

# Studies on Toxicokinetics of <sup>3</sup>H-Sulfolane in Rat after Oral Administration

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**Published on Journal of West China University Medical Society 19, 61-64. 1988.**

## Abstract

In this paper, the absorption, distribution and excretion of <sup>3</sup>H-sulfolane in rats were studied by the radioactivity trace method. The results showed that the curve of blood <sup>3</sup>H-sulfolane concentration versus time fitted a one-compartment open model with first order rate by curve fitting, statistics and computer. The toxicokinetic parameters of <sup>3</sup>H-sulfolane in blood were as follows:  $K_a$  4.48h<sup>-1</sup>,  $K_e$  0.025h<sup>-1</sup>,  $T_{1/2K_a}$  0.15h,  $T_{1/2K_e}$  27.37h, AUC 1667.89 ng/ml.h, CL 24.47ml/h,  $V_d$  4.84 L/kg,  $T_{max}$  1.16h and  $C_{max}$  41.01 ng/ml. The experiment showed that sulfolane was absorbed rapidly and completely by the gastrointestinal tract. The small intestine was the major part of absorption. The level of radioactivity was the highest in the liver, then the levels of radioactivity in the kidney, lung, thyroid gland, adrenal gland, pancreas, spleen, heart, muscle, brain, testis and fat decreased gradually. <sup>3</sup>H-sulfolane easily passed through the blood-brain barrier and placenta barrier. <sup>3</sup>H-sulfolane was eliminated in urine and feces, especially in the former,  $K_e$  of urine, and feces were 0.01899 and 0.01172 respectively. The half-life periods of urinary and fecal elimination were 36.5h and 59h.

## Introduction

Sulfolane is a stable inert organic solvent, often used as desulfurating agent in the removal of sulfur from natural gas streams in natural gas production. The sulfolane-contained wastewater discharged from the gas processing facilities often results in surface water pollution. Several studies of the toxicity of sulfolane have been reported by foreign researchers. In order to further understand its metabolism, the absorption, distribution and excretion of sulfolane in rats were studied using <sup>3</sup>H-sulfolane.

## Materials and Methods:

### Materials:

1.  $^3\text{H}$ -sulfolane, 95.3 % radiochemical purity, 1.733 mCi/mg (2.6m Ci/ml) specific radioactivity, from Laboratory of Isotopes, Institute of Atomic Energy, Chinese Academy of Sciences.

Freshly make 40 $\mu$  Ci/ml solution with 1/10 LD<sub>50</sub> sulfolane as carrier before use.

## 2. Test animal:

SD adult rats were provided by West China University Medical School and fasted 12 hours before experiment. Intra-gastric administration dosage was 40 $\mu$ Ci/100g bodyweight. Rats were allowed to eat and drink freely during experiment.

## Methods:

### 1. Gastrointestinal tract absorption

Twelve rats were anesthetized with 1% urethane and then their bellies were cut open. The stomach cardia and pylorus, 7cm segment of jejunum and ileum of each rat were ligated respectively. 0.2ml (8 $\mu$ Ci)  $^3\text{H}$ -sulfolane was injected into each ligated segment and stomach. Every three ligated stomach, jejunum, and ileum were cut, taken out and put into 20ml anhydrous alcohol at 0, 1, 4, 10 hour respectively. All these stomach, jejunum, and ileum samples were in anhydrous alcohol extraction for 24 hours. 0.2ml extract was then taken for sample preparation from each sample.

### 2. $^3\text{H}$ -sulfolane toxicokinetic and distribution in organs

Fifty five rats were orally administered  $^3\text{H}$ -sulfolane at a time and then draw 0.1ml blood via femoral artery at 5, 15, 30 minutes, 1, 2, 4, 6, 8, 12, 24, 48 hours respectively. At the same time the samples from liver, kidney, adrenal gland, spleen, pancreas, brain, heart, lung, thyroid gland, fat, testicles, and muscle were taken and washed with normal saline, each organ tissue sample was weighed out 50mg for sample preparation.

### 3. $^3\text{H}$ -sulfolane distribution in pregnant rat and embryo rat

The pregnant rats were killed 2 hours after orally administered  $^3\text{H}$ -sulfolane. 0.1ml blood and 50mg each above organ tissue was taken for sample preparation.

### 4. Rat bile, urine and feces

Three male rats were anesthetized with 1% urethane and then biliary tract plunging tubes were setup. The bile was collected every 10 minutes within 72 hours after orally administered  $^3\text{H}$ -sulfolane. Another five male rats were orally administered  $^3\text{H}$ -sulfolane, kept in cage, urine and feces were collected every 10 minutes within 72 hours. Total amount of urine and feces were also recorded. 0.1mL urine and 50 mg milled dry feces were taken out for sample preparation.

### 5. Sample preparation and radioactivity measurement

The above blood, organ tissues and feces samples were digested with formic acid, hydrogen peroxide and octanol. And they were incubated at 75°C for 1 hour. After cooling, 0.1ml extract solution from each sample was taken into a test tube. Each tube was added with 5 ml Dimethylbenzene Scintillation solution, and then shaken and let stood. Finally, the tubes were put into Beckman 9800 Liquid Scintillation Counter for radioactivity measurement. The results were reported in  $\mu\text{g}/\text{ml}$  or  $\mu\text{g}/\text{g}$ .

## Results

### 1. Gastrointestinal tract absorption

The post-absorption residues measured at 0 hour in the stomach, jejunum and ileum samples were considered 100%. The absorbed rate % at 1, 4, 10 hours respectively were calculated from the post-absorption residues measured in these stomach, jejunum and ileum samples (See Table 1).

### 2. The curve of $^3\text{H}$ -sulfolane concentration in blood versus times

The results measured at different times were graphed against time in Figure 1. The toxicokinetic parameters of blood  $^3\text{H}$ -sulfolane after orally administration were calculated using a one-compartment open model with first order rate. The results were listed in Table 2. The experiments showed that the level of  $^3\text{H}$ -sulfolane was the highest about 1 hour after orally administration and then decreased gradually presented in Figure 1 and Table 2.

### 3. $^3\text{H}$ -sulfolane distribution in different organ tissues

The experiments showed that the  $^3\text{H}$ -sulfolane were actually present in every organ and the level of  $^3\text{H}$ -sulfolane was the highest about 1 hour after orally administration and then decreased gradually as shown in Figure 2.

When  $^3\text{H}$ -sulfolane reach highest, the level of  $^3\text{H}$ -sulfolane was the highest in the liver, and then in the kidney, lung, other organs also shown in Figure 2. The  $^3\text{H}$ -sulfolane still can be found in every organ at 48 hours after orally administration.

The toxicokinetic parameters of  $^3\text{H}$ -sulfolane in tissues after orally administration can also be calculated using a one-compartment open model with first order rate. The  $T_{1/2K_e}$  in the brain tissue has highest value ( $31.22\pm 4.68$ ), showing the  $^3\text{H}$ -sulfolane stay in the brain for the longest time.

### 4. $^3\text{H}$ -sulfolane distribution in pregnant rat and embryo rat

The  $^3\text{H}$ -sulfolane blood concentration in pregnant rat was almost the same as in embryo rat. The placenta was also found contained relatively higher  $^3\text{H}$ -sulfolane concentration. The results were listed at Table 3.

## 5. Rat bile, urine and feces

The bile excretion contained low level of  $^3\text{H}$ -sulfolane. The 72 hours bile accumulative excretive amount was only 3% of total administration dosage but the urine and feces accumulative excretive amounts were 31% and 15% of total administration dosage respectively. According to the toxicokinetic of  $^3\text{H}$ -sulfolane in the urine and feces excretion, the kinetic constant  $K_e$  of urine, and feces were 0.01899 and 0.01172 respectively. The half-life periods of urinary and fecal elimination were 36.5 hours and 59 hours respectively.

## Discussion

The kinetic constant  $K_a$  is  $4.48\text{h}^{-1}$  for the  $^3\text{H}$ -sulfolane absorption rate after orally administration. The half-life period for absorption  $T_{1/2}K_a$  is 0.15 hour. The peak time  $T_m$  is 1.16 hour, indicating that sulfolane can be absorbed quickly. The Gastrointestinal tract absorption experiment also showed that  $^3\text{H}$ -sulfolane was absorbed rapidly and completely by the gastrointestinal tract because the  $^3\text{H}$ -sulfolane is water soluble compound. The small intestine was the major part of absorption as shown in Table 1.

Figure 2 showed that the  $^3\text{H}$ -sulfolane were actually present in every organ and the level of  $^3\text{H}$ -sulfolane was found the highest in the liver, and then in the kidney and lung. The  $^3\text{H}$ -sulfolane still can be found in every organ at 48 hours after orally administration. Based on the chronic toxicity study cited in reference 3, pathological examinations indicated 2.5mg/kg sulfolane can cause a significant change in fatty deposits in the liver tissue of the test guinea pigs, leading to dysfunction of their livers. This matched the highest concentration of  $^3\text{H}$ -sulfolane found in liver, indicating that the liver is one of the organs damaged.

According to the Figure 1, 2, the  $^3\text{H}$ -sulfolane concentration in blood was almost the same as in brain. The half-life periods of elimination in brain is longer, indicating that  $^3\text{H}$ -sulfolane stays in brain for a longer period of time. Based on the acute toxicity studies of sulfolane, the test rats demonstrated rigid tails, twitching, convulsions and other nerve poisoned symptoms [3], indicating that  $^3\text{H}$ -sulfolane maybe easily passed through the blood-brain barrier.

According to the Table 3, the  $^3\text{H}$ -sulfolane blood concentration in pregnant rat was almost the same as in embryo rat, indicating that  $^3\text{H}$ -sulfolane maybe easily passed through the placenta barrier. It is proven that many toxic compounds affect the embryo more than its mother [4]. A sulfolane deformation experiment also indicated that the high level sulfolane can be absorbed by embryo rats and caused the bone deformation of embryo rats. This research also indicated that sulfolane easily passed through the placenta barrier. Therefore more attention should also be needed for toxic effect on embryo in future sulfolane toxicity study.

Figure 3 showed that the  $^3\text{H}$ -sulfolane was found more in the urine than in bile excretion, indicating that some of the  $^3\text{H}$ -sulfolane were not absorbed by gastrointestinal tract and moved out of the rat bodies along with feces.

In sum, this study provides a scientific evidence for the full evaluation of sulfolane toxicity and mechanism.

## References

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