HETA 91-104-2229
JUNE 1992
FLORIDA HOSPITAL
ORLANDO, FLORIDA

NIOSH INVESTIGATORS:
John Decker, R.Ph., M.S.
Ruth A. Shults, R.N., M.P.H.

I. SUMMARY

In response to a Florida Hospital management request, representatives of the National Institute for Occupational Safety and Health (NIOSH) conducted an industrial hygiene and medical evaluation of health care workers' (HCWs) exposures to aerosolized ribavirin (AR). The evaluation was conducted during three visits to Florida Hospital: February 2-4, 1991, April 3-5, 1991, and October 18-20, 1991.

Ribavirin is a synthetic nucleoside that is used to treat severe respiratory syncytial virus (RSV) infections.[1] Ribavirin has been shown to be teratogenic and embryolethal several species.[2,3,4,5] However, no published studies have linked ribavirin to fetal abnormalities or fetal loss in humans.

Florida Hospital was utilizing an aerosol containment device on most, but not all administrations of AR. The use of personal protective equipment, including disposable respirators, was required by hospital policy and was practiced by most HCWs.

One hundred forty-eight urine samples from 44 HCWs were analyzed for ribavirin. Forty pairs of pre-workshift and post-workshift samples were statistically analyzed. Post-shift urinary ribavirin concentrations, equal to or above the limit of quantification of 0.01 micromoles of ribavirin per liter of urine (µmol/L), were found in 13 of 20 (65%) post-shift urine samples from nurses and in three of 20 (15%) samples from respiratory therapists (RTs). In previously published studies of occupational exposure, ribavirin has not been detected consistently in other body fluids of HCWs. Urinary ribavirin was detected in some HCWs despite the use of aerosol containment systems and implementation of a respiratory protection program.

Creatinine-corrected post-shift urinary ribavirin values ranged from <0.001 to 0.140 micromoles of ribavirin per gram of creatinine (µmol/g), with a mean of 0.017 µmol/g. The mean post-shift value for nurses was 0.030 µmol/g while the mean for RTs was 0.004 µmol/g.

Analysis of covariance was used to compare the mean post-shift urinary ribavirin value among nurses and RTs after adjusting for pre-shift urinary ribavirin values. Nurses had significantly higher post-shift urine values than RTs. The mean post-shift urinary ribavirin value, from all HCWs, was significantly lower on the October visit than on the February and April visits.

Forty-six full-shift and short-term personal air samples for AR were collected from nurses and RTs. Fifty area air samples were collected. Among nurses, full-shift personal samples ranged from 18.7 to 31.0 micrograms per cubic meter ($\mu g/m^3$) during administration with the Aerosol Delivery Hood® (ADH) alone, non-detected to 13.2 $\mu g/m^3$ for the ADH enclosed by the Demisitifer® scavenging tent, 12.0 to 28.2 $\mu g/m^3$ for the croup tent, and <3.3 - 4.8 $\mu g/m^3$ for the ventilator.

Analysis of Variance and Tukey's Honestly Significant Difference Test were used to compare the full-shift mean personal breathing zone (PBZ) concentrations among nurses. There were statistically significant differences in mean PBZ concentrations among the evaluated methods of ribavirin aerosol administration. The mean ribavirin concentration associated with administration through the ADH alone (24.9 $\mu g/m^3$) was significantly greater than the ADH/Demistifier® combination (6.4 $\mu g/m^3$) or the ventilator (4.3 $\mu g/m^3$). The mean concentration associated with the croup tent (22.9 $\mu g/m^3$) was also significantly greater than the ADH/Demistifier® combination or the ventilator.

Air Sampling results demonstrated that engineering controls and appropriate work practices can appreciably reduce health care workers exposures to aerosolized ribavirin. The finding of detectable concentrations of ribavirin in the urine demonstrate the need to use effective engineering controls and to strictly adhere to good work practices. Although more data is necessary, biological monitoring for ribavirin may be useful in assessing the overall effectiveness of control methods. Recommendations to minimize ribavirin exposures appear in Section IX of this report.

KEYWORDS: SIC 8062 (General Medical and Surgical Hospitals), ribavirin, Virazole®, 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboximide, aerosolized drugs, aerosolized pharmaceuticals, health care workers, aerosol containment system, urinary ribavirin.

II. INTRODUCTION

On February 2-4, 1991, April 3-5, 1991, and October 18-20, 1991, representatives of the National Institute for Occupational Safety and Health (NIOSH) visited Florida Hospital in response to a request by hospital management to evaluate employee exposures to aerosolized ribavirin (AR). The objectives of the NIOSH investigation were to characterize workers' exposure to aerosolized ribavirin and to evaluate engineering controls, work practices, and personal protective equipment.

Florida Hospital is an 801-bed medical center and teaching hospital. The investigation was conducted in the pediatric intensive care unit (PICU), where AR is administered to infants and children.

This final report includes information previously reported to Florida Hospital in letters dated May 16, 1991 and November 1, 1991, and an interim report dated January 1992. Participants in the biological monitoring were informed of their individual results via letter during May 1991 - June 1992.

III. BACKGROUND

The medical administration of pharmaceutical aerosols is rapidly expanding. Asthma, chronic obstructive pulmonary disease, and pulmonary infections are frequently treated with aerosols of sympathomimetics, beta-agonists, corticosteroids, and antimicrobials. The advantages to the patient include rapid onset of therapeutic action, optimized delivery of the drug to the site of action, and reduction in unwanted systemic side-effects. Aerosol delivery methods, however, can result in exposures to the health care worker (HCW). The difficulty in controlling the spread of aerosols, along with their small particle size, contributes to the risk of occupational exposure.

Much of the concern about occupational exposure to pharmaceutical aerosols has centered on the use of ribavirin. The adverse reproductive effects of ribavirin exposure in animal studies have raised concerns among HCWs who administer ribavirin, many of whom are in their reproductive years. However, no published studies have linked ribavirin to fetal abnormalities or fetal loss in humans.

In previous studies, ribavirin has not been consistently detected in body fluids of HCWs.[6,7,8] The lack of data demonstrating uptake of the drug following occupational exposure has raised questions as to the extent of the potential health risk posed by ribavirin.[9,10] Differing opinions regarding the need for ribavirin-exposed HCWs to wear personal protective equipment have been expressed in the scientific literature.[9,11] In its "Aerosol Consensus Statement-1991", the American Association for Respiratory Care recommended that HCWs wear full barrier protection including respirators.[11] In contrast, the American Academy of Pediatrics stated in its "Ribavirin Therapy for Respiratory Syncytial Virus" policy that the use of gloves and gowns is unnecessary, and "...the use of a mask designed to block absorption of particulate droplets with ribavirin might provide added protection."[9] No occupational exposure criteria for ribavirin have been published by the Occupational Safety and Health Administration (OSHA), NIOSH, or the American Conference of Governmental Industrial Hygienists (ACGIH).

A. *Uses of Ribavirin*

Ribavirin is a synthetic nucleoside that is licensed by the U.S. Food and Drug Administration (FDA) for the short-term treatment of severe respiratory syncytial virus (RSV) infections.[1] Its antiviral activity is thought to result from inhibition of RNA and DNA synthesis, which subsequently inhibits protein synthesis and viral replication.[12] Ribavirin has also been used to treat both influenza B pneumonia and RSV pneumonia in immunocompromised adults.[13,14] Clinical trials have studied the use of ribavirin in the treatment of influenza in otherwise healthy adults.[15,16]

Ribavirin is commercially available as a sterile, lyophilized powder, which is initially reconstituted by injecting additive-free sterile water into a vial containing six grams of ribavirin. The initial solution is transferred to a sterile wide-mouthed flask, which serves as the reservoir for the aerosol generator and is further diluted to a final volume of 300 milliliters (mL) [20 milligrams (mg) per mL].

Ribavirin aerosol is generated by a Small Particle Aerosol Generator® (Model SPAG-2® nebulizer) marketed by the drug manufacturer (ICN Pharmaceuticals, Inc, Costa Mesa, California). The SPAG-2® nebulizer delivers AR at a rate of approximately 14 liters per minute (L/min). According to the manufacturer, when the recommended starting solution of 20 milligrams of ribavirin per milliliter (mg/mL) sterile water is used, the average concentration of aerosol generated by the unit is expected to be 190 milligrams per cubic meter (mg/m^3).[17] The small particle size of the ribavirin aerosol (1.0-1.3 micrometer mass median aerodynamic diameter) permits deep penetration of the drug into the patient's lungs.[8]

The aerosol can be delivered to the patient by a variety of methods, including face mask, head hood (i.e. Aerosol Delivery Hood®), croup or mist tent, oxygen hood, or direct coupling to tracheostomy. During these applications, aerosol may escape into the environment and be inhaled by hospital staff caring for the patient or working nearby.

B. *Shift Assignments and Hospital Policies*

As the primary health care providers, nurses generally have the highest potential for exposure to AR. At Florida Hospital, the Pediatric Intensive Care Unit (PICU) nurses worked 12-hour shifts, while respiratory therapists (RTs) worked 8-hour shifts. Nurses cared for one or two patients receiving ribavirin, and they spent about 20 to 40 percent of the shift, or 2.5 to 5 hours, giving bedside care. When not providing care, they sat at a make-shift desk directly outside the patient's room. RTs were generally assigned to one patient receiving ribavirin, and they spent approximately 1 to 1.5 hours per shift in the patient's room. During the remainder of the shift, the RTs worked in other areas of the hospital.

Setting-up and dismantling the ribavirin delivery system was the responsibility of the RTs. This procedure entailed transferring the ribavirin solution to the SPAG-2® units's reservoir, securing the reservoir in the unit, turning on the unit, checking/adjusting the air flow settings to the manufacturer's specifications, and ensuring that the delivery equipment was secure and functioning properly. The child

was then placed into the administration device. AR was delivered from the SPAG-2® to the Aerosol Delivery Hood® (ADH) or tent through tubing.

Every three to five hours, the RTs checked the patient's vital signs, the solution volume, and nebulizer function. Bronchodilator medications were also administered at this time, if ordered by the physician. The RT visits usually lasted 15 to 45 minutes.

The hospital's written ribavirin policy stated that employees involved with ribavirin administration were required to wear isolation gowns, shoe covers, latex gloves, a cap, and 3M 9970® high efficiency particulate air (HEPA) disposable respirators (NIOSH/MSHA Approval number TC-21C-437, 3M Occupational Health and Environmental Safety Division, St. Paul, Minnesota), while in the treatment rooms. The hospital's written respirator policy met the requirements of the OSHA standard for respiratory protection (29 CFR 1910.134 and 30 CFR 11) and was implemented as stated in the policy.[18] Qualitative respirator fit testing was performed with saccharine. The hospital policy also stated that the aerosol generator (SPAG-2®) must be turned off at least five minutes before the administration hood or tent was opened.

C. *Administration Devices and Engineering Controls*

The hospital had recently implemented several engineering controls related to ribavirin administration. Newly constructed ventilation systems in ribavirin treatment rooms were designed to provide 22 air changes per hour while maintaining negative pressure with respect to the adjacent hallway. The return air was vented to the outside of the building.

The ADH, supplied by the drug manufacturer, is a rigid plastic shell that is set upon the bed. The child's head is then placed inside the hood. The unit is equipped with an evacuation system which is intended to remove ribavirin from the area where the child's body enters the hood. The supply of AR from the SPAG-2®, however, is not dependent on the operational status of the evacuation system.

A Demistifier® isolation tent (Peace Medical, Inc., Orange, New Jersey), which scavenges ribavirin aerosol escaping from the ADH, was being used on a trial basis by the hospital. During administration of ribavirin, the plastic isolation tent was placed over the ADH. Air within the tent was exhausted into the room after passing through a high-efficiency particulate air (HEPA) filter system (flow rate reportedly 150 cubic feet per minute).[19]

IV. EVALUATION CRITERIA

A. *Toxicology of Ribavirin*

In animal studies, ribavirin has been shown to be teratogenic and embryolethal in rats, mice, and hamsters, and embryolethal in rabbits.[2,3,4,5] One study which evaluated teratogenic effects in baboons did not show teratogenic effects.[20]

However, because of the small number of test animals, the study may not provide adequate evidence to evaluate reproductive outcome. Three studies in rats showed degenerative or histopathologic testicular effects. Eight other studies in rats, mice, dogs, and monkeys induced no testicular effects.[21] Ribavirin was found to be toxic to lactating animals and their offspring.[22]

Ribavirin has not been linked to fetal abnormalities in humans; however, given the wide spectrum of teratogenic potential in several animal species, avoidance of ribavirin prior to pregnancy, during pregnancy, and during lactation has been recommended.[22,23] At present, the potential reproductive health effects of occupational exposure to ribavirin are unknown.

Adverse effects occur infrequently in patients receiving AR; the more commonly reported effects include respiratory and cardiovascular disturbances, rash, and skin irritation.[22,24] Hemolytic anemia and suppression of erythropoiesis can occur when the drug is given orally or parenterally.[22]

Acute effects due to environmental exposure to ribavirin aerosol include rhinitis, headache and eye irritation.[22] The drug has been found to precipitate on contact lenses, causing eye irritation in employees wearing contact lenses.[22,25]

B. *Pharmacokinetics of Ribavirin*

Following inhalation, ribavirin is deposited in the respiratory tract. It is then redistributed from the respiratory tract into the circulation with eventual accumulation in erythrocytes. The extent of accumulation following inhalation has not been established, but following oral administration of a single dose of ribavirin, plasma and erythrocyte levels initially increased in parallel. Within two hours after administration, the plasma levels began to fall while erythrocyte levels continued to rise. Erythrocyte levels rose to a plateau at about four days and then declined with an apparent half-life of 40 days.[26]

Ribavirin is believed to be metabolized in the liver. The major route of elimination of ribavirin and its metabolites appears to be renal. In healthy adults with normal renal function, excretion of ribavirin administered orally indicates that approximately 53% of a single dose is excreted within 72-80 hours. An additional 15% is excreted in the feces.[22,23] No data are available regarding cutaneous or mucocutaneous absorption.

C. *Exposure Recommendations - Ribavirin*

No occupational exposure standard for ribavirin has been recommended by NIOSH, OSHA, or the ACGIH. The California Department of Health Services has suggested that an occupational exposure limit, based on a risk assessment model, can be calculated by applying a safety factor of 1000 to the no observed effect level (NOEL) in the most sensitive animal species.[27,28] Using the model, a limit of 2.7 $\mu g/m^3$ as an eight-hour time-weighted average (TWA) has been proposed by the California Department of Health Services. This calculation was based on a minute ventilation of 19 liters, an employee weight of 58 kilograms, and a pulmonary ribavirin retention

rate of 70%. The model was based on pharmacokinetic data collected after administration of therapeutic doses, which may not be a correspond to low-dose occupational exposure. Although NIOSH has not issued an official policy statement on the subject, there is concern that the existing animal data may be inadequate to establish a NOEL.

D. *Room Ventilation Recommendations*

The American Institute of Architects (AIA) Committee on Architecture for Health has published ventilation recommendations for hospitals. Isolation rooms are recommended to have a minimum of six total air changes per hour and should be under negative pressure. Regular patient rooms are required to have a minimum of two total air changes per hour.[29] These guidelines, however, do not address ventilation for rooms used to administer aerosolized pharmaceuticals.

V. METHODS

A. *Biological Monitoring Methodology*

1. Background

Previous studies of ribavirin exposure in HCWs have attempted to measure ribavirin and/or its metabolites in urine, plasma, and erythrocytes. Harrison et al. collected 30 urine, 30 erythrocyte, and 30 plasma samples from ten ribavirin-exposed HCWs.[6] Ribavirin was detected in only one erythrocyte sample (at a concentration of 0.44 µg/mL) collected from a nurse five days after exposure.
In a previous NIOSH study, ribavirin was measured in the urine of one of three ribavirin-exposed HCWs, but not in plasma or erythrocytes.[30] In this study, investigators decided to collect only urine from ribavirin-exposed HCWs. Based on the pharmacokinetics seen in clinical trials, NIOSH investigators chose to collect three urine specimens from each participant: prior to exposure (pre-shift), immediately following exposure (post-shift), and 24 to 48 hours post-exposure (next day).

Methods used for measuring ribavirin in biological samples in previous studies had limited ability to detect and quantify low concentrations of the drug due to interferences in the assay. In this study, a laboratory method that combines high pressure liquid chromatography (HPLC) and radioimmunoassay (RIA)[31] was used to measure ribavirin in urine. This was the first large-scale use of the new laboratory method.

As the primary health care providers, nurses generally have the highest potential for exposure to AR. In addition, PICU nurses at Florida Hospital routinely worked 12-hour shifts, while RTs worked 8-hour shifts. Based on the longer duration of exposure of nurses, NIOSH investigators hypothesized that nurses would have higher post-shift urine ribavirin levels than RTs.

2. Participants

NIOSH investigators requested that all ribavirin-exposed HCWs at Florida Hospital submit urine samples. HCWs received their patient assignments prior to being recruited for the study and without regard to their willingness to participate in the study. Each participant completed a brief questionnaire to document his or her job title, work area, and recent history of ribavirin exposure.

3. Sample Collection

In order to avoid contamination of urine with ribavirin from their hands, HCWs were instructed to wash their hands prior to contributing a urine specimen. Urine was collected in disposable paper cups and placed in a clean glass or plastic transport tubes without preservative. The samples were frozen and shipped by overnight express to the contract laboratory.

4. Laboratory Analytical Method

Two hundred microliter aliquots of urine were injected into the HPLC column to remove endogenous compounds that could cause interference during radioimmunoassay (RIA). The eluent containing ribavirin was then pipetted into RIA assay tubes, along with a known amount of tritium-labeled (radioactive) ribavirin, diluted rabbit antiribavirin serum, and buffer solutions.

During RIA, the tritium-labeled ribavirin competed with the ribavirin from the urine sample for a limited number of binding sites specific for ribavirin in the antiribavirin serum. The amount of ribavirin from samples and standards was then determined after separation of the bound and unbound tritiated ribavirin by liquid scintillation counting. A standard curve was prepared and the quantity of ribavirin in the samples was determined. The limit of quantification for the method is 0.01 micromole ribavirin per liter urine (μmol/L). This assay was developed in 1983[31] and has recently been combined with HPLC to increase the specificity of the method.

5. Creatinine Correction of Urine Samples

Twenty-four hour urine samples (all urine excreted over a 24-hour period) would generally provide the most accurate measurement of HCWs' excretion of ribavirin. However, because it was impractical to collect 24-hour urine samples, "spot" urine samples were used. To "standardize" the concentration of substances, (to make the results comparable from one time to another and from one person to another), it is common practice to correct the results for the dilution of the urine. Creatinine correction is the preferred standardization method for very concentrated and very dilute urine samples.[32,33] Creatinine is a normal metabolic product that is excreted by the kidney at a daily rate that is constant for an individual.

A creatinine-corrected urinary ribavirin result was obtained by dividing the urinary ribavirin value by the creatinine concentration. The creatinine-corrected urine ribavirin value (URV) was reported in micromoles of ribavirin per gram of creatinine (μmol/g).

6. Data Analysis

The "next day" urine samples were not statistically analyzed because over 50% of the participants did not provide a sample.

For statistical analyses, the creatinine-corrected urinary ribavirin values were used regardless whether the uncorrected value was above or below the LOQ. Using these data points as rough estimates of concentrations below the LOQ avoided the need to work with truncated distributions. Generally, methods become increasingly less precise at lower levels; the LOQ is a rough estimate of the region where the imprecision begins to increase more sharply.

Some of the HCWs had cared for patients who were receiving ribavirin therapy before the NIOSH team arrived to begin biological monitoring. Because some participants had prior exposure and others did not, it was necessary to control for the pre-shift urinary ribavirin levels. Analysis of covariance (ANCOVA) was used to test whether nurses had a higher mean post-shift urinary ribavirin value (URV) compared to RTs after adjusting for pre-shift levels. Logarithmic transformations of the post-shift URVs were used to obtain normality.

Linear regression was performed to test for an association between the results of full-shift personal breathing zone (PBZ) ribavirin air concentrations of nurses and their corresponding post-shift URVs, while controlling for visit number and pre-shift URVs. The logarithmic transformation of the PBZ levels and post-shift URVs were used to obtain normality.

B. *Air Sampling Methodology and Laboratory Analysis*

1. Background

NIOSH investigators collected personal breathing zone (PBZ) samples for ribavirin analysis from nurses and RTs who administered AR. Each patient had a private room. The monitoring was conducted in conjunction with four administration methods: (1) Aerosol Delivery Hood® (ADH) with ICN evacuation device in operation, (2) ADH and Pup® tent enclosed by the Demistifier® scavenging tent, (3) croup tent, and (4) direct coupling to a ventilator. The ICN scavenging system was not in operation when the Demistifier® was used. Ventilation measurements were made to characterize the effect of room ventilation on AR concentrations. A summary of the number and types of air samples is presented in Table 1.

2. Site Visit of February 2-4, 1991

During the February visit, three children received ribavirin for treatment of RSV infection. One child was treated with the ADH enclosed by the Demistifier® scavenging tent, the second was treated in a croup tent in which the ribavirin aerosol was supplied directly into the tent, and the third child was treated with the ADH alone.

The nurses' short-term PBZ samples were collected while full-shift sampling was in progress. Area air samples were collected within the treatment rooms and the nurses' station, which was located across the hall from the ribavirin patient rooms. Three bulk samples of ribavirin solution were collected from the SPAG-2® before administration for analysis.

3. Site Visit of April 3-5, 1991

During the April visit, three children were administered ribavirin; one via an ADH enclosed by a Demistifier® scavenging tent, and two via ventilators through tracheostomies. No scavenging devices, such as the Demistifier®, were used with the ventilator administration.

Five PBZ samples for AR were collected from three nurses and two RTs assigned to the infant receiving ribavirin aerosol in the ADH enclosed by the Demistifier® scavenging tent. Eleven area air samples were collected. Because of an equipment malfunction in the SPAG-2® which severely reduced the delivery of AR, the results of these air samples will not be reported; they are not included in Table 1. The measured concentrations inside the ADH were much less than the concentration recommended by the drug manufacturer. In addition, the volume of ribavirin solution was later found to be much less than recommended by the manufacturer.

Five sets of short-term samples were collected from within the ADH and the Demistifier® tent. These five sets of samples were collected on 37-millimeter glass fiber filters at a flow rate of 1.0 liters per minute (L/min) for ten minutes within the ADH and for 15 minutes within the Demistifier® tent.

4. Site Visit of October 18-20, 1991

During the October visit, three children were administered ribavirin. One was treated via an ADH enclosed by the Demistifier® scavenging tent. The second was treated within a Pup® tent (Peace Medical), in which the ribavirin aerosol was supplied directly into the tent (the Demistifier® scavenging tent was placed over the Pup® tent). The third patient was treated with an ADH equipped with the ICN evacuation device alone (no Demistifier®).

Three samples from inside the ADH, and two from inside the Demistifier® were collected at a flow rate of 1 L/min for 5 and 10 minutes, respectively.

5. Participants and Sample Types

Personal samples were collected in the workers' breathing zone. Full-shift samples were generally collected from nurses, who provided care continually throughout their shift. Short-term samples were generally collected from RTs, who provided care approximately four times per shift. Exposure monitoring was conducted only on employees.
In-mask sampling of the respirators was not conducted.

6. Air Sampling Methodology

Air sampling for AR was performed according to NIOSH method 5027, utilizing 37-millimeter (mm) diameter, 1.0 micrometer (µm) glass fiber filters.[34] AR was collected on the filters at a flow rate of 2.0 L/min for full-shift personal and area samples. A flow rate of 3.0 L/min was utilized for the short-term samples.

7. Laboratory Analysis

The glass fiber filters containing ribavirin were extracted with 3 mL sulfuric acid solution (pH = 2.5) in an ultrasonic bath and analyzed by high performance liquid chromatography (HPLC) using a cation exchange resin column. The HPLC was equipped with an ultraviolet detector set at 210 nanometers wavelength.

8. Statistical Analysis of Results

Analysis of Variance (ANOVA) was used to simultaneously compare the mean exposures resulting from administration by four different methods (ADH alone, ADH/Demistifier®, croup tent, ventilator). Full-shift PBZ concentrations of nurses working with the different administration methods were statistically compared. A statistical test similar to a pairwise t-test (Tukey's Honestly Significant Difference test[35]) was used to expand upon the ANOVA to determine where the differences among the administration methods lay.

C. *Ventilation Evaluation*

During all three NIOSH visits, smoke tubes were used to observe the direction of airflow between the treatment rooms and the adjacent hallway, to determine if ribavirin could potentially migrate out of the treatment rooms.

During the April 1991 visit, room ventilation flow rates were measured in the ADH/Demistifier® treatment room (#6322) using an Shortridge Instruments Airdata® flow meter (CFM-88, Series 8400). Four sets of measurements (supplies and exhausts) were made between 1305 hours on April 4 and 0650 hours on April 5, 1991. Measurements were recorded with the front door closed and the bathroom door open (usual position).

The patients receiving ribavirin by ventilator were not in the specially designed ribavirin treatment rooms. No measurements were made in these rooms.

During the last visit in October 1991, ventilation flow rates (supplies and exhausts) were measured again in each of the treatment rooms (rooms 6321, 6322, and 6330-PICU bed #7) with the same Shortridge Instruments AirData Flow Meter. Measurements were made with the front door closed and the bathroom door open.

VI. RESULTS and DISCUSSION

A. *Biological Monitoring Results*

1. Laboratory Method Ninety-four percent (44/47) of the eligible HCWs provided at least one urine sample; a total of 148 urine samples from ribavirin-exposed HCWs were analyzed for ribavirin and creatinine. Using data from laboratory control and replicate field samples, NIOSH chemists estimated the lowest value at which the amount of ribavirin in the urine could be accurately quantified, the limit of quantification (LOQ), to be 0.01 micromoles per liter of urine (μmol/L). At levels below the LOQ, the precision with which the laboratory method measures ribavirin is reduced. All of the urine ribavirin values were creatinine-corrected, and the corrected values were used in statistical analyses regardless whether the uncorrected value was above or below the LOQ.

2. Statistical Analysis Eight pairs of urine results (pre-shift and post-shift) from the April visit were excluded from statistical analysis because the SPAG-2® in the room in which the HCWs worked malfunctioned, delivering AR at well below the therapeutic dosage (see Section V, 3). None of the air samples taken in the room had detectable amounts of ribavirin.

   Some HCWs worked two shifts during one of the three-day sampling periods, and therefore they contributed two pairs of urine samples during one visit. Multiple pairs of results obtained from an individual during the same visit were not considered to be independent of each other. Only the first pair of urine results per HCW per visit was included in the statistical analysis.

   Two HCWs each contributed one set of samples during each of two visits, and a third HCW contributed one set of samples on each of the three visits. The effect of repeated samples was controlled for in the ANCOVA model.

   Two additional HCWs provided post-shift, but not pre-shift urines. Neither HCW had been exposed to ribavirin in the 14 days prior to the shift during which the sampling was conducted; therefore, each pre-shift ribavirin was assigned a value of "0.000" and resulting pairs were included in the analysis. A value of "0.000" was assigned because actual concentrations (whether above or below the LOQ) were used in the statistical analysis of the samples.

Following exclusions, 40 pairs of urine samples from 36 HCWs were available for statistical analysis (Table 2). The samples were collected from 19 RTs (12 male and 7 female) and 17 nurses (1 male and 16 female). Ages ranged from 22 years to 53 years, with a mean age of 39 years. Thirteen of the 20 (65%) post-shift urinary ribavirin levels from nurses, and three of 20 (15%) from RTs were at or above the limit of quantification (LOQ) of 0.01 µmol/L of urine.

The urinary ribavirin levels were then adjusted for creatinine to correct for the effect of urine concentration as described in the methods section. The creatinine-corrected urinary ribavirin values (URVs), reported in micromoles of ribavirin per gram of creatinine (µmol/g), ranged from <0.001 - 0.140 µmol/g, with a mean of 0.017 µmol/g and a standard deviation of 0.031 µmol/g over all three visits (Table 3). The mean post-shift value for nurses was 0.030 µmol/g with a standard deviation of 0.039 µmol/g, and the mean for RTs was 0.004 µmol/g with a standard deviation of 0.008 µmol/g. Figure 1 presents the creatinine-corrected post-shift URVs by visit number (visit one, two, or three) and job title (nurse or RT).

Initial analysis indicated no difference in post-shift URVs between male and female workers, after adjusting for differing pre-shift URV, visit number, and job title. Therefore, gender was omitted from the final ANCOVA model.

Independent variables in the final model included pre-shift URVs, visit number, and job title. Job title was significant ($p = 0.0006$, df = 1, 35), after adjusting for all the other variables, indicating that nurses indeed had a higher mean post-shift URV than RTs. Also, the mean post-shift URV (adjusted for pre-shift URVs) was significantly lower for the October visit than for the February ($p = 0.0032$, df = 1, 32), while the mean post-shift URV were not significantly lower for the April visit than for the February ($p = 0.2891$, df = 1, 32). The reduction of the post-shift URVs on the October visit may have may been due to the use of administration methods that lowered exposures and to improved work practices.

Time-weighted averages (TWAs) of full-shift PBZ air sampling and post-shift URVs were available for 11 nurses over 13 work shifts. Figure 2 is a plot of the logarithmic transformations of PBZ air levels (along the horizontal axis) and post-shift URVs (along the vertical axis). The URVs are negative because they are the logarithmic transformations of fractions. The six nurses sampled during the February visit worked with several types of administration units including the Demistifier®, croup tent, and the Aerosol Delivery Hood® (ADH) without the Demistifier®. All three nurses sampled during the April visit cared for patients who were on ventilators. Three of the four nurses sampled on visit three worked with the Demisifier®, and the remaining nurse worked with the ADH.

Linear regression was performed to test for an association between the PBZ ribavirin concentrations of nurses and their corresponding post-shift URVs, while controlling for the pre-shift URVs, and visit number. The logarithmic transformation of the post-shift URVs and the PBZs were used to obtain

normality. The analysis showed that, after adjusting for pre-shift URVs and visit number, no linear relationship was present between the nurses' PBZ ribavirin concentrations and their post-shift URVs ($p = 0.5409$, df = 1,8).

Several factors may have weakened the relationship between PBZ and urinary ribavirin levels. Five of the thirteen (38%) post-shift URVs included in the regression analysis had ribavirin levels below the LOQ of 0.01 µmol/L or urine; all five URVs were collected on the second and third visits. Three of the five URVs had corresponding PBZ air concentrations below the LOQ. As mentioned previously, the laboratory method used to measure ribavirin is less precise at levels below the limit of quantification. Therefore, it is probable that, due to the decreased accuracy of URVs and PBZ air levels at extremely low levels of exposure, reliable statistical analysis is not possible. It is also possible that there is no dose-response relationship between occupational exposure to AR and urinary ribavirin levels.

NIOSH investigators did not record whether respirators were used at all times by all study participants. Although most nurses consistently wore 3M 9970® respirators while NIOSH investigators were present, at least three nurses during visits one and two did not. One nurse reported that she sometimes needed to enter the patient's room immediately, and in such cases, she would not take the time to put on the respirator.

While the wearing of respirators did not affect the measured PBZ air concentrations (the samples were collected outside of the respirator), their use probably decreased the actual inhaled exposure and dose of ribavirin. The relationship between air concentrations and urinary ribavirin levels was probably weakened by the use of respirators, since the level of protection provided by respirators can vary significantly between individuals. In-mask sampling would be necessary to estimate each HCW's actual exposure to ribavirin. No in-mask air sampling was done in this study.

One of the nurses sampled on the third visit was caring for a patient when it was noticed that the tube that delivered AR to the patient was disconnected, causing AR to be released into the treatment room. The nurse reconnected the tube as soon as it was noticed, and she did not know how long it had been disconnected. The nurse wore a respirator each time she entered the room. Although her PBZ ribavirin concentration was equivalent to concentrations measured on visit one, her post-shift URV was less than those seen on visit one (Figure 2). The proper wearing of a respirator may explain why the nurse absorbed less ribavirin than other nurses who were exposed to similar concentrations of AR.

Prior to the third NIOSH visit in October 1991, several events occurred which NIOSH investigators believe may have contributed to the decline in ribavirin air levels and URVs among HCWs. The hospital had recently discontinued the practice of staffing the PICU with nurses from contract agency. (During the February visit, two of the contract nurses had expressed to a NIOSH investigator that they did not plan to conceive, so they did not see the need in

wearing respirators to protect against ribavirin exposure.) Some of the staff nurses had expressed a desire not to care for patients receiving ribavirin, citing concern about possible birth defects. Staff meetings were being held to address these issues and to update the medical and nursing staff on hospital policy for caring for patients with respiratory syncytial virus. NIOSH investigators believe that the climate of heightened awareness concerning ribavirin may well have influenced HCWs, thereby improving their work practices and resulted in reducing ribavirin exposure.

B. *Personal Air Sampling Results - All Visits*

Table 4 summarizes all the personal air monitoring results. Since most of the employees wore NIOSH/MSHA approved 3M 9970® HEPA disposable respirators while working in the treatment rooms, the actual exposures were presumably less than the PBZ concentrations that are reported. Tables 5 and 6 present a detailed list of personal full-shift and short-term sample results.

The reported limits of detection were 0.3, 2.0, and 1.0 µg/sample for the February, April, and October visits, respectively. The reported limits of quantitation were 0.8, 4.0, and 3.1 µg/sample, for the February, April, and October visits, respectively.

1. Comparison of Different Methods of Administration

Figure 3 presents the full-shift, time-weighted averages of personal breathing zone concentrations among nurses who administered ribavirin by different methods. The use of the scavenging tent, which enclosed the ADH, lowered PBZ exposures for both nurses and RTs. The mean (arithmetic mean of the TWAs), full-shift, time-weighted average breathing zone concentration for nurses was 6.4 $\mu g/m^3$ (range: non-detected - 13.2 $\mu g/m^3$) with the use of the scavenging tent, verses 24.9 $\mu g/m^3$ (18.7 - 31.0 $\mu g/m^3$) without the scavenging tent. The ribavirin concentrations in the full-shift RT sample was below the limit of detection (LOD) with the scavenging tent, versus 5.9 $\mu g/m^3$ without the scavenging tent. The croup tent administration resulted in a full-shift mean breathing zone concentration of 22.9 $\mu g/m^3$ (12.0 - 28.2 $\mu g/m^3$). Comparatively low exposures (full-shift mean of 4.3 $\mu g/m^3$ for nurses) occurred with the ventilator administration. None of the three short-term air samples from the respiratory therapists had detectable ribavirin. This finding was not unexpected, since the pediatric ventilator was essentially a closed system with a filter on the exhalation circuit.

2. Statistical Analysis of Different Administration Methods

Analysis of Variance (ANOVA) was used to simultaneously compare mean AR exposures of the different administration methods (ADH, ADH/Demistifier®, croup tent, and ventilator). Full-shift personal breathing (PBZ) zone concentrations among nurses were statistically compared. The overall ANOVA was significant ($F = 10.09$, $p = 0.0017$, $df = 3,11$). For the purpose of statistical data analysis, values below the LOD were assigned the LOD value divided by the square root of two.

Tukey's Honestly Significant Difference test (similar to a pairwise t-test) was used to expand on the ANOVA results. The test was used to determine where the differences ($\alpha = 0.05$, df = 11) in AR exposures among the administration methods lay. Administration with the ADH alone resulted in statistically significant greater exposures than the ADH/Demistifier® combination. The croup tent and ADH resulted in exposures that were significantly greater than the ventilator administration. The croup tent was significantly greater than the ADH/Demistifier®. All other pair-wise comparisons (ADH vs. croup tent, etc.) were not statistically significant.

3. Discussion of Highest and Lowest Exposures

The highest full-shift personal exposure (78.0 $\mu g/m^3$) was collected from a nurse caring for two children, one child treated with the ADH alone and one in the ADH enclosed by the Demistifier® scavenging tent. The nurse did not always turn the aerosol generator off five minutes before opening the administration device. The highest short-term exposures (Table 6 - means of 58.1 and 77.0 $\mu g/m^3$) occurred with the croup tent, which was reasonable to expect since a substantial amount of ribavirin remained inside the relatively large tent when it was opened by the HCW.

Short-term samples collected from one RT while using the ADH alone had ribavirin concentrations below the limit of quantitation (LOQ) (<12.1 $\mu g/m^3$). The RT routinely turned off the aerosol generator and left the room for 10 to 15 minutes before starting his work. During this interim period, a large percentage of AR was probably removed by the room ventilation system (all air in treatment room was exhausted directly to the outside). The ventilation system provided a measured 18-19 air changes per hour (ACH). Approximately seven minutes are required for 90% removal efficiency of airborne contaminant, assuming 19 air changes per hour and perfect mixing.[36] In addition to the flushing effect of the ventilation system, the level of ribavirin exposure is probably related to the proximity of the employee to the administration hood during the shut-off period before the hood is opened.

C. *Area Air Sampling Results*

1. Site Visit of February 2-4, 1991

Table 7 lists the results of area air samples within the treatment rooms and the nurses' station. Measurable levels of ribavirin (average: 9.7 $\mu g/m^3$) were found at the nurses' station, indicating that the level of negative pressure within the treatment rooms relative to the hallway was insufficient. Smoke tube tests also indicated that the pressure in the treatment rooms was neutral or under marginally negative pressure. AR was not transmitted to the nurses' station through the ventilation system since the air in the treatment rooms was exhausted directly to the outside.

An area air sampler was placed on each side of the croup and the Demistifier® tents. As expected, the average ribavirin concentrations were highest on the

side of the tent that was opened when the children required attention. Full-shift, time weighted averages (concentrations computed over the actual sample period) on either side of the croup tent were 54.0 and 40.0 $\mu g/m^3$; for the Demistifier®, the values were 17.0 and 9.8 $\mu g/m^3$. Area air concentrations of ribavirin were generally lower for the Demistifier® than for the croup tent. In all but one measurement, area air concentrations at the sides of the Demistifier® tent were lower than with the ADH alone.

Two bulk samples of ribavirin solution, collected before placement into the SPAG-2® unit, were analyzed to determine the ribavirin concentration. The sample taken from room 6322 contained 20 milligrams per milliliter (mg/mL). The sample taken from room 6321 was damaged during shipment. A sample collected from the SPAG-2® in room 6322 at the end of the shift contained 32 mg/mL. The mechanism is probably the dilution air blowing continuously through the reservoir, and causing evaporation of water.[8]

Ventilation Observations Rooms 6320 and 6322 were marginally negative with respect to the adjacent hallway (air was moving into treatment room). Room 6321 was under weakly positive pressure with respect to the hallway (air movement out of the treatment room). All supply and return vents were functioning.

2. Site Visit of April 3-5, 1991

Ribavirin concentrations of all PBZ and area samples collected in association with the child receiving ribavirin aerosol in the ADH enclosed with the Demistifier® were below the LOD.

Short-term air sampling for ribavirin was conducted inside the ADH to determine if there was a relationship between occupational exposures and hood concentrations. The results of five 5-minute samples inside the ICN hood ranged from 4.9 to 25 mg/m^3, well under the concentration of 190 mg/m^3 recommended by the manufacturer. The amount of ribavirin solution used in the aerosol generator was later found to be much less than expected, according to a telephone conversation in May 1991 with the Director of Respiratory Care. The PBZ and area air samples had non-detectable levels of ribavirin and probably were not representative of typical air concentrations.

Administration of ribavirin to a patient through a Bear Cub® ventilator was also conducted during the April visit. A scavenging unit was not used during this administration. The results of area air samples in the treatment room ranged from non-detected to 12.9 $\mu g/m^3$. Concentrations at the nurses' station were non-detected to <2.4 $\mu g/m^3$. Specific results can be found in Table 8.

Ventilation Observations Measurements were made in the treatment room with the Demistifier® (room 6322). Using an estimated room volume of 1330 cubic feet, room air changes per hour (ACH) were calculated using the exhaust measurements for the room. The room air was reportedly exhausted to the outside. The results, which ranged from 18-19 ACH, were in excess of the

minimum rates (6 ACH) recommended by the AIA. The results of ventilation measurements can be found in Table 9. Smoke tube tests indicated that room 6322 was under negative pressure with respect to the adjacent hallway.

Smoke tube tests indicated that the rooms used for the ventilator patients (PICU #3 and #6) were under very slight negative pressure. The patients receiving ribavirin by ventilator were not in the specially designed ribavirin treatment rooms. Room ventilation flow rates were not measured in these rooms, since the location and design of the return and supply diffusers did not permit the use of air flow measurement equipment.

3. Site Visit of October 18-20, 1991

Some samples collected inside the ADH were less than the expected concentration of 190 mg/m^3, specified by the drug manufacturer.[37] Five-minute sample results ranged from 30 to 78 mg/m^3 ribavirin with the nebulizer air flow set at 7 L/min (see Table 8). However, the amount of ribavirin solution used by the SPAG-2® was within the expected range. Other investigators have found that AR concentrations within the administration hood vary as a function of time and nebulizer air flow.[8] AR concentrations within the treatment hood might also vary depending on the sampling methodology and location within the administration hood. Two samples collected from inside the Demistifier® unit had ribavirin concentrations of 1.5 mg/m^3 (1500 $\mu g/m^3$) and 2.4 mg/m^3 (2400 $\mu g/m^3$).

Ventilation Observations Ventilation flow rates were measured in each of the treatment rooms (6321, 6322, and 6330-PICU bed #7). Measurements were recorded with the front door closed and the bathroom door open. Table 9 lists the results, which ranged from 18 to 22 ACH in rooms 6321 and 6322 and 10-11 ACH in room 6330 (PICU #7). The room ventilation rates were well in excess of the minimum rate (6 ACH) recommended by the American Institute of Architects (AIA) for isolation rooms.[34] Using tissue paper to visually observe the air flow direction at the doorway, it was observed that all of the treatment rooms were under negative pressure at the doorway.

D. *Study Limitations*

NIOSH investigators requested that work practices remain as usual during each site visit. While this policy increases the comparability of the results, the differing shift durations, ribavirin exposure in the days immediately prior to the start of the study, and working more than one shift during the study period by some HCWs may have weaken the association between exposure and excretion of ribavirin, thereby placing limitations on the interpretation the biological monitoring data.

Most employees wore high efficiency disposable respirators during the NIOSH visits, but a few HCWs were observed wearing surgical masks instead of respirators while in patients' rooms. NIOSH investigators did not record whether respirators were used at all times by all study participants; therefore the effect of wearing a respirator on URVs could not be evaluated.

While the use of respirators did not affect the personal breathing zone air concentrations, their use presumably decreased urinary ribavirin levels by decreasing the actual exposure and inhaled dose. Since the same type of respirator worn by different individuals will usually result in various levels of protection, the use of respirators presumably weakened the PBZ-URV relationship. In addition, the level of protection afforded by surgical masks against ribavirin was unknown (probably inferior); therefore, the effect of surgical masks on exposure and urinary ribavirin concentrations was also unknown.

HCWs did not change clothes prior to providing post-shift urine samples, so contamination from their uniforms could have occurred. However, HCWs wore isolation gowns over their uniforms while in patients' rooms, so the potential for contamination of urine from ribavirin on the uniform was presumably reduced.

Twenty-four of the 40 (60%) post-shift urinary ribavirin levels, prior to creatinine-correction, were less than the LOQ of 0.01 µmol/L urine. The laboratory method used to measure ribavirin is less precise at levels below the limit of quantification. Therefore, the use of these values in the data analysis weakened any possible PBZ-URV relationship.

The findings of this study may not be generalizable to other hospitals. The above average levels of room ventilation in most of the treatment rooms at Florida Hospital probably lowered ribavirin air concentrations significantly. In hospitals that do not have ribavirin treatment rooms with ventilation rates comparable to Florida Hospital, it is likely that ribavirin usage using similar administration equipment will result in higher AR exposures than those measured at Florida Hospital.

VII. CONCLUSIONS

In previously published studies, ribavirin has not been consistently detected in body fluids of HCWs.[6,7,8] During this NIOSH evaluation, a laboratory method for quantifying ribavirin in biological samples, developed at the University of California, San Diego, Antivirals Assay Laboratory, was used. Post-shift urinary ribavirin concentrations prior to creatinine correction, equal to or above the limit of quantification of 0.01 µmol/L of urine, were found in 13 of 20 (65%) post-shift urine samples from nurses and in three of 20 (15%) of the samples from RTs.

The mean post-shift urinary ribavirin value, adjusted for pre-shift urinary ribavirin values, from all visits combined, was significantly higher in nurses than in respiratory therapists. The mean post-shift urinary ribavirin value, from all HCWs, was significantly lower on the October visit than on the February and April visits. NIOSH investigators believe that the HCWs' heightened awareness of the potential health effects of ribavirin may have positively influenced the use of engineering controls and work practices to reduce stray aerosol emissions. The study results suggest that, when controls and work practices are consistently applied, HCWs' exposure to aerosolized ribavirin can be reduced appreciably.

Although patient-care considerations typically determine the route of ribavirin administration, hospital staff should be aware that in this study, PBZ exposures were greatest when ribavirin was administered by croup tent or ADH, and least with the ventilator or ADH/Demistifier® combination.

Variables that can affect HCWs' exposure to AR include the method of administration, use of scavenging devices, and implementation of certain work practices, such as turning off the aerosol generator before opening the administration device. Other factors that may affect exposure but were not fully evaluated include the concentration of AR produced by the aerosol generator, room ventilation rates, and effectiveness of the respirators.

Environmental concentrations of AR at Florida Hospital were generally lower than concentrations measured during other NIOSH investigations[38,39,40] and published studies of ribavirin exposure.[6,7,8] NIOSH investigators believe that the use of engineering controls and appropriate work practices contributed to the lower observed concentrations in this study. Further biological monitoring of workers exposed to differing concentrations of AR is necessary to more fully evaluate relationship between occupational exposure and urinary ribavirin concentrations.

During the investigation, Florida Hospital was utilizing engineering controls to reduce ribavirin exposure among HCWs. Work practice policies, including turning off the aerosol generator prior to providing care to the patient and permitting alternative job assignments for individuals who were actively trying to conceive or who were lactating, were practiced with some inconsistency. The use of personal protective equipment, including disposable respirators, was required by hospital policy and was practiced by most HCWs.

VIII. RECOMMENDATIONS

The following recommendations are offered to minimize exposure of HCWs and other individuals who may enter rooms where ribavirin is administered.

1. Training programs should be developed to educate health care workers about potential risks of ribavirin exposure. Education should not be limited to direct care personnel, but should include ancillary personnel such as phlebotomists, housekeepers, maintenance staff, and others who enter the room during treatment or must clean contaminated rooms, waste, and bedding. The staff should be educated to recognize situations that could result in increased occupational exposure. Female HCWs who are pregnant, lactating, or who may become pregnant, and male HCWs whose sexual partner is not actively avoiding pregnancy should be counseled about risk reduction strategies, such as alternate job assignments. Family members and visitors, who may stay in the room for long periods of time during treatment, should be notified of potential health effects to ribavirin.

2. Various ribavirin administration and scavenging systems result in different levels of environmental contamination. All administration systems should include a mechanism to reduce environmental exposures to ribavirin. It is the responsibility of hospital management to implement more effective control measures as they become

available. Administration and scavenging equipment should be inspected by respiratory therapy staff on a regular basis.

3. Rooms where ribavirin is administered should conform to the American Institute of Architects recommendations for isolation rooms.[29] Rooms should provide a minimum of six total air changes per hour, and should be under negative pressure. Room air should be exhausted to the outside rather than recirculated to other areas of the hospital. At Florida Hospital the air from the specially designed isolation rooms is reportedly exhausted to the outside.

4. Air pressure in the ribavirin treatment rooms should be evaluated before therapy begins and daily thereafter. Ideally, ribavirin treatment should begin only if room air pressure is negative with respect to the hallway. This can be accomplished by observing the direction of airflow at the doorway by holding a piece of tissue paper at the cracked doorway.

5. The aerosol generator should be turned off for a minimum of five minutes prior to the HCW entering the room to provide routine care (unless urgent or emergent problems require immediate access to the patient). This could be accomplished by placement of a remote switch outside the room.

6. During aerosol therapy, ribavirin precipitate is deposited on the patient and on the surrounding area. To prevent the dust from becoming airborne, care should be taken when ribavirin-contaminated clothing, bedding, or equipment is handled.[41] Although dermal absorption is not thought to be significant, dermal exposure should be avoided to prevent unintentional oral ingestion or ocular contact. The use of personal protective equipment, including gloves, gowns, and air-tight goggles should be considered.

7. Ribavirin has been found to deposit on contact lenses,[25] so HCWs should be discouraged from wearing lenses when working with ribavirin. If contacts are worn, air-tight goggles should be used.[22]

8. Individual hospitals may choose to use respirators to further reduce HCW exposure to ribavirin. NIOSH/MSHA-approved high efficiency particulate half-mask respirators, assigned to HCWs based on the results of quantitative fit tests, were found by in-mask sampling to reduce exposure to aerosolized ribavirin to the analytical limit of detection.[38] OSHA standard (29 CFR 1910.134) requires that all occupational respirator use must take place within the context of a respiratory protection program that includes evaluation of worker fitness to use a respirator, training, fit testing, and maintenance. Surgical masks should not be relied upon to provide personal protection from occupational exposure to ribavirin.[42]

   Disposable respirators, such as the 3M 9970® respirator, have an assigned protection factor of five (See Appendix A).[43] The assigned protection factor is the minimum anticipated protection provided by a properly functioning respirator to a given percentage of properly fit-tested and trained users. A respirator with an assigned protection factor of five will presumably reduce the exposure for most wearers five-fold. Florida Hospital's respiratory protection policy specifies a qualitative

saccharine fit-test; therefore, the assigned protection factor for respirators when used in conjunction with this type of fit-testing is five. However, it should be noted that a substantial percentage of persons using a particular type of respirator may not achieve an adequate face to faceseal fit.[38] On the other hand, a portion of workers using a particular type of respirator will achieve a superior faceseal fit, resulting in actual worker protection factors greater than five.

9. In order to help reduce exposure of HCWs to ribavirin, medically unnecessary use of it should be avoided. Accordingly, medical staff should remain mindful of the American Academy of Pediatrics recommendations and other current knowledge regarding ribavirin therapy.[9]

IX. REFERENCES

1. Food and Drug Administration [1986]. Ribavirin aerosol approved for severe cases of RSV in infants and young children. FDA Drug Bulletin 16(1):7.

2. Kilham L, Ferm V [1977]. Congenital abnormalities induced in hamster embryos with ribavirin. Science 195:413-4.

3. Hillyard I [1980]. The preclinical toxicology and safety of ribavirin. In: Smith RA, Kirkpatrick W, eds. Ribavirin: a broad spectrum antiviral agent. New York: Academic Press, pp 59-71.

4. Ferm V, Willhite C, Kilham L [1978]. Teratogenic effects of ribavirin on hamster and rat embryos. Teratology 17:93-102.

5. Kochhar D, Penner J, Knudsen T [1980]. Embryotoxic, teratogenic, and metabolic effects of ribavirin in mice. Teratology and Applied Pharmacology 52:99-112.

6. CDC [1988]. Assessing exposures of health-care personnel to aerosols of ribavirin-California. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control. MMWR 37(36):560-563.

7. Bradley J, Connor J, Compogiannis L, Eiger L [1990]. Exposure of health care workers to ribavirin during therapy for respiratory syncytial virus infections. Antimicrob Agents Chemother 34(4):668-670.

8. Arnold S, Buchan R [1991]. Exposure to ribavirin aerosol. Appl Occup Environ Hyg 6(4):271-279.

9. American Academy of Pediatrics [1991]. Ribavirin therapy of respiratory syncytial virus. In: Committee on Infectious Diseases, American Academy of Pediatrics. Report of the Committee on Infectious Diseases. Elk Grove, IL: American Academy of Pediatrics, pp. 581-587.

10. Infectious Diseases and Immunization Committee, Canadian Paediatric Society [1991]. Ribavirin: is there a risk to hospital personnel? Can Med Assoc J 144(3):285,286.

11. American Association for Respiratory Care [1991]. Aerosol Consensus Statement-1991. Respiratory Care 36(9):916-921.

12. Smith R [1984]. Background and mechanisms of ribavirin action. In Smith R, Knight V, Smith J, eds. Clinical applications of ribavirin. Orlando, FL: Academic Press, pp 1-18.

13. Bell M, Hunter J, Mostafa S [1988]. Nebulized ribavirin for influenza B Viral pneumonia in a ventilated immunocompromised adult. Lancet 2: 1084-1085.

Nov 5, 1988.

14. Murphy D, Rose C [1989]. Respiratory syncytial virus pneumonia in human immunodeficiency virus-infected man (letter). JAMA 261:1147.

15. Smith C, Fox J [1980]. Double-blind evaluation of ribavirin in naturally occurring influenza. In Smith R, Kirkpatrick W, eds. Ribavirin: a broad spectrum antiviral agent. New York: Academic Press, pp 147-164.

16. Gilbert B, Wilson S, Knight V, et.al. [1984]. Ribavirin small particle aerosol treatment of influenza in college students 1981-1983. In: Smith R, Knight V, Smith J, eds. Clinical applications of ribavirin. Orlando, FL: Academic Press, pp. 125-143.

17. ICN Pharmaceuticals, Inc. [1987]. Small particle aerosol generator model SPAG-2 6000 series instructions for use. Costa Mesa, California: ICN Pharmaceuticals, Inc. Operators Manual Part No. 9018.

18. Code of Federal Regulations. 29 CFR 1910.134 (Respiratory protection). Washington, DC: U.S. Government Printing Office, Federal Register.

19. Peace Medical [1990]. Demistifier® isolation chamber manufacturer's literature. Peace Medical Company, Orange, New Jersey.

20. Gallagher R, Givan N, Hazelden K, McGregor D, Ridgway P, de S. Wickramaratne G [March 1977]. Teratogenicity testing in baboons of virazole. Unpublished report from ICN Pharmaceuticals.

21. Marks M [1990]. Adverse drug reactions: United States experience II. Pediatr Infect Dis J 9:(suppl):S117-S118.

22. American Hospital Formulary Service [1990]. AHFS Drug Information. Bethesda, MD: American Society of Hospital Pharmacists, Inc., pp 372-379.

23. Waskin H [1991]. Toxicology of antimicrobial aerosols: A review of aerosolized ribavirin and pentamidine. Respir Care 36:1026-1036.

24. Janai H [1990]. Adverse drug reactions: United States experience I. Pediatr Infect Dis J 9:(Suppl):S115-S116.

25. Diamond S, Dupuis L[1989]. Contact lens damage due to ribavirin exposure (letter). Drug Intell Clin Pharm 23:428-429.

26. Catlin D, Smith R, Samuels A [1980]. ^{14}C-ribavirin: distribution and pharmacokinetics studies in rats, baboons, and man. In: Smith R,Kirkpatrick W, eds. Ribavirin: a broad spectrum antiviral agent. New York: Academic Press, pp 83-98.

27. California Department of Health Services [1988]. Health care worker exposure to ribavirin aerosol: field investigation FI-86-009. Berkeley, CA: California Department of Health Services, Occupational Health Surveillance and Evaluation Program.

28. Federal Register [1986]. Environmental Protection Agency guidelines for the health assessment of suspected developmental toxicants. Washington DC: U.S. Government Printing Office. Federal Register 51(185):34028-34040.

29. American Institute of Architects [1987]. Guidelines for construction and equipment of hospital and medical facilities. Washington DC: The American Institute of Architects Press.

30. Deitchman S [1990]. Letter of April 6, 1990, to Michael Brady, Columbus Children's Hospital, Columbus, OH. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Hazard Evaluation and Technical Assistance Branch. HETA 89-145.

31. Austin RK, Trefts PE, Hintz, Connor JD, Kagnoff MF [1983]. Sensitive radioimmunoassay for the broad-spectrum antiviral agent ribavirin. Antimicrob. Agents Chemother. 24(5):696-701.

32. Elkins H, Pagnotto L, Smith H [1974]. Concentration adjustments in urinalysis. Am Ind Hyg Assoc J 35:559-565.

33. Lauwerys R [1983]. Industrial chemical exposure: guidelines for biological monitoring. Davis, CA: Biomedical Publications, pp 6-7.

34. NIOSH [1984]. Ribavirin: Method 5027 (issued 5/15/89). In: Eller P, ed. NIOSH Manual of Analytical Methods, 3rd ed. Cincinnati, OH: U.S. Department of Health and Human Services. Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication No. 84-100.

35. Neter WW, Wasserman W, Kutner M [1990]. Applied Linear Statistical Models, 3rd ed. Homewood, IL: Irwin Publishers, pp 580-581.

36. CDC [1990]. Guidelines for preventing the transmission of tuberculosis in health-care settings, with special focus on HIV-related issues. MMWR 39 No. RR-17.

37. Schumacher M, Dowd A, eds. [1992]. 1992 Physicians Desk Reference. Montvale, New Jersey: Medical Economics Data.

38. NIOSH [1991]. Health Hazard Evaluation Report: Wichita, KS. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. NIOSH Report No. HETA 90-155-2169, NTIS No. PB-92-164-227.

39. Boiano, J [1988]. Letter of November 21, 1988, to Patricia Branson, Children's Hospital Medical Center, Cincinnati, OH. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Hazard Evaluation and Technical Assistance Branch. HETA 88-120.

40. Bryant, C [1990]. Letter of April 19, 1990, to Michael Mihailoff, Milton S. Hershey Medical Center, Hershey, PA. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. Hazard Evaluation and Technical Assistance Branch. HETA 89-099.

41. Prows CA [1989]. Ribavirin's risk in reproduction-how great are they? Matern Child Nurs J 14:400-404.

42. Tuomi T [1985]. Face seal leakage of half masks and surgical masks. Am Ind Hyg Assoc J 46:308-12.

43. NIOSH [1987]. NIOSH respirator decision logic. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication No. 87-108.

X. AUTHORSHIP AND ACKNOWLEDGEMENTS

Report Prepared by:	John Decker, R.Ph., M.S. Industrial Hygienist Industrial Hygiene Section
	Ruth A. Shults, R.N., M.P.H. Health Officer Medical Section
Statistician:	Deanna K. Wild, M.S, M.B.A. Statistician (Health) Support Services Branch Statistical Services Section
Chemist:	Alexander W. Teass, Ph.D. Section Chief Applied Biology Branch Analytical Toxicology Section Division of Biomedical and Behavior Science
Urine Protocol Author:	Scott D. Deitchman, M.D., M.P.H. Medical Officer Medical Section
Originating Office:	Hazard Evaluations and Technical Assistance Branch Division of Surveillance, Hazard Evaluations and Field Studies
Air Sample Analysis:	DataChem Laboratories, Inc. 960 Levoy Drive Salt Lake City, Utah 84123
Urine Sample Analysis:	James Connor, M.D. University of California, San Diego Department of Pediatrics, 0609-E Antivirals Assay Laboratory 9500 Gilman Drive La Jolla, California 92093

XI. DISTRIBUTION AND AVAILABILITY OF REPORT

Copies of this report may be freely reproduced and are not copyrighted. Single copies of this report will be available for a period of 90 days after the date of this report from the NIOSH Publications Office, 4676 Columbia Parkway, Cincinnati, OH 45226. To

expedite your request, include a self-addressed mailing label along with your written request. After this time, copies may be purchased from the National Technical Information Service, 5285 Port Royal Road, Springfield, VA 22161.

Information regarding the NTIS stock number may be obtained from the NIOSH Publications Office at the Cincinnati address. Copies of this report have been sent to:

1. Florida Hospital
2. Employee representatives
3. OSHA, Region IV
4. Public Health Service, NIOSH Region IV
5. Food and Drug Administration
6. United States Pharmacopeia/The National Formulary (USP/NF)

For the purpose of informing affected employees, copies of this report shall be posted by the employer in a prominent place accessible to the employees for a period of 30 calendar days.

Table 1
Air Sampling Summary
Florida Hospital
Orlando, Florida
HETA 91-104

	February 2-4, 1991	April 3-5, 1991	October 18-20, 1991
Patients			
Administration Unit			
Number of Personal Full-shift Air Samples			
Number of Personal Short-term Air Samples			
Number of Area Air Samples			

1 Due to an equipment malfunction that severely reduced the amount of ribavirin provided to the patient, all the samples collected from nurses and RTs were below the limit of detection. The values in this column reflect only administration of ribavirin by ventilation.

Table 2
Biological Sampling Summary
Florida Hospital
Orlando, Florida
HETA 91-104

	February 2-4, 1991	April 3-5, 1991	October 18-20, 1991
Patients	3 infants	1 infant 2 older children	2 infants 1 older child
Administration Unit	Croup tent ADH alone ADH/Demistifier	ADH/Demistifier Ventilator	ADH/Demistifier Pup/Demistifier ADH alone
Urine Sample Sets Statistically Analyzed[1]	12	7	21
Nurses (#female)	7 (7 F)	4 (4 F)	9 (8 F)
RTs[2] (# female)	5 (0 F)	3 (1 F)	12 (6 F)

[1]Sample set = pre-shift and post-shift
[2]Respiratory therapists

Table 3
Mean Post-shift Urinary Ribavirin Values
Nurses and Respiratory Therapists n=40
Florida Hospital
Orlando, Florida
HETA 91-104

Mean Post-shift Urinary Ribavirn Values

Job Title	Combined (μmol/g)[1] n=40	Visit 1 (μmol/g) n=12	Visit 2 (μmol/g) n=7	Visit 3 (μmol/g) n=21
Nurses	0.030 (0.039)[2]	0.070 (0.045)[2]	0.007 (0.004)[2]	0.009 (0.005)[2]
RT[3]	0.004 (0.008)	0.005 (0.003)	0.014 (0.019)	0.002 (0.002)
Total	0.017 (0.031)	0.042 (0.047)	0.009 (0.012)	0.005 (0.005)

[1] Micromoles of ribavirin per gram of creatinine
[2] Standard deviation
[3] Respiratory Therapists

Table 4
Summary Data
Aerosolized Ribavirin
Personal Exposure Concentrations
Florida Hospital
Orlando, Florida
HETA 91-104

Administration Method	Job Category	Number of Samples	Sample Type	Range of Conc. ($\mu g/m^3$)[1]	Mean of Conc. ($\mu g/m^3$)[2]
ADH + tent[3]	Nurses	8	Full-shift	ND - 13.2[4]	4.4
ADH + tent	Nurses	2	Short-term	11.9 - 13.9	12.9
ADH + tent	RT[5]	1	Full-shift	ND	ND
ADH + tent	RTs	6	Short-term	8.3 - 55.5	22.0
Croup Tent	Nurses	4	Full-shift	12.0 - 28.2	22.9
Croup Tent	Nurses	2	Short-term	58.8 - 95.2	77.0
Croup Tent	RTs	4	Short-term	33.3 - 83.3	58.1
ADH alone & ADH + tent	Nurse	1	Full-shift	78.0	78.0
ADH alone	Nurses	2	Full-shift	18.7 - 31.0	24.9
ADH alone	RTs	2	Short-term	<7.4-<12.1	<12.1
ADH alone	RT	1	Full-shift	5.9	5.9
Bear Cub Ventilator	Nurses	3	Full-shift	<3.3 - 4.8	4.3
Bear Cub Ventilator	RTs	3	Short-term	ND	ND

[1] "Range of Conc." refers to the range in concentrations of the individual samples, expressed in micrograms per cubic meter ($\mu g/m^3$).
[2] "Mean of Conc." refers to the arithmetic mean of the individual samples.
[3] "ADH + tent" refers to an Aerosol Delivery Hood enclosed by the Peace Medical Demistifier isolation tent. This scavenging tent was placed over the ADH. The ADH did not have the ICN evacuation apparatus connected.
[4] "ND" means non-detected. ND concentrations were treated as zero for calculating the "Mean of Conc."
[5] "RTs" signifies respiratory therapists.

Table 5
Personal Samples for Ribavirin
Full-Shift Samples
Florida Hospital
Orlando, Florida
HETA 91-104

Job Title/Unit	Date	Sample Period	Sample Time (min)	Time in room (min)	Percent Time in Room	Conc. ($\mu g/m^3$)[1]	TWA Conc.[2]
Nurse[3] Demistifier	2/2/91	1904-2246 2246-0645	222 479	80 160	36 33	11.3 12.8	12.4
Nurse[3] Demistifier	2/3/91	0739-1337 1445-1839	358 236	170 65	47 28	9.8 8.5	9.3
Nurse[3] Demistifier	2/3/91	1915-2320 2320-0629	185 369	175 85	95 23	22.4 7.9	13.2
Nurse[4] Demisitifier	10/18/91	1640-2255	375	30	8	ND	ND
RT[4] Demistifier	10/18/91	1724-2305	341	50	14	ND	ND
Nurse[4] Demistifier	10/18/91	0756-1451	415	75	18	ND	ND
Nurse[4] Demistifier	10/19/91	0729-0955 1245-1646	146 242	60 115	41 47	ND ND	ND ND
RT[5] ADH alone	10/18/91	0750-1447	417	60	14	5.9	5.9
Nurse[5] ADH alone	10/18/91	1532-1807	157	58	36	18.7	18.7
Nurse ADH alone	10/18/91	0734-1228	294	50	17	31.0	31.0
Nurse[4] Croup Tent	2/2/91	1906-2245 2245-0645	221 480	55 150	25 31	33.9 25.6	28.2
Nurse[4] Croup Tent	2/3/91	0708-1315 1315-1600	367 165	130 44	35 27	36.8 9.1	28.2
Nurse[4] Croup Tent	2/3/91	1915-2319 2319-0629	244 430	135 112	55 26	38.9 14.0	23.0
Nurse[4] Croup Tent	2/4/91	0730-1510	460	178	39	12.0	12.0
Nurse Ventilator	4/3/91	1403-1903	300	150	50	<3.3	<3.3
Nurse Ventilator	4/3/91	1944-0620	636	192	30	4.7	4.7
Nurse Ventilator	4/4/91	1951-0620	630	480	76	4.8	4.8
Nurse [3,4] Croup & Demist	2/2/91	1525-1856	211	61	28	43.7	43.7
Nurse[3,6] ADH[7] & Demist	2/4/91	0730-1505	455	255	56	78.0	78.0

[1] Conc. ($\mu g/m^3$) = ribavirin concentration in micrograms per cubic meter air, computed over the sampling period.
[2] TWA Conc = Time-weighted average concentration of ribavirin in micrograms per cubic meter air, computed over the entire work shift.
[3] Administration in room 6322
[4] Administration in room 6321
[5] Administration in room 6330
[6] Administration in room 6320
[7] ADH = Aerosol Delivery Hood, ICN Pharmaceuticals

Table 6
Personal Samples for Ribavirin
Short-term Samples
Florida Hospital
Orlando, Florida
HETA 91-104

Job Title	Administration Unit	Sampling Date	Sampling Time (minutes)	Concentration ($\mu g/m^3$)[1]
RT[2]	Croup Tent	2/2/91	8	83.8
RT	Croup Tent	2/2/91	14	71.4
RT	Croup Tent	2/2/91	15	44.4
RT	Croup Tent	2/3/91	32	33.3
Nurse	Croup Tent	2/2/91	88	95.2
Nurse	Croup Tent	2/3/91	47	58.8
RT	Demistifier[3]	2/2/91	30	33.3
RT	Demistifier	2/2/91	36	55.5
RT	Demistifier	2/3/91	32	9.4
RT	Demistifier	2/3/91	28	11.9
RT	Demistifier	2/3/91	10	8.3
RT	Demistifier	2/4/91	20	13.3
RT	Demistifier	10/19/91	38	<40.7
Nurse	Demistifier	2/2/91	22	11.9
Nurse	Demistifier	2/3/91	48	13.9
RT	ADH[4]	2/4/91	36	<7.4[5]
RT	ADH	2/4/91	22	<12.1[5]
RT	Ventilator[6]	4/3/91	30	ND[7]
RT	Ventilator	4/4/91	25	ND
RT	Ventilator	4/4/91	40	ND

[1] "$\mu g/m^3$" indicates micrograms per cubic meter air over the specified sample time.
[2] "RT" signifies Respiratory Therapist.
[3] "Demistifier" indicates scavenging tent (Peace Medical, Inc.) placed over the Aerosol Delivery Hood.
[4] "ADH" is the Aerosol Delivery Hood (ICN Pharmaceuticals).
[5] "<" signifies that indicated value below the Limit of Quantitation of 3.1 μg/sample.
[6] "Bear Cub" is a pediatric ventilator, administered through tracheotomy.
[7] "ND" signifies that value is below the Limit of Detection of 1 μg/sample.

Table 7
Ribavirin Area Air Samples
Florida Hospital, Orlando, Florida
February 2,3,4, 1991
HETA 91-104

Sampling Location or Room Number	Date	Sample Period	Conc. ($\mu g/m^3$)[1]	Average Conc.[2]
Nurses' Station. Across hall from treatment rooms	2/2/91	1515-1907	4.3	
		1915-2247	2.2	
		2247-0647	8.6	
	2/3/91	0710-1242	9.0	
		1242-1845	13.9	
		1845-0629	15.9	
	2/4/91	0756-1504	4.7	9.7
Room 6321, Croup tent. 3 ft. from tent & floor. Employees worked from this side of the tent.	2/2/91	1517-1911	47.2	
		1916-2250	52.9	
		2250-0649	92.3	
	2/3/91	0715-1241	32.2	
		1241-1849	28.5	54.0
Room 6321, Croup tent. Sampler set near SPAG. 2 ft. from tent, 3 ft. from floor.	2/2/91	1919-2249	38.1	
		2249-0645	52.6	
	2/3/91	0712-1243	46.8	
		1243-1849	36.9	
		1858-0630	33.3	
	2/4/91	0759-1506	35.1	40.0
Room 6321, Croup. Above tent on light fixture.	2/2/91	1529-1910	84.7	84.7
Room 6322, Demistifier. Near SPAG, 3 ft. from floor, 2 ft. from tent. Employees worked from this side of tent.	2/2/91	1525-1856	33.5	
		1921-2253	21.2	
		2253-0650	16.6	
	2/3/91	0719-1245	16.9	
		1254-1850	15.1	
	2/4/91	0758-1507	8.4	17.0
Room 6322, Demistifier. 3 ft. from tent & floor.	2/2/91	1922-2254	11.8	
		2254-0650	13.6	
	2/3/91	0716-1245	10.6	
		1254-1850	11.0	
		1900-0630	7.2	9.8
Room 6322, Demistifier. Above tent on light fixture	2/2/91	1520-1911	82.3	82.3
Room 6320, ICN Hood alone Sampler 4 ft. off floor, 3 ft. from hood.	2/4/91	0800-1507	32.8	32.8

[1] "$\mu g/m^3$" indicates micrograms per cubic meter air over the actual sampling period.

[2] "Average Conc." indicates time weighted average concentration of ribavirin in micrograms per cubic meter air for the entire group of samples within each section.

Table 8
Ribavirin Area Air Samples
Florida Hospital, Orlando, Florida
April 3-5 and October 18-19, 1991
HETA 91-104

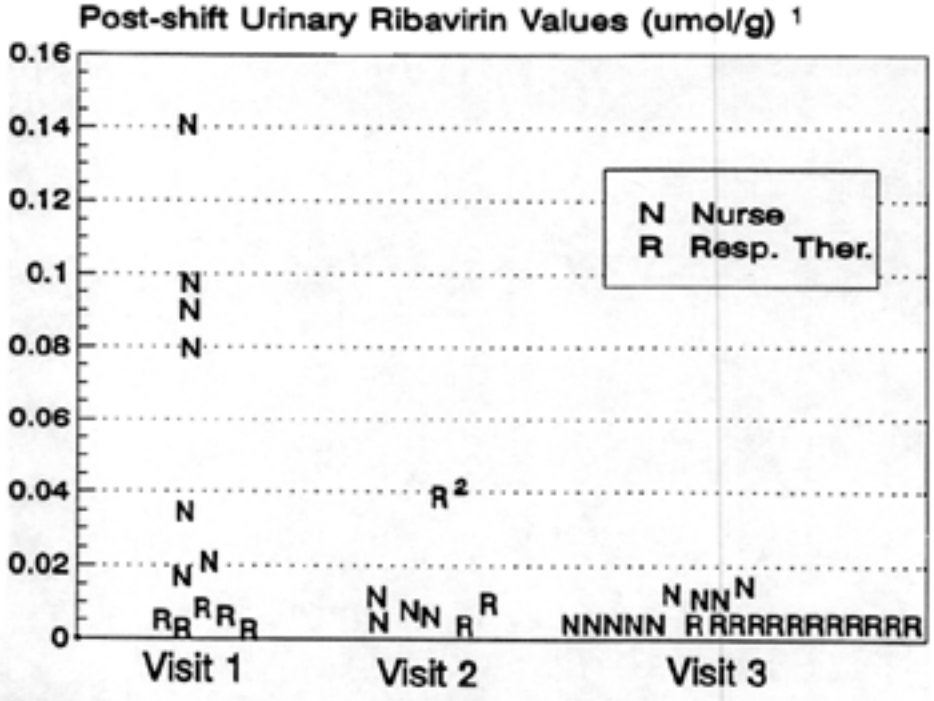
Sampling Location or Room Number	Date	Sample Period	Conc. ($\mu g/m^3$)[1]
Nurses' Station, across hall from ICU #6	4/4/91	0740-1920	ND[2]
	4/4/91	1946-0621	<2.4
Head of bed, Bear Cub Ventilator, Room ICU #6	4/3/91	1305-1902	11.2
	4/3/91	1925-0622	12.9
	4/4/91	0654-1921	ND
	4/4/91	1950-0622	11.1
Nurses' Station, across hall from 6320 & 6321	10/18/91	0707-1746	ND
	10/18/91	1804-0650	ND
	10/19/91	0720-0955	ND
Nurses' Station, across hall from 6330.	10/18/91	0746-1746	ND
	10/18/91	1805-0100	ND
Room 6321, Demistifier enclosing ADH, 4 feet from tent, 3 feet off floor.	10/18/91	0712-1746	ND
	10/18/91	1804-0650	ND
	10/19/91	0720-0955	37.3
	10/19/91	1249-1647	ND
Room 6322, Demistifier enclosing Pup tent.	10/18/91	0710-1500	16.0
Room 6330, ADH alone, 4 feet away, 3 feet off floor	10/18/91	0735-1747	161.8
	10/18/91	1806-0653	ND
Room 6321, inside ADH	10/18/91	1622-1627	64,000
Inside the Demistifier	10/18/91	1622-1632	1,500
Room 6321, inside ADH	10/19/91	1020-1025	30,000
Inside the Demistifier	10/19/91	1020-1030	2,400
Room 6322, inside ADH	10/19/91	0730-0735	78,000

[1] Conc. ($\mu g/m^3$) = ribavirin concentration in micrograms per cubic meter air, computed over the sampling period.
[2] ND = below the limit of detection of 0.8 $\mu g/m^3$/sample.

Table 9
Room Ventilation Measurements
Pediatric Intensive Care Unit
Florida Hospital, Orlando, Florida
HETA 91-104

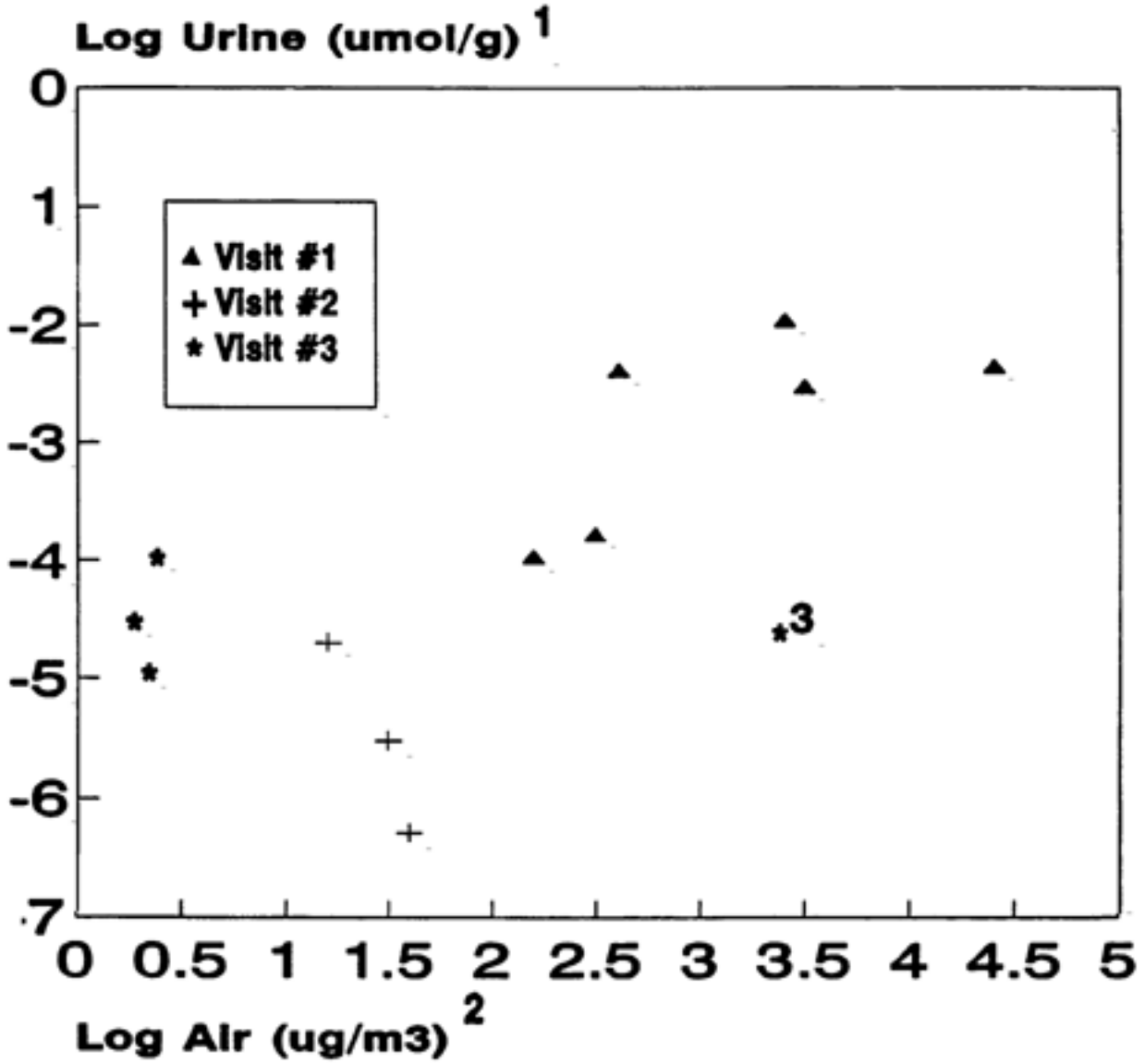
Room Number and Date	Supply (cfm)	Return (cfm)	Bathroom Exhaust (cfm)	Air Changes per Hour
6322 4/3/91	414	-357	-74	19
6322 4/4/91	234	-331	-71	18
6322 4/4/91	228	-342	-72	19
6321 10/18/91	271	-358	-93	20
6321 10/19/91	257	-371	-97	21
6322 10/18/91	443	-367	-124	22
6322 10/19/91	369	-295	-95	18
6330 PICU #7 10/18/91	171	-229	none	10
6330 PICU #7 10/19/91	167	-243	none	11

Figure 1
Post-shift Urinary Ribavirin Values
Nurses and Respiratory Therapists n=40
Florida Hospital
Orlando, Florida
HETA 91-104



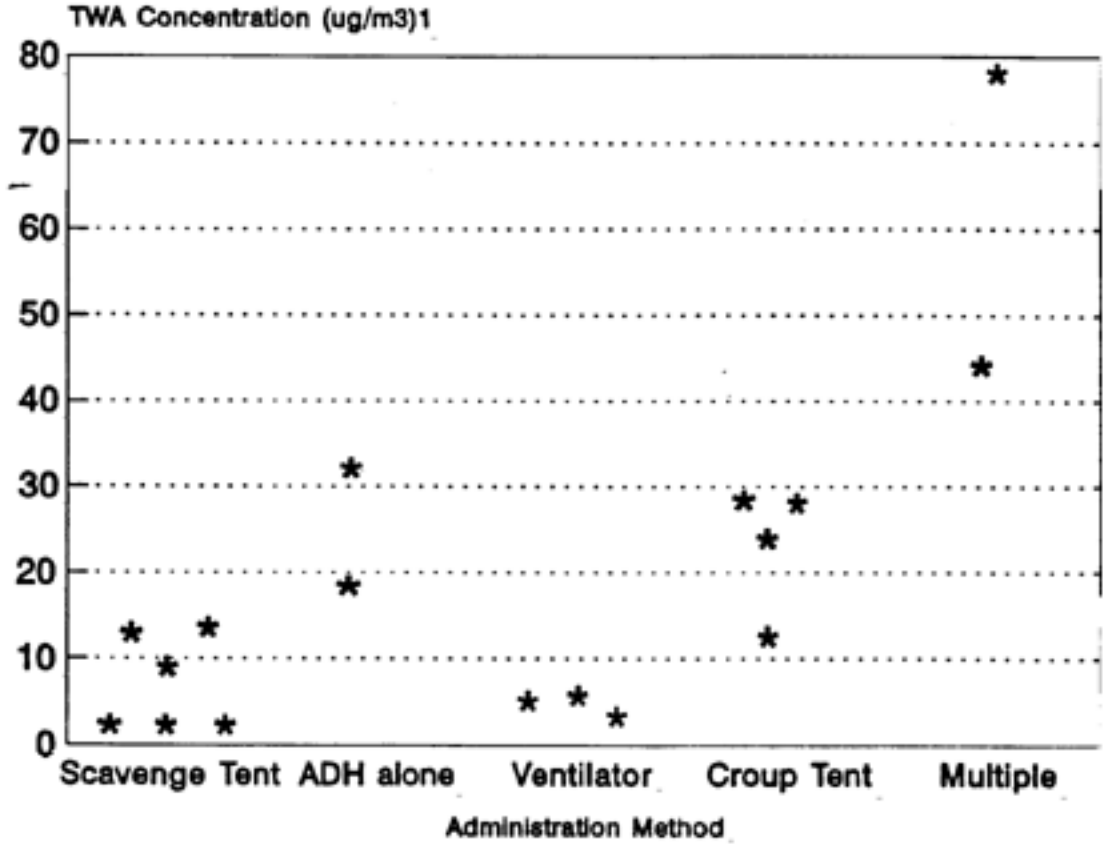
1 Micromoles of ribavirin per gram of creatinine
2 HCW reported that he briefly disconnected ventilator tubing to do testing

Figure 2
Full-shift Personal Air Samples vs.
Post-shift Urinary Ribavirin Values
Nurses n=13
Florida Hospital
Orlando, Florida
HETA 91-104



1 Log of post-shift urinary ribavirin values, adjusted for pre-shift values.
2 Log of time-weighted averages of personal air samples.
3 Administration tube was disconnected, spilling ribavirin into the room.

Figure 3
Aerosolized Ribavirin
Personal Breathing Zone Concentrations
Full-Shift Samples from Nurses
Florida Hospital
Orlando, Florida
HETA 91-104



1 TWA Concentration = Time-weighted average concentration of ribavirin in micrograms per cubic meter air, computed over the entire work shift.

APPENDIX A

Because differences exist among the various classes of respirators with regard to their protective capabilities, respirators are assigned protection factors as guidance for their selection. A protection factor is the ratio of the concentration of a contaminant in the environment surrounding a respirator wearer to the concentration of the contaminant inside the respirator wearer's facepiece. The majority of assigned protection factors are based on quantitative fit factors rather than workplace protection factors. **Quantitative fit factors** are determined from tests in which a group of respirator wearers perform a specific regimen of head and body movements for a short period of time while in a laboratory test chamber containing a challenge aerosol. A **workplace protection factor** is a measure of the protection provided in a workplace under the actual conditions of that workplace by a properly functioning respirator which is correctly worn and used.[1] An **assigned protection factor** (APF) is the minimum expected workplace level of respiratory protection that would be provided by a properly functioning respirator, or class of respirators, to a stated percentage of properly fitted and trained users.[2] Table 4 lists APFs for various classes of respirators.[3] Most APFs are not based on measurements of actual field (workplace) performance; the majority of APFs are based solely on quantitative fit factors. To date, it should be noted that no relationship between quantitative fit test results and measured workplace performance testing has been established.[3]

The maximum use concentration for a respirator is generally determined by multiplying the assigned protection factor of a respirator by a contaminant's lowest occupational limit (i.e., Permissible Exposure Limit of the Occupational Safety and Health Administration, Recommended Exposure Limit of NIOSH, and Threshold Limit Value of the American Conference of Governmental Industrial Hygienist). Alternatively, the minimum level of protection necessary for a specific occupational application can be calculated after exposure estimates have been determined for environmental contaminants. This is usually done by dividing the highest 8-hour time-weighted average (TWA) exposure estimate of an airborne contaminant by the contaminant's lowest occupational exposure limit. Then a class of respiratory protection is selected with an assigned protection factor equal to or exceeding the required level of protection. For example, if a set of industrial hygiene samples collected during a particular operation produced 8-hour TWA exposure estimates ranging from 8 to 50 mg/m^3 for a contaminant with an occupational exposure limit of 10 mg/m^3, then a respirator with an assigned protection factor of at least 5 (50/10 = 5) would be selected. Such a respirator would reduce the highest exposure concentration to an in-mask concentration equal to, or less than, the contaminant's exposure limit for the majority of respiratory wearers.

TABLE A-1. --Assigned protection factor classification of respirators for protection against particulate exposures[1]

(Adapted from *NIOSH Respirator Decision Logic* manual)

Assigned protection factor	Type of respirator
5	Single use or quarter mask[2] respirator
10	Any air-purifying half-mask respirator including disposable[3] equipped with any type of particulate filter except single use[2,4]
	Any air-purifying full facepiece respirator equipped with any type of particulate filter[5]
	Any supplied-air respirator equipped with a half-mask and operated in a demand (negative pressure) mode[2]
25	Any powered air-purifying respirator equipped with a hood or helmet and any type of particulate filter Any supplied-air respirator equipped with a hood or helmet and operated in a continuous flow mode4
50	Any air-purifying full facepiece respirator equipped with a high efficiency filter[2]
	Any powered air-purifying respirator equipped with a tight-fitting facepiece and a high efficiency filter[4]
	Any supplied-air respirator equipped with a full facepiece and operated in a demand (negative pressure) mode[2]
	Any supplied-air respirator equipped with a tight-fitting facepiece and operated in a continuous flow mode[4]
	Any self contained respirator equipped with a full facepiece and operated in a demand (negative pressure) mode [2]
1,000	Any supplied-air respirator equipped with a half-mask and operated in a pressure demand or other positive pressure mode[2]
2,000	Any supplied-air respirator equipped with a full facepiece and operated in a pressure demand or other positive pressure mode[2]
10,000	Any self-contained respirator equipped with a full facepiece and operated in a pressure demand or other positive pressure mode[2]
	Any supplied-air respirator equipped with a full facepiece operated in a pressure demand or other positive pressure mode in combination with an auxiliary self-contained breathing apparatus operated in a pressure demand or other positive pressure mode

1 Only high efficiency filters are permitted for protection against particulates having exposure limits less than 0.05 mg/m3.

2 The assigned protection factors (APF's) were determined by Los Alamos National Laboratories (LANL) by conducting quantitative fit testing on a panel of human volunteers [6].

3 An APF factor of 10 can be assigned to disposable particulate respirators if they have been properly fitted using a quantitative fit test.

4 APF's were based on a workplace protection factor (WPF) data or laboratory data more recently reported than the LANL data.

5 The APF was based on consideration of efficiency of dust, fume, and/or mist filters.

APPENDIX REFERENCES

1. Myers WR, Lenhart SW, Campbell D, Provost G [1983]. Letter to the editor, Topic: respirator performance terminology. Am Ind hyg Assoc J 44:B25-26.

2. Guy HP [1985]. Respirator performance terminology. Am Ind Hyg Assoc J 46:B22 & B24.

3. NIOSH [1987]. NIOSH respirator decision logic. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Standards Development and Technology Transfer. DHHS (NIOSH) Publication Number 87-108.