ADME NTP Study S0179 Propylene glycol mono-t-butyl ether

The contract laboratory used the synonym propylene glycol t-butyl ether and abbreviated the test article as PGtBE.
Species: adult male Fischer 344 (F-344) rats and $B6C3F_1$ mice.
Vehicles: intravenous, isotonic saline; oral, water; dermal, acetone.

CASRN 57018-52-7

Radiolabeled with carbon-14 on carbon 3 of the propanol moiety; 1-tert-butoxy-2[3-^{14}C]propanol.

Propylene glycol mono-t-butyl ether Studies Performed:

1. Single 3.8 mg/kg oral gavage dose in rats with sacrifice 72 hours postdose.

2. Single 37.7 mg/kg oral gavage dose in rats with sacrifice 72 hours postdose.

3. Single 377.1 mg/kg oral gavage dose in rats with sacrifice 72 hours postdose.

4. Single 4714 ug/cm^2 dermal administration to rats over an area of 8.4 cm^2 (~ 39.5 mg/rat) and mice over an area of 0.8 cm^2 (~ 3.76 mg/mouse) with dose site covered and sacrifice 72 hours postdose.

5. Single 37.8 mg/kg intravenous bolus dose in rats with sacrifice 60 minutes postdose.

The rat toxicokinetic and bile excretion data following intravenous administration of 37.8 mg/kg and 37.7 mg/kg PGtBE, respectively, were given in figures and are not shown here.

The toxicokinetic parameters were calculated using the program PK-PARAM. The plasma concentration of PGtBE at time t=0 was determined by regression of the data from the distribution phase of the apparent biexponential elimination. AUC(0-∞) was calculated by the linear trapezoidal method. Clearance (Cl) was calculated as Dose/AUC(0-∞) and the volume of distribution at steady state (Vd_{ss}) was calculated as Dose x AUMC/AUC^2. K_{el} was determined by unweighted linear regression.

The parameters are mean clearance (Cl), volume of distribution at steady state (Vd_{ss}), mean elimination half-life ($T_{1/2}$), and area under the curve from 0 to infinity ($AUC_{(0-\infty)}$).

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Table 1. The Distribution of Dosed Radioactivity in Male Fischer 344 rats 72 hours Following Dose Administration of a Single Oral Dose of [^{14}C]Propylene Glycol t-Butyl Ether at 377.1, 37.7 and 3.8 mg/kg[a]

Dose (mg/kg)	Urine	Feces	$^{14}CO_2$	Tissues	Total Recovery
377.1	48.1 ± 4.2	11.3 ± 3.2	21.6 ± 2.2	4.8 ± 0.3	86.8 ± 3.5
37.7	58.6 ± 5.6	3.9 ± 2.1	25.9 ± 2.2	4.9 ± 0.3	93.7 ± 3.0
3.8	67.3 ± 1.4	3.4 ± 0.8	24.6 ± 0.7	5.7 ± 0.2	101.6 ± 0.8

[a] Values are mean and standard deviation of dosed radioactivity for 3 rats.

Table 2. Tissue Distribution of Dosed Radioactivity in Male Fischer 344 Rats Following a Single Oral Dose of [^{14}C]-Propylene Glycol t-Butyl Ether (377.1 mg/kg).

Tissue	% of Dose[a]	T/B[b]
Blood	0.28±0.02	1.00
Brain	0.02±0.00	0.87
Heart	0.01±0.00	1.35
Kidney	0.08±0.00	2.90
Liver	0.39±0.01	2.63
Lung	0.03±0.00	2.32
Spleen	0.02±0.00	2.69
Muscle	1.72±0.34	1.12
Testes	0.04±0.00	1.13
Skin	1.18±0.20	2.42
Lg. Intestine	0.06±0.01	2.45
Sm. Intestine	0.11±0.00	2.73
Stomach	0.04±0.00	2.35
Fat	0.62±0.09	1.84
Lg. Int. Contents	0.05±0.02	N.D.
Sm. Int. Contents	0.17±0.00	N.D.
Stomach Contents	0.01±0.00	N.D.

The tissue burden of total radioactivity derived from the dosed compound was calculated from estimates of the fraction of body weight from blood (8%), muscle (50%), skin (16%) and adipose (11%).
[a]Mean and standard deviation of dosed radioactivity for 3 rats.
[b]Mean ratio of ^{14}C in tissue to ^{14}C in blood.
N.D. Not determined

Table 3. Tissue Distribution of Dosed Radioactivity in Male Fischer 344 Rats Following a Single Oral Dose of [^{14}C]-Propylene Glycol t-Butyl Ether (37.7 mg/kg).

Tissue	% of Dose[a]	T/B[b]
Blood	0.29±0.00	1.00
Brain	0.03±0.00	1.24
Heart	0.02±0.00	1.79
Kidney	0.10±0.00	3.60
Liver	0.40±0.04	3.26
Lung	0.04±0.00	3.46
Spleen	0.02±0.00	3.75
Muscle	1.90±0.18	2.50
Testes	0.05±0.00	1.47
Skin	0.95±0.18	2.04
Lg. Intestine	0.09±0.02	3.52
Sm. Intestine	0.15±0.04	4.21
Stomach	0.04±0.00	3.31
Fat	0.42±0.05	1.31
Lg. Int. Contents	0.10±0.05	N.D.
Sm. Int. Contents	0.23±0.06	N.D.
Stomach Contents	0.01±0.00	N.D.

The tissue burden of total radiioactivity derived from the dosed compound was calculated from estimates of the fraction of body weight for blood (8%), muscle (50%),
skin (16%) and adipose (11%).
[a]Mean and standard deviation of dosed radioactivity for 3 rats.
[b]Mean ratio of ^{14}C in tissue to ^{14}C in blood.
N.D. Not determined

Table 4. Tissue Distribution (at 72 hr) of Dosed Radioactivity in Male Fischer 344 Rats Following a Single Oral Dose of [^{14}C]-Propylene Glycol t-Butyl Ether (3.8 mg/kg).

Tissue	% of Dose[a]	T/B[b]
Blood	0.28±0.04	1.00
Brain	0.02±0.00	0.80
Heart	0.01±0.00	1.37
Kidney	0.09±0.00	2.69
Liver	0.39±0.04	2.43
Lung	0.05±0.00	3.07
Spleen	0.02±0.00	2.89
Muscle	2.04±0.18	1.20
Testes	0.04±0.00	1.03
Skin	1.39±0.18	2.24
Lg. Intestine	0.11±0.02	2.51
Sm. Intestine	0.15±0.02	2.58
Stomach	0.04±0.00	2.63
Fat	0.57±0.12	1.84
Lg. Int. Contents	0.05±0.05	N.D.
Sm. Int. Contents	0.24±0.06	N.D.
Stomach Contents	0.06±0.00	N.D.

The tissue burden of total radioactivity derived from the dosed compound was calculated from estimates of the fraction of body weight for blood (8%), muscle (50%), skin (16%) and adipose (11%).
[a]Mean and standard deviation of dosed radioactivity for 3 rats.
[b]Mean ratio of ^{14}C in tissue to ^{14}C in blood.
N.D. Not determined

Table 5. The Recovery of Dosed Radioactivity in Male Fischer 344 rats and Male $B6C3F_1$ Mice 72 hours Following a Single Topical Administration of [^{14}C]Propylene Glycol t-Butyl Ether (4714 ug/cm^2)[a]

Species	Urine	Feces	$^{14}CO_2$	Skin-Mounted Trap	Total Recovery
Rat	1.8 ± 0.3	0.1 ± 0.0	1.0 ± 0.1	99.5 ± 1.4	102.6 ± 1.8
Mouse	2.0 ± 0.8	0.4 ± 0.1	5.4 ± 1.6	91.8 ± 2.2	99.8 ± 1.0

[a] Values are mean and standard deviation of dosed radioactivity for 3 animals.

Table 6. Pharmacokinetic Parameters of Propylene Glycol t-Butyl Ether Following IV Administration to Male Fischer 344 Rats at 37.8 mg/kg.

Parameter	Rat Number 92-3809	92-3810	92-3811	92-3813	Mean±SD
Cl (ml/min/kg)	21.1	23.5	25.5	30.4	25.1±4.0
Vd_{SS}	0.39	0.53	0.42	0.49	0.46±0.06
K_{el}	2.48	2.14	2.89	2.76	2.57±0.33
$T_{1/2}$	0.28	0.32	0.24	0.25	0.27*
$AUC_{(0-\infty)}$ (µg.hr/ml)	29.95	26.82	24.71	20.71	25.55±3.89

*Harmonic mean = 0.693/mean K_{el}
N=4 rats