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TOXICOLOGY AND APPLIED PHARMACOLOGY 91, 256–265 (1987)

Intestinal Absorption of Trichloroethyl...

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TATSUYA HOBARA, HARUO KOBAYASHI, SUSUMU IWAMOTO, AND TSU...

Department of Public Health, Yamaguchi University School of M...

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Intestinal Absorption of Trichloroethylene in Dogs. HOBARA, T., KOBAYASHI, H., KAWAMOTO, T., IWAMOTO, S., AND SAKAI, T. (1987). *Toxicol. Appl. Pharmacol.* **91**, 256–265. In order to examine the intestinal absorption of trichloroethylene (TRI), we developed the intestinal circulation system of dogs and administered TRI solution at three concentrations (0.1, 0.25 and 0.5%) to the three parts of the intestinal tract (jejunum, ileum, and colon) of the operated dogs. We measured TRI and its metabolites, free-trichloroethanol, trichloroacetic acid, and conjugated trichloroethanol, in serum or blood, urine, bile and circulating solutions. The absorption rates of TRI from the intestine were 50–70% of the administered volume of TRI 2 hr after administration in all groups, and all parts of intestine readily absorbed TRI. Moreover, there were no significant differences in the absorption rates of TRI and water between the jejunum and ileum, and ileum and colon, respectively. The excretion rates of TRI and its metabolites in urine and bile were very low (0.1–0.4%) compared with the volume of absorbed TRI from the intestine 2 hr after administration in all groups. The high degree of absorption of TRI should be considered when threshold limits for TRI in the drinking water, the surface water, and the ground water are established.

An important industrial chemical for the past 60 years, trichloroethylene (TRI)[1] is used as a solvent for vapor decreasing of fabricated metal parts, as a solvent in the textile industry, and as a lubricant, among other uses. There are numerous surveys concerning TRI toxicity to animals and humans (Waters *et al.*, 1977; Nomiyama and Nomiyama, 1979; Kimbrough *et al.*, 1985). In recent years, it is reported that this substance is a carcinogen in B6C3F1 mice (NCI, 1976; NTP, 1983).

TRI production by chemical companies has been increasing every year. During and after use, large amounts of TRI are released into rivers, the ground, and the sea. TRI is a stable substance that is only slightly degraded by light, heat, water, natural bacteria, and microorganisms. It has a slow decomposition rate in the dark in dilute aqueous solution (Dilling *et al.*, 1975). Therefore, TRI pollution of surface water as well as ground water is increasing year by year, creating serious problems in many advanced nations (IARC, 1979). In contrast, relatively little is known about its absorption from the gastrointestinal tract (D'Souza *et al.*, 1985). For this reason, we administered TRI solutions at three concentrations (0.1, 0.25, and 0.5%) to the three segments of intestinal tracts (jejunum, ileum, and colon) of operated dogs. We measured TRI and its metabolites, free trichloroethanol (F-TCE), trichloroacetic acid (TCA), and conjugated trichloroethanol (Conj-TCE), in the serum or blood, urine, bile, and circulating solutions.

[1] Abbreviations used: TRI, trichloroethylene; CH, chloral hydrate; F-TCE, free trichloroethanol; Conj-TCE, conjugated trichloroethanol; TCA, trichloroacetic acid; T-TCE, total trichloroethanol; ECG, electrocardiogram.

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TOXICOLOGY AND APPLIED PHARMACOLOGY 91, 256–265 (1987)

Intestinal Absorption of Trichloroethylene in Dogs

TATSUYA HOBARA, HARUO KOBAYASHI, TOSHIHIRO KAWAMOTO, SUSUMU IWAMOTO, AND TSUNEMI SAKAI

Department of Public Health, Yamaguchi University School of Medicine, 1144 Kogushi, Ube 755, Japan

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Intestinal Absorption of Trichloroethylene in Dogs. HOBARA, T., KOBAYASHI, H., KAWAMOTO, T., IWAMOTO, S., AND SAKAI, T. (1987). *Toxicol. Appl. Pharmacol.* **91**, 256–265. In order to examine the intestinal absorption of trichloroethylene (TRI), we developed the intestinal circulation system of dogs and administered TRI solution at three concentrations (0.1, 0.25 and 0.5%) to the three parts of the intestinal tract (jejunum, ileum, and colon) of the operated dogs. We measured TRI and its metabolites, free-trichloroethanol, trichloroacetic acid, and conjugated trichloroethanol, in serum or blood, urine, bile and circulating solutions. The absorption rates of TRI from the intestine were 50–70% of the administered volume of TRI 2 hr after administration in all groups, and all parts of intestine readily absorbed TRI. Moreover, there were no significant differences in the absorption rates of TRI and water between the jejunum and ileum, and ileum and colon, respectively. The excretion rates of TRI and its metabolites in urine and bile were very low (0.1–0.4%) compared with the volume of absorbed TRI from the intestine 2 hr after administration in all groups. The high degree of absorption of TRI should be considered when threshold limits for TRI in the drinking water, the surface water, and the ground water are established.

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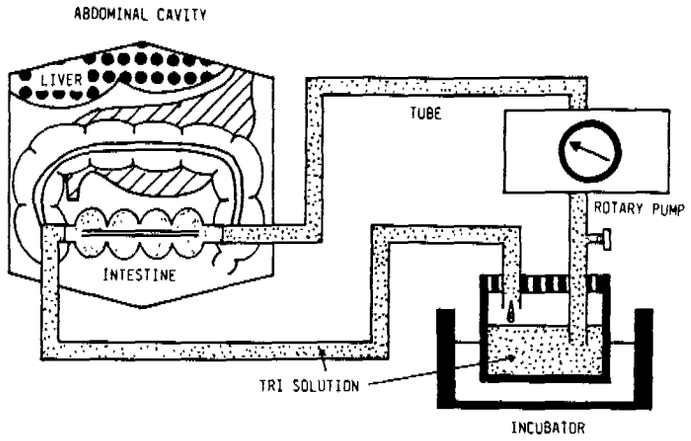

FIG. 1. Intestinal circulation system.

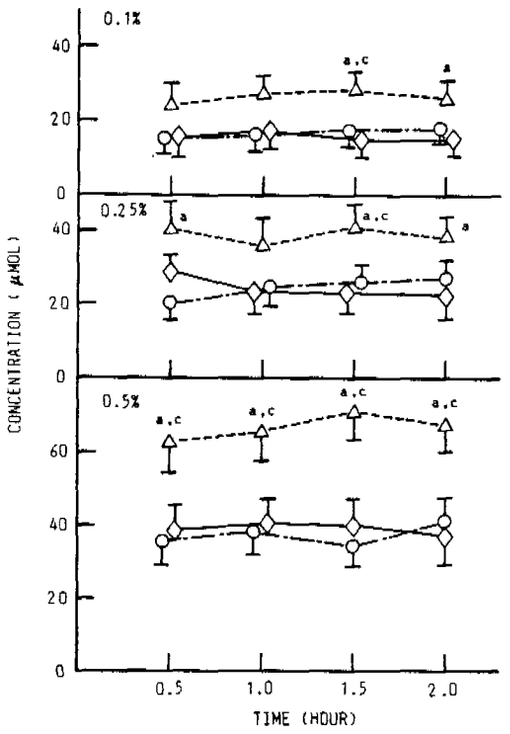

FIG. 2. Trichloroethylene concentrations in the blood after administration of 0.1, 0.25, and 0.5% trichloroethylene solution (mean ± SD; $n = 5$). ◇, Jejunum; ○, ileum; △, colon. a. Significant difference between the jejunum and colon ($p < 0.05$). c, Significant difference between the ileum and colon ($p < 0.05$).

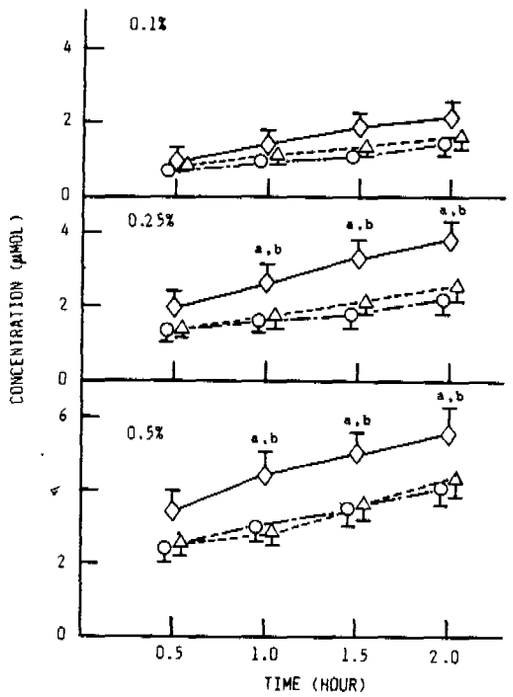

FIG. 3. Free trichloroethanol concentrations in serum after administration of 0.1, 0.25, and 0.5% trichloroethylene solution (mean ± SD; $n = 5$). ◇, Jejunum; ○, ileum; △, colon. a. Significant difference between the jejunum and colon ($p < 0.05$). b, Significant difference between the jejunum and ileum ($p < 0.05$).

TABLE 1

GAS CHROMATOGRAPHIC OPERATING CONDITIONS FOR ANALYSIS OF TRICHLOROETHYLENE, TRICHLOROETHANOL, AND TRICHLOROACETIC ACID (SHIMADZU GC-7AG WITH FLAME IONIZATION DETECTOR (FID) AND ELECTRON CAPTURE DETECTOR (ECD))

	Column	Column packing	Oven temperature	Injection temperature	Carrier gas and flow rate	Detector
Trichloroethylene	3.0 mm ϕ × 2.0 m (glass)	25% Silicone DC-550 Celite 545 AW 60–80 mesh	150°C	170°C	N_2, 60 ml/min	FID
Trichloroethanol and trichloroacetic acid	3.2 mm ϕ × 2.0 m (glass)	5% OV-17 Gaschrom Q 100–120 mesh	110°C	180°C	N_2, 40 ml/min	ECD (Ni-63)

METHODS

Animals. Sixty adult male and female mongrel dogs (8–12 kg body wt) were used. Each dog was anesthetized with 25–30 mg/kg of sodium pentobarbital given intravenously. Tracheal intubations were performed and cannulas were connected with a volume-type respirator (Aika-R-60). The respiratory rate was 20 cycles/min, and

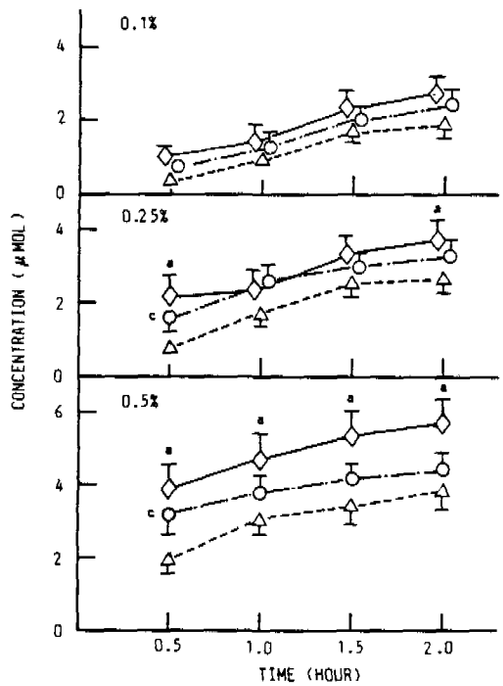

FIG. 4. Conjugated trichloroethanol concentrations in serum after administration of 0.1, 0.25, and 0.5% trichloroethylene solutions (mean ± SD; $n = 5$). ◇, Jejunum; ○, ileum; △, colon. a, Significant difference between the jejunum and colon ($p < 0.05$). c, Significant difference between the ileum and colon ($p < 0.05$).

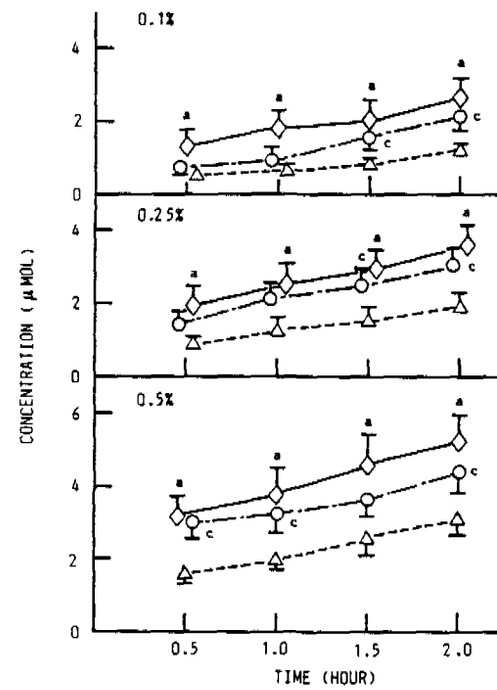

FIG. 5. Trichloroacetic acid concentrations in serum after administration of 0.1, 0.25, and 0.5% trichloroethylene solutions (mean ± SD; $n = 5$). ◇, Jejunum; ○, ileum; △, colon. a. Significant difference between the jejunum and colon ($p < 0.05$). c, Significant difference between the ileum and colon ($p < 0.05$).

HYLENE, TRICHLOROETHA-
)ETECTOR (FID) AND ELEC.

e	Carrier gas and flow rate	Detector
	N_2, 60 ml/min	FID
	N_2, 40 ml/min	ECD (Ni-63)

pentobarbital given intra-
is were performed and can-
olume-type respirator (Ai-
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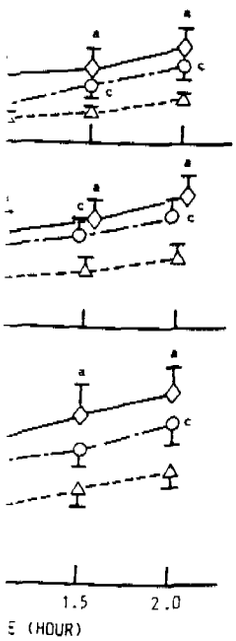

oncentrations in serum
and 0.5% trichloroeth-
5). ○, Jejunum; ○, il-
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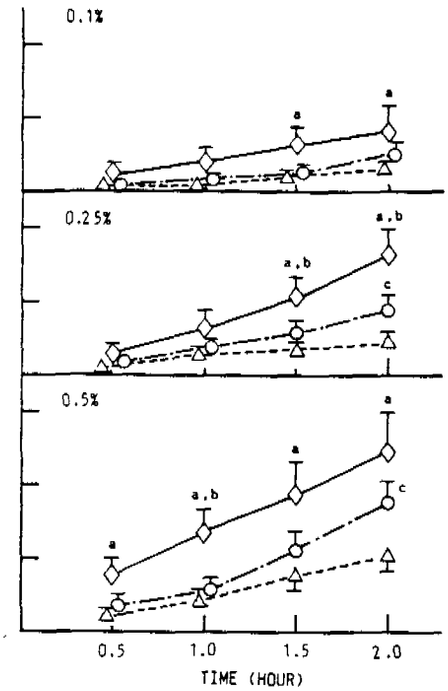

. 6. Free trichloroethanol concentration in urine af-
dministration of 0.1, 0.25, and 0.5% trichloroethyl-
olutions (mean ± SD; $n = 5$). ◇, Jejunum; ○, ileum;
olon. a, Significant difference between the jejunum
colon ($p < 0.05$). b, Significant difference between
jejunum and ileum ($p < 0.05$). c, Significant differ-
e between the ileum and colon ($p < 0.05$).

idal volume was adjusted to yield a peak inspiratory pressure of 10 cm H_2O (Kobayashi *et al.*, 1984). A catheter was inserted into the left femoral artery and connected to a strain-gauge transducer (Nihon Koden MP-0.5) to measure arterial blood pressure. The electrocardiogram (ECG) was recorded from the three standard limb leads and monitored with a memory scope (Nihon Koden VM-645R). The heart rate was obtained from the R-R interval in the ECG.

Intestinal circulation system. As shown in Fig. 1, the abdominal wall was cut transversely along the bottom of the diaphragm with an electric surgical unit (Asahiika Co.). After the intestine was cut at a length of 30 cm, the contents were emptied and the inside was washed with a 1% phosphate buffer (pH 7.0). Both sides of the intestine were connected with Teflon tubes (1 cm $\phi \times 40$ cm), as shown in Fig. 1, and the opposite sides of the intestine were closed. The jejunum, ileum, and colon were used for TRI administration. The jejunum was defined as the first 30 cm after the stomach, the ileum was defined as 30 cm retrograde from the ileocecal region, and the colon was defined as the first 30 cm from the ileocecal region. Phosphate buffer solution was circulated with a rotary pump (Travenol Co.) at 300 ml/min. After the solution had circulated to the intestine, the abdominal wall was closed and both sides of the tubes were left in place. Then solutions containing 0.1, 0.25, or 0.5% (weight/volume) were perfused through the intestine. At concentrations of TRI below 0.1%, we could not measure F-TCE and TCA in blood, urine, or bile. The volume of each solution was 500 ml. TRI was added to polyoxyethylene sorbitan monooleate (Tween 80, 1:1) and adjusted to pH 7.0 with a phosphate buffer. These mixed solutions were soluble in water. TRI and Tween 80 were obtained from Katayama Chemical Co., Inc., and had a purity of more than 99%.

Sampling of blood, urine, bile, and solution. Arterial blood samples (6 ml) were obtained from the right femo-

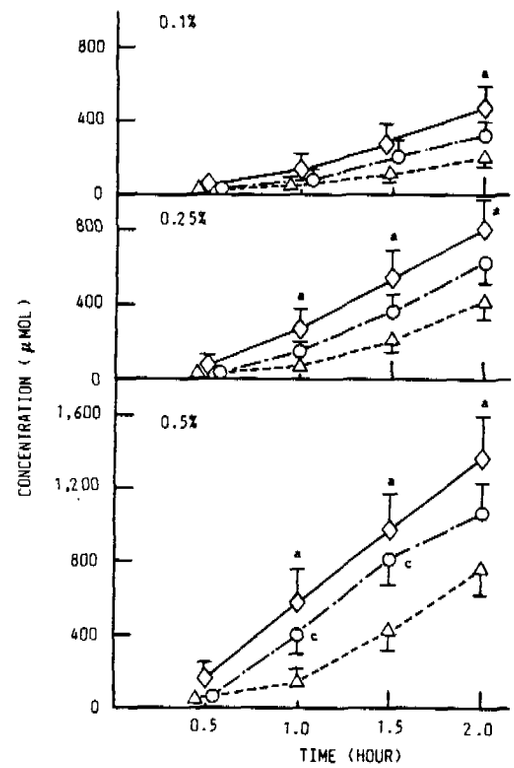

FIG. 7. Conjugated trichloroethanol concentration in urine after administration of 0.1, 0.25, and 0.5% trichloroethylene solutions (mean ± SD; $n = 5$). ◇, Jejunum; ○, ileum; △, colon. a, Significant difference between the jejunum and colon ($p < 0.05$). c, Significant difference between the ileum and colon ($p < 0.05$).

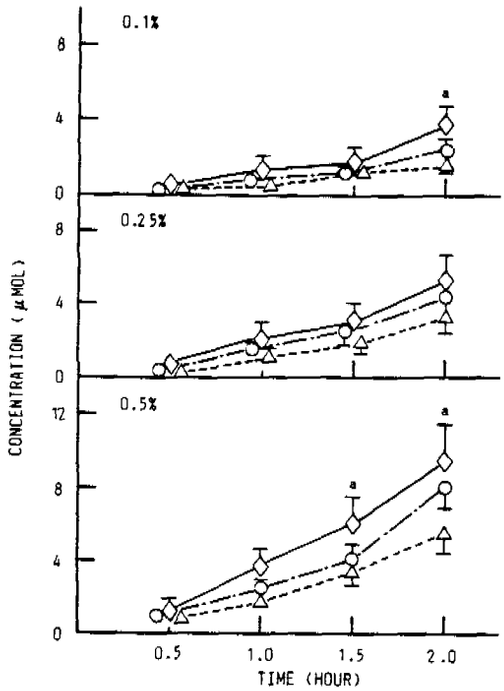

FIG. 8. Trichloroacetic acid concentration in urine after administration of 0.1, 0.25, and 0.5% trichloroethylene solutions (mean ± SD; $n = 5$). ◇, Jejunum; ○, ileum; △, colon. a, Significant difference between the jejunum and colon ($p < 0.05$).

ral artery once before administration of TRI and at 30, 60, 90, and 120 min after administration. Urine was collected with a urinary catheter, which was inserted through the urethra into the bladder (Hobara *et al.*, 1986a). Urine was collected five times, from 30 min before administration to 2 hr after administration. Bile was collected every 30 min until 2 hr after administration of each concentration of TRI (Hobara *et al.*, 1982b, 1986b). Three-milliliter samples of the circulating solutions were collected from the outlet (Fig. 1) every 30 min until 2 hr after administration. The volume of excreted urine and bile was constant for all TRI groups, about 1.0 ml/kg/hr.

Analysis. The analytical methods for the determination of F-TCE, total trichloroethanol (T-TCE) containing F-TCE and Conj-TCE, and TCA were described by Humbert and Fernandez (1976). Conj-TCE was calculated from the differences between T-TCE and F-TCE. The method for determining TRI has been described previously (Hobara *et al.*, 1982a). F-TCE, T-TCE, and TCA were measured periodically in the serum, urine, bile, and solution, while TRI was measured in the blood, urine, bile, and solution. The gas chromatographic conditions are shown in Table 1.

Statistical analysis. All data are presented as the mean ± standard deviation of the mean. The data were compared by ANOVA and Newman–Keul's test. p values < 0.05 were regarded as significant.

RESULTS

Intestinal Circulation System

The intestinal circulation system did not result in significant differences in blood pressure, heart rate, ECG, glutamic oxaloacetic transaminase and glutamic pyruvic transaminase, alkaline phosphatase, erythrocyte and leukocyte counts, hematocrit, blood urea nitrogen, and creatinine. Moreover, no abnormal findings were observed in the ECG pattern. This operation does not require special-

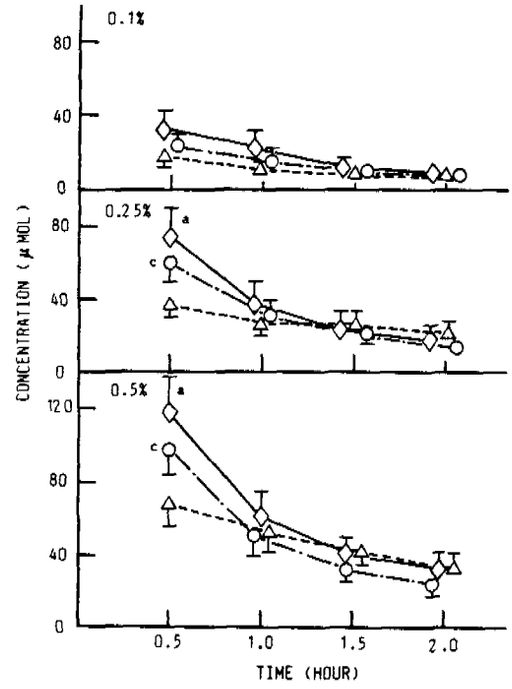

FIG. 9. Trichloroethylene concentration in bile after administration of 0.1, 0.25, and 0.5% trichloroethylene solutions (mean ± SD; $n = 5$). ◇, Jejunum; ○, ileum; △, colon. a, Significant difference between the jejunum and colon ($p < 0.05$). c, Significant difference between the ileum and colon ($p < 0.05$).

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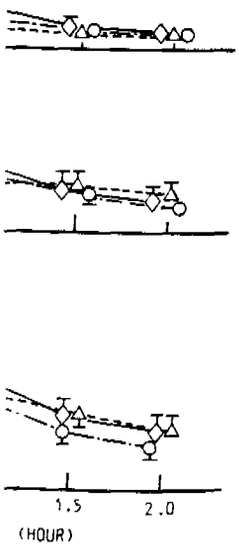

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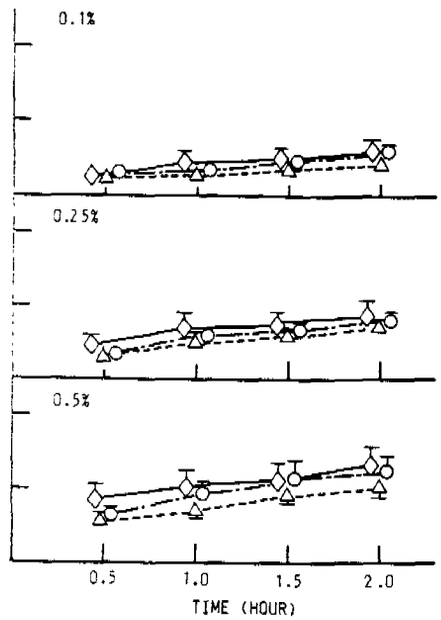

10. Free trichloroethanol concentration in bile af-
ministration of 0.1, 0.25, and 0.5% trichloroethyl-
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anges in TRI and Its Metabolites in Blood
or Serum

Figures 2, 3, 4, and 5 show the changes in TRI, F-TCE, Conj-TCE, and TCA in the blood or serum after administration of 0.1, 0.25, and 0.5% TRI through the jejunum, ileum, and colon. TRI values were measured in the blood, while those of F-TCE, TCA, and Conj-TCE were measured in the serum.

According to these observations, TRI remained constant in the blood, while F-TCE, Conj-TCE, and TCA increased gradually with time. Depending on the time, the concentration of TRI was 10 to 30 times higher than those of F-TCE, Conj-TCE, and TCA in all groups. In terms of each region of administration, the blood concentration of TRI in the colon group was higher than those in the ileum and jejunum groups, while the F-TCE and Conj-TCE levels of the jejunum were higher than those of the colon and ileum. TCA levels in the jejunum and ileum were higher than that of the colon. Absorption of TRI, F-TCE, TCA, and Conj-TCE increased with increasing concentrations of TRI, but the increases were not proportional to the increases in TRI concentration in the perfusing solutions.

Changes of TRI and Its Metabolites in Urine, Bile, and Circulating Solution

Figures 6, 7, and 8 show the changes in F-TCE, Conj-TCE, and TCA in the urine, re-

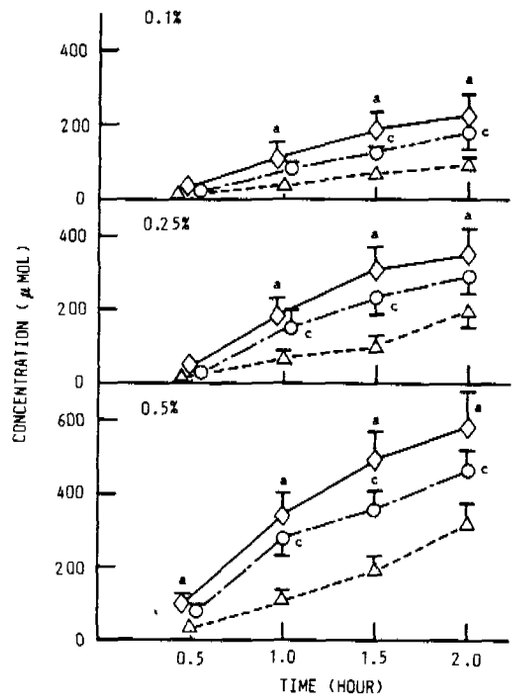


FIG. 11. Conjugated trichloroethanol concentration in bile after administration of 0.1, 0.25, and 0.5% trichloroethylene solutions (mean ± SD; n = 5). ◇, Jejunum; O, ileum; Δ, colon. a. Significant difference between the jejunum and colon ($p < 0.05$). c. Significant difference between the ileum and colon ($p < 0.05$).

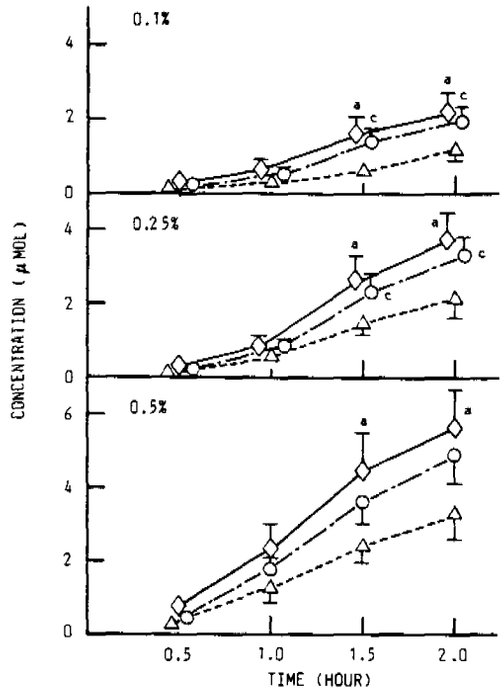


FIG. 12. Trichloroacetic acid concentration in bile after administration of 0.1, 0.25, and 0.5% trichloroethylene solution (mean ± SD; $n = 5$). ◇, Jejunum; ○, ileum; △, colon. a, Significant difference between the jejunum and colon ($p < 0.05$). c, Significant difference between the jejunum and ileum ($p < 0.05$).

spectively, after circulation of 0.1, 0.25, and 0.5% TRI through the jejunum, ileum, and colon. F-TCE, Conj-TCE, and TCA increased with time of perfusion in all urine samples. The levels of Conj-TCE were much higher than those of F-TCE or TCA. TRI was not detected in the urine. Urine levels of F-TCE, Conj-TCE, and TCA ranked with respect to region of administration were jejunum > ileum > colon. Urinary concentrations of metabolites increased as the concentration of TRI increased.

Figures 9, 10, 11, and 12 show changes in TRI, F-TCE, Conj-TCE, and TCA in the bile after administration of 0.1, 0.25, and 0.5% TRI. TRI decreased, F-TCE remained constant, and TCA and Conj-TCE increased with time of perfusion. The concentrations of Conj-TCE were dramatically higher than those of F-TCE and TCA. In terms of the biliary excretion of TRI and its metabolites, the region of administration was jejunum > ileum > colon. Concentration dependency was observed.

Figure 13 shows the changes in the concentration of TRI in the circulating solutions after administration of 0.1, 0.25, and 0.5% TRI. The decrease in TRI concentration over time was linear. No apparent differences could be observed with respect to the region of administration.

Absorption and Excretion of the TRI and Its Metabolites

The data in Table 2 show that 10% of the water and 50–70% of TRI were absorbed in

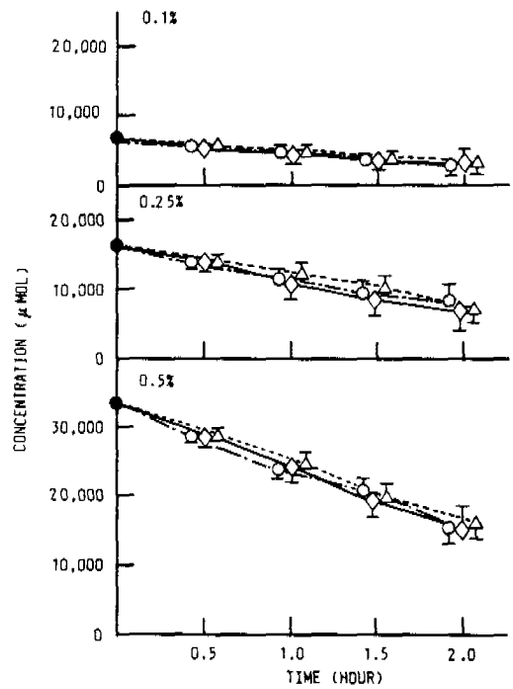


FIG. 13. Trichloroethylene concentration in circulating solutions after administration of 0.1, 0.25, and 0.5% trichloroethylene solutions (mean ± SD; $n = 5$). ◇, Jejunum; ○, ileum; △, colon.

TABLE 2

ABSORPTION RATES OF TRICHLOROETHYLENE (TRI) WATER IN THE JEJUNUM, ILEUM, AND COLON 2 hr R ADMINISTRATION OF TRI AND PHOSPHATE ER (CONTROL) (MEAN ± SD; $n = 5$).

ion and lution	Percentage absorbed	
	Water	TRI
num		
ontrol	11.3 ± 2.6	—
1% TRI	9.8 ± 1.9	56.1 ± 15.3
25% TRI	10.1 ± 2.8	67.4 ± 21.2
5% TRI	9.2 ± 2.4	61.3 ± 15.7
m		
ontrol	9.0 ± 2.1	—
.1% TRI	10.6 ± 3.7	64.2 ± 14.8
.25% TRI	9.8 ± 3.1	59.6 ± 12.3
.5% TRI	8.8 ± 2.2	57.8 ± 13.0
lon		
Control	12.1 ± 2.9	—
0.1% TRI	9.9 ± 1.4	59.3 ± 11.0
0.25% TRI	10.1 ± 2.3	61.8 ± 15.7
0.5% TRI	10.6 ± 2.7	56.4 ± 13.2

2 hr. These values were calculated from the difference between the original concentration and that at 2 hr. No significant differences were observed between the different regions of the intestine or between different TRI concentrations. The amount of TRI absorbed was about 5 mg/intestine (cm)/hr in the 0.1% TRI groups, 12–15 mg in the 0.25% TRI groups, and 20–24 mg in the 0.5% TRI groups, respectively. Moreover, that of water was 0.8 ml/intestine (cm)/hr in all regions.

Table 3 shows the percentage of excretion to the absorbed TRI from the intestine in the urine and bile 2 hr after administration. The amount of urine and bile excreted was constant in all groups, i.e., about 1 ml/kg hr. The total excretion of TRI and its metabolites in bile and urine during the 2-hr experiment, was 0.3–0.4% of the absorbed TRI for the jejunum, 0.2–0.3% for the ileum, and 0.1–0.2% for the colon. More than 90% of the biliary and urinary metabolites were in the form of Conj-TCE in all groups.

DISCUSSION

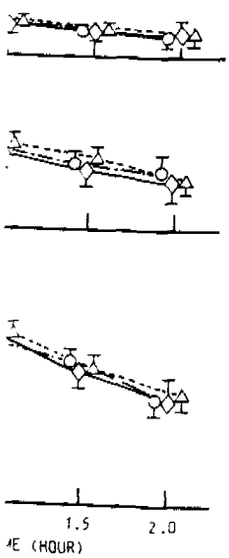
In the present study, we found no significant differences in the biological and physiological parameters before and after operation in the anesthetized dogs. Moreover, the respiratory rate and tidal volume were controlled by the respirator. Thus, we believe the results obtained in this model are comparable to those anticipated in normal dogs.

It is well known that the intestinal absorption rates of substances are different in different segments of the intestine. Some substances are well absorbed in the stomach or the jejunum and others are better absorbed from the colon or the ileum (Yoshimura and Ogata, 1970). Because of this, we investigated TRI absorption rates from the three segments of the intestine. No significant differences among the three segments of the intestine were found with respect to the absorption rate of TRI. However, blood concentrations

TABLE 3

CUMULATIVE EXCRETION RATIO OF TRICHLOROETHYLENE (TRI) AND ITS METABOLITES TO THE ABSORBED AMOUNTS OF TRI FROM THE INTESTINE IN THE BILE AND URINE 2 hr AFTER ADMINISTRATION OF TRI (MEAN; $n = 5$)

Region and solution	Cumulative excretion ratio to absorbed amounts of TRI at 2 hr	
	Urine (%)	Bile (%)
Jejunum		
0.1% TRI	0.26	0.17
0.25% TRI	0.15	0.09
0.5% TRI	0.19	0.11
Ileum		
0.1% TRI	0.15	0.11
0.25% TRI	0.12	0.08
0.5% TRI	0.13	0.07
Colon		
0.1% TRI	0.09	0.06
0.25% TRI	0.07	0.04
0.5% TRI	0.08	0.04



centration in circulat- of 0.1, 0.25, and 0.5% ± SD; $n = 5$). ○, Jeju-

of TRI were higher following absorption from the colon than from the ileum and jejunum. This situation was reversed for the TRI metabolites. These data indicate that TRI metabolism was different in each absorptional segment of the intestine and that the intestine itself might play some part in TRI metabolism.

D'Souza *et al.* (1985) administered TRI intravenously and orally to the rats and measured TRI in the blood over time. They reported that TRI was rapidly absorbed after oral dosing, with blood concentrations peaking between 6 and 10 min. It was suggested that TRI was probably absorbed through gastrointestinal membranes by passive diffusion, since it was a small, unchanged, lipid-soluble molecule. In our present examination, all segments of the intestine readily absorbed TRI and the blood TRI concentration was constant at 2 hr. The decrease in TRI concentration over time was linear in the circulating solution. We could not determine if TRI was absorbed passively in our system. Since TRI is a lipophilic substance, the lymphatic system of the intestine might play a major role in the absorption of TRI.

In our previous reports, about 50% of the absorbed TRI was excreted in expired air in 1 hr after exposure to TRI (Hobara *et al.*, 1982a). The percentage of TRI and its metabolites in urine to the total amount of TRI absorbed by the lungs was about 0.7% at 1 hr after TRI exposure (Hobara *et al.*, 1983). These figures indicated that absorbed TRI is partly excreted into the expired air, while its metabolites (F-TCE, TCA, Conj-TCE, and others) are excreted into the urine and bile (Dekant *et al.*, 1984; Green and Prout, 1985). Moreover, excretion of TRI into bile was observed in this study as well as in our previous studies (Hobara *et al.*, 1982b, 1986b). There are many differences among the species in TRI metabolism (Mueller *et al.*, 1982; Prout *et al.*, 1985). Therefore, the data obtained in these animals studies may not directly be applied to humans.

TRI has been identified as a water contaminant in several water supplies surveyed by the U.S. EPA. The contaminating levels of TRI in the drinking water are generally in the low ppb. However, it is likely that TRI is readily absorbed by humans. This factor must be considered in calculating human risk from TCE exposure.

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