U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
CENTER FOR DISEASE CONTROL
NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH
CINCINNATI, OHIO 45202

HEALTH HAZARD EVALUATION DETERMINATION
REPORT NO. 73-173-244
BORDEN CHEMICAL COMPANY
LEOMINISTER, MASSACHUSETTS

DECEMBER 1975

I. TOXICITY DETERMINATION

It has been determined that a number of employees who have been exposed to the enzyme, trypsin, at the Borden Chemical Company have developed allergic sensitization. Episodic exposure to trypsin has resulted in respiratory impairment in those employees who have become sensitized and mild upper respiratory tract irritation among other employees who have not been sensitized. Detrimental health effects from this exposure were observed and it is possible that more can be anticipated if proper medical screening and material handling is not strictly enforced. This determination is based on interviews with exposed employees, skin tests, pulmonary function tests, observation of work practices, and available medical literature relevant to trypsin.

Further, it has been determined that several employees who were engaged in the handling of the surfactant, Nekal B-78, have periodically experienced upper airway irritation, gagging and shortness of breath. This problem exists as a result of poor work practices. No serious health consequences from this exposure were observed and none are anticipated. This determination is based on interviews with exposed employees, observations of work practices, and on available information relevant to surfactants as health hazards.

No environmental measurements were conducted.

II. DISTRIBUTION AND AVAILABILITY OF THE DETERMINATION REPORT

Copies of this Determination Report are available upon request from the Hazard Evaluation Services Branch, U.S. Post Office Building, Room 508, 5th and Walnut Streets, Cincinnati, Ohio 45202. Copies have been sent to:

a. Borden Chemical Company, Leominister, Massachusetts
b. U.S. Department of Labor - Region I
c. NIOSH - Region I
d. Authorized Representative of Employees

For the purposes of informing the "affected employees," the employer will promptly "post" the Determination Report in a prominent place where "affected employees" work for a period of 30 calendar days.

III. INTRODUCTION

Section 20(a)6 of the Occupational Safety and Health Act of 1970, 29 U.S.C. 669(a)(6), authorizes the Secretary of Health, Education, and Welfare, following written request by any employer or authorized representative of employees, to determine whether any substance normally found in the place of employment has potentially toxic effects in such concentrations as used or found.

The National Institute for Occupational Safety and Health (NIOSH) received such a request from an authorized representative of employees from the Borden Chemical Company, Leominister, Massachusetts.

The alleged hazard, as reported in the original request for Health Hazard Evaluation, involved 24 operators, 12 helpers and 6 packers. These employees were exposed to Nekal B-78 which is a surfactant and trypsin which is a proteolytic enzyme.

IV. HEALTH HAZARD EVALUATION

A. General

The Borden Chemical Company in Leominister, Massachusetts was visited on January 7, 1974, by a NIOSH physician, Dr. Phillip Lee Polakoff. A brief preliminary meeting was held with management and labor representatives to explain the nature of the visit and to obtain background information. Following this meeting, a survey of the entire plant was undertaken, with special attention focused on those areas where the agents Nekal B-78 and trypsin were used.

B. Description of the Process

At this plant, The Borden Chemical Company is engaged in the manufacture of various types of polyvinyl chloride (PVC) resin.

Nekal B-78 and porcine trypsin are used on the second floor of the production facility immediately adjacent to the reactor vessels.

In the area where the surfactant is weighed out the workers involved in this process complained of upper airway irritation, gagging and shortness of breath. The problem appears simply to be one of poor

handling practices. All the workers questioned stated that once out of the area where the Nekal B-78 is used, they only occasionally experienced symptomatology. In the area where Nekal B-78 is being weighed, the ventilation system is a makeshift, localized type which appeared to be inadequate.

Porcine trypsin, the second alleged hazardous substance, is a proteolytic enzyme derived from hog pancreas. Until May 1973, trypsin was hand-weighed from a supply barrel and carried upstairs to the blending tank. Since May 1973, supplies of trypsin have been received as pre-weighed, four-pound plastic bags, which are dumped directly into the blending tank. There are a limited number of protective masks available for use during this process. There are no gloves available for use while handling this enzyme.

Prior to May 1973, there were two well-documented cases of allergy to trypsin in this plant. These cases had been evaluated by a local allergist. Another three to five people said they were adversely affected by trypsin. One of these has also been documented as being sensitized by the allergist. Since the change in trypsin handling, there has been an appreciable decrease in complaints and no new cases of hypersensitivity have been reported.

In summary, based on the initial observational survey, it was the opinion of the NIOSH investigator that the problem with Nekal B-78 is one of poor material handling and could be easily eliminated. The problem related to trypsin was more difficult and required more thorough medical evaluation to judge its severity. In the past relative little work has been done on the biologic effects of trypsin or other biologic enzymes. Thus, because of the scarcity of toxicological information on typsin and the number of symptomatic workers, it was felt that a more in-depth study of trypsin hypersensitivity should be carried out.

C. Evaluation Methods

1. Medical

Based on the results of the initial observational survey, a follow-up medical survey was conducted on April 10, 1974. The investigators on this trip included Phillip L. Polakoff, M.D., Harvey Colten, M.D., Associate Professor of Immunology, Harvard School of Medicine, and David Wegman, M.D., Occupational Health Officer, State of Massachusetts. On this occasion a study population was defined and consisted of fourteen (14) workers wo had been exposed to airborne hog trypsin in

the course of their work for periods of two weeks to fifteen years. Of these fourteen, three had been transferred to other jobs because of respiratory symptoms associated with the trypsin exposure. Six employees who had never been exposed to trypsin and eight staff members of the Allergy Division at the Children's Hospital Medical Center, Boston, Massachusetts served as controls. Informed consent was obtained from each of these participants.

A questionnaire modified from the British Medical Research Council Questionnaire on Pulmonary Disease was answered by each employee. Venous blood samples were obtained for determination of $alpha_1$ antitrypsin (a test used as a diagnostic aid in determining genetic predisposition to emphysema) and for the presence of precipitating antibodies against hog trypsin. Scratch tests, using a specially prepared (for this study) hog trypsin antigen were performed on all participants to determine immediate type hypersensitivity.

On the basis of these preliminary screening studies, eight individuals (four symptomatic workers and four control individuals) were selected for more extensive investigations, i.e., pulmonary function tests, and inhalation challenge tests which were conducted at Children's Hospital Medical Center, Boston, Massachusetts. (The four symptomatic individuals all had positive skin tests and responded in the questionnaires that they were adversely affected by exposure to the trypsin.)

2. Environmental

During the initial survey bulk samples of trypsin and the PVC resin which contained trypsin were obtained. Both samples were taken to the NIOSH laboratories in Cincinnati where their pH and particle size distribution were determined.

D. Toxicology

Nekal B-78 (sodium alkyl napthalene sulfonate) is a surfactant. Little has been reported concerning the toxicology of this particular sulfonate, but in general, sulfonates have the potential to cause skin, mucous membrane irritation and dermatitis.

Trypsin is an active proteolytic enzyme and therefore should be handled with special precautions. Proteolytic enzymes can cause "burns" of the skin and/or mucosa. The "burns" result in a sloughing of the outer layers of the skin. Enzyme burns vary in severity from those that are minor in nature, allowing employees to return to work immediately, to those resulting in time lost.

These burns are similar to thermal burns and are handled medically in a similar manner. Enzyme burns of the mucosa of the mouth, nasal passages and eyelids are especially troublesome and must be treated immediately.

Allergic sensitivity to enzymes is a well-documented phenomenon, usually manifest as asthma. Personnel with known enzyme sensitivity should not be exposed to enzymes in their work.

Occupational health standards as promulgated by the U.S. Department of Labor currently do not exist for either Nekal B-78 or trypsin.

E. Evaluation Results

1. Clinical Manifestations

Four symptomatic employees reported the acute onset of shortness of breath and wheezing (Tables 1 and 2) when exposed to trypsin dust. Two of the four reported an associated nonproductive cough and one described rhinitis, nasal pruritis and conjunctivitis. Three of the symptomatic individuals have since developed wheezing and shortness of breath unrelated to the industrial exposure. They also continued to note an exacerbation of symptoms to trypsin exposure, and two reported marked symptomatic improvement over weekends.

2. Skin Tests

Of the twenty-eight individuals tested, four had evidence of immediate hypersensitivity to trypsin by scratch testing (Tables 1 and 2). Only one of these had positive reactions to other antigens. These four employees, who were all symptomatic, responded with wheal, or wheal and flare reactions to both active and inactivated trypsin preparations. None responded to SBTI (soybean trypsin inhibitor) control solution.

3. Pulmonary Function Tests

All control subjects and the symptomatic employees had normal initial pulmonary function tests except for patient III who had a moderately reduced MMFR (maximal mid-expiratory flow rate suggestive of small airway obstruction). One employee with a history of myocardial infarction was not subjected to inhalation challenge. Through the successive steps of challenge with PSB (phosphate buffered saline), SBTI (soybean trypsin inhibitor) and SBTI-inactivated trypsin solutions, the controls showed no change in lung function.

Their MEFV (maximal expiratory flow volume) curves remained unaltered, as shown by the maximal expiratory flow measured at 50% of vital capacity. The sensitized patients had no response to inhalation challenge with the control solutions or with 1 ug/ml inactivated trypsin aerosol. Patient III complained of chest tightness and difficulty breathing after two breaths of 10 ug/ml inactivated trypsin aerosol. Patients I and II developed a cough and mild breathing difficulty in response to three breaths of 10 ug/ml and one breath of 100 ug/ml inactivated trypsin aerosol, respectively. Marked changes in pulmonary function accompanied the onset of respiratory symptoms in the three patients. On the average, vital capacity and forced expiratory volume decreased by 25% and 27%, respectively, and the MMFR by 37%. Changes in total lung capacity and functional residual capacity were variable but residual volume increased by 33% to 102% (Table 3). These changes characteristic of airway obstruction, were reversed by inhalation of 1/200 isoproterenol. All the subjects were notified of their performances on these tests.

4. Environmental Samples

Particle size for both the PVC resin containing trypsin and trypsin itself were all respirable, i.e., the size ranged from 1.2 microns to 3.0 microns. The pH for trypsin was 5.05; for PVC 260 5.89; and for Nekal, 5.70.

V. RECOMMENDATIONS

It is strongly recommended that workers exposed to trypsin dust receive annual skin tests and interviews to detect the development of medical symptomatology suggestive of allergy. These steps would facilitate the early detection of sensitization. Adequate respiratory protection and stringent work practices to reduce exposure to trypsin is imperative to minimize the development of future cases of sensitivity.

Further, it is recommended that known asthmatics and those individuals with a strong atopic history should not be allowed to work in the areas where enzymes are employed. Pre-employment screening procedures will facilitate the exclusion of these high risk individuals. Any employee who develops signs and/or symptoms of allergy to trypsin dust should be removed from the work area and should be medically evaluated. If the employee is judged to be allergic to trypsin, he should not be further exposed. Any employee with a positive skin test should not be further exposed.

VI. AUTHORSHIP AND ACKNOWLEDGMENT

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TABLE 1

SURVEY OF TRYPSIN SENSITIVITY

Patient	Age	Sex	Allergic History	Respiratory Symptoms	Exposure to Trypsin Dust (years)	Skin Tests	
						Trypsin*	Other
I	29	M	+	+	3-1/2	+	+
II	41	M	-	+	4-1/2	+	-
III	33	M	+	+	5	+	-
IV	52	M	+	+	5	+	-
V	28	M	+	+	7	-	-
VI	46	M	-	+	11-1/2	-	-
VII	31	M	-	-	4-1/2	-	-
VIII	26	M	+	-	2	-	+
IX	30	M	+	-		-	-
X	33	M	-	-	1/26	-	+
XI	26	M	-	-	3/26	-	-
XII	20	M	-	-	1-1/2	-	-
XIII	36	M	-	-	1/2	-	-
XIV	39	M	-	-	15	-	-
XV	26	F	-	-	0	-	-
XVI	19	F	-	-	0	-	-
XVII	39	M	-	-	0	-	-
XVIII	44	M	-	-	0	-	-
XIX	34	M	-	-	0	-	-
XX	27	M	-	-	0	-	-
XXI-XXVIII**			+(5/8)	-(8/8)	0(8/8)	-(8/8)	+(4/7)

* SBTI inactivated trypsin

** CHMC Allergy Staff

TABLE 2

SENSITIVITY TO HOG TRYPSIN

Patient	Symptoms	Skin Tests (wheal/flare, mm) with solutions**					α_1 anti-trypsin	
		A	B	C	D	E	(% nl)***	Pi type
I	S,W,C	8/35	6/30	15/35	0	10/30	100	M
II	S,W,N,E	ND****	ND	8/25	0	ND	80	MS
III	S,W,C	10/20	8/20	12/25	0	7/15	100	M
IV	S,W	10/-	7/-	7/-	0	7/-	77	M
V	± C	0	0	0	0	0	175	M
XXI	0	0	0	0	0	0	ND	
XXII	0	0	0	0	0	0	ND	
XXIII	0	0	0	0	0	0	ND	

* S= shortness of breath; W= wheezing; C= cough; N= rhinitis; E= conjunctivitis.

** Solution A= trypsin 1.0 mg/ml; B= trypsin 0.25 mg/ml; C= SBTI inactivated trypsin 1 mg/ml; D= SBTI 1 mg/ml; E= trypsin heated 37°C for 2 hours.

*** Normal Range 47-153.

**** Not done.

TABLE 3

PASSIVE TRANSFER OF SENSITIVITY TO HOG TRYPSIN

Intradermal Injection	Heat Inactivation**	Dilution	Absorption	Skin response* (mm bluing)
Serum from	0	1/10	0	4 x 6
	+	1/10	0	0
Patient I	0	1/10	anti-IgE	2 x 2
	0	1/10	anti-IgG	6 x 8
Serum from	0	undiluted	0	9 x 10
Patient II	+	undiluted	0	1
Serum from Control Subject XXIII	0	undiluted	0	0
PBS				0

* 15 min. after intradermal injection of 0.05 ml of SBTI inactivated trypsin solution, diluted to 0.25 mg/ml.

** 56°C for 1 hour.

TABLE 4

PULMONARY FUNCTION TESTS BEFORE AND AFTER TRYPSIN AEROSOL CHALLENGE

	PATIENT					
	I		II		III	
	Before	After	Before	After	Before	After
Spirometry						
Vital Capacity, liters	5.60	4.20	4.00	3.20	4.84	3/44
Forced Expiratory Volume (1 sec), liters	4.29	3.00	3.00	2.47	3.13	2.10
Maximal Midexpiratory Flow Rate, liters/min	203	137	160	113	115	0.60
Body Plethysmography						
Total Lung Capacity, liters	7.18	6.47	5.29	4.91	6.32	6.45
Residual Volume, liters	1.58	2.27	1.29	1.71	1.48	3.01
RV/TLC, percent	22	36	24	35	23	47
Functional Residual Capacity, liters	3.38	3.07	2.59	3.01	3.02	3.85