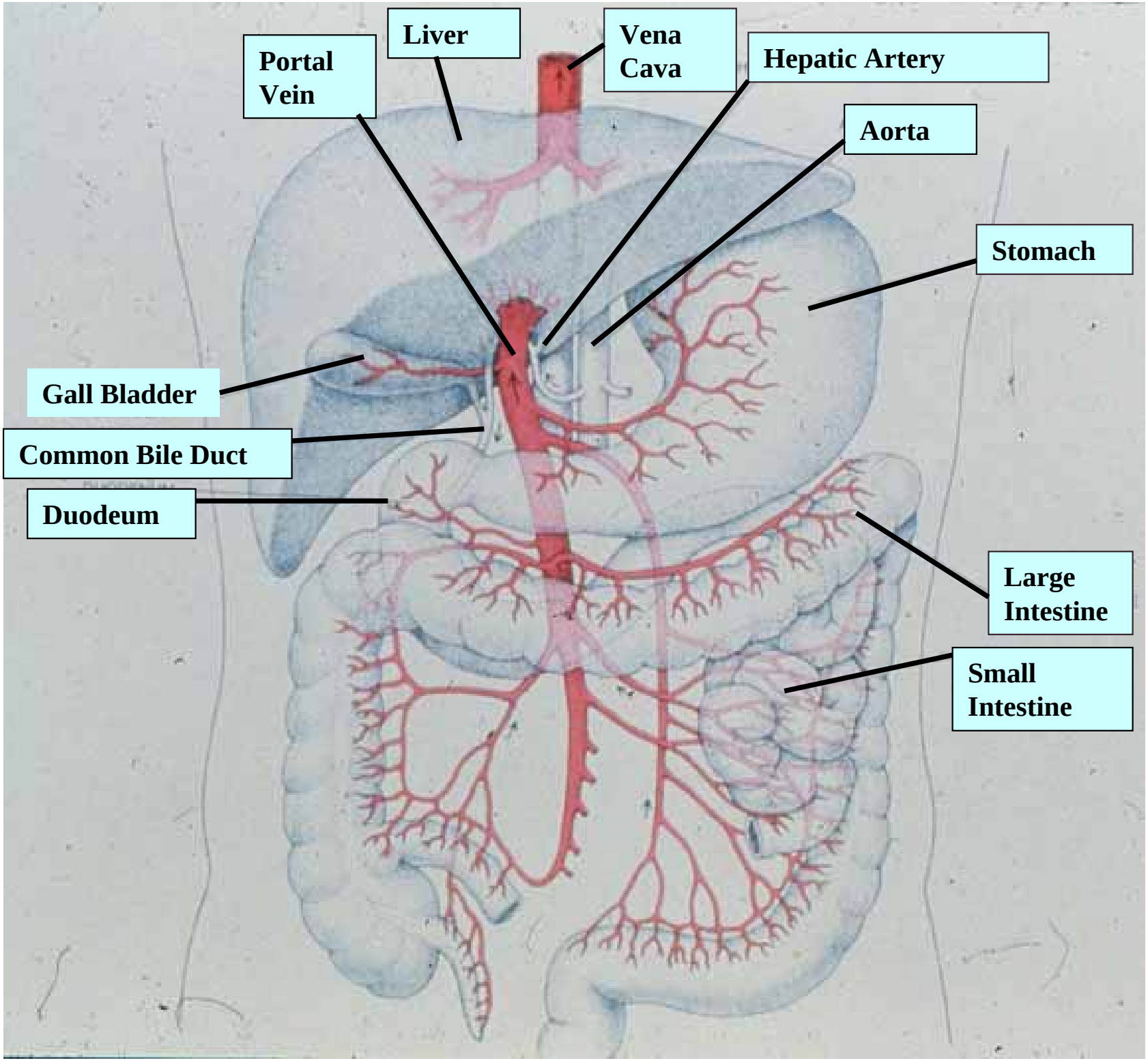
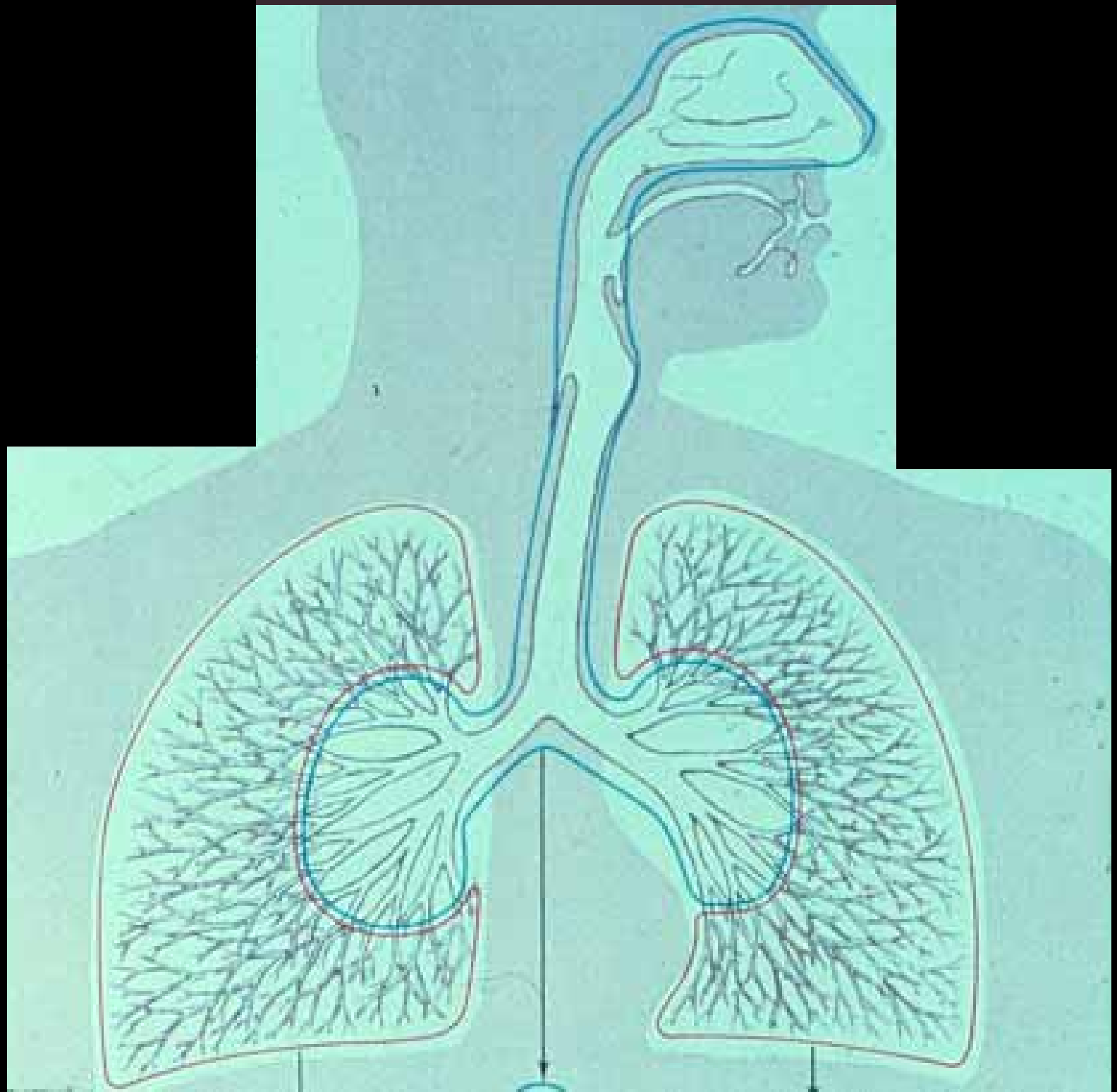
PRESYSTEMIC ELIMINATION OF ORAL TRICHLOROETHYLENE


Liver
Vena Cava
Portal Vein
Hepatic Artery
Aorta
Stomach
Gall Bladder
Common Bile Duct
Duodeum
Large Intestine
Small Intestine



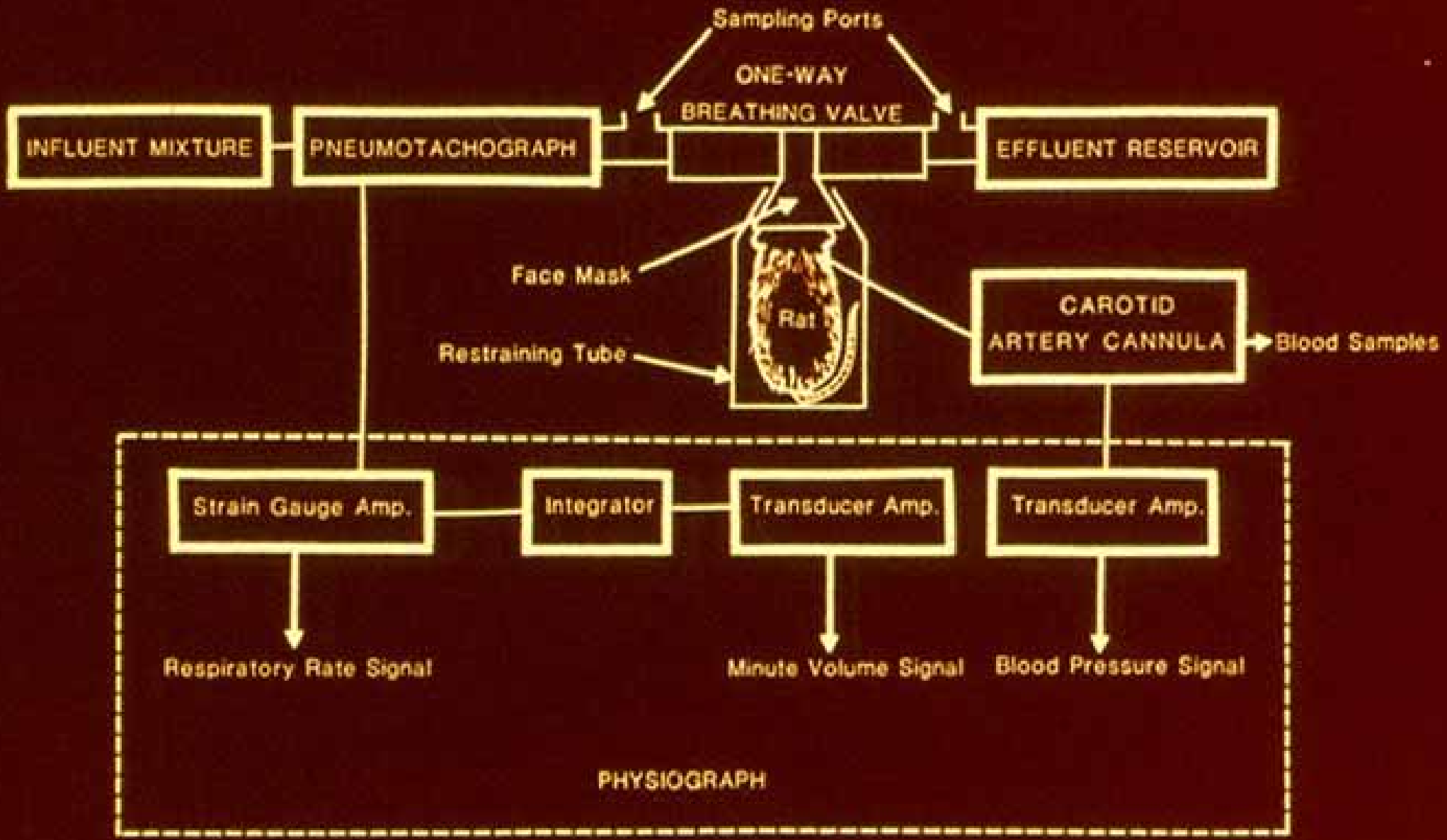
Are the results of inhalation studies Applicable Qualitatively or Quantitatively to situations where chemicals are ingested?

ROUTE to ROUTE COMPARISON

EXPERIMENTAL APPROACH

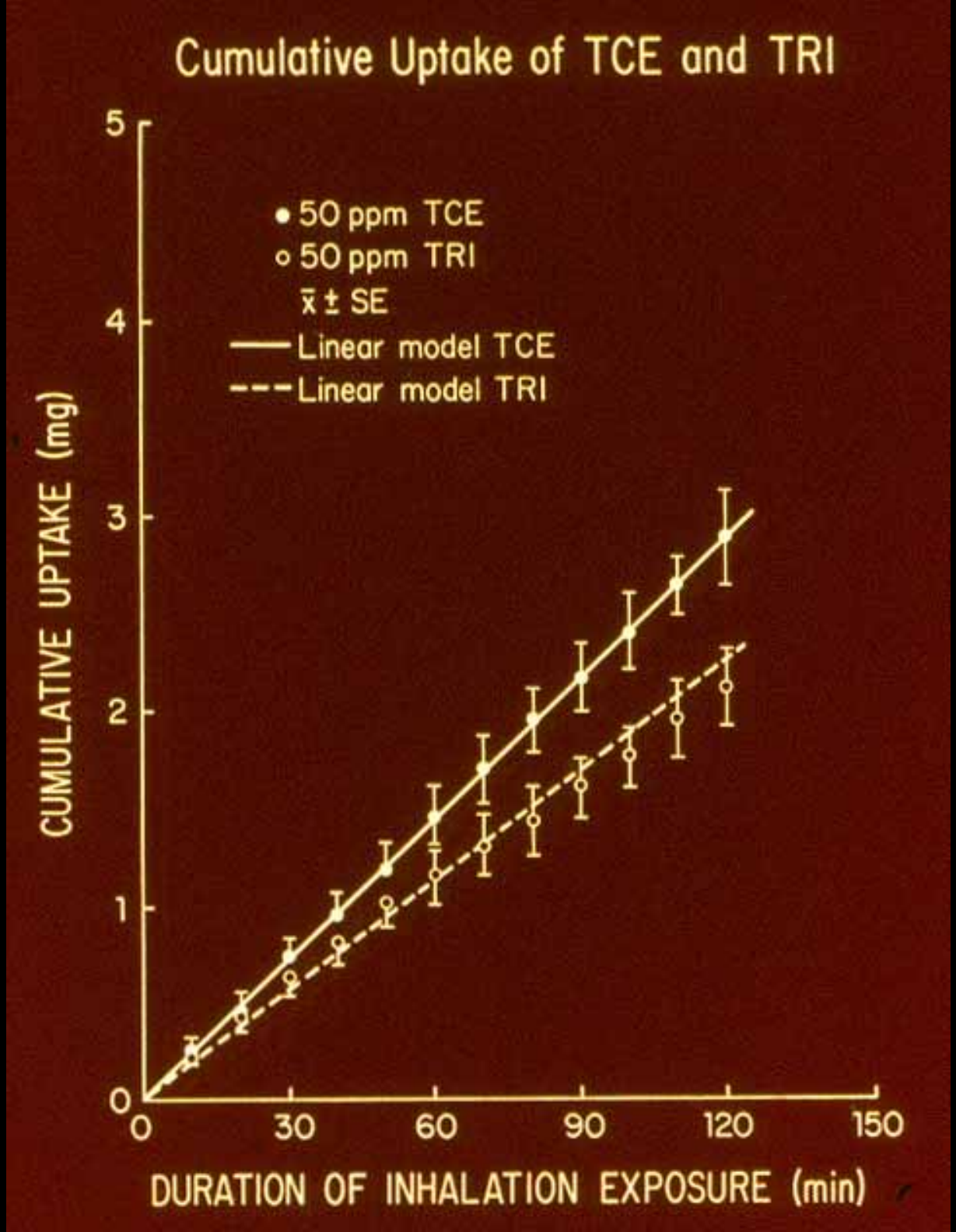
Administer Equivalent doses over the Same time-frame by Inhalation and Gastric Infusion

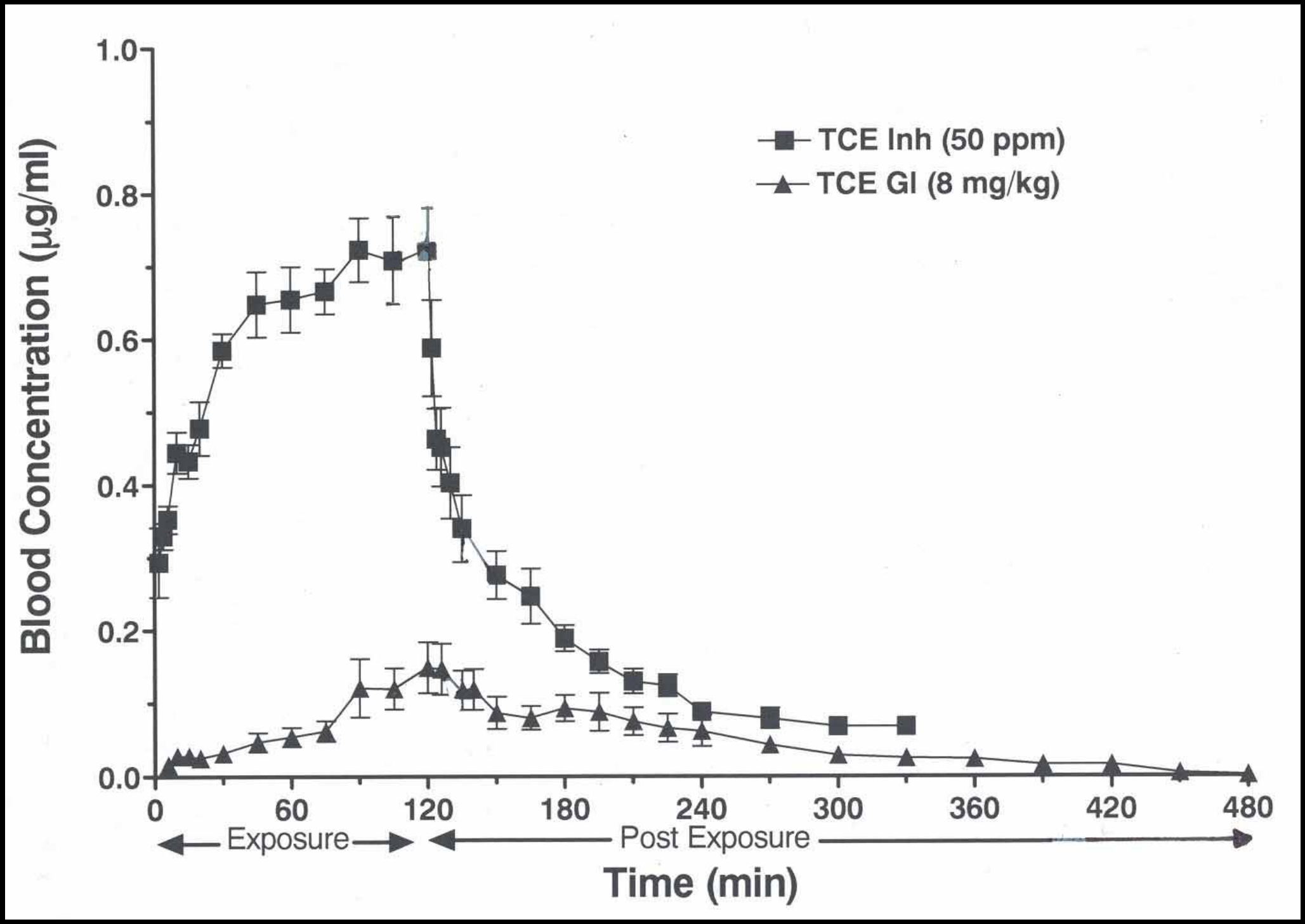
INHALATION EXPOSURE SYSTEM

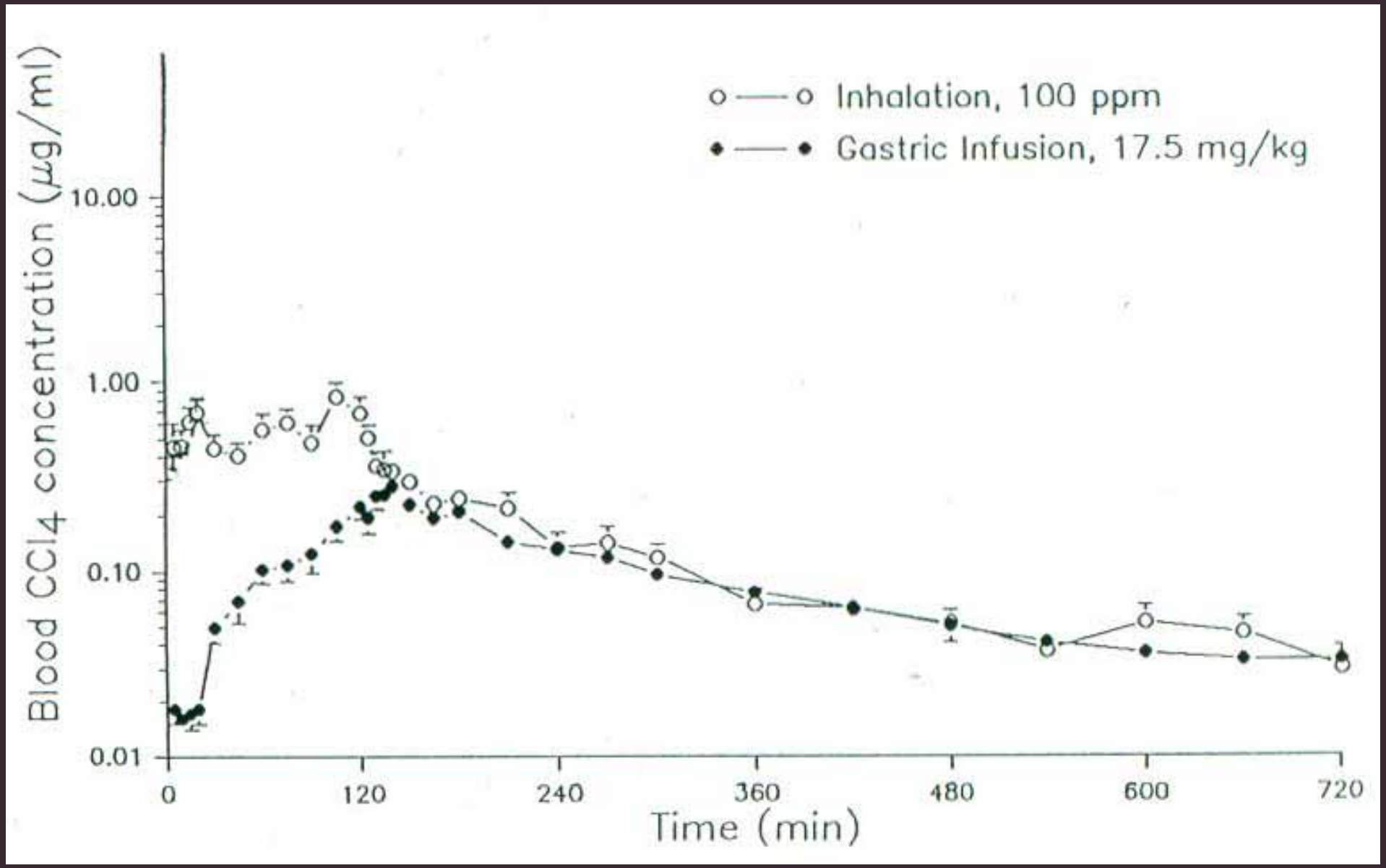


Amount Retained (MG) =

INHALED CONC. – ALVEOLAR CONC. X MINUTE VOLUME

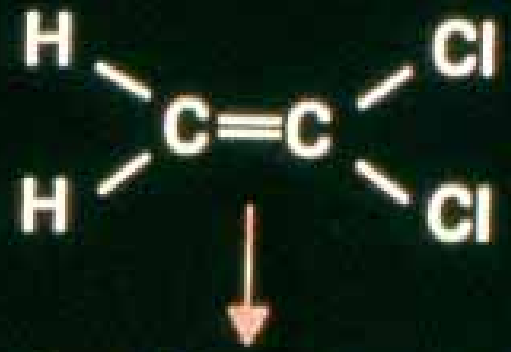

Cumulative Uptake of TCE and TRI
• 50 ppm TCE
○ 50 ppm TRI
x̄ ± SE
Linear model TCE
Linear model TRI
CUMULATIVE UPTAKE (mg)
0
1
2
3
4
5
0
30
60
90
120
150
DURATION OF INHALATION EXPOSURE (min)


TCE Inh (50 ppm)
TCE GI (8 mg/kg)
Blood Concentration (µg/ml)
1.0
0.8
0.6
0.4
0.2
0.0
0
60
120
180
240
300
360
420
480
Exposure
Post Exposure
Time (min)


Inhalation, 100 ppm
Gastric Infusion, 17.5 mg/kg
Blood CCl4 concentration (μg/ml)
10.00
1.00
0.10
0.01
0
120
240
360
480
600
720
Time (min)

Work Supported by COOPERATIVE AGREEMENTS CR 816258 & 820447 Between U.S. EPA Health Effects Research Laboratory (RTP, NC) and University of Georgia (Athens, GA)

1,1-DCE METABOLIC PATHWAY



Reactive Metabolite(s)

(Electrophile -epoxide?)

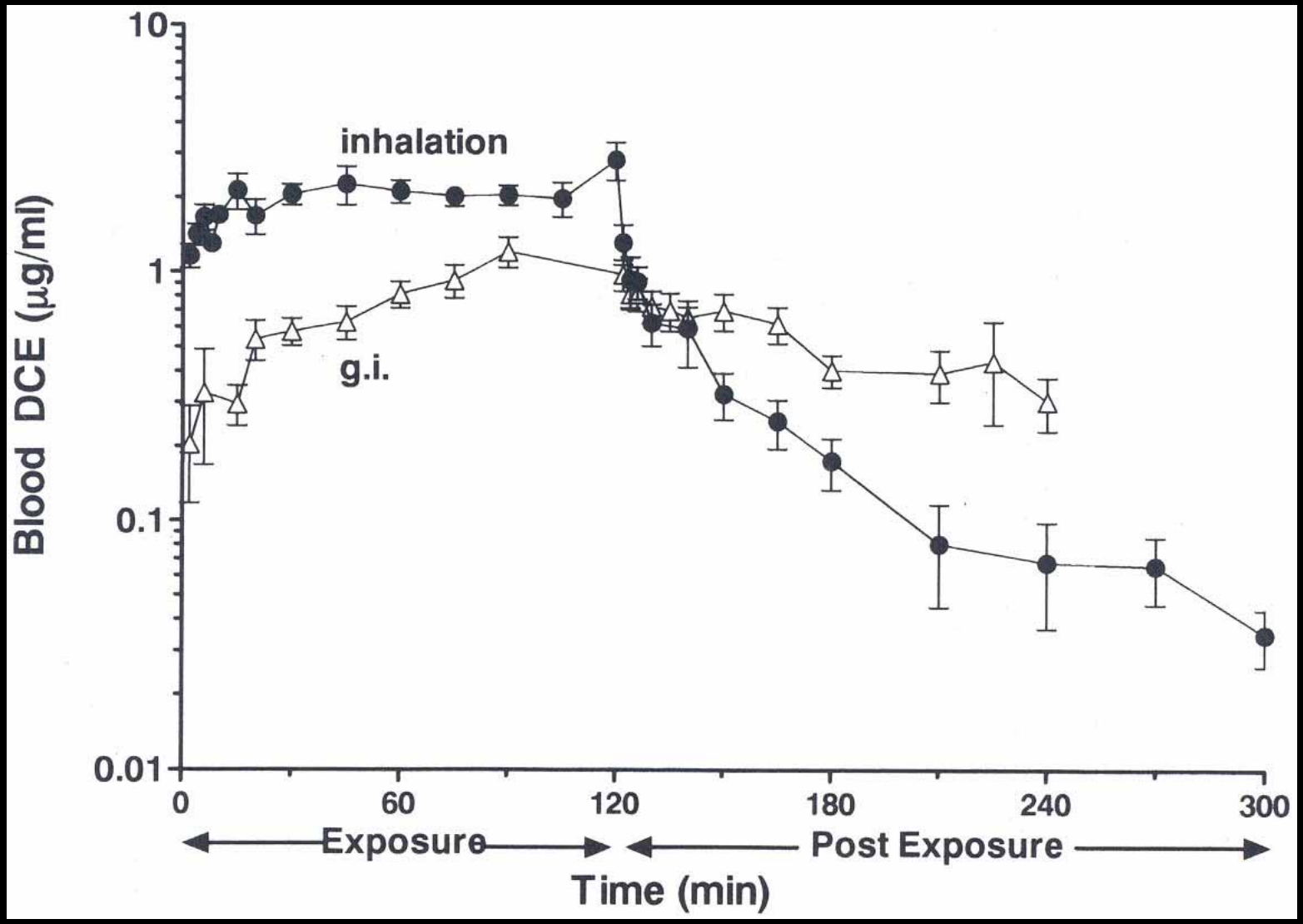
Detoxification

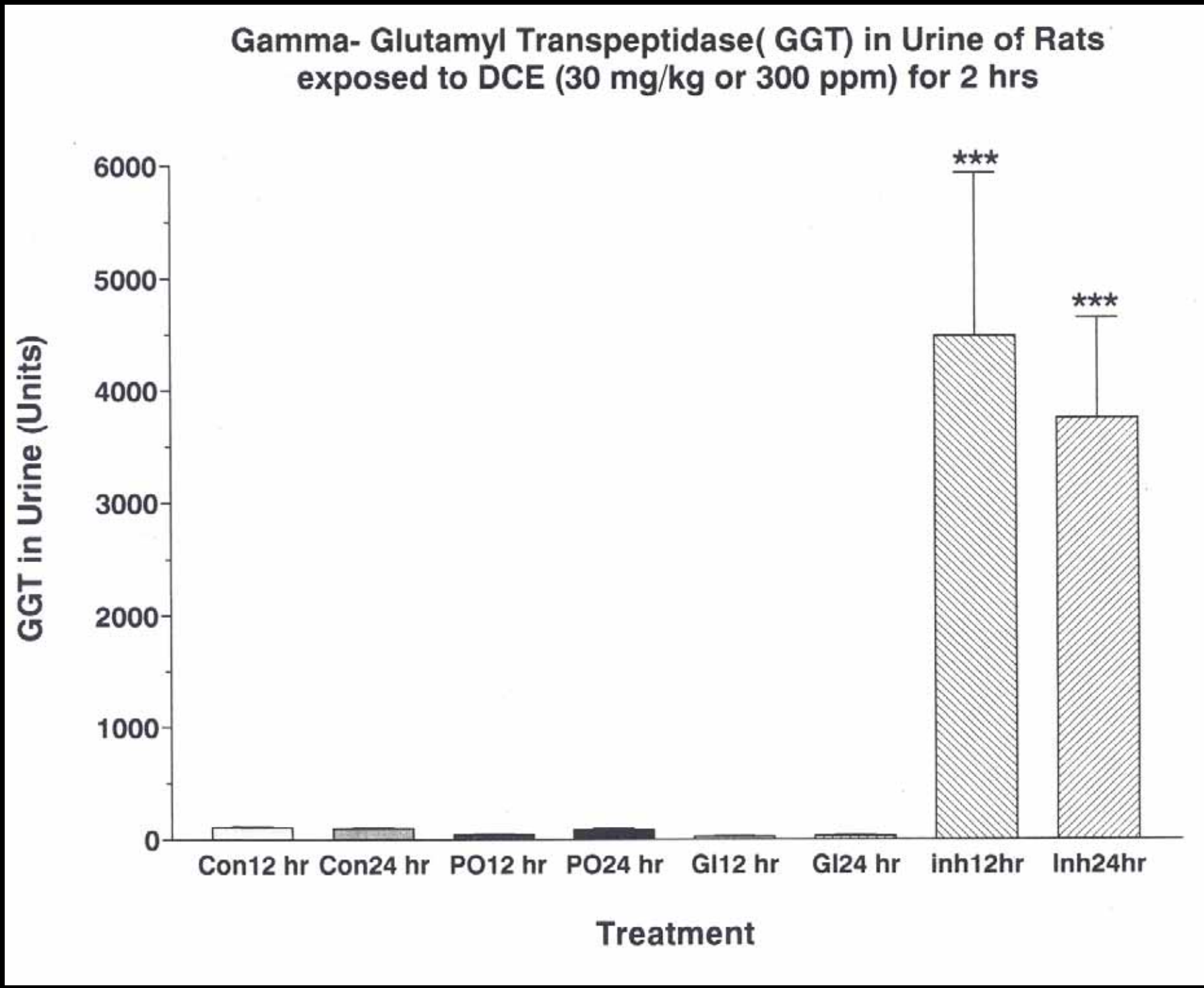
- Conjugation with GSH
- Urinary mercapturic acid excretion

Toxicity

- Covalent binding to tissue nucleophiles

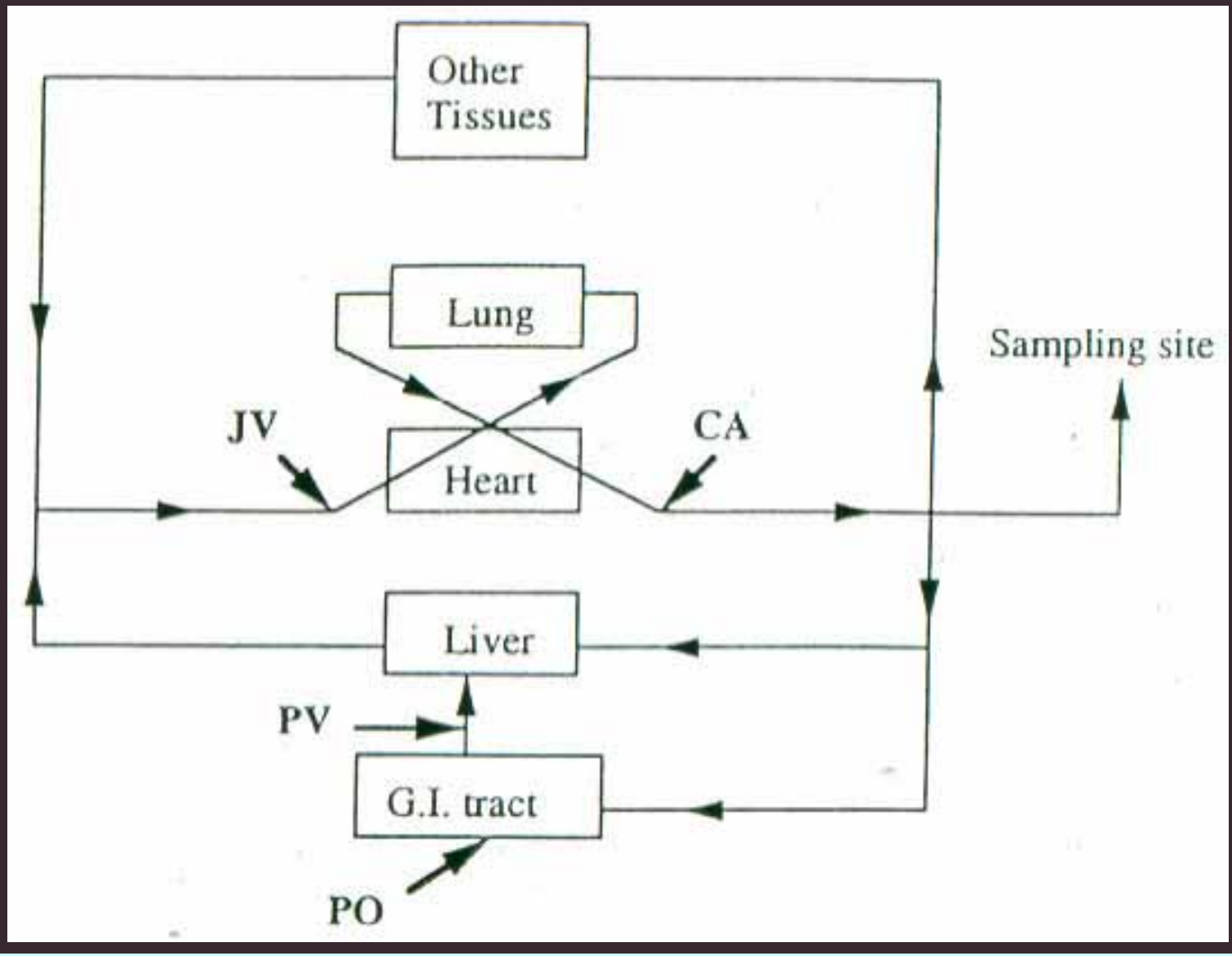
INHALATION of 300 ppm and GASTRIC INFUSION of 30 mg/kg 1,1-DICHLOROETHYLENE over 2 Hours



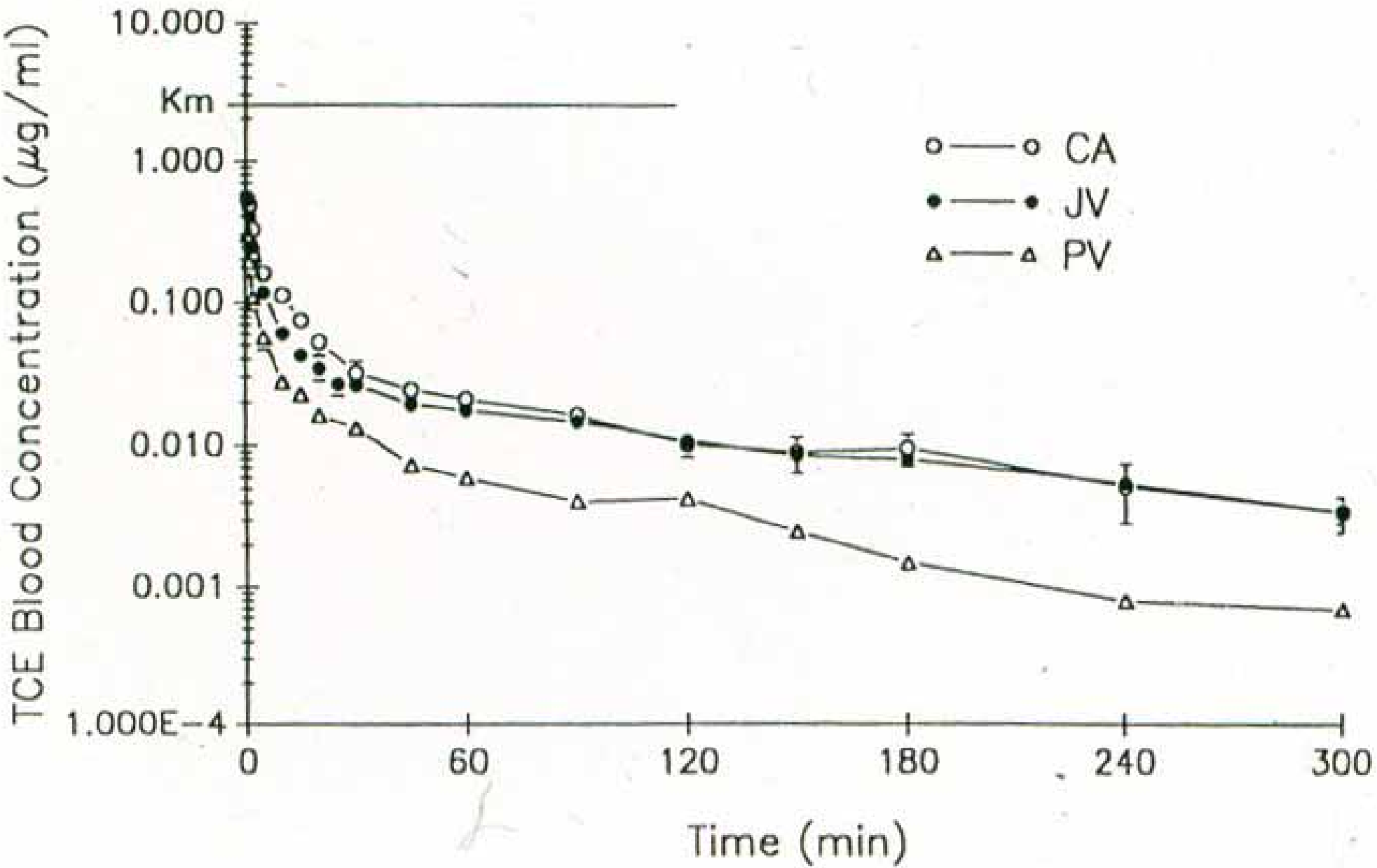

Gamma- Glutamyl Transpeptidase(GGT) in Urine of Rats
exposed to DCE (30 mg/kg or 300 ppm) for 2 hrs
GGT in Urine (Units)
6000
5000
4000
3000
2000
1000
0
***
***
Con12 hr
Con24 hr
PO12 hr
PO24 hr
GI12 hr
GI24 hr
inh12hr
Inh24hr
Treatment

Objective

- **Ascertain the Relative Contribution of the LIVER & LUNGS to 1st Pass Elimination of each of series of VOCs**



TCE administration and sampling sites in the rat.



Blood TCE conc. vs. Time Profiles after adm. of 0.71 mg/kg by diff. Routes

First-Pass Elimination of TCE in Rats[a]

Eliminating organ	TCE Dose (mg/kg)					
	0.17	0.33	0.71	2.0	8.0	16.0
Lungs	NC	NC	5.7	4.8	7.4	8.0
Liver	57.5	45.0	42.6	25.2	10.8	NC
Total	59.5	53.6	49.5	45.3	36.7	13.6

[a] Values are expressed as percentage of administered dose. They are based on bioavailability (corresponding area ratios), corrected by $t_{\frac{1}{2}}$.

The liver is capable of removing virtually ALL of a VOC so long as the dose (rate) is not High enough to saturate its metabolism.

Andersen, M. E. (*TAP*, 1981)

Objective

- **To determine the effect of rate of oral drug administration on the pharmacokinetics and first pass metabolism of TRI and TCE.**

Methods

- Male Sprague-Dawley rats received
  - TRI via Gastric Infusion or Oral Bolus
    - 6 MG/KG
    - 48 MG/KG
  - TCE via Gastric Infusion or Oral Bolus
    - 10 MG/KG
    - 50 MG/KG

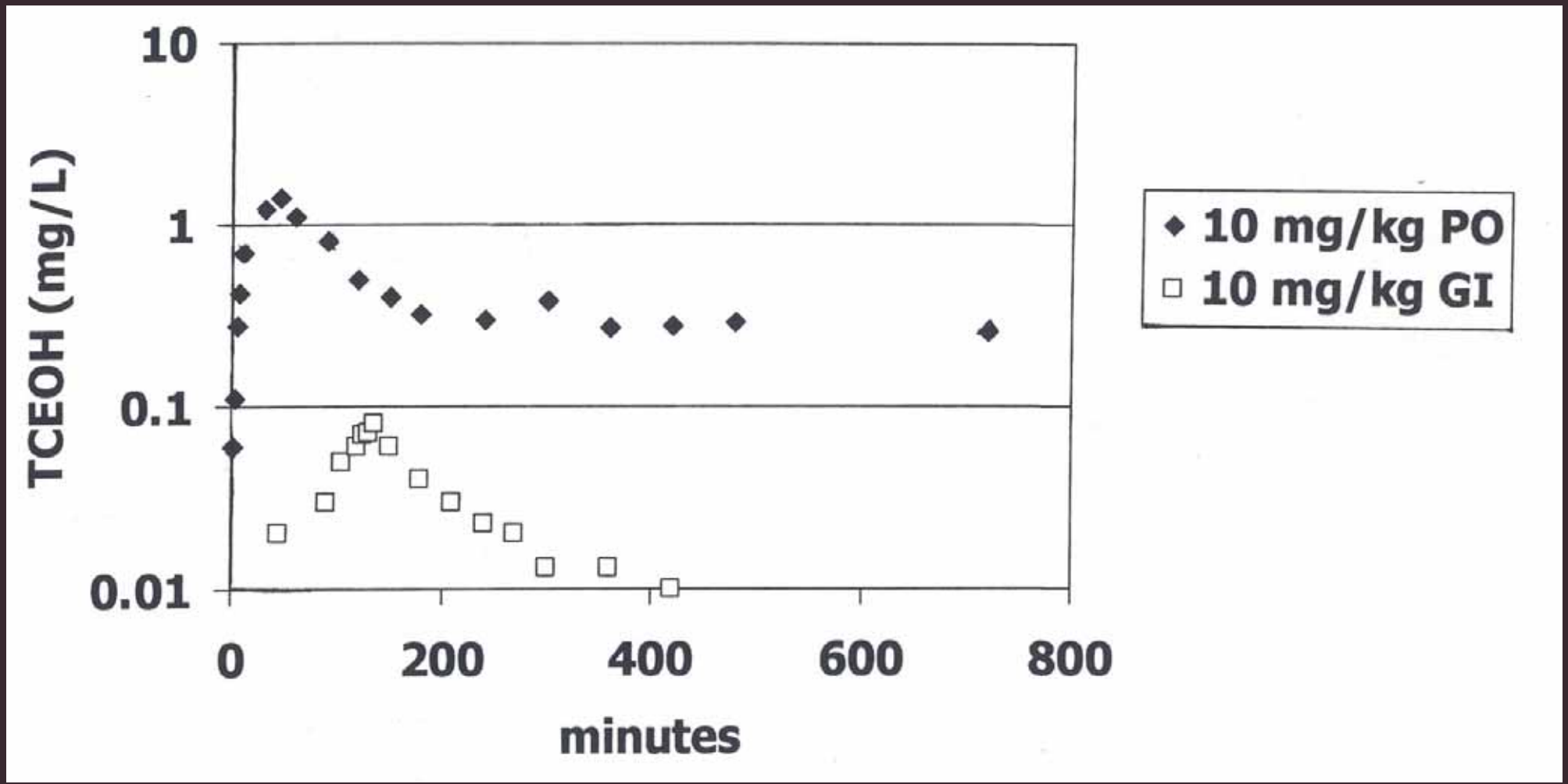
Methods

- **TCE, trichloroethanol (TCEOH) and trichloroacetic acid (TCA) were determined by Gas Chromatography**
- **Pharmacokinetics analysis was performed with WINNONLIN**

TRI Bioavailability

	6 mg/kg	48 mg/kg
PO	96 %	106 %
GI	98 %	89 %

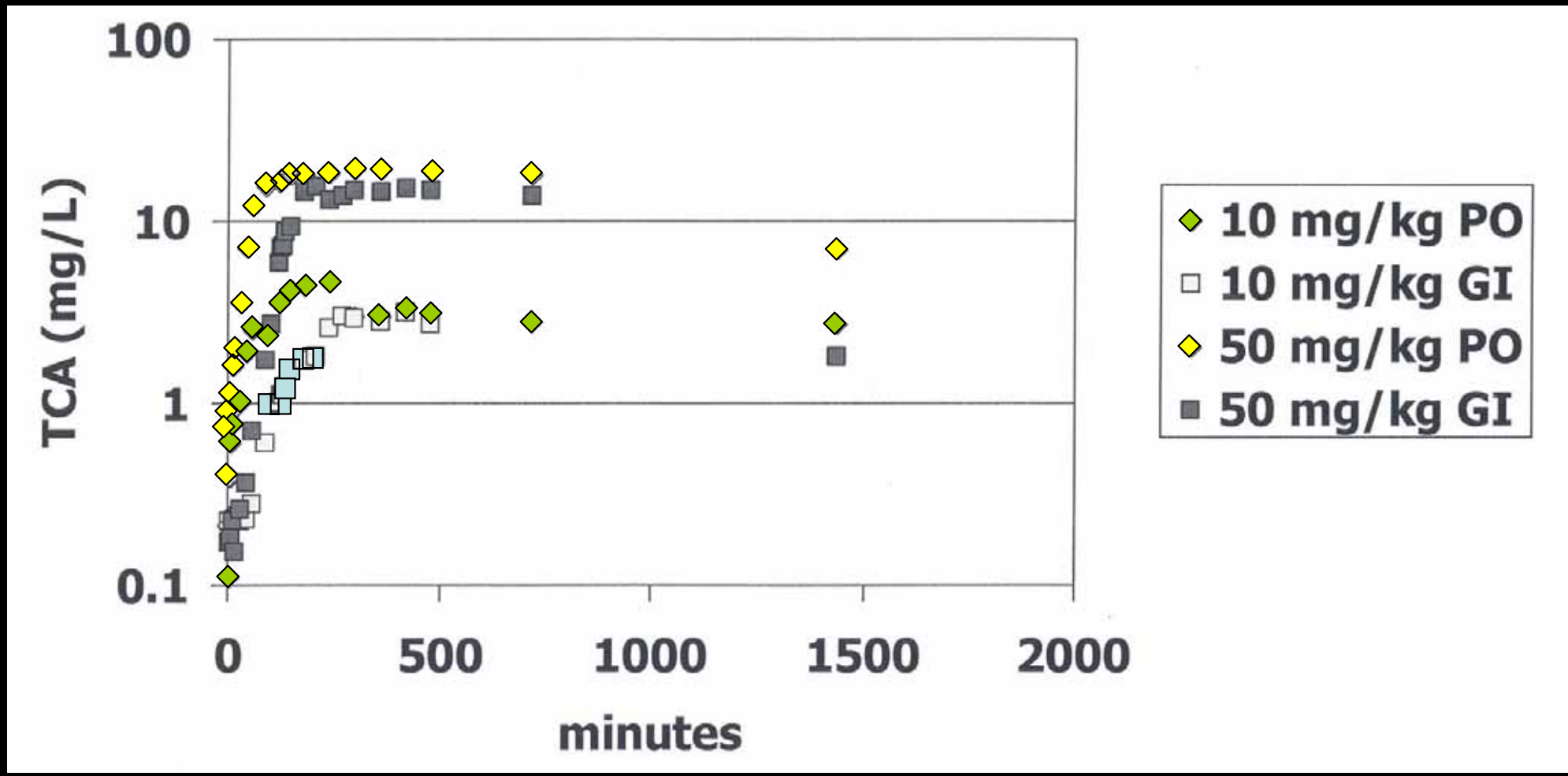
TCEOH: GI vs. Oral Bolus of TCE



TCEOH Pharmacokinetics

Dose (mg/kg)	Cmax (mg/L)	Tmax (minutes)	AUC (mg*min/L)
10 PO	1.4 ± 0.5	36 ± 12	262 ± 90
10 GI	0.44 ± 0.1	162 ± 29	86 ± 15
50 PO	4.2 ± 0.9	66 ± 16	903 ± 54
50 GI	1.9 ± 0.9	140 ± 12	433 ± 214

TCA: GI vs. Oral Bolus of TCE



TCA Pharmacokinetics

Dose (mg/kg)	Cmax (mg/L)	Tmax (minutes)	AUC (mg*min/L)
10 PO	5.0 ± 1.5	266 ± 76	2091 ± 846
10 GI	3.5 ± 1.2	358 ± 136	951 ± 290
50 PO	19.4 ± 1.1	330 ± 79	17033 ± 4834
50 GI	15.4 ± 2.3	356 ± 94	9342 ± 5522

SIGNIFIANCE OF 1st-PASS ELIMATION OF ENVIRONMENTAL DOSES OF TCE

Amount of TCE reaching Extrahepatic Organs may be NIL.

Cancer Risk in organs (other than Kidneys) may be NIL.

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