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OCCUPATIONAL SAFETY CONSIDERATIONS WITH HYDRAZINE FUELS

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ABSTRACT

A simple pharmacokinetic model and a specially designed dermal vapor exposure chamber which provides respiratory protection were used to determine the rate of penetration of hydrazine and 1,1-dimethylhydrazine (UDMH) vapor through the skin of rats. Parameters for the pharmacokinetic model were determined from intravenous and inhalation exposure data. The model was then used to estimate the skin permeation coefficient for hydrazine or UDMH vapor from the dermal-vapor exposure data. This analysis indicates that UDMH vapor has a relatively high permeability through skin (0.7 cm/hr), a value somewhat higher than was obtained for hydrazine by the same procedure (0.09 cm/hr). Based on these skin permeability results, a skin-only vapor exposure limit giving protection equivalent to the inhalation Threshold Limit Value (TLV) could be calculated. The current TLV's for UDMH and hydrazine are 0.5 and 0.1 ppm, respectively. The corresponding skin-only TLV equivalents, for personnel wearing respiratory protection, are 32 ppm for UDMH and 48 ppm for hydrazine. Should the proposed lowering of the TLV's for these compounds to 0.01 ppm be adopted, the equivalent skin-only TLV's would become 0.64 ppm for UDMH and 4.8 ppm for hydrazine.

INTRODUCTION

Aerzine-50, a 50:50 by weight blend of UDMH and hydrazine, is an important fuel used in the Titan series missile. UDMH and hydrazine are caustic liquids which produce severe chemical burns. Therefore, personnel working with these fuels must wear protective clothing suitable to prevent liquid contact with the skin or eyes. In addition, inhalation of the fuel vapors has been shown to produce both acute and chronic toxicity, including carcinogenicity¹. As a result, the American Conference of Government Industrial Hygienists (ACGIH) currently recommends TLVs of 0.1 ppm for hydrazine and 0.5 ppm for UDMH, and is considering lowering the TLVs for both chemicals to 0.01 ppm². Thus respiratory protection is also necessary whenever significant concentrations of vapor may be present.

Because of uncertainty concerning the significance of dermal exposure to fuel vapor, it has often been the practice in the past to require that personnel working with these fuels wear a cumbersome, self-contained ensemble to provide full-body protection against vapor. This self-contained ensemble seriously degrades performance, so there is interest in establishing when protection of the skin from fuel vapors is needed, and when inhalation protection and prevention of liquid contact will suffice. Other than direct irritation of the skin, which occurs at levels well above the TLV, the principal issue concerning dermal exposure to fuel vapor is the potential for systemic toxicity due to penetration of vapor through the skin as compared to inhalation. The purpose of the current study was to estimate a dermal equivalent of the permissible hydrazine inhalation exposure level in order to establish realistic guidelines for ensuring the personal safety of individuals potentially exposed to hydrazine or UDMH vapors.

METHODS

Details of the experimental methods have been reported previously^{3,4}, so only a brief description is provided here. For the dermal vapor exposures, rats were exposed to hydrazine or UDMH vapors in a specially designed chamber³ which provided respiratory protection by the use of masks, but allowed exposure of the whole body, which had been closely clipped of fur, to the chamber atmosphere. The same chamber was used for the inhalation exposures, but the use of masks was omitted and the fur was not clipped. Male Fischer 344 rats (200 to 280 g) were trained to wear a harness and, for the dermal exposures, latex face mask prior to the exposures. Twenty-four hours before the exposure, jugular cannulas were surgically implanted and exteriorized at the back of the neck. Just prior to the exposure, six rats were placed in the chamber and the cannulas were routed outside the chamber for blood collection during the exposure. For intravenous exposures, hydrazine or UDMH was introduced in a saline vehicle. Blood samples were drawn through a jugular cannula at 0.5, 1, 2, and 4 hours after injection. Analysis of blood samples involved

derivitization with chlorobenzaldehyde³ or acetone⁴, followed by gas chromatography.

A relatively simple one-compartment open pharmacokinetic model was used to relate the measured blood concentrations during exposure to the total amount of chemical (hydrazine or UDMH) in the animal and the total amount metabolized. Two processes were incorporated in the model: slowly reversible chemical reaction with components of the blood and tissues, and irreversible clearance of free chemical by a saturable process. Incorporation of these two processes into the model was necessary to provide a coherent description of all of the data from the three exposure routes. The total amount of unreacted chemical in the animal (A_{free}) at a given time is determined by integrating the following equation with initial condition $A_{free} = 0$, for the vapor exposures, or $A_{free} = \text{dose (mg)}$, for the intravenous exposures:

$$dA_{free}/dt = R_{skin} + R_{inh} - R_x - R_{clear}$$

where:

R_{skin} = rate of penetration through skin

$$= P * A * C_{dermal}$$

R_{inh} = rate of inhalation

$$= Q_{alv} * C_{inhal}$$

R_x = rate of reaction

$$= K_r * C_{free} * V_d - K_d * A_x$$

R_{clear} = rate of clearance

$$= V_{max} * C_{free} / (K_m + C_{free})$$

In these equations, P is the skin permeation coefficient (cm/hr), A is the skin area (cm²), C_{dermal} is the chamber concentration for the dermal vapor exposures (mg/ml), Q_{alv} is the alveolar ventilation rate (L/hr), C_{inhal} is the chamber concentration for the inhalation exposures (mg/L), C_{free} is the concentration of unreacted chemical in the blood (mg/L), K_r is the rate constant for reaction with blood and tissue components (/hr), V_d is the volume of distribution in the animal (L), K_d is the rate constant for reversal of the reaction with blood or tissue (/hr), A_x is the amount of reacted chemical (mg), V_{max} is the maximum clearance rate for free chemical (mg/hr), and K_m is the Michaelis-Menton constant for the clearance process (mg/L). Two major assumptions of the model are that the rate constants for reaction are the same in blood and tissues, and that the hydrazone derivative procedure effectively reverses the reaction with blood components so that the measured concentration is the sum of free and reacted chemical:

$$C_{measured} = C_{free} + A_x/V_d$$

Q_{alv} and A were calculated on the basis of empirically derived relationships to body weight, with typical values of about 6.7 L/hr and 260 cm², respectively. The volume

of distribution was set to total body water (65% of body weight). The kinetic constants K_r , K_d , V_{max} , and K_m were established by iterative fitting of the inhalation and intravenous exposure data sets. Although these parameters are highly correlated, their affects on the behavior of the model were sufficiently distinct to estimate each of the parameters relatively independently. The final step was to estimate P from fitting the dermal vapor exposure data. The numerical integration and non-linear parameter estimation was performed with SIMUSOLV (Mitchell and Gauthier Associates, Inc., Concord MA) on a VAX 8530.

RESULTS

The model was able to provide a reasonably good representation of the intravenous and inhalation data for UDMH (Figs. 1 and 2) using parameter values of $K_r=11/\text{hr}$, $K_d=1.9/\text{hr}$, $V_{max}=8.7 \text{ mg/hr}$, and $K_m=0.6 \text{ mg/L}$. Although the model somewhat overestimates the blood concentrations at early times in the inhalation exposure, it predicts the correct steady-state behavior and performs remarkably well at describing the complex intravenous kinetics. The value of the skin permeation coefficient that yielded the best agreement between the model and the dermal vapor exposure data was 0.7 cm/hr (Fig. 3).

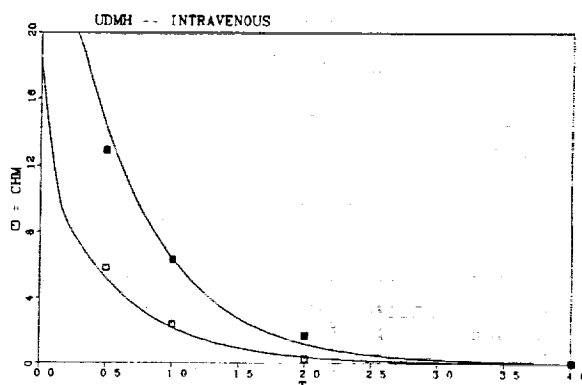


Figure 1. Model-Predicted (curves) and Experimental (symbols) Blood Concentrations of UDMH for Intravenous Doses of 24 mg/kg (upper curve, solid symbols) and 12 mg/kg (lower curve, open symbols).

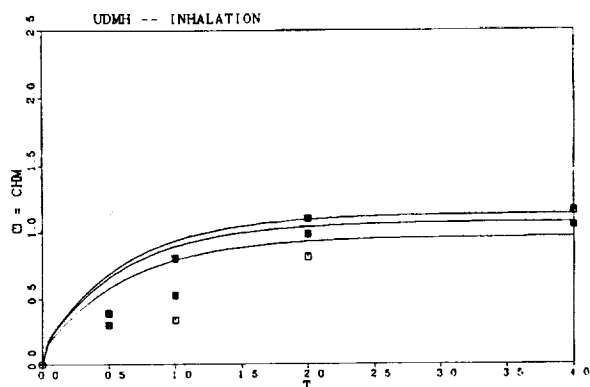


Figure 2. Model-Predicted and Experimental Blood Concentrations of UDMH for Inhalation Exposures at 108 ppm (upper curve, solid symbols), 104 ppm (middle curve, crossed symbols) and 95 ppm (lower curve, open symbols).

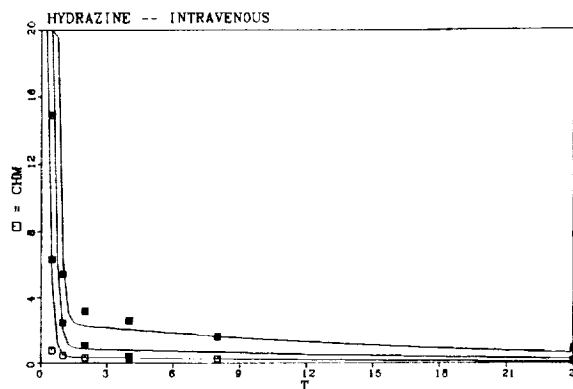


Figure 4. Model-Predicted and Experimental Blood Concentrations of Hydrazine for Intravenous Doses of 12 mg/kg (upper curve, solid symbols) and 6 mg/kg (lower curve, open symbols).

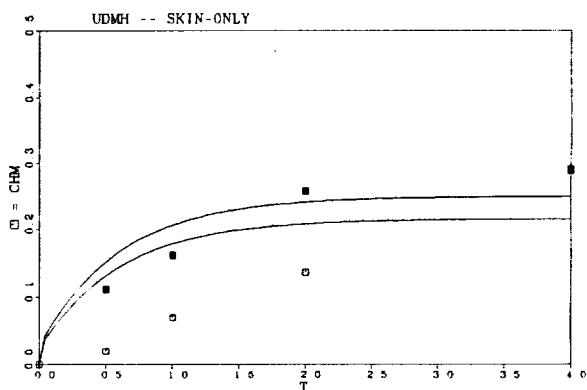


Figure 3. Model-Predicted and Experimental Blood Concentrations of UDMH for Skin-Only Vapor Exposures at 1028 ppm (upper curve, solid symbols) and 895 ppm of UDMH vapor (lower curve, open symbols).

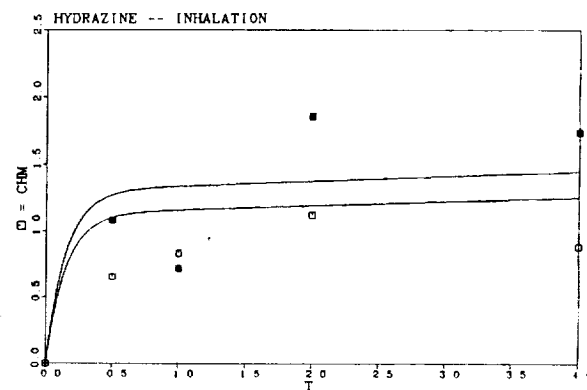


Figure 5. Model-Predicted and Experimental Blood Concentrations of Hydrazine for Inhalation Exposures at 10.7 ppm (upper curve, solid symbols) and 9.3 ppm (lower curve, open symbols).

An earlier analysis for hydrazine⁵ obtained a value of 0.06 cm/hr, but that analysis used a very different pharmacokinetic model. To assess the impact of the change of model, the model described above was used to re-evaluate the hydrazine data. The new model was able to provide a general description of the hydrazine data as well (Figs. 4 and 5), using parameter values of $Kr = .031$, $Kd = .055$, $V_{max} = 3.1$, and $K_m = 50$. The only other change required was to restrict the volume of distribution to the blood volume (5% of body weight). The value of P determined with the new model was 0.092 (Fig. 6), in good agreement with the earlier value.

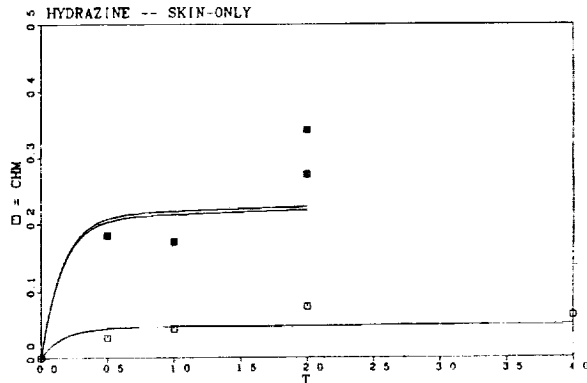


Figure 6. Model-Predicted and Experimental Blood Concentrations of Hydrazine for Skin-Only Vapor Exposures at 486 ppm (upper curve, solid symbols), 476 ppm (middle curve, crossed symbol), and 105 ppm (lower curve, open symbols).

Once we have established the skin permeation coefficients, we can calculate the relative importance of the dermal and inhalation routes of exposure for systemic toxicity. Assuming that the rat is a good model for skin absorption in the human, a measure of the rate of uptake of chemical through the skin is simply $P \cdot A$, where A is the exposed skin area for humans, generally taken to be 2 m^2 . The equivalent measure of uptake for inhalation is just Q_p , which is commonly taken to be 800 L/hr . The ratio of inhalation to dermal uptake is then $Q_p / (P \cdot A)$. Applying this formula to UDMH, the ratio of inhalation to dermal uptake is then 64, and the similar ratio for hydrazine, using $P=0.09$, is 487. Multiplying these ratios by the current TLVs, we obtain estimates for the equivalent skin-only exposure levels of 32 ppm for UDMH and 48 ppm for hydrazine. At the proposed TLVs of 0.01 ppm, the skin-only equivalents would be 0.64 ppm and 4.8 ppm, respectively.

DISCUSSION

The approach described above for estimating safe skin-only vapor exposure levels relies on a number of assumptions. The principal assumption is that skin permeation coefficients measured in rats are representative of human skin values. While there is some evidence that human skin is at least as good a barrier to chemical vapors as rat skin⁶, the exact relationship has not yet been established for water soluble chemicals. The adequacy of the rat as a model for skin absorption in humans is therefore an important source of uncertainty which should be considered in deriving human exposure guidelines. Another key assumption in this approach is that the skin and lungs act only as routes of entry for a chemical whose effects are systemic. The method would be inappropriate for a chemical which had direct effects either on the skin or in the lungs at the concentrations of interest. In the case of hydrazine and UDMH there are no significant contact site effects at the level of the TLV.

Given the assumptions discussed above, this same approach can be generally applied to other toxic chemicals. Provided that skin permeation coefficients for the vapor are either known or can be determined, the calculation of the skin-only equivalent to a given inhalation exposure guideline is straightforward. This approach could provide a method for use by ACGIH or OSHA in assigning quantitative skin notations. A similar approach can also be used to determine appropriate personal protection for potential short-term exposures as a part of emergency response planning⁷.

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