# COMPARISON OF DERMAL AND INHALATION ROUTES OF ENTRY FOR ORGANIC CHEMICALS

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## ABSTRACT

The quantitative comparison of the chemical concentration inside the body as the result of a dermal exposure versus an inhalation exposure is useful for assessing human health risk and deciding on an appropriate protective posture. In order to describe the relationship between dermal and inhalation routes of exposure, a variety of organic chemicals were evaluated. The types of chemicals chosen for the study were halogenated hydrocarbons, aromatic compounds, non-polar hydrocarbons and inhalation anesthetics. Both dermal and inhalation exposures were conducted in rats and the chemicals were in the form of vapors. Prior to the dermal exposure, rat fur was closely clipped and during the exposure rats were provided fresh breathing air through latex masks. Blood samples were taken during 4-hour exposures and analyzed for the chemical of interest. A physiologically based pharmacokinetic model was used to predict permeability constants (cm/hr) consistent with the observed blood concentrations of chemical. The ratio of dermal exposure to inhalation exposure required to achieve the same internal dose of chemical was calculated for each test chemical. The calculated ratio in humans ranged from 18 for styrene to 1180 for isoflurane. This methodology can be used to estimate the dermal exposure required to reach the internal dose achieved by a specific inhalation exposure. Such extrapolation is important since allowable exposure standards are often set for inhalation exposures, but, occupational exposures may be dermal.

## INTRODUCTION

Dermal penetration may be the primary mode of entry for occupational and environmental chemicals (1). This is particularly true in occupational settings where workers are provided with respiratory protection but have skin exposed to chemical vapors. In situations where the chemical vapor concentrations are high enough and exposure is long enough, the amount of chemical absorbed into the body through the skin can produce a chemical body burden up to or exceeding the levels achieved by an inhalation exposure at the threshold limit value (TLV). Since the skin can function as a significant route of entry for chemicals which have regulated inhalation exposure standards, it is important to quantitatively assess sthe contribution of dermal penetration to the internal dose of chemical resulting from an exposure (2). In order to compare the internal chemical dose following inhalation and the internal dose following dermal exposure, physiologically based pharmacokinetic (PBPK) models are used to account for the uptake, biodistribution, metabolism and elimination of chemicals. The models are built by connecting a series of physiological compartments which have descriptions of blood flow, tissue volume and if appropriate, metabolism (3). Such a description allows for tracking the chemical mass balance as well as the kinetics of the physiological processes impacting the fate of the chemical. When combined with appropriate laboratory data, the PBPK model provides a useful tool for comparing the amount of chemical absorbed following inhalation or dermal exposure.

The total amount of chemical absorbed is the primary piece of information required to make the quantitative comparison between different routes of chemical exposure and allows for derivation of a dermal exposure that would yield a chemical body burden equivalent to that produced by a selected inhalation exposure.

RESULTS

Chemical concentration profiles in rat blood during dermal exposure to chemical vapors combined with use of a physiologically based pharmacokinetic model provided the information needed to calculate dermal permeability constants for the chemicals used in the study (Table 1).

Table 1. Dermal Vapor Penetration

| Chemical | Permeability(cm/hr) |
|---|---|
| Styrene | 1.75 |
| Dibromomethane | 1.32 |
| Bromochloromethane | 0.79 |
| m-xylene | 0.72 |
| Tolene | 0.72 |
| Perchloroethylene | 0.67 |
| Methylene chloride | 0.28 |
| Benzene | 0.15 |
| Halothane | 0.05 |
| Hexane | 0.03 |
| Isofurane | 0.03 |

Similar chemical concentration profiles in rat blood during an inhalation exposure and use of a PBPK model allowed for calculation of the internal dose that resulted from the exposure. The ratios of dermal to inhalation exposure concentration which yield identical internal doses or chemical body burden are shown in Table 2.

Table 2. Extapolation Ratios

| Chemical | Ratio (Dermal/Inhalation) Rat | Human |
|---|---|---|
| Styrene | 10 | 18 |
| Dibromomethane | 14 | 23 |
| Bromochloromethane | 22 | 39 |
| m-xylene | 25 | 42 |
| Tolene | 24 | 43 |
| Perchloroethylene | 26 | 46 |
| Methylene chloride | 62 | 110 |
| Benzene | 113 | 202 |
| Halothane | 339 | 682 |
| Hexane | 408 | 990 |
| Isoflurane | 448 | 1180 |

CONCLUSION

Dermal exposure to chemicals of occupational or environmental interest can result in an internal dose or chemical body burden which may be unacceptable based on the internal dose received following an inhalation exposure for which exposure limits exist. The use of a physiologically based pharmacokinetic model combined with the generation of kinetic data during dermal and inhalation chemical exposures, allows for the calculation of an extrapolation ratio. The extrapolation ratio is the ratio of the dermal and inhalation exposure concentrations required to produce the same internal dose of chemical. Therefore, the extrapolation ratio can be used to assign a dermal TLV for chemical vapor exposure if an inhalation TLV exists.

REFERENCES


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