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OFFICE OF
PREVENTION, PESTICIDES AND TOXIC
SUBSTANCES

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MEMORANDUM

SUBJECT: Study Review - Newton, J. G. and Breslin, A. B. X. (1983) Asthmatic reactions to a commonly used aerosol insect killer. Med. J. Aust; 1:378-380

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Objective: There were three stated objectives to this study. To study the response of asthmatic participants to exposure to insecticides containing pyrethrins and tetramethrin; to study the time-course of exacerbation of asthma following exposure to the insecticide; and to evaluate bronchial reactivity to histamine after exposure to the insecticide.

Study Design: Experimental, intentional dosing study.

Methods: In this study, seven participants diagnosed with asthma and a history of chest tightness were evaluated for airway narrowing and chest tightening before and after a controlled exposure to aerosol insecticide sprays.

Selection criteria: Participants were selected into the study using the following criteria: (a) proven bronchial asthma; (b) history of chest tightness upon exposure to aerosol fly-killer insecticides; (c) aged between 18 and 75 years old; (d) well-controlled, mild or moderate asthma; (e) not pregnant or not at risk of pregnancy during time of study; and (f) no history of cardiac disease.

Dosing Regimen: Participants were exposed to an aerosol insecticide (Mortein Pressure Pak insect killer containing 3.0 g/kg pyrethrins, 0.9 g/kg tetramethrin, 15 g/kg piperonyl butoxide, 7.5 g/kg N-octyl-bicycloheptene dicarbonyls, propellants (chlorofluorocarbons and hydrocarbons) and solvents (non water based)). The spray rate was measured as 1.59 g/second. The maximum concentration reached in a 7m³ room was 6.7 mg/l which was determined after a 30 seconds continuous spray duration within the testing room.

On Day 1 upon arrival, participants were evaluated as to their medical history. Testing regimen began with a challenge of histamine to determine the concentration needed to evoke a 20% reduction in forced expiratory volume in one-second (FEV₁), a measure of non-specific bronchial hyper-reactivity (referred to as PC₂₀). This information is noted as “before challenge” PC₂₀ (mg/ml).

Upon entering the testing chamber, three baseline readings including FEV₁, vital capacity (VC), and maximum mid-expiratory flow rate (MMEFR) were measured on a spirometer. Then, the aerosol insecticide was sprayed into the chamber for 5 seconds duration. Participants were asked to remain inside the chamber for 5 minutes after cessation of the spray. Upon leaving the chamber, spirometry was repeated and then again after 5 minutes subsequent to leaving the chamber. If no asthmatic reaction occurred, participants were asked to return to the chamber for an additional 10, 20, or 30 seconds of spray duration with an additional 5 minutes of exposure inside the chamber before leaving the chamber. Exposures were stopped at any point if an asthmatic attack occurred and spirometry was performed every five minutes until the reading returned to the baseline values. If no asthmatic reaction developed after 30 seconds duration of spray exposure, spirometric values were measured every 5 minutes for 30 minutes, then at 15 minutes intervals for 30 minutes, and then every half hour for at least 2 hours.

Upon return to the testing site on Day 2, histamine challenge was again performed (24 hours after first histamine challenge), and a two-fold difference in PC₂₀ would be considered a significant change in airway hyperreactivity post Day 1 exposure. Those participants who developed a significant asthmatic reaction to the insect spray were repeated with a placebo (water) to ensure that the reaction was specific to the pressurized insect spray and not due to stress, repeated forced expiration, and/or confinement in the provocation room.

If a participant displayed a significant fall in FEV₁, he was asked to return on Day 3 and underwent provocation 60 minutes after inhalation of 2 mg of atropine methonitrate (a bronchodilator) using the same testing regimen as Days 1 and 2.

Statistical Analyses: No statistical analysis was performed. Simple counts and proportions across exposure groups were completed.

Results: Selected participants ranged in age from 24 to 71 years old and included 5 females and 2 males. All participants were test negative to an Aspergillus precipitins test and the skin-prick tests showed four females were atopic (allergic reaction) to various allergens.

Authors reported the aerosol insect killer produced symptoms in all participants. Participants complained of chest tightness associated with severe non-productive cough, sneezing, rhinorrhoea, and lachrymation, which they described as “asthma.” This sensation usually began after one or two five-minute exposures in the provocation room and continued for up to one hour after challenge. These symptoms usually resolved within five minutes after leaving the provocation room.

One study participant coughed for about 30 minutes after a 10 second spray, while another had rhinorrhoea and sneezing for about one hour after challenge. Those study participants who developed a significant asthmatic reaction to the insect spray were repeated with a placebo (water) on Day 2 and none of the study participants showed significant changes in lung-function values on the placebo day.

There were no significant changes in the histamine reactivity after bronchial provocation with the insect killer. Three study participants showed some evidence of airway-narrowing. This was seen as a significant fall in their MMEFR (24-60%). Only one of these three had significant fall in FEV₁ (35%). Other study participants did not show significant changes in VC, FEV₁, or MMEFR. The only study participant to show a significant fall in FEV₁ returned on Day 3 and underwent provocation 60 minutes after inhalation of 2 mg of atropine methonitrate. The study participant experienced chest tightness, coughing and significant fall in MMEFR and FEV₁. The time sequence was similar to that in the challenge on Day 1.

Authors' Conclusions: In discussion, the authors noted that all participants reported chest tightness and 6/7 also experienced severe cough in association with the tightness; however, chest tightness did not correlate with significant changes in pulmonary function (i.e., FEV₁ or bronchial hyperreactivity) in these participants.

None of the participants were observed with changes in lung function values upon challenge with a placebo, indicating the stress of the testing procedure itself was not likely contributing to the lung measures. There were no significant changes in the histamine reactivity after bronchial provocation with the insect killer. In addition, inhalation of a bronchodilator (atropine methonitrate) did not block the asthmatic reaction to the insecticide suggesting the insecticide did not change the non-specific hypersensitivity to histamine and the asthmatic reaction might be due to some other factors.

Study Observations and Limitations:

1. Limited ability to gain information about the variability in response in an asthmatic sub-population given the small sample size (n=7).
2. A number of potential additional variables that could affect asthmatic response were not measured or included in the analysis – these include smoking history, occupational history and/or age.
 - a. Smoking or exposure to passive smoking alone can aggravate asthma symptoms and no information provided as to the smoking status of 7 participants (never, former, current).
 - b. The study does not mention the occupation of the study participants, as some occupations have been shown to induce or exacerbate asthma.
 - c. The age range (24-71 years) makes interpretation of the results even more difficult, since age by itself plays a major role in changes in pulmonary functions.
3. There were no significant changes in the histamine reactivity after bronchial provocation with the insect killer. It should be noted, histamine is no longer used in such studies because of its potential effects on multiple organs in the body.
4. The technology used in spirometry is outdated. Currently, many computer systems are available to perform much more accurate measurements of pulmonary functions parameters, compared to what was used in this study. Therefore, if more updated measurement tools had been used and a more valid experimental design employed, the results may have been different.
5. Lack of correlation between reported clinical symptoms and quantitative pulmonary function testing, introduces uncertainty about the nature of the response and is not sufficiently addressed by the authors.
6. Although the Agency recognizes the study should be considered in light of the diagnostic standards of the day, the authors considered an $FEV_1 > 20\%$ a significant drop to define an asthmatic response. We note, current guidelines of the American Thoracic Society (ATS) classify a drop of $>30\%$ as mild asthma.

Reviewer Conclusions: The study appears to be scientifically valid and provides some information on the potential relationship between human exposure to pyrethrins/pyrethroids and human asthmatic and respiratory responses. It should be considered in a qualitative weight of evidence approach. The limitations of the study, however, including the small sample size, additional variables involved in the etiology of asthma, and the unaddressed inconsistency between qualitative and quantitative measured responses, prevent its serving as a definitive study for determination of causality or as a basis for a quantitative human health risk assessment with a dose response analysis.