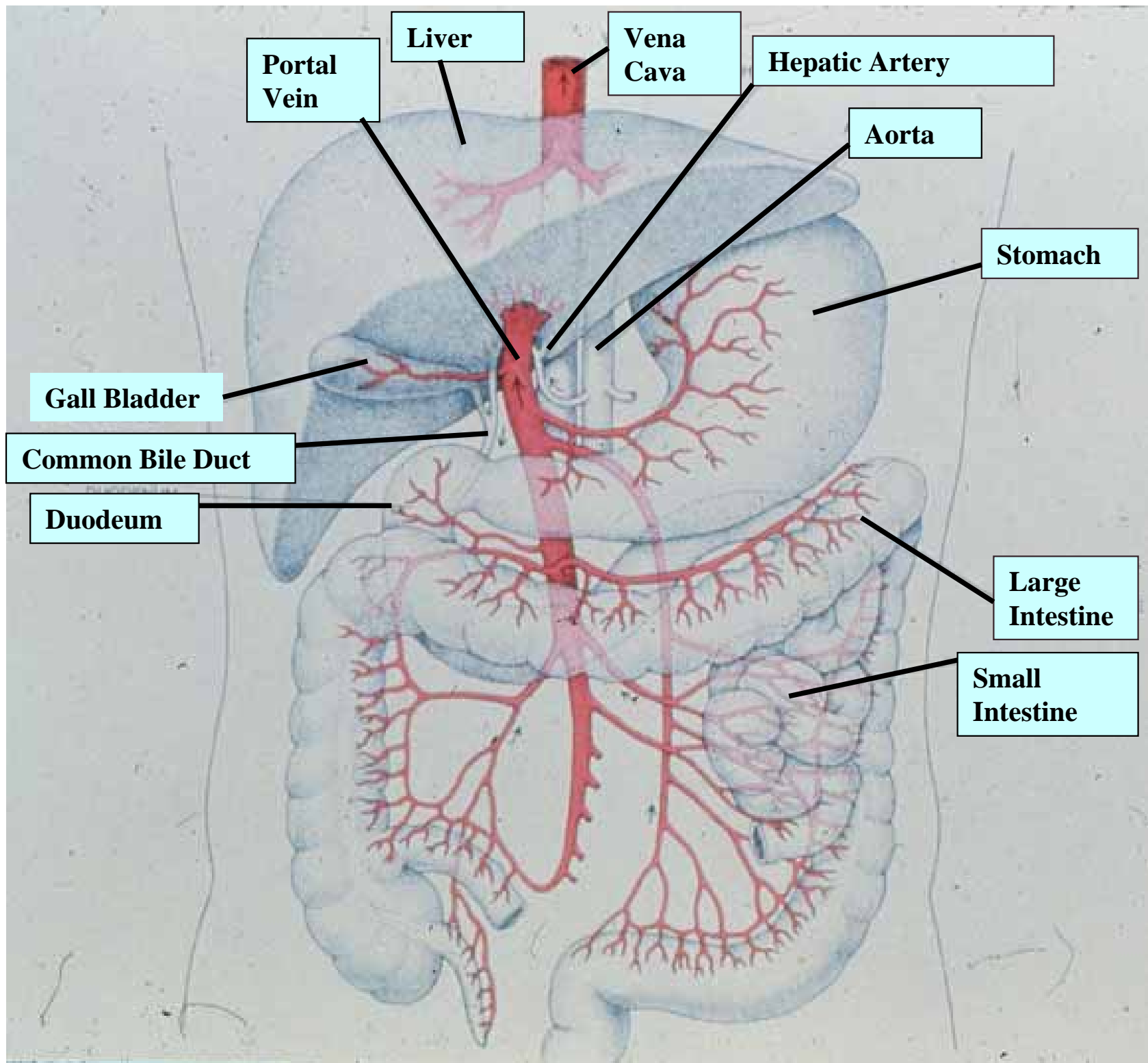
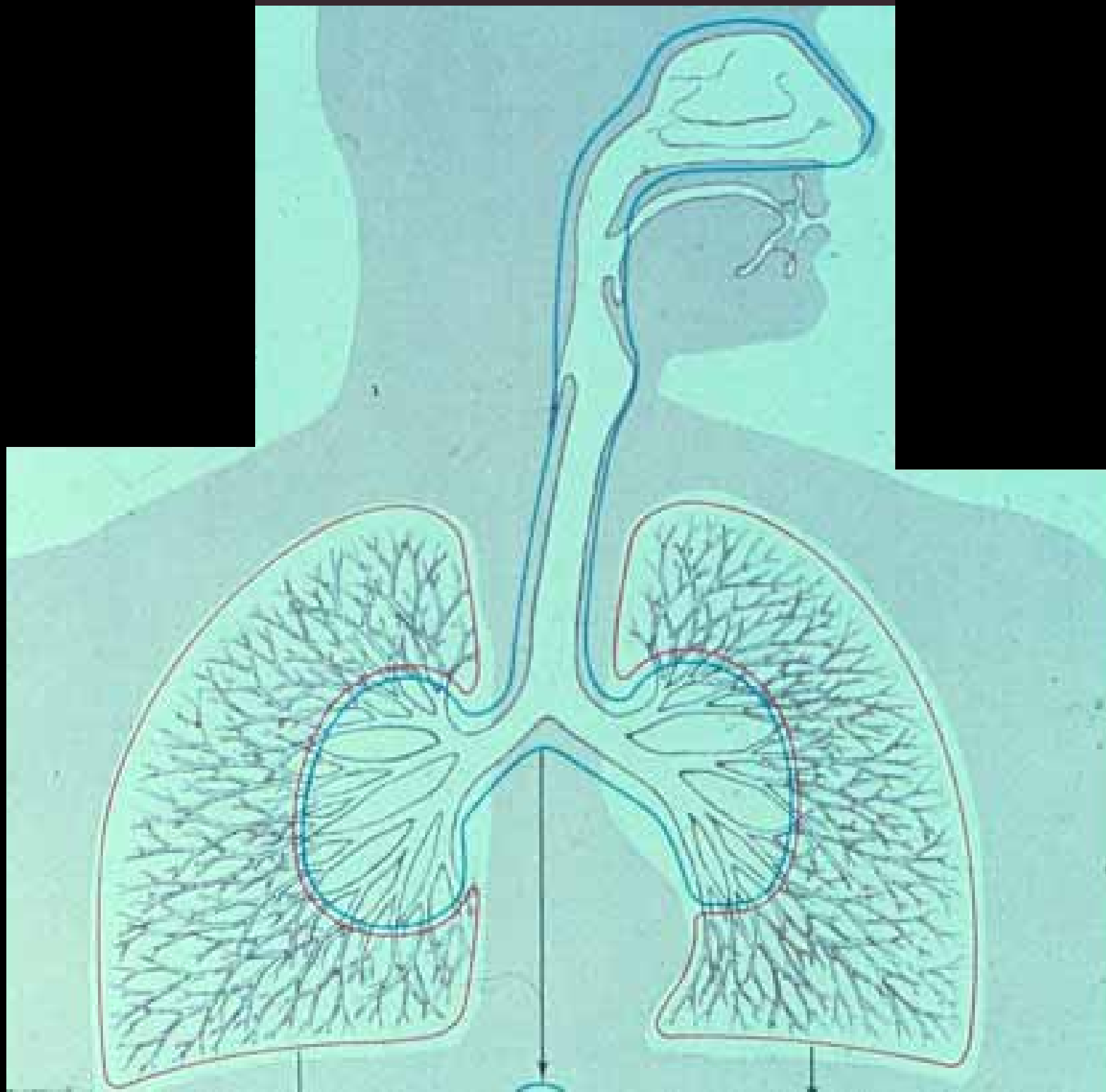


PRESYSTEMIC ELIMINATION OF ORAL TRICHLOROETHYLENE





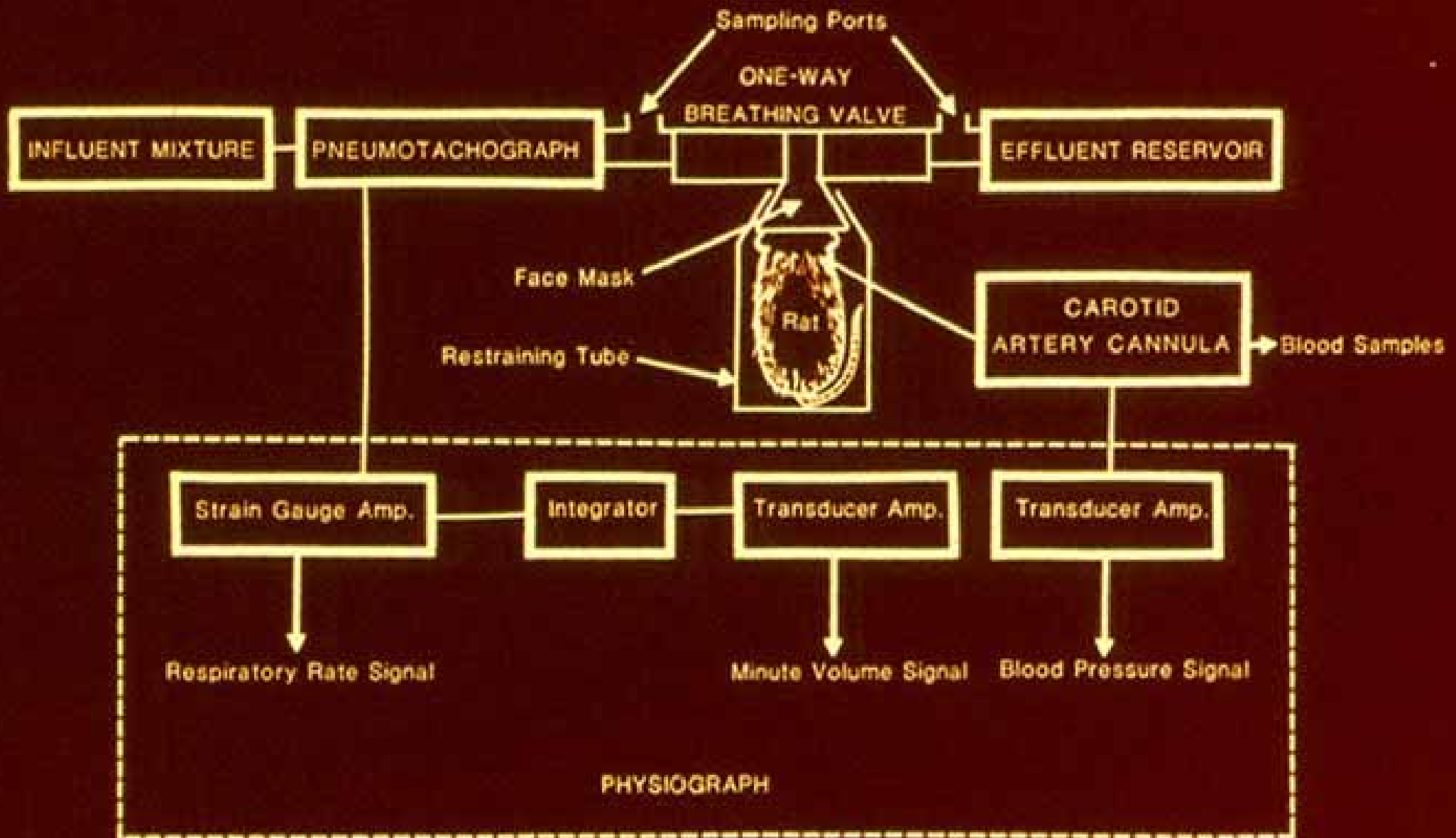
**Are the results of inhalation studies
Applicable Qualitatively or
Quantitatively to situations where
chemicals are ingested?**

ROUTE to ROUTE COMPARISON

EXPERIMENTAL APPROACH

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

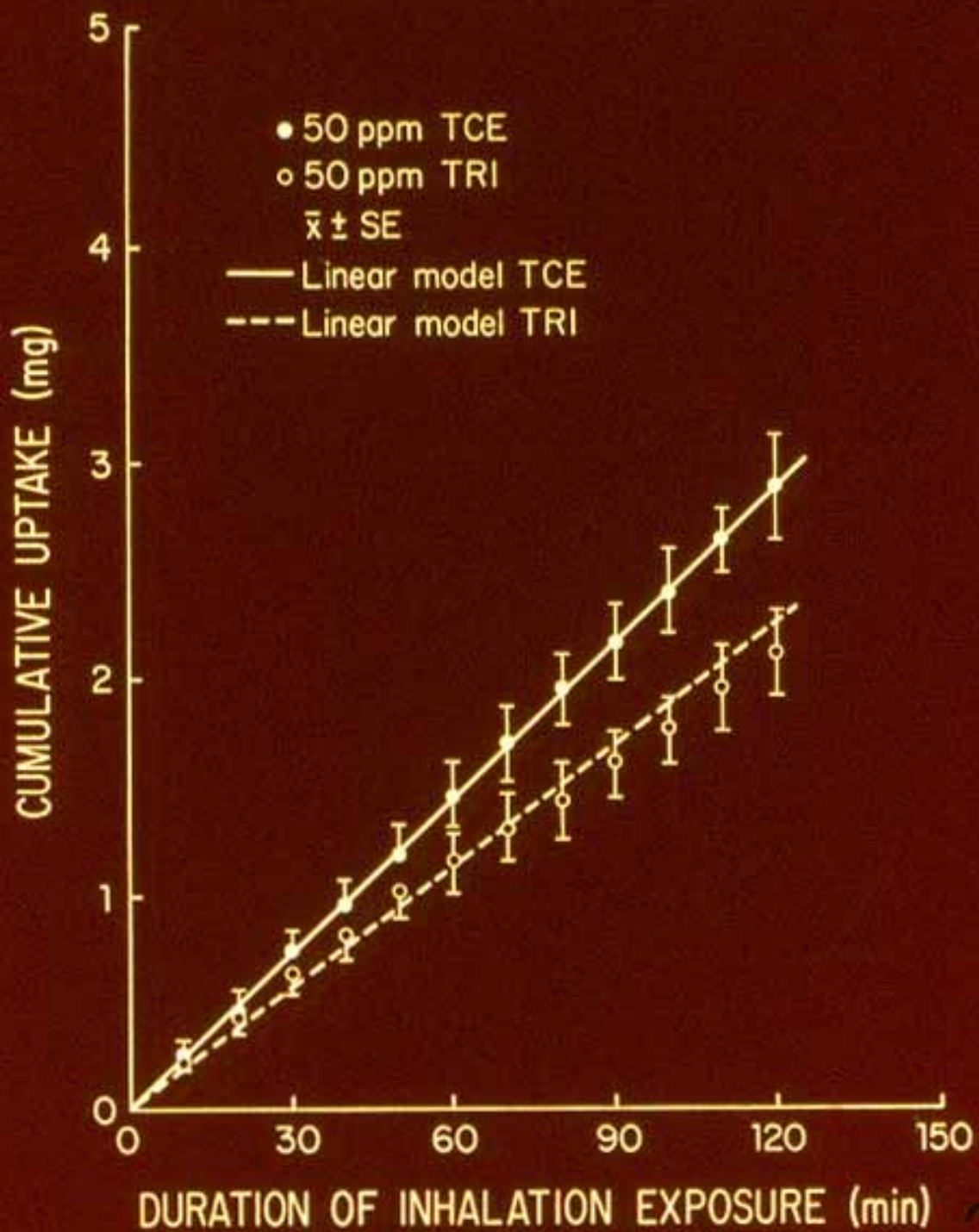
INHALATION EXPOSURE SYSTEM

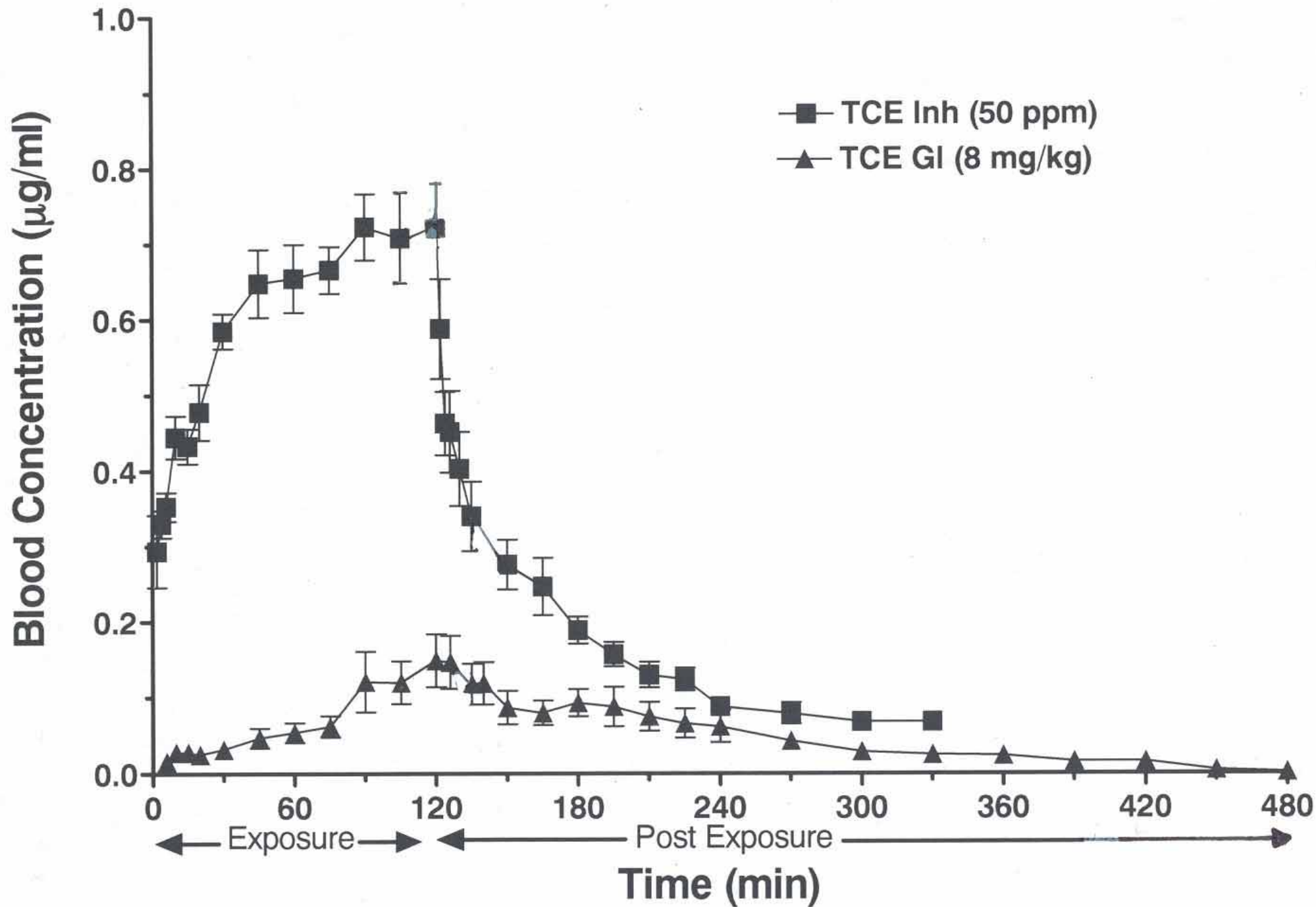


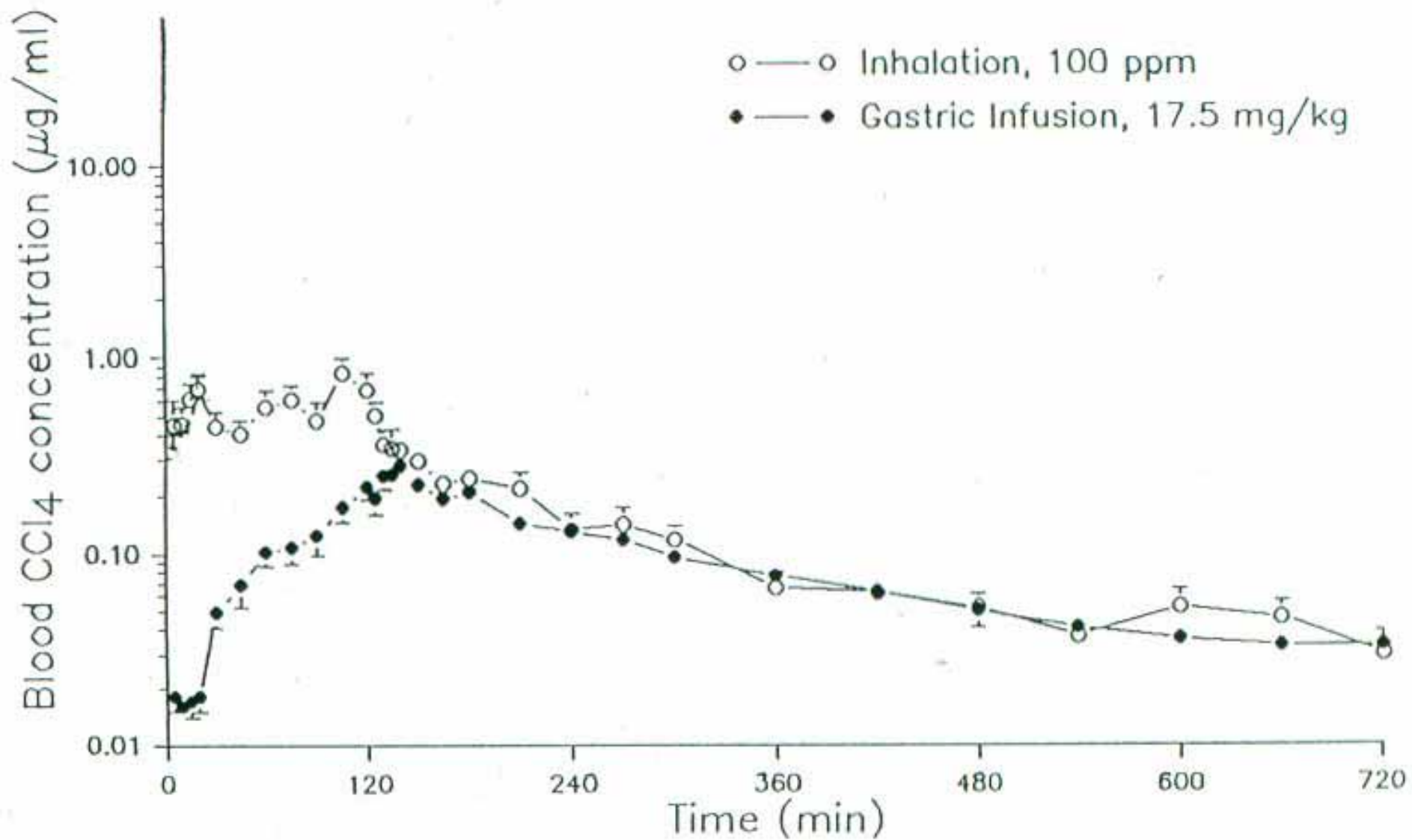
Amount Retained (MG) =

INHALED CONC. – ALVEOLAR CONC. X MINUTE VOLUME

Cumulative Uptake of TCE and TRI

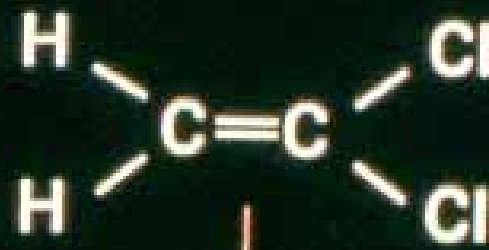






**Work Supported by COOPERATIVE
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Between U.S. EPA Health Effects
Research Laboratory (RTP, NC) and
University of Georgia (Athens, GA)**

1,1-DCE METABOLIC PATHWAY



Reactive Metabolite(s)

(Electrophile
-epoxide?)

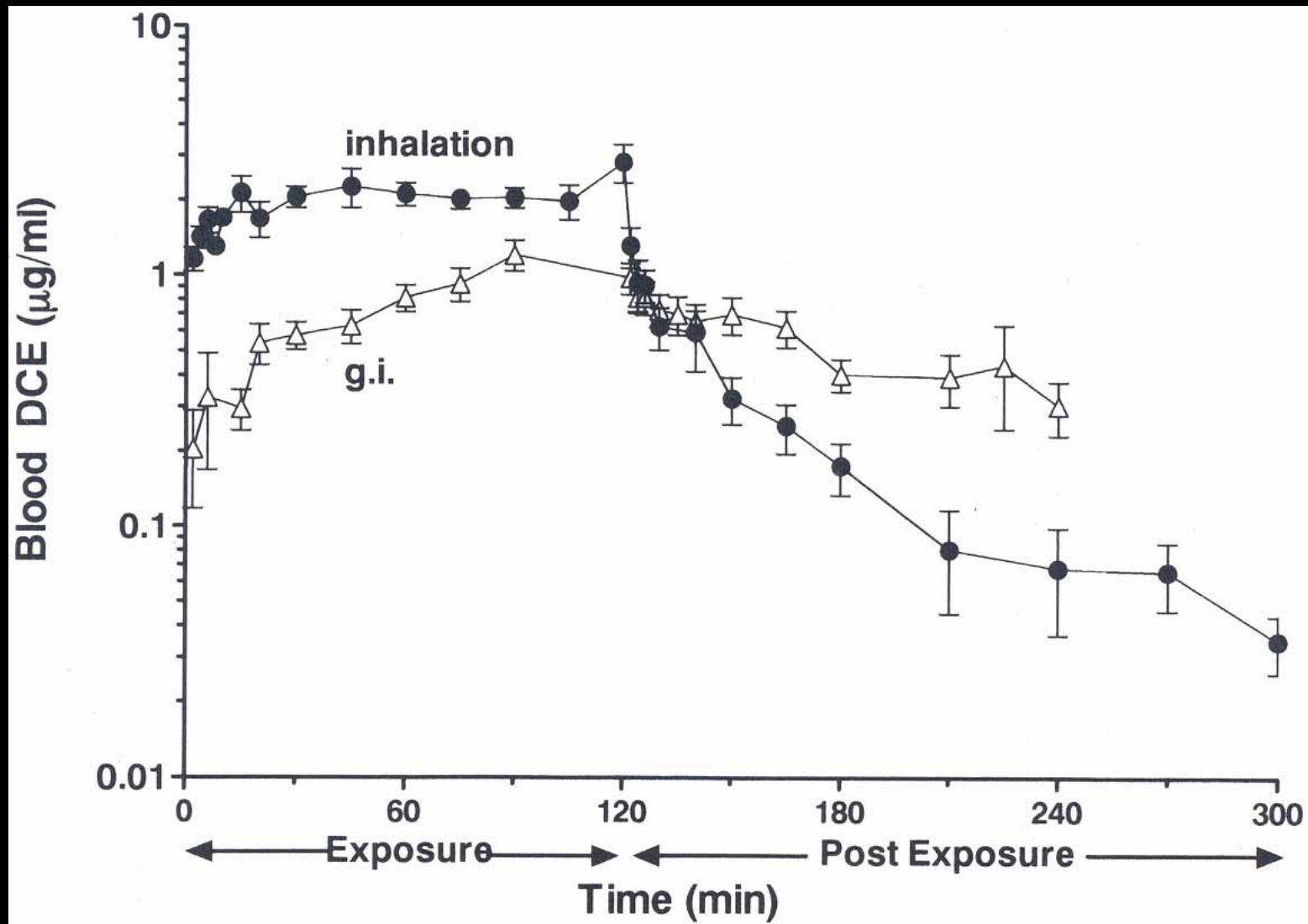
Detoxification

- Conjugation with GSH
- Urinary mercapturic acid excretion

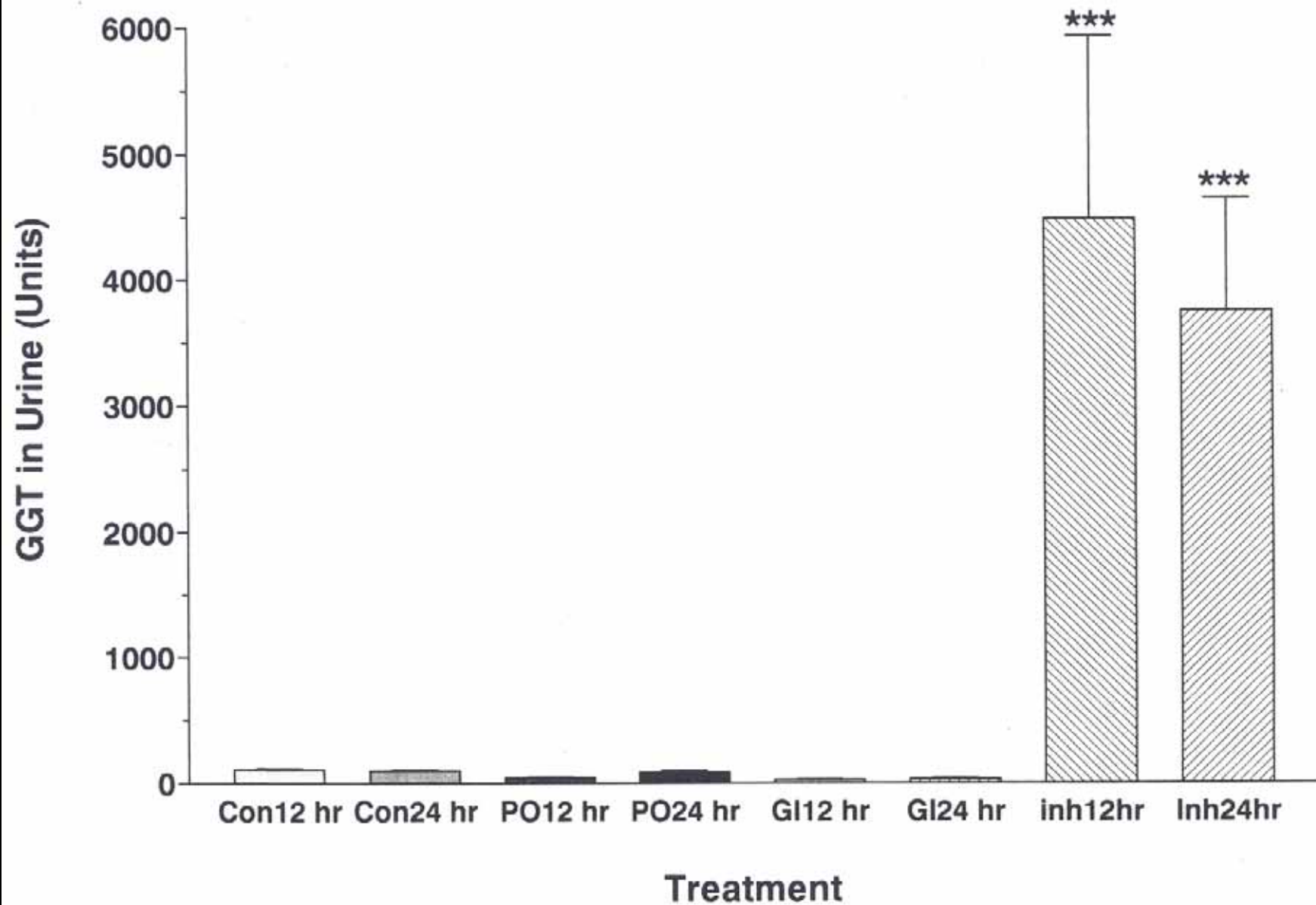
Toxicity

- Covalent binding to tissue nucleophiles

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

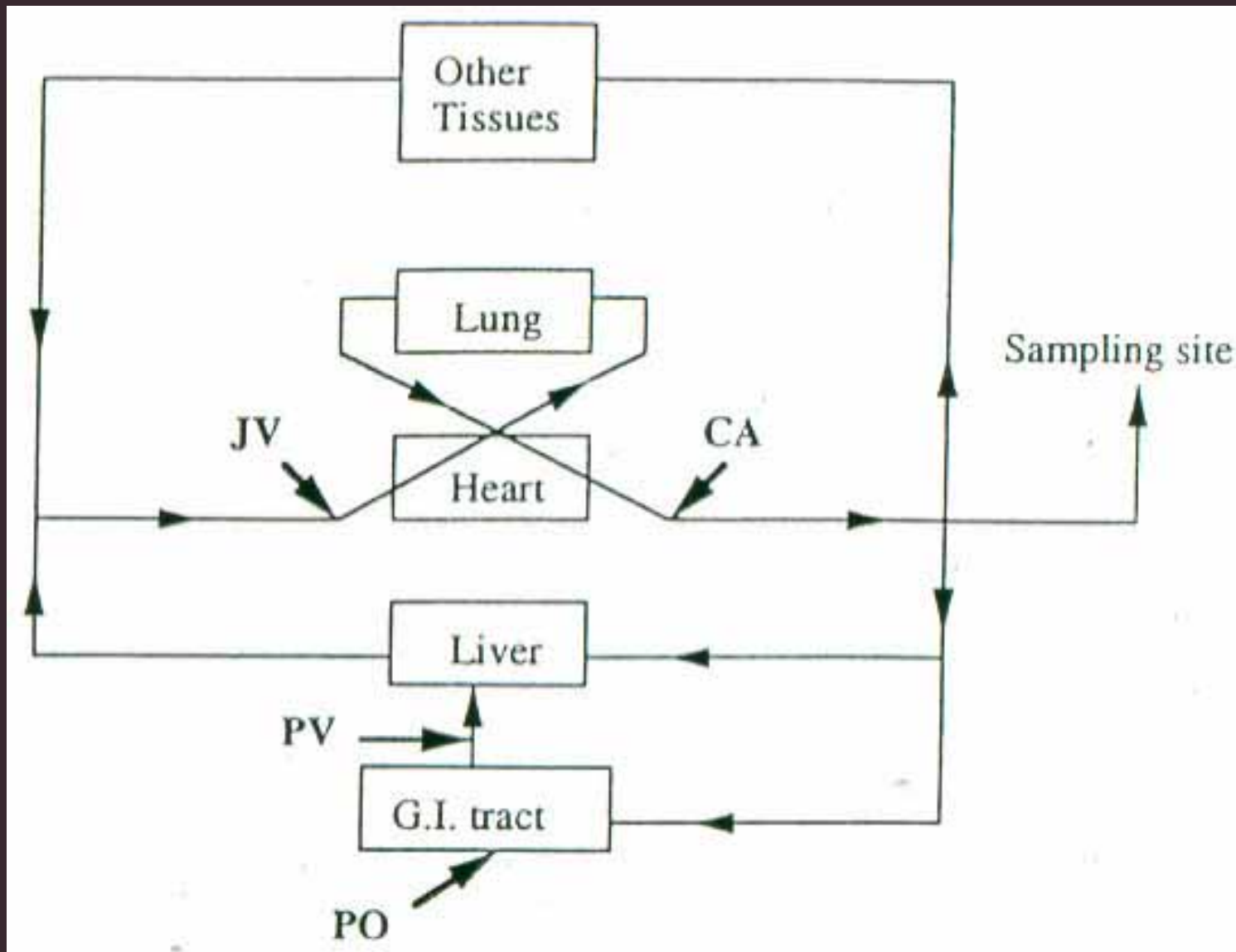


Gamma- Glutamyl Transpeptidase(GGT) in Urine of Rats exposed to DCE (30 mg/kg or 300 ppm) for 2 hrs

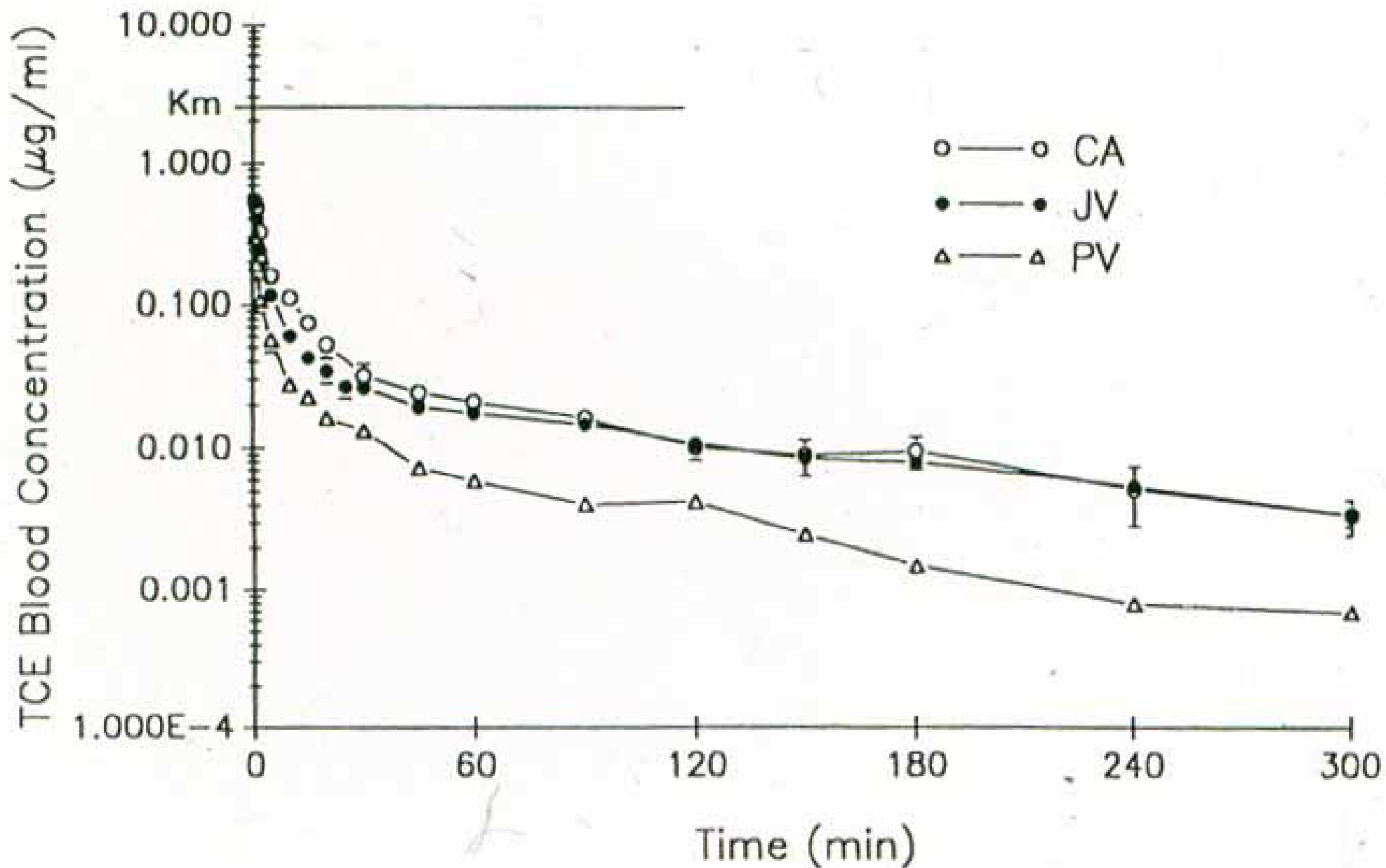


Objective

- ★ **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 $t_{1/2}$.

**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**

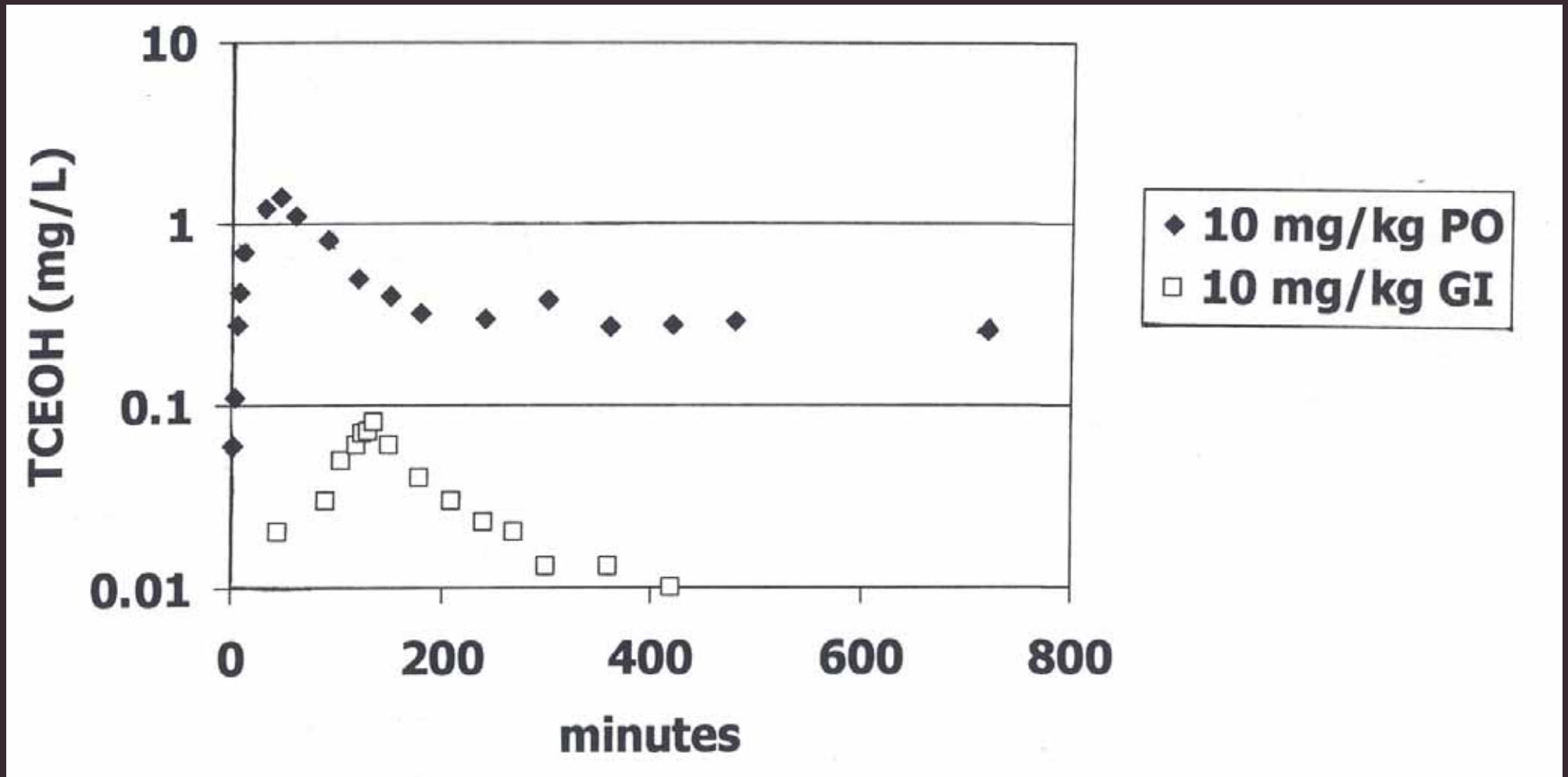
Methods

- **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 %

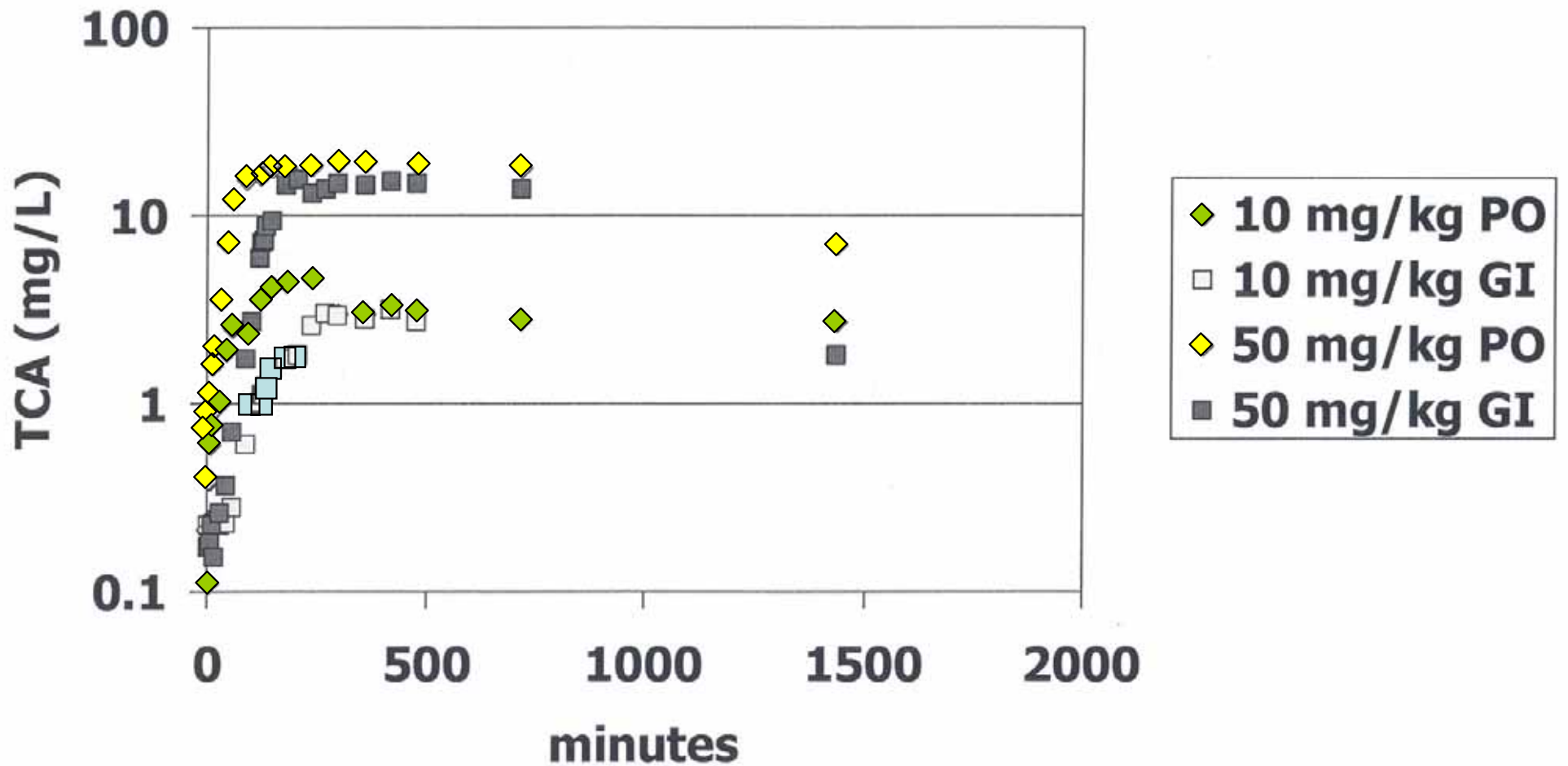
TCEOH: GI vs. Oral Bolus of TCE



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

**SIGNIFICANCE OF 1st-PASS
ELIMINATION 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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