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Limited research has been conducted on dermal exposure and risk assessment, owing to the lack of reliable measurement techniques and data for quantitative risk assessment. We investigated the magnitude of dermal exposure to jet propulsion fuel 8 (JP-8), using naphthalene as a surrogate, on the US Air Force fuel-cell maintenance workers. Dermal exposure of 124 workers routinely working with JP-8 was measured using a non-invasive tape-strip technique coupled with gas chromatography–mass spectrometry analysis. The contribution of job-related factors to dermal exposure was determined using multiple linear regression analyses. Average whole body dermal exposure to naphthalene (as a marker for JP-8) was \(7.61 - 2.27 \ln(\text{ng m}^{-2})\). Significant difference \((P < 0.0001)\) between the high-exposure group \([8.34 - 2.23 \ln(\text{ng m}^{-2})]\) and medium- and low-exposure groups \([6.18 - 1.35 \ln(\text{ng m}^{-2})\) and \(5.84 - 1.34 \ln(\text{ng m}^{-2})\), respectively] was observed reflecting the actual exposure scenarios. Skin irritation, use of booties, working inside the fuel tank and the duration of JP-8 exposure were significant factors explaining the whole body dermal exposure. This study clearly demonstrates the efficiency and suitability of the tape-strip technique for the assessment of dermal exposure to JP-8 and that naphthalene can serve as a useful marker of exposure and uptake of JP-8 and its components. It also showed that the skin provides a significant route for JP-8 exposure and that actions to reduce exposure are required. Studies to investigate the relative contribution of dermal uptake of JP-8 on total body dose and the toxicokinetics of dermal exposure to JP-8 are underway.

Keywords: dermal; exposure assessment; jet fuel; JP-8; naphthalene (CAS 91-20-3); skin; stratum corneum; tape stripping

INTRODUCTION

Military activities require the use of hazardous chemicals, and consequently, result in emissions into the air, soil and water. Jet propulsion fuel 8 (JP-8) is the major fuel used by the US Air Force (USAF) and the North Atlantic Treaty Organization. JP-8 has been recognized as a major source of chemical exposure for fuel-cell maintenance workers (ATSDR, 1998; Carlton and Smith, 2000). Although the widespread use of JP-8 and its potential for causing adverse health effects has prompted several toxicological studies (ATSDR, 1998; NRC, 2003), only limited research has been conducted on JP-8 exposed populations (Carlton and Smith, 2000; Pleil et al., 2000; Egeghy et al., 2003; Rhodes et al., 2003; Serdar et al., 2003, 2004). In none of these human studies was the health impact of dermal exposure to JP-8 investigated, although it occurs commonly during aircraft fueling and fuel-cell maintenance in the military, and in some cases is unavoidable.

Knowledge of JP-8 exposure, uptake, metabolism and its potential health effects on humans is limited. In humans, symptoms and/or health effects reported with JP-8 exposure include nausea, headache, fatigue and neurobehavioral changes (Smith et al., 1997; Zeiger and Smith, 1998), neurocognitive changes (Tu et al., 2004), psychiatric disorders (Knave et al., 1976; Mindus et al., 1978; Struwe et al., 1983), posture balance problems (Smith et al., 1997), effects on reproductive (Reutman et al., 2002) and immune (Rhodes et al., 2003) systems and skin irritation (Serdar et al., 2003, 2004). The National Research
Council has concluded that inhalation of JP-8 vapor does not present a carcinogenic risk but dermal exposure may present a risk for skin cancer and sensitization (NRC, 2003).

Despite the increasing number of studies conducted on JP-8, none of them has focused on quantification and assessment of dermal exposure to JP-8 on humans. The low vapor pressure and slower rate of evaporation of JP-8 compared with its predecessor JP-4 provides an increased duration of dermal contact and can lead to increased dermal exposure. During some operations, fuel-cell maintenance workers wear cotton overall to avoid the induction of static electricity. The wicking properties of the cotton, however, enhance dermal exposure. This study was designed to measure the magnitude of JP-8 dermal exposure in the USAF fuel-cell workers using a laboratory tested non-invasive tape-stripping of stratum corneum (Chao and Nylander-French, 2004).

MATERIALS AND METHODS

Study population

This study was conducted on six USAF bases, as a part of a broad USAF project (TIEHH, 2001), to investigate acute dermal exposure to JP-8 on fuel-cell maintenance workers. The study was approved by the institutional review boards of all of the participating investigators. Although 339 USAF personnel subjects enrolled in the overall USAF project, a total of 124 subjects were recruited with informed consent into this dermal exposure study. These Air Force members worked with or were exposed to JP-8 to various degrees while performing their military duties. Demographic, job tasks, the use of protective equipment and work environment related information was collected using questionnaires. Work diaries detailing work tasks and durations were also recorded. The average age of the subjects was 24.6 ± 4.98 years. Of all subjects, 116 were male (93.5%), 107 were Caucasians (86.3%), 53 were smokers (42.7%) and 62 complained about skin irritation (50.0%). Personal protective equipment included use of respirators (n = 96, 77.4%), cotton overalls (n = 98, 79.0%) and boots (n = 40, 32.3%).

Four main job titles, namely entrants, attendant, runners and other field workers were identified according to the work diary. Entrants performed tank door removal, bolt removal, foam removal, foam replacement, fuel tank entry and cleaning, necessary repairs, depuddling, and were required to wear self-contained breathing apparatus. Attendants and runners worked outside the fuel tank to assist entrants (e.g. removal of foams). Other field workers performed maintenance with occasional contact with JP-8. Attendants, runners and other field workers did not generally wear respirators during work. In order to categorize the exposure levels, the subjects were assigned into three exposure groups (high, medium and low). The high-exposure group consisted of entrants (n = 85). Anyone who entered a fuel tank, regardless of any other additional jobs performed, was classified into the high-exposure category. The medium-exposure group consisted of subjects who were attendants and/or runners assisting the entrants but did not perform fuel-tank entry (n = 19). The low-exposure group consisted of the other field workers (n = 20) who had only occasional contact with JP-8.

Sample collection and analysis

Chemicals. Naphthalene (C_{10}H_{8}, CAS 91-20-3), one of the major components in JP-8 (0.26–1% v/v), was chosen as a marker of dermal exposure to JP-8. Naphthalene has also been used as a marker for JP-8 exposure in previous human studies (Egeghy et al., 2003; Serdar et al., 2003, 2004; Chao and Nylander-French, 2004; Mattorano et al., 2004). Naphthalene (99%+, scintillation grade) and naphthalene-d_8 (98+atom% D) were obtained from Aldrich Chemical Co. (Milwaukee, WI). Acetone (nanograde) was obtained from Mallinckrodt Baker, Inc. (Paris, KY).

Dermal samples. Tape-strip samples were collected from three exposed body regions with the greatest potential for dermal exposure, as identified by the subject and confirmed by visual inspection by the investigators, in an air-conditioned clean room after the end of work shift. The median time between the end of work and sampling was 28 min (mean and standard deviation 41 ± 31 min). For each subject, body regions sampled included three of the following body surfaces: forehead, neck, shoulders, arms, hands, legs, knees, feet or buttocks. Within each body region, three successive tape-strip samples were taken from a single site using Cover-Roll tape precut to size 4 cm × 2.5 cm (Beiendorf AG, Germany). The tape-strip technique has been described in detail elsewhere (Chao and Nylander-French, 2004; Mattorano et al., 2004). In brief, the tape was applied onto the skin surface with a constant pressure and retained for 2 min before it was removed at ~45° angle using clean forceps. The tape was folded and placed into a labeled scintillation vial containing 5 ml acetone and 20 μl of 25 μg ml^{-1} naphthalene-d_8 (internal standard). Three blank tapes per subject were processed along with dermal tape-strip samples as a quality control measure. No cross-contamination was observed in any of the blank samples.

Tape-strip samples were analyzed using a published gas chromatography–mass spectrometry (GC–MS) method (Chao and Nylander-French, 2004). Tape-strip samples were analyzed in the order they were collected, i.e. all the first tape-strip
samples were analyzed first, then the second tape-strip samples and finally, the third tape-strip samples. Results of the three sequential tape-strip samples from the first 30 subjects showed that when the naphthalene recovery in the first tape-strip from that sampling site was below the limit of detection (LOD), the naphthalene recovery in the second and third tape-strips were both below LOD. Thus, if the naphthalene recovery in the first tape-strip sample was below LOD, the second and third tape-strips from the same site were not analyzed. For the statistical analyses, a value of 2/3 of the LOD was assigned to all the tape-strip samples detected to be below LOD, whereas the unanalyzed second and third tape-strip samples were assigned a value of zero.

Statistical analyses

All statistical analyses were performed using SAS system software (V.8.1, SAS Institute, Cary, NC, USA) at a significance level of 0.05. Dermal exposure data were log-transformed (natural) to best satisfy normal distribution assumption. The amount of naphthalene removed with the three successive tape-strip samples was adjusted for the surface area of that particular region sampled in order to estimate the regional dermal exposure to naphthalene under the assumption of uniform exposure within that region. For each subject, the regional surface areas were estimated by Lund and Browder chart (Deitch, 1999) and Haycock’s formula (Haycock et al., 1978). The whole body dermal exposure to naphthalene (ng m\(^{-2}\)) was calculated by summing the estimated regional dermal naphthalene concentration of the three sampled regions (e.g. arm, neck and leg), and assuming that no exposure to the other unsampled regions occurred.

A one-way analysis of variance was used to investigate differences in dermal exposure to naphthalene between different exposure groups, job titles, use of personal protective equipment (respirator, cotton overalls and booties) or smoking status. Multivariate linear-regression analyses with stepwise selection were used to investigate the effects of potential covariates on dermal exposure to naphthalene. The response variable was regressed on each independent variable separately to eliminate unlikely predictors (P < 0.25). The remaining independent variables were examined to achieve the final model (P < 0.05). Collinearity was investigated by eigenvalues and condition indices. Possible outliers were examined by student residuals.

RESULTS

Effects of exposure category

Dermal exposure was observed in various regions of the body. Hands and arms were the most frequently exposed and hence, the most sampled regions, accounting for 70.5% of all sampled regions (Table 1). The highest regional dermal exposure was observed on the buttocks of one subject and believed to be the result of sitting in a puddle of JP-8 during work. Overall, dermal exposure to naphthalene was different among the sampled regions (P < 0.0001). However, no statistical difference was observed in dermal exposure to naphthalene between left and right arms, legs or feet (for all P > 0.0725).

Descriptive statistics for the estimated whole body dermal exposure to naphthalene are presented in Table 2. The average whole body dermal naphthalene level was 7.61 ± 2.27 ln(ng m\(^{-2}\)), ranging from 4.61 ln(ng m\(^{-2}\)) to 15.4 ln(ng m\(^{-2}\)). Our results showed that dermal exposure to naphthalene was significantly different among the three exposure groups (P < 0.0001). The geometric mean exposure level was 10-fold higher in the high-exposure group (4180 ng/m\(^2\) with geometric standard deviation (GSD) of 9.35) than in the medium-exposure group (485 ng/m\(^2\) with GSD of 3.87), and 13-fold higher than in the low-exposure group (343 ng/m\(^2\) with GSD of 3.80). However, no significant difference was observed on dermal exposure to naphthalene between subjects in the medium- and the low-exposure groups (P = 0.5920). There was no observed statistical difference in dermal exposure for subjects within the same exposure group regardless of job title (for all P > 0.3568). However, entrants who were also attendants and runners during the work day (job title 1) and entrants who also were attendants during the work day (job title 2) had a significantly increased dermal exposure to naphthalene when compared with attendants and runners (job title 5), attendants only (job title 6) and other field workers (job title 7) (for all P < 0.0148). Entrants (job title 4) had a significantly increased dermal exposure when compared with attendants (job title 6; P < 0.0286) and other field workers (job title 7; P < 0.0078) and borderline increased exposure when compared with attendants and runners (job title 5; P < 0.0721).

Effects of personal and work-related factors

Two multivariate linear-regression models were applied to evaluate the effects of personal and job-related factors on dermal exposure to naphthalene. The first model consisted of all the subjects whereas the second model consisted of the subjects in the high-exposure group only (Table 3). The first model (n = 118) had four significant predictors in the final regression model: (i) skin irritation, (ii) use of booties, (iii) work inside fuel tank and (iv) the duration of JP-8 exposure, which represents the time between the start of work and dermal sampling (in minutes). All the same covariates, except work inside fuel tank, were also included in
the second model \((n = 82)\) since all the subjects in the high-exposure group performed fuel tank entry. Subjects who complained about skin irritation because of contact with JP-8 or performed fuel-tank entry had a significantly increased dermal exposure to naphthalene \((P < 0.0001)\). Also, subjects who did not wear booties had a higher dermal exposure to naphthalene than workers who wore booties \((P < 0.0047)\). The duration of JP-8 exposure was observed to be an inversely significant factor in both of the final models \((P = 0.0329\) and \(0.0059)\) denoting, as expected, that with an increased penetration time, less naphthalene was available in the upper layers of the stratum corneum for tape stripping.

The observed non-significant covariates included personal demographics (age, gender, weight, height, race), job-related factors (primary job, purpose of work and tasks performed, e.g. held ventilation tubing, depuddled, removed bolts, removed foams, removed bolts, removed foams, removed foams, removed foams).
removed tank door, replaced foams), use of other personal protection equipment (cotton overall, respirator, goggles, gloves, aprons) and smoking status (yes or no).

**DISCUSSION**

We have previously shown that dermal JP-8 exposure, using naphthalene as a marker, can be measured by the tape-strip technique, which removes the upper layers of the stratum corneum, when coupled with GC–MS analysis (Chao and Nylander-French, 2004; Mattorano et al., 2004). This approach allows the determination of the quantity of JP-8 retained in the upper layers of the stratum corneum following exposure, thus providing a measure of absorbed dermal dose available for metabolism and systemic circulation. Here we have shown that this approach can be used to measure dermal exposure to JP-8 in an occupational exposure setting. The dermal exposure estimates corresponded well with exposure scenarios. The regression models used indicated that the dermal exposure estimates were highly correlated with a potential health risk (skin irritation), protection control (use of booties), work situation (work inside the fuel tank) and the exposure duration. Furthermore, the results of this study as well as our laboratory experiments (Chao and Nylander-French, 2004) have shown that JP-8 components penetrate into the skin rapidly with minimum evaporation from the skin surface.

For this study, we adjusted the amount of naphthalene in the tape-strip samples by the surface area of the sampled region and thus, were able to account for individual differences in exposed surface areas and to derive individual specific dermal exposure estimates. This adjustment can be considered an improvement over the OECD protocol (OECD, 1997), which uses the surface area of the 80th percentile male for all subjects and thus, fails to account for individual variation. With this approach, we were able to correlate dermal exposure estimates with four significant predictors (skin irritation, use of booties, work inside the tank and exposure time) in the linear regression models. Since JP-8 has been reported to cause skin dryness, burning and irritation, skin irritation was expected to be one of the most important covariates explaining dermal exposure to naphthalene. In addition, work inside the fuel tank contributed significantly to JP-8 dermal exposure. Entrants performing work inside the fuel tank wearing cotton overall unavoidably contact JP-8. Hence, increased dermal exposure to JP-8 on different body regions was expected. The use of booties significantly lowered dermal exposure to naphthalene for subjects whose foot or leg was used for exposure monitoring (n = 35, P = 0.0107). JP-8 penetrates readily into the skin (Chao and Nylander-French, 2004), and with increased time between the start of work and the tape-strip sampling, we detected less naphthalene in the upper layers of stratum corneum. This was also observed in a study of pesticide exposure by Doran et al. (2003) who emphasized the importance of time in assessing dermal exposure in agriculture setting.

We chose to present this data using surface area adjusted dermal exposure estimates under the assumption of uniform exposure within the sampled region and assumed no dermal exposure to the unsampled regions and thus, determined dermal exposure to naphthalene using conservative estimates. We also tested another, less conservative, approach in which we applied the average dermal exposure from the three sampled regions to other unsampled regions that resulted in higher dermal exposure estimates (data not shown). In both cases, the high-exposure group had significantly higher exposure than the medium- or low-exposure group (P < 0.0001) and no significant difference was observed between the medium- and low-exposure groups. Although our approach using conservative estimates most probably underestimated the exposure, we were still able to show a statistically

<table>
<thead>
<tr>
<th>Subjects</th>
<th>n</th>
<th>Overall $R^2$</th>
<th>Predictor variable</th>
<th>Parameter estimate</th>
<th>Standard error</th>
<th>P-value</th>
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<tbody>
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<td>All</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Work inside fuel tank$^b$</td>
<td>1.90</td>
<td>0.417</td>
<td>&lt;0.0001</td>
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<td></td>
<td></td>
<td></td>
<td>Time$^c$</td>
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<td>0.003</td>
<td>0.0329</td>
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<td>High exposure group</td>
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<td>Booties$^b$</td>
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<td>0.0047</td>
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<td>Time$^c$</td>
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<td>0.004</td>
<td>0.0059</td>
</tr>
</tbody>
</table>

$^a$Number of subjects.
$^b$Dicotomous variable: yes/no.
$^c$Duration of JP-8 exposure (the time between the start of work and dermal sampling) in minutes.

Table 3. Regression models of the whole body dermal exposure to naphthalene [ln(ng m$^{-2}$)].
significant difference in dermal exposure to naphthalene among the exposure groups and job titles (Table 2).

To date, no occupational exposure limit has been established for dermal exposure to JP-8 or in general, owing to the lack of reliable data for quantitative risk assessment (Nielsen and Grandjean, 2004). Therefore, standardization and validation of dermal exposure assessment methods are essential to develop more comparable and accurate exposure estimates. The tape-strip technique for dermal sampling has been used to investigate the biological activities and structure of stratum corneum (van der Molen et al., 1997; Beisson et al., 2001), to determine the chemical penetration (Rougier et al., 1986; Rougier and Lotte, 1993) and chemical contamination (Nylander-French, 2000; Cullander et al., 2001; Chao and Nylander-French, 2004; Mattorano et al., 2004) in the skin. It is an inexpensive, non-invasive means of sampling the skin and has recently been proposed by the US Food and Drug Administration as part of a standard method to evaluate bioequivalence of topical dermatological dosage forms (Shah et al., 1998).

In this study, we have demonstrated that the tape-strip technique is an effective and non-invasive method to quantify dermal exposure to JP-8 in an occupational setting. This approach can be easily applied onto any environmentally or occupationally exposed population (including children) to assess dermal exposure. Other existing dermal sampling methods (i.e. patches, skin swabs, washing and fluorescent tracers) provide data on the amount or mass of materials potentially deposited on the skin (reviewed in Nylander-French, 2003). However, these methods fail to provide data as to what has been absorbed into stratum corneum layers. Thus, the tape-strip method has the potential to meet the criteria required to standard dermal exposure assessment. However, more data are required to show the applicability of this method for other compounds and potential exposure settings.

We conclude that the fuel-cell workers investigated here had extensive dermal exposure to JP-8 and thus, action may be required to minimize exposure and potential health effects. In addition, this study clearly demonstrates the efficiency and suitability of the tape-strip method for the assessment of dermal exposure. Further study is warranted to investigate the toxicokinetics of dermal exposure to JP-8 and the contribution and importance of dermal exposure to JP-8 on total body dose and systemic exposure.

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