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Whole-body autoradiography and allied tracer techniques in distribution and elimination studies of some organic solvents: benzene, toluene, xylene, styrene, methylene chloride, chloroform, carbon tetrachloride and trichloroethylene.

by [Bergman K](#)

Key terms: [allied tracer technique](#); [benzene](#); [carbon tetrachloride](#); [chloroform](#); [distribution](#); [elimination](#); [methylene chloride](#); [organic solvent](#); [styrene](#); [toluene](#); [trichloroethylene](#); [whole-body autoradiography](#); [xylene](#)

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WHOLE-BODY AUTORADIOGRAPHY AND ALLIED TRACER TECHNIQUES IN
DISTRIBUTION AND ELIMINATION STUDIES OF SOME ORGANIC SOLVENTS

BENZENE, TOLUENE, XYLENE, STYRENE, METHYLENE CHLORIDE,
CHLOROFORM, CARBON TETRACHLORIDE AND TRICHLOROETHYLENE

by

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A B S T R A C T

BERGMAN, K. Whole-body autoradiography and allied tracer techniques in distribution and elimination studies of some organic solvents: Benzene, toluene, xylene, styrene, methylene chloride, chloroform, carbon tetrachloride and trichloroethylene. *Scand. j. work environ. & health* 5(1979): suppl. 1, 263 p. Whole-body autoradiography has been used to study the distribution and fate of ^{14}C -labeled benzene, toluene, xylene, styrene, methylene chloride, chloroform, carbon tetrachloride and trichloroethylene in mice after inhalational exposure. Total radioactivity, including the volatile part of the solvents, was registered using low-temperature (-80°C) autoradiographic techniques. Non-volatile metabolites of the solvents were registered by autoradiography of dried, evaporated tape-fastened sections. In addition, dried, evaporated tape-fastened sections were extracted with water, trichloroacetic acid and a series of organic solvents and autoradiographed to register organs where metabolites were firmly bound. In another facet of the study, the quantitative elimination of the solvents and their metabolites via various routes was investigated. The expiration of unchanged solvents was subject to mathematical and computerized compartmental pharmacokinetic analysis.

All solvents were rapidly taken up in fatty and nervous tissues where they were retained for different periods of time largely dependent on their fat solubility. Unexpectedly long retention times were noted for the chlorinated solvents, particularly for chloroform, which showed a specific long-term retention in the cerebellum, meninges and spinal nerves, indicating interactions with specific nervous tissue receptors. Solvent metabolites appeared rapidly in several organs, mainly the liver and kidney, and were excreted both via urine and bile. Toluene and xylene metabolites were completely extractable whereas firmly bound metabolites were registered after inhalation of benzene, styrene and all chlorinated solvents, notably in the liver and kidney but also in the bronchi of the lung.

Three-compartment pharmacokinetics were observed for the majority of the solvents selected for study although a two-compartment model was found to fit the elimination rate curves for styrene, methylene chloride and chloroform in the exhaled air. The fat solubility of the solvents was found to influence their pharmacokinetics since lower rate constants were generally obtained for the expiration of more fat soluble solvents.

Key words: autoradiography, benzene, carbon tetrachloride, chloroform, distribution, methylene chloride, pharmacokinetics, toluene, trichloroethylene, solvents, styrene, xylene.

I N T R O D U C T I O N

The organic solvents comprise a large variety and number of chemicals of great commercial and industrial importance. Chemically, most of the organic solvents can be classified as aliphatic or aromatic hydrocarbons, halogenated aliphatic hydrocarbons, alcohols, ethers, esters, ketones or glycol derivatives. The widespread use of organic solvents is based on their excellent ability to dissolve fats, oils, waxes, lacquers, resins and similar materials, which makes them indispensable as chemical "tools" in industry, for degreasing, cleaning and extraction purposes and as constituents in products often encountered in every-day life. Some solvents also serve as starting materials and intermediates in chemical syntheses.

Toxicologically, the organic solvents have attracted attention mainly as health hazards in occupational exposure. However, the extensive use of solvents in many commercial products also makes them a threat, although less serious, to the health of the general public. The deliberate inhalation of solvent vapors for inebriation purposes in "sniffing" has also been shown to be injurious to health (17, 46, 78, 90, 157, 159, 228, 232, 253, 322, 365, 468). The presence of solvent residues in processed foods has been discussed as a possible

hazard (267). Organic solvents have also been identified among our ubiquitous environmental pollutants (111, 267).

The physical and chemical characteristics of most organic solvents, such as high volatility and fat solubility and low molecular weight, confer upon them certain common properties and effects upon contact with the living organism. The most probable mode of contact with solvents is via inhalation of their vapors, which are readily absorbed from the respiratory tract. They easily penetrate the blood-brain barrier and localize in the lipid-rich cells of both the central and peripheral nervous system. Acute as well as, in some cases, chronic exposure to organic solvents is known to cause deleterious effects on the nervous system. Nervous system effects are generally considered to be caused by the solvents themselves, although reactive intermediates formed during the biotransformation of solvents have recently been suggested as mediators of chronic neurotoxic effects (366). Biotransformation of organic solvents is also known to give products with the capacity to injure other organs, notably the liver and the kidney.

The general effects, uptake, biotransformation and elimination of many organic solvents have been the subject of quite an intensive study ever since the turn of the century. The achieved knowledge has been comprehensively collected and reviewed in several works such as those by Browning (51), Gerarde (146) and von Oettingen (299). During the last years, the growing concern for the health hazards associated with occupational exposure to organic solvents has

led to an intensified experimental and epidemiological research.

A survey of the literature on organic solvents reveals that very little has been done as regards the distribution of organic solvents and their metabolites in the body. The investigation presented in this monograph has been done with the aim to study the distribution, specific localizations and retention of some organic solvents and their metabolites in the living organism. For this purpose modified whole-body autoradiographic techniques have been used. Information about the distribution of solvents and their metabolites is of great value in understanding the mechanisms of solvent toxicity and explaining the organ injuries reported after exposure to solvents. Knowledge of the specific localizations of solvents and their metabolites can also reveal new sites of action of these substances. In another facet of the investigation, the distribution patterns were compared and correlated to the excretion of the solvents via different routes. These studies provide insight into the transfer of organic solvents in the body and may also be of help in elucidating their toxicity.

The selection of solvents for study has been based on their reported toxicity and/or extent of use for different purposes. The aromatic hydrocarbons make up an important group among the organic solvents. Benzene, well known for its toxic effects on the blood-forming tissues, together with its homologs and suggested replacers toluene and xylene were chosen as representatives of the aromatic hydrocarbon solvents (Chapter II). Styrene, suspected to possess mutagenic and carcinogenic properties as well as neurotoxicity, was also

included (Chapter III). Chlorinated hydrocarbon solvents, of bad reputation as hepato-renal and nervous system poisons, are represented by methylene chloride, chloroform and carbon tetrachloride (Chapter IV) and trichloroethylene (Chapter V). Part of the results have been presented at the Conference on Autoradiography in Pharmacology and Toxicology, Uppsala, May 1977 (40) and at the ILO Symposium on the Control of Air Pollution in the Working Environment, Stockholm, September 1977 (39).