2 ± 0.1
	<i>Dose excreted (cumulative %)</i>		
0-4	1.2 ± 2.4	1.4 ± 2.9	0.9 ± 1.1
0-8	4.5 ± 2.8	4.0 ± 5.0	2.5 ± 2.8
0-12	4.8 ± 2.7	10.3 ± 1.6	8.5 ± 1.4
0-24	10.2 ± 2.9	10.5 ± 1.8	9.3 ± 1.7
0-32	10.7 ± 2.7	11.2 ± 1.6	9.5 ± 1.4
0-48	11.4 ± 2.7	11.3 ± 1.6	9.7 ± 1.4

<sup>a</sup>Mean ± SD of data from four mice.

<sup>b</sup>Mice were given two 3000 mg/kg doses of ethanol by gavage, 4.45 hr apart. [ $^{14}\text{C}$ ]EC was administered at 15 min following the first ethanol dose.

<sup>c</sup>Mice were treated with ethanol by gavage at 3000 mg/kg/day for 10 days, followed by a 24 hr washout period, then dosed with [ $^{14}\text{C}$ ]EC.

<sup>d</sup>Samples in which radioactivity was less than twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.

**Table 26: Urinary excretion of  $^{14}\text{C}$  radioactivity by mice after ethanol treatment at a dose level of 3000 mg/kg p.o. for 0, 1 and 10 days and administration of [ $^{14}\text{C}$ ]EC at 119 mg/kg i.v.<sup>a</sup>**

Time (hr)	Day		
	1 <sup>b</sup>	10 <sup>c</sup>	Control
	<i>Dose excreted (%)</i>		
0-4	6.4 ± 1.1	4.1 ± 3.5	0.0 ± 0.0 <sup>d</sup>
4-8	4.1 ± 3.9	4.0 ± 4.7	0.0 ± 0.0
8-12	0.6 ± 0.7	1.4 ± 1.6	7.7 ± 5.2
12-24	4.9 ± 1.9	0.9 ± 0.9	4.1 ± 5.2
24-32	0.6 ± 0.4	0.4 ± 0.4	0.8 ± 1.3
32-48	1.1 ± 0.4	0.4 ± 0.2	0.3 ± 0.2
	<i>Dose excreted (cumulative %)</i>		
0-4	6.4 ± 1.1	4.1 ± 3.5	0.0 ± 0.0
0-8	10.5 ± 3.5	8.1 ± 3.8	0.0 ± 0.0
0-12	11.1 ± 3.9	9.5 ± 2.4	7.7 ± 5.2
0-24	16.0 ± 4.0	10.4 ± 2.3	11.9 ± 1.7
0-32	16.5 ± 4.2	10.8 ± 2.4	12.6 ± 1.0
0-48	17.6 ± 4.1	11.2 ± 2.4	12.9 ± 1.0

<sup>a</sup>Mean ± SD of data from four mice.

<sup>b</sup>Mice were given two 3000 mg/kg doses of ethanol by gavage, 4.45 hr apart. [ $^{14}\text{C}$ ]EC was administered at 15 min following the first ethanol dose.

<sup>c</sup>Mice were treated with ethanol by gavage at 3000 mg/kg/day for 10 days, followed by a 24 hr washout period, then dosed with [ $^{14}\text{C}$ ]EC.

<sup>d</sup>Samples in which radioactivity was less than twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.

**Table 27: Fecal excretion of <sup>14</sup>C radioactivity following administration of [<sup>14</sup>C]EC at 4.75 mg/kg i.v. to rats pretreated with 5% ethanol in drinking water for 0-30 days**

Time (hr)	Ethanol pretreatment (days)					Control <sup>a</sup>
	0	1	3	10	30	
<i>Dose excreted (%)<sup>b</sup></i>						
0-4	0.0 ± 0.0 <sup>c</sup>	0.0 ± 0.0	0.1 ± 0.2	0.2 ± 0.1	0.0 ± 0.0	0.0 ± 0.0
4-8	0.1 ± 0.1	0.1 ± 0.1	0.0 ± 0.0	0.1 ± 0.1	0.0 ± 0.1	0.0 ± 0.0
8-12	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1
12-24	0.4 ± 0.2	0.5 ± 0.2	0.4 ± 0.1	0.2 ± 0.2	0.3 ± 0.1	0.3 ± 0.1
<i>Dose excreted (cumulative %)</i>						
0-4	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.2	0.2 ± 0.1	0.0 ± 0.0	0.0 ± 0.0
0-8	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.2	0.3 ± 0.1	0.0 ± 0.1	0.0 ± 0.0
0-12	0.1 ± 0.1	0.2 ± 0.1	0.2 ± 0.2	0.3 ± 0.1	0.1 ± 0.1	0.1 ± 0.1
0-24	0.5 ± 0.1	0.6 ± 0.3	0.6 ± 0.3	0.6 ± 0.2	0.3 ± 0.1	0.4 ± 0.2

<sup>a</sup>These animals were kept for 30 days without ethanol pretreatment, then dosed with EC.

<sup>b</sup>Mean ± SD of data from four animals.

<sup>c</sup>Samples in which radioactivity was below twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.

**Table 28: Fecal excretion of  $^{14}\text{C}$  radioactivity following administration of [ $^{14}\text{C}$ ]EC at 119 mg/kg i.v. to rats pretreated with 5% ethanol in drinking water for 0-30 days**

Time (hr)	Ethanol pretreatment (days)					Control <sup>a</sup>
	0	1	3	10	30	
<i>Dose excreted (%)<sup>b</sup></i>						
0-4	0.0 ± 0.0 <sup>c</sup>	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.1	0.0 ± 0.0	0.0 ± 0.0
4-8	0.1 ± 0.2	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.1	0.1 ± 0.1
8-12	0.3 ± 0.5	0.1 ± 0.1	0.2 ± 0.1	0.1 ± 0.1	0.2 ± 0.1	0.2 ± 0.1
12-24	2.2 ± 3.1	0.2 ± 0.1	0.3 ± 0.1	0.2 ± 0.2	0.2 ± 0.2	0.3 ± 0.2
<i>Dose excreted (cumulative %)</i>						
0-4	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.1	0.0 ± 0.0	0.0 ± 0.0
0-8	0.1 ± 0.2	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1
0-12	0.4 ± 0.5	0.1 ± 0.1	0.2 ± 0.1	0.1 ± 0.1	0.3 ± 0.1	0.2 ± 0.1
0-24	2.6 ± 3.6	0.3 ± 0.2	0.5 ± 0.1	0.4 ± 0.2	0.5 ± 0.2	0.5 ± 0.3

<sup>a</sup>These animals were kept for 30 days without ethanol pretreatment, then dosed with EC.

<sup>b</sup>Mean ± SD of data from four animals.

<sup>c</sup>Samples in which radioactivity was below twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.

**Table 29: Fecal excretion of  $^{14}\text{C}$  radioactivity following administration of [ $^{14}\text{C}$ ]EC at 4.75 mg/kg i.v. to mice pretreated with 5% ethanol in drinking water for 0-30 days**

Time (hr)	Ethanol pretreatment (days)					Control <sup>a</sup>
	0	1	3	10	30	
	<i>Dose excreted (%)<sup>b</sup></i>					
0-4	0.0 ± 0.0 <sup>c</sup>	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.3 ± 0.4	0.1 ± 0.1
4-8	0.0 ± 0.0	0.0 ± 0.0	0.8 ± 1.5	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1
8-12	0.1 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.6 ± 0.7	0.4 ± 0.2	0.4 ± 0.4
12-24	0.3 ± 0.1	0.4 ± 0.5	0.2 ± 0.1	0.3 ± 0.1	0.3 ± 0.2	0.7 ± 0.4
	<i>Dose excreted (cumulative %)</i>					
0-4	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.3 ± 0.4	0.1 ± 0.1
0-8	0.0 ± 0.0	0.0 ± 0.0	0.8 ± 1.5	0.1 ± 0.1	0.3 ± 0.4	0.1 ± 0.1
0-12	0.1 ± 0.1	0.2 ± 0.1	1.0 ± 1.4	0.6 ± 0.7	0.7 ± 0.4	0.5 ± 0.4
0-24	0.3 ± 0.1	0.6 ± 0.4	1.2 ± 1.4	0.9 ± 0.8	1.0 ± 0.4	1.2 ± 0.8

<sup>a</sup>These animals were kept for 30 days without ethanol pretreatment, then dosed with EC.

<sup>b</sup>Mean ± SD of data from four animals.

<sup>c</sup>Samples in which radioactivity was below twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.



**Table 30: Fecal excretion of  $^{14}\text{C}$  radioactivity following administration of [ $^{14}\text{C}$ ]EC at 119 mg/kg i.v. to mice pretreated with 5% ethanol in drinking water for 0-30 days**

Time (hr)	Ethanol pretreatment (days)					Control <sup>a</sup>
	0	1	3	10	30	
<i>Dose excreted (%)<sup>b</sup></i>						
0-4	0.0 ± 0.0 <sup>c</sup>	0.1 ± 0.1	0.0 ± 0.0	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1
4-8	0.0 ± 0.0	0.0 ± 0.0	0.2 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.0 ± 0.0
8-12	0.2 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.3 ± 0.2
12-24	0.1 ± 0.1	0.2 ± 0.0	0.6 ± 0.8	0.4 ± 0.2	0.3 ± 0.1	0.5 ± 0.1
<i>Dose excreted (cumulative %)</i>						
0-4	0.0 ± 0.0	0.1 ± 0.1	0.0 ± 0.0	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1
0-8	0.0 ± 0.0	0.1 ± 0.1	0.2 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1
0-12	0.2 ± 0.1	0.1 ± 0.2	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.4 ± 0.2
0-24	0.3 ± 0.2	0.3 ± 0.2	0.9 ± 0.8	0.6 ± 0.2	0.5 ± 0.1	0.9 ± 0.1

<sup>a</sup>These animals were kept for 30 days without ethanol pretreatment, then dosed with EC.

<sup>b</sup>Mean ± SD of data from four animals.

<sup>c</sup>Samples in which radioactivity was below twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.

**Table 31: Fecal excretion of  $^{14}\text{C}$  radioactivity by rats treated with ethanol for 0, 1 and 10 days and administration of [ $^{14}\text{C}$ ]EC at 4.75 mg/kg i.v.<sup>a</sup>**

Time (hr)	Day		
	1 <sup>b,c</sup>	10 <sup>d</sup>	Control
	<i>Dose excreted (%)</i>		
0-4	0.3 ± 0.4	0.0 ± 0.0 <sup>e</sup>	0.0 ± 0.0
4-8	0.2 ± 0.2	0.1 ± 0.1	0.1 ± 0.1
8-12	0.2 ± 0.2	0.1 ± 0.1	0.1 ± 0.1
12-24	7.5 ± 4.3	0.5 ± 0.0	0.4 ± 0.2
24-32 <sup>f</sup>	0.4 ± 0.7	0.0 ± 0.1	g
32-48 <sup>f</sup>	4.0 ± 2.7	0.2 ± 0.1	g
	<i>Dose excreted (cumulative %)</i>		
0-4	0.3 ± 0.4	0.0 ± 0.0	0.0 ± 0.0
0-8	0.5 ± 0.4	0.1 ± 0.1	0.1 ± 0.1
0-12	0.6 ± 0.4	0.2 ± 0.1	0.1 ± 0.1
0-24	8.1 ± 4.3	0.7 ± 0.0	0.5 ± 0.1
0-32 <sup>f</sup>	9.6 ± 4.7	0.8 ± 0.1	g
0-48 <sup>f</sup>	13.6 ± 6.7	0.9 ± 0.1	g

<sup>a</sup>Mean ± SD of data from four rats, unless otherwise indicated.

<sup>b</sup>Rats were given two doses of ethanol, the first 3000 mg/kg, the second 2000 mg/kg, administered at 7.45 min after the first dose. [ $^{14}\text{C}$ ]EC was administered at 15 min following the first ethanol dose.

<sup>c</sup>Radioactivity collected in feces is unusually high. We suspect cross-contamination.

<sup>d</sup>Rats were dosed with ethanol by gavage at 3000 mg/kg/day for 10 days, followed by a 24 hr washout period, then dosed with [ $^{14}\text{C}$ ]EC.

<sup>e</sup>Samples in which radioactivity was below twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.

<sup>f</sup>Mean of data from three rats.

<sup>g</sup>Control rats were sacrificed at 24 hr.

**Table 32: Fecal excretion of  $^{14}\text{C}$  radioactivity by rats after ethanol treatment at a dose level of 3000 mg/kg p.o. for 0, 1 and 10 days and administration of [ $^{14}\text{C}$ ]EC at 119 mg/kg i.v.<sup>a</sup>**

Time (hr)	Day		
	1 <sup>b</sup>	10 <sup>c</sup>	Control
	<i>Dose excreted (%)<sup>d</sup></i>		
0-4	0.0 ± 0.0 <sup>d</sup>	0.0 ± 0.0	0.0 ± 0.0
4-8	0.1 ± 0.2	0.1 ± 0.3	0.1 ± 0.2
8-12	0.0 ± 0.0	0.2 ± 0.1	0.3 ± 0.5
12-24	0.6 ± 0.3	0.5 ± 0.1	2.2 ± 3.1
24-32	0.2 ± 0.2	0.1 ± 0.0 <sup>e</sup>	f
32-48	0.3 ± 0.3	0.2 ± 0.1 <sup>e</sup>	f
	<i>Dose excreted (cumulative %)</i>		
0-4	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
0-8	0.1 ± 0.2	0.1 ± 0.3	0.1 ± 0.2
0-12	0.1 ± 0.2	0.3 ± 0.1	0.4 ± 0.5
0-24	0.7 ± 0.4	0.8 ± 0.2	2.6 ± 3.6
0-32	0.9 ± 0.3	0.9 ± 0.3	f
0-48	1.1 ± 0.6	1.1 ± 0.3	f

<sup>a</sup>Mean ± SD of data from four rats, unless otherwise indicated.

<sup>b</sup>Rats were given two doses of ethanol, the first 3000 mg/kg, the second 2000 mg/kg, administered at 7.45 min after the first dose. [ $^{14}\text{C}$ ]EC was administered at 15 min following the first ethanol dose.

<sup>c</sup>Rats were dosed with ethanol by gavage at 3000 mg/kg/day for 10 days, followed by a 24 hr washout period, then dosed with [ $^{14}\text{C}$ ]EC.

<sup>d</sup>Samples in which radioactivity was below twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.

<sup>e</sup>Mean of data from three rats.

<sup>f</sup>Control rats were sacrificed at 24 hr.

**Table 33: Fecal excretion of  $^{14}\text{C}$  radioactivity by mice after ethanol treatment at a dose level of 3000 mg/kg p.o. for 0, 1 and 10 days and administration of [ $^{14}\text{C}$ ]EC at 4.75 mg/kg i.v.<sup>a</sup>**

Time (hr)	Day		
	1 <sup>b</sup>	10 <sup>c</sup>	Control
	<i>Dose excreted (%)</i>		
0-4	0.0 ± 0.0 <sup>d</sup>	0.0 ± 0.1	0.0 ± 0.0
4-8	0.2 ± 0.2	0.0 ± 0.1	0.1 ± 0.1
8-12	0.3 ± 0.2	0.2 ± 0.1	0.3 ± 0.2
12-24	0.4 ± 0.2	0.2 ± 0.3	0.2 ± 0.1
24-32	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.1
32-48	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1
	<i>Dose excreted (cumulative %)</i>		
0-4	0.0 ± 0.0	0.0 ± 0.1	0.0 ± 0.0
0-8	0.2 ± 0.2	0.1 ± 0.1	0.1 ± 0.1
0-12	0.5 ± 0.4	0.2 ± 0.2	0.3 ± 0.2
0-24	0.9 ± 0.6	0.4 ± 0.3	0.5 ± 0.1
0-32	0.9 ± 0.6	0.4 ± 0.3	0.5 ± 0.1
0-48	0.9 ± 0.6	0.6 ± 0.3	0.6 ± 0.1

<sup>a</sup>Mean ± SD of data from four mice.

<sup>b</sup>Mice were given two 3000 mg/kg doses of ethanol by gavage, 4.45 hr apart. [ $^{14}\text{C}$ ]EC was administered at 15 min following the first ethanol dose.

<sup>c</sup>Mice were treated with ethanol by gavage at 3000 mg/kg/day for 10 days, followed by a 24 hr washout period, then dosed with [ $^{14}\text{C}$ ]EC.

<sup>d</sup>Samples in which radioactivity was less than twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.

**Table 34: Fecal excretion of <sup>14</sup>C radioactivity by mice after ethanol treatment at a dose level of 3000 mg/kg p.o. for 0, 1 and 10 days and administration of [<sup>14</sup>C]EC at 119 mg/kg i.v.<sup>a</sup>**

Time (hr)	Day		
	1 <sup>b</sup>	10 <sup>c</sup>	Control
	<i>Dose excreted (%)</i>		
0-4	0.0 ± 0.0 <sup>d</sup>	0.0 ± 0.0	0.0 ± 0.0
4-8	0.0 ± 0.0	0.1 ± 0.2	0.0 ± 0.0
8-12	0.2 ± 0.2	0.3 ± 0.2	0.2 ± 0.2
12-24	0.3 ± 0.1	0.2 ± 0.2	0.2 ± 0.2
24-32	0.0 ± 0.0	0.1 ± 0.1	0.1 ± 0.1
32-48	0.2 ± 0.1	0.1 ± 0.1	0.1 ± 0.1
	<i>Dose excreted (cumulative %)</i>		
0-4	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
0-8	0.0 ± 0.0	0.1 ± 0.2	0.0 ± 0.0
0-12	0.2 ± 0.2	0.5 ± 0.1	0.2 ± 0.2
0-24	0.5 ± 0.0	0.6 ± 0.1	0.4 ± 0.2
0-32	0.5 ± 0.0	0.7 ± 0.1	0.5 ± 0.2
0-48	0.7 ± 0.1	0.8 ± 0.2	0.6 ± 0.2

<sup>a</sup>Mean ± SD of data from four mice.

<sup>b</sup>Mice were given two 3000 mg/kg doses of ethanol by gavage, 4.45 hr apart. [<sup>14</sup>C]EC was administered at 15 min following the first ethanol dose.

<sup>c</sup>Mice were treated with ethanol by gavage at 3000 mg/kg/day for 10 days, followed by a 24 hr washout period, then dosed with [<sup>14</sup>C]EC.

<sup>d</sup>Samples in which radioactivity was less than twice background for the system or the total radioactivity was <0.1% of the dose were considered to contain zero percent.

**Table 35: Recovery of <sup>14</sup>C radioactivity following i.v. administration of [<sup>14</sup>C]EC to rats and mice pretreated with ethanol**

Species	Dose (mg/kg)	First study						Third study	Fourth study	
		Ethanol pretreatment (days)							Control <sup>a</sup>	Control
		0	1	3	10	30	Control <sup>a</sup>			
<i>Dose recovered (%)<sup>b</sup></i>										
Rat	4.75	105.7 ± 11.4	92.7 ± 4.7	91.8 ± 2.8	95.1 ± 17.0	86.2 ± 30.9	84.1 ± 3.6	148.0 ± 21.7	92.5 ± 4.1	c
	119	96.7 ± 12.4	85.0 ± 6.4	92.6 ± 3.1	93.7 ± 15.2	91.4 ± 6.9	74.5 ± 20.5	99.8 ± 1.3	90.5 ± 8.8	c
Mouse	4.75	112.4 ± 4.0	94.4 ± 4.7	94.3 ± 6.1	98.1 ± 3.0	88.3 ± 9.4	96.2 ± 3.3	92.8 ± 8.0	85.6 ± 2.1	96.4 ± 2.3
	119	107.2 ± 2.0	83.3 ± 1.9	89.6 ± 2.2	88.1 ± 9.6	89.8 ± 2.3	94.1 ± 6.6	98.2 ± 4.9	79.4 ± 0.5	102.1 ± 1.4

<sup>a</sup>These animals were kept for 30 days without ethanol pretreatment, then dosed with EC.

<sup>b</sup>Mean ± SD of data from at least three animals.

<sup>c</sup>No control animals were used in this study. Control values from the first study were used for comparison.