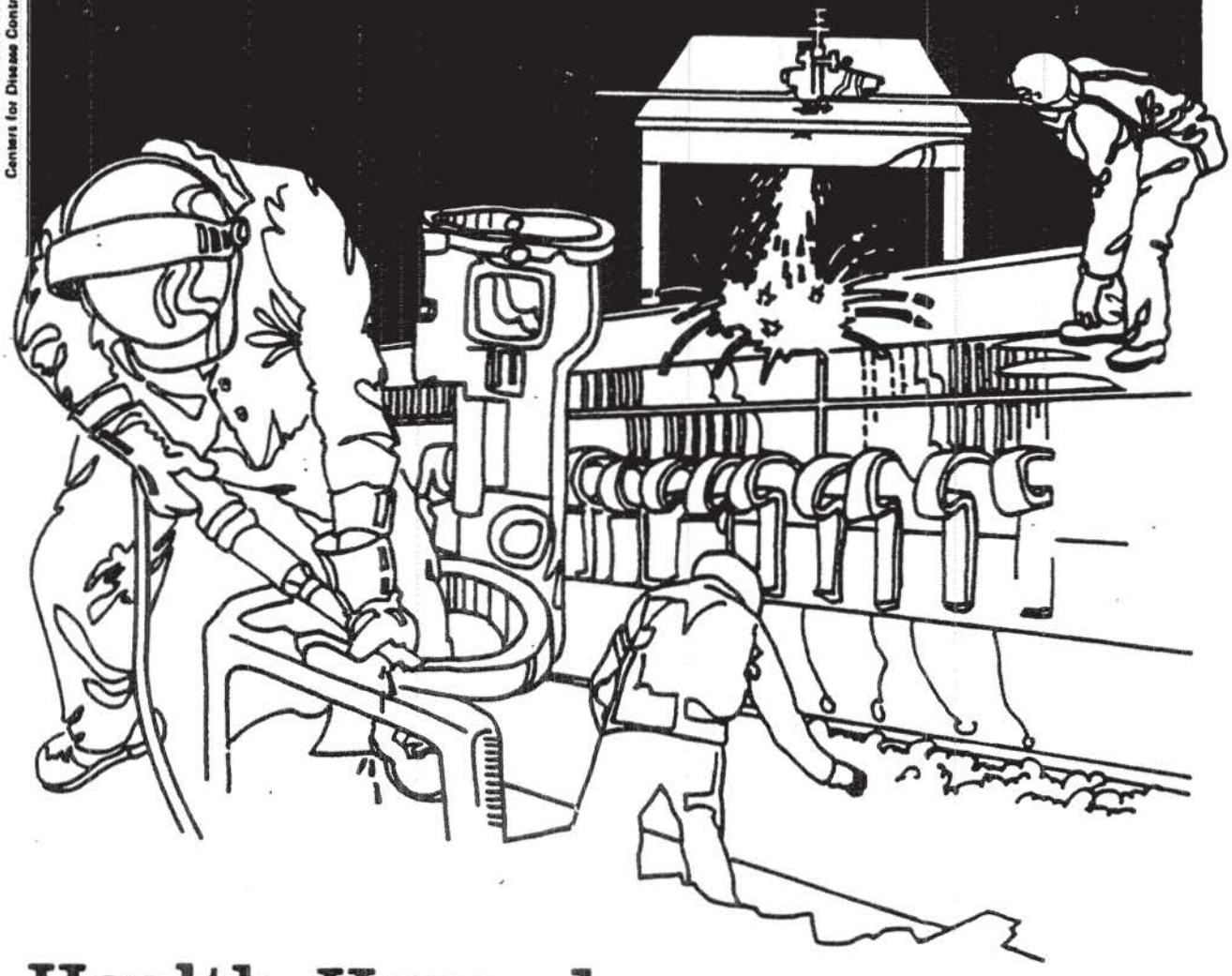
FILE COPY

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES ■ Public Health Service
Centers for Disease Control ■ National Institute for Occupational Safety and Health

NIOSH



Health Hazard Evaluation Report

HETA 83-019-1562
BERLEX LABS.
WAYNE, NEW JERSEY

PREFACE

The Hazard Evaluations and Technical Assistance Branch of NIOSH conducts field investigations of possible health hazards in the workplace. These investigations are conducted under the authority of Section 20(a)(6) of the Occupational Safety and Health Act of 1970, 29 U.S.C. 669(a)(6) which authorizes the Secretary of Health and Human Services, following a written request from 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 Hazard Evaluations and Technical Assistance Branch also provides, upon request, medical, nursing, and industrial hygiene technical and consultative assistance (TA) to Federal, state, and local agencies; labor; industry and other groups or individuals to control occupational health hazards and to prevent related trauma and disease.

HETA 83-019-1562
SEPTEMBER, 1985 REVISED
BERLEX LABS.
WAYNE, NEW JERSEY

Investigators:
Raja Igliewicz, RN, MS
Michael Schmidt, MD
Peter Gann, MD

I. SUMMARY

In October, 1982, the National Institute for Occupational Safety and Health (NIOSH) received a request to evaluate workers involved in the production of a drug, quinidine gluconate at Berlex Laboratories, Wayne, N.J. These workers had developed work-related skin rashes and respiratory symptoms. Staff from the Occupational Health Program of the New Jersey State Department of Health performed the investigation under a cooperative agreement with NIOSH. Walk-through inspections of the plant and preliminary interviews were conducted by a physician and industrial hygienist during January and February, 1983. Extensive environmental sampling and detailed medical interviews were conducted during June - August, 1983. Follow-up medical testing (including serum immunology tests and skin prick tests) and employee interviews were performed in April, 1984.

The medical findings show a large number of workers (33 of 47 questioned, or 70%) complaining of respiratory and skin symptoms (itchy rash, itchy stuffy nose, red painful eyes, chest tightness and wheezing). The primary cause of the symptoms appeared to be an irritant effect from exposure to quinidine. A subgroup of skin symptoms (7 of 37 or 19%) were caused by an allergic contact dermatitis.

Environmental sampling data consisting primarily of airborne quinidine in the worker's breathing zone show that quinidine air levels are essentially low (less than 0.2 mg/m3) in the packaging area of the plant, but that there are substantially higher levels of quinidine (up to 5.0 mg/m3) in manufacturing that may contribute to symptomology experience by workers in these areas. Specific engineering and work practices modifications that are discussed in Section VII should help lower these quinidine levels.

On the basis of environmental and health data collected, we have determined that a health hazard exists for employees at this facility due to exposure to quinidine powder. Allergic contact dermatitis as well as skin and respiratory mucous membrane irritation were identified. Recommendations for modification of work practices, engineering controls and medical surveillance are made.

Key Words: SIC 2834, Pharmaceutical Industry, quinidine, skin sensitivity, mucous membrane irritation, allergy.

II. INTRODUCTION

In October, 1982, the National Institute for Occupational Safety and Health (NIOSH) received a request for a Health Hazard Evaluation from Local 8-149 of the Oil, Chemical, and Atomic Workers Union (OCAW) which represents wage employees at Berlex Laboratories in Wayne, New Jersey. During the previous two years, a number of workers involved in the production of a drug, quinidine gluconate, were reported to have work-related skin rashes and respiratory symptoms. The requestors sought more information about the nature and circumstances of these health effects attributed to quindine exposure.

The evaluation was assigned to the New Jersey State Department of Health under a Cooperative Agreement. Walkthrough inspections of the plant and preliminary interviews were conducted by a physician and industrial hygienist during three visits in January and February, 1983. During June-August, 1983 follow-up visits for environmental sampling and detailed medical interviews were conducted. In April 1984, another visit took place where several physicians and an industrial hygienist conducted follow up medical testing and employee interviews.

This report summarizes the findings of the walkthrough visits, environmental sampling, and medical interviews. Recommendations are made in the areas of exposure control and medical surveillance.

III. BACKGROUND

Berlex Laboratories, Inc., a subsidiary of Schering AG (West Germany), has produced a variety of pharmaceuticals at its plant in Wayne, New Jersey since 1980. Prior to that, the facility was owned and operated by Cooper Laboratories, another pharmaceutical firm. Many Cooper employees were retained by Berlex, and several product lines were retained as well. No quinidine drugs were handled at the Wayne facility until Berlex assumed ownership. There are approximately 130 employees at the facility, about 63 of whom are involved in quinidine production.

Berlex manufactures a variety of pharmaceuticals including several quinidine preparations. Quinaglute Duratabs (quinidine gluconate) have been manufactured and packaged at the Wayne plant since July, 1981.

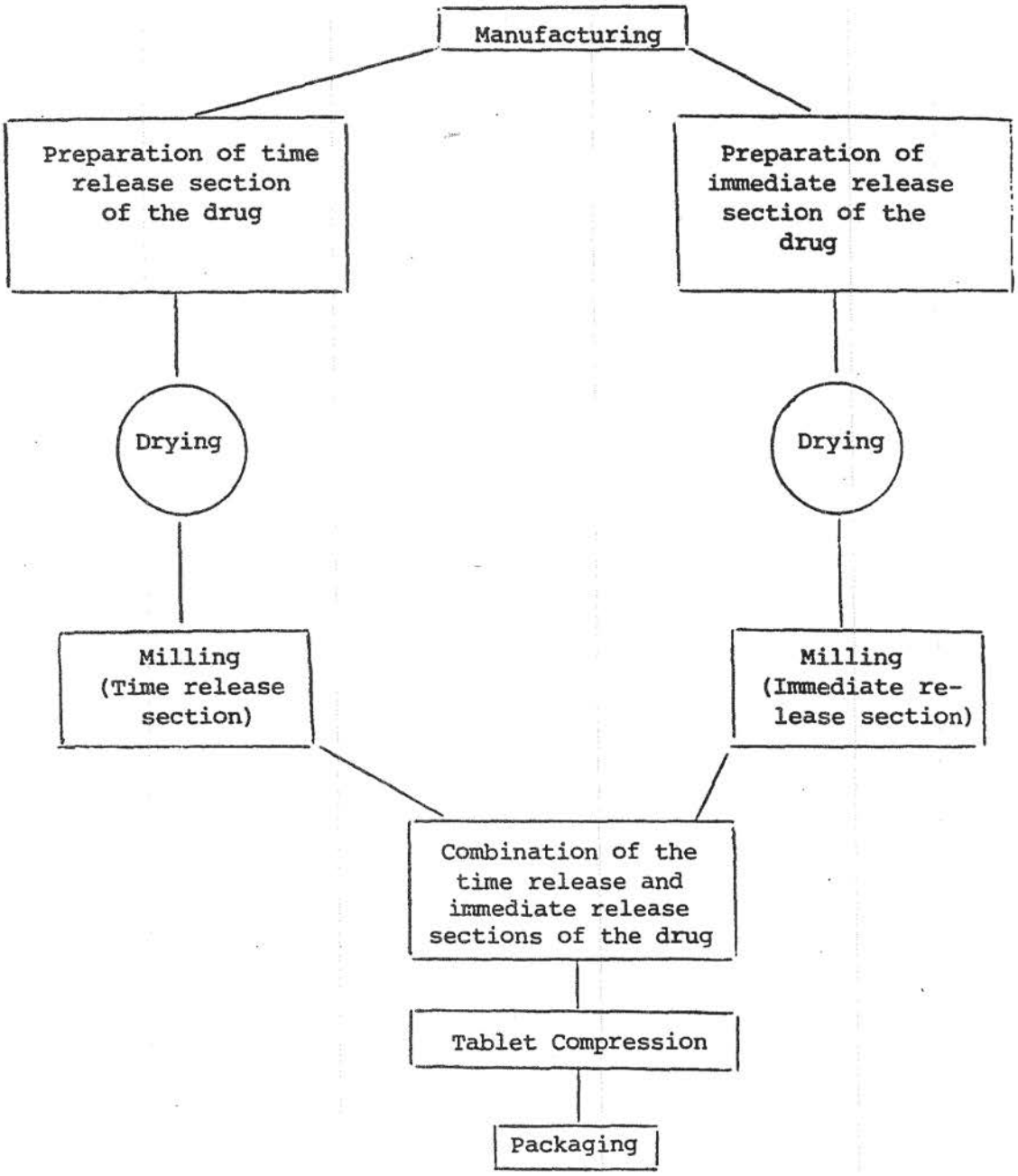
Prior evaluations of the quinidine production areas have been conducted by the Occupational Safety and Health Administration (OSHA), OSHA Consultative Services, the Hartford Insurance Company, and Berlex Laboratories itself. Results of these evaluations indicate that there was a reduction of dust concentrations after OSHA citations were made.

Each Quinaglute Dura-Tab contains 324 mg quinidine gluconate (equivalent to 202 mg quinidine base) in a tablet matrix specially designed to allow prolonged release of the drug in the gastrointestinal tract. The manufacturing process is divided into two sections; in one section the active drug is suspended in sugar, in the other it is suspended in wax. The sugar component is combined with the wax component to produce the prolonged release drug. Nowhere in the plant is raw quinidine itself manufactured; feedstocks are shipped from overseas.

Quinidine is a drug commonly used for the treatment of cardiac arrhythmias. When taken orally, it is possible that a patient may develop one or more of a

FIGURE I

FLOW CHART OF QUINAGLUTE PRODUCTION AND PACKAGING AREAS



variety of side effects. The most common side effects are gastrointestinal: diarrhea, nausea, and vomiting. The drug can also cause cinchonism (a syndrome associated with quinine toxicity characterized by headache, dizziness and tinnitus) and rarely can cause rashes, fever, hepatitis and a decrease in platelet count (1).

There are only two reports available showing quinidine health effects in exposed workers (2,3). In both cases allergic contact dermatitis was diagnosed by skin patch testing. No reports were found demonstrating a skin or respiratory irritant effect from quinidine. There is one report of quinine, a very closely related chemical, causing both allergic contact dermatitis as well as non-allergic dermatitis (4).

At the time of this study, Berlex Laboratories had conducted some medical tests on quinidine exposed employees. Thirty seven workers had been tested for skin allergy to quinidine using skin patch tests. In addition, 5 employees had been given informal inhalation challenge tests for respiratory allergy to quinidine. The results of the patch testing are included in the analysis. Because the inhalation tests were not conducted in controlled circumstances, these results are not included. However the company did report that 3 of the five employees tested had positive results.

Description of Process

The following is a brief description of the stages in the manufacturing process. These stages are shown schematically in Figure 1. The purified raw quinidine gluconate used to produce the drug comes to the plant warehouse in sealed drums. Periodically, quantities are weighed out in a room adjacent to the warehouse and brought to production areas.

The time release section of the drug is prepared as a homogeneous mix, and is manufactured by combining granulating fluid, a wax-like ingredient and quinidine gluconate. The heated wax mixture flows into a dip pan in which a chilled drum rotates. A thin film adheres to the chilled drum, from which it is scraped off. The resultant solid is spread onto paper-lined trays which are stacked on drying racks. The racks are then placed in a drying room.

After drying, the quinidine time release section is ground into a powder in the milling room. This process involves manual loading of the time release product into trays that feed into a grinder. Dust is controlled by using an elephant hose extension attached to a dust collector. After the material is ground, it is automatically fed into a plastic-lined drum with a fitted sleeve. The ground material is manually scooped out of drums and deposited onto trays once again. These trays are located on a spreading table with an attached slot exhaust ventilation system connected to another dust collector. Periodically one of the workers in this room sweeps the floor. The stacks of trays containing the milled time release power are again dried.

The immediate release section of the drug is formulated in another room. This granulation is prepared by blending quinidine gluconate, other ingredients and granulating fluid in a mixer. The mixture is discharged from the bottom of the mixer into plastic-lined drums. The operator then manually scoops the immediate release granulation onto drying trays. The trays are stacked in an oven for drying.

The next step in the process involves milling of the immediate release section mix. The granulation is fed into a mill for grinding. The finished granulation is then discharged into drums.

The final stage in the formulation of the drug is conducted in the blending room. Other ingredients, time release drug granules, and immediate release drug granules are loaded into a blender. The blender is run and then lubricant is added through a mesh screen. The dust generated around the blender is swept into a pile and collected for reconciliation. The powdery blend is then fed into plastic-lined drums.

The Quinaglute Dura-Tabs are then formed into tablets by a tablet compression machine, which is located in a separate room. The blended material is poured from drums into a hopper located on a mezzanine above the tablet compression machine. The operator monitors the compression machine and periodically removes tablets for quality testing. The finished tablets are collected in drums.

The drug is packaged in three areas: On one packaging line a machine covers five tablets with a strip of foil and workers pack these strips in boxes. On another packaging line, bottles are filled with tablets. This line is located in a tablet filling room which is under negative pressure in order to confine quinidine dust to the area. Dust control also includes a dust collector and plexiglass shields. The third packaging line also involves filling bottles with Quinaglute tablets. There are 48 packaging workers; 4 have been excluded from quinidine processes due to previous reactions to Quinaglute.

According to management records, each day 10 chemical operators are involved in manufacturing quinidine products. A total of 15 operators are available for Quinaglute manufacture; therefore each day 5 operators rotate into production of other drugs. The number of personnel exposed to quinidine are broken down by job and percent of time exposed in Table 1.

TABLE 1

	Available Personnel	% of Time Exposed to Quinidine
chemical operators	14.75*	53%
press operators	2.25*	78%
manufacturing porter	1	85%
packaging	44	8%
packaging porter	1	22%

*one chemical operator works as a press operator 25% of time.

Throughout the entire operation workers were supplied with appropriate personal protective equipment and Berlex policy dictated that the equipment be worn. The personal protective equipment worn by the workers includes: T-cloth oversuits, Tyvek oversuits, 3M 8710 dust masks, 3M 8712 organic vapor respirators, filtered air-supplied respirators, and cotton glove liners covered by latex gloves. Earmuffs are supplied for noisy operations such as milling. The personal protective equipment provided for each job was found to be appropriate.

IV. METHODS OF EVALUATION

A. Environmental

Industrial hygienists from the New Jersey State Department of Health collected personal and area samples on June 14, 15, and 16 and July 5, 7, and 27, 1983 to evaluate exposure to quinidine. The quinidine was collected and analyzed in accordance with the analytic procedure developed by Berlex Laboratories (Appendix 1).

Personal and area samples of airborn quinidine were collected using a sampling train consisting of a 37 millimeter glass fiber filter with a two piece polystyrene monitor case (without a support pad). Dupont P 4000 and P 2000 air sampling pumps calibrated for 2 liters per minute were used. Total dust samples were collected so that the results could be compared to data that was collected from previous studies.

B. Medical

During the initial walkthrough visits, a physician conducted preliminary interviews of 20 quinidine-exposed workers and obtained information on suspected and probable cases of quinidine allergy from the company's physicians. During June 14-16, 1983, more extensive medical interviews were conducted by a physician and nurse on 47 workers. This group of 47 individuals were volunteers from areas with potential quinidine exposure. Special emphasis was placed on including those workers known to be symptomatic. Therefore, the sample cannot be considered representative. Appendix 2 contains a copy of the questionnaire used.

Serum quinidine levels were determined before and after a workday (June 14, 15 or 16) on 12 individuals; 8 with quinidine exposure and 4 controls. Two additional exposed workers had pre and post-shift serum quinidine levels collected on July 27. Blood was collected by venipuncture and serum was removed after centrifugation. Samples were analyzed at National Medical Services in Willow Grove, Penna. (6). Quinidine has a half-life of 6-7 hours in the blood (1), therefore on a given morning, the previous day's exposure should largely have been elimated.

During a follow-up visit on April 12, 1984, brief interviews were conducted to gather information concerning quinidine associated symptoms during the interim period of nine months. These questionnaires were administered to 27 workers, 23 who had been previously surveyed, and 4 additional volunteers who had not been previously involved.

At this time, physicians conducted skin prick tests to clinically detect a possible immediate type hypersensitivity response to quinidine. Blood was also collected for serum immunoassays to detect various types of antibodies that could be involved in quinidine associated reactions.

These tests were conducted on the group of 27 workers described above. Skin testing was done by the skin prick method using quinidine-HSA and quinidine gluconate (dilutions of 10-4, 10-3, 10-2), common inhalants (ragweed, timothy, dust), a positive control (Histamine) and a negative control (saline).

A blood sample was collected by veni-puncture, centrifuged, and sent for analysis to the Division of Immunology of the University of Cincinnati Medical Center in Cincinnati, Ohio. The assays included:

1. Measurements of specific IgE to quinidine by RAST using quinidine-human serum albumin (Qu-HSA) conjugates;

2. Measurements of specific IgG to quinidine by ELISA using Qu-HSA conjugates;

3. Measurements of total antibody binding to I-125 Qu-HSA conjugates.

V. EVALUATION CRITERIA

No studies of environmental levels of quinidine have been reported and there are no established exposure criteria for the airborne drug. Blood levels of quinidine have been reported for the clinical use of the drug. Levels known[1] to have a pharmacologic effect on heart tissue are above 1.5 ug/ml in blood serum[1].

Therefore, air levels identified in this study provide information on the relative levels of quinidine in different job titles and areas of the plant. This information may be used to evaluate the reasons for symptoms in different plant groups, and to provide base line exposure information to evaluate the effectiveness of additional control technology as it is introduced.

VI. FINDINGS

A. Environmental

Observations showed that personal protective equipment including respiratory protection and skin protection (coveralls and gloves) were consistently worn by employees. Thus, the actual dose received by individual operators was significantly lower than the airborne levels measured.

Measured airborne concentrations of quinidine ranged from 0.003 mg/m3 to 5.098 mg/m3. These numbers are time-weighted averages assuming exposure for an 8-hour work day and 40 hours per week. The results of the personal air samples, grouped according to job location, are given in Table 2 .

The mean or average exposure measured in manufacturing was 1.33 mg/m3 and the mean exposure in packaging was 0.12 mg/m3. The individual sampling results are presented in Appendix 3.

Exposures of chemical operators in the time-release room were 2.5 mg/m3 and 2.65 mg/m3. These levels were measured while adding quinidine gluconate into the mixing kettle. During time release grinding, one chemical operator had a morning exposure of 6.17 mg/m3 and an afternoon exposure of 3.59 mg/m3. These levels reflect exposure during the transfer of wax chips onto the feeding

tray. In the preweigh area, one worker was exposed to 3.74 mg/m3 while weighing quinidine powder for a period of twenty-five minutes.

The highest exposure level measured in the plant occurred during the routine monthly cleaning of the dust collector. A personal air sample measured in the chemical operator's breathing zone indicated that he was exposed to 9.22 mg/m3 of quinidine while he vacuumed the interior of the dust collector. Several workers reported experiencing upper respiratory irritation and excessive fatigue while performing this particular job.

In the Packaging Area, quinidine air levels were low and engineering controls appeared to be effective. The highest exposure in packaging occurred in the secondary tablet and capsule room. Exposure to one machine operator was measured as 1.24 mg/m3. She spent half her time adding tablets into a rotating sieve and the other half on the labelling machine. Heavy dusting was noted at the base of the turntable and dust was generated when the pills were added to the turntable. Two elephant trunk ventilation hoses were present; however, one was not attached to the front of the machine.

TABLE 2

Personal Quinidine Exposure Results

Production Area	Date Sampled	# of Persons Sampled	# of Samples	Range	TWA $_3$ (mg/m^3 Quinidine)
Time Release Prep	June 14	2	4	.01-2.65	2.00
Time Release Grind	June 15	2	4	.26-6.17	2.81
Immediate Release Grind	June 16	2	4	.03-9.22	1.71
Mezzanine	June 14	1	2	.03-2.20	1.26
Immediate Release Mixer	June 15	2	4	.04-.19	0.09
Blending	July 27	2	4	.28-.49	0.37
Pre Weigh	July 27	1	1	-	3.74
Tableter	June 14	1	2	.03-.04	0.035
Foil Wrap Packaging	June 15	5	10	.00-.06	0.028
Foil Wrap Packaging	June 16	3	3	.01-.01	0.011
Small Bottle Filling	July 5	4	4	.00-.14	0.042
Large Bottle Filling	July 7	5	5	.04-1.24	0.33

B. Medical

Blood quinidine levels measured before and after a work shift were determined for 14 individuals. Levels were non-detectable in all but 2 of the people tested. One was an exposed chemical operator and the other was a presumably non-exposed control. Findings in both cases were 0.04 mcg/ml, which is only slightly above the detection limit of 0.02 mcg/ml. These findings were not considered significant.

Of the 47 people interviewed, 31 were men (average age 39), and 16 were women (average age 47). Forty percent of these workers were smokers and 34% had family or personal histories of atopy (predisposition to allergy) The workers reported experiencing a wide range of symptoms. The nine most prevalent symptoms reported are shown in Table 3 with the number of people reporting each one.

TABLE 3

Symptoms Reported

Symptoms	Number of Reports of Symptoms
Itchy rash	23
Itchy stuffy nose	19
Red painful eyes	13
Painful nose	10
Chest tightness	9
Wheezing	7
Tinnitus	6
Nosebleed	5
Sore throat	5

In order to study the relationship between symptom response and allergy test results, three categories of cases were identified based on symptom reports. The definitions of these case categories are:

Upper respiratory cases: itchy stuffy nose.

Lower respiratory cases: wheezing or chest tightness plus cough.

Skin cases: itchy rash or hives.

Out of the 47 workers interviewed, 33 (70%) fit into one or more of the case definitions. These 33 cases were divided into 6 subcategories by symptoms and are shown by job position at time of symptom onset in Table 4.

TABLE 4

Symptoms Reported

Job position at time of symptom onset	Upper Resp. Only	Lower Resp. Only	Skin Only	Upper Resp. and Skin	Lower Resp. and Skin	Upper, Lower Resp. and Skin	Tota
Chemical operator	2	1	3	4	1	1	12
Assembler packer	3		2	3	1		9
Maintenance			2	1			3
Material handler, porter			1	1		1	3
Other (manager, lab)	1	1	2	1			5
None	1*						1
Total	7	2	10	10	2	2	33

*one person's work area unknown at time of symptom onset

Patch testing performed by a Berlex physician was completed on 37 workers and results are presented by symptom category in Table 5. The tests were positive in 7 out of 37 (19%). All of those with positive patch tests reported skin symptoms. It should also be noted that results were reported as equivocal in 5 participants.

TABLE 5

Patch Test Results by
Symptom Category

Symptoms	Patch Test +	-	?	Total
Upper Resp. only		4	2	6
Lower Resp. only		2		2
Skin only	3	7		10
Upper Resp., Skin	2	6		8
Lower Resp., Skin	1		1	2
Upper Resp., Lower Resp., Skin	1	1		2
None		5	2	7
Totals	7	25	5	37

Both atopic status (predisposition to allergy) and smoking history were considered possible confounding factors for the analysis. To detect any association between symptoms and a history of atopy or atopic family background a series of two by two tables were constructed. In examining each of the symptom groups separately or together, no associations were found at a significance level of p=.05 using a chi square test or Fisher's Exact Test.

In addition, a two by two table was also constructed to determine if smoking (which could mask a true association between respiratory symptoms and quinidine exposure) was associated with upper or lower respiratory symptoms. No association was detected indicating that the symptoms reported could not be explained by smoking alone.

During the follow-up plant visit on April 12, questionnaires were administered to 27 workers (23 previous cases and 4 new volunteers). Of 23 previously symptomatic people interviewed, 10 no longer had symptoms. Six of these 10 continued to have the same amount of contact with quinidine as when inteviewed the previous year.

Nonetheless, symptoms were once again found in workers from all job categories. Furthermore, the questionnaire demonstrated the following general characteristics in the 14 symptomatic cases. Two felt that their symptoms began immediately after coming to work. The other twelve reported that symptoms began an average of 2.8 hours after the start of work. The symptoms continued throughout the workshift for all 14 symptomatic cases. Nine out of 15 workers had symptoms after coming home from work. The symptoms improved on weekends for 10 out of 14 cases and in 12 out of 14 the symptoms significantly improved on vacations.

There were no positive responses to the specific allergy tests conducted by NIOSH. Of the 21 individuals given the skin prick test, and the 19 workers (15 previous cases and 4 new volunteers) given antibody binding tests (RAST, ELISA and total antibodies) none tested positive.

VII. DISCUSSION

Since this was the first time that personal exposure to quinidine was measured at Berlex, the environmental data should serve as a baseline for evaluating the effectiveness of engineering controls and improved work practices. The mean or average exposure measured in manufacturing was 1.33 mg/m3 and the mean exposure in packaging was 0.12 mg/m3. Since appropriate personal protective equipment was used, the levels found reflect only air concentrations, not effective dose to the individual worker monitored.

The tests designed to measure quinidine levels in the blood of workers handling quinidine before and after the workshift were essentially negative. The results of the serum quinidine determinations (.02 ug/ml-.04 ug/ml) show that exposure levels during the manufacture of quinidine drugs were far below the levels required to produce a pharmacologic effect (therapeutic level usually = 1.5 - 5 ug/ml). Thus, symptoms looked at in this study were limited to hypersensitivity (skin and general allergies) and irritative symptoms (upper and lower respiratory system and skin).

Several problems in the evaluation of the data collected were also considered. First, only those people reporting symptoms were included in the study; thus no rates of illness in the population could be calculated. Second, because of work assignment policies, individuals included in the study worked in several different jobs on any one day, as well as over their work history at Berlex; thus no exposure groups could be easily identified. Third, some individuals who had become symptomatic in the past had been removed from exposure (either by a change in job assignment or by termination); thus there may have been fewer people in the present population with illness.

In spite of these limitations, the study does help to describe a syndrome associated with quinidine exposure. It cannot however determine the rates of disease in the exposed population. Nor can the study identify a specific exposure level at which one would expect no symptoms. Airborne quinidine levels reflect the potential for exposure, with or without the additional use of protective equipment. Our findings of the presence of symptoms, in spite of the use of PPE, indicates that the protection provided by these means is insufficient and that further reduction of airborne levels is warranted.

In order to determine the clinical spectrum and severity of quinidine hypersensitivity present in Berlex workers, selected individuals received blood tests (total IgE, RAST and ELISA) and appropriate skin tests (patch and prick) to detect allergies. The skin patch test was used to detect delayed hypersensitivity reactions related specifically to the skin (i.e. contact dermatitis). The skin prick test and the three blood immunology tests detect an immediate type hypersensitivity response in the whole body (i.e. asthma). Of the three blood tests, the RAST is designed to detect specific quinidine allergy.

Patch testing, which was conducted on 37 workers at Berlex, was positive in 7 cases, although 24 workers reported quinidine associated skin symptoms. Thus it

appears that a subgroup of the affected people had delayed hypersensitivity to quinidine and developed the typical allergic contact dermatitis hours after exposure.

In addition, the symptoms at Berlex suggested that something other than allergic contact dermatitis may have been occurring. In addition to the delayed response, workers reported skin symptoms sometimes immediately after exposure. Many reported skin itching and redness without evidence of actual lesions in the skin and several workers reported respiratory symptoms. These responses suggested the possibility of a Type 1 IgE mediated (immediate type) reaction. However, the results of the serum immunoassays for IgE or IgG associated with quinidine were negative which strongly suggests that a Type 1 reaction was not responsible. This conclusion was further supported by the negative skin prick test results.

An alternative explanation for the symptoms displayed would be that quinidine is a direct irritant of the skin and respiratory mucous membranes. While the irritant effects of quinidine have not been documented, quinine, a close chemical relative of quinidine, is an irritant (5). Quinine has also been shown to be responsible for cases of irritant dermatitis in pharmaceutical workers (4). Questionnaire responses in our study suggest skin and mucous membrane irritation in some of the quinidine exposed workers. These symptoms began within hours after onset of exposure to quinidine, tended to be worse upon high exposure and abated after removal from quinidine exposure, improving significantly on weekends and vacations.

Our questionnaire data also revealed that in most cases the symptoms were minor and did not require treatment or involve lost work-time. It may be expected, however, that the more severely affected individuals would have left the exposed areas before this study was conducted, leaving only the unaffected, or mildly affected workers. The symptoms were not confined to any particular job in the plant although our impression was that the percentage of workers with symptoms was higher among chemical operators and maintenance workers than among packaging workers. This would coincide with the reported quinidine air levels and potential for skin contact.

Neither smoking history nor atopic status appeared to influence the risk of quinidine associated symptoms. However, it is possible that a true effect of atopic status on risk may have been obscured by misclassification of subjects due to the imprecision of questionnaire data.

It is of interest that of 23 previous cases investigated (all of whom had symptoms in June 1983), ten no longer had symptoms during the follow-up study in April 1984. The 23 workers had not changed job positions nor had their status changed regarding quinidine contact. No cases had sought further physician contact and symptom characteristics had not changed from the previous year.

If one assumes that a reporting bias is not present, these findings might be explained by an improvement in engineering controls, work practices or both. It is also possible that the workers may have developed a tolerance to quinidine, especially if their symptoms were due to an irritant effect. The reason for this change could not be included from the available information.

In summary, the quinidine associated symptoms identified by NIOSH seem to primarily have an irritant etiology while a subgroup of skin symptoms can be explained by an allergic contact dermatitis mechanism.

VIII. RECOMMENDATIONS

A. Environmental

On the basis of the findings of skin contact dermatitis and respiratory irritation symptoms identified in this study, a number of exposure reduction measures are recommended:

1. In the grinding room, the elephant hose currently in use without a hood attachment is not an effective control. An appropriate dust collection hood should be designed and installed .

2. An industrial vacuum cleaner equipped with a high efficiency filter should be available to clean up dust in the grinding room. Sweeping dust from the floor and surfaces creates unnecessary dust exposure.

3. All existing ventilation equipment should be properly attached for efficient dust collection. A regular (weekly) preventive maintenance program should be designed and instituted to ensure that equipment is properly installed and functioning.

4. A drum dumping system similar to the one used in the final mix blending room should be installed in the time release section room to eliminate the need for hand scooping the quinidine powder. The system should be installed with adequate local exhaust ventilation.

5. Additional controls should be installed on the final mix blender to reduce dust escaping from the machine. The temporary seal presently in use appeared ineffective as accumulated dust was visible on the final mix blender.

6. When the final mix blender is discharged into drums, a visible cloud of dust was generated. This dust discharge may be reduced by filling the drums only 3/4 full.

7. The secondary tablet and capsule filling machine should be fitted with enclosures to prevent dust generation. A plexiglass enclosure could be installed and the metal band should be sealed to the base of the machine. Also, a tighter contact should be developed between the bottles and the feed lines.

8. Significant dust was also generated as pills traveled down metal tracks on the sample/unit dose packaging system. This machine should also be fitted with a plexiglass enclosure.

9. The use of floor fans to cool workers in the sample/unit dose packaging room creates unnecessary dust exposure. Installation of air conditioning units should be considered if heat is high in these areas.

10. Both the Pre Weigh and Mezzanine areas should be further evaluated to identify the sources of airborne quinidine. Work process observation and additional sampling may be necessary for this evaluation.

11. High exposure to quinidine was demonstrated during cleaning of the dust collector, indicating the need for a more efficient method. More frequent cleaning of the dust collector would eliminate large buildups of dust. Also, according to the Berlex Standard Operating Procedures Manual, the filters are vibrated prior to cleaning to loosen any accumulated dust to facilitate vacuuming. The instructions require waiting for a few minutes prior to opening the access cover to allow the dust to settle. It is suggested that the filters be vigorously vibrated at lease two hours before cleaning to allow more complete dust settling.

12. In addition to these dust control measures, workers should have available to them facilities to maintain good personal hygiene. Berlex has installed a unique air shower booth that flushes the worker's body and oversuit with air. This air shower should remove contamination from the worker's body and oversuit with air. This air shower should remove contamination from the worker's clothing. However, the installation of adequate water shower facilities for both exposed men and women may significantly improve hygiene and reduce the incidence of contact dermatitis. Sufficient time for showering at the end of each work shift must also be allowed.

13. The current environmental sampling program at Berlex is based on area sampling alone. While this type of sampling may be useful in identifying sources of air contamination, it does not evaluate personal exposure levels. A personal air sampling protocol should be instituted by Berlex to help quantify individual exposure levels.

B. Medical

1. Medical surveillance for pharmacologic effects of quinidine (such as "cinchonism") is not required since exposures are far below the exposure experienced by patients taking the drug orally.

2. The evidence does not support the exclusion of atopics or persons with history of allergy from employment in quinidine areas.

3. Engineering controls and work practices should be designed to minimize respiratory and skin contact and quinidine as the majority of quinidine-associated symptoms appear to have an irritant etiology.

4. Patch testing should be done on employees who develop skin symptoms to identify those workers with an allergic contact dermatitis. Workers with symptoms and positive patch test results for quinidine should be transfered to areas with no potential for quinidine exposure.

5. The evidence does not support a protocol to screen workers prior to development of symptoms.

BIBLIOGRAPHY

1. Physicians Desk Reference. Medical Economics Company. 1982, p.673

2. Fernstrom AI: Occupational Quinidine Contact Dermatitis, A Concept Apparently Not Yet Described. Acta Derm-Venereol 1965;45:129-134.

3. Wahlberg JE, Boman A: Contact Sensitivity to Quinidine Sulfate from Occupational Exposure. Contact Dermatitis 1981;7:27:31

4. Hardie RA, Savin JA, White DA, et al: Quinine Dermatitis: Investigation of a Factory Outbreak. Contact Dermatitis 1978;4:121-124.

5. Goodman LS, Gilman A: The Pharmacological Basis of Therapeutics, MacMillan Pub. Co. 1979, pp 686-687, 1062-1063.

6. Flood JG, Bowers GN, McComb RB: Simultaneous Liquid Chromatographic Determination of 3 Anti Arrythoric Drugs: Disopyramid, Lydocaine and Quinidine. Clinical Chemistry 1980; 26:197-200.

AUTHORSHIP AND ACKNOWLEDGEMENTS

Report Prepared by:

Raja Iglewicz, R.N., M.S.
Michael Schmitt, M.D., M.P.H.

Occupational Health Program
New Jersey State Department of Health
CN 360
Trenton, N.J. 08625

Peter Gann, M.D.

Acknowledgements:

Kenneth Rosenman, M.D., Director
Occupational and Environmental
Health Services,

Occupational Health Program
New Jersey State Department of Health
CN 360
Trenton, N.J. 08625

Kathleen O'Leary, M.S.
Chief Occupational Health Program

Jerry Roseman, M.S.

Joseph Schirmer, M.S.

Noah Seixas, M.S.

Linda Glazner, R.N., M.P.H.

Timothy Liveright, M.D.

Michael Cohen, M.D.

Department of Immunology University
of Cincinnati Medical Ctr.
Cincinnati, Ohio

DISTRIBUTION AND AVAILABILITY OF REPORT

Copies of this report are currently available, upon request, from NIOSH, Division of Technical Services, Information Resources and Dissemination Section, 4676 Columbia Parkway, Cincinnati, Ohio 45226. After 90 days, the report will be available through the National Technical Information Service (NTIS), Springfield, Virginia 22161.

Copies of this report have been sent to:

1. Local 8-149 Oil, Chemical and Atomic Workers Union (OCAW)
2. Berlex Laboratories, Wayne, New Jersey
3. Occupational Health Program, New Jersey State Department of Health
4. NIOSH Region II
5. U.S. Department of Labor, OSHA, Region II

For the purpose of informing the affected employees, copies of this report shall be posted by the employer in a prominent place, accessible to employees, for 20 calendar days.

APPENDIX 1

QUINIDINE ANALYSIS METHOD

HPLC ASSAY OF RESIDUAL QUINIDINE GLUCONATE IN AIR FILTERS

A) Reagents

1) Acetonitrile (chromatographic grade)
2) Methanol (reagent grade)
3) Glacial Acetic Acid (reagent grade)
4) Sodium Acetate Anhydrous (reagent grade)
5) 0.01 M Sodium Acetate:

   a) Accurately weigh 820 mg (± 5 mg) of sodium acetate anhydrous and transfer to a 2000 ml beaker. Add 1000 ml of water and mix to dissolve.

6) Mobile Phase: To 760 ml of 0.01 M Sodium Acetate solution, add 230 ml of acetonitrile and 10 ml glacial acetic acid. Mix well and filter through a 0.45 u teflon filter.

NOTE: If the mobile phase and samples are not filtered, the system will clog with particulate matter giving rise to a higher operating pressure and an erratic baseline due to erratic flow. The higher pressure can also damage the column.

7) 50% Methanol Solution: Add 300 ml of reagent grade methanol to 300 ml of water in a 1000 ml beaker. Mix well. Let cool to room temperature.

B) Preparation of Standard Solutions

1) Quinidine Gluconate - Accurately weigh approximately 12 mg of quinidine gluconate USP into a 200 ml volumetric flask. Add approximately 160 ml of 50% methanol solution and shake well to dissolve. Bring to mark with 50% methanol solution and mix well. Transfer 3.0 ml to a 100 ml volumetric flask and bring to mark with 50% methanol solution and mix well.

C) Sample Preparation - Transfer the filter from the air sample cassette and quantitatively transfer to a glass stoppered centrifuge tube. Add 5.0 ml of 50% methanol solution to the tube and shake for 5 minutes. Filter.

D) Procedure - Inject 20 ul of quinidine gluconate standard solution and sample solution. Measure each peak height in millimeters or in the area.

HPLC Chromatographic Conditions

Column: 30 cm x 4 mm Water u-Bondapak C_{18} or similar column
Mobile Phase: 0.01M Sodium acetate: Acetonitrile: Acetic acid (76:23:v/v)

Detection: UV:240 nm
Attenuation: 0.2 AUFS or as necessary
Flow: 2.0 ml/min. or as necessary
Injection: 20 ul or as necessary
Chart Speed: 30 cm/hr

Perkin Elmer Sigma 10B Chromatography Data Station Parameters

Attentuation: 1
Base Code: 0
Chart Speed: 7 mm/min

Base sensitivity, area sensitivity, run time, and retention time must be determined prior to analysis.

NOTE: Chromatographic conditions may be altered for desired separation. Quinidine gluconate elutes first at 4.6 minutes followed closely by dihydroquinidine at 5.5 minutes.

E) Calculation

Concentration of quinidine gluconate.

$$\frac{N \times Cs \times 5\ ml}{M} = \text{ppm quinidine gluconate}$$

Where

N = peak height in mm or peak area of quinidine gluconate in air filter solution

M = peak height in mm or peak area of quinidine gluconate reference standard solution

Cs= micrograms per ml quinidine gluconate reference standard solution final dilution.

APPENDIX 2

QUESTIONNAIRES

JUNE, 1983

QUESTIONNAIRE

1. Name: _____

2. Address: _____

3. Phone: _____ 4. Date of Interview _____

5. Age: _____ Race: _____ Sex: _____

6. Estimated Height: _____ Estimate Weight: _____

OCCUPATIONAL HISTORY

Name ______________________ I.D. No. __________

Now I would like some information about each of the jobs, part time or full time, that you held for three months of more after completing your education. Please include work in the armed services. We will start with your first full time job after leaving school and come up to your most recent job.

Put C in current job	Q-1 What was the name and address of the Company/Employer you worked for? Q-2 What did they do or manufacture? Q-3 What was your job title?	Q-4 Mo/Yr Start Q-5 Mo/Yr Stop Q-6 Was job full time or part time	Q-7 What were the duties?	Q-8 Were you exposed to Fumes, (Show Card)	Q-9 Did You Wear Protective Clothing/Equipment?
FIRST JOB	1. 2. 3.	4. 5. 6. ☐ Part-Time ☐ Full-Time	7.	8. ☐ Yes—Specify ☐ No	9. ☐ No ☐ Yes, Spec.
	1. 2. 3.	4. 5. 6. ☐ Part-Time ☐ Full-Time	7.	8. ☐ Yes—Specify ☐ No	9. ☐ No ☐ Yes, Spec.
	1. 2. 3.	4. 5. 6. ☐ Part-Time ☐ Full-Time	7.	8. ☐ Yes—Specify ☐ No	9. ☐ No ☐ Yes, Spec.
	1. 2. 3.	4. 5. 6. ☐ Part-Time ☐ Full-Time	7.	8. ☐ Yes—Specify ☐ No	9. ☐ No ☐ Yes, Spec.
	1. 2. 3.	4. 5. 6. ☐ Part-Time ☐ Full-Time	7.	8. ☐ Yes—Specify ☐ No	9. ☐ No ☐ Yes, Spec.

Any adverse effects noted from above jobs? List by Job Number.

Ever Live Near Plant, Mine or Facility that could have released hazardous material?

☐ Yes ☐ No

Where ____________________

Any of your hobbies involve adverse exposure?

☐ Yes ☐ No

When ____________________

Exposures ____________________

Anyone in the family work in a trade where hazardous materials could have been brought home (viz, asbestos, lead, beryllium, vinyl chloride, etc.)? ☐ Yes ☐ No

If yes, what materials ____________________

JOBS AT BERLEX (Start With Date Of Hire)

	JOB TITLE	LOCATION	ACTIVITY	DURATION MO/YR - MO/YR	CONTACT WITH QUINIDINE?
1.					
2.					
3.					
4.					
5.					

When did you first work with quinidine? Never did MO/YR _____

Process: _____

When did you stop working with quinidine? Never did MO/YR _____

Reason stopped _____

MEDICAL HISTORY

Has a doctor told you that you have any of the following?

	Yes	No	Onset	Specify
Heart disease	___	___	_____	_____
High blood pressure	___	___	_____	_____
Irregular heartbeat	___	___	_____	_____
Hay fever (nasal, eye)	___	___	_____	_____
Skin allergy	___	___	_____	_____
Asthma	___	___	_____	_____
Other Chronic Medical Condition	___	___	_____	_____

Do any of your first degree relative (parents, siblings, children) have hay fever, asthma, or eczema? Yes___ No___

Specify _____

Have you taken any medicines regularly for at least 3 months during the past 3 years? Yes___ No___

Specify_____

MEDICAL HISTORY (Continued)

Have you taken any medicines regularly for at least 3 months during the past 3 years? Yes___ No___

Specify_____

Have you ever been skin tested for quinidine allergy? Yes__ No__

Type of test (patch or prick)

Doctor _____

Date _____

Have you ever been tested for allergy by inhaling quinidine? Yes__ No___

Doctor _____

Date _____

Do you smoke?	Yes__ No___
Have you quite smoking?	Yes__ No___
What is (was) your average packs/day?	_____
How many years have you smoked?	_____

While working with quinidine, have you taken any of the following drugs?

	Dates	Problems
anticoagulants (blood thinners)	_____	_____
barbiturates	_____	_____
digitalis or digoxin	_____	_____
drugs to correct heartbeats	_____	_____

During the past two years, have you had any of the following, outside of regular colds and flu? (circle if yes)

	Onset	Duration	Doctor?	Relationship to Work
Temporary blurred vision				
Difficulty seeing colors				
Red, painful eyes				
Itchy, stuffy nose				
Painful nose				
Nosebleeds				
Sore throat				
Ringing in the ears				
Room spinning sensation				
Temporary hearing loss				
Chest tightness				
Wheezing				
Cough				
Irregular heartbeat				
Nausea or vomiting				
Diarhea or constipation				
Hives				
Bruise spots				
Itchy rash				

Sites _____

Describe _____

Symptoms (Continued)

	Onset	Duration	Doctor?	Relationship to Work ?
Rash worsened by the sun				
Sites				
Joint swelling/stiffness				
Low back pain				
Headache				
Unusual fatigue				
Dizziness				
Weight loss (unintended)				
Fever				

Other _____

_____

Do you notice, or have you noticed in the past, any particular symptoms associated with quinidine exposure? _____

_____

_____

APRIL, 1984

State of New Jersey
DEPARTMENT OF HEALTH
JOHN FITCH PLAZA
CN 360, TRENTON, N.J. 08625

J. RICHARD GOLDSTEIN, M.D.
COMMISSIONER

CONSENT FORM

I have been informed that the National Institute of Occupational Safety and Health in cooperation with the New Jersey State Department of Health is conducting a study of selected employees at Berlex. This study involves obtaining information from me about my work and health, and being examined by a physician. The study may require approximately 30 minutes before and after work of my time to complete.

I understand that I will be notified in writing after the study, and that my private physician may be contacted if I want. All the information will be summarized and shared with the Union and Management without any identifying information.

I have agreed to take part in this study and to give information understanding that:

1. My responses will be kept completely confidential.
2. My participation is voluntary and I am free to discontinue participation at any time.
3. Questions can be answered by talking to Ms. Raja Iglewicz at (609) 984-1863.

Participant Signature: _____

Date: _____ Witness: _____

Private Physician Name: _____

Address: _____
(Street)

_____
(City) (State) (Zip)

QUESTIONNAIRE

1. Name: _____

2. Address: _____ _____

3. Phone: _____ 4. Date of Interview _____

5. Age: _____ Race: _____ Sex: _____

JOBS AT BERLEX SINCE JUNE 1983 (LAST INTERVIEW)

	JOB TITLE	LOCATION	ACTIVITY	DURATION MO/YR - MO/YR	CONTACT WITH QUINIDINE
1.					
2.					
3.					
4.					
5.					

SINCE JUNE 1983,

Have you ever been skin tested for quinidine allergy? Yes__ No__

Type of test (patch or prick)

Doctor _____

Date _____

Result _____

SINCE JUNE 1983,

Have you ever been tested for allergy by inhaling quinidine?
Yes__ No___

Doctor _____

Date _____

RESULT _____

SINCE JUNE 1983,
have you had any of the following,
outside of regular colds and flu? (circle if yes)

	Onset	Duration	Doctor?	Y, N	Do these symptoms begin immediately after coming to work?	Do these symptoms begin hours after coming to work?	If yes, how many hours?	If so, how many hours do these symptoms last at work?	Do these symptoms continue after coming home from work?	If so, for how many hours?	Are these symptoms better on the weekends?	Are these symptoms better on vacation?	Days
Red, painful eyes													
Itchy, stuffy nose													
Painful nose													
Nosebleeds													
Sore throat													
Temporary hearing loss													
Chest tightness													
Wheezing													
Cough													
Nausea or vomiting													
Hives													
Bruise spots													
Itchy rash													
Sites													
Describe													

APPENDIX 3

SAMPLING RESULTS

TABLE I
BERLEX SAMPLING DATE - JUNE 14, 1983

Employee	Work Area	Sampling Time (minutes)	Total Volume (liters)	Concentration mg/m³		Comments Work Activities
Chemical operator (personal sample)	Time Release Section Room	264	533.3	2.531*	AM	Homogeneous melt is made by adding granulating fluid, other ingredients, and quinidine gluconate to kettle, and then mixing. Heated melt distributed on rollers, knife edge flakes off thin flakes onto a trough. Flakes are spread on paper lined trays and trays are put into a drying room.
		83	167.7	0.006	PM	
		347	701.0	1.93	TWA[1]	
Chemical operator (personal sample)	Time Release Section Room	283	566	2.650*	AM	
		83	166	0.209	PM	
		366	732	2.096	TWA	
	(Area Sample) Time Release Section Room	425	850	0.246		
Chemical operator (personal sample)	Grinding Room #2 Immediate Release Section Mix	159	321.2	0.330	AM	Chops up clumps of immediate release section containing quinidine gluconate with a spatula. Hand feeds trays of the powder mixture to grinder that grinds up this section of the drug; mixture is discharged into a sleeve attached to a plastic lined 55 gallon drum. Drum is then moved into hallway.
		304	351.5	0.021	PM	
		463	672.7	0.127	TWA	
Chemical operator (personal sample)	Grinding Room #2 Immediate Release Section Mix	160	336	1.166*	AM	
		171	342	0.045	PM	
		332	618	0.585	TWA	
	(Area Sample) Grinding Room #2 Immediate Release Section Mix	147	308.7	0.196		
Press operator (personal sample)	Tablet Compression Room, Tablet Comperssion Machine	215	430	0.034	AM	Monitors tablet compressing machine. Tablets fall automatically into drums, each containing about 33,000 tablets. Periodically removes tablets for quality testing.
		179	358	0.036	PM	
		394	788	0.0349	TWA	
	(Area Sample) Tablet Compression Room	407	494	0.129	AM	
		180	360	0.031	PM	
		587	854	0.0989	TWA	
	(Area Sample) Equipment Room Manufacturing	405	826.2	0.042	TWA	Storage room located in manufacturing.
	(Area Sample) Changing Room	401	802	0.052	TWA	Room used for changing into clothing and donning of personal protective gear.
Press operator (personal sample)	Mezzanine Charging Powder to Hopper	147	301.4	0.271	AM	Loads drums of the final mix of Quinaglute powder into a hopper which feeds into the tablet compressing machine.
		154	315.7	2.20*	PM	
		301	617.1	1.26	TWA	
	(Area Sample) Mezzanine	200	410.0	0.131	AM	
		157	321.9	0.017	PM	
		357	731.9	0.081	TWA	

C-concentration t-time T-total time

$\overline{T}$

*Areas of concern

TABLE 2
BERLEX SAMPLING DATE - JUNE 15, 1983

Employee	Work Area	Sampling Time (minutes)	Total Volume (liters)	Concentration mg/m^3		Comments Work Activities
Chemical operator (personal sample)	Grinding Room (Time Release Section)	235 167 402	470 334 804	6.17* 3.59* 5.098*	AM PM TWA	The time release flakes are loaded onto a feeding tray that feeds into a grinder. Material is ground up, fed automatically into plastic lined drum with a fitted sleeve. Ground time release section is mannually deposited onto trays that are moved into a drying room. Periodically one worker sweeps up the floors.
Chemical operator (personal sample)	Grinding Room (Time Release Section)	224 167 391	425.6 317.3 742.9	0.592 0.255 0.448	AM PM TWA	
Area Sample	Grinding Room #2 (Time Release Section) Total Dust	196 145 341	392 290 682	1.91* 2.59* 2.20*	AM PM TWA Total Dust	
Area Sample	Grinding Room #2 (Time Release Section)	196 145 341	398 294.4 692.4	0.317 0.085 0.218	AM PM TWA Quinidine Gluconate	
Chemical operator (personal sample)	Blender Mixing Room (Immediate Release Section)	209 137 346	424.3 278.1 702.4	0.035 0.191 0.097	AM PM TWA	Formulation of immediate release section includes blending of quinidine, granulating fluid, and other ingredients in a mixer. Mixture is discharged into plastic lined drums. Immediate release section is manually spread onto drying trays. Trays are placed in the drying room.
Chemical operator (personal sample)	Blender Mixing Room (Immediate Release Section)	201 137 338	402 274 676	0.069 0.102 0.082	AM PM TWA	
	Blender Mixing Room (Area Sample)	196 133 329	411.6 279.3 690.9	0.013 0.005 0.0097	AM PM TWA	
Quality assurance inspector (personal sample)	Sample/Unit Dose Packaging Line	209 190 199	418 380 798	0.003 0.026 0.014	AM PM TWA	Spends 2-5 minutes each hour on sample strip packaging line. Looks for defects, picks up 4 strips (20 tablets) and puts it in dessicator to check for leakage.
Assembly packer 2 (personal sample)	Sample/Unit Dose Packaging Line	225 208 433	450 416 866	0.023 0.017 0.020	AM PM TWA	Takes strips of wrapped tablets off of conveyor and places in small trays. Hands trays with about 8 strips to machine operator.
Material handler (personal sample)	Sample/Unit Dose Packaging Line	211 208 419	422 416 838	0.055 0.050 0.052	AM PM TWA	Scoops tablets from box - shakes them in sieve and dumps into filling machine hopper. Helps fill tablet packages - stacks packages into boxes. Stacks boxes on pallets.

Machine operator (personal sample)	Sample/Unit Dose Packaging Line	227 207 434	454 414 868	0.036 0.038 0.037	AM PM TWA	Checks the foil strips to make sure all the tablets are there. Makes sure they are properly labelled with name and code.
Assembly packer 1 (personal sample)	Sample/Unit Dose Packaging Line	229 207 436	458 414 872	0.018 0.018 0.018	AM PM TWA	Lets some strips go to Assembler Packer (2) - takes other strips and places in trays. Also slides strips into boxes.
	Sample/Unit Dose Packaging Line Area sample on table in corner right next to sieving operation	251 200 451	502 400 902	0.022 0.021 0.0216	TWA	
	Sample/Unit Dose Packaging Line Area sample close to hopper where tablets are added.	250 200 450	500 400 900	0.043 0.121 0.078	AM PM TWA	A local exhaust vent with flexible tubing was installed but is not adequately hooked up because it hampers machine vibration necessary to transfer tablets from hopper to sealing head.

TABLE 3
BERLEX SAMPLING DATE - JUNE 16, 1983

Employee	Work Area	Sampling Time (minutes)	Total Volume (liters)	Concentration mg/m³		Comments Work Activities
Chemical operator (personal sample)	Immediate Release Section Grinder	233 159 392	466 318 784	0.954* 0.026 0.578*	AM PM TWA	AM activities Chops up clumps of immediate release section containing quinidine gluconate with a spatula. Hand feeds trays of the power mixture to grinder that grinds up this section of the drug. Mixture is discharged into a sleeve attached to a plastic lined 55 gallon drum. Drum is then moved into the hallway.
Chemical operator (personal sample)	Immediate Release Section Grinder	226 103 329	452 206 658	0.243 9.22* 3.05*	AM PM TWA	
Area Sample	Immediate Release	219	438	0.354	AM	PM activities 12:21 - 2 PM Cleaned dust collector unit. Empty collecting tray, vacuumed cloth bags and cleaned vacuum.
	Washroom (Cleaning Dust Collector)	107	212.4	1.010*	PM	
Area Sample	Washroom (Cleaning Dust Collector) Total Dust	106	212	3.58	PM	Cleaning dust collector unit.
	Sample/Unit Dose Packaging Line Area sampling (On Packaging Machine)	419	850.6	0.039	TWA	Packaging Area
Machine operator (personal sample)	Sample/Unit Dose Packaging Line	412	824	0.013	TWA	Checks foil strips to make sure all the tablets are there. Makes sure they are properly labelled with name and code.
Assembly packer (personal sample)	Sample/Unit Dose Packaging Line	407	805.9	0.010	TWA	Takes strips of wrapped tablets off of conveyor and places them in small trays. Hands trays with about 8 strips to operator.
Assembly packer (personal sample)	Sample/Unit Dose Packaging Line	404	808	0.011	TWA	Also takes strips of tablets, places them in trays. Slides strips into boxes.
Area Sample	(Area Sample) on Guard's Desk in hallway	466	932	Negative		Guard station (located in hallway, guards the entrance to the manufacturing area.

TABLE 4
BERLEX SAMPLING DATE - JULY 5, 1983

Employee	Work Area	Sampling Time (minutes)	Total Volume (liters)	Concentration mg/m^3		Comments Work Activities
Area Sample	Primary Tablet and Capsule Trade Unit Packaging Line (Located behind and under feeding hopper)	233	466	0.021	TWA	The primary tablet and capsule trade unit packaging line contains a tablet and capsule filling room which is under negative pressure so that Quinaglute dust is confined in the room. Dust control includes a five horsepower dust collector unit and plexiglass shields.
Area Sample	Primary Tablet and Capsule Trade Unit Packaging Line (On top of filling machine)	232	464	0.005	TWA	
Machine operator (personal sample)	Primary Tablet and Capsule Trade Unit (One hour spent in filling room)	226	452	0.014	TWA	Monitors the flow of tablets into bottles. Periodically removes defective tablets from the machine. Rotates operation every hour.
Machine operator (personal sample)	Primary Tablet and Capsule Trade Unit Packaging Line (One hour spent in packaging room)	223	446	0.144	TWA	Same as above.
Sterile operator II (personal sample)	Primary Tablet and Capsule Trade Unit Packaging Line	217	434	0.005	TWA	Operates the capping machine. Periodically goes into tablet and capsule filling room to assist the flow of bottles.
Assembly packer (personal sample)	Primary Tablet and Capsule Trade Unit Packaging Line	216	432	0.003	TWA	Packs bottles into a box.

TABLE 5
BERLEX SAMPLING DATE- JULY 7, 1983

Employee	Work Area	Sampling Time (minutes)	Total Volume (liters)	Concentration mg/m^3		Comments Work Activities
Machine operator (personal sample)	Secondary Tablet and Capsule Trade Unit Packaging Line	371	742	1.239*	TWA	Spends 1/2 time at filling machine on secondary tablet and capsule trade unit packaging line adding tablets into rotating perforated disc. Spends other 1/2 time on labelling machine.
Packer (personal sample)	Secondary Tablet and Capsule Trade Unit Packaging Line	367	734	0.106	TWA	3 separate packaging stations. (1) Individual takes glass bottles to be filled, holds them over airjets. (2) After bottles are filled by filling machine, packer inserts cotton, puts caps on bottles. (3) Bottles are labeled and instructions are attached and bottles are boxed.
Packer (personal sample)	Secondary Tablet and Capsule Trade Unit Packaging Line	365	730	0.155	TWA	
Packer (personal sample)	Secondary Tablet and Capsule Trade Unit Packaging Line	361	722	0.083	TWA	All packers rotate from station to station on an hourly basis.
Material handler (personal sample)	Secondary Tablet and Capsule Trade Unit Packaging Line	363	726	0.035	TWA	Seals completed boxes. Brings in empty bottles and bins or drums of tablets. In general conveys materials to and from other employees.
Area Sample	Secondary Tablet and Capsule Trade Unit Packaging Line (Located on wall ledge about 6 feet high and 3 feet behind filling machine)	360	720	0.049	TWA	
Area Sample	Secondary Tablet and Capsule Trade Unit Packaging Line (Located on filling machine)	360	720	0.206	TWA	

TABLE 6
BERLEX SAMPLING DATE - JULY 27, 1983

Employee	Work Area	Sampling Time (minutes)	Total Volume (liters)	Concentration mg/m^3		Comments Work Activities
Chemical operator (personal sample)	Final Mix	242	484	0.283	AM	Adds immediate and time release sections of product and other necessary ingredients to blender; final mix is then blended. Lubricant is added to the blender via a mesh screen. Dust on the floor is swept and suctioned into the dust collector unit.
	Blender	113	226	0.398	PM	
		355	710	0.320	TWA	
Chemical operator (personal sample)	Final Mix	242	508.2	4.25	AM	
	Blender	113	237.3	2.53	PM	
	(Total Dust)	355	745.5	3.70	TWA (Total Dust)	
Chemical operator (personal sample)	Final Mix	240	482.4	0.394	AM	After the final mix is blended, the blend is removed from the mixer, placed in 55 gallon drums lined with polyethylene bags. Cloud of dust is generated when the drum is almost filled. A dust collection system is employed at this operation.
	Blender	109	219.1	0.493	PM	
		349	701.5	0.425	TWA	
Chemical operator (personal sample)	Final Mix	240	480	0.75	AM	
	Blender	109	218	4.31	PM	
	(Total Dust)	349	698	1.86	TWA (Total Dust)	
	Final Mix Blender Area Sample (Located on ventilation dust collector) (Total Dust)	227	454	0.53	(Total Dust)	
	Final Mix Blender	227	454	0.092	AM	
	Area Sample	102	204	0.063	PM	
	(Located on ventilation dust collector)	329	658	0.083	TWA	
Chemical operator (personal sample)	Preweigh	25	50	3.74*	TWA	Weigh specific amounts of quinidine gluconate into small barrels.