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**HETA 98-0048-2688**  
**The Children's Hospital**  
**Denver, Colorado**

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**John Decker, C.I.H.**

## 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.

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## ACKNOWLEDGMENTS AND AVAILABILITY OF REPORT

This report was prepared by John Decker of the Hazard Evaluations and Technical Assistance Branch, Division of Surveillance, Hazard Evaluations and Field Studies (DSHEFS), Atlanta Field Office. Field assistance was provided by William Daniels of the Denver Field Office. Analytical support was provided by Data Chem Laboratories, Inc. Desktop publishing by Pat Lovell. Review and preparation for printing was performed by Penny Arthur.

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**Health Hazard Evaluation Report 98-00480-2688**  
**The Children's Hospital**  
**Denver, Colorado**  
**April 1998**

**John Decker, C.I.H.**

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## **SUMMARY**

In response to a request from Denver's Children's Hospital management, the National Institute for Occupational Safety and Health (NIOSH) conducted an industrial hygiene evaluation of health care workers' exposures to aerosolized ribavirin. Ribavirin is a synthetic nucleoside that is used to prevent and treat respiratory syncytial virus (RSV) infections in infants and children. The specific request was for NIOSH to evaluate exposures to ribavirin and determine if N-95 disposable respirators should be used to provide supplemental protection against exposure to the drug. At Children's Hospital, ribavirin is frequently administered through an Airlife™ face mask enclosed by an aerosol scavenging system (a NOVA Tenthouse™ cube attached to the hospital's suction system).

Five personal breathing zone (PBZ) and 14 area air samples for ribavirin were collected over two administrations on December 10-11, 1997. Additionally, a Met-One™ particle counter was used to determine counts of airborne particles 0.3 to 3 microns in diameter during the administrations.

A trace amount of ribavirin (between the analytical limit of detection and quantification) was detected on one attending nurse's personal PBZ sample on December 10, 1997. Ribavirin was not detected on the other four PBZ samples, including the three samples from respiratory therapists. The respiratory therapists spent only a few minutes in the patient's room, and based on the small air volumes sampled, the analytical limits of detection (LODs) for these samples were relatively high, ranging from 100 to 500 micrograms per meter air ( $\mu\text{g}/\text{m}^3$ ). No occupational exposure criteria for ribavirin has been established by NIOSH, the Occupational Safety and Health Administration (OSHA), or the American Conference of Governmental Industrial Hygienists (ACGIH).

Ribavirin was found on all area samples inside the room, except one. These results indicate that some ribavirin was leaking from the Tenthouse enclosure surrounding the patient receiving ribavirin. Ribavirin was found near the return vents in the room (range: 20.5 to 76.9  $\mu\text{g}/\text{m}^3$ ) and at the visitor's chair (11.7 and 13.8  $\mu\text{g}/\text{m}^3$ ). Non-detectable to trace quantities of ribavirin were found immediately outside the door to the patient's room. Concentrations were higher for samples taken very near the Tenthouse (243 and 1125  $\mu\text{g}/\text{m}^3$ ).

Particle count measurements made with the Met-One™ suggest that the Tenthouse cube-bed seal is an important determinant of the amount of ribavirin escaping the containment system. Higher particle counts were observed when the administration mask came off the patient, and the bed-cube seal was disrupted.

Despite engineering controls and appropriate hospital policies, employees continue to have some potential for exposure to ribavirin aerosol during administrations. On the days of the NIOSH visit, only one patient was receiving ribavirin treatment once per day. Multiple administrations throughout the day could result in a higher cumulative exposures, as could spending more time in the room when caring for more difficult patients. Several recommendations to reduce potential exposures are offered in this report, including training of staff to maintain the best-possible Tenthouse-bed seal, reevaluation of the exhaust airflow rates from the scavenging system to ensure containment, and utilizing respirators while in the administration room. Although the magnitude of risk-reduction attained by reducing exposures is not known, taking measures to reduce potential exposures is suggested.

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.

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## INTRODUCTION

In response to a management request dated November 10, 1997, the National Institute for Occupational Safety and Health (NIOSH) conducted a site visit at The Children's Hospital, Denver, Colorado, on December 9-12, 1997, to evaluate health care workers' exposures to aerosolized ribavirin (Virazole®). The specific request was for NIOSH to evaluate the exposure conditions and determine whether N-95 respirator masks should be used to provide supplemental protection against exposure to the drug. Ribavirin is a synthetic nucleoside that is used to prevent and treat respiratory syncytial virus (RSV) infections in infants and children. Concern about occupational exposure to ribavirin has centered around potential adverse reproductive effects. An interim letter, dated March 3, 1998, was sent to Children's Hospital; it discussed most of the information contained in this report.

## BACKGROUND

The Children's Hospital is a 199-bed pediatric medical and surgical hospital in Denver which administers ribavirin to immunosuppressed children (primarily bone marrow transplant patients) for prevention and treatment of RSV infection. Ribavirin was originally marketed for short-term treatment of RSV infection in infants, but new information concerning the lack of clinical efficacy for this purpose has changed prescribing recommendations.<sup>1</sup> However, ribavirin continues to be prescribed for treatment and prophylaxis of RSV in bone marrow transplant patients because of its reported clinical efficacy in this application.<sup>2</sup> Approximately six children per year receive ribavirin at Children's Hospital, and it is usually administered for 3-4 months at a time. The children receiving ribavirin at Denver Children's Hospital are typically several years

old (average age: 7 years old). A two-gram dose of ribavirin is administered to patients over two hours, and one to three treatments per day are given depending on whether the patient is currently infected or is receiving a maintenance dosage following resolution of RSV infection. Ribavirin is also administered to children in the hospital's outpatient clinic.

The ribavirin solution is prepared in the pharmacy by injecting sterile water into a 6-gram vial of lyophilized ribavirin powder to produce a concentration of 60 milligrams per milliliter (mg/mL). Two grams of ribavirin (about 33 mL) is transferred to a 60-mL syringe, which is then delivered to the patient's room. A respiratory therapist sets up the administration equipment and begins the administration. The ribavirin aerosol is generated by a Small Particle Aerosol Generator (SPAG-2™) marketed by the drug manufacturer (ICN Pharmaceuticals, Inc., Costa Mesa, California). The SPAG-2 delivers aerosolized ribavirin (as a solid particulate aerosol) at a flow rate of 13-14 liters per minute (L/min). The nebulizer airflow rate is generally set at 6 - 6.5 L/min, and the drying airflow rate is set at 7 L/min (both as measured with a rotameter on the SPAG-2). At Children's Hospital, the ribavirin is frequently administered to the patient through a loose-fitting vinyl Airlife™ Face Mask (Cat. No. 001220, Baxter Healthcare Corporation, Valencia, California). The small particle size of the ribavirin aerosol (1.0 - 1.3 microns mass median aerodynamic diameter) permits deep penetration into the patient's lungs.

The scavenging system consists of a NOVA Tenthouse™ (18" x 18" x 18" clear plastic cube) connected to a regulator on the hospital's suction system. The patient's face and upper torso are enclosed by the Tenthouse. A Pall HME 15-22 bacterial/viral filter (Pall Biomedical, Inc., Fajardo, Puerto Rico) removes the escaping ribavirin before it enters the suction system. The filter is advertised by

the manufacturer to have a 99.999% bacterial/viral removal efficacy. When the scavenging system is activated, the regulator suction is set to the maximum setting, although the airflow rate at this setting had not been determined by hospital personnel. The ribavirin is administered until all the solution in the reservoir is gone (approximately two hours). The Tenthouse, tubing, filters, etc. are changed and discarded every 24 hours. Hospital policy states that staff are to wait five minutes after turning off the SPAG before opening the Tenthouse and working on the patient.

To protect the patients from infection, the rooms in the bone marrow transplant unit are under positive pressure relative to the hallway. Air supplied to the room (reportedly 25 air changes per hour) is filtered through high efficiency particulate air (HEPA) filters and delivered as laminar flow over the patient's bed.

All hospital staff and visitors are required to wash their hands and put on gowns before entering the bone marrow transplant unit. Gowns, gloves (Triflex® non-sterile vinyl) and surgical masks (Technol® high filtration isolation masks) are required when entering the patient's room (whether or not ribavirin is being administered) to protect the patient from infection. To prevent transmission of RSV outside the patient's room, the gloves and surgical masks are discarded when leaving the room, and the gown is changed. Technol® Model PF 95-170 N-95 half-mask respirators are available for staff to wear during ribavirin administration in lieu of surgical masks.

## METHODS

Personal breathing zone (PBZ) and area air sampling for aerosolized ribavirin was conducted during two 2-hour treatments on December 10 and 11. The sampling was conducted according to NIOSH method 5027,

utilizing 37-millimeter diameter, 1 micron glass fiber filters.<sup>3</sup> The ribavirin was collected on the filters at a flow rate of 2.0 liters per minute (L/min) using battery-powered Gillian™ high flow air pumps. Calibration of the pumps before and after sampling was conducted with a Bios™ dry flow calibrator. Additionally, the Bios was used to determine the suction airflow rate from the Tenthouse. For each treatment, personal air monitoring was conducted on the nurse attending the patient and the respiratory therapist. The personal sampling for the respiratory therapists was conducted only during the time that they were in the room, since the respiratory therapists left the area during the administration. On each day, area air monitoring was conducted at six locations in the room and immediately outside the door to the room.

The filter samples were sent to a NIOSH contract laboratory for analysis. The samples were extracted with a 3- mL solution of sulfuric acid (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.

A Met-One™ model 227 hand-held particle counter was used to determine particle counts during ribavirin administration. Since the air in the patient's room was HEPA filtered, nearly all the particles being counted could be assumed to be ribavirin aerosol. This was verified by measuring the particulate counts in the room prior to ribavirin administration. The monitor was set to count particles 0.3 microns (μ) and larger, as well as particles 3.0 μ and larger.

## EVALUATION CRITERIA

In animal studies, ribavirin has been shown to be teratogenic and embryolethal in rats, mice, and hamsters, and embryolethal in rabbits.<sup>4,5,6,7</sup> Three studies in rats showed degenerative or histopathologic testicular effects. Eight other studies in rats, mice, dogs, and monkeys induced no testicular effects.<sup>8</sup> Ribavirin has been found to be toxic to lactating animals and their offspring.<sup>9</sup>

Adverse effects occur infrequently in patients receiving aerosolized ribavirin; the more commonly reported effects include respiratory and cardiovascular disturbances, rash, and skin irritation.<sup>10</sup> Hemolytic anemia and suppression of erythropoiesis can occur when the drug is given orally or parenterally.

Acute effects due to environmental exposure to ribavirin aerosol include rhinitis, headache, and eye irritation.<sup>7</sup> The drug has been found to precipitate on contact lenses, causing eye irritation in employees wearing contact lenses.<sup>11</sup>

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.<sup>7,12</sup> A pharmacokinetic study conducted under the support of the drug's manufacturer suggested that typical occupational exposures to ribavirin would result in body burdens of 0.1% to 1% of the levels reported to be toxic in laboratory animals.<sup>13</sup> The manufacturer's product insert for ribavirin administration indicates "it should be assumed that Virazole [ribavirin] may cause fetal harm in humans."<sup>14</sup> At present, the potential reproductive health effects from occupational exposure to ribavirin are unknown.

No occupational exposure criteria for ribavirin has been established by NIOSH, the Occupational Safety and Health Administration (OSHA), or the American Conference of

Governmental Industrial Hygienists (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.<sup>15,16</sup> Using the model, a limit of 2.7 micrograms per cubic meter air ( $\mu\text{g}/\text{m}^3$ ) as an 8-hour time-weighted average (TWA) has been proposed. This calculation was based on a respiratory rate of 19 liters per minute, 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 correspond to lower-dose occupational exposure. Other investigators have proposed higher limits (91  $\mu\text{g}/\text{m}^3$  as an 8-hour TWA) by using different estimates of the NOEL and applying a safety factor of 100.<sup>17,18</sup>

## RESULTS

The results of air monitoring can be found in Tables 1 and 2. A trace amount of ribavirin (between the limits of detection and quantification) was detected on the attending nurse's PBZ sample on December 10. The other four PBZ samples on December 10 and 11, including the three samples from the respiratory therapists, had no detectable ribavirin. The respiratory therapists spent only a few minutes in the patient's room, so based on the small air volumes sampled, the limits of detection (LODs) for these samples were relatively high, ranging from 100 to 500  $\mu\text{g}/\text{m}^3$ . When caring for patients with difficult illnesses, respiratory therapists and nurses may spend more time in the room. Additionally, on the days of the NIOSH visit, only one patient was receiving ribavirin treatment once per day. Multiple administrations throughout the day or more time in the patient's room per administration could result in higher cumulative exposures. Therefore, because of



the high LODs and short sampling times, only limited conclusions can be made from these samples.

Ribavirin was found on all area samples inside the room, except one. These results indicate that some ribavirin was leaking from the Tenthouse enclosure into the room. Concentrations were higher (243 and 1125  $\mu\text{g}/\text{m}^3$ ) in samples taken very near the Tenthouse. Ribavirin was also found near the return vents in the room (15.5 to 44.7  $\mu\text{g}/\text{m}^3$ ) and at the visitor's chair (11.7 and 13.8  $\mu\text{g}/\text{m}^3$ ). Non-detectable to trace quantities of ribavirin were found immediately outside the door to the patient's room.

**Table 1**  
HETA 98-0048, Children's Hospital  
Denver, Colorado  
December 10, 1997 - Room 560

Area Sample Location or Job Title for Personal Sample	Sample Time (minutes)	Concentration ( $\mu\text{g}/\text{m}^3$ ) <sup>a</sup>
Outside door to room	128	ND <sup>b</sup> (<3)
Return vent near door	132	20.5
IV Pole - opposite window	129	50.4
Side of bed on window side	130	76.9
Visitors' chair near window	132	11.7
Return vent near window	132	15.5
On edge of Tenthouse	115	243
Attending nurse	135 ( was in room 35 minutes)	(7) <sup>c</sup>
Respiratory Therapist	15 (set up of equipment)	ND <sup>b</sup> (<100)
Limit of Detection (based on sample volume of 260 liters)		3
Limit of Quantification (based on 260 liters)		11

<sup>a</sup> Time-weighted concentration over time sampled; micrograms per cubic meter air

<sup>b</sup> ND = non-detected

<sup>c</sup> Between limit of detection and quantification

**Table 2**  
 HETA 98-0048, Children's Hospital  
 Denver, Colorado  
 December 11, 1997 - Room 560

Area Sample Location or Job Title for Personal Sample	Sample Time (minutes)	Concentration ( $\mu\text{g}/\text{m}^3$ ) <sup>a</sup>
Outside door to room	151	(6.6) <sup>b</sup>
Return vent near door	134	44.7
IV Pole - opposite window	131	18.3
Over bed from light frame	132	ND
Visitor's chair near window	134	13.8
Return vent near window	134	36.9
On edge of Tenthouse	120	1125
Attending nurse	130	ND <sup>c</sup> (< 3)
Respiratory therapist #1	3	ND (< 500)
Respiratory therapist #2	11	ND (< 136)
Limit of Detection (based on sample volume of 260 liters)		3
Limit of Quantification (based on 260 liters)		11

<sup>a</sup> Time-weighted concentration over time sampled, micrograms per cubic meter air

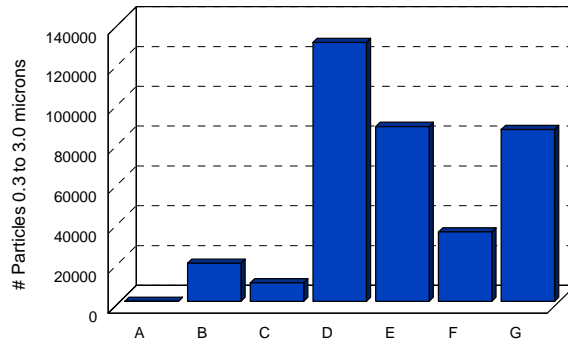
<sup>b</sup> Sample concentration between the limit of detection and quantification

<sup>c</sup> ND = non-detected

Figures 1 and 2 provide the results of the particle count measurements from the Met-One particle counter. Each bar in Figures 1 and 2 represents an average of 3-5 measurements at that location. Very low counts were measured before ribavirin administration was begun. As shown in Figure 1, there was some variability in the count depending on measurement location and the integrity of the bed-cube seal. Measurements B and C, taken shortly after administration was started, suggest the bed-

cube seal was good. In measurements D, E, F, and G, the bed-cube seal had been disrupted, and additional amounts of particulate were escaping. In Figure 2, the initial set-up of the bed-cube seal was better, and less particulate was measured. Higher particulate levels were measured later in the administration after the patient had moved about and removed his mask, affecting the bed-cube seal.

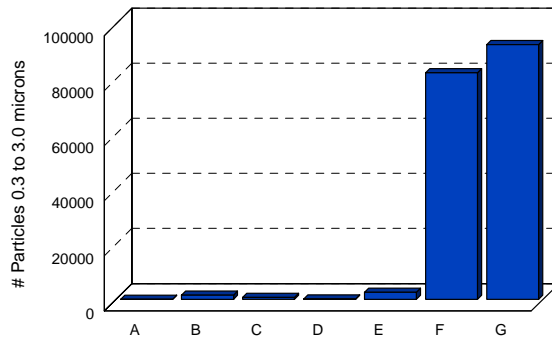
**Figure 1**  
**Particle Counter Results - December 10, 1998**  
**Denver Children's Hospital**



Sampling Locations:

- A = General room - over bed before administration (used room 559)
- B = Administration started - at foot of bed
- C = Near cube - opposite side of bed from window
- D = Under bed-cube seal on bed
- E = Immediately above cube
- F = General room counts 3 feet from foot of bed
- G = Near scavenger hoses on wall

**Figure 2**  
**Particle Counter Results - December 11, 1998**  
**Denver Children's Hospital**



Sampling Locations:

- A = Near ceiling under HEPA filters before administration was started
- B = Near bedding after cube was assembled and placed on bed
- C = Ribavirin started, measurements around bed-cube seal
- D = Top of cube during administration
- E = Ribavirin stopped for a few minutes and cube opened to administer IV medication
- F = Mask came off patient during administration... bed-cube seal disturbed
- G = Foot of bed during situation described under "F."

Measurements of the suction flow rate with the Bios Calibrator indicated the airflow was 30.5 L/min. This measurement was taken following completion of a ribavirin administration to a RSV patient. Since the ribavirin is administered at a flowrate of 13-14 L/min, a net 16-17 L/min is exhausted from the Tenthouse cube. It was noted that a hole (about 1/2" in diameter) was manufactured into the top of the cube for patient comfort. However, because the administration given on the bed is directly below the laminar airflow from the HEPA filters, air may be entering the cube through this hole, affecting the relative air pressure in the cube. It was unclear whether this situation poses a significant problem with regard to the escape of ribavirin into the room air.

## DISCUSSION AND CONCLUSIONS

Prior to the NIOSH visit, The Children's Hospital in Denver had implemented several policies to reduce potential exposures to ribavirin. For instance, the protocol of waiting 5 minutes after turning off the aerosol generator likely reduces airborne exposures. In addition, the hospital's use of a containment system is probably reducing exposures to some degree. The high airflow rate in the isolation rooms appears to be removing much of the escaped ribavirin aerosol before it can migrate out of the positive-pressure rooms. Although negative-pressure rooms would assure better containment of airborne contaminants such as ribavirin, this option is not available because of the need for the infection control measure of keeping the room air pressure higher than that of the hallway.

Differing opinions regarding the need for ribavirin-exposed health care workers to wear personal protective equipment have been expressed in the scientific literature.<sup>19,20</sup> In its "Aerosol Consensus Statement-1991," the

American Association for Respiratory Care recommended that health care workers wear full barrier protection including respirators.<sup>21</sup> This position was restated in their 1996 AARC Clinical Practice Guideline.<sup>21</sup> 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"(this recommendation did not consider infection control needs for bone marrow transplant patients).<sup>22</sup> Previous NIOSH health hazard evaluations have offered facility-specific recommendations for reducing exposure to aerosolized ribavirin.<sup>23,24</sup> These recommendations have included training of staff potentially exposed to ribavirin, using aerosol containment systems, administering ribavirin in negative-pressure isolation rooms (when other engineering controls are not available), turning off the aerosol generator 5 minutes before giving routine care, implementing measures to avoid ocular and dermal contact, and considering particulate respirator masks to reduce exposure (although NIOSH does not have a formal respirator recommendation for ribavirin aerosol exposure). Although the magnitude of risk-reduction attained by implementing these measures is not known, utilizing available measures to reduce exposures is reasonable and prudent.

## RECOMMENDATIONS

1. The Met-One particle count data suggest that the integrity of the Tenthouse cube-bed seal is an important determinant of the amount of ribavirin escaping from the containment system. In one instance, it appeared that additional ribavirin may have been escaping when the administration mask briefly came off the patient (during monitoring on December 11). The respiratory therapists and the nurses

should be educated on these issues, so that the best possible set-up is maintained during administration.

2. A higher suction airflow rate from the Tenthouse cube may improve the integrity of the containment system. Additional evaluation of exhaust flow rates and relative pressures between the inside and outside of the cube are necessary. However, before changes are made, the impact on the dosage of ribavirin to the patient should be considered.

3. Although NIOSH does not have an official policy regarding the use of respirators during ribavirin administration, the use of any particulate respirator is preferable to a surgical mask. The N-95 filter respirators are capable of filtering aerosols in the size range of ribavirin aerosol. A non-valved respirator (one without an exhalation valve) may be more appropriate when considering the infection control needs of the patient. A respiratory protection program consistent with OSHA regulations should be implemented for staff using respirators, including disposable types.

4. As the ribavirin aerosol ages, it sometimes agglomerates and precipitates on surfaces. When taking down the cube after administration, the respiratory therapists should disassemble the unit gently so that the amount of re-aerosolized ribavirin is minimized. Using a N-95 respirator during this activity would also be a reasonable precaution.

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