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Study on the Kinetics of Styrene and Styrene Oxide in Rats and Mice

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Report

Study on the kinetics of styrene and styrene oxide in rats and mice

Study performed for the
ECETOC Task Force Styrene

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Study on the kinetics of styrene and styrene oxide in rats and mice

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* S = styrene; SO = styrene-7,8-oxide

1. SUMMARY

This report describes experiments on the kinetics of styrene (S*) and styrene-7,8-oxide (SO*) in Sprague-Dawley rats and B6C3F1 mice. The pharmacokinetic parameters for S and SO determined in this study permit quantitative description of the major pathways of S and SO in the organism of rat and mouse under various conditions of exposure.

For this purpose the two compounds were given at appropriate dose levels to the animals by inhalative, intravenous, intraperitoneal and oral route. In vivo data were generated using experimental approaches like closed chamber gas uptake studies, plasma level measurements, repeated pretreatment or inhibiton of metabolism prior to dosing. In vitro techniques were used to determine the partition coefficients for both compounds in systems comprising liquids/air; tissues/air and tissues/blood.

Results are used to calculate the kinetic parameters for both compounds. Summary tables of kinetic data for S and SO are presented in the report. The following conclusions are drawn:

A quantitative relation between exposure to S or to SO and occurrence of SO in the organism has been found.

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* In the whole report these abbreviations will be used:
S = styrene; SO = styrene-7,8-oxide

The Area Under the concentration-time Curve of SO in blood of rats and mice (AUC_{SO}) is considered to be a surrogate of the effective dose of SO. Based on this different scenarios of exposure to S or SO were analyzed.

From these results it appears that systematically available SO acts not as a potent carcinogen.

2. INTRODUCTION

Styrene (S) is an important chemical used in the production of polymers, copolymers and reinforced plastics. Exposure mainly occurs via inhalation in industries and operations producing or using styrene. A full description of the toxicology of styrene is given in several reviews: WHO (1983); BUA report on styrene (1989); MAK documentation for (1987). Information out of this literature is used in the following text without specific references.

Various studies have shown that the uptake of S is rapid and that it is distributed in the body via systemic circulation. S is mainly metabolized to SO and subsequently to various side chain oxidation products (e.g. mandelic acid, phenylglyoxylic acid). Concern about the carcinogenic potential of S has been related to the occurrance of SO as an intermediate metabolite of S. However, the results of controlled laboratory studies with animals (up to now 11 long-term studies) and various epidemiology studies have not provided clear evidence for the carcinogenicity of S.

As SO is formed from inhaled S in the body, explanations for the above findings could be:

- the epoxide is very efficiently detoxified resulting in extremely low systemic concentrations in the organism

- the epoxide is much less biologically active than other aliphatic epoxides or arene oxides

The kinetics of S and SO is important to describe quantitatively the fate of these substances in the exposed organism.

During the exposure to styrene (S) via inhalation the concentration of styrene-7,8-oxide (SO) in the organism is determined by the following factors:

- concentration of S in the atmosphere
- inhalation rate of S
- exhalation rate of S
- metabolic rate of S to SO
- rate of conversion of SO to other side chain oxidation products

The uptake of S via inhalation depends on the ventilation rate, the cardiac output, and the blood/air partition coefficient.

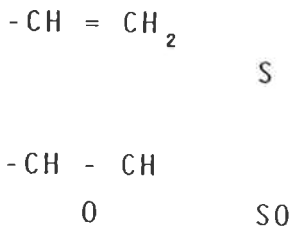
The metabolic rate of S depends upon site of metabolism, rate of blood flow to that site, the tissue/blood partition coefficient, substrate concentration as well as kinetic characteristics of the metabolizing enzymes. Similar considerations apply to the further conversion of SO.

At high substrate concentrations enzymatic processes always exhibit saturation kinetics. At low concentrations a metabolic rate often is limited by transport to metabolizing enzymes, with blood flow or ventilation rate as possible rate-determining steps and not by enzymatic capacity. Therefore, different routes of exposure to S or SO can lead to very dissimilar blood concentrations of SO, resulting in divergent biological effects.

A quantitative description of these relationships can be obtained by pharmacokinetic investigations using a closed chamber system. Accordingly in this study experiments have been performed with rats and mice under different conditions of exposure (to S and SO) to allow the prediction of blood concentrations of SO. These have been subsequently verified in additional experiments.

3. MATERIAL AND METHODS

3.1. Test Articles

Name:	Styrene (S) Styrene-7,8-oxide (SO)
Chemical Structures:	
Molecular Formulas:	S: C_8H_8 SO: C_8H_7O
Origin:	Aldrich
Batch Lot No.:	see raw data
Purity:	S > 99%; SO > 98%
Aggregate State:	S: liquid SO: liquid
Stability:	stable in inorganic solvents for at least 4 weeks
Storage:	-20°C in the dark

Preparations of test articles:	Undiluted S without further parification was used for inhalation experiments. SO was either used undiluted or for in vivo experiments dissolved in corn oil.

3.2. Test System

Animals:	1) Rats 2) Mice
Strain:	1) Sprague-Dawley 2) B6C3F1; NMRI*
Origin:	GSF, Neuherberg
Sex:	male
Weight:	Rats: about 160 - 300 g; Mice: 20 - 30 g checked immediately before dosing

* NMRI mice: origin GSF Neuherberg; due to limited supply of B6C3F1 mice these animals were used for experiments to measure tissue/blood partition coefficients; all other experiments were done with B6C3F1 mice.