Effect of Occupational Exposure to Rayon Manufacturing Chemicals on Skin Barrier to Evaporative Water Loss

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Abstract: Effect of Occupational Exposure to Rayon Manufacturing Chemicals on Skin Barrier to Evaporative Water Loss: Tzu-Chieh CHOU, et al. Department of Environmental and Occupational Health—To evaluate the effects of the occupational exposure to rayon manufacturing chemicals (RMC, containing predominantly carbon disulfide (CS2) and minor sulfuric acid) in a rayon factory on the basal transepidermal water loss (TEWL), barrier integrity (BI), and sequential increasing TEWL profiles. Six Thais and five Chinese workers in the spinning department of a rayon manufacturing plant and five healthy unexposed controls were recruited as the test subjects. An area of 4.5 × 5.5 cm on the mid-side of the volar forearm on the right hand was stripped by means of moderate pressure with commercially available adhesive tape by the same technician throughout the experiment. The skin was progressively stripped until glistening. TEWL was measured at every three and five tape strips on the right hand. The corresponding site on the left hand was measured parallel as the self-control. We found significant differences in basal TEWL and in BI between Chinese workers and Chinese controls, and between Thai workers and Chinese workers, respectively. Two-stage patterns of progressive TEWL profiles were found in such a chronic and repeated occupational exposure to RMC containing CS2. The occupational exposure to RMC could result in the perturbation of the skin barrier function. Basal TEWL might be more sensitive to chronic skin irritant exposure. The TEWL profile achieved to the glistening stage might be necessary to avoid erroneous pattern estimation. Due to the lack of Thais control in this study, the racial difference in response to the RMC warrants further study. (J Occup Health 2004; 46: 410–417)

Key words: Transepidermal water loss, Barrier integrity, Tape stripping, Occupational exposure, Rayon manufacturing

Skin diseases, accounting for about 9–35% among all occupational diseases1–5, have long been considered the most prevalent diseases in occupational environments. Irritant contact dermatitis is the most common form of occupational skin disease and constitutes nearly 80% of all occupational dermatitis in the US6. Any pathological changes in skin will result in the destruction of skin barrier function7–10. Basal transepidermal water loss (TEWL) has been widely used as an index in the evaluation of skin barrier function11. A great number of studies have reported significantly positive associations between the dermal absorption of xenobiotics and the basal TEWL rates12–14. Barrier integrity (BI), the number of tape stripplings which increase TEWL to a certain value (e.g. 20 g/m²/h) has been reported to be able to differentiate the skin barrier function among races15, 16, but the application of these two skin barrier indices in exposure to occupational hazards very is limited.

Cumulative evidence showed that the location of the skin barrier function mainly lies within the stratum corneum17, 18. By repeatedly depriving the stratum corneum with an adhesive tape stripping technique, a sequential increasing profile of TEWL can be obtained. Such a TEWL increasing profile can be further utilized to evaluate the functional barrier properties of different layers of the stratum corneum19–21.

Numerous chemicals frequently used in industry have...
shown that they can cause perturbation of the skin barrier in either animal experiments or human volunteer studies. The conclusions drawn from the above studies were mainly based on acute exposure and short-term observation. There is a need to evaluate the skin barrier function in subjects who have been occupationally exposed to skin irritants in occupational settings for a certain period chronically and repeatedly. Several lines of evidence also indicate that resistance to the chemical perturbation of the skin barrier is race-dependent.

This study tried to assess the skin barrier characteristics in rayon workers who have long been occupationally exposed to carbon disulfide (CS₂) during manufacturing processes. Some organic solvents have been documented to cause skin irritation. Wigger-Alberti and associates have demonstrated that the interaction due to the sequential exposure to sodium lauryl sulphate (SLS) and toluene could cause an increase in TEWL and induce skin irritation. Drexler and colleagues have found increased pathological skin problems among the workers exposed to rayon manufacturing materials. Our recent studies demonstrated that workers occupationally exposed to rayon manufacturing chemicals (RMC, containing predominantly CS₂ and minor sulfuric acid) could result in hand dermatitis and further found that those rayon workers who had skin diseases tended to have higher levels of 2-thiothiazolidine-4-carboxylic acid, used as a biomarker of exposure, in post-shift urine than those who had healthy skin, given their CS₂ exposures were the same. It is of importance to evaluate various skin barrier function indicators of the basal TEWL, BI and sequentially increasing TEWL profile among workers who have been occupationally exposed to RMC in comparison with un-exposed controls. The effects of difference in race on the above skin barrier indicators were also evaluated.

Materials and Methods

Subject recruitment

According to the findings in literature and in our previous studies, employees working in the spinning department of a rayon factory are readily exposed to considerably high levels of RMC. In the spinning department, a viscose solution containing predominantly CS₂ and minor sulfuric acid, is then pumped through a platinum nozzle into a warm viscose bath at a very high speed, and a continuous rayon thread is generated in the spinning department. Although wearing impermeable rubber gloves, the workers complained that the rayon solution spilled over onto the surface of their hands and front forearm occasionally because of the need to put their hands into the rayon solution to collect the thread every one-and-a-half hours.

To evaluate the effects of repeated occupational exposure to viscose-related chemicals on the forearms, all the workers in the spinning department (all male, n=11) and five healthy male un-exposed controls matched by social-economic status were enrolled in this study. Eleven workers (age range 26–52 yr/o) included two race groups, Thais (n=6) and Chinese (n=5). All the exposure subjects worked uninterruptedly in the spinning department for no less than a year. All the controls (age range 24–25 yr/o) were recruited without any remarkable historical exposure to any organic solvents. All subjects were instructed not to apply any cosmetics or topical drugs to the test sites for at least 24 h before the commencement of the study. Informed consent was obtained from each subject prior to the experiment.

Tape stripping and transepidermal water loss (TEWL) measurement

An area of 4.5 x 5.5 cm on the mid side of the right volar forearm was stripped with moderate pressure on commercially available adhesive tape (Scotch No. 845 book tape, 3M, USA) by the same technician throughout the experiment. The skin, without any notable diseases or wounds in prior examination, was progressively stripped until glistening, which indicated near complete deprivation of the stratum corneum.

An evaporimeter (Tewameter 210®, Courage & Khazaka, Cologne, Germany) was used to measure TEWL, as used in our previous studies. Prior to the measurement, all subjects were instructed to sit still in a room with atmospheric temperature and relative humidity of 26.6 (± 1.1)°C and 53.4 (± 11.6)% respectively, to maintain a physiologically calm condition for 30 min. Moreover, TEWL was performed in the daily time-zone between 3:00 and 6:00 p.m. to avoid endogenic variation of evaporation water loss due to a different circadian rhythm. The corresponding site on the left hand was measured parallel as the self-control. TEWL was measured at every three and five tape strips on the right hand and left hand, respectively. TEWL was determined at every five strips instead of every three after 21 strips for the Thais because their TEWL had reached a relatively steady state. The experimental protocol was approved by the Institute Review Board (IRB) of the National Cheng Kung University before the commencement of the study.

Data analyses

Basal TEWL and BI were compared under different exposure conditions (workers vs. controls) and races (Thais vs. Chinese). BI was defined as the number of progressive tape stripings at which TEWL reached 39.4 g/m²h by Tewameter 210®, equivalent to 20.0 g/m²h measured by EP1. Mann-Whitney’s U test was applied to examine whether there were any significant differences in TEWL and BI. Spline regression analyses were used to determine the knot (the number of tape strips) at which the TEWL of Thais was higher than that of Chinese. The daily rhythm of TEWL was also evaluated.
strippings at which two segmental lines get connected). The knot was chosen as the point where two segmental lines receive the greatest summation of the square of correlation coefficients ($=R_1^2+R_2^2$). Statistica Software (Release 5, StatSoft, OK, USA) and S-Plus 2000 (Release 1, Mathsoft, Seattle, WA, USA) were used throughout data analyses.

Results

The coefficient of variance (CV%=$\frac{SD}{mean} \times 100\%$) for all the TEWL measurements on the left hand was found to be 12.1 ($\pm$5.0)%, indicating considerably stable TEWL measurements throughout the experiments. Basal TEWL in Thai workers, Chinese workers, and Chinese controls were 11.0 ($\pm$1.9), 14.8 ($\pm$3.9), and 8.9 ($\pm$2.1) g/m²h, respectively (mean ($\pm$SD)). When examined by Mann-Whitney’s U test, no significant differences were found in any one-by-one comparisons except between Chinese workers and Chinese controls ($p<0.05$, Fig. 1a), indicating that basal TEWL might be more sensitive in distinguishing the exposure status than race. On the other hand, BI was found to be 68.8 ($\pm$18.9), 28.2 ($\pm$8.4) and 27.6 ($\pm$8.3) for Thai workers, Chinese workers and Chinese controls, respectively. No significant differences were found except the comparison of BI in Thai workers and Chinese workers ($p<0.01$, Fig. 1b), suggesting that in contrast to basal TEWL, BI might be more sensitive in the differentiation of the races than the exposure status.

The progressive tape stripping TEWL profile showed that the TEWL measurements, basically increased, followed by the increases in the number of progressive tape strippings for all three groups (Fig. 2). The considerably wide ranges of TEWL measurements at a given fixed number of tape strippings for any group showed substantial inter-individual variability in the change in skin barrier function in relation to the number of strippings. Seemingly two linear segments of TEWL profiles were found for all test groups. The knots (number of tape strippings at which two linear segments get connected) were 36, 18 and 15 for Thai workers, Chinese workers and Chinese controls, respectively (refer to Table 1).

Fig. 1. The comparison of basal TEWL (Fig. 1a) and barrier integrity (BI, Fig. 1b) among Thai workers, Chinese workers, and Chinese controls. Note used in the Figure: \[ mean, I: \pm S.D., p \] value was calculated by Mann-Whitney’s U test, *: $p<0.05$, **: $p<0.01$

Fig. 2. TEWL profile patterns among three study groups. ●: measurements of the Thai workers, ■: measurements of the Chinese workers, ▲: measurement of the Chinese controls, ——: TEWL profile pattern among Thai workers estimated by simple linear regression, ——: TEWL profile pattern among Chinese workers estimated by simple linear regression, ——: TEWL profile pattern among Chinese controls estimated by simple linear regression. The knots (number of tape strippings at which two linear segments get connected) were 36, 18 and 15 for Thai workers, Chinese workers and Chinese controls, respectively (refer to Table 1).
which the number of tape strippings=0) were 11.90 (±0.57), 14.44 (±0.86) and 8.45 (±1.00) for Thai workers, Chinese workers and Chinese controls, respectively. These estimates were close to the experimental measurements of 11.0 (±1.9), 14.8 (±3.9) and 8.9 (±2.1), indicating that the accuracy of the equations’ predictions was acceptable. The increases in TEWL per tape stripping (slope=b1 and b2) at the first stage and at the second stage for Thai workers were 0.22 g/m²h, 0.60 g/m²h (Table 2). For Chinese workers, they were 0.53 g/m²h and 1.42 g/m²h. Compared to those for Chinese workers, the slopes for Chinese controls in the first stage was higher (0.76 vs. 0.53) and lower in the second stage (1.16 vs. 1.42), showing a steeper increase in the beginning of tape stripping and a milder increase in the later stage. The ratios of the 2nd slope to 1st slope, an index estimating the relative increasing speeds of two segmental stages, were 2.73, 2.68, and 1.53 for Thai workers, Chinese workers and Chinese controls, respectively. Almost the same slope ratios for Thai workers and Chinese workers (≈2.7) suggested that the effects resulting from the rayon manufacturing insults on different races might be similar although Thais showed much more resistance to the chemical perturbation of skin barrier function at both stages (1st stage: 0.22<0.53, 2nd stage: 0.60<1.42). Compared to that for Thai workers and Chinese workers, the ratio for Chinese controls was apparently lower (b2/b1=1.53). Overtly lower slopes in both stages for Thai workers than from either Chinese workers or Chinese controls were observed. The increasing slope at the initial stage (about less than 40 tape strippings) for Thais were significantly less than that for two Chinese groups, suggesting more resistance of skin barrier function to adhesive taping in Thais than in

Table 1. Using spline regression analyses to estimate the knot of two segmental lines of TEWL profile

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Knot</th>
<th>R₁²</th>
<th>R₂²</th>
<th>R₁²+R₂²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thai workers</td>
<td>30</td>
<td>0.44</td>
<td>0.49</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>0.47</td>
<td>0.48</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>36†</td>
<td>0.51</td>
<td>0.45</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>0.51</td>
<td>0.43</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>0.53</td>
<td>0.38</td>
<td>0.91</td>
</tr>
<tr>
<td>Chinese workers</td>
<td>12</td>
<td>0.29</td>
<td>0.64</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>0.46</td>
<td>0.60</td>
<td>1.06</td>
</tr>
<tr>
<td></td>
<td>18†</td>
<td>0.57</td>
<td>0.55</td>
<td>1.12</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>0.52</td>
<td>0.43</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>0.54</td>
<td>0.34</td>
<td>0.88</td>
</tr>
<tr>
<td>Chinese controls</td>
<td>9</td>
<td>0.39</td>
<td>0.54</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>0.56</td>
<td>0.47</td>
<td>1.03</td>
</tr>
<tr>
<td></td>
<td>15†</td>
<td>0.65</td>
<td>0.39</td>
<td>1.04</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>0.67</td>
<td>0.32</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>0.62</td>
<td>0.26</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Notes: Knot: the number of tape strippings at which two segmental lines connected. R: correlation coefficient. † represent the highest summation of the square of correlation coefficient (R₁²+R₂²)

Table 2. Using simple regression approach to the best fit of the TEWL profile to the glistening stage among three groups

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Knot</th>
<th>n₁</th>
<th>a₁ (SD)</th>
<th>b₁ (SD)</th>
<th>R₁</th>
<th>n₂</th>
<th>a₂ (SD)</th>
<th>b₂ (SD)</th>
<th>R₂</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thai workers</td>
<td>36</td>
<td>62</td>
<td>11.90 (0.57)***</td>
<td>0.22 (0.03)***</td>
<td>0.71***</td>
<td>81</td>
<td>-3.46 (5.27)***</td>
<td>0.60 (0.07)***</td>
<td>0.67***</td>
<td>2.73</td>
</tr>
<tr>
<td>Chinese workers</td>
<td>18</td>
<td>35</td>
<td>14.44 (0.86)***</td>
<td>0.53 (0.08)***</td>
<td>0.75***</td>
<td>37</td>
<td>-4.71 (7.19)***</td>
<td>1.42 (0.22)***</td>
<td>0.74***</td>
<td>2.68</td>
</tr>
<tr>
<td>Chinese controls</td>
<td>15</td>
<td>26</td>
<td>8.45 (1.00)***</td>
<td>0.76 (0.11)***</td>
<td>0.80***</td>
<td>33</td>
<td>5.22 (7.50)***</td>
<td>1.16 (0.26)***</td>
<td>0.63***</td>
<td>1.53</td>
</tr>
</tbody>
</table>

n₁, n₂: sample size; a₁,a₂: intercept; b₁,b₂: regression coefficient; R₁,R2: correlation coefficient, ***p<0.001
most Chinese. The differences between TEWL patterns for Chinese workers and Chinese controls were less insignificant than those between Thais and Chinese (Fig. 2), indicating the racial difference might be an important factor in the consideration of chemical insults to the skin barrier function.

Discussion

Skin barrier function is one of the essential mechanisms protecting human beings from environmental hazards via the dermal route. A great number of studies have demonstrated that skin barrier function is associated with the skin absorption potential. Studies regarding the change in skin barrier function in relation to tape stripping were mainly carried out by using either animals or human volunteers. The studies incorporating humans who are truly exposed in occupational settings were, however, very limited. The exposed subjects in this study worked in the spinning department for at least a full year and their forearms and hands were exposed to CS₂-containing viscose solution occupationally in a chronic and repeated way. More than 70% of the workers have suffered from contact dermatitis on the hands because of having little chance to remove the viscose irritants spilled on them. In contrast, with the availability of rapid wiping off of the viscose irritants, only less than 6% of them reported contact dermatitis on forearms (published elsewhere and data not shown). These facts show that viscose solution containing CS₂ was able to cause skin perturbation and the exposure of forearms might be frequent, repeated but relatively low. Such an exposure scenario was different from those normally conducted for human volunteers as well as for murine species.

Quite a few studies have demonstrated that skin barrier function measurements can be affected by many factors, such as host variables (race, age, gender, and pathological skin condition), and measurement conditions (temperature, humidity, air convection, and time zone tested). A fixed range of temperature, humidity, and time zone were constantly provided in the measurement for all participants in this study. Moreover, all the test subjects were of the same gender (male) as well as the TEWL measurements on the left-hand site (as the control site) remaining considerably stable. Therefore, the TEWL measurements in this study were reliable to some extent.

A significant difference in basal TEWL was found between Chinese workers and Chinese controls (p<0.05, Fig. 1a) but not between Thai workers and Chinese workers (p=0.14), suggesting that basal TEWL might be more sensitive in the evaluation of the change in skin barrier function resulting from chronic exposure to chemical insults. Our findings were consistent with those in the study conducted by Coenraads et al. in 1986. After 12-wk continuous occupational exposure, they found, compared to unexposed groups, the basal TEWL significantly increased in those exposed to mineral oils, slightly but not significantly increased in those exposed to water-soluble oils among metal industry workers. No distinction between African-American and non-African-American in basal TEWL was also reported by Reed and associates.

BI has been defined as barrier capacity and was measured by the numbers of tape strippings to remove the same thickness of stratum corneum. In this study, BI, but not basal TEWL, was found significantly different in Chinese workers and Thai workers (p<0.01, Fig. 1b), indicating that BI might be more sensitive to the racial differences than basal TEWL. Similar findings of greater numbers of tape strippings needed to remove the same thickness of stratum corneum for the black than for the white were affirmed by other researchers. In this study, Thais (with darker skin) have shown more resistance to progressive tape stripping than Chinese (with lighter skin) in both BI (Fig. 1b) and progressive TEWL profiles (Fig. 2), indicating the different skin types in different races might affect resistance to the mechanical insults. This finding was supported by the conclusions drawn from other studies: more corneocyte layers and lipid contents of stratum corneum were found in black skin than in white skin. The study reported by Reed and colleagues also demonstrated higher capability for skin types V/VI to defy skin barrier perturbation by serious tape stripping than for skin types II/III. All the above findings affirmed that darker skins have more resistance to skin barrier function perturbation. Due to the lack of Thai controls in this study, the racial difference in response to the RMC, however, warrants further study.

Slightly different profile patterns for the Chinese workers and Chinese controls were found (Fig. 2). The TEWL profile pattern for Chinese workers, compared to that for Chinese controls, showed a less steep increase in the first linear stage but a more rapid increase in the second linear stage. Fluhr and colleagues applied sequential D-Square strippings on hairless mice after treatment with 1-hexadecyl-3-trifluoroethylglycero-sn-2-phosphomethanol (MJ33) and they found a similar two-stage TEWL increasing pattern. Kao and colleagues also obtained a similar two-stage TEWL increasing trend with topically applied clobetasol (0.05%) on hairless mice. In these cases, MJ33 was functioned as a permeability barrier homeostasis disrupter and clobetasol a potent glucocorticoid, a well-known barrier homeostasis deteriorator. In the present study, the workers have long been exposed to skin irritants containing CS₂ occupationally, which have been also associated with perturbing the skin barrier. There were slightly different TEWL to sequential tape strips patterns in Chinese controls and exposed Chinese. These chemicals have been documented to cause damage to skin barrier homeostasis in short-term exposure, but the effects of
chemical irritant exposure in a chronic and repeated way on superficial layers of stratum corneum (mainly comprising stratum disjunctant) might be different from deeper ones (mainly comprising stratum compactum). Nevertheless, given substantial inter-individual variability, the use of more study subjects in each group to investigate the effects of occupational exposure to the skin irritants on profile pattern is warranted. Regarding the considerable variability in TEWL measurements revealed in this study, this was also reported by numerous investigators who used a fixed number of sequential tape strips\textsuperscript{20,21). Comparing the TEWL profile to the stage of a given fixed TEWL value or fixed number of strips in previous studies\textsuperscript{19–21), the complete TEWL profile to the glistening stage, i.e., nearly completely removing the stratum corneum by progressive tape stripping was achieved in this study\textsuperscript{52). Table 3 shows the estimation of the TEWL profile if the experiment was carried only to the same stage (i.e., stop at TEWL=39.4 g/m\textsuperscript{2}h) as the previous studies, and the TEWL profile would present only one linear stage for all three groups (Table 3). Compared to Table 2, the TEWL profile in Table 3 for Thai workers, Chinese workers, and Chinese controls shows very similar estimates of intercepts (12.12 vs 14.53 vs 8.83) and slopes (0.21 vs 0.50 vs 0.83) in the first linear stage, but the slopes in the second stage show overtly rapid increases (about 2.7, 2.7 and 1.5 times higher than in the first stage) suggesting faster depletion of skin barrier function in the second stage, which cannot be observed by tape stripping only stopped at 39.4 g/m\textsuperscript{2}h as in previous studies\textsuperscript{15,16). It is well known that the bottommost region of the stratum corneum has been demonstrated to be responsible for preventing evaporative water loss on the basis of lipid analysis and barrier properties\textsuperscript{50). This study demonstrated that the complete TEWL profile for progressive tape stripping completed to the glistening stage appears to be meaningful. The rayon manufacturing solution contained saturated CS\textsubscript{2} and CS\textsubscript{2} has been documented as a skin irritant\textsuperscript{31). Concerning the findings of the study, it might be hypothesized that the skin exposed to RMC (saturated CS\textsubscript{2} solution) could chronically and repeatedly result in more resistance to the perturbation in the superficial stratum corneum layers, but more serious damage to the deeper stratum corneum layers, which were more critical to skin barrier function. Taken together, this study concluded that basal TEWL might be more sensitive to repeated low-dose chemical exposure. BI might be more sensitive to the racial differences, but due to the lack of the Thai controls in this study, the racial difference in response to the RMC warrants further study. Two-stage patterns of progressive TEWL profiles were found in such a chronic and repeated occupational exposure to RMC containing CS\textsubscript{2. The TEWL profile achieved to the glistening stage might be necessary to avoid erroneous pattern estimation. Owing to substantial inter-individual variability, the use of more test subjects to investigate the effects of RMC on skin barrier function is warranted. Acknowledgments: This study was jointly supported by the National Science Council (Grant number: NSC-92-2320-B-238A-001, NSC-92-2320-B-006-093) and the Institute of Occupational Safety and Health, Council of Labor Affairs (Grant number: IOSH89-A307), Taiwan. The authors sincerely thank Mr. Roger Wu, Mr. You-Ming Chu, and Ms. Jing-Fang Hsu for their assistance with fieldwork. We also thank the workers and employers of the rayon factory for their participation and cooperation. References

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