Cough in Hot Pepper Workers*

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Study objective: To determine whether there is an effect on the prevalence of respiratory symptoms, an alteration in lung function, or an increase in the cough threshold to capsaicin among workers chronically exposed to hot chili (Capsicum) peppers.

Design: Cross-sectional study of responses to a structured questionnaire, lung function assessed by spirometry and cough threshold to inhalation of capsaicin aerosol in a group of occupationally-exposed Capsicum workers as compared to non-exposed employees of the same work site.

Setting: Spice manufacturing facility.

Participants: Twenty-two Capsicum-exposed and 19 nonexposed workers.

Measurements and main results: When evaluated by questionnaire, 13 (59 percent) of the Capsicum-exposed workers reported cough as compared to 4 (21 percent) of the nonexposed workers (p<0.05). Baseline FEV, and FVC did not differ between the two groups. Cough threshold, as assessed by the lowest concentration of inhaled capsaicin eliciting cough, was related to workplace exposure (p=0.05), displaying a bimodal pattern of higher and lower cough thresholds among the Capsicum workers as compared to a unimodal distribution among the nonexposed workers. Within the exposed group, a higher cough threshold was significantly related to male gender (p=0.03) and was associated to a lesser extent with dietary preference for hot food (p=0.09) and cumulative cigarette smoking (p=0.07). Conclusion: Chronic occupational exposure to chili peppers is associated with complaints of cough but does not alone lead to decreased responsiveness of capsaicin-sensitive nerves when assessed by cough threshold. The cough response to capsaicin inhalation may be modified by the effects of multiple, potentially interactive factors.

(Chest 1991; 99:27-32)

SP = substance P; HPLC = high pressure liquid chromatography; ATS = American Thoracic Society

Capsaicin is the active chemical moiety in hot chili or cayenne peppers (Capsicum annum and related species) that accounts for the "hot" sensation associated with their consumption.1 Capsaicin's actions appear to be mediated through the release of the neurosecretory agent, SP, and other neuropeptides from afferent "nociceptive" nerve endings.2 These neuropeptides have many direct and indirect inflammatory effects including vasodilation, increased vascular permeability and neutrophil chemotaxis.3,4 Pre-treatment of animals with capsaicin diminishes the response of capsaicin-sensitive nociceptive nerve endings to capsaicin and to nonspecific noxious stimuli, a tachyphylactic effect that is related to the depletion by capsaicin of neuropeptide stores in the nerve endings.5 Capsaicin-sensitive nerves in the airways may play an important role in inflammation, airway reactivity and cough.3 Cough is of particular interest because of the afferent pathways that appear to mediate this reflex.6 Sensory nerve endings supplied by unmyelinated C-fibers that are of the cough reflex are highly responsive to capsaicin.6 In humans, capsaicin inhalation causes cough in a dose-dependent and reproducible manner.7-10 This capsaicin response can be quantified as a "cough threshold," the lowest concentration inducing cough upon inhalation of serially increasing concentrations of capsaicin. Systemic pretreatment of guinea pigs with capsaicin significantly reduces the cough response to inhaled capsaicin.6 In humans, however, tachyphylaxis is not observed after repeated inhalations of capsaicin, despite the observation that certain other inhaled stimuli of cough, such as citric acid aerosol, do indeed elicit tachyphylaxis.9 It is not known whether chronic exposure to capsaicin, in contrast to brief repeated inhalation, would reduce responsiveness and raise the cough threshold. It is also unknown whether such chronic exposure would modify other capsaicin-sensitive airway responses affecting inflammation or responsiveness to irritative stimuli.

Spice workers processing Capsicum peppers comprise a group unique in its chronic inhalational exposure to capsaicin. For this reason we undertook a study of chili pepper workers to assess whether they exhibited a different prevalence of respiratory or irritant symptoms as compared with a group without such exposure. We also examined whether workplace Capsicum exposure was associated with a modified response to capsaicin inhalation challenge as measured by the cough threshold. We hypothesized that if chronic capsaicin inhalation depleted inflammatory neuropeptides from nerve endings in the airways, Capsicum-exposed workers would display an increased capsaicin cough threshold and might have fewer com-
plaints of upper airway irritation, such as nonspecific or seasonal rhinitis.

METHODS

Study Site

With the cooperation of a large spice manufacturing company and the local union representing employees, we studied workers at a facility processing Capsicum peppers, together with administrative personnel from the same company. Subject participation was voluntary and carried out on company time. The study protocol was reviewed and approved according to standard institutional guidelines for human subject experimentation. We carried out subject recruitment in the following manner: written flyers announcing the study were circulated to the potential study population together with a voluntary sign-up list. Cough was not identified as a focus of study interest. Potential subjects were aware that a modest reimbursement would be provided for participation.

Work Process

Peppers processed included locally grown red peppers with a relatively low capsaicin content used for “sweet paprika” and imported smaller-sized “hot” red peppers used for chili. Pepper “hotness,” based on capsaicin content verified through HPLC, is traditionally measured in the spice industry in “Scoville units.” The peppers processed in the facility ranged from less than 100 to 100,000 Scoville units per pepper. Processing of peppers included emptying sacks of dried peppers, operating sifting and grinding equipment, “cooking” ground chili, bulk packing in drums and warehousing of the final product. The “cooking” processing step included blending and heating ground chilies together with salt and sugar to achieve a desired flavor, color and texture.

Capsicum processing involved two small work crews over a day and a swing shift. The processing of the hottest high Scoville unit chilies is seasonal in nature lasting several months out of each year. These peppers had come in to processing for the season two to three weeks prior to our study. Capsicum processing took place in one section of a large structure; in other sections of the building workers carried out sorting and packing of flaked and powdered onion and garlic. The processing structure was not partitioned. All sifting, grinding and mixing operations in the facility were closed systems. There was no general environmental ventilation and no air conditioning in the processing structure.

Administrative personnel who served as a nonexposed comparison group worked in areas isolated from processing. All but two worked in one air-conditioned office building on the factory grounds. The job responsibilities of these personnel included accounting, secretarial and various administrative activities although several did have duties such as safety that took them into production areas at various times.

Questionnaire Survey

We carried out a structured 10- to 15-minute interview with each subject. The questionnaire covered demographics, work history, work practices, history of lower and upper respiratory symptoms and medical history, dietary intake and tolerance of hot, spicy food and cigarette smoking history. Interviews were carried out in either English or Spanish according to the preference of the subject.

Capsaicin Challenge

After the interview, we carried out spirometry and inhalation challenges. In the case of the Capsicum-exposed workers (except for one manager tested with controls), this took place in an enclosed room in the production building. For the nonexposed administrative workers, spirometry and challenge took place in an air-conditioned room one day later. Each subject performed spirometry according to standard ATS criteria (Vitalograph, Birmingham, England).

Subjects then carried out a series of incremental inhalational challenges with nebulized solutions of capsaicin. Challenge was stepwise beginning with diluent (1 percent ethanol in normal saline solution), followed by increasing concentrations of capsaicin beginning at 2.8 × 10⁻⁴ M and increasing by half-log steps. Subjects were asked to inhale deeply from the nebulizer (DeVilbis Pulmosonic nebulizer model 25; single-breath volume delivery, 0.013 ml) over 3 s in a single breath. If no cough was elicited by this single-breath inhalation, the next half-log higher concentration of capsaicin was nebulized. Challenge with inhaled capsaicin continued until cough was produced; higher concentrations of capsaicin were not inhaled after the concentration that first elicited cough. In all cases cough occurred immediately upon inhalation of the “threshold” dose of capsaicin. Cough was pronounced and often consisted of a volley of coughs in a paroxysm. Tape recordings were made of the inhalation challenge for later review by an observer blinded to the purpose of the study. Upon reaching a cough threshold, subjects then repeated the FVC spirometry maneuver. Although this took place within 1 to 3 min of the last capsaicin dose, we applied no fixed standard time interval to the repeat spirometry. The spirometry was intended in part to divert the subjects’ attention away from cough as a response of study interest. All exposed subjects and all but four control subjects (administrative personnel with health and safety oversight) were unaware that cough was a specific subject of research interest in the investigation.

Capsaicin (ICN Biochemicals, Cleveland, OH) was prepared in a stock solution of 7.5 mg capsaicin in 250 ml of 1 percent ethanol in normal saline solution. This solution was prepared prior to its field use and kept refrigerated. On each day of the two days of testing, fresh dilutions were prepared from the stock solution. The stock solution had a calculated concentration of capsaicin of 8.8 × 10⁻⁴ M. We tested its actual capsaicin concentration against a known standard through HPLC according to the standard quality control procedures of the spice manufacturing facility where we carried out our study.¹¹ The tested concentration of the stock solution was 5.8 × 10⁻⁴ M. We report dose-response concentration levels based on this determination.

Forced vital capacity and FEV₁ were calculated manually from the spirometric record. Predicted spirometric values were derived from the equations of Goldman and Becklake.¹² No adjustments for racial factors were made.

Subsequent to the field study at the chili pepper processing facility, we carried out a series of cough threshold challenges in normal volunteer subjects (laboratory controls) in order to generate baseline data for another study. We performed these challenges using a similar sequential concentration protocol. We carried out multiple cough threshold determinations with each subject, all challenges being at least one day apart.

Data Analysis

Questionnaire, spirometry and cough threshold data were coded and key entered into a personal computer. Because we defined “cough threshold” as the lowest concentration of inhaled capsaicin at which cough was elicited, each subject could be defined at any given capsaicin concentration dichotomously (cough threshold at this dose, yes[1] or no[0]). Each subject in the field study therefore could have only one threshold value assigned: at this concentration the subject would be assigned a “1”; the subject received a “0” at all other concentrations. We compared the cough threshold responses among chili-pepper exposed with the nonexposed workers, testing this difference with the chi square test. We compared the proportion of other dichotomous or categorical variables among Capsicum-exposed as compared with nonexposed subjects with the chi square or Fisher’s exact test. Differences in continuous variables were tested with the t test or, in the case of pre- and post-capsaicin inhalation challenge, the paired t test. We used the results of repeated challenges in laboratory controls to serve as a measure of
the range of cough threshold responses. We did not utilize test-based statistics for this comparison that would have treated multiple challenges in the same individual as independent observations.

In order to further explore factors potentially associated with cough threshold, we also carried out a logistic regression analysis in the Capsicum-exposed and nonexposed groups separately. We undertook this analysis to explore possible co-factors associated with an apparent bimodal pattern of cough threshold response. In order to differentiate between levels of cough threshold response, we assigned the cough threshold at a concentration of 3 × 10⁻⁶ M capsaicin a value of "0" and the cough threshold at any concentration above this level a value of "1." This defined cough threshold dichotomously, allowing a logistic regression analysis of potential predictors of higher as compared with lower concentration of inhaled capsaicin cough threshold. We tested predictor variables for which there was reason to hypothesize a possible effect on cough threshold, including age, gender, diet and cigarette smoking.

We made no adjustments for multiple comparisons. We analyzed the data utilizing a standard computerized statistical package.

RESULTS
We studied 22 Capsicum-exposed and 19 nonexposed administrative workers. The Capsicum-exposed workers represented all but two of those eligible for the study; the 19 nonexposed workers volunteered from an administrative population of 59 (32 percent).

As Table 1 demonstrates, the Capsicum-exposed workers, although similar in age to the nonexposed comparison group, differed significantly in a number of other ways. The Capsicum-exposed group was predominantly male and Hispanic. Although the cigarette smoking prevalence (defined as having ever smoked cigarettes regularly) was similar between the groups; pack years of smoking were significantly fewer among the Capsicum-exposed as compared with the nonexposed workers.

Among the upper and lower respiratory complaints presented in Table 2, cough was significantly more prevalent among the exposed as compared with the nonexposed workers. Although "nasal stuffiness" tended to be common among exposed workers as well, "hay fever or sinus trouble" displayed an opposite trend, with significantly less use of nasal medications reported by the capsaicin-exposed group. Any episode of past wheezing was similar in both groups and treated asthma was reported only by one nonexposed subject.

Table 2—Respiratory Symptoms Among Capsicum and Non-Exposed Workers

<table>
<thead>
<tr>
<th>Respiratory Variable</th>
<th>Capsicum</th>
<th>Nonexposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough during the day, n(%)*</td>
<td>13 (59)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Cough disturbing sleep, n(%)</td>
<td>3 (14)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Chest discomfort or tightness, n(%)</td>
<td>5 (23)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Dyspnea, n(%)</td>
<td>5 (23)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Nasal stuffiness or runny nose, n(%)</td>
<td>13 (59)</td>
<td>6 (32)</td>
</tr>
<tr>
<td>Hay fever or sinus trouble, n(%)</td>
<td>5 (23)</td>
<td>9 (47)</td>
</tr>
<tr>
<td>Ever having wheezing, n(%)</td>
<td>5 (23)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Ever treated for asthma, n(%)</td>
<td>0 (0)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Use of nasal medications, n(%)*</td>
<td>1 (5)</td>
<td>6 (32)</td>
</tr>
<tr>
<td>Use of cough or chest medications, n(%)</td>
<td>1 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Last flu or cold, median months</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>

*p≤0.05, Capsicum-exposed as compared with nonexposed workers.

Table 3—Spirometry Among Capsicum and Nonexposed Workers

<table>
<thead>
<tr>
<th>Spirometry Result</th>
<th>Capsicum</th>
<th>Nonexposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-capsaicin challenge baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁, % predicted, mean ± SD %</td>
<td>89 ± 14</td>
<td>92 ± 11</td>
</tr>
<tr>
<td>FVC, % predicted, mean ± SD %</td>
<td>107 ± 15</td>
<td>109 ± 8</td>
</tr>
<tr>
<td>FEV₁/FVC, mean ± SD %</td>
<td>85 ± 5</td>
<td>84 ± 8</td>
</tr>
<tr>
<td>Change from baseline, post-challenge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall in FEV₁, mean ml ± SD</td>
<td>−64 ± 210</td>
<td>−37 ± 110</td>
</tr>
</tbody>
</table>

*p≤0.05, Capsicum-exposed as compared with nonexposed workers.
the Capsicum-exposed workers suggests a bimodal distribution, as opposed to the distribution of thresholds among the nonexposed workers. The two patterns of response were significantly different (chi square = 5.98; p = 0.05). Because Capsicum-exposed workers reporting daytime cough in the structured interview might have represented a higher exposure group, we analyzed them separately. These subjects (n = 13) demonstrated an even more marked bimodal response pattern with six having a cough threshold of $3 \times 10^{-7}$ M capsaicin, seven having a threshold of $3 \times 10^{-8}$ M and none having an intermediate threshold. This pattern was significantly different from all of the other workers studied (n = 28 [chi square = 8.2; p = 0.02]). Tape recordings of 18 of the 22 Capsicum-exposed and 17 of the 19 nonexposed subjects were reviewed; six recordings were lost due to technical failure. The median number of coughs at threshold was 2.5 among the Capsicum-exposed and three among the nonexposed group of workers.

Seven laboratory control subjects (four men and three women aged 22 to 32 years) performed 44 separate cough challenge studies with a minimum of six studies per subject. Among these 44 challenges, two (5 percent) exhibited a threshold outside the range observed in the field study at the chili processing facility. Although within-individual variation in response over time was present, there was no pattern of increasing or decreasing threshold over time with sequential challenge testing.

Because cough threshold among the Capsicum-exposed workers suggested a bimodal pattern, we analyzed this response further through a logistic regression analysis. Among Capsicum workers, male gender was significantly associated with a higher cough threshold (p = 0.03). Increasing dietary preference for spicy food (p = 0.09) and cumulative pack years of cigarette smoking (p = 0.07) also were associated with a higher cough threshold, although each was of borderline statistical significance. Neither full-time Capsicum production line grinding, mixing or packing (n = 9) nor hours per day handling peppers (mean = 5.5 ± 3.1) were significantly predictive of higher cough threshold among those in the exposure group. We also analyzed the following potential predictors and found them to be unrelated to cough threshold among Capsicum-exposed workers: age, current cigarette smoking status, workplace exposure to onions or garlic, baseline FEV1:FVC ratio, post capsaicin challenge change in FEV1.

Among the 19 non-Capsicum-exposed comparison group, male gender, hot food preference, and pack-years of smoking each displayed an inverse relationship to higher cough threshold (a trend opposite to that observed among the exposed workers), although none of these associations was statistically significant at the 0.10 level.

**DISCUSSION**

These data do not support the hypothesis that chronic exposure to Capsicum leads to a predictable decrease in capsaicin responsiveness. We observed a bimodal pattern of cough threshold in Capsicum-exposed workers, with some of the exposed workers demonstrating a higher cough threshold than would be consistent with the hypothesis of Capsicum-in-
duced hyporesponsiveness, while others responded to a lower concentration of inhaled capsaicin, opposite the effect predicted. Workplace exposure to Capsicum appeared to interact with other factors, such that gender, dietary capsaicin and cigarette smoking were associated with higher capsaicin cough threshold within the Capsicum-exposed group, potentially contributing to the bimodal pattern of response.

Interpretation of these findings should be tempered by four important limitations in this study: lack of quantifiable Capsicum work-exposure data; demographic differences between the Capsicum-exposed and nonexposed subjects that might have confounded the study; the small study population examined; and the potential difficulties in quantifying the cough response to inhaled capsaicin. We will consider each of these factors as they might potentially affect the results of this study.

We did not have the benefit of industrial hygiene sampling allowing quantification of airborne capsaicin levels in the Capsicum processing facility where we carried out this study. The increased prevalence of cough among those working there supports the impression of exposure sufficient enough to produce some effect. Zuskin et al., 13, 14 in a study of spice workers in Yugoslavia, also found a significantly higher prevalence of chronic cough among exposed as compared with control subjects, although exposures in that group included caraway, cinnamon, parsley, ginger and mace in addition to Capsicum, garlic and onions. We were unable to show a dose-response within the exposure group when we analyzed production line as compared with other Capsicum job duties or when we used hours per day directly handling the peppers as an exposure measure. This may reflect such a ubiquitous exposure as to preclude observation of an exposure gradient. It also suggests that worker self-selection to higher or lower exposure jobs within the Capsicum-exposed group does not appear to explain the observed bimodal response pattern. It may be that capsaicin exposure in the facility studied was insufficient alone to produce the hypothesized effect, whereas higher exposure levels might indeed do so. However, as naive subjects, our study team all experienced eye irritation and persistent cough on the day of our in-plant study. Several weeks later, handling the questionnaires that had been filled out in the plant continued to produce slight irritation from residue dust released upon handling them.

The comparison group of nonexposed workers differed from the Capsicum-exposed workers in important ways, such as in cumulative cigarette smoking and in dietary preference for capsaicin-containing foods. We intentionally have avoided the misleading label of "controls" and would cast the interpretation of results in that light. For example, the decreased use of nasal medications among the Capsicum workers may simply reflect cultural patterns of behavior rather than capsaicin attenuation of rhinitis symptoms. For the purposes of our study, the important differences in the groups, particularly the high dietary intake of capsaicin-containing foods, is a relative advantage in interpreting negative results. It suggests that this study population represents a "maximal" environmental capsaicin group, with exposure both in the diet and through occupational inhalation. Although onion and garlic workers in the facility probably represented a group with a gender, age and ethnic mix closer to that of the chili pepper processors, the potential ability of onion and garlic to stimulate capsaicin-sensitive receptors makes that population inappropriate for comparison with the chili processors.

Small study size is an important consideration in interpretation of these results. Capsicum processing is a limited employment category which precludes large study populations. It should be emphasized that small study populations do not increase the probability of an alpha error (identifying an association as "unlikely to be due to chance" when in fact the null hypothesis should be accepted). 15 Therefore, although negative results must be viewed in the light of the limited power of the small study population of chili pepper processing workers, the observed differences that were statistically significant cannot be discounted because of small study size. However, we have made multiple comparisons and have emphasized two associations (smoking and diet with cough threshold) of borderline statistical significance. Furthermore, the analysis of higher as compared with lower thresholds of response among the Capsicum-exposed workers was not based on any a priori assumptions. It should be considered as hypothesis-generating rather than supporting or detracting from the original study aim.

Finally, it must be stated that there is no established methodology for assessing "cough threshold." 79, 10, 16, 17 Other investigators have given capsaicin both by single breath and by continuous breathing over several minutes, assessing the outcome as number of coughs at a given dose or as an absolute threshold. Our method was reproducible and adaptable to field conditions. In repeated challenges, our laboratory controls appeared to respond over a similar range to the chili pepper facility workers assessed under field conditions and did not demonstrate a pattern over time indicating suggestibility, tolerance or a learning effect. Measurement of cough threshold to inhaled capsaicin does not assess other mechanisms that might produce cough. In particular, cough could have been a symptom of occupational asthma. However, our other observations argue against occupational asthma explaining the prevalence of cough by questionnaire or the bimodal pattern of capsaicin challenge responses. We did not
observe any marked effect of Capsicum exposure on lung function as measured by spirometry either at baseline or in response to capsaicin inhalation. This is consistent with experimental evidence suggesting that capsaicin-induced bronchoconstriction and cough may be mediated by different pathways. The 24 percent fall in FEV₁ observed in one of the exposed workers may represent an isolated case of occupational sensitization to capsaicin. Although we are unaware of documented cases of occupational asthma due to Capsicum, rhinitis with occupational Capsicum exposure and positive RAST tests to paprika and cayenne pepper has been reported. In contrast to this one subject, among the remaining subjects no spirometric pattern suggesting asthma was observed nor was there increased reporting of asthma or wheezing by the questionnaire survey. We did not assess nonspecific airway reactivity, but the capsaicin inhalation would have been likely to identify those with an immediate specific response to this substance had they been sensitized in the workplace.

With these caveats in mind, we find the bimodal pattern of cough threshold response among the Capsicum-exposed workers intriguing. Inhalation of Capsicum on the job in and of itself does not appear to uniformly modify the cough threshold assessed by capsaicin challenge. It may be that capsaicin-sensitive responses are modified by the effects of multiple, potentially interactive factors, only one of which is the chronic inhalation of chili pepper dust. For example, cigarette smoking has been shown to affect responses mediated by capsaicin-sensitive nerves in the lung, including cough. Furthermore, increased capsaicin responsiveness as measured by cough has been reported in nonsmokers. Although the effect of dietary capsaicin on the lung has not been studied, modification of other neural responses has been observed. Gender may also play a role in capsaicin-mediated responses: an association of female gender to cough has been previously reported in studies of angiotensin-converting enzyme effects, with lowered cough threshold to inhaled capsaicin among those symptomatic to cough.

Chili worker's cough is an occupational syndrome of limited prevalence but with interesting attributes. The effects of ongoing Capsicum exposure may provide clues to the actions of capsaicin that prove useful in understanding the cough reflex and the role of afferent nerves in its control.

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