

Elimination study

Uptake. The dose of styrene-8- ^{14}C administered to mice by inhalation, as calculated from the difference between the amount of radioactivity added to the inhalation apparatus and the amount of radioactivity recovered from the apparatus by washings with scintillation fluid, was $0.42 \pm 0.02 \mu\text{Ci}$ or $107.6 \pm 5.8 \text{ mg/kg}$ (mean value of three mice $\pm$ S.E.M.). The uptake of styrene was from this value calculated to be $29.8 \pm 1.6\%$ (mean value of three mice $\pm$ S.E.M.).

Elimination in the exhaled air. The amount of radioactivity exhaled as unchanged styrene during 8 hours after inhalation was $29462 \pm 2093 \text{ dpm}$ or $2.9 \pm 0.2\%$ of the calculated dose. During the same period of time $72562 \pm 3682 \text{ dpm}$ or $7.2 \pm 0.4\%$ of the dose was recovered as $^{14}\text{CO}_2$ (mean values of three mice $\pm$ S.E.M.). The time course of the cumulative elimination of unchanged styrene-8- ^{14}C and $^{14}\text{CO}_2$ in the exhaled air is shown in Fig. III:6. None of the elimination curves reached a plateau during the time of the experiment. No radioactivity was recovered as ^{14}CO . The semilogarithmic plot of the elimination rate of styrene in the exhaled air against time is shown in Fig. III:7. Computerized non-linear regression analysis gave a very good fit of the experimental data to a two-exponential curve with an initial rapid decrease of elimination rate (0-45 min) followed by a slower decrease (45-480 min). The computer calculated equation for the curve was:

$$Y = 0.0186 \cdot e^{-0.0447 \cdot t} + 0.0093 \cdot e^{-0.0025 \cdot t}$$

with apparent half-lives of:

$$t_1 = 15.5 \text{ min}, t_2 = 275.8 \text{ min}$$

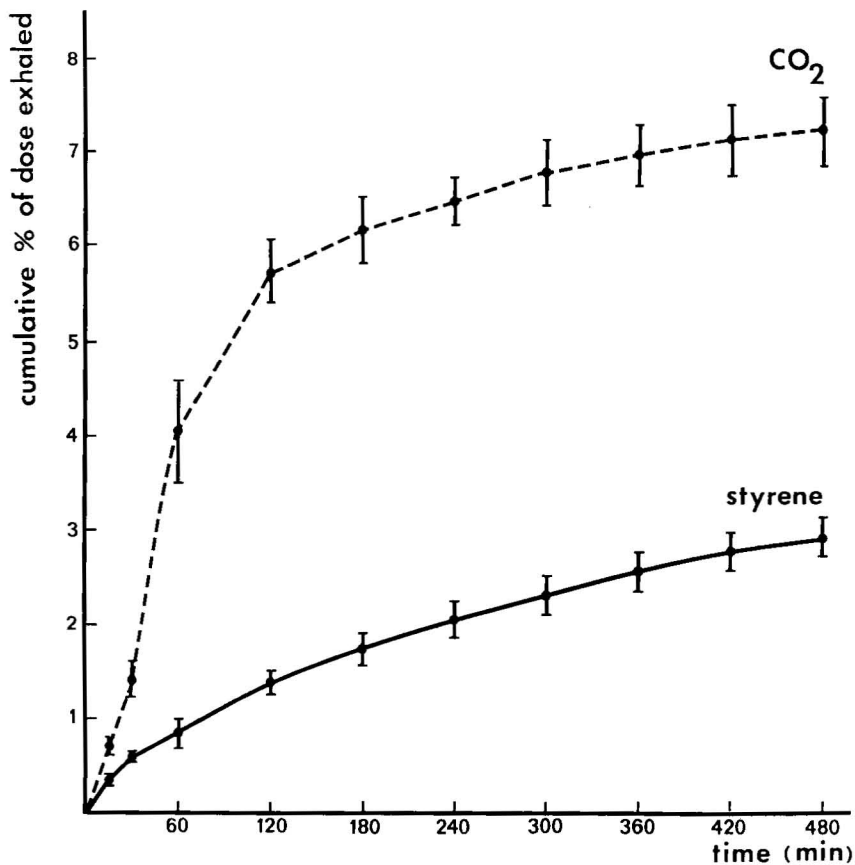


Fig. III:6. The cumulative elimination of styrene-8-¹⁴C and ¹⁴CO₂ in the exhaled air. Mean values of three mice $\pm$ S.E.M.

Elimination in urine. A large proportion of the dose, $64.4 \pm 4.2\%$ ($651.4 \pm 41.9 \cdot 10^3$ dpm) was recovered in the urine in 8 hours (mean value of three mice $\pm$ S.E.M.).

Tissue radioactivity levels. The remaining radioactivity in different tissues 8 hours after inhalation is shown in Table III:1. The radioactivity levels are generally low although relatively high concentrations are still present in the liver, kidney, lung and fatty tissues.

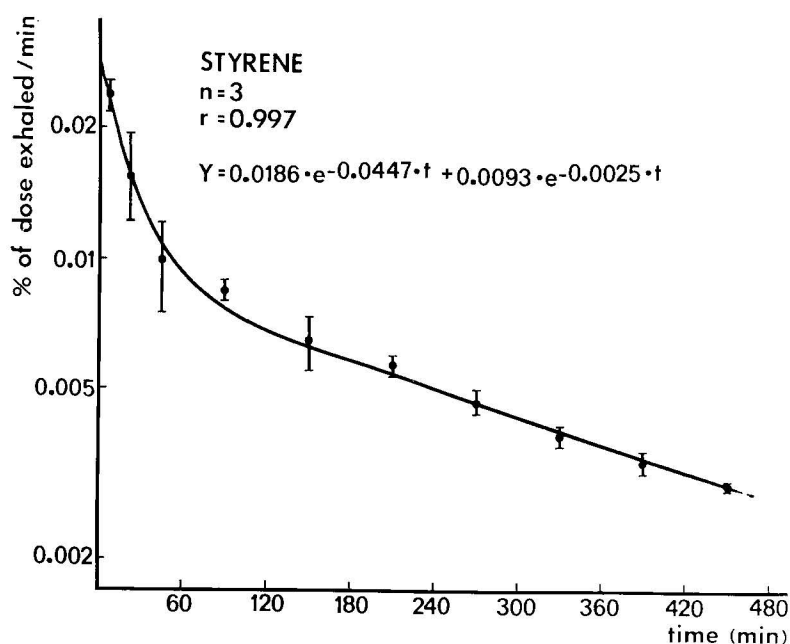


Fig. III:7. Elimination rate curve for styrene in the exhaled air. Mean values $\pm$ S.E.M.

The uptake of styrene by mice may seem unexpectedly low in light of the high blood solubility of styrene (Appendix 2). The uptake by mice is only about half of that reported for humans (31, 130). A reasonable explanation for the low uptake obtained in this study is the highly irritating properties of styrene vapors which affects the respiratory frequency of the mice (as discussed for toluene and xylene in Chapter II) and the short exposure time, 10 minutes, used in the experiment.

Both animal (89, 117) and human (413) experiments indicate that a small proportion of the dose, 2-3%, is exhaled as unchanged styrene. Only one study reports the expiration of CO₂ as a breakdown product of styrene (89). The results of this study agree with previous findings in that about 3% of

Table III:1. The retention of radioactivity in selected tissues of mice 8 h after inhalation of styrene-8- ^{14}C (dose: $2.97 \pm 0.16 \mu\text{l} = 1011.3 \pm 54.2 \cdot 10^3 \text{ dpm}$). Mean values of three mice $\pm$ S.E.M.

tissue	dpm/g	total radioactivity (dpm)
brain	1578 ± 166	682 ± 91
liver	6043 ± 225	8490 ± 441
lung	4413 ± 110	889 ± 65
spleen	1689 ± 130	188 ± 32
kidney	5457 ± 262	2303 ± 145
pancreas	2344 ± 118	413 ± 17
white fat	5942 ± 486	-
brown fat	3120 ± 195	-
blood	$1348 \pm 219^{(1)}$	-

(1) dpm/ml

the dose was recovered as expired unchanged styrene and about 7% of the dose as CO_2 . Since the expiration of neither styrene nor CO_2 was complete in 8 hours (Fig. III:6) the final values may be expected to be higher. The two-compartment pharmacokinetic model for styrene obtained from the elimination rate of unchanged styrene in the exhaled air in this study agrees with the results of Withey and Collins (474), who found an initial rapid decrease of styrene concentrations in rat blood up to about 40 minutes after intravenous injection followed by a slower decrease up to about 3 hours. If styrene concentrations in rat blood in the study by Withey and Collins and the

elimination rate of styrene in the exhaled air of mice in this study had been followed. for longer periods of time, a third even slower phase of the elimination curves would probably have been observed. The very high fat solubility of styrene (Appendix 2) and low vapor pressure at body temperature (Appendix 1) and its consequently slow release from body fat is reflected in the lack of a plateau in the cumulative elimination curve of styrene in the exhaled air (Fig. III:6) and is also probably the reason why the third part of the elimination curve, assumed to represent the final elimination of styrene from fatty tissues, has not appeared within the time of the experiment. This is also supported by autoradiographic results where styrene was clearly visible in body fat as long as 24 hours after inhalation.

The rapid and extensive excretion of styrene metabolites in the urine, as shown in this elimination study and by autoradiography, has been reported for rats and rabbits in earlier studies (89, 117, 197). Danishefsky and Willhite (89) also noted the fecal excretion of radioactivity after administration of styrene-8-¹⁴C to rats. This was also obvious in mice as shown by autoradiography. At 8 hours after inhalation the autoradiographic distribution picture was dominated by the high concentration of radioactivity in the intestinal contents. However, relatively high radioactivity levels were registered both by autoradiography and liquid scintillation counting at 8 hours after inhalation also in the body fat, explained by the high fat solubility of styrene, and in the liver, lung and kidney, probably due to the firm binding of styrene metabolites in these tissues.