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ORIGINAL ARTICLE

Health Effects of Ultraviolet Irradiation in Asthmatic Children's Homes

JONATHAN A. BERNSTEIN, M.D.,[1,*] R. CARTER BOBBITT, M.D.,[1] LINDA LEVIN, PH.D.,[2] ROGER FLOYD, PH.D.,[1] MICHAEL S. CRANDALL, C.I.H.,[3] ROBERT A. SHALWITZ, M.D.,[4] ANAND SETH, PH.D.,[4] AND MARK GLAZMAN, PH.D.[4]

[1]*Department of Internal Medicine, Division of Immunology, Allergy Section*
[2]*Department of Environmental Health, Epidemiology and Biostatistics, University of Cincinnati College of Medicine*
[3]*Indoor Environmental Services, Cincinnati, Ohio*
[4]*General Innovations and Goods, Inc., Columbus, Ohio, USA*

Objective. Centrally installed ultraviolet (UV) irradiation units were investigated to determine the potential health benefits in mold-sensitized asthmatic children. *Methods*. Nineteen mold-sensitized asthmatic children 5 to 17 years of age with home central ventilation systems were enrolled in a 28-week double-blinded placebo controlled cross-over trial. Clinical outcome measurements included morning and evening peak expiratory flow rates (PEFR), PEFR variability, change in forced expiratory volume in 1 second (FEV_1), change in total rhinoconjunctivitis and asthma symptom scores, change in rhinoconjunctivitis and asthma quality-of-life scores, and total (rescue and controller) medication use from baseline and between time periods. Environmental outcomes included changes in temperature, relative humidity, dew point, and indoor airborne mold and bacterial counts from baseline and between time periods. Analysis of variance (ANOVA) and regression analysis and t test were used to evaluate relationships between environmental exposure(s) and clinical outcome measurements during each study period. *Results*. Twelve male and seven female children, average age 10.6 years, were enrolled. A statistically significant improvement in PEFR variability in subjects receiving CREON2000 units followed by placebo units was observed ($p < 0.05$) across both treatment periods. Within group analysis during treatment period 1, a statistically significant improvement in reduction of asthma symptom scores, the number of days with asthma symptoms, total asthma medication use, and PEFR variability were observed in subjects receiving CREON2000 units versus placebo units ($p < 0.05$). No significant differences were observed between the CREON 2000 and placebo units for other clinical or environmental outcome measurements. *Conclusions*. Central UV irradiation was effective at reducing airway hyperresponsiveness manifested as PEFR variability and some clinical symptoms. A larger cohort controlled longitudinal study to validate the clinical health effects of UV irradiation as a primary indoor environmental intervention for allergic asthma is necessary to confirm this finding.

Keywords ultraviolet irradiation, CREON2000, asthma, rhinoconjunctivitis, quality of life, mold exposure, bacteria exposure, health effects

INTRODUCTION

The prevalence of asthma and allergies has increased 75% between 1980 and 1994 in the United States with the greatest increase in children (approximately a 160% increase) (1, 2). The rising prevalence of asthma is reflected in increased hospitalization rates and overall health care costs (2). It is widely believed that an important contributing factor to the rising prevalence of asthma is poor indoor air quality.

Indoor environments are sources of many common allergens including dust mites, mold spores, cockroaches, and pets and their by-products, all of which have been linked with adverse health effects. The relationship between allergen exposure, sensitization, and the development of asthma is strengthened by numerous studies that have found that a reduction or elimination of the offending allergen(s) improves clinical outcomes (3, 4).

Studies have demonstrated a relationship between airborne mold spore levels and asthma exacerbations (5–7). This relationship is supported by numerous epidemiologic studies that have identified a significant relationship between home dampness and increased respiratory infections and asthma (8–11). The difficulty in establishing a causal effect between indoor mold exposure and respiratory problems including asthma has been largely due to multiple confounding variables that make it difficult to design clinical trials (8).

Spread of airborne microbial agents has been well documented to be reduced by ultraviolet (UV) irradiation systems installed inside ventilation air duct systems (12–16). Ultraviolet irradiation has proven to be more effective and economically feasible than other approaches in reducing levels of indoor microorganisms. Current commercially available UV air disinfection systems have low energy efficiency and reliability because particles suspended in the air accumulate on the surface of the lamp, which reduces or eliminates their germicidal effectiveness (17–19). The CREON2000 Photonic Air Disinfection system (US patent 5,635,133; European patent 0848617) has been demonstrated to continuously operate efficiently because of a pre-filter system that removes dust from the treated air thereby preventing dust accumulation on the lamps over time (20).

Very few studies have been conducted to determine the health benefits of UV air disinfection systems. Menzies et al. conducted a study to investigate whether UV irradiation of drip pans and cooling coils in ventilation systems of office buildings was effective at reducing microbial contamination, thereby reducing work-related symptoms (21). A double-blind multiple cross-over study was conducted with 771

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*Corresponding author: Jonathan A. Bernstein, M.D., University of Cincinnati, 231 Albert Sabin Way, M.L. 563, Cincinnati, Ohio 45267-0563, USA; E-mail: Jonathan.Bernstein@uc.edu

individuals. Ultraviolet units were turned on and off for 4-week intervals over 48 weeks. The authors found that UV irradiation was associated with overall fewer work-related symptoms and specifically respiratory and mucosal symptoms. This effect was observed to be greatest among atopic workers and non-smokers. The authors of this study emphasized the cost-benefits of installing central UV units in office buildings to reduce costs associated with missed days from work or decreased productivity at work as a result of building-related illness (21). The overall purpose of this study was to test the hypothesis whether central UV irradiation installed in homes of mold-sensitized asthmatic children could have a practical effect on asthma outcomes.

TABLE 1.—Study timeline.

Office visits	1	2	3		4			5
Procedure/week	−4	−2	0	8	10	14	22	24
Informed consent	X							
Inclusion/exclusion criteria	X							
Health assessment (QOL and environmental questionnaires, physical examination, spirometry)		X			X			X
Distribute symptom/PEFR diaries		X		X			X	
Collect symptom/PEFR diaries			X		X			X
Randomization to CREON2000 or placebo		X						
Air and settled dust sampling		X			X			X
Turn on CREON2000 and placebo units			X			X		
Washout period; switch CREON2000 and placebo units in homes					X			

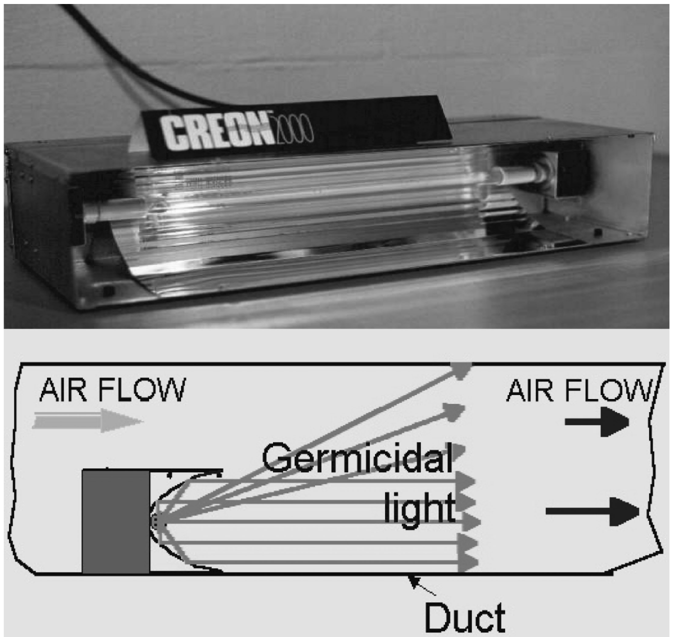
METHODS

Study Design

Nineteen mold-sensitized children with mild to moderate/severe asthma ($FEV_1 > 50\%$) from 17 homes were enrolled by rolling admission into a double-blinded placebo controlled cross-over trial conducted over a 28-week period. Subjects were recruited from middle to upper class communities and all homes were less than 50 years old. An average of 5 people lived in each home. Environmental outcomes were obtained in 17 homes as two sibling pairs were enrolled. Baseline measures were obtained before randomization of subjects into one of two groups; group1 received the CREON2000 intervention first (A) then placebo (B), and group 2 received placebo first (B) then CREON2000 intervention (A). Subject-specific daily measurements of clinical outcomes and environmental variables were obtained for three consecutive 2-week periods: baseline, and follow-up visits 4 (weeks 8–10) and 5 (weeks 22–24). Clinical outcome measurements included morning and evening peak expiratory flow rates (PEFR), PEFR variability (PEFRvar) defined as: daily highest PM PEFR—daily highest AM PEFR/daily average PEFR, change in FEV_1, change in total rhinoconjunctivitis and asthma symptom scores, change in rhinoconjunctivitis and asthma quality-of-life scores and total asthma medication use from baseline and between time periods. All PEFR and FEV_1 measurements were performed on awakening in the morning before taking any asthma medications and before bedtime before taking any asthma medications. Subjects were questioned at each visit regarding recent viral infections/colds to control for this variable. Environmental outcomes included changes in temperature, relative humidity, dew point, and indoor airborne mold and bacterial counts from baseline and between time periods.

To be enrolled, children had to be capable of performing and recording daily PEFR measurements and symptoms of asthma and rhinoconjunctivitis (RC) and be sensitized to at least one indoor mold allergen (*Aspergillus* and *Penicillium*) and one other indoor perennial allergen (dust mite, cockroach). Other inclusion criteria included permanent residency in their home for 1 year after the initiation of the study, having a central ducted heating and air-conditioning system with a standard furnace filter, and the presence of a total asthma symptom score of four. A standard furnace filter grade was not required as baseline clinical and air sampling measurements accounted for any confounding effect of variables other than UV irradiation on clinical or environmental outcomes. Asthma symptoms included chest tightness, shortness of breath, wheeze, and cough and were each rated on a 0- to 4-point scale (0 = no symptoms, 1 = mild symptoms that are noticeable but not effecting daily activities; 2 = moderate symptoms that are bothersome but tolerable; 3 = severe symptoms that are difficult to tolerate and interfere with daily activities and sleep; 4 = continuous symptoms that are unbearable preventing daily activities and sleep). Children were excluded if there was (1) passive indoor smoke exposure or they themselves were active smokers; (2) pre-existing extensive remediation in the home (i.e., dehumidifiers, HEPA filters); (3) active fireplaces or other sources of air particulates (wood burning stoves, kerosene heaters . . .); (4) active "in duct" humidifiers; (5) sensitization to pets present in the home or; (6) other coexisting chronic respiratory illnesses (e.g., cystic fibrosis). Children were maintained on the asthma and rhinitis medications they were taking at the time of their enrollment throughout the study.

The study time line is summarized in Table 1. There were four office visits. At visit one (4 weeks pre-study initiation), all subjects and their legal guardian signed an informed consent approved by the Sterling Institutional Review Board and were confirmed that they met study inclusion criteria, which included at least a 12% post-bronchodilator change in FEV_1 and positive skin prick test for specific IgE to common seasonal and perennial allergens. Families were instructed not to change their weekly cleaning routine. During visit one, testing was also performed for dust mite, cat, dog, cockroach, *Aspergillus fumigatus*, *Penicillium notatum*, *Cladosporium herbarum*, and *Alternaria alternata* unless they had been tested in the past 6 months. A wheal ≥3 mm with erythema was considered significant in the presence of a positive histamine and negative saline control. At visit two (2 weeks pre-study initiation), each subject and/or their legal guardian completed a detailed health questionnaire, Juniper asthma and rhinoconjunctivitis (RC) quality-of-life (QOL) questionnaires, a disease non-specific (SF-36) QOL questionnaire, and an environmental questionnaire. These questionnaires were also completed at weeks 10 (visit 4) and 24 (visit 5). Health questionnaires asked specific questions regarding the number of scheduled or unscheduled doctor office visits, medication usage (particularly short acting beta-agonists, oral corticosteroids, and antibiotics), wheezing episodes,



***The placebo unit was identical but incorporated a blue light.**

FIGURE 1.—The CREON2000 Ultraviolet Unit*.

upper or lower respiratory infections, emergency room visits or hospitalizations for asthma, or other health-related problems. During visit 2 and again at visits 4 (week 10) and 5 (week 24), all children received a physical examination and spirometry. Children and their parent(s) were instructed on how to record morning and evening PEFRs and asthma and RC symptom scores and total (rescue and controller) medication use over 2-week periods in a diary they were provided. Subjects were provided a mini-Wright PF meter (Clement Clark, Columbus, Ohio, USA). Each daily recording was intended to reflect an 8-hour indoor exposure period over the course of the study. Symptom scores were also recorded after returning from outside the home for comparison. PEFR and symptom diaries were collected during visits 3 (week 0), 4 (week 10), and 5 (week 24).

At visit 2, subjects were randomized to either a placebo or active CREON2000 unit group. At that point, a technician was instructed to install either the CREON2000 or a sham "blue light" system in the home's ventilation duct system (Figure 1) along with a HOBO electronic data logger (Onset Computer Corp., Pocasset, MA, USA) in each child's bedroom to continuously monitor for temperature, relative humidity, and dew point beginning two weeks before study initiation. The investigators, subjects, and industrial hygienists were all blinded as to which home received the real or sham UV unit in their home during a specific time period. An outdoor logger was used to continuously monitor these parameters throughout the study.

Air and bulk dust sampling was performed in each child's bedroom sometime between the second and third visits (−2 to 0 weeks) before turning on the CREON2000 or placebo units. This process was again repeated beginning 2 weeks before their fourth (weeks 8 to 10) and fifth (weeks 22 to 24) visits. Air and bulk samples collected during these time intervals reflected each subject's indoor exposure during the 2-week period when they were recording PEFR and symptom scores. At 10 weeks, active units were exchanged for sham units and vice versa. After a 4-week washout period, units were turned back on.

Air Sampling

Air was drawn through an Andersen single-stage (N6) impactor using an SKC AirChek Hi-Lite 30 Constant Flow Sampler (Eighty Four, PA, USA) to measure culturable fungi in each home. A second Anderson sampler was used to simultaneously collect a sample for bacterial culture analysis. The pumps were calibrated at a nominal flow rate of 28.3 liters per minute (lpm) using a BIOS International DryCal DC-Lite primary flowmeter. The impactor was connected to the pump using Tygon tubing (Saint-Gobain Performance Plastics, Valley Forge, PA, USA), and air samples were collected over 3 to 5-minutes time periods (∼85 liter to 141.5 liter sample volume) on 2% malt-extract agar (2% MEA) for fungal culture or Trypticase soy agar (TSA) with 0.4 g/L cyclohexamide for bacterial culture. Carpet dust samples were collected in the child's bedroom using a standard vacuum cleaner with a side hose in which a dust trap was inserted. P&K Microbiology Services, Cherry Hill, New Jersey, analyzed all air samples for mold and bacteria levels.

Dust Analysis

Sixty milligrams of sieved dust was placed in a 5-mL tube, and 3 mL of extraction buffer was added to make a 1:50 dilution. Tubes were vortexed and incubated for 1 hour at room temperature. Dilutions of the supernatant to 1:150 and 1:5,000 were made. Each dust sample was analyzed quantitatively for dust mite, cat, dog, cockroach, *Aspergillus, Penicillium, Alternaria*, and *Cladosporium*levels using methods established by Allergen Alert™ (Cincinnati, Ohio, USA), which is a competitive-inhibition ELISA using polyclonal antibodies (Greer Laboratories, Lenoir, NC, USA). Plates were read at 405 nm, and a standard curve was plotted on semi-logarithmic paper. Sample unknowns were read from the straight portion of the standard curve, multiplied by the dilution of the sample, and converted to μg/g of dust.

Statistical Analysis

Data entered into an excel database was used to create a SAS dataset for running the SAS Proc analyses. Averages of outcome variables for each subject during each 2-week treatment period were analyzed. Non-parametric and parametric statistical methods were applied. ANOVA, regression analysis, and the unpaired and paired *t* tests methods were used to analyze continuous data. For the ordinal data, Wilcoxon paired signed rank test was used to compare within group changes in the health outcomes and carry-over effects. A two-sample Mann-Whitney test was used to compare changes in health outcomes between the CREON2000 and placebo groups within the first treatment period. The data was adjusted for baseline measurements in the ANOVA models. Analyses were carried out using the SAS procedures PROC MIXED, PROC GLM, PROC TTEST and PROCNPAR1WAY.

TABLE 2.— Demographic characteristics of the study population (A = CREON2000; B = Placebo).

	Group1: A → B ($n = 11$)	Group2: B → A ($n = 8$)	All ($n = 19$)
Mean age (yrs)	9.6	12.0	10.6
(Min-max)	(5–17)	(7–15)	(5–17)
Gender (%male)	73	63	68
Race (%AA)	55	50	53

*One subject dropped out due to an asthma exacerbation and one due to non-compliance with the study protocol.

RESULTS

Table 2 summarizes the demographic information of subjects that participated in this study. A total of 21 subjects were enrolled but only 19 completed the study. The two subjects dropped out of the study due to non-compliance and a severe asthma exacerbation, respectively. In both cases, the subjects failed to record the necessary PEFR and symptom scores in their diaries, and therefore they were not included in the analysis. One-half of the subjects were Caucasian and the other half were African American. Sixty-eight percent of the participants were male. Seventeen homes were evaluated as two homes had two siblings in each home.

Table 3 summarizes the mean and median values for all baseline clinical outcomes measured in this study. There were no significant mean differences between the CREON2000 and placebo groups for the clinical outcomes except FEV_1 which was lower for group 1 compared to group 2, indicating that subject randomization was successful.

Table 4 summarizes the clinical differences between the CREON2000 and placebo groups within treatment period 1 and treatment period 2 for all clinical outcomes. During the baseline run-in period, PEFRvar was 9.6% ± 13.6% and 9.8% ± 3.8% in the CREON2000 and placebo groups, respectively. The effects of CREON2000 and Placebo were significantly different for PEFR variability ($p < 0.05$) based on Wilcoxon signed rank test of subject differences (treatment period 1-treatment period 2). There was also a positive trend for improvement in FEV_1 from baseline to treatment period 1 for the CREON2000 group compared to placebo.

Initial data analysis indicated that group 1 subjects, who initially received the CREON2000 in their homes during treatment period 1, had a carry over effect during treatment period 2 due to the active intervention. In addition, the time interval between the two study treatment periods was 2.5 to 3 months; treatment period 1 occurred during the spring-summer season, and treatment period 2 occurred during the late summer–autumn season. Therefore, seasonal variation, which is known to have a significant impact on the dynamics of allergic asthma, further complicated the initial analysis. To eliminate the carry over effect from the active intervention and the extension of the study into a different season, statistical analysis was performed that focused only on changes in clinical outcomes between the CREON2000 and placebo groups during treatment period 1. The non-parametric methods, Wilcoxon signed rank test, and Mann-Whitney U-test, were used for this analysis as the data were not normally distributed.

Table 5 summarizes the differences in clinical outcomes within treatment period 1 between the CREON2000 and placebo groups. Peak expiratory flow rate variability decreased by 1.4 % in the CREON2000 group and increased by 1.3% in the placebo group. This change represented a 15.1% relative reduction in PEFRvar in the CREON2000 group and a 15.6% relative increase in the placebo group (Tables 4 and

TABLE 3.—Baseline clinical outcomes recorded over a 2-week interval.

	Mean (SD)		Median, (min, max)	
Characteristic	CREON2000	Placebo	CREON2000	Placebo
		Pulmonary function testing		
PEFRvar	0.096 (0.136)	0.098 (0.039)	0.046 (0.009, 0.47)	0.112 (0.030, 0.137)
FEV_1, l/s	1.7 (1.04)	2.17 (0.44)	1.4 (0.6, 4.5)	2.37 (1.5, 2.6)
		Asthma symptom severity scores		
Wheezing	0.77 (0.53)	0.75 (0.98)	0.75 (0, 1.61)	0.38 (0.07, 3.0)
Shortness of breath	0.63 (0.35)	0.87 (0.88)	0.68 (0, 1.04)	0.64 (0.07, 2.71)
Chest tightness	0.46 (0.31)	1.05 (0.65)	0.39 (0, 1.0)	1.04 (0.07, 1.82)
Cough	1.06 (0.42)	1.29 (0.82)	0.93 (0.18, 0.71)	1.06 (0.43, 3.0)
		Days with asthma symptoms		
Days of wheeze	7 (4.90)	4.75 (4.28)	6 (0.0, 14)	4 (1.0, 14)
Days of shortness breath	6.09 (4.07)	6.63 (4.68)	6 (0.0, 14)	6.5 (0.5, 14)
Days of chest tightness	4.64 (3.92)	8.19 (4.28)	4.5 (0.0, 14)	9.5 (1.0, 12.5)
Days of cough	8.95 (3.36)	9.38 (2.80)	8.5 (2.0, 13.5)	9.5 (5.0, 13)
		RC symptom severity scores		
Stuffy nose	0.96 (0.78)	1.21 (0.83)	1 (0, 2.43)	1.11 (0.29, 3.0)
Runny nose	0.64 (0.57)	1.15 (1.03)	0.39 (0, 1.89)	1.02 (0.0, 2.75)
Itchy/watery eyes	0.67 (0.57)	1.1 (0.88)	0.46 (0.07, 1.86)	0.94 (0.18, 2.36)
Sneezing/ itchy nose	1.07 (0.62)	1.44 (0.79)	1 (0.36, 2.31)	1.29 (0.46, 2.61)
Post-nasal drip	0.76 (0.57)	1.13 (0.72)	0.71 (0, 0.82)	1.32 (0.21, 1.94)
		Total medication use (# Inhalations)		
Doses	47.6 (39.2)	61.6 (36.4)	42 (2,126)	75 (12, 104)
QOL-RC	45.9 (23.7)	65.1 (43.4)	36 (12, 90)	50 (20, 131)
QOL-A	107.4 (31.7)	104.8 (31.1)	109 (59, 161)	108 (39, 141)

CREON2000 group, $n = 11$; Placebo group, $n = 8$.

QOL-A: asthma quality-of-life questionnaire; QOL-RC = rhinoconjunctivitis quality of life questionnaire. Baseline means of groups CREON2000 and Placebo for each outcome were not significantly different ($p > 0.05$) based on unpaired t tests adjusted for unequal variances. Baseline medians of groups CREON2000 and Placebo for FEV_1 were significantly different ($p < 0.05$) based on Mann-Whitney U test.

TABLE 4.—Mean (SD) and median values (min, max) of clinical outcomes by intervention sequence.

Variable	N	Baseline	Treatment period 1	Treatment period 2
PEFR % variability*				
Group1: A → B	11	9.6 (13.6)	8.2 (12.1)	8.9 (8.8)
		4.6 [0.9, 47]	3.7 [1.0, 40.4]	5.3 [0.4, 30]
Group2: B → A	8	9.8 (3.9)	11.1 (6.2)	7.0 (5.1)
		11.2 [3.0, 13.7]	10.5 [3.5, 20.0]	5.0 [0.7, 20]
FEV1†				
Group 1: A → B	11	1.7 (1.1)	1.9 (1.2)	1.8 (1.0)
		1.4 [0.6, 4.5]	1.5 [0.6, 4.9]	1.4 [0.8, 4.5]
Group 2: B → A	8	2.2 (0.4)	2.3 (0.4)	2.3 (0.4)
		2.4 [1.5, 2.6]	2.4 [1.6, 3.0]	2.3 [1.8, 2.9]
Total RC scores				
Group 1: A → B	11	8.1 (5.3)	4.4 (2.4)	3.9 (2.3)
		8.1 [1.8, 19.1]	4.6 [0.4, 10.0]	3.9 [0.1, 7.8]
Group 2: B → A	8	12.1 (7.9)	7.7 (7.4)	7.7 (7.1)
		13.5 [3.4, 25.5]	7.9 [0, 17.6]	8.2 [0, 19.6]
Total asthma scores				
Group 1: A → B	11	5.9 (2.7)	1.9 (2.1)	2.5 (2.4)
		5.4 [2.4, 10.5]	1.2 [0, 6.2]	1.6 [0, 6.6]
Group 2: B → A	8	7.9 (6.3)	4.9 (5.3)	4.9 (5.4)
		5.5 [2.1, 21.8]	2.8 [0, 12.9]	3.1 [1, 13.5]
QOL-RC				
Group 1: A → B	11	45.9 (23.7)	26.0 (15.5)	28.2 (18.6)
		36 [12, 90]	23 [8, 56]	28 [4, 62]
Group 2: B → A	8	12.1 (7.9)	44.3 (32.2)	47.3 (28.1)
		50 [20, 131]	23 [10, 92]	28 [25, 97]
QOL-A				
Group 1: A → B	11	107.4 (31.7)	125.7 (27.3)	125.3 (29.1)
		109 [59, 161]	133 [65, 151]	136 [92, 160]
Group 2: B → A	8	104.8 (31.1)	135.6 (17.6)	129.1 (16.0)
		108 [39, 141]	139 [78, 159]	135 [106, 146]

A = CREON2000; B = Placebo; PEFR = peak expiratory flow rate; FEV_1 = forced expiratory flow rate in the first second of exhalation; RC=rhinoconjunctivitis; QOL-A = asthma quality of life; QOL-RC = rhinoconjunctivitis quality of life.

*The effects of CREON2000 and Placebo were significantly different for PEFR variability ($p < 0.05$) based on Wilcoxon signed rank test of subject differences (treatment period 1—treatment period 2).

†Baseline medians of groups 1 (A → B) and 2 (B → A) for FEV_1 were significantly different ($p < 0.05$) based on Wilcoxon signed rank test.

‡The carry-over effects from treatment period 1 to treatment period 2 (A for group 1 and B for group 2) were significantly different for FEV_1 ($p < 0.05$) based on Wilcoxon signed rank test of subject totals across time (treatment period 1 + treatment period 2).

5). The between-group difference within treatment period 1 of 30.7% was statistically significant (Table 5; $p < 0.03$).

The differences between individual asthma symptom severity scores (averaged night and day time symptom scores) and number of days with asthma in the CREON2000 and placebo groups are summarized in Table 5. At baseline the shortness of breath severity scores were 0.63 and 0.87 in the CREON2000 and placebo groups, respectively. After the intervention within treatment period 1, asthma severity scores decreased by 0.47 in CREON2000 group and by 0.29 in placebo group. The change represented a 75% reduction in asthma severity scores in the CREON2000 group compared to a 33% reduction in the placebo group. The between-group difference was statistically significant ($p < 0.05$). A significant effect of CREON2000 was also detected for chest tightness. The mean values for chest tightness severity scores after treatment period 1 decreased by 78% and 48% in CREON2000 and placebo groups, respectively. The between-group difference was statistically significant ($p < 0.05$). No statistical between-group differences were detected for wheezing, cough, or rhinoconjunctivitis symptoms (data not shown).

At baseline, the numbers of days a child had shortness of breath were 6.09 and 6.63 in the CREON2000 and the placebo groups, respectively. After treatment period 1, the number of days a child had shortness of breath, decreased by 4.5 and 1.44 days in the CREON2000 and placebo groups, respectively (Table 5). This change, representing a 74% reduction in the number of days a child had shortness of breath in the CREON2000 group and a 22% reduction in the placebo group, was statistically significant ($p < 0.05$). A similar effect was observed for the CREON2000 on the number of days a child experienced chest tightness. The number of days with chest tightness was reduced by 78% and 45% in the CREON2000 and placebo groups, respectively. The between-group difference was statistically significant ($p < 0.05$).

During the baseline run-in period, total asthma medication use (controller and rescue medications over the 2-week evaluable period) was 47.6 and 61.6 in the CREON2000 and placebo groups, respectively. After treatment period 1, total asthma medication use decreased by 24.3 and 8.2 in the CREON2000 and placebo groups, respectively. This change represented a 51% reduction in total asthma medication use by the CREON2000 group compared to a 13% reduction in the placebo group. The between-group difference was statistically significant ($p < 0.05$) Other clinical outcome measurements including quality-of-life (QOL) scores revealed no statistically significant differences between CREON2000 and placebo groups within treatment period 1. Operation of the CREON2000 system in the homes of asthmatic children with central ventilation systems over the duration of the study was found to be very safe as there were no adverse events reported by any of the subjects.

Table 6 summarizes the mean temperature, relative humidity, dew point, indoor and outdoor mold, and bacteria levels at baseline and during each treatment period for groups 1 and 2. The means of interventions A and B were not significantly different for any variables based on analysis of variance adjusted for carry-over and period effects, with or without baseline adjustment. Although, not statistically significant, there was a definite trend for reduction of both indoor mold and bacterial levels with CREON2000 compared with placebo for both groups (A → B and B → A) (Table 6). This is more clearly appreciated when all of the combined mold and bacterial levels measured for both treatment periods during the CREON2000 active intervention are compared to the levels measured during the placebo group intervention (Table 7).

Carpet dust analysis, performed in all homes at baseline and during each period for dust mite, cat, dog, cockroach, and four common indoor molds (*Alternaria, Aspergillus, Penicillium, and Cladosporium*), revealed no significant difference in allergen concentrations compared to baseline regardless whether the home initially received CREON2000 or the placebo (data not shown).

Discussion

This preliminary cross-over study was able to demonstrate that the CREON2000 ultraviolet irradiation system was safe and more effective than placebo at improving the clinical outcomes PEFRvar over both treatment periods. Asthma symptom scores and the number of days children experienced shortness of breath and chest tightness were noted to improve for the CREON2000 group compared to the placebo group within treatment period 1 only. The finding that other

TABLE 5.—Differences in clinical outcomes between CREON2000 and placebo groups over a 2-week interval during treatment period 1.

Characteristic	CREON2000	Placebo	Difference	p-value
Pulmonary function testing				
PEFRvar				
Mean (SD)	0.082 (0.121)	0.113 (0.062)	−0.031	
Median (min, max)	0.037 (0.010, 0.404)	0.105 (0.035, 0.200)	−0.068	0.03
FEV_1, l/s				
Mean (SD)	1.89 (1.12)	2.29 (0.44)	−0.4	
Median (min, max)	1.5 (0.6, 4.9)	2.37 (1.6, 3.0)	−0.87	0.32
Asthma symptom severity scores				
Wheezing				
Mean (SD)	0.23 (0.36)	0.40 (0.70)	−0.17	
Median (min, max)	0.0 (0.0, 1.11)	0.02 (0.0, 1.61)	−0.02	0.4
Shortness of breath				
Mean (SD)	0.16 (0.24)	0.58 (0.66)	−0.42	
Median (min, max)	0 (0.0, 0.64)	0.22 (0.0, 1.48)	−0.22	0.04
Chest tightness				
Mean (SD)	0.1 (0.17)	0.55 (0.64)	−0.45	
Median (min, max)	0 (0.0, 0.50)	0.3 (0.0, 1.63)	−0.3	0.04
Cough				
Mean (SD)	0.47 (0.50)	0.93 (1.09)	−0.46	
Median (min, max)	0.43 (0.0, 1.64)	0.71 (0.0, 3.18)	−0.28	0.26
Days with asthma symptoms				
Days of wheeze				
Mean (SD)	2.86 (4.55)	3.69 (6.23)	−0.83	
Median (min, max)	0 (0.0, 14.0)	0.25 (0.0, 14.0)	−0.25	0.24
Days when child had shortness of breath				
Mean (SD)	1.59 (2.50)	5.19 (5.48)	−3.60	
Median (min, max)	0 (0.0, 7.5)	2.75 (0.0, 12.0)	−2.75	0.02
Days of chest tightness				
Mean (SD)	1.05 (1.65)	4.88 (5.32)	−3.83	
Median (min, max)	0 (0.0, 5.0)	3.5 (0.0, 13.0)	−3.50	0.04
Days when child had cough				
Mean (SD)	5.23 (5.04)	5.81 (5.34)	−0.06	
Median (min, max)	5 (0.0, 14.0)	7 (0.0, 14.0)	−2.00	0.28
Total medications use (no. of inhalations)				
Mean (SD)	23.3 (29)	53.4 (17.9)	−30.1	
Median (min, max)	12 (0, 79)	50 (28, 73)	−38	0.04

TABLE 6.— Mean values (SD) of environmental variables by intervention sequence.

Variable	N*	Baseline	Treatment period 1	Treatment period 2
Temp (°C)				
Group 1: A → B	8	23.4 (0.8)	23.4 (1.3)	21.6 (2.1)
Group 2: B → A	8	22.6 (1.8)	24.0 (1.4)	22.8 (0.4)
%RH†				
Group 1: A → B	8	52.4 (4.5)	49.5 (10.9)	46.2 (5.7)
Group 2: *B* → A	8	47.3 (4.7)	52.8 (9.6)	39.4 (6.8)
DP(°C)†				
Group 1: A → B	8	12.9 (1.5)	11.8 (4.8)	9.3 (2.5)
Group 2: B → A	8	10.7 (2.0)	13.5 (2.6)	8.0 (2.6)
Indoor mold††				
Group 1: A → B	9	462.2 (401.0)	228.2 (153.3)	279.5 (337.0)
Group 2: B → A	8	555.8 (1175.6)	202.1 (78.5)	184.3 (71.6)
Indoor bacteria††				
Group 1: A → B	9	588.4 (650.6)	337.0 (328.4)	99.4 (73.2)
Group 2: B → A	8	732.2 (650.9)	710.3 (460.7)	453.4 (404.5)
Outdoor mold				
Group 1: A → B	9	1595.2 (1607.2)	1427.4 (1636.3)	763.1 (851.0)
Group 2: B → A	8	655.3 (418.2)	813.7 (604.8)	782.0 (906.7)
Outdoor bacteria				
Group 1: A → B	9	132.4 (172.6)	176.9 (242.2)	116.5 (105.6)
Group 2: B → A	8	795.5 (1445.5)	118.4 (85.8)	126.0 (154.2)

A = CREON2000; B = Placebo; Temp = temperature; RH = relative humidity; DP = dew point.

*N = number of homes at baseline. There were 2 subjects in one home from each group.

†Baseline means of groups 1 (A → B) and 2 (B → A) were significantly different ($p < 0.05$) for RH and DP only, based on unpaired t tests adjusted for ≠ variances.

††Due to the extreme skewness of the distributions of indoor and outdoor mold and bacteria, medians of mold and bacteria variables were also tested and were not significantly different by Wilcoxon rank sum test ($p > 0.05$). However, a trend for reduced indoor mold and bacteria counts was observed with the CREON2000 intervention compared to the placebo intervention.

clinical outcome variables including some asthma symptoms, RC symptom scores, or QOL scores were not significantly improved is consistent for what has been reported by other investigators (25–28). Moy et al. found no correlation between FEV_1 and health related QOL measurements and Shingo et al. found very poor correlation between total beta-agonist use, which is considered a measurement of a patient's perception of asthma symptoms, and FEV_1 (26, 27). The likely explanation is that these single endpoints do not adequately describe asthma variability. In contrast, PEFR variability captures several endpoints over the course of a study and is therefore more reflective of the dynamic nature of asthma (25).

The lack of a positive effect at improving other health and environmental factors can also be explained by several limitations of the study design. First, this study was significantly hampered by a small sample size and the necessity for using a cros-over study design due to budgetary restraints. Although there were 19 subjects enrolled in this study, data from each group (A → B; B → *A*) had to be analyzed separately to account for any potential carry over effect from the active (CREON2000) intervention. Menzies et al. avoided these limitations by enrolling hundreds of subjects and incorporating several 4-week periods where the indoor air was treated off and on with UV irradiation (21).

Secondly, there are many variables that are very difficult to control over time during environmental intervention studies of this type including enrollment across seasons, differences in housing characteristics, indoor hygiene (cleaning routines), out of home activities, indoor and outdoor seasonal

TABLE 7.—Combined mold and bacterial levels measured for both treatment periods during the CREON2000 active intervention compared to the levels measured during the placebo group intervention.

		Average mold, CFU/m^3					Average bacteria, CFU/m^3				
		Mean	STD	Min	Max	*N*	Mean	STD	Min	Max	*N*
Intervention	Location										
CREON	Outdoors	1161.6	1386.2	88.5	4482.0	17	155.9	211	0.0	881.0	17
	Indoors	210.1	125.0	6.0	496.0	17	384.9	382	89.	1630	17
Placebo	Outdoors	783.9	738.4	53.0	2929.5	17	117.2	112	0	393	17
	Indoors	247.7	260.2	6.0	960.5	17	350.9	432	12.	1455	17
Baseline	Outdoors	1268.0	1344.1	154.5	4700.0	17	449	1012	0	4359	17
	Indoors	527	819	60.0	3595	17	687	677	0	2784	17

CFU/m^3: colony forming units per cubic meter.

variations in relative humidity, temperature, and airborne mold and bacteria levels. To circumvent many of these problems, we focused on changes in clinical parameters measured after the child spent approximately 8 hours in their bedroom (i.e., all PEFRs and symptom scores were collected at night before bedtime and in the morning after awakening). Furthermore, we attempted to choose relatively strict inclusion/exclusion criteria to ensure that our subject population was as homogeneous as possible. Baseline means of all clinical outcome differences between the CREON2000 and placebo groups indicate successful randomization of subjects in the presence of these confounding variables. Therefore, the significant differences in clinical outcomes observed between the CREON2000 and placebo groups during treatment period 1 should be attributed to the effect of the active intervention.

Another potential but likely insignificant confounder was selection of the "blue light" as a placebo. Interestingly, blue light has previously been reported to have a modest fungicidal/bactericidal effect, which could have blunted the effect of UV irradiation on improving clinical outcome parameters and in reducing airborne mold spores and bacteria levels (29). However, a blue light was selected so subjects would be blinded as to whether they received an active CREON2000 unit or placebo. A similar problem was encountered in a previous study investigating the effect of HEPA filtration on reducing airborne cat allergen levels and improving asthma outcomes (30). These investigators used a carbon filter in their placebo air cleaner, which may have lessened the significance of their findings (30). Despite this unforeseen problem, there was a definite trend for reduction of indoor mold and bacteria levels when the active CREON2000 unit was on. Future studies would need to incorporate more sampling periods to better assess the relationship between intervention with the CREON2000, reduced indoor airborne fungal, and bacterial levels and observed health effects.

In summary, the results of this small cross-over double-blinded, placebo-controlled study indicates that trials of this type, although challenging, are feasible. Our data indicating that the CREON2000 central ultraviolet system was effective and safe at improving PEFRvar and reducing some asthma symptoms, the number of asthma symptom days, and total asthma medication use are encouraging and support pursuing further research into the health benefits of this specific intervention in a larger clinical trial. Future studies should be designed as longitudinal, parallel, double-blind placebo control trials with sufficient power to better elucidate the health effects of central UV irradiation as an environmental control intervention for asthma.

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