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# Memorandum

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From: Roy M. Fleming, Sc.D., Director, Research Grants Program RMF
Office of Extramural Programs, NIOSH, D30

Subject: Final Report Submitted for Entry into NTIS for Grant 5 R01 OH003134-03.

To: William D. Bennett
Data Systems Team, Information Resources Branch, EID, NIOSH, P03/C18

The attached final report has been received from the principal investigator on the subject NIOSH grant. If this document is forwarded to the National Technical Information Service, please let us know when a document number is known so that we can inform anyone who inquires about this final report.

Any publications that are included with this report are highlighted on the list below.

Attachment
cc: Sherri Diana, EID, P03/C13

List of Publications None

**Title:** Physiologic Sampler for Airborne Health Hazards
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**Abstract:**
Physiologic sampling offers a potential significant improvement in exposure assessment methods applied in workplaces. A physiologic sampler device continuously adjusts the air-sampling rate in proportional to a worker's inhaled air volume. This study resulted in the development of a new physiologic sampling pump (PSP) for personal air sampling on workers. Laboratory and field evaluations of the PSP conducted for this project demonstrated the flexibility, utility, and application of this new device. This study also evaluated the Rapid Exhaled Gas Analyzer (REBA) as a tool for measuring human breath samples. Ten volatile organic compounds in spiked breath samples were examined for applicability with this device (ethanol, ethylbenzene, n-hexane, methy ethyl ketone, methy tert-butyl ether, m-xylene, 1,1,1-trichoroethane, trichloroethylene, and toluene). Detection limits were determined for all compounds and were sufficiently low to indicate that REBA could monitor these solvents at levels appropriate for their BEI (Biologic Exposure Index) as define by the ACGIH biologic monitoring committee. The quantification accuracy was good in many cases, but values were under-predicted for some compounds (n-hexane and 1,1,1-trichloroethane). This finding suggests that further refinement in quantification methods and validation of sampling methods is needed for these compounds.

**Publications**
No publications to date.

# Final report:

# Physiologic Sampler for Airborne Health Hazards

## NIOSH Grant RO1-OH03134

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## 1 SIGNIFICANT FINDINGS

This report documents the findings of the research project titled "Physiologic Sampler for Airborne Health Hazards (NIOSH RO1-OH03134). The concept of a physiologic sampler is a significant adaptation of the usual personal sampling methods applied in workplaces. A physiologic sampler is a device that continuously adjusts the air-sampling rate in proportional to a worker's inhaled air volume. This study resulted in the development of a new physiologic sampling pump (PSP) for personal air sampling. This device was mainly aimed at sampling organic solvents (or other compounds) collected on adsorbent media. Various physiologic signals were tested to control the pump in the laboratory study, but heart rate proved the most feasible for field applications. Laboratory and field evaluations of the PSP conducted for this project demonstrated the flexibility, utility, and application of this new device.

Construction workers are likely candidates for physiologic sampling since they engage in physically demanding work that can result in the release of contaminants in the breathing zone. Construction workers are exposed to a variety of solvents from paints, adhesives, and cleaning agents, as well as dusts, mists and fumes. In the pilot testing of the PSP, one subject was a carpentry shop worker performing painting activities. A pilot study of construction drywall workers demonstrated the feasibility of measuring heart-rate on active subjects, and also showed the high metabolic loads experienced by these workers. The workers expended energy at close to their maximum sustained aerobic capacity, which leads to dramatic elevations in their breathing rates.

In parallel to the development of a physiologic sampler, this project evaluated a novel device for biological monitoring of breath samples: the Rapid Exhaled Breath Analyzer (REBA). REBA is based on commercially available technology and was developed from non-NIOSH funding,. REBA was designed to provide near real-time "direct reading" capabilities for breath sampling of a variety of volatile solvents. The evaluation conducted by this project showed that REBA could detect essentially all volatile solvents for which BEI's (Biological Exposure Index) have been defined by the ACGIH biological monitoring committee.

Like biological monitoring, the purpose of physiologic sampling is to obtain better estimates of individual dose and body burden compared to traditional air samples. Physiologic sampling is highly relevant to situations where workers engage in intense physical activity, since this increases breathing rates and metabolic loads. When work activities generate or release contaminants, creating a positive correlation between increased breathing and air concentrations, traditional sampling methods can dramatically underestimate exposures. Simulation studies by Hart found that even a modest correlation of 0.6 between air concentrations and breathing rate could produce a 6 fold under-estimation of inhaled dose[17].

The specific aims of the study are addressed in order in Sections 2, 3 and 4 in the body of the report. The specific aims of this study were:

(1) Develop a physiologic sampling device to collect air samples at a flow rate proportional to an individual's pulmonary ventilation rate and which can be worn as a free ranging personal monitor suitable for construction workers;

(2) Evaluate a novel instrument, the Rapid Exhaled Breath Analyzer (REBA), for monitoring expired air from solvent exposed construction workers;

(3) Conduct a field pilot study using the physiologic sampler and REBA to analyze breath samples from solvent-exposed workers.

The primary aim of this project was the development and validation of the PSP in a laboratory study. This is documented in Section 2. Section 2.1 develops the theory behind a PSP and proposes a new measure of exposure: the Physiologic Volume Weighted Average (PVWA). This measure of exposure may be interpreted like a traditional "Time-Weighted Average" used by Industrial Hygienists, but it accounts for individual differences in exposure due to variations in breathing rates.

Section 2.2 describes the design of the PSP and hardware evaluation. A digital microprocessor operates the PSP and all operations are controlled by user programmable software. Section 2.22 documents a series of breakthrough experiments conducted to test the performance of charcoal tube sampling with a PSP. In addition, at toluene levels that are realistic in today's work environments, the odds of breakthrough occurring are low. The ability of a charcoal tube to capture toluene is unaffected by variations in the PSP flow rates and depends on the average flow rate over a sampling period. At average flow rates up to 1.0 LPM over 2 hours, air concentrations less than 112 ppm (more than double the TLV) did not lead to breakthrough. The PSP was designed to operate below this break through level. There was an apparent non-linear relationship between the breakthrough mass and average flow rate above 1 LPM. Since only three flow rates were tested in this experiment, the nature of this curve was not well defined by the study results. Field tests using the PSP did not experience any breakthrough problems.

Section 2.3 describes the laboratory validation study. The PSP performed extremely well in the laboratory. Various physiologic signals were coupled with PSP sampling methods to estimate minute ventilation in the laboratory. These are referred to in this document as the PSP calibration methods. Not all of these calibration methods, however, were acceptable for use of the PSP device in the field. The heart rate methods were found most applicable for field trials, but these still have significant limitations. The Direct HR calibration method probably was not complex enough, and the predictive equation used in the indirect HR method was not accurate enough, to meet the stringent requirements set for the laboratory studies. However, both methods have good predictive value for estimating breathing rates, and either of these methods can be considered for field applications. The PSP was used on 30 laboratory subjects without difficulty and the indirect heart rate method (see section 2.3.2) was used on field subjects without difficulty.

Section 3 documents the evaluation of the Rapid Exhaled Gas Analyzer (REBA), the second aim of this study. REBA was designed to perform gas-phase Fourier Transform InfraRed (FTIR) analysis on human breath samples. In the original aims of this project the REBA was intended for use in the field pilot study. However, this objective was not feasible, since all the construction workers we had access to used respiratory protection, which prevented any meaningful elevated exposures. Instead, the validation was conducted on spiked breath samples. Ten volatile organic compounds (VOC) were examined for applicability to FTIR spectroscopy (ethanol, ethylbenzene, n-hexane, methyl ethyl ketone, methyl tert-butyl ether, m-xylene, 1,1,1-trichloroethane, trichloroethylene, tetrachloroethylene, and toluene). Three sets of detection limits (LOD) were determined. $LOD_1$ were generated from partial least squares (PLS) calibration methods using spectroscopic software, $LOD_2$ from spiked breath samples, and $LOD_3$ from blank breath samples. Mixed expired breath samples from 4 subjects were spiked at varying levels with four different VOC (hexane, methyl ethyl ketone, m-xylene and 1,1,1-trichloroethane) to validate spectral data and test overall accuracy. Breath samples spiked with m-xylene were validated by GC/FID. PLS-derived $LOD_1$ ranged from 0.06 - 2.47 ppm. Spiked breath sample $LOD_2$ ranged from 0.52 - 1.21 ppm. Blank breath LOD measurements ranged from 0.17 - 1.70 ppm, except for ethanol, which had an LOD of 11.2 ppm. Predicted concentrations for carbon dioxide (slope = 1.06), m-xylene (slopes = 1.18, 1.21), and methyl ethyl ketone (slope = 0.93) were fairly accurate, while concentrations were underpredicted for n-hexane (slope = 0.69) and 1,1,1-trichloroethane (slopes = 0.58-0.66).

Section 4 describes the field studies, which focused on measuring heart rate as an indicator of physiologic work load. Both field studies demonstrated the feasibility of measuring heart rate as the PSP control signal on free ranging workers. A pilot study of construction drywall workers was done first to test the feasibility of measuring heart rate on active subjects. This study showed that heart rate data was reliably obtained and the monitoring equipment was acceptable to workers. The results also showed these workers experienced very high metabolic loads and expended energy at close to their maximum aerobic capacity, which would lead to dramatic elevations in their breathing rates.

The field testing of the PSP was successful in showing the feasibility of this sampling device. Although the indirect heart rate method used in this study has limited accuracy, the idea behind it warrants further study. The advantage of this calibration method is its inherent simplicity. One only needs to know the weight of the worker and measure his/her resting heart rate. Further, a worker can wear a heart rate monitor during a work shift without interference. This heart rate can be logged via a wristwatch device (for estimating the total pulmonary ventilation over the entire work shift), or the detected signal can be sent to a PSP device. With the exception of the anomaly regarding missed heartbeats for Subject #1, the PSP performed exceptionally in the field studies using the indirect heart rate method. However, based on the small size and protocol limitations of this pilot field study, conclusions regarding a possible correlation between air concentration and minute ventilation of a worker cannot be drawn.

## 1.1 USEFULNESS OF FINDINGS

This research could lead to a number of significant and useful improvements in exposure assessment aimed at disease prevention in the workplace. Using a PSP to characterize exposure intensity, the exposure metric (the PVWA) becomes more "meaningful". It does so by better classifying subjects with regard to exposure, by being closely related to inhaled dose, and by being flexible enough to remain meaningful across a wide range of exposure-disease relationships. In addition (for these same reasons), using the PVWA in conjunction with exposure-time will yield more meaningful cumulative exposure metrics for chronic disease studies. More accurately characterizing exposure in occupational epidemiological studies would improve their ability to identify exposure-disease relationships. This would yield more accurate risk assessments, due to both the improved understanding of exposure-response relationships and provide a better summary of exposure in regard to the population on which the risk assessment is being performed. This, in turn, would lead to higher quality data that regulatory agencies may use as a basis for setting standards.

The introduction of physiologic sampling devices suitable for field use could have a significant impact on the practice of Industrial Hygiene, outside of their potential effect on exposure-disease relationships. Routine use of PSPs could refine task-based sampling by highlighting differences in work rates from various tasks, as well as the different ambient air concentrations related to particular tasks. This would allow hygienists to focus interventions more accurately on the tasks with the greatest exposure potential. In addition, heart rates could be measured prior to air sampling in order to stratify workers with regard to different work rates. Finally, PSPs allow two ways of identifying the most highly exposed population in a sampling campaign: by comparing either the PVWAs or the cumulative inhaled doses. Cumulative inhaled dose has the advantage that minute ventilation does not have to be estimated for an individual or an entire group to relate air concentrations to body burden. This may provide an advantage for chronic toxicants, since a total dose estimate (similar to that used in radiation dosimetry) may be a better indicator of hazard.

## 1.2 ABSTRACT

This report presents the findings of the research project titled "Physiologic Sampler for Airborne Health Hazards (NIOSH RO1-OH03134). Physiologic sampling offers a potential significant improvement in exposure assessment methods applied in workplaces. A physiologic sampler device continuously adjusts the air-sampling rate in proportional to a worker's inhaled air volume. This study resulted in the development of a new physiologic sampling pump (PSP) for personal air sampling on workers. Laboratory and field evaluations of the PSP conducted for this project demonstrated the flexibility, utility, and application of this new device. This study also evaluated the Rapid Exhaled Gas Analyzer (REBA)as a tool for measuring human breath samples. Ten volatile organic compounds (VOC) in spiked breath samples were examined for applicability with this device (ethanol, ethylbenzene, n-hexane, methyl ethyl ketone, methyl tert-butyl ether, m-xylene, 1,1,1-trichloroethane, trichloroethylene, tetrachloroethylene, and toluene). Detection limits (LOD) were determined for all compounds and were sufficiently low to indicate that REBA could monitor these solvents at levels appropriate for their BEI (Biological Exposure Index) as defined by the ACGIH biological monitoring committee. The quantification accuracy was good in many cases but values were under-predicted for some compounds (n-hexane and 1,1,1-trichloroethane). This finding suggests that further refinement in quantification methods and validation of sampling methods is needed for these compounds.

## 2 PHYSIOLOGIC SAMPLER DEVELOPMENT

### 2.1 PHYSIOLOGIC SAMPLING PUMP THEORY

The purpose of this section is: (1) to derive the inhaled dose equations for samples collected on both a traditional sampling pump (TSP) and a physiologic sampling pump (PSP), (2) to derive an equation that relates the sampling results from a PSP to the current regulatory framework, (3) to detail the characteristics of an ideal PSP, and (4) to describe why heart rate might function well as a surrogate for minute ventilation.

#### *2.1.1.1 Inhaled Dose Estimates Using TSP versus PSP*

Three primary variables affect the magnitude of the inhaled dose of a worker: the air concentration, the minute ventilation of a worker, and time. Since air concentration and minute ventilation both fluctuate over time, these variables must be inside the integral in an ideal inhaled dose equation. The inhaled dose D in a time interval T is mathematically defined as the following:

$$D = \int_0^T (C \cdot \dot{V}_i) dt$$

*Equation 2-1: Ideal inhaled dose equation, where C = air concentration, and $\dot{V}_i$ = minute ventilation.*

This ideal inhaled dose equation is able to capture the instantaneous changes of ambient air concentration and minute ventilation. Unfortunately, TSPs capture only the changes in air concentration over time. Since minute ventilation is not inherently accounted for when using TSPs, it must be estimated and factored into the inhaled dose equation after the sampling is complete. Mathematically, this can be represented by removing the minute ventilation variable from the integral, thereby treating it as a constant (mean minute ventilation), as shown in Equation 2.

$$D_{TSP} = \overline{\dot{V}}_i \int_0^T (C) dt$$

*Equation 2-2: Inhaled dose equation when using a traditional sampling pump.*

There are three important weaknesses in our current estimation of inhaled dose (equation2):

1) Minute ventilation is represented by a constant mean value. While some situations exist in which this assumption is reasonable (e.g. sedentary workers), for many jobs this assumption is not legitimate.

2) Mean minute ventilation must be estimated. To incorporate work rate into dose estimates, one must assign a value for minute ventilation. Minute ventilation must be estimated for many different populations and there are very few data available for this purpose, making the accuracy of the derived inhaled dose uncertain. Applying estimates to an entire job category would ignore any individual differences in minute ventilation.

3) The equation does not account for any correlation between minute ventilation and air concentration. While there has been little work done regarding such a correlation, one could imagine several mechanisms that could lead to either a positive correlation or negative correlation between air concentration and minute ventilation.

A positive correlation between minute ventilation and air concentration could result from a situation where the contaminant generation is tied to what the worker is doing; for example, when an increase in work rate causes an increase in contaminant generation. This situation might exists for painters if the harder they work (and thereby increase their minute ventilation), the more contaminant they generate (and therefore increase the local air concentration). If the air concentration of a contaminant is independent of a worker's work rate (and therefore their minute ventilation), then there would be no correlation between air concentration and minute ventilation. A negative correlation could occur if increasing air concentrations tended to lower the work rate and therefore the minute ventilation. For example, if the air contaminant of interest had a negative side effect, (e.g. irritant) then workers might alter (consciously or otherwise) their activity to work harder when the air concentration is lower. One could extend this hypothesis to day-to-day community exposures as well. For example, if people tend to exercise at times when the air pollution is lower, then there would be a negative correlation; on the other hand, some people might tend to exercise when air pollution is higher, possibly because of better weather conditions. Assuming a single constant minute ventilation rate in either cases could significantly over or under-estimate exposures.

Unfortunately there is no data in the literature to judge the existence (or non-existence) of such a correlation. Thus, it is difficult to quantify the potential effect of such a correlation on actual inhaled doses. However, this issue is critical to the decision regarding PSP development. If a significant correlation does not occur in the real world, then TSPs for personal monitoring do not need to be modified; the individual minute ventilation rates can be monitored independently of air sampling. If, on the other hand, a significant correlation exists, then a PSP is needed. This issue will become more clear with an understanding of the potential benefits of PSPs.

PSPs, as opposed to TSPs, can integrate minute ventilation into the inhaled dose estimate since pump rate changes in proportion with minute ventilation. Thus, the minute ventilation variable remains inside the integral in the inhaled dose equation for PSPs:

$$D_{PSP} = k\int_0^T (C \cdot \dot{Q})\,dt$$

*Equation 2-3: Inhaled dose equation when using a physiologic sampling pump, where $k$ = the proportionality constant between the pulmonary ventilation and the pump flow rate, and $\dot{Q}$ = the pump flow rate.*

When minute ventilation is accounted for in this manner, all of the weaknesses previously mentioned with regard to TSPs no longer apply.

### *2.1.1.2 PSP Measurements in Relation to TWAS*

Time-weighted averages are the most common measure of exposure intensity. Their frequency of use has, to some degree, been driven by the use of TWAs in official and unofficial standards (PELs and TLVs, respectively). TWAs are calculated by averaging the ambient air concentration over time, as shown in Equation 2-4.

$$TWA = \frac{1}{T}\int_0^T C\ dt$$

*Equation 2-4: Time weighted average equation.*

The relationship of personal sampling data to TWAs is very important because collected samples must be evaluated as to whether the exposure levels are acceptable or unacceptable. Since TWAs are the most common exposure metrics used for this purpose (e.g. PELs and TLVs), it would be convenient to be able to calculate a similar exposure metric using PSP data. Based on an understanding of how TWAs are calculated using TSP data (Equation 2-4) and an understanding of the relationship of how PSPs differ from TSPs, one can generate an equivalent exposure metric called the Physiologic Volume Weighted Average, or PVWA :

$$PVWA = \frac{1}{V_{TOT}}\int_0^{V_{TOT}} C\ dV$$

*Equation 2-5: Physiologic volume weighted average equation, where $V$ = inhaled volume and $V_{TOT}$ = total inhaled volume over the work shift.*

A PVWA applies to samples collected on a PSP and is equivalent to the TWA except that the worker's minute ventilation is incorporated into the PVWA.

The first logical question is, how will PVWAs differ from TWAs? The answer is that they will not differ unless there is a correlation between air concentration and minute ventilation. If there is a positive correlation then the PVWA would be greater than the TWA, and vice versa; in either of these situations, the TWA could not accurately quantify the inhaled dose. Even if there is no correlation, and the PVWA equals the TWA, the PVWA is still useful. To demonstrate this, the estimated inhaled dose equations can be re-written to incorporate TWAs and PVWAs:

$$D_{TSP} = \bar{V}_i \cdot T \cdot TWA$$

*Equation 2-6: Inhaled dose equation for samples collected on traditional sampling pumps, incorporating the TWA value.*

$$D_{PSP} = V_{TOT} \cdot PVWA$$

*Equation 2-7: Inhaled dose equation for samples collected on physiologic sampling pumps, incorporating the PVWA value.*

If the TWA equals the PVWA, then it appears that Equations 2-6 and 2-7 would be mathematically equivalent. The difference comes from the fact that a PSP provides an estimate of the total inhaled volume for each worker. As noted earlier, if no correlation exists between minute ventilation and air concentration (and the TWA equals the PVWA) then a PSP is unnecessary. Air concentrations can be obtained via a TSP, and minute ventilation can be obtained independently of any sampling device.

### *2.1.1.3 Heart Rate as a Predictor of Minute Ventilation*

Currently, inhaled volume is estimated by attempting to determine the average work rate of a job. It is not measured directly because the equipment necessary to do so (a pneumo-tachometer or flow meter mask) is a burden for both the worker and the industrial hygienist. The use of heart rate to predict pulmonary ventilation, while not a novel idea, has not been investigated thoroughly enough to be used by Industrial Hygienists in the field. This section provides an overview of the physiological relationship between heart rate and minute ventilation.

The respiratory system is composed of a series of branching airways that conduct air from outside the body to the gas-exchanging regions within the lungs, the alveoli. The volume of air inhaled and exhaled is called the tidal volume. Ventilation is intricately linked to cellular respiration by the pulmonary and peripheral circulatory systems,[1] and ultimately reflects the oxygen requirements and carbon dioxide production of the body. The lungs must maintain precise control of these two critical gases in order to allow the body to maintain homeostasis under widely varying conditions. For example, when greater quantities of oxygen are utilized by mitochondria within muscle cells, there is a greater production of carbon dioxide, the peripheral circulation dilates, blood flow increases due to an increase in stroke volume and heart rate, and minute ventilation increases due to an increase in tidal volume and breathing frequency.[1] Tidal volume is the primary means by which minute ventilation increases, especially at low exercise intensity.[1,5] As the tidal volume begins to exceed half of the vital capacity, frequency plays a larger part of the increase in minute ventilation. Frequency has been characterized as having a curvilinear relationship with minute ventilation.[1]

At the start of exercise, the profile for minute ventilation can be divided into three phases. The first phase is a rapid increase in minute ventilation that commences in the first 15-20 seconds according to Åstrand *et al.*, and in the first 5-15 seconds according to Miyamoto *et al.*[5,6] Åstrand *et al.* credits the hypothalamic center with this phase, suggesting that the signals sent to the muscles to initiate exercise are paired with signals sent to the respiratory control centers. The second phase is exponential, whereby the degree of rise is related to the severity of the exercise. The carotid bodies, which are peripheral chemoreceptors, are thought to mediate this phase. The third phase is one of steady-state, whereby at exercise levels below the anaerobic threshold, the minute ventilation is linked closely to the carbon dioxide production.[5] At the end of exercise, this profile is reversed. The fast response phase leads to a sharp drop in minute ventilation, followed by a slower, exponential phase. Finally, minute ventilation plateaus at a level related to the new exercise level (or rest).

The cardiovascular system is responsible for the transport of oxygen and carbon dioxide between the alveoli and the cells undergoing respiration. When cellular respiration increases (i.e. during an increase in work rate), the distribution of perfusion in the body changes and the cardiac output is increased. Cardiac output, which is defined as the flow of blood from the heart per unit time, is determined by the stroke volume and heart rate. Stroke volume (the volume of blood ejected per heart beat from either ventricle) increases immediately upon the start of exercise, the magnitude of which is dependent on several factors such as age, fitness and body size. After this initial increase in stroke volume, additional increases in cardiac output are attributed to increases in heart rate.[1]

Heart rate begins to increase within 10 seconds from the onset of exercise.[1,6] During this time period, the heart rate increases on the order of 10-35% of the total change. Like the phases of minute ventilation, an exponential phase follows this fast response. The fast response drop after the end of exercise is longer, and ranged from 10-30 seconds in studies conducted by Miyamoto et *al.*.[6]

Just as minute ventilation is tightly coupled with oxygen demand and carbon dioxide elimination, so too is cardiac output. Since they are both linked to the same source (an increase in muscle activity), they must be fairly tightly coupled to each other. Since stroke volume is reasonably fixed, we will consider heart rate a surrogate for cardiac output. While both heart rate and minute ventilation respond to changes in muscular activity, there is a lag between the change in heart rate and change in minute ventilation. This lag is not simple to describe and depends on many factors, such as the rate of change of work rate and the pattern of change.

*Bakker et al.*, for example, examined the dynamics of minute ventilation and heart rate in response to sinusoidal (at seven different frequencies) and impulse workloads in four men. For all subjects and all conditions, the heart rate lag was **smaller** than the ventilation lag. Therefore, they concluded that the heart rate responds faster to changes in work load than does the minute ventilation.[7] Other authors support this conclusion and add that "the time constant of the heart rate change is shorter than that of the corresponding ventilation change."[5]

The relationship between heart rate and minute ventilation remains tightly linked under both steady state and non-steady state conditions.[3,8,9] Satoh et al., for example, found that under steady state conditions, the average correlation coefficient between heart rate and minute ventilation was 0.97. Under non-steady state conditions, Treese *et al.* found that the mean correlation coefficient between heart rate and minute ventilation was 0.9, and that the data was best-fit by using a linear curve after log-transforming the minute ventilation data.[8]

Mermier *et al.* also studied the relationship between heart rate and ventilation under non-steady state; they examined the 15-second averages of each variable while subjects performed both progressive and non-progressive exercise tests. Like Treese et al., they found that the within-subject relationship between these factors was curvilinear, and was best characterized by a linear regression of the logarithm of minute ventilation versus heart rate. One additional finding of interest was that the relationship between minute ventilation and heart rate remained constant, regardless of the pattern of workloads (e.g. progressive versus non-progressive). This finding is an important indicator that a heart rate- minute ventilation calibration curve derived via progressive exercise testing can be meaningfully applied to non-progressive activity (as would be expected in a work environment). In addition, they concluded that "during averaging times of 15 seconds, minute ventilation remains tightly coupled to heart rate."[9] This conclusion is important in terms of the PSP design and will be referred to in Chapter 2.

McCool and Paek studied the within-subject minute ventilation to heart rate relationship at steady state for four different activities (cycling, arm cranking, lifting and pulling). They concluded that "the minute ventilation-heart rate relationship calibrated during one type of activity can be used to predict ventilation during another type of activity."[10] Samet *et al.* concluded otherwise; they found that minute ventilation increased more steeply with upper body exercise as compared to lower body exercise.[11] Note that this discrepancy is extremely important, because the ability to apply a calibration performed on an ergometer to a variety of activities that workers may perform is directly related to the accuracy of using heart rate to estimate minute ventilation.

McCool *et al.* and Samet *et al.* cannot both be right; other literature tends to support the conclusion, by Samet *et al.*, that the slope of the minute ventilation-heart rate relationship is steeper for upper body exercise. For example, Taguchi and Horvath found that for a given heart rate, minute ventilation is higher for upper body exercise as compared to lower body exercise. They attributed the larger increase in ventilation to higher muscle spindle activity and stimulation of mechanoreceptors; this would stimulate the respiratory center, thereby inducing reflex ventilation.[12]

McCool *et al.* suggest that the reason their results differed from Samet *et al.* might have been due to the fact that their subjects had a much more restricted range of heart rates.

#### *2.1.1.4 Advantages and Disadvantages to Heart Rate*

There are both advantages and disadvantages of using heart rate as a surrogate measure of minute ventilation. The advantages include:

1. Heart rate is very easy to measure; three electrodes embedded in a band can easily detect the R-wave when wrapped around a subject's chest. Subjects are not likely to resist wearing a heart rate monitoring band. Since there is one R-wave per heartbeat, one can time the period between R-waves and determine the frequency (or beats per minute).

2. Heart rate is tightly coupled to minute ventilation under both steady state and non-steady state condition, even when using a 15-second averaging period.

3. Large numbers of exercise tests have been performed which could lead to an extensive enough database to develop a reliable predictive equation between heart rate and ventilation.

The disadvantages also are important to emphasize:

1. Heart rate is not actually a measure of lung volume changes or airflow.

2. The relationship between heart rate and minute ventilation varies between subjects. Thus, this relationship must be predicted in some manner, either by use of a predictive equation or via individual calibrations.

3. The slope of the minute ventilation-heart rate relationship probably is steeper for arm exercise than for leg exercise. Minute ventilation could be underestimated when workers perform upper body activities if the ventilation-heart rate calibration curve was developed using exercise tests using lower body exercise. A relatively small error may occur at lower work rates, but at higher work rates it could be significant.

### 2.2 HARDWARE DESIGN

The physiologic sampling pump developed in this research has a sophisticated digital controller, called the Physiologic Sampler Control Unit (or PSCU)„ which received signals from the following devices: a cardiotachometer, a pneumotachometer, and a respiratory inductive plethysmograph (RIP). The cardiotachometer signal provided a measure of heart rate, and both the pneumotachometer and RIP provided signals related to minute ventilation. By running a BASIC program incorporating calibration curves that related each signal to minute ventilation, the PSCU was able to estimate minute ventilation based on any (or all) of these signals. Every 15 seconds the minute ventilation estimates were updated and a new voltage was sent to a traditional sampling pump that had been modified to change its pump rate in response to the voltage sent from the PSCU; this voltage always corresponded to a flow rate that was $1/40^{th}$ of the estimated minute ventilation.

A commercial personal sampling pump ( a Gilian "Gilair 5" ) was selected as the basis for this device. This pump was selected because it has the capability to give a wide dynamic range of flow rates, from approximately 75 ml per minute to a maximum of about 7.5 liters per minute. In addition, the analog control loop provided very stable and tight control of the pump flow over this

range. We arranged to obtain complete schematics for the pump from the manufacturer; by agreement we cannot reveal details of the internal control circuit because the manufacture considers this information proprietary.

A simple modification was devised that adapted the pump into a variable flow device. A resistor network was attached in the control loop at a point in the circuit nominally connected to the wiper of the flow control potentiometer. A shielded signal lead attached to the network was brought outside the case. An analog DC control signal between 0 and 100 mV injected via the signal lead into the pump feedback control loop varies the pump rate. This external control signal overrides the normal flow control setting when supplied by a low impedance source, such as the output of a linear amplifier. A benefit of this modification scheme was that the pump would continue to operate normally if no connection was made to the external signal input. Further, when the pump was under external voltage control, the feedback circuit remained closed loop, so that the flow regulation, pressure compensation, and fault sensing circuits continued to function normally. The net result is that the modified pump functions as a linear DC proportional controlled sampling device.

A second component of the physiologic sampler system is the Physiologic Sampler Control Unit (PSCU). The PSCU accepts a physiologic input signal and produces an analog output signal to control the pump. The PSCU has to provide a number of system functions including:

- Conditioning the analog or digital physiologic input signals;
- Converting the input signals to a calibrated measure of minute ventilation for the individual subject;
- Converting the minute ventilation to a proportional calibrated flow rate for the pump;
- Data logging the pump flow rate over time to record the total sample volume;
- Sending an appropriate output signal to control the pump at specified time intervals.

These functions were implemented with a digital micro-controller and custom designed input-output hardware. The micro-controller used for the PSCU was a Tattletale model 4A (Onset Computer, Falmouth MA). The Tattletale 4A provides the following standard features: 8-channel, 12-bit analog-to-digital conversion, onboard clock/timer, 16 digital input/output lines, 2 channel serial interface (programmable UART), 32 K of non volatile RAM data storage, and a regulated 5 volt supply. Operating current is strongly dependent on the operating program activities; typical power requirements are 7 to 15 volts DC at a current of about 20 mA (although much lower power operation is possible).

Functions for this compact (2.25x 3.75 inch) micro-controller device are programmable in TxBASIC, a compiled BASIC-style language customized for the controller features. Control programs are written on a laptop or desktop PC, compiled, and downloaded into the Tattletale via a standard RS-232 interface connection. Functions in TxBASIC allow the user to provide input or control the operating program when the terminal is connected. When the terminal is disconnected, the program will operate unattended until the terminal connection is re-established. Data logging is done in a compact binary format, with time stamping of each record. The binary format is expanded to ASCII format for downloading. Retrieval of logged data is accomplished over the same RS-232 serial interface with a PC attached as a terminal.

In addition to the standard features of the Tattletale 4A, a number of auxiliary circuit functions were needed. The four main functions were: 1) input signal conditioning; 2) digital to analog conversion for the pump control signals; 3) output signal drivers; 4) and auxiliary power supply.

These functions were developed on auxiliary "piggy-back" circuit boards that plugged directly onto a buss connector for the Tattletale 4A.

The digital-to-analog converter for the PSCU used an Analog Devices AD7225. This chip provides 4 independent analog output channels with 8-bit resolution, which allows the PSCU to independently control up to 4 sampling pumps. Input lines are addressed sequentially via a 74HC595 serial shift register and the 4 outputs are updated all at once when latched. The outputs are buffered by a CA660 CMOS quad operational amplifier to provide low impedance signals to the pumps.

The input signal conditioning board accepts signals from a pneumo-tachometer, a Respiratory Inductive Plethysmograph (RIP), or a cardiotachometer to measure heart rate. The pneumo-tachometer and RIP signals are analog voltages, which are processed by a LM324 quad operational amplifier. The pneumo-tachometer signal resembles a positive rectified sinusoid. The DC offset of the pneumo-tachometer signal is level-shifted to +0.5 volts and the signal range is adjusted to span from 0 to +4.5 volts at the A/D converter. The RIP provides two bipolar sinusoidal analog signals, one signal for each band, corresponding to changes in the rib cage or abdominal cross section area. The DC zero crossing of the RIP signals are level-shifted to an offset of +2.5 volts and the signal range is adjusted to span from 0 to +5 volts at the A/D converter.

The cardiotachometer signal is broadcast from a small, wireless transmitter unit (Polar Inc) strapped to the subject's chest with an elastic band. The heart rate input is a 15 ms digital pulse corresponding to the R-wave detected from the electrocardiogram. The receiver unit inside the PSCU can detect the 5 kHz transmitter signal up to 3 feet away. The heart beat input is processed by a 7473 flip flop operating in toggle mode to provide an alternating-stepped 5V transition for each heart beat. This arrangement eliminates the need for interrupts or high-speed digitization to reliably detect the heart beat. Software timing of the inter-beat interval using the internal clock provides a beat-by-beat estimate of heart rate.

Figure 2-1 shows a block diagram of the PSP system. Output lines "A" through "D" represent analog control signals connected to the modified sampling pumps (two are illustrated in the diagram). The heart rate input is always connected and automatically enabled when a pulse from the wireless link is detected. The pneumo-tachometer and RIP inputs normally are grounded and enabled only when connected to an input signal.

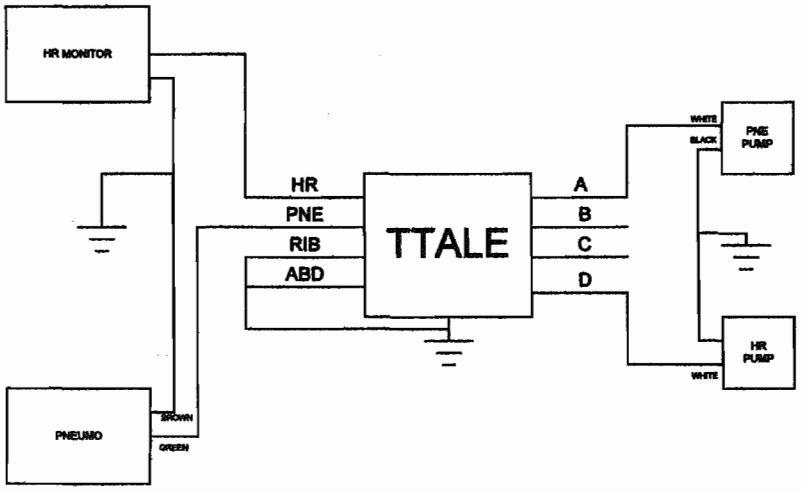



*Figure 2-1: Block diagram of Physiologic Sampler showing PSCU and Pump connections*

### 2.2.1 PUMP RESPONSE CHARACTERISTICS

An important step in the development if this PSP system was to assess the ability of the pump hardware to accurately respond with the appropriate flow rate to the control program signal. Two types of testing were conducted, steady state tests to evaluate the ability of the PSP produce a repeatable calibrated flow response, and dynamic testing to evaluate the ability of the PSP to follow transient changes in flow. Both tests are important since the pump must respond in a controlled manner in order to obtain an accurate estimate of the total air volume collected during a sampling session.

#### *2.2.1.1 Steady state Response*

The steady state response of the PSP system was evaluated by calibrating the pumps compared to a bubble meter (Gilibrator) primary standard. A TX basic program generated several different control voltages at the D/A converter and sent these to the pump. The actual control voltage was monitored with a digital voltmeter (Fluke Inc.) during calibration. Only a limited range of flow rates was needed so the primary calibration was limited to the range of zero to 3.5 l/min. At low flow rates, the non-linear pump response was best described by a quadratic function. Figure 2-2 shows the calibration data of all four pumps, along with a calibration curve fitted to the response for Pump B. Individual pump coefficients were stored in the tattletale non-volatile memory.

In addition, a self-calibrating software procedure was implemented for routine field applications. A mass flow meter connected downstream of the pump provided the flow rate standard, and this electrical signal flow rate signal was connected into an analog input (Pneumo-tachometer input). After the user entered the linear calibration equation for the mass flow meter signal, the software would automatically step the pump through a range of control voltages while monitoring the flow rate signal. The software would then automatically generate the pump calibration coefficients from a least squares fit of the data and save the coefficients in the micro-controller memory.

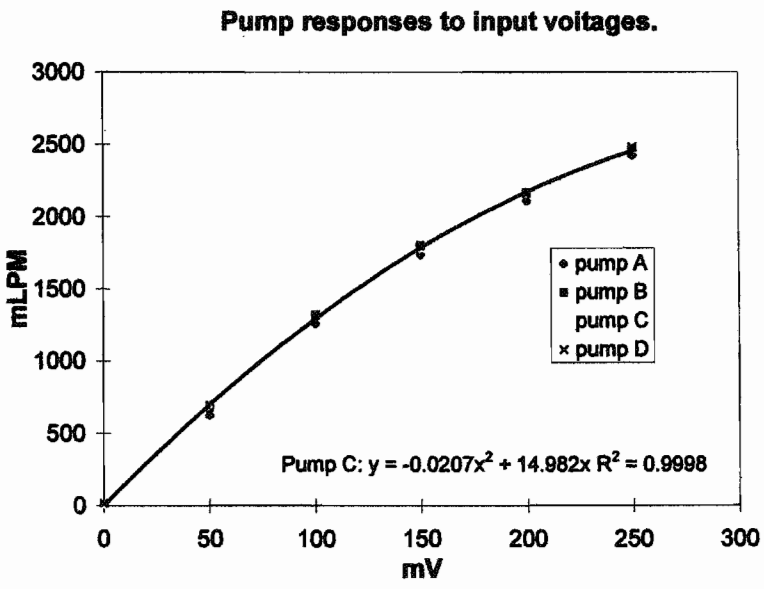



*Figure 2-2: Steady state calibration response of pumps, calibration line shown for pump B*

### *2.2.1.2 Dynamic response*

It is important to understand the dynamic behavior of the pump to assess the error associated with the pump's response to an input voltage. The inability of the pump to respond instantaneously to a new input voltage is a characteristic of many Electro-mechanical systems. Usually these systems can be described as either a first order linear system or a second order linear system. A first order linear system can be characterized by the differential equation:

$$\tau\frac{dx}{dt} + x(t) = y(t) \qquad \textit{Equation 2-8}$$

Where y(t) is the input at time t, x(t) is the output at time t, and $\tau$ is the time constant of the system.[15] The third component in this equation, $\tau$ dx/dt, is the transient response, where $\tau$ is the time constant of the system.

The equation relating the response of a first order linear system to a rising step input is:

$$x(t) = X_f + (X_i - X_f) \cdot e^{-t/t} \qquad \textit{Equation 2-9}$$

Where x(t) is the output response, $X_f$ is the final value of x after the transients have died out, $X_i$ is the initial value of x, just after the step was imposed, and $\tau$ is the time constant of the system.[16] Graphically, the output of a first order system in response to a positive step input is an exponentially rising curve.

A series of experiments was conducted to determine whether the pumps responded to the changes in voltage from the PSCU as a first order system. In the process, we also evaluated the approximate time constant of the system response. These tests were complicated by the fact that the pump flows were measured using mass flow meters, instruments that also had a first order response.

Two Txtools programs were written that would instruct the PSCU to generate of a series of voltage steps. The first program had voltage steps that were 15 seconds in length, and the second program was identical except that the voltage steps were 60 seconds long. The PSCU output voltages to each pump (A through D) were first calibrated with a digital voltmeter. Next, each pump was tested three times using Vtest15s. A mass flow meter was attached upstream and its output voltage was digitally recorded at 100 Hz sampling rate on a personal computer using Dataq software and hardware (Dataq Inc.). Finally, the Vtest60 program was sent to pumps "A" and "C" two times, hereafter referred to as "Run 1" and "Run 2". During Run 1, the mass flow meter was located upstream of the pump. For Run 2, however, a valve was used to select whether the pump pulled air through the mass flow meter or not. For each 60-second voltage step in the Vtest60 program, the air was pulled through the mass flow meter for only the last 30 seconds to decouple the mass flow meter transient response from the pump response.

The mass flow meter output voltages for Runs 1 and 2 were overlaid to allow for a comparison of the combined pump - mass flow meter responses and the mass flow meter alone. Note that after 30 seconds into each step, we assumed the pump response had stabilized so that the mass flow meter response would not be linked to the pump response.

The time constant for the mass flow meter (whose published value was 0.08 seconds) and the time constant for the pump and mass flow meter in series were calculated. The time constant for the pump could then be estimated by assuming the time constants would be additive.

Figure 2-3 shows the responses recorded from all four pumps to the same input voltage applied for 15 seconds per step. Note that except for an offset difference (due to the mass flow meters), the responses appear to be indistinguishable. The signals were further examined to compare pump responses during a positive step and negative step. These tests indicated that the pump and mass flow meter system behaved in a symmetrical fashion and there was no evidence of hysteresis.

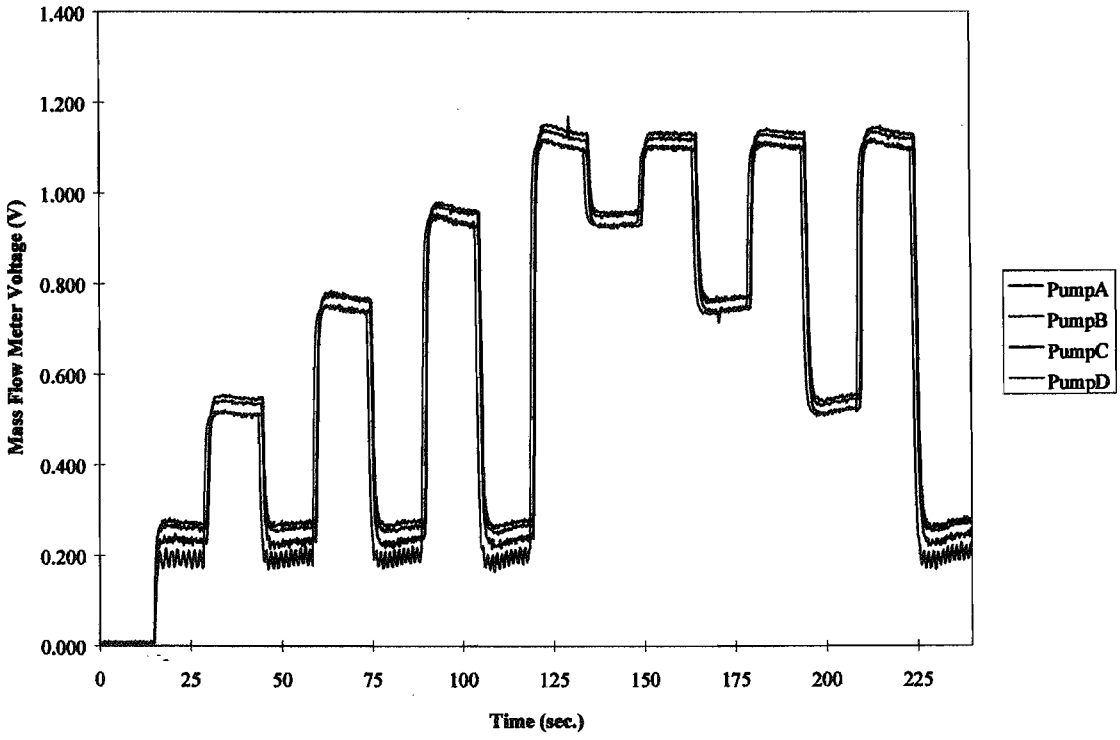



*Figure 2-3: Mass flow meter voltages for pumps A, B, C, and D, using 15-second steps.*

Figure 2-4 displays the mass flow meter data obtained using the pump "A". The test results illustrated two test conditions: (1)when the mass flow meter measured the pump flow throughout the procedure, and (2) when the mass flow meter was introduced at 30 seconds into each step. Figure 2-5, shows one of the steps shown in the previous Figure in more detail. In Figure 2-5 the mass flow meter response alone at 30 seconds is shifted in time to overlay the combined pump and mass flow meter response at 0 seconds into the step (under Condition #1).

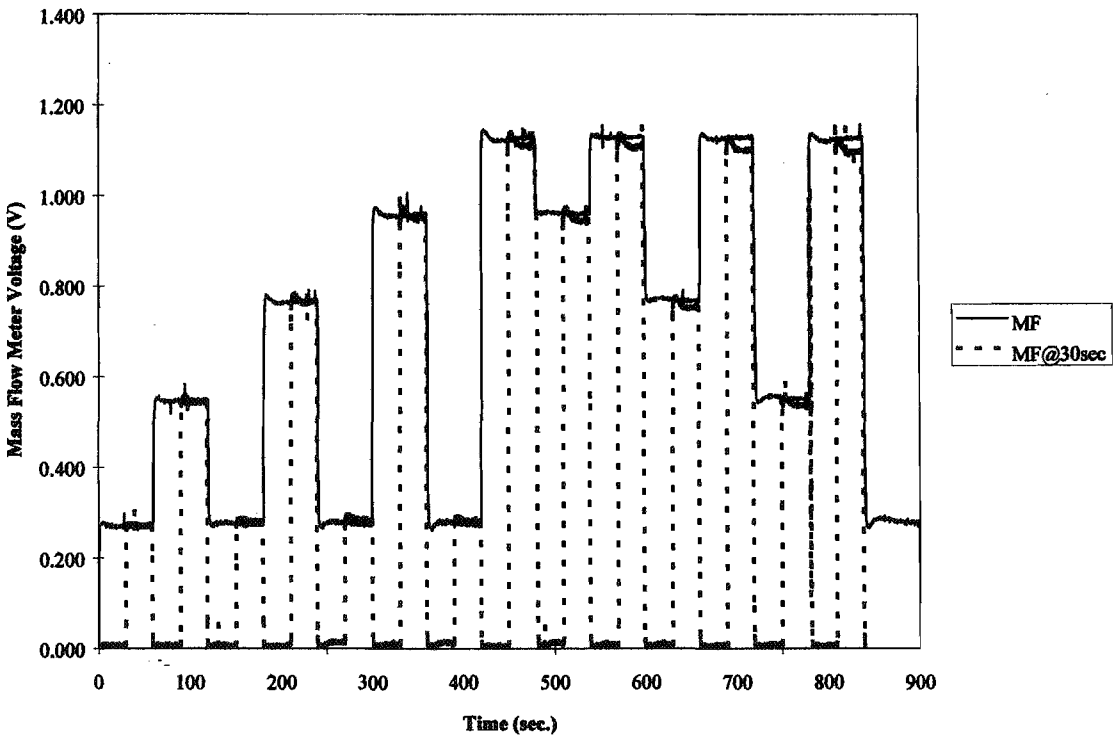



Figure 2-4: Mass flow meter voltage during step input to GilAir5, under two conditions: (1) flow through mass flow meter was continuous (solid line), (2) flow through mass flow meter was commenced at 30 seconds into each voltage step (dotted line).

Based on these tests the response of the pump-mass flow meter system is predominantly a first order linear system, with at most a very small second-order component. Figures 2-4 and 2-5 suggests that the second order component can be attributed to the mass flow meter response. The mass flow meter documentation states that the mass flow meter time constant is 0.08 seconds. The time constant for the mass flow meter in this experiment was calculated to be approximately 0.08 seconds, as expected. The time constant for the pump-mass flow meter system was then calculated using the data from Condition #1 for the same input step. This time constant for the combined flow meter and pump system was approximately 0.33 seconds and by superposition, the time constant for the pump was estimated to be 0.25 seconds.

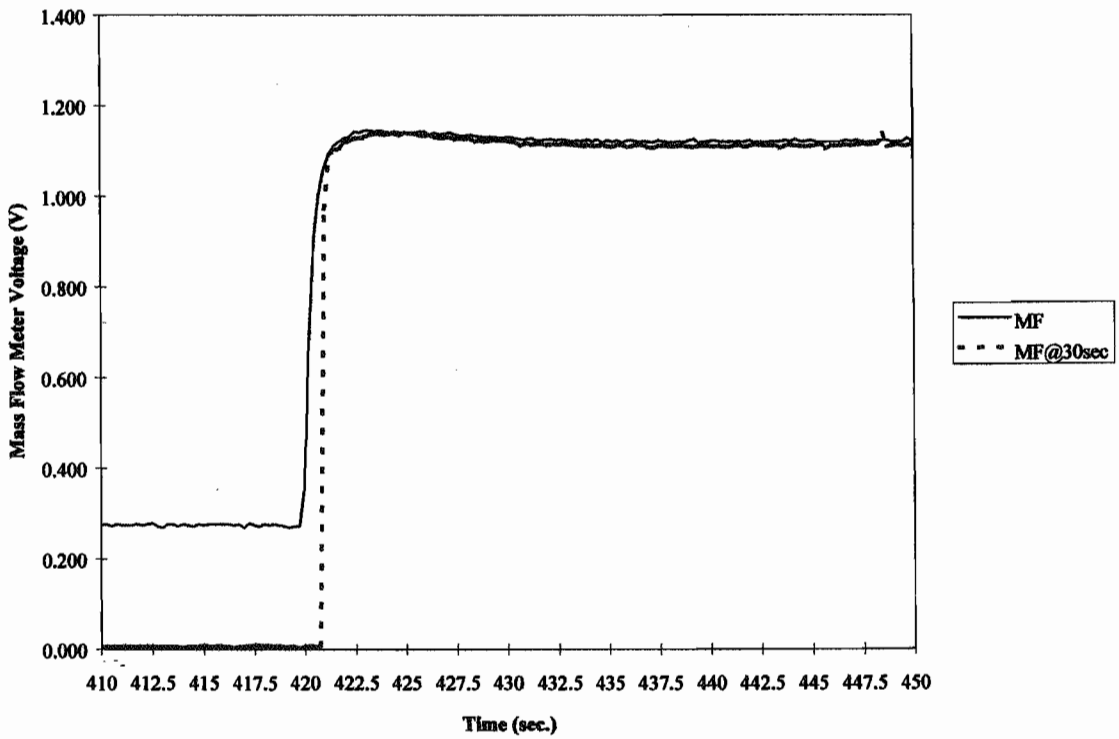



Figure 2-5: The data from the largest step in Figure 4, with mass flow meter response at 30 seconds into step shifted to overlap with original recorded values.

Since it takes three to four time constants for a system to stabilize, we can assume that the pump stabilizes at each new flow rate within a second. In this testing, the pump responded immediately to a step voltage change, stabilizing at its new flow rate within a second or less. There was no evidence of overshoot in the response or of oscillation in the feedback control. The magnitude of the error resulting from "wind-up time" was not significant for the protocol that the subjects performed. This conclusion was based on the results indicating that the mass flow meter results were not significantly different from the PSCU data logged results.

### 2.2.2 CHARCOAL TUBE BREAKTHROUGH CHARACTERISTICS

A physiologic sampling pump varies its pump rate in proportion to a worker's estimated inhalation rate. This raises the question, in regard to sampling methods, of whether a variable flow rate affects the breakthrough point of a charcoal tube.

Charcoal tubes are divided into two sections: the front section and the back section. The front section contacts air first and is designed to capture organic compounds in the sampled air. The back section is necessary in order to validate that none of the contaminant of interest was able to pass through the front section without being captured. Therefore, in order to determine whether the mass collected on the front section of a charcoal tube is reflective of the true mass of contaminant in the air sampled, the back section must be analyzed. Breakthrough has occurred when the contaminant is found on the back section of the charcoal tube.

The primary purpose of this experiment was to validate that the breakthrough point of a charcoal tube is unaffected by the variability of the pump flow rate.

A secondary purpose of this experiment was to validate that if the laboratory subjects had actually been exposed to toluene contaminated air (at realistic levels) then the samples would not have been compromised due to breakthrough problems.

### *2.2.2.1 Methods*

For this experiment, the data from three laboratory subjects were used. The subjects were selected based on the variance and mean of the flow rate of the pump controlled by the predicted minute ventilation values (based on the Indirect HR Method). In addition, a constant flow condition was added (e.g. no variance) where the average flow rate was set to correspond to that of the subject that had the highest variance of flow rate (Subject #29). The statistics for these four conditions are displayed below in Table 2-1.

*Table 2-1: Four conditions tested in this experiment.*

| Condition # | Subject # | Average pump flow rate | Variance of pump flow rate |
|---|---|---|---|
| 1 | 1 | 0.51 | 0.01 |
| 2 | 17 | 1.01 | 0.08 |
| 3 | 29 | 0.74 | 0.15 |
| 4 | N/A | 0.74 | 0 |

A solvent generator was used to create air of known toluene concentrations. This generator introduced toluene via a syringe pump into a mixing chamber with a known clean airflow rate. The syringe pump flow rate and clean airflow rate could be adjusted to provide a wide variety of known air concentrations.

A charcoal tube was attached to a sampling port downstream of the mixing chamber. The charcoal tube, in turn, was connected to a physiologic sampling pump (or traditional sampling pump, in the case of the Condition #4).

The sampling time for each charcoal tube was two hours. Conditions #1-3, entailed sending subject data to the PSP. The two hours of data for the breakthrough experiments were generated by sending the 40 minutes of data (collected for each laboratory subject) to the PSP three times in series; the methods for the process of loading the PSCU with the program LABPSP and sending the subject data to the PSP were described in the laboratory validation section.

For Condition #4, the TSP was set to a flow rate of 0.74 liters per minute using a primary standard. The TSP then pulled air through each charcoal tube for a total of two hours.

Samples were collected for each Condition at varying air concentrations until two samples closely bracketing the breakthrough point were found. To ascertain when breakthrough occurred, the back section of each tube was desorbed and the desorption solution was sent to the University of Washington's Environmental Health Analytical Laboratory for qualitative analysis. If the solution contained a higher concentration of toluene than the desorption solution from a blank tube, breakthrough was determined to have occurred.

The expected masses of toluene on the two charcoal tubes bracketing the breakthrough point for each Condition was calculated using Equation 2-10.

$$\text{Expected Mass (mg)} = \frac{C \cdot V \cdot MW \cdot (1/24.04)}{1000}$$

*Equation 2-10. Expected mass (in mg) collected on a charcoal tube. C= air concentration (in ppm), V= sampled air volume (in L), and MW= molecular weight.*

To confirm that the expected masses on the charcoal tubes were accurate, the front sections of the charcoal tubes at each breakthrough point were desorbed and analyzed for toluene per NIOSH Method 1500. The only variation on the method was that the charcoal from the front section of each tube was added to 2-ml of desorption solution, as opposed to 1-ml. The concentrations of the five standards ranged from 0.1-ml to 0.5-ml toluene per ml of desorption solution.

### *2.2.2.2 Results*

The expected masses of the two samples bracketing the breakthrough point will be referred to as the breakthrough mass. The air concentrations and breakthrough masses for all four sampling conditions are listed in Table 2-2.

*Table 2-2: Expected masses of toluene loaded onto charcoal tubes that were under and over the breakthrough point for each sampling condition.*

| Condition # | Under or Over Breakthrough Point | Average pump flow rate | Variance of pump flow rate | Air conc. (ppm toluene) | Expected mass (mg) |
|---|---|---|---|---|---|
| 1 | Under | 0.51 | 0.01 | 366 | 86 |
| 1 | Over | 0.51 | 0.01 | 376 | 88 |
| 2 | Under | 1.01 | 0.08 | 112 | 52 |
| 2 | Over | 1.01 | 0.08 | 118 | 54 |
| 3 | Under | 0.74 | 0.15 | 250 | 86 |
| 3 | Over | 0.74 | 0.15 | 255 | 88 |
| 4 | Under | 0.74 | 0 | 255 | 86 |
| 4 | Over | 0.74 | 0 | 260 | 88 |

Note that Conditions #3 and #4 differ only in the variance of the flow rate (the most variance exhibited by all subjects versus no variance) and that the breakthrough mass was the same. The breakthrough mass was also the same for Conditions #1 and #3, where the average flow rates were 0.51 LPM and 0.74 LPM, respectively. The breakthrough mass for Condition #2, however, was much lower than that of the other Conditions (~ 60%).

The validity of the expected masses was confirmed by GC analysis of the front sections of the charcoal tubes. The recovered masses reported in Table 2-3 are consistent with charcoal tube desorption characteristics. Note that not all the toluene collected by the charcoal will desorb off the charcoal into the desorption solution; this established characteristic adds to the error inherent in charcoal tube analysis.

*Table 2-3: Recovered masses and apparent desorption efficiencies for the front sections of the charcoal tubes surrounding the breakthrough point for all four conditions.*

| Condition # | Under or Over Breakthrough Point | Expected mass (mg) | Recovered mass (mg) | Desorption Efficiency (%) |
|---|---|---|---|---|
| 1 | Under | 86 | 81 | 94 |
| 1 | Over | 88 | 80 | 91 |
| 2 | Under | 52 | 40 | 77 |
| 2 | Over | 54 | 45 | 83 |
| 3 | Under | 86 | N/A | N/A |
| 3 | Over | 88 | N/A | N/A |
| 4 | Under | 86 | 82 | 95 |
| 4 | Over | 88 | 82 | 93 |

The recovered masses for Condition #3 are not available due to error during the desorption process; unfortunately it was not possible to repeat the samples. There is no reason to expect, however, that the recovered masses would not be similar to Conditions #1 and 3, which had the same expected masses.

### *2.2.2.3 Summary of Breakthrough Experiments*

The breakthrough mass was not affected by the variability of the pump flow rate. There was an apparent non-linear relationship between the breakthrough mass and average flow rate. As only three flow rates were tested in this experiment, the nature of this curve was not well defined by the results. At flow rates of 0.51 and 0.74 LPM the breakthrough mass remains stable. However, at some point between 0.74 and 1.01 LPM the breakthrough mass begins to drop. One could hypothesize that there is a critical flow rate above which the air does not have enough contact time with the charcoal in the front section to bind reliably; therefore, some organic contaminant is able to pass through to the back section where it may be captured.

Over a two hour period at an average flow rate of 1.0 LPM, air concentrations less than 112 ppm did not lead to breakthrough. The high air concentrations used in this experiment were necessary to create a situation that would lead to breakthrough so that the sampling characteristics might be understood. However, these air concentrations for toluene are unlikely in the real world. The PEL is toluene is 50 ppm and the action level is 25 ppm; thus, even using one charcoal tube to sample for 8 hours no breakthrough is expected at toluene concentrations equal to the action level. The ability of a charcoal tube to capture toluene is unaffected by the variability of the flow rate of the pump. In addition, at toluene levels that are realistic in today's work environments, the odds of breakthrough occurring are low.

## 2.3 LABORATORY VALIDATION ON ACTIVE HUMAN SUBJECTS

The physiologic sampling pump (PSP) developed by Yost, Hart, and Lopez is described in detail in the previous section. In brief, a modified GilAir 5 sampling pump is controlled by a signal from a PSCU computer that can be programmed to control the pump rate. The pump rate varies in proportion to an estimate of the minute ventilation of the person wearing the PSP. The PSCU in this laboratory experiment was designed to accept input signals from the following devices: (1) a pneumotachometer (providing an instantaneous flow rate signal), (2) a cardiotachometer (providing heart rate data), and (3) a respiratory inductive plethysmograph (providing two signals which

correspond to the cross-sectional area of the chest and abdominal cavities). This design allowed for the evaluation of different methods for estimating the minute ventilation.

Using these three input signals, five methods were used for estimating the minute ventilation (hereafter referred to as "Methods"). Each Method, along with the input signal from which it was derived and its purpose for being included in the study, is listed below:

1. Pneumotachometer Method. Derived from the pneumotachometer signal. Designed to provide a reference for how well the PSCU processing performs compared to the raw signal (Primary Standard). Abbreviated "Pneumo Method".

2. Direct Heart Rate Method. Derived from the heart rate signal and an individually calibrated heart rate-minute ventilation calibration curve. Designed to provide a means of (A) assessing the potential of using heart rate as a surrogate for minute ventilation with this particular PSP design, and (B) comparison for the Indirect Heart Rate Method. Abbreviated "Direct HR Method".

3. Indirect Heart Rate Method. Derived from the heart rate signal and an original predictive equation relating minute ventilation to heart rate. The primary focus of this study. Abbreviated "Indirect HR Method"

4. Respiratory Inductive Plethysmograph Method. Derived from the respiratory inductive plethysmograph signals and a calibration curve relating these signals to minute ventilation. Designed to provide a comparison for heart rate-based estimates, although not deemed practical for use in the field at this time. Abbreviated "RIP Method".

5. Satoh's Heart Rate Method. Derived from the heart rate signal and a predictive equation relating minute ventilation to heart rate that was published by Satoh *et al.*[3] Designed to provide a comparison for the predictive equation used in the Indirect Heart Rate Method. Abbreviated "Satoh's Method".

All of these Methods were calculated by the PSCU (based on input signals) and provided estimates of minute ventilation. In order to evaluate these Methods meaningfully, the "true" minute ventilation was necessary. For this purpose, the Primary Standard was generated. The Primary Standard was the integrated, positively rectified pneumotachometer signal (corresponding to inhaled minute ventilation). The only difference between the Primary Standard and the Pneumo Method was the signal processing location (Dataq Software for the Primary Standard and the PSCU for the Pneumo Method). Differences between the Primary Standard and the Pneumo Method, therefore, could be specifically attributed to the PSCU processing of the pneumotachometer signal.

One notable PSP design issue is the balance between the averaging time for the input signals and the update period for the output voltage to the pump. The shorter the averaging period, the better the PSP will be able to capture peak exposures; unfortunately, this must be balanced against the error introduced by "wind-up time". This particular error is inherent in a pump that changes pump rate; there must be a transient period during which the pump rate approaches the steady-state pump rate for a given input voltage. The more frequently the pump rate is altered, the more error will accumulate. A 15-second averaging period for the input signal was selected for two reasons: (1) it would be long enough to limit the error associated with pump response transients just mentioned, and (2) research performed by Mermier *et al.* concluded that 15-second averages of heart rate and minute ventilation were closely linked (see theory section).[9]

A laboratory simulation was performed in order to collect human subject data to send to the PSP. The human subjects bicycled on an ergometer in order to simulate workers changing work rates on the job. This section presents the methodology for each calibration equation development and the laboratory simulation. Next, the method for performing concordance analysis will be described, and will serve to facilitate evaluation of the hypotheses. Finally, we will summarize the implications for the future of physiologic sampling pumps. Further details on the methods and the software referred to in this section are described in Hart (1998) [17].

### 2.3.1 HUMAN SUBJECT CHARACTERIZATION

Potential subjects were recruited via fliers posted on the Environmental Health bulletin board and outside a busy café close to the laboratory. Interested parties were interviewed over the phone in a standard manner. They were then scheduled for either one or two sessions and were sent a confirmation notice and a map. Seven male and seven female subjects were scheduled for one testing session. In addition, eight males and eight females were scheduled for two testing sessions, at least one week apart.

To track each subject session and ensure that each step was carried out, a checklist was used. The checklist included the following processes: preparation, subject handling, data collection, data processing, and sample collection. Prior to a subject's arrival, the pneumotachometer was heated for at least thirty minutes and then calibrated using a glass rotameter as a secondary standard (which was calibrated against a primary standard, a spirometer). A three point calibration curve was generated, relating pneumotachometer voltage to airflow rate. During calibration, the air was set to flow in the direction the air flows during subject inspiration; the pneumotachometer was positioned such that this airflow direction produced a positive voltage in the pneumotachometer.

When subjects arrived they were asked to read and sign the human subject consent form. The project was also described to the subject verbally, to provide them with a better feel for the purpose of their session. Subjects then filled out the subject history macro, which was reviewed before proceeding further. Summary statistics for the age, height, weight, and BMI for males and females are provided in Tables 2-4 and 2-5, respectively.

*Table 2-4: Summary of male subjects' age, height, weight, and body mass index.*

| MALES | Mean | Minimum | Maximum |
|---|---|---|---|
| Age (yr) | 31.1 | 26 | 43 |
| Height (cm) | 182.5 | 165 | 193 |
| Weight (lb) | 186.9 | 152 | 285 |
| BMI | 25.5 | 21 | 40 |

*Table 2-5: Summary of female subjects' age, height, weight, and body mass index.*

| FEMAL | Mean | Minimu | Maximu |
|---|---|---|---|
| Age (yr) | 29.5 | 20 | 60 |
| Height | 166.0 | 155 | 173 |
| Weight | 137.7 | 115 | 190 |
| BMI | 22.6 | 19 | 32 |

Of the male subjects, seven classified themselves as above average in health, while the remaining eight decided they experienced normal health. One subject had mild exercise induced asthma; no other diseases were reported. None of the subjects reported taking any medication. Fourteen

subjects were Caucasian and one subject was Asian (Subject #8). Only one male subject smoked (Subject #30), and he had a twelve-year history of smoking one pack per day. Subjects classified their fitness based on the number of times per week they regularly exercised: sedentary (no exercise), average (exercise 1-3 times per week), active (exercise 4-5 times per week), and athletic (exercise 6-7 times per week). Two males were classified as sedentary, five as average, five as active, and three as athletic.

Of the female subjects, eight claimed they experienced above average health, and the remaining seven reported being of normal health. The only disease reported among the women were two cases of hypothyroidism. One subject smoked, Subject #32, although she only reported smoking two packs per month for approximately four years. Fourteen subjects were Caucasian and one was Filipino (Subject #32). In terms of their fitness, only one female was classified as sedentary, eight had average fitness, five were active, and one was athletic. The two smokers were not obvious outliers with the exception that the Direct Method significantly overpredicted the minute ventilation for the female smoker; this subject was also the only non-Caucasian female.

### 2.3.2 INDIRECT HEART RATE CALIBRATION

The relationship between heart rate and minute ventilation within a subject is very stable. This relationship can be fit with a straight line between heart rate and the logarithm of minute ventilation. Satoh, Higashi, Sakurai, and Omae developed an equation of this form using data from 34 healthy male subjects ( Equation 2-11).

$$\text{Log } \dot{V}\,i = (9.38 \bullet (HR - HR_0) + 4.22 \bullet H + 1.19 \bullet W + 2.22 \bullet A + HR_0) \times 10^{-3} - 0.0439$$

*Equation 2-11. Satoh, Higashi, Sakurai, and Omae's equation to relate heart rate (HR) to minute ventilation ($\dot{V}\,i$). $HR_0$ = resting heart rate (per minute), $H$ = height (cm), $W$ = weight (kg), $A$ = age (yr).*[3]

The database compiled for our study was much larger, however, and consisted of 181 subjects. The data were accessed through the Gas Exchange Laboratory at the Harbor-UCLA Medical Center. Subject data were systematically abstracted from original records. Prior to data collection, a matrix was developed to guide the subject selection (see Table 2-6). Each cell was a unique combination of sex, age, health, and activity level (a surrogate measure of fitness). The goal for the data collection was to try to select five subjects per matrix cell.

The subjects were drawn from three different sources: (1) asbestos-exposed individuals referred to the laboratory to take part in an Asbestos Case-Control study, (2) control subjects pulled from the local community for use in a variety of studies, including the Asbestos study, and (3) patients referred to the laboratory for clinical reasons. All of the controls were healthy; the remaining subjects were classified as healthy, mildly diseased, or severely diseased based on the physiologic data and the physician's written comments. As a general rule, subjects were considered to be "mildly diseased" when they had some condition, such as asthma, diabetes or obesity, that was not severe enough to cause a major lifestyle change. When subjects had diseases that did seriously impede their health and lifestyle, such as pulmonary vascular disease or cardiovascular disease, they were considered to be "severely diseased".

Table 2-6 shows the actual number of subjects in the database for each matrix cell. The database contained data on 138 males and 43 females. 118 of these subjects were determined to have "Normal" health, 46 were "Mildly Diseased", and the remaining 17 were "Severely Diseased".

*Table 2-6: Subject matrix showing the number of subjects in database for each matrix cell.*

| **Health** | Normal | Normal | Normal | Normal | Mild | Mild | Mild | Severe |
|---|---|---|---|---|---|---|---|---|
| **Activity** | Sedentary | Avg. | Active | Athletic | Sedentary | Avg. | Active | Sedentary |
| Exer.Freq. | 0/wk | 1-3/wk | 4-5/wk | >5/wk | 0/wk | 1-3/wk | 4-5/wk | 0/wk |
| **Males:** | | | | | | | | |
| Age <30 | 4 | 5 | 1 | 5 | 2 | 0 | 1 | 3 |
| Age 30-39 | 3 | 9 | 4 | 3 | 4 | 1 | 4 | 0 |
| Age 40-49 | 8 | 5 | 4 | 3 | 3 | 0 | 5 | 3 |
| Age 50-59 | 5 | 8 | 7 | 2 | 4 | 2 | 4 | 5 |
| Age ≥50 | 4 | 9 | 0 | 0 | 1 | 1 | 3 | 3 |
| **Females:** | | | | | | | | |
| Age <30 | 3 | 1 | 2 | 0 | 2 | 1 | 0 | 1 |
| Age 30-39 | 2 | 2 | 2 | 2 | 1 | 1 | 0 | 0 |
| Age 40-49 | 5 | 2 | 2 | 1 | 1 | 1 | 1 | 2 |
| Age 50-59 | 2 | 1 | 1 | 0 | 2 | 1 | 0 | 0 |
| Age ≥50 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |

All of the subjects performed an incremental work rate test as described in Principles of Exercise Testing and Interpretation.[1] The 30-second averages of heart rate, breathing frequency, and minute ventilation were recorded over the span of the test (10-20 minutes).

For all subjects, the following data were collected (weight was missing for one subject):

- sex
- age
- height
- weight
- maximum oxygen capacity
- maximum heart rate
- maximum oxygen pulse
- maximum minute volume
- estimated overall health
- estimated fitness level
- predicted maximum oxygen capacity

The following additional data were also collected when available:

- predicted maximum heart rate
- predicted maximum oxygen pulse
- blood pressure at rest
- blood pressure at maximum exercise
- arterial oxygen pressure at rest and at maximum exercise
- alveolar-arterial oxygen pressure difference at rest and at maximum exercise
- arterial end-tidal carbon dioxide pressure difference at rest and at maximum exercise
- the physiologic deadspace to tidal volume ratio
- current smoking status
- smoking history
- subject history of respiratory disease or cardiovascular disease
- vital capacity
- inspiratory capacity

- forced expiratory volume in 1 sec. (FEV1)
- maximum ventilatory volume
- use of heart medications

### 2.3.3 INDIRECT CALIBRATION EQUATION DEVELOPMENT

The database was first filtered to eliminate questionable subject data. In order to assess the data's validity, the variability of each subject's data across time was examined. When there was significant, unexplained variation, the data were deemed potentially erroneous. Of the original 182 subjects, 72 were eliminated for analytical purposes. In order to evaluate this screening process, the percentage of subjects removed was calculated for all categorical variables. It was found that a larger percentage of those removed were taking heart rate influencing medication, or were severely diseased. It is entirely reasonable that these two groups of subjects would have less stable or predictable relationships between heart rate and minute ventilation; this fact lends credence to the screening process, although there is no absolute way to check its validity.

The predictive equation model was developed by performing a stepwise regression on the filtered database (of 110 subjects) using SPSS®. The final equation included the change in heart rate and weight as variables. Note that the following variables were tested to determine if they should be included in this equation, and were rejected: sex, age, height, BMI (body mass index), resting heart rate, health, and fitness.

$$\dot{V}i = \exp(A \bullet (HR - HR0) + B \bullet W + C)$$

*Equation 2-12: Predictive equation model for the indirect heart rate calibration method.* $\dot{V}i$ *= minute ventilation,* $HR$ *= heart rate (beats per minute),* $HR_0$ *= resting heart rate, and* $W$ *= weight in kilograms.*

The coefficients for Equation 2-12 (A, B, and C) were determined by using a bootstrap statistical method as outlined by Efron, and LePage and Podgorski.[13,14] A bootstrap method was required in order to deal with the autocorrelation between minute ventilation and heart rate within-subject. Since the data were recorded as 30 second averages and each subject exercised for different periods of time, there were various numbers of pairs of heart rate and minute ventilation data for each subject. Inherently, these 30 second averages were autocorrelated, thus nullifying the assumption of independence necessary for the application of more traditional statistical methods. In order to calculate a linear regression without log-transforming the minute ventilation data, the statistical package S-Plus was used. Essentially, the following series of four steps was executed as desired:

1) One row of data for each subject was randomly selected.

2) The selected rows were extracted from the database and stored in a matrix.

3) A linear regression was performed on the extracted data.

4) The coefficients from the log-linked regression analysis were stored in another matrix.

This process produced a distribution of coefficients for each term in the predictive equation. The mean value of each distribution was then used in the final predictive equation.

### 2.3.4 DIRECT HEART RATE CALIBRATION

Subjects were asked to remove their shirts in order to attach the monitoring equipment. A band containing three electrodes, used to detect each heart beat, was strapped around their chests, just below the breast area. Water was applied to each electrode face to enhance conduction of the signal.

Next, the mouth unit was attached to the subject's head (see Figure 2-6). This mouth unit was composed of a PVC T-fitting, where one end was connected to a plastic mouthpiece and the opposite end to a tygon tube leading to a saliva-collection bottle. Perpendicular, and pointing up when the subject had the mouthpiece in his/her mouth, was the pneumotachometer. Webbing and elastic were used to strap this mouth unit to the subject's head. One band wrapped around the back of the subject's neck and was secured to the top of the T-fitting on the opposite side of the stem from the subject. After this band was tightened, a second band, made of elastic and originating from in front of the T-fitting's stem, was placed over the top of the subject's head and attached behind the neck to the first strap via Velcro. This point of attachment was reinforced with a simple barrette. Two or three more barrettes were used to secure the second band to the subject's hair.

*Figure 2-6: Mouth unit attached to a subject's head.*

In order to relate the subjects' heart rates to their actual minute ventilation (for the Direct HR Method), a calibration curve linking these two variables was required. This curve was generated by recording the signals from the heart rate monitor and pneumotachometer using software (Codas AT and Advanced Codas) and hardware (data acquisition card, Model DI-420 Parallel Port Module) produced by Dataq Instruments, for a total of 12 minutes: 2 minutes while sitting on a bicycle ergometer at rest, 5 minutes while biking at 40 Watts, and 5 minutes while biking at 80 Watts. After the subject session was complete, the Codas file was processed using a batch file. This batch file accomplished two things: first, the moving average of the heart rate was calculated, and, second, the moving average of the positively rectified minute ventilation signal was computed. One minute sections from each work rate period, corresponding to 45 to 105, 345 to 405, and 645 to 705 seconds from the start of the calibration file, were saved as a new file. An Excel macro named HRcal opened this file and generated a three-point calibration curve between the logarithm of the minute ventilation and the heart rate (Equation 2-13).

$$\text{Log}\,(\dot{V}\,i) = A \bullet HR + B$$

*Equation 2-13: Predictive equation model for the direct heart rate calibration method.* $\dot{V}\,i$ *= minute ventilation and* HR *= heart rate (beats per minute).*

Another macro, PREDHRLOGVI used the resting heart rate and weight of the subject to predict the minute ventilation at each of the three steady-state heart rates using Equation 2-12 (Indirect Calibration Equation). Then, the actual data points, the measured calibration curve, and the predicted calibration curve were all plotted on a second graph, allowing visual comparison of the two calibration curves.

### 2.3.5 RESPIRATORY INDUCTIVE PLETHYSMOGRAPH CALIBRATION

After the electrodes were attached to a subject for the direct heart rate calibration process, each subject donned a stress-test shirt. Stress-test shirts are tank-top shaped and made of an elastic mesh that stays tight against the body. The two RIP bands were placed over this shirt, one located around the chest and one located around the abdomen. The bands were attached to the shirt at four points (two in front, two in back) using straps made of webbing and Velcro. These Velcro straps prevented vertical shifting of the bands, without interfering with their expansion/contraction due to breathing movements.

The RIP calibration protocol involved two steps. For the first step, subjects were asked to perform three isovolume maneuvers while sitting on the ergometer. The maneuvers consisted of the subjects plugging their noses and holding their breath while moving their abdomens in and out several times. Each maneuver was performed at a different lung volume: for the first maneuver, the subjects breathed out slightly first, for the second they simply plugged their noses and closed their mouths at a neutral state, and, finally, for the third, they inhaled slightly first. The band signals during each maneuver were recorded using hardware and software from Codas.

The isovolume maneuvers aid in determining the relationship between the band signals and the cross-section area of the torso. Theoretically, if the lung volume does not change, then any negative change in the cross-sectional area of the abdomen (caused by the subject moving the abdomen in) would cause a corresponding positive change in the cross-sectional area of the ribcage, and vice versa. Since the signals are related to the cross sectional area of the bands, a plot of the abdominal signal versus the ribcage signal during an isovolume maneuver should be a line with a negative slope. The intercept should be related to the volume of air contained in the lungs during the procedure.

The second step of the calibration procedure required the subjects to sit on the ergometer at rest for two minutes, while the pneumotachometer and RIP band signals were recorded. This data could then be used to relate the derivative of the RIP signals to a known flow rate (provided by the pneumotachometer signal);

because the RIP signals are related to volume, the derivative of each signal is required to relate them to a flow rate.

This protocol involving isovolume maneuvers and two minutes period at rest was conducted twice: before and after the laboratory simulation.

The calibration curve was developed after the subject session was complete. First, the calibration files were processed using a batch file entitled RIP.bat; this calculated the derivative of each band signal and stored it in the Codas file. Then a portion of the data from each isovolume maneuver and the breathing at rest period was extracted. This data was then processed via the macros ISO and RIPCAL (Appendices M and N, respectively). The ISO macro opened all three isovolume maneuver files and calculated the line coefficients relating the abdominal signal to the ribcage signal for each. These three sets of data and their lines of best fit were plotted on a graph. The most consistent isovolume data set was selected to relate the abdominal signal to the ribcage signal. The slope and intercept for the selected data were then recorded for later use in the RIPCAL macro.

The RIPCAL macro opened the breathing at rest data, used the slope and intercept derived from the ISO macro to calculate the abdominal and ribcage calibration coefficients (abdominal coefficient = -slope/intercept, ribcage coefficient = 1/intercept), and multiplied the derivatives of the abdominal and ribcage signals by their respective calibration coefficients to get the adjusted derivative values. These two adjusted derivative values were then summed to get the final calibrated RIP values, which were plotted against the corresponding minute ventilation values in order to produce the final RIP calibration curve.

### 2.3.6 LABORATORY SIMULATION

In order to compare the Methods listed in the Background to this section, minute ventilation, heart rate, and RIP data for all 30 subjects were collected over a 40 minute sampling period that involved four work rates. This sampling period commenced immediately following the heart rate calibration data collection, after the subjects were given a water break. The mouth unit was re-attached, the nose clip was re-fastened, and the sampling period was started.

The 40 minute sampling period was broken into 8 five-minute sections, with the following work rates assigned to each section: 0 Watts, 40 Watts, 0 Watts, 80 Watts, 40 Watts, 0 Watts, 120 Watts, and 0 Watts. The cardiotachometer and pneumotachometer signals were recorded at 125 samples per second using the Dataq software and hardware. When biking, subjects were required to pedal at 50 rotations per minute; a metronome set to 100 beats per minute provided an auditory cadence, and the pedaling rate could be visually confirmed via a display on the ergometer itself. Subjects were allowed to stand during the 0 Watt sections. In addition, they were allowed to read if they wished to and could do so while biking steadily at 50 rotations per minute. Music, however, was not allowed.

A series of computer programs were used to process the data. A batch file TXDAT.bat, was used to process the sampling period data. The processed file was then copied using a comma-delimited format, opened in Word, and saved as a text file (after the Codas header was removed). The subject data were sent to the PSCU via a Pentium computer, running a QuickBASIC program called Senddat.bas. This program sends the data from any comma delimited file to a digital-to-analog converter at a rate of 125 samples per second per channel. Prior to sending a subject's data, this program was used to send zero volts to both the RIP and pneumotachometer channels of the PSCU. Three Txtools programs, Analog0 for the RIP abdominal signal, Analog2 for the pneumotachometer signal, and Analog6 for the RIP ribcage signal, were run on a laptop Pentium computer to measure the voltage offsets of the PSCU.

A TxBASIC program titled LABPSP was downloaded into the PSCU and started. This program prompted the user to input several values, including the PSCU offsets, the four GilAir5s' calibration coefficients, the direct heart rate calibration coefficients, the isovolume slope, the RIP calibration coefficients, and the subject's age, height, weight and resting heart rate. The program's sampling protocol was initiated manually, to correspond with the start of the Pentium computer sending a subject's data file to the PSCU. The program then calculated and recorded the 15-second averages of minute ventilation estimates for each Method.

After each subject's 40 minute sampling period had been sent to the PSCU, the 15 second averages were downloaded from the PSCU to the laptop Pentium computer and saved as an Excel file. All five estimates were weighted by the averaging time and then summed over the sampling period to attain the total inhaled volume values. The raw pneumotachometer data were processed in order to calculate the Primary Standard value. The processing of this signal involved summing the positively rectified data over the sampling period and applying the pneumotachometer calibration curve.

Mass flow meters were used to validate that the volume of air pulled through charcoal tubes attached to the PSPs were proportional to the PSCU estimated total inhaled volumes. The PSCU was connected to four sampling pumps; these pumps were driven by the following Methods: (1) Pneumo Method, (2) Direct Method, (3) Indirect Method, and (4) RIP Method. Four GilAir5 pumps were labeled with an identifier: A, B, C, and D. The four mass flow meters were also individually labeled: 1, 2, 3 and 4. The mass flow meters were calibrated against a primary standard, a Gilibrator. The mass flow meters were attached upstream of the charcoal tube and allowed to warm up for at least 15 minutes prior to use. The pumps and mass flow meters were randomly assigned each data set, in order to eliminate any pump or mass flowmeter bias. The output voltages of the four mass flow meters were logged using the Dataq Instruments software and hardware.

### 2.3.7 CONCORDANCE ANALYSIS

The PSCU results from all methods (Pneumo Method, Direct HR Method, Indirect HR Method, RIP Method, and Satoh's Method) were compared to the Primary Standard by examining the components of concordance: location shift, scale shift, precision, and accuracy. In addition, the Indirect HR Method was compared to the Direct HR Method in a similar manner.

Location shift centers around zero; values less than or greater than zero signify that the comparison method underestimates or overestimates total inhaled volume compared to the standard method. The statistical significance of location shift was determined by performing a paired T-test between the two methods of interest. Scale shift is simply the ratio of the standard deviation of the comparison method to the standard deviation of the standard method. Values greater than one suggest that the variability of the comparison method is greater than the standard method. The statistical significance of scale shift was calculated by performing a linear regression through a scatter plot of data pairs for the methods and testing the null hypothesis that the slope was not significantly different from one. The precision is the Pearson correlation coefficient and the accuracy is a combination of both the location shift and the scale shift. The overall concordance is simply a product of the precision and the accuracy.[15]

### 2.3.8 INDIRECT CALIBRATION RESULTS

The bootstrap process produced a population of coefficients. Histograms for the coefficients, overlaid with a normal curve, are displayed in Figures 2-7, 2-8, and 2-9.

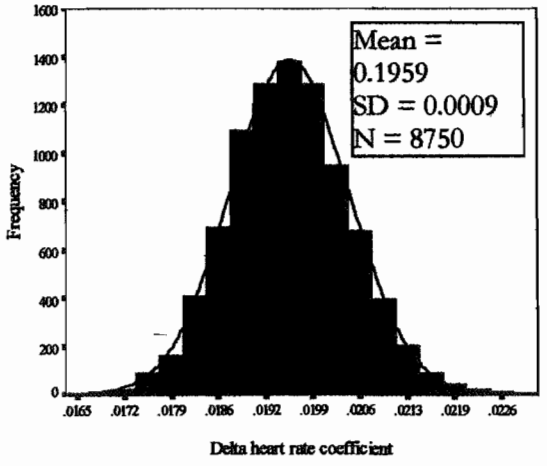



*Figure 2-7: Histogram of delta heart rate coefficients.*

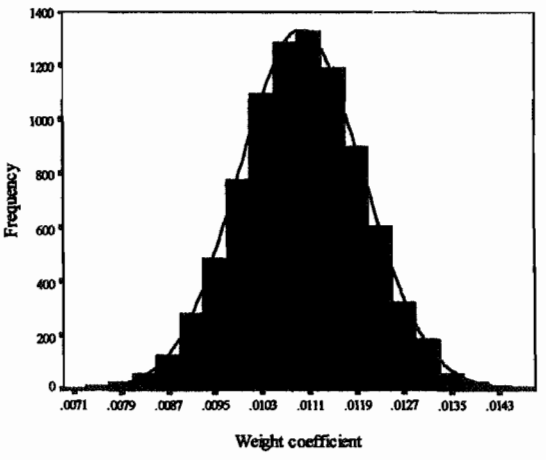



*Figure 2-8: Histogram of weight coefficients.*

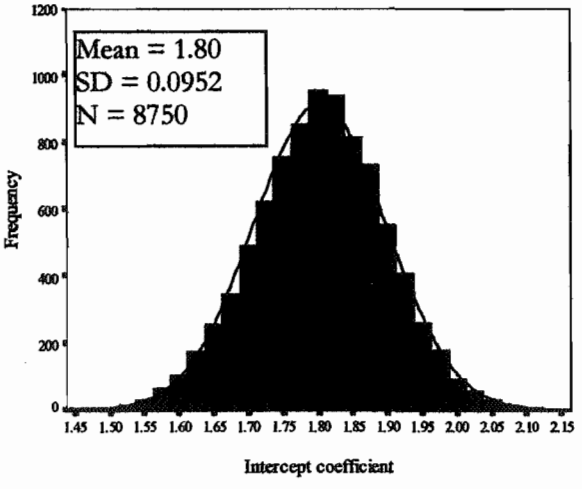



*Figure 2-9: Histogram of intercept coefficients.*

The final predictive equation was derived by entering Equation 2-12.

$$\dot{V}i = e^{0.01959 * (HR-HR0) + 0.01094 * W + 1.8029}$$

*Equation 2-14: Final predictive equation relating minute ventilation to heart rate derived from a large database of physiologic data.* $\dot{V}i$ *= minute ventilation,* $HR$ *= heart rate (beats per minute),* $HR_0$ *= resting heart rate, and* $W$ *= weight in kilograms.*

### 2.3.9 DIRECT HEART RATE CALIBRATION RESULTS

The average steady-state heart rate and minute ventilation values at 0 Watts, 40 Watts, and 80 Watts were significantly different between subjects (p-values of 0.004, 0.001, and 0.000 for heart rate and 0.021, 0.038, and 0.016 for minute ventilation).

The change in resting heart rate within-subject averaged 1.3%, but ranged from -22% to +32%.

The average, minimum, and maximum steady-state values for heart rate and minute ventilation at all three work rates for the first session are displayed in Table 2-7. Second session data was not included in these statistics so as not to weight the averages twice for the sixteen subjects that performed a second session.

*Table 2-7: First session steady-state heart rate and minute ventilation statistics for 0, 40, and 80 Watts.*

| | Work | Average | Minimu | Maximu |
|---|---|---|---|---|
| **Heart Rate (BPM)** | **0 Watts** | 81.6 | 57.4 | 114.7 |
| | **40 Watts** | 92.0 | 60.7 | 137.0 |
| | **80 Watts** | 117.9 | 78.1 | 149.3 |
| **Minute Ventilation** | **0 Watts** | 9.2 | 4.7 | 12.8 |
| | **40 Watts** | 16.8 | 12.5 | 30.8 |
| | **80 Watts** | 26.9 | 19.0 | 33.4 |

### 2.3.10 CALIBRATION CURVE COMPARISON RESULTS

For each subject session, the minute ventilation estimates for the steady state heart rate value corresponding to 0, 40 and 80 Watts of work were derived using both the Indirect Method and the Direct Method. Figure 2-10 shows a comparison of these values. Clearly, over the heart rate range corresponding to 0 to 80 Watts of work, the minute ventilation estimates based on the Indirect Method are higher than those derived using the Direct Method. The difference between the two estimates versus heart rate is displayed in Figure 2-11. The Methods differ most at lower work rates, and start to converge as work rate is increased.

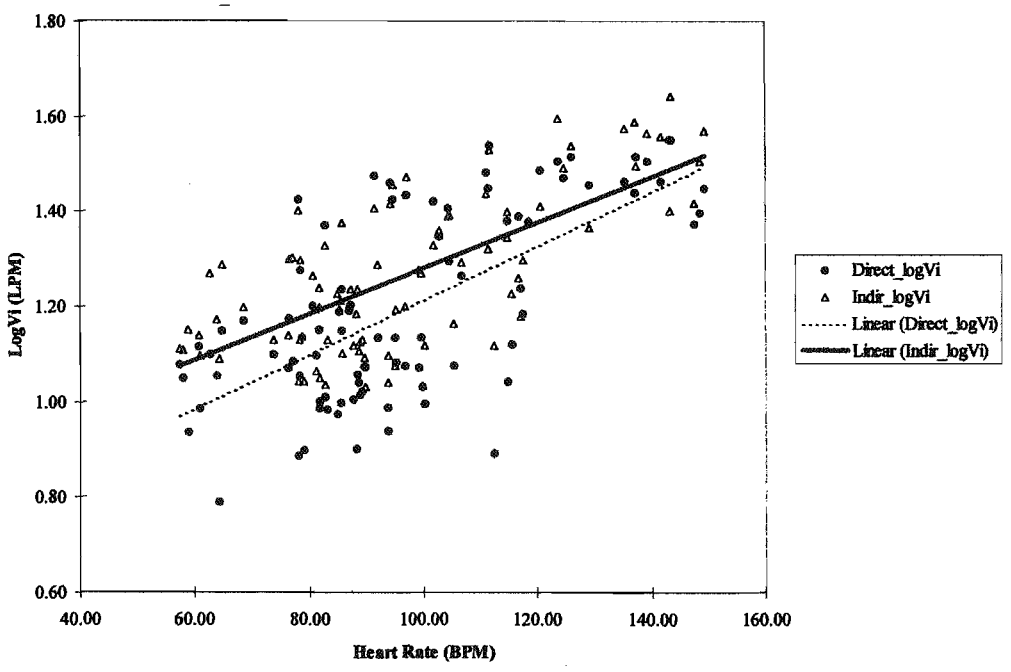



*Figure 2-10: Plot of the log minute ventilation of each heart rate calibration (Indirect and Direct HR Method) versus heart rate.*

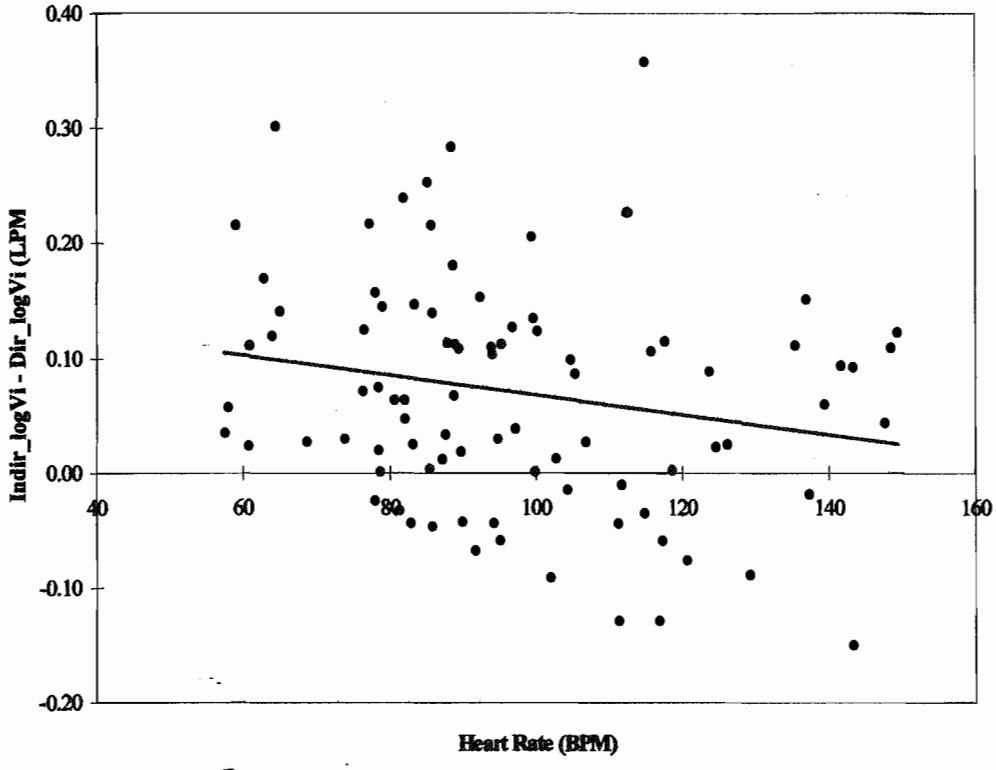



*Figure 2-11: Plot of the difference of the log minute ventilation (Indirect HR Method - Direct HR Method) versus heart rate.*

Several MANOVAs were performed to determine if sex, health status or fitness affected this difference between the Methods' estimates of minute ventilation. It was determined that only fitness had a significant effect. This effect is exceedingly apparent in Figure 2-12, where the difference between the minute ventilation estimates (Indirect Method - Direct Method) is stratified by fitness. In this figure, the fitness categories were collapsed into two categories: (1) exercise 0 to 3 times per week, and (2) exercise more than 3 times per week. Each Method also was examined separately to determine if there were any significant between subject effects for sex, health, or fitness; no significant effects were discovered.

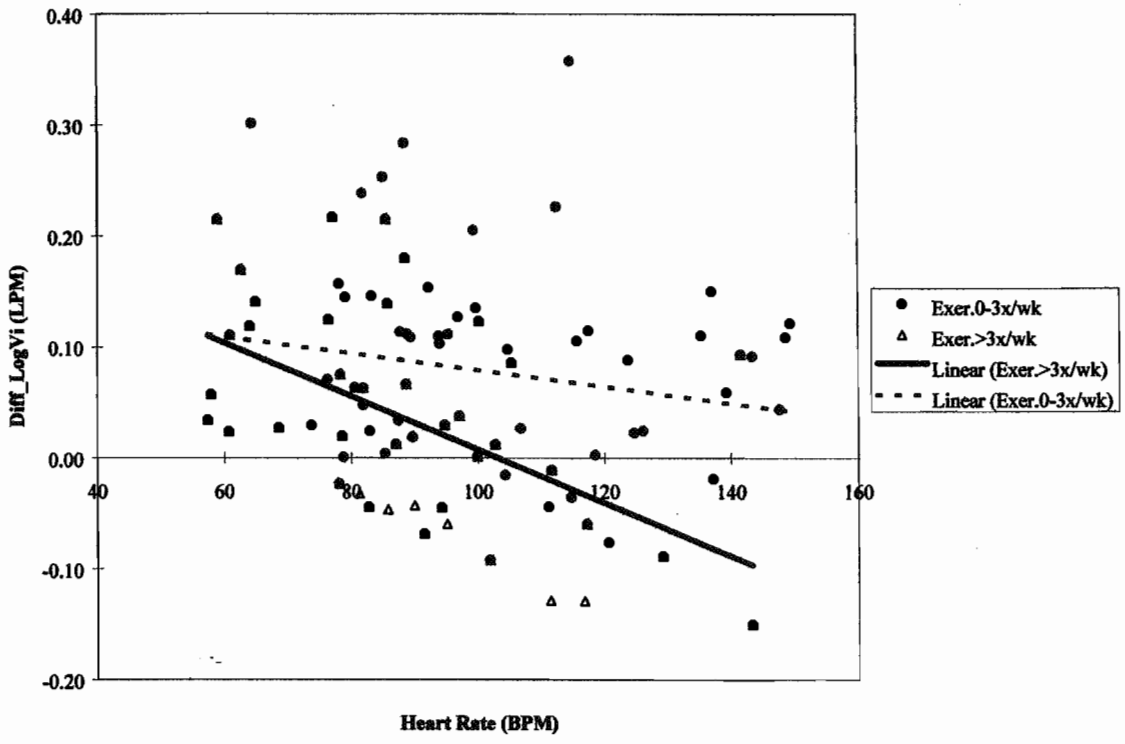



*Figure 2-12: Difference in minute ventilation estimates (Indirect HR Method - Direct HR Method), stratified by subject's fitness (exercise 0-3 times per week or exercise more than 3 times per week).*

### 2.3.11 PSCU TOTAL INHALED VOLUME RESULTS

The PSCU estimates of total inhaled volume (liters of air inhaled over the 40 minute sampling period), from the first session for each subject, are summarized in Table 2-8. Results from the second session for the 16 subject that performed a second testing session are summarized in Table 2-9. Note that these estimates are derived from the PSCU data files, not from the mass flowmeter data (with the exception of the Primary Standard whose values were derived as described in Methods). Figures 2-13 and 2-14 show graphs of the data in Table 2-8. Figure 2-13 shows data from the Pneumo and PIP Method plotted against the Primary Standard values; both methods represent a direct measurement of minute ventilation or changing lung volume. These methods have little bias since they are centered on the unity line, but the RIP method has considerable scatter and a much lower correlation compared to the Pneumo method. Figure 2-14 shows data from the three heart rate methods plotted against the Primary Standard values. The heart rate methods are not direct measurement of minute ventilation, and all have some tendency to over or underestimate minute ventilation compared to the unity line. Satoh's method in particular has almost no predictive value (low slope) and dramatically underestimates minute ventilation.

*Table 2-8: PSCU estimates of total inhaled volume (in liters) for all 30 subjects.*

| Subject | Primary | Pneumo | Direct | Indirect | RIP | Satoh's |
|---|---|---|---|---|---|---|
| 1 | 773 | 757 | 922 | 929 | 697 | 479 |
| 2 | 616 | 602 | 743 | 951 | 582 | 512 |
| 5 | 715 | 701 | 876 | 820 | 628 | 455 |
| 6 | 641 | 628 | 805 | 953 | 721 | 537 |
| 7 | 660 | 645 | 611 | 792 | 750 | 399 |
| 8 | 807 | 789 | 460 | 712 | N/A | 321 |
| 9 | 602 | 590 | 610 | 737 | 581 | 462 |
| 10 | 762 | 747 | 836 | 881 | 870 | 500 |
| 11 | 789 | 775 | 1023 | 1070 | 732 | 671 |
| 12 | 795 | 778 | 920 | 894 | 659 | 560 |
| 13 | 757 | 742 | 909 | 697 | 776 | 411 |
| 14 | 699 | 685 | 813 | 982 | 730 | 588 |
| 15 | 624 | 613 | 865 | 658 | N/A | 382 |
| 16 | 665 | 653 | 648 | 685 | 629 | 422 |
| 17 | 936 | 918 | 886 | 1351 | 923 | 475 |
| 18 | 707 | 694 | 732 | 698 | 661 | 378 |
| 19 | 800 | 785 | 984 | 927 | 756 | 413 |
| 20 | 607 | 593 | 778 | 794 | 629 | 455 |
| 21 | 739 | 723 | 822 | 1007 | 354 | 586 |
| 22 | 670 | 654 | 746 | 708 | 707 | 415 |
| 23 | 598 | 585 | 691 | 982 | 540 | 631 |
| 24 | 659 | 646 | 553 | 726 | 602 | 372 |
| 25 | 731 | 715 | 819 | 1078 | 804 | 606 |
| 26 | 756 | 745 | 845 | 829 | 705 | 404 |
| 27 | 709 | 694 | 768 | 702 | 638 | 410 |
| 28 | 680 | 672 | 715 | 861 | 725 | 503 |
| 29 | 706 | 694 | 908 | 1180 | 637 | 616 |
| 30 | 823 | 807 | 873 | 825 | 699 | 488 |
| 31 | 844 | 829 | 929 | 853 | 837 | 403 |
| 32 | 861 | 846 | 1362 | 938 | 678 | 498 |

*Table 2-9: PSCU estimates of total inhaled volume (in liters); 16 subjects in second sampling period.*

| Subject | Primary | Pneumo | Direct | Indirect | RIP | Satoh's |
|---|---|---|---|---|---|---|
| 1 | 791 | 777 | 656 | 809 | 685 | 411 |
| 10 | 675 | 661 | 800 | 922 | 646 | 521 |
| 11 | 876 | 861 | 1186 | 1016 | 836 | 631 |
| 13 | 823 | 808 | 793 | 681 | 810 | 399 |
| 14 | 798 | 785 | 836 | 914 | 683 | 545 |
| 16 | 777 | 764 | 887 | 854 | 603 | 540 |
| 17 | 834 | 820 | 978 | 1611 | 856 | 578 |
| 20 | 586 | 573 | 705 | 849 | 455 | 489 |
| 21 | 779 | 768 | 918 | 1008 | N/A | 587 |
| 22 | 709 | 695 | 767 | 816 | 604 | 485 |
| 25 | 734 | 718 | 883 | 1071 | 703 | 601 |
| 28 | 728 | 716 | 826 | 845 | 607 | 492 |
| 29 | 816 | 800 | 1096 | 1085 | 636 | 558 |
| 30 | 725 | 710 | 771 | 997 | 1662 | 602 |
| 31 | 790 | 775 | 729 | 723 | 762 | 335 |

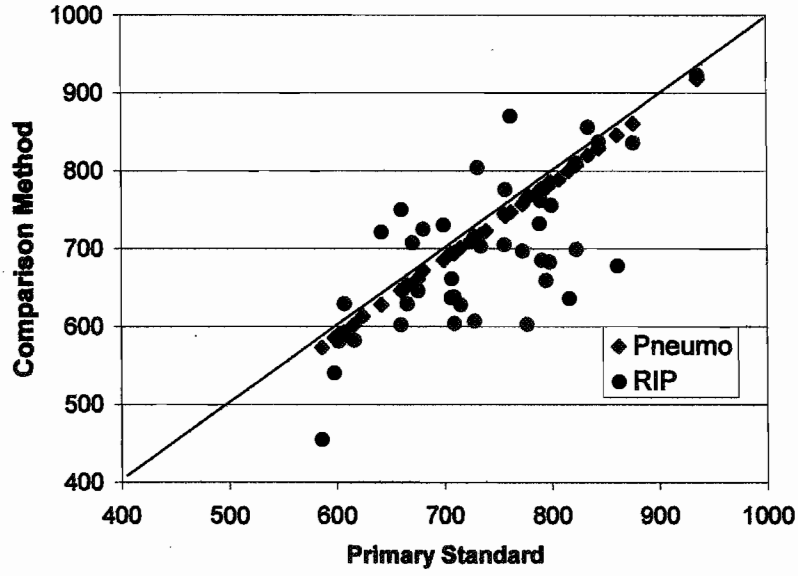



*Figure 2-13: Plot of Pneumo Method and RIP Method versus Primary Standard PSCU results. The line is a line of unity for the Primary Standard.*

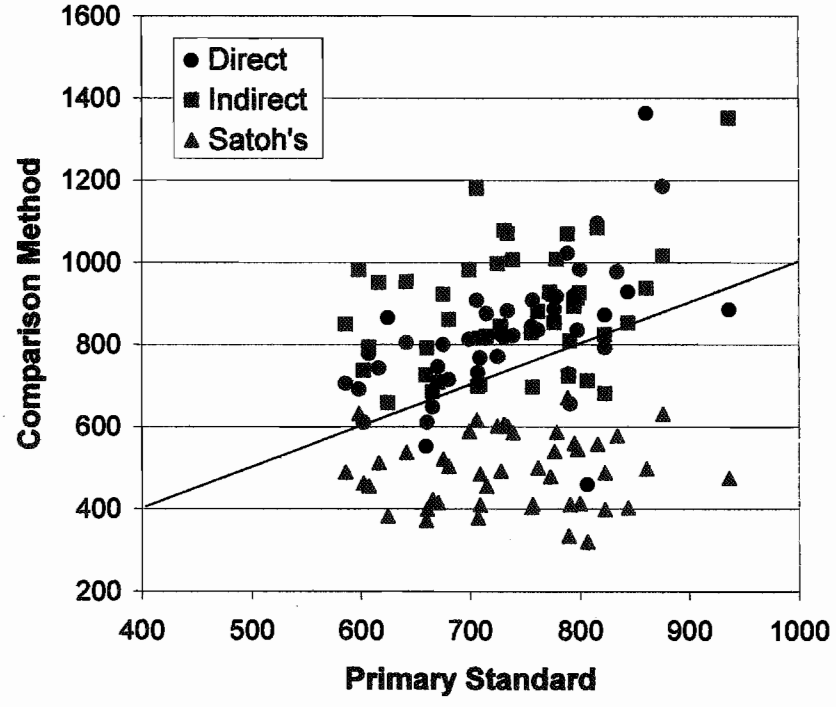



*Figure 2-14: Plot of Direct HR Method, Indirect HR Method , and Satoh's Method versus Primary Standard PSCU results. The line is a line of unity for the Primary Standard.*

### 2.3.12 MASS FLOWMETER TOTAL INHALED VOLUME RESULTS

The mass flowmeter total inhaled volume (liters of air inhaled over the 40-minute period) results from the first session for each subject are summarized below in Table 2-10.

| Subj | Pneumo | Direct | Indirect | RIP |
|---|---|---|---|---|
| 1 | 781.64 | 979.17 | 907.36 | 693.23 |
| 2 | 587.25 | 773.88 | 899.87 | 544.14 |
| 5 | 688.58 | 940.03 | 769.23 | 549.99 |
| 6 | 597.94 | 826.02 | 916.72 | 546.55 |
| 7 | 602.25 | 678.69 | 813.59 | 708.45 |
| 8 | 864.27 | 525.02 | 703.53 | |
| 9 | 564.52 | 686.92 | 705.04 | 580.79 |
| 10 | 774.87 | 882.75 | 866.13 | 851.59 |
| 11 | 740.19 | 1102.11 | 1033.97 | 700.82 |
| 12 | 780.36 | 937.32 | 848.21 | 541.56 |
| 13 | 753.36 | 1012.39 | 616.18 | 743.04 |
| 14 | 632.99 | 883.67 | 1026.76 | 741.93 |
| 15 | 644.94 | 924.21 | 577.87 | |
| 16 | 565.42 | 721.48 | 646.82 | 599.14 |
| 17 | 922.14 | 953.55 | 1323.18 | 907.58 |
| 18 | 715.00 | 764.93 | 722.63 | 592.18 |
| 19 | 783.20 | 1017.78 | 914.12 | 689.58 |
| 20 | 637.86 | 836.71 | 717.36 | 627.79 |
| 21 | 724.37 | 881.72 | 1030.03 | 341.57 |
| 22 | 601.98 | 830.11 | 719.28 | 759.03 |
| 23 | 619.21 | 766.93 | 1015.02 | 526.04 |
| 24 | 624.71 | 634.65 | 781.01 | 590.74 |
| 25 | 729.45 | 897.39 | 1104.50 | 727.97 |
| 26 | 737.50 | 895.14 | 738.57 | 696.40 |
| 27 | 723.44 | 824.51 | 695.43 | 566.52 |
| 28 | 681.31 | 757.97 | 823.06 | 664.65 |
| 29 | 663.05 | 958.61 | 1168.00 | 598.66 |
| 30 | 811.45 | 917.91 | 827.30 | 638.15 |
| 31 | 808.56 | 948.94 | 804.59 | 822.98 |
| 32 | 827.15 | 1397.00 | 915.69 | 637.75 |

. *Table 2-10: Mass flowmeter estimates of total inhaled volume (in liters) for all 30 subjects.*

### 2.3.13 CONCORDANCE ANALYSIS RESULTS

The various methods were compared using a concordance analysis[15]. This analysis is similar to a regression and Pearson correlation coefficient. The correlation is always higher than the concordance, and is a measure of precision in the data. Concordance adjusts the correlation for shifts in location of the data cloud (shift away from a unity line) and shifts in scale (shifts from a unity slope in the line). From this analysis a measure of accuracy (ideal value = 1) and precision (Ideal value =1) for each method can be obtained.

The concordance components relating the five methods for estimating minute ventilation to the Primary Standard are displayed in Table 2-11. In addition, this Table compares the Indirect HR Method to the Direct HR Method, for purposes of assessing the ability of the Indirect HR Method to correspond with what was individually measured in the laboratory.

*Table 2-11: Concordance component values for first session PSCU results. Statistically significant location and scale shifts are marked with asterisks (** for a P-value < 0.01, * for a P-value < 0.05).*

| Standard | Comparison | Location Shift | Scale Shift | Prec. | Accuracy | Concordance |
|---|---|---|---|---|---|---|
| Primary | Pneumo | -0.168** | 0.984** | 1.000 | 0.986 | 0.986 |
| | Direct HR | 0.768** | 1.954** | 0.544 | 0.654 | 0.356 |
| | Indirect HR | 1.283** | 1.908** | 0.402 | 0.491 | 0.197 |
| | RIP | -0.381 | 1.303 | 0.525 | 0.903 | 0.473 |
| | Satoh's | -2.845** | 1.047** | -0.023 | 0.198 | -0.005 |
| Direct HR | Indirect HR | 0.361 | 0.976* | 0.402 | 0.939 | 0.377 |

The Pneumo Method had the highest concordance (0.986), as expected. It had a slight downward bias (as evidenced by a location shift of -0.169), but it had perfection precision. The Direct and Indirect HR Methods had a much lower concordance than the Pneumo Method (0.356 and 0.197, respectively). They both overestimated total inhaled volume by a significant magnitude and had essentially twice the standard deviation (reflected by a scale shift of approximately 2). Their precision was about half that of the Pneumo Method. The RIP Method was not significantly different from the Primary Standard in terms of its location shift and scale shift, but its precision was still unacceptably low (0.525). This method was much more accurate than the Direct and Indirect HR Methods, however. Satoh's Method significantly underestimated total inhaled volume and had no precision.

The Indirect HR Method, compared to the Direct HR Method, was not significantly different in terms of its location shift. Its scale shift, on the other hand, was significant. The accuracy was extremely high (0.939), but the overall concordance was only 0.377 due to its low precision.

An additional comparison of the Direct HR Method to the Primary Standard was made when restricting the subjects in the analysis to Caucasian subject (excluding Subjects #8 and #32). These concordance analysis results are displayed in Table 2-12.

*Table 2-12: Comparison of concordance component values for first session PSCU results, of Direct HR Method to Primary Standard, when including all subjects versus only Caucasian subjects. Statistically significant location and scale shifts are marked with asterisks (** for a P-value < 0.01, * for a P-value < 0.05).*

| Subjects Included | Comparison to Primary Std. | Loc. Shift | Scale Shift | Prec. | Accuracy | Concordance |
|---|---|---|---|---|---|---|
| All | Direct HR | 0.768 | 1.954** | 0.544 | 0.654 | 0.356 |
| Caucasian | Direct HR | 0.847 | 1.376** | 0.677 | 0.709 | 0.480 |

Note the much lower scale shift when the analysis is restricted to Caucasian subjects. An F-test was performed to compare the variances of the total inhaled volume results for both sets of Direct HR data (all subjects versus Caucasians subjects only); the variance was significantly smaller when only Caucasians were included. The potential implication of these results will be addressed in the Discussion.

Table 2-13 uses concordance components to compare mass flowmeter estimates of total inhaled volume to PSCU estimates.

*Table 2-13. Concordance component values for first session PSCU versus mass flowmeter results. The location and scale shifts were not statistically significant at the 0.01 level.*

| Standard (PSCU) | Comparison (mass flow) | Loc. Shift | Scale Shift | Prec. | Accuracy | Concordance |
|---|---|---|---|---|---|---|
| All Methods | All Methods | 0.025 | 1.056 | 0.967 | 0.998 | 0.965 |

Note that the location shift and scale shift were insignificant at the 0.01 level. This explains the almost perfect accuracy (0.998). The precision, while not perfect, was extremely high (0.967). The overall concordance was therefore 0.965.

Figure 2-15 displays the relationship of the mass flowmeter estimates of total inhaled volume to the PSCU estimates. Note that the line in the graph represents a line of unity and is not a regression line.

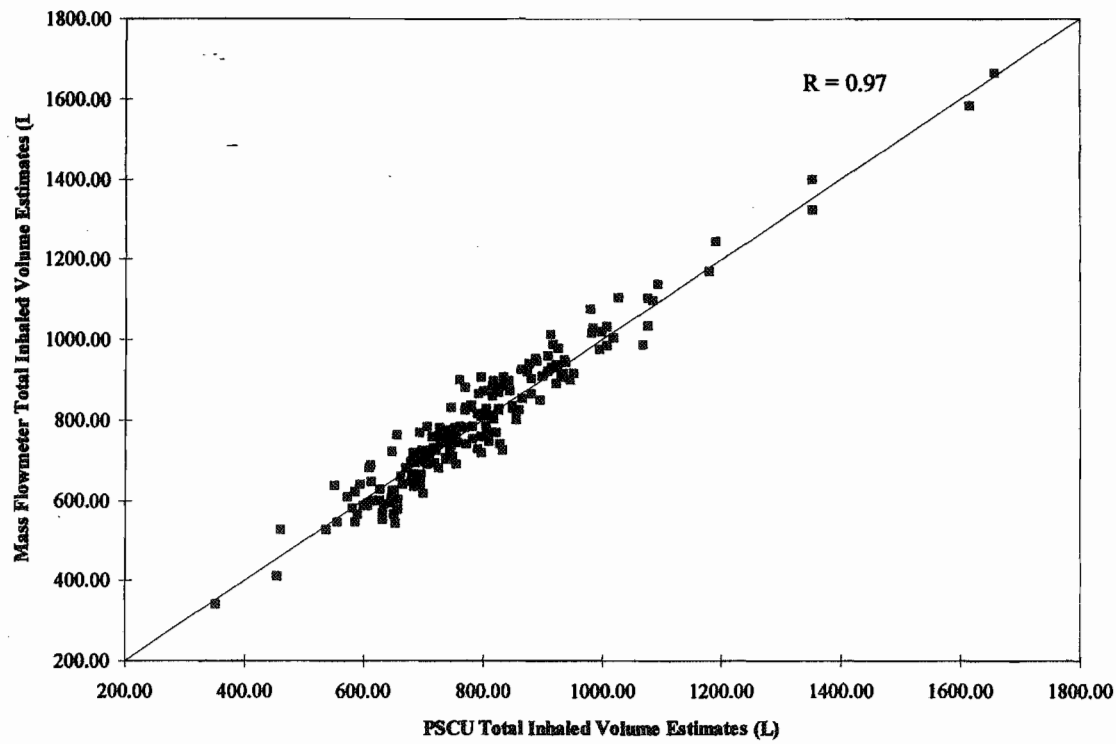



*Figure 2-15. Relationship of mass flowmeter to PSCU total inhaled volume estimates. The line is a line of unity for the PSCU estimates.*

### 2.3.14 DISCUSSION

This set of experiments was successful in demonstrating that the PSP system works as expected. The Pneumo Method estimates had 100 percent precision and 98.6 percent accuracy when compared to the Primary Standard. The slight loss of accuracy appears to be caused by an electrical bias in the PSCU; this bias could easily be corrected.

When the PSP used any of the Methods other than the Pneumo Method to estimate minute ventilation, the results were not impressive. Clearly, they all fell far short of the goal (an accuracy of at least 80 percent and a precision of at least 90 percent). The RIP Method was the only Method that met the accuracy goal (with an accuracy of 90.3 percent); however, all the Methods had poor precision (ranging from –2.3 to +54.4 percent).

The use of heart rate to estimate minute ventilation was not successful. Since, theoretically, the Direct HR Method should produce more accurate minute ventilation estimates (because it is individually calibrated), it assists in the evaluation of the potential of using heart rate as a surrogate. Based on the concordance analysis results, it is known that the Direct HR Method had a significant location shift and scale shift. There are several possible reasons for this:

1. The calibration curves were generated at the start of the subject session, right after subjects were fitted with the sampling equipment. It is reasonable to assume that the subjects would be more anxious during this calibration period (and therefore have a higher heart rate) than during the sampling protocol. If their heart rate for a given work rate was over-inflated for this reason, then the resulting calibration curve would tend to overestimate minute ventilation after they became more relaxed.

2. The calibration curve was based on the data ranging from 0 to 80 Watts of work and the subjects performed work at 120 Watts during the sampling protocol.

3. The calibration curve was derived using steady-state values; for a significant portion of the sampling protocol, the subjects were not at steady-state.

4. The calibration curve was only based on three data points.

Figures 2-16 and 2-17 show cases that could be explained by reasons listed above. Each figure shows a timeline of minute ventilation estimates from both the Pneumo Method and the Direct HR Method. Subject #11's data is displayed in Figure 2-16 and Subject #18's data is displayed in Figure 2-17. For Subject #11, the Direct HR Method overestimated minute ventilation for the entire length of the session.

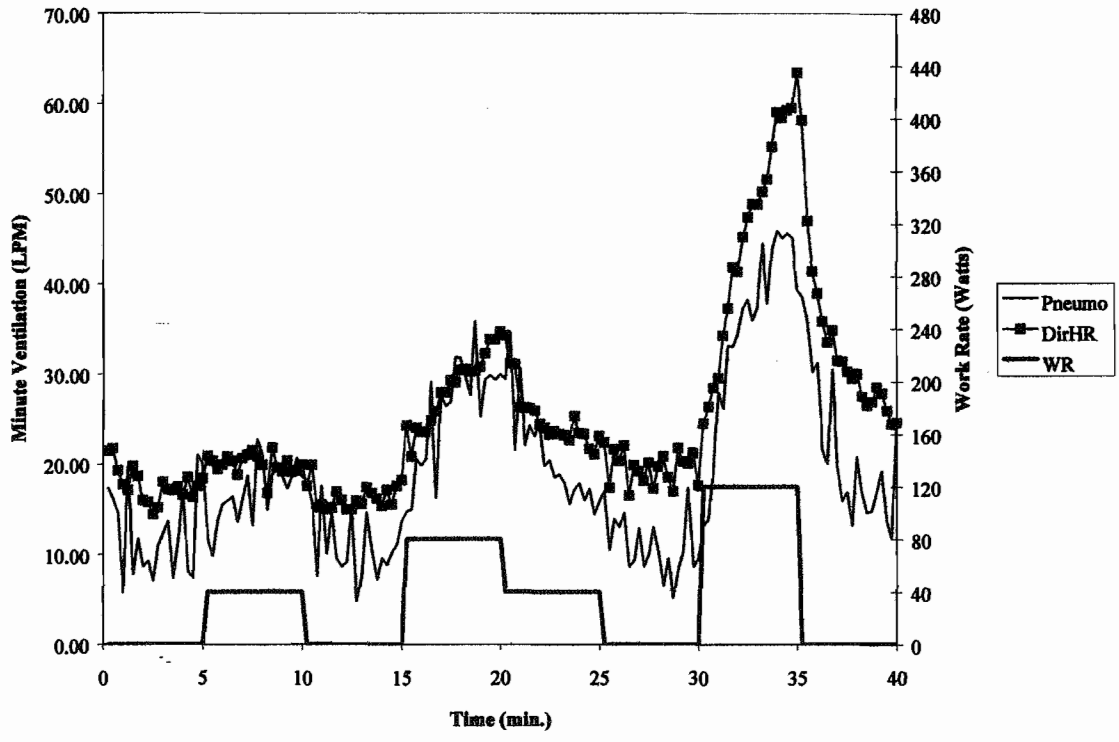



*Figure 2-16. Timeline of minute ventilation estimates for Subject #11 using the Pneumo Method and Direct HR Method.*

For Subject #18, the Direct HR Method does a much better job of tracking the Pneumo Method (see Figure 2-17). There are two interesting things to note in this graph. First, the Direct HR Method clearly overestimates minute ventilation when the subject is biking at 120 Watts (see the period from 30 to 35 minutes). Second, the lag of the respiratory system to a change in work rate is evident; the Direct HR Method's estimates always respond first. This leads to overestimation of minute ventilation at the start of a positive step (see 15 minutes on the graph) and an underestimation of minute ventilation at the start of a negative step (see 20 minutes on the graph).

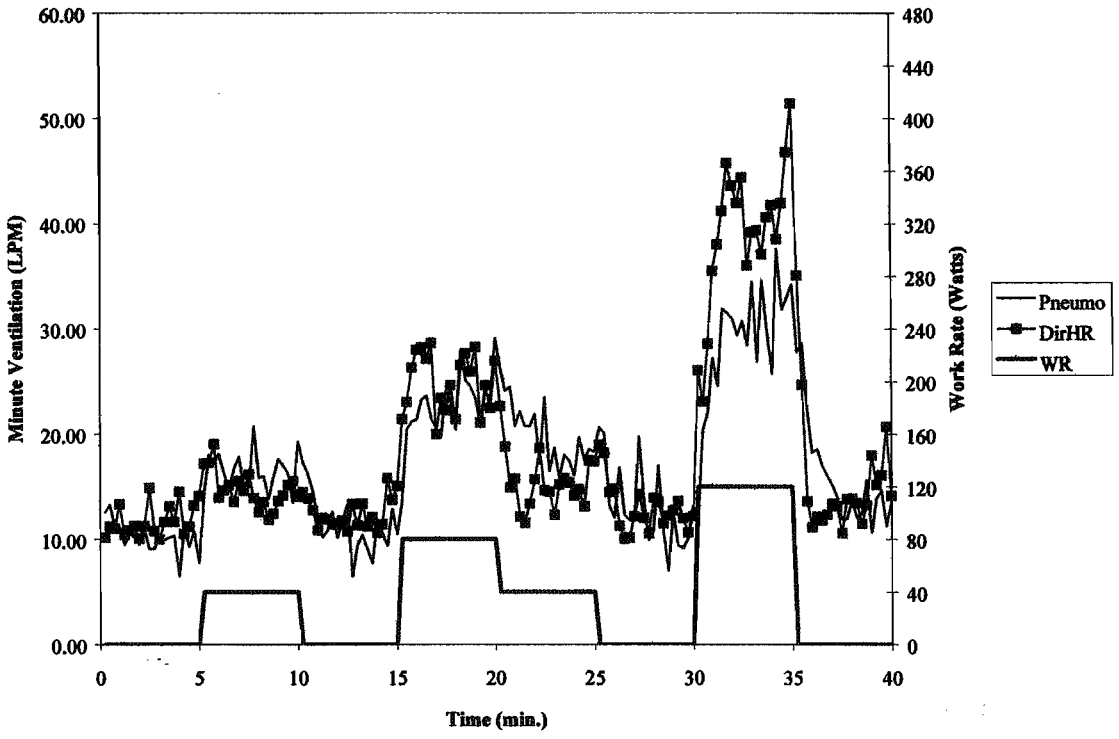



*Figure 2-17. Timeline of minute ventilation estimates for Subject #18 using the Pneumo Method and Direct HR Method.*

When examining the relationship of the Direct HR Method to the Primary Standard (Table 2-8), there are two obvious outliers; these outliers represent the only non-Caucasian subjects. While this could be attributed to coincidence, it is interesting to note that Satoh's Method, which was derived using Asian subjects, was essentially useless in predicting minute ventilation in this experiment. The implication is that perhaps people of different races have different heart rate to minute ventilation relationships, and that they cannot be characterized in the same manner. Were this hypothesis true, one would expect Satoh's Method to produce a total inhaled volume estimate close to the Primary Standard value for the Asian subject in this experiment; this is not the case, however.

As expected, the concordance analysis showed that the Indirect HR Method had less accuracy and less precision than the Direct HR Method. It would be unreasonable, after all, to expect a predictive equation to perform better than an individually determined calibration curve. The Indirect HR Method tended to overestimate minute ventilation compared to the Direct HR Method (as evidenced by the positive location shift noted in the concordance analysis). The Indirect HR Method actually had a very high accuracy when the Direct HR Method was used as its standard (93.9%). The low precision, however, brought down the concordance value to 0.377. It should be noted that the Indirect HR Method did perform as well as, or in some cases, better than, the Direct HR Method for some subjects. Figure 2-18 shows a case where the Indirect HR Method performs almost identically to the Direct HR Method, although they both overestimate the true minute ventilation.

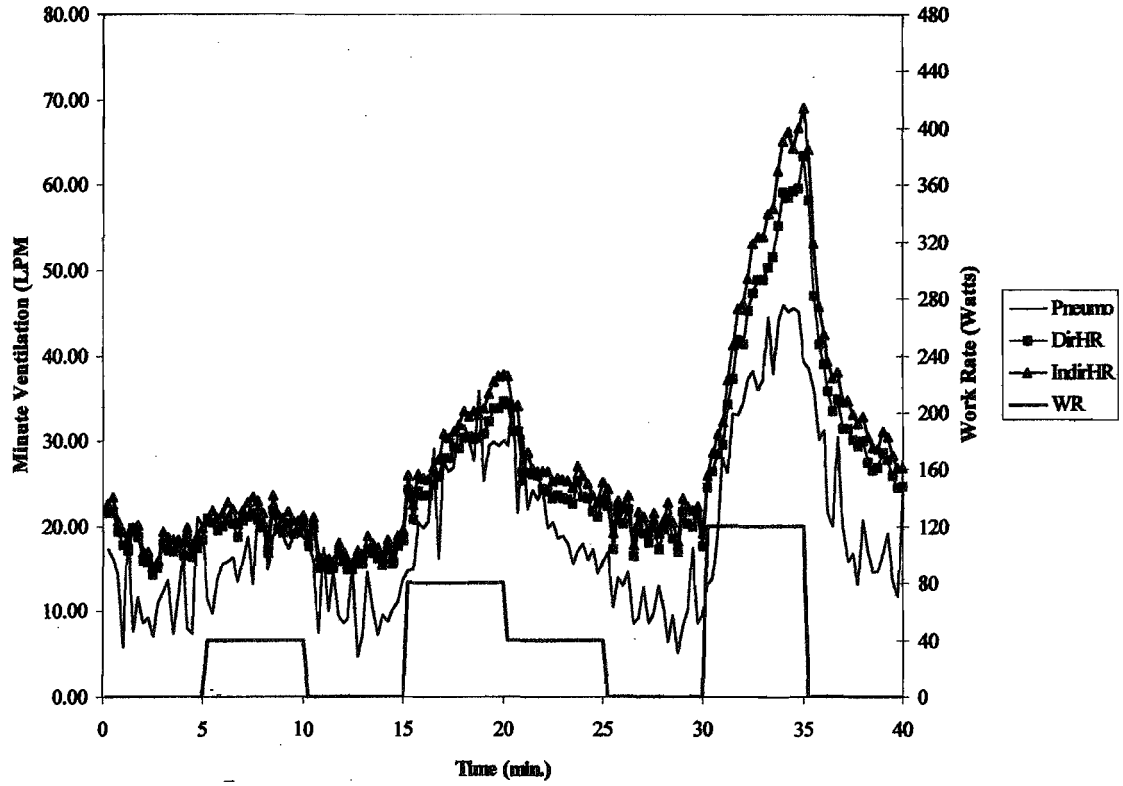



*Figure 2-18. Time line of Pneumo Method, Direct HR Method, and Indirect HR Method, for Subject #11.*

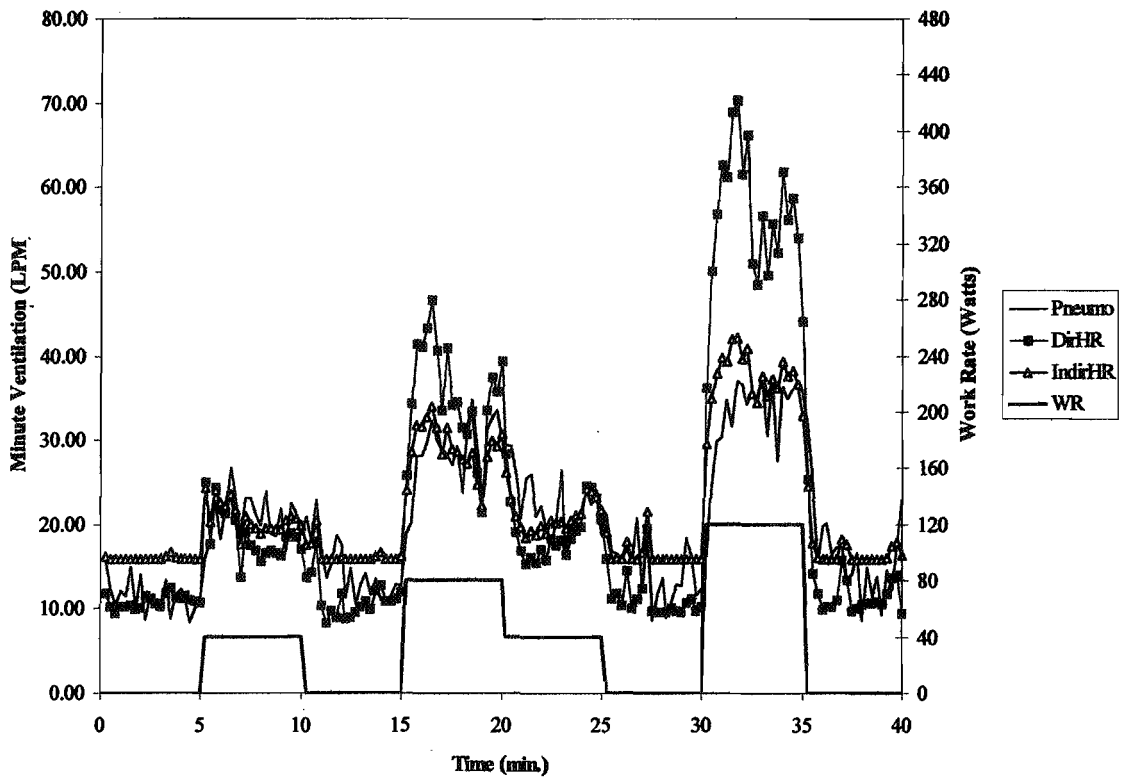



*Figure 2-19. Time line of Pneumo Method, Direct HR Method, and Indirect HR Method, for Subject #30.*

Figure 2-19 shows a case where the Indirect HR Method performs better than the Direct HR Method. Figure 2-19 also provides an example of what happens when the estimated resting heart rate for a subject is actually higher than the true value. When the heart rate falls below the pre-determined resting heart rate, the minute ventilation estimates are clipped, as seen at each of the rest periods in Figure 24 (0 to 5 minutes, 10 to 15 minutes, 25 to 30 minutes, and 35 to 40 minutes). This effect could have contributed to (1) inflating the location shift and (2) decreasing the precision of this method.

The calibration curve comparison results suggest strongly that fitness should be a significant factor in predicting the heart rate to minute ventilation relationship. The reason that it was not found significant in the predictive equation likely relates to the imprecise method of estimating fitness level for the database population. Since the data was extracted from records, the subjects were separated into four fitness categories based on the written comments of the physician and/or the maximum oxygen consumption values. When the Direct HR Method was examined for a fitness effect, it was not determined to be significant either; this could have resulted from the limited characteristics of and/or size of the laboratory population. The method of categorizing fitness (by number of times the subject exercised per week) could also have led to enough misclassification of fitness to prevent an effect from being observed.

Of all the methods, the RIP performed the best, but even after a potential outlier (Subject #21) was removed, it failed to meet the critical precision value of 90 percent. For Subject #11, the RIP Method performed extremely well and closely tracked the Pneumo Method's estimates (Figure 2-20). Yet for Subject #32, the RIP Method did not track the minute ventilation very accurately (Figure 2-21). The respiratory inductive plethysmograph had several characteristics that presumably contributed to the low precision of the RIP Method. The RIP bands, even attached to the stress test shirt, tended to move. The abdominal band, in particular, would often ride up over a roll of abdominal tissue, thereby affecting the calibration of the system. The Velcro was often stretched to the point of failure. ( In some cases the Velcro came off the bands altogether, thereby accounting for the missing RIP Method data for Subjects #8, 15, and 21.)

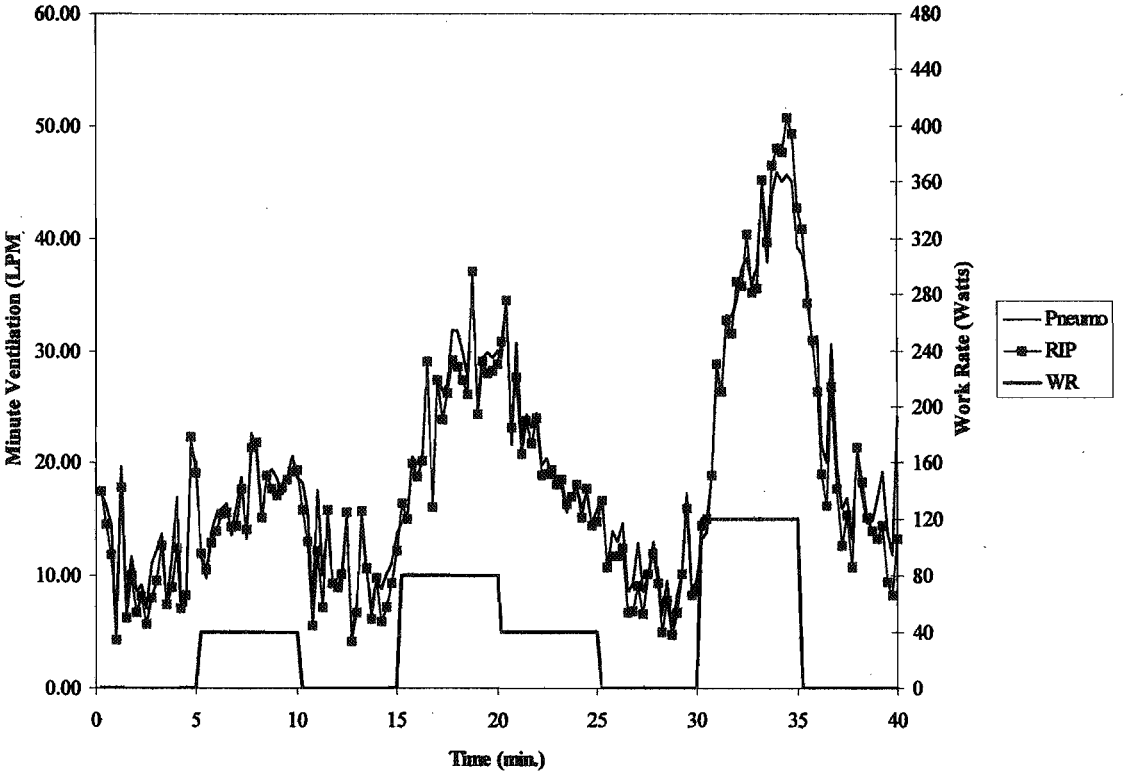


*Figure 2-20. Timeline of minute ventilation estimates for Subject #11 using the Pneumo Method and the RIP Method.*

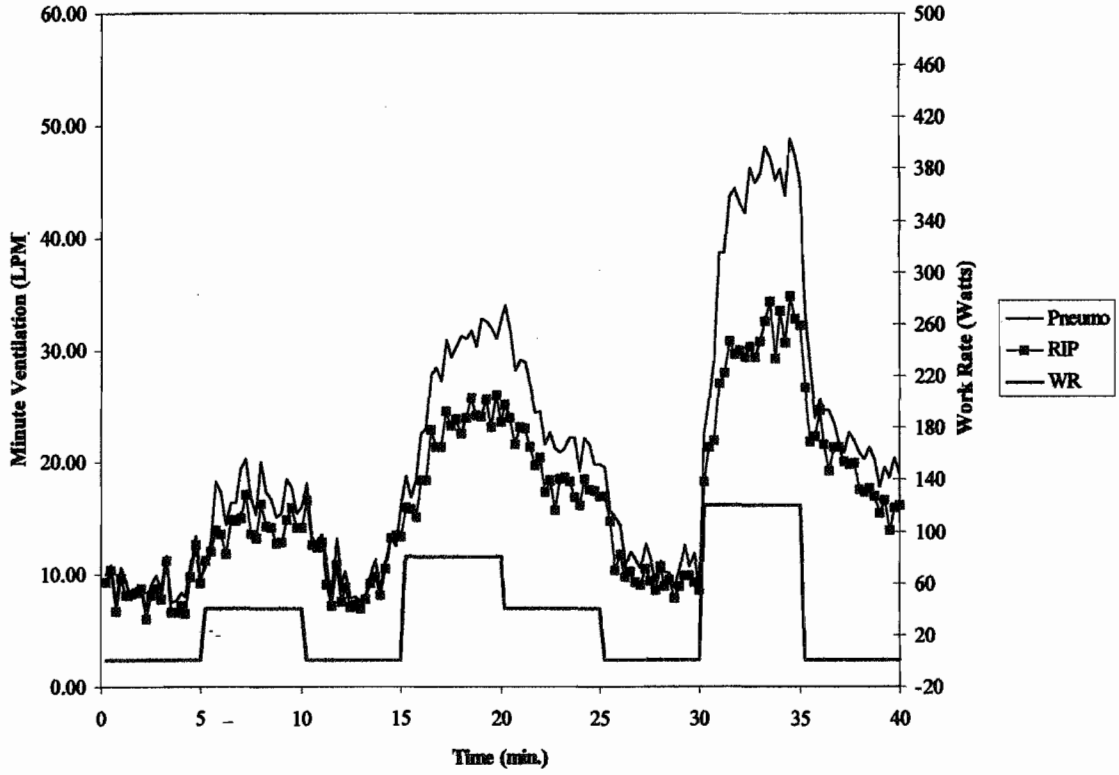



*Figure 2-21. Timeline of minute ventilation estimates for Subject #32 using the Pneumo Method and the RIP Method.*

The RIP Method presents many difficulties that make it impractical for use the field. One of the main reasons it was included in this study was to provide some reasonable measure with which to compare the heart rate-based Methods. One also must keep in mind that the laboratory subject population was very restricted; the subjects were mostly Caucasian, in good health, and 20 to 30 years old. In addition, the exercise protocol that each subject performed was the same. The combination of a limited study population and identical protocol means that the ranges of the results are very restricted; these conditions could have conceivably inflated the accuracy and precision results.

With the understanding that the heart rate-based Methods examined in this experiment were not sufficient for use in the field, the question arises as to how to improve upon them. The goal is, of course, a predictive equation; however, if we cannot fulfill the accuracy and precision goals using individually determined calibration curves, then developing a predictive equation would be pointless. Therefore, focusing on a Direct HR Method first would be prudent.

One could go two ways when attempting to improve upon the Direct HR Method described in this experiment. The first would be to add levels of complexity to the calibration protocol: (1) increase the number of work rate levels to increase the number of data points, and (2) add work rates greater than 80 Watts. This approach assumes that steady-state values remain the basis of the calibration curve.

The second way would be to focus on the transient relationship of minute ventilation to heart rate rather than the steady-state relationship. Introductory work on such a method, which used a transfer function, was performed, but it was determined that this method surpassed the scope of this investigation.

### 2.3.15 SUMMARY

The PSP itself performed extremely well in this laboratory study. Not all of these calibration methods, however, were acceptable for use of the PSP device in the field. The heart rate methods were found most applicable for field trials, but these still have significant limitations. The Direct HR calibration method probably was not complex enough, and the predictive equation used in the indirect HR method was not accurate enough, to meet the stringent requirements set for these laboratory studies. However, both methods have predictive value for estimating breathing rates, and either of these methods can be considered for preliminary field applications. The PSP was used on 30 laboratory subjects without difficulty and the indirect heart rate method (see section 2.3.2) was used on field subjects without difficulty. Even if a heart rate-based Method was optimized, it would not eliminate the error associated with the heart rate leading the minute ventilation response. This probably is not a serious problem, because such errors should largely average out over a sampling session.

Although the Indirect Method used in this study is did not meet laboratory standards, the idea behind it warrants further study. The advantage of this calibration method is its inherent simplicity. One only needs to know the weight of the worker and measure his/her resting heart rate. A worker can wear a heart rate monitor during a work shift with minimal interference. Either this heart rate signal can be logged via a wristwatch device (for estimating the total pulmonary ventilation over the entire work shift), or the detected signal can be sent to a device such as a physiologic sampling pump.

### 2.3.16 REFERENCES FOR SECTION 1 AND 2


[1] Wasserman, K., Hansen J.E., Sue, D.Y., Whipp, B.J., and R. Casaburi. Principles of exercise testing and interpretation, 2nd Ed. Lea & Febiger, 1994.

[2] Kucharski, R. *A personal dust sampler simulating variable human lung function.* British Journal of Industrial Medicine, 37:194-196, 1980.

[3] Satoh, T., Higashi, T., Sakurai, H., and Omae K. *Development of a new exposure monitoring system considering pulmonary ventilation (DEM 1).* Keio Journal of Medicine, 38(4):432-443, 1989.

[4] Levine, M.S. *A respiration-modulated personal air sampling pump.* Applied Occupational Environmental Hygiene, 9(12):994-1005, 1994.

[5] Åstrand, P. and K. Rodahl. Textbook of work physiology: Physiological bases of exercise, 3rd Ed. McGraw-Hill Book Company, 1986.

[6] Miyamoto, Y., Tatsuhiko, T., Takahashi, T., and T. Mikami. *Transient changes in ventilation and cardiac output at the start and end of exercise.* Japanese Journal of Physiology, 31:153-168, 1981.

[7] Bakker, H.K., Struikenkamp, R.S., and G.A. de Vries. *Dynamics of ventilation, heart rate, and gas exchange: sinusoidal and impulse work loads in man.* Journal of Applied Physiology: Respiratory and Environmental Exercise Physiology, 48(2):289-301, 1980.

[8] Treese, N., MacCarter, D., Adbulut, O., Coutinho, M., Baez, M., Liebrich, A. and J. Meyer. *Ventilation and heart rate response during exercise in normals: relevance for rate variable pacing.* PACE 16:1693-1700, 1993.

[9] Mermier, C.M., Samet, J.M., and Lambert, W.E. *Evaluation of the relationship between heart rate and ventilation for epidemiologic studies.* Archives of Environmental Health, 48(4):263-269, 1993.

[10] McCool, F.D. and Paek, D. *Measurements of ventilation in freely ranging subjects.* Health Effects Institute Research Report, 59:1-17, 1993.

[11] Samet, J.M. *Assessment of heart rate as a predictor of ventilation.* Health Effects Institute Research Report, 59:19-55, 1993.

[12] Taguchi, S. and S.M Horvath. *Metabolic responses to light arm and leg exercise when sitting.* European Journal of Applied Physiology, 56:53-57, 1987.

[13] Efron, B. *Bootstrap methods: another look at the jackknife.* The Annals of Statistics, 7(1):1-26, 1979.

[14] LePage, R. and K. Podgorski. *Giving the boot, block and shuffle to statistics.* Scientific Computing and Automation, March:28-34, 1994.

[15] van Belle, G., Gibson, K., Nochlin, D., Sumi, M., and E.B. Larsen. *Counting plaques and tangles in Alzheimer's disease: Concordance of technicians and pathologists.* Journal of the Neurological Sciences, 145: 141-146, 1997.

[16] Basic Electronic Circuit Analysis. Johnson and Hilburn. Inglewood Cliffs, NJ: Prentice-Hall, 1978.

[17] Hart, C.K. Theory and Evaluation of a new Physiologic Sampling Pump. Dissertation, Doctor of Philosophy, 1998, Department of Environmental Health, University of Washington, Seattle WA 98195

# 3 EVALUATION OF THE RAPID EXHALED GAS ANALYZER (REBA) FOR DETECTING ORGANIC SOLVENTS IN EXPIRED BREATH

The aim of this study was to test the performance of a new instrument, called the Rapid Exhaled Gas Analyzer (REBA), which is designed to perform gas-phase FTIR analysis on human breath samples. Ten volatile organic compounds (VOC) were examined for applicability to FTIR spectroscopy (ethanol, ethylbenzene, n-hexane, methyl ethyl ketone, methyl tert-butyl ether, m-xylene, 1,1,1-trichloroethane, trichloroethylene, tetrachloroethylene, and toluene). Three sets of detection limits (LOD) were determined. $LOD_1$ were generated from partial least squares (PLS) calibration methods using spectroscopic software, $LOD_2$ from spiked breath samples, and $LOD_3$ from blank breath samples. Mixed expired breath samples from 4 subjects were spiked at varying levels with four different VOC (hexane, methyl ethyl ketone, m-xylene and 1,1,1-trichloroethane) to validate spectral data and test overall accuracy. Breath samples spiked with m-xylene were validated by GC/FID.

PLS-derived $LOD_1$ ranged from 0.06 - 2.47 ppm. Spiked breath sample $LOD_2$ ranged from 0.52 - 1.21 ppm. Blank breath LOD measurements ranged from 0.17 - 1.70 ppm, except for ethanol, which had an LOD of 11.2 ppm. Predicted concentrations for carbon dioxide (slope = 1.06), m-xylene (slopes = 1.18, 1.21), and methyl ethyl ketone (slope = 0.93) were accurate, while concentrations were under-predicted for n-hexane (slope = 0.69) and 1,1,1-trichloroethane (slopes = 0.58-0.66).

## 3.1 INTRODUCTION

In recent years, biological monitoring has grown into one of the most direct and relevant approaches to exposure assessment. Within the realm of biomonitoring, breath analysis is of interest as a possible estimate of body burden for many volatile organic compounds (VOC). Breath monitoring, like other biomonitoring methods, can reflect the uptake of contaminants from all routes of exposure, yet is less invasive than blood or urine analysis and supplies a much less complex matrix to analyze.[1] It thus provides distinct comfort and logistic advantages over these other methods, although some workers may express concern over ethanol monitoring without worker consent. When combined with a suitable air monitoring program, one can determine the occupational contribution to internal dose. Presently, the majority of breath sampling methods require a laboratory setting with the resulting analyses usually requiring several days. The use of a direct reading instrument could greatly enhance the applicability of breath analysis to field use.

Mølhave and Pedersen evaluated the use of a photoionization detector as a direct reading instrument for breath analysis, but found the instrument to be poorly selective for individual compounds in a mixed atmosphere, with a limit of detection (LOD) for toluene around 5 ppm.[4] Also, as early as 1962, infrared methods have been used to detect VOC in breath, though not in a direct-reading application.[5] Franzblau *et al.* illustrated a semi-direct breath analysis technique for methanol using Fourier Transform infrared (FTIR) gas phase spectroscopy, which shows promise.[6] FTIR spectroscopy provides many advantages for breath monitoring. Because FTIR measures the entire infrared spectrum instantaneously (known as multiplexing), it can provide quick and accurate identification and quantitation of mixture components with multiple compounds at low concentrations, while also quantifying water vapor and carbon dioxide. It is furthermore quite sensitive, with reported limits of detection (LOD) near 10-500 ppb, depending on the compound and calibration method.[7,8]

The basic assumption underlying breath analysis is that there is equilibrium of volatile components between the alveolar air and the pulmonary arterial (capillary) blood.[1] The primary goal of all breath sampling is to accurately determine a compound's alveolar concentration, which can then be used as an index of blood level--the most common indicator of body burden. The partial pressure of a contaminant in blood will equal its partial pressure in the alveolar air when this equilibrium is established, which, for most VOC

usually occurs within 0.3 seconds.[9,10] The equilibrium concentrations are related by a compound's blood:air partition coefficient, denoted by $K_{BA}$. Kelman has shown that compounds with $K_{BA} > 10$ generally exhibit a good correlation between the venous blood and alveolar air concentrations.[11] Sato states that in general, compounds with high molecular weights or high boiling have high $K_{BA}$, although no simple relationship exists between a compound's physical properties such as molecular weight or boiling point and it's $K_{BA}$.[12]

Many types of breath sampling strategies have been studied,[1,4,6,9,13,17-20] and most have been thoroughly reviewed by Wilson (1986). They include end-expired air, alveolar air, mixed expired air, and rebreathed air. Of these, mixed-expired air samples are of particular interest because of their simplicity in acquisition and applicability to FTIR. Mixed expired breath samples have lower amounts of carbon dioxide than other types of breath samples (rebreathed air, breath holding), so there is less interference in the infrared spectrum. Mixed-expired air consists of alveolar air diluted by air retained in the respiratory dead space (mouth, nose, pharynx, trachea, and bronchi).[1] Alveolar air (end-expired air) constitutes about two-thirds of the tidal volume, so the concentration of a solvent in mixed expired air is approximately two-thirds of the concentration in alveolar air (exception: very water-soluble solvents, such as ethanol, where dead space is very small).[1] This is normally true unless dead space air also contains the analyte, so it is of great importance that mixed expired air sampling be done in a clean environment. Assessment of mixed expired air generally employs a carbon dioxide normalizing factor to standardize any variability between breath samples and to adjust for dead space dilution. By obtaining each subject's mean end-tidal carbon dioxide concentration, the mixed expired breath concentration can be converted to its estimated alveolar concentration.[13] Standard carbon dioxide concentrations used as normalization factors range from 5% to 5.5%.[14-16] Mixed expired breath samples are normalized to each subject's end-tidal breath carbon dioxide concentration by the following formula:

$$(1)\quad Normalized[compound] = \left(\frac{ET[CO_2]}{sample[CO_2]}\right) \times sample[compound]$$

where $ET[CO_2]$ is the subject's end-tidal breath carbon dioxide concentration, $sample[CO_2]$ is the measured carbon dioxide concentration in the breath sample, and sample[compound] is the compound's measured concentration in the breath sample.[13]

Fourier-Transform Infrared spectroscopy, which first attained commercial use in the late 1960s, is an infrared spectral analysis technique that provides many advantages for measuring complex mixtures, such as breath samples.[21] FTIR instruments differ from traditional dispersive IR instruments in two ways. First, FTIRs have a much higher signal to noise ratio because they allow the entire IR beam, rather than a fraction passing through a slit, to strike the sample.[21] Second, FTIR spectrometers can measure the all wavelengths in the IR spectrum at once, in a process called multiplexing, that vastly reduces the time needed to acquire a spectrum. Obtaining a spectrum rapidly offers the added benefit of co-averaging many spectra of the same sample. Because most instrument noise is a randomly fluctuating variable in time, co-averaging many spectra reduces noise and increases the distinction of the desired signal. One disadvantage of FTIR instruments, in regards to dispersive IR spectrometers, is that a background spectrum cannot be obtained simultaneously. A background spectrum must be obtained separately or sequentially from a sample spectrum and then subtracted to produce the desired transmission or absorbance spectrum. Temporal and environmental fluctuations in bench conditions can adversely affect this correction for background. FTIR instruments have already been demonstrated as potential remote sensing equipment for industrial and environmental atmospheres (known as open-path FTIR).[22] Its application to breath monitoring is not as well-developed: the only compound investigated thus far is methanol.[6]

Carbon dioxide and water are both strong infrared absorbers across broad bands of frequencies, and the fact that they are found in relatively high concentrations in breath may limit considerably the quantitation of breath contaminants using FTIR spectroscopy. The regions of a breath spectrum available for quantitation thus are restricted to 920-820, 1250-1100, 1970-2220, and 3400-2425 $cm^{-1}$, although significant interference from water overtones begins at 2950 $cm^{-1}$. This means that only about 30-40% of any breath spectrum has the total mid-IR band available as usable information. Table I shows the VOC included in the study and the regions used for quantitation.

Table I. VOC selected for study and region of IR spectrum used for quantitation (in wavenumbers).

| Compound | Region (cm-1) |
|---|---|
| Carbon Dioxide | 2081-2074 |
| Ethanol | 1150-950 |
| Ethylbenzene | 3138-2806 |
| n-Hexane | 3013-2808 |
| Methyl Ethyl Ketone (MEK) | 1240-1110 |
| Methyl tert-Butyl Ether (MTBE) | 1137-1049 |
| m-Xylene | 3100-2813 |
| Tetrachloroethylene (PERC) | 940-875 |
| Toluene | 3150-2825 |
| 1,1,1-Trichloroethane (TCA) | 1163-1036 |
| Trichloroethylene (TCE) | 865-815 |
| Water | 1969-1964 |

These ten organic solvents were selected for this study using several criteria. Six of the selected compounds (ethylbenzene, n-hexane, 1,1,1-trichloroethane, tetrachloroethylene, toluene, and trichlorethylene) represent six of seven compounds found in the 1995-1996 ACGIH Biological Exposure Indices with exhaled breath analysis as a possible determinant of occupational exposure. The four remaining solvents (ethanol, methyl ethyl ketone, methyl tert-butyl ether [MTBE], and m-xylene) were chosen for the purpose of comparing LOD between differing functional groups, because they are common industrial solvents, and because ethanol and MTBE can be considered biomonitoring confounders due the possibility of non-occupational exposure.

To determine whether FTIR shows good promise for use in breath monitoring, measures of its utility were compared with other methods of breath analysis. Two of these measures are a method's limit of detection (LOD) and its accuracy (predictive ability). A basic definition of the LOD is the minimum concentration level that can be determined to be statistically different from an analytical blank.[23] When applied to traditional IR spectroscopy, the LOD is the concentration of analyte that produces a detector response exceeding instrument noise by three times the noise's standard deviation

($3\ SD_{noise}$). At this level, there exists a 7% chance of producing a false negative or false positive determination.[24] In this study, FTIR LOD for 10 VOC were estimated in three ways. The first procedure ($LOD_1$) used the upper 95% confidence limit of the intercept from least square regressions representing predicted versus actual concentrations of reference spectra. The second procedure ($LOD_2$) used the upper 95% confidence limit of the intercept from a least squares regression between actual and FTIR-determined concentrations of spiked breath samples. The third procedure ($LOD_3$) used the average predicted concentration of two repeated blank background breath samples when quantified for a particular compound

using its calibration method. These three procedures of LOD determination have been shown to provide a more likely estimation of the performance characteristics of FTIR than $\overline{X}_{noise} + 3\ SD_{noise}$.[24]

Next, the FTIR's accuracy was assessed by comparing results for spiked samples that were also analyzed independently on a gas chromatograph/flame ionization detector (GC/FID). In this study, four VOC with differing functional groups (hexane, methyl ethyl ketone, m-xylene, and 1,1,1-trichloroethane (TCA)) were used to validate the results from FTIR quantitation methods. All four compounds' sample concentrations were determined by injecting known amounts of analyte into known volumes of mixed expired breath.. Two sets of mixed expired breath samples (both spiked with m-xylene) were analyzed by GC/FID to verify the sample preparation method.

The hypothesis tested in this work asserts that FTIR can accurately determine solvent concentrations in mixed-expired breath samples at levels likely to be encountered in industry. The objectives of this study are: 1) to determine the limits of detection for ten volatile organic compounds of differing functional groups using three different methods, 2) to validate four of the FTIR quantitation methods with spiked breath samples, and 3) to compare the prediction of mixed expired breath samples spiked with m-xylene between FTIR and GC/FID.

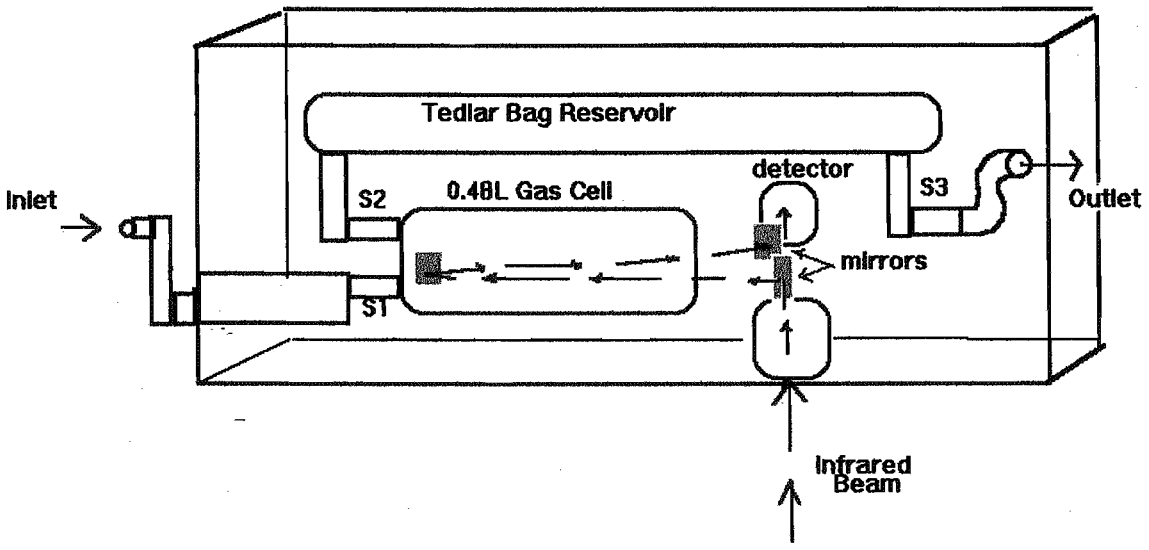
### 3.2 METHODS

The FTIR instrument in this project incorporates a custom-designed gas cell into a standard optical bench. The optical bench is a Nicolet Magna 550 spectrometer, which provides 0.5 $cm^{-1}$ wavenumber resolution over the spectral range of 7400 to 550 $cm^{-1}$. The optical bench is completely sealed and desiccated to insure the integrity of the KBr optics. The bench is fitted with a liquid nitrogen cooled mercury-cadmium-telluride (MCT) infrared detector. The stainless steel gas cell has a 0.48 liter total volume and the optical path is 4.8 meters. The gas cell and associated piping (also stainless steel) are enclosed within Plexiglas™ and kept at a temperature of 38.5° C (± 0.1°) to prevent moisture condensation in the breath sample. The gas cell is also equipped with a two liter Tedlar® bag that serves as a reservoir for the collection of rebreathed breath samples. The inlet and outlet of the cell are fitted with check valves to assure unidirectional sample flow during sample analysis. The purge valve allows the cell to be flushed with dry nitrogen or another suitable gas between breath samples. A schematic diagram of the instrument is shown in Figure 1.

All spectra incorporated a background spectrum that was collected immediately before the collection of a set of sample spectra. When there were changes in compounds or time intervals longer than fifteen minutes between spectrum collections, a new background was obtained prior to sample spectra collection.

Calibration spectra for carbon dioxide and water were generated using the optical bench. FTIR spectra were acquired by introducing bag atmospheres to the cell using Gilian GilAir5® personal sampling pump connected to the cell outlet. Carbon dioxide atmospheres were created using a compressed gas mixture (10.1% $CO_2$ in $N_2$, Scott Specialty Gases) in successively diluted concentrations (using a 2 L Hamilton Super Syringe and dry $N_2$) in pre-flushed 25 L Tedlar® bags. Water spectra were generated by installing a General Eastern Hygro M1 dew point hygrometer onto the downstream port of the gas cell. A 25 L Tedlar® bag of $N_2$ was kept in a styrofoam box furnished with a heating pad to keep bag temperatures above 37° C. Successive microliter amounts of distilled water were injected into the bag. At each injection stage, the atmosphere was allowed to equilibrate, then drawn into the cell where it was analyzed. It was then drawn through the hygrometer to determine the dew point. The dew point temperature data were converted to volume fraction water vapor concentrations using a psychometric table.

*Figure 1. Side view diagram of the gas cell assembly. All piping is stainless steel, except outlet, which is Tygon®. S1, S2, and S3 are solenoid valves to provide unidirectional sample flow and control between mixed expired and rebreathing sample modes.*




All reference VOC spectra were obtained from searching available spectral libraries. Spectra for ethylbenzene, hexane, methylene chloride, m-xylene, methyl ethyl ketone, tetrachloroethylene, trichlorotheylene and toluene were obtained by downloading FTIR spectra from the Environmental Protection Agency/Arnold Engineering Development Center (EPA/AEDC) Spectral Database, located at the website http://info.arnold.af.mil:80/epa/refcas.htm. Spectra for ethanol were obtained from EXAMS (Expert Air Monitoring System, James B. D'Arcy, Automotive Safety and Health Research, General Motors Corporation).

Spectra were analyzed using a spectral software program (Galactic Industries PLSplus/IQ™ for GRAMS/386). A separate quantitation method was constructed for each compound. Each method was designed to measure carbon dioxide, water vapor, and the VOC of interest, and used a total of 14-20 calibration spectra. Five calibration spectra of carbon dioxide ranged from 0 to 10.1 % v/v. Five calibration spectra for water vapor ranged from 2.1 to 4.2 % v/v. Reference spectra for the selected VOC ranged from 4-10 in number and several orders of magnitude in concentration range to bracket expected breath concentrations (below expected LOD levels and above levels associated with "likely" occupational exposure).

A separate quantitation method was constructed solely for carbon dioxide because it had much better accuracy alone than when included into a VOC's method. Before being incorporated into a quantitation file, all spectra were first converted into file types that could be handled by the software (using the GRAMS/386 file converter). They then had to be matched for resolution and data range. Ethanol spectra were quantified at 1 $cm^{-1}$ resolution and a data range of 3400 - 550 $cm^{-1}$. All other spectra were quantified at

0.5 $cm^{-1}$ resolution and a data range of 4000 -550 $cm^{-1}$. For each VOC's quantitation method, spectra that represented differing levels of concentrations were required. These were obtained by multiplying a

compound's standard spectrum by differing factor levels to obtain a set of standard spectra at concentrations ranging from the expected LOD and including higher breath levels attributable to occupational exposure.

The FTIR quantitation method used in this study is a type of factor analysis known as Partial Least Squares (PLS). PLS is a robust FTIR quantitation method that is relatively unaffected by the presence of impurities and can identify multiple components in a mixture.[25] It is the method of choice for spectra that contain mixtures with overlapping peaks and interactions between sample components. In addition, it is ideally suited for noisy spectra (like those of breath) and spectra that may contain artifacts. PLS uses scores and factors that represent variation in the calibration spectra, not the spectra themselves.[25] These variation spectra are then used to construct the calibration curve. PLS quantitation method factors were optimized by running maximum factor cross validation models to obtain the optimum number of factors, then reconstructed using these optimized factors. The cross validation model was a diagnostic algorithm that repeatedly recalculates the calibration curve leaving one standard out at a time.

Human subjects provided blank breath samples for the purpose of spiking with VOC. Four (3 male and 1 female) human subjects were recruited under currently granted permission of the University of Washington Human Subjects Research Committee. These subjects were non-smoking adults between the ages of 23 and 28 and provided informed consent prior to participation in this experiment.

Prior to sample collection, all Tedlar® bags were flushed with near maximum volumes of dry nitrogen, placed in an incubator at 41° C for a minimum of 45 minutes, and then emptied via the laboratory vacuum. This flushing procedure was repeated 4 times. During sample collection, bag volumes were determined by displacement of air from an airtight Plexiglas® box using a 13.5 liter respirometer (Warner E. Collins, Inc.). Two of the subjects were asked to exhale normally into nine 10-liter Tedlar® bags. The two other subjects were asked to exhale normally into four 10-liter Tedlar® bags and five 25-liter Tedlar® bags. After collection, all bags were homogenized by vigorous agitation. Carbon dioxide concentrations were then measured using an Ametek CD-3A direct reading carbon dioxide meter, removing approximately 0.03-0.06 L of the sample volume during this measurement. The bags were then placed in the incubator for one hour to ensure complete volatization of the injected VOC and good mixing of the VOC and the breath atmosphere.

After incubation, the bags were spiked (injected) with appropriate amounts of liquid contaminant to achieve the desired final breath concentration. To increase the accuracy and precision of the amount injected, all contaminants were dissolved in larger liquid volumes of carbon disulfide ($CS_2$). It was determined that this solvent does not interfere with the infrared absorbances of the compounds of concern.

Separately, mean end-tidal carbon dioxide levels for each subject were obtained by having the subject sit in a comfortable upright position and relax while breathing through a mouthpiece and wearing a noseclip. Exhaled air was continuously monitored using an Ametek CD-3A direct reading carbon dioxide analyzer, which was connected to the midstream sampling port on the mouthpiece. Data were recorded electronically utilizing Labview 2.2 software for the Macintosh. Mean end-tidal carbon dioxide concentrations were calculated by averaging the concentration maxima of approximately 60-90 consecutive breaths.

Validation of spiked breath concentrations by GC/FID were performed only for m-xylene. The m-xylene validation served as a relative confirmation of the spiked breath concentrations for the other three compounds. After one hour of incubation following spiking, the bags' contents were drawn through SKC 100/50 mg charcoal tubes using Gilian pumps while still in the incubator. Pump flow rates were calibrated using a bubbleburet and a stopwatch, and ranged from 0.46 to 0.49 L/min. Sample volumes were corrected to body temperature. Charcoal tubes were subsequently desorbed with a carbon disulfide (Omnisolve® spectrophotometry grade, EM Science) solution containing 50 ppm n-propylbenzene (Aldrich) as an internal standard. The front and back sections of charcoal from each sample and bag blank tube were transferred to 4 mL glass vials with Teflon® lined caps. The glass vials were pre-filled with desorption solution using a

Brinkman Dispensette® dispenser set to deliver 2 mL. Desorbates were sonicated for 5 minutes. After 1 hour at room temperature, desorbates were transferred to 1.5 mL autosampler vials and analyzed for m-xylene on a Hewlett-Packard 5890 Series II Gas Chromatograph with a Flame Ionization Detector (GC/FID), equipped with J&W Scientific DB5MS wax column (30 m length, 0.25μm film thickness, 0.25 mm inside diameter). Species concentration in simulated mixed exhaled air was then normalized to simulated alveolar concentration utilizing each subject's mean end-tidal $CO_2$ normalizing factor.

The levels of hexane, MEK, m-xylene, and TCA in the spiked breath samples were chosen as likely exhaled breath concentrations resulting from corresponding occupational exposure levels or at recommended concentrations denoted in the 1995 ACGIH Biological Exposure Indices. For example, TCA in the breath samples were spiked at four levels: 40, 15, 5, and 2 ppm. The BEI for TCA is 40 ppm, and levels were selected to span the range from anticipated LOD to likely occupational exhaled breath concentrations.

### 3.3 RESULTS

Prior to comparing the results of FTIR analysis with the concentrations calculated from known amounts of injected analytes, it was necessary to validate the preparation method used to produce simulated breath atmospheres. The concentrations in each bag atmosphere at five levels (0, 0.5, 2, 5, and 10 ppm) for subjects 3 and 4 were validated for m-xylene using GC/FID. There was an excellent correlation between the preparation method calculation and GC/FID results ($r^2 = .986$, $y = 0.977x - 0.078$, t-test for intercept =0 $t = -0.407$, $p > .50$, t-test for slope = 1. $t = -0.599$, $p > .50$). Subject 3 had one disparate reading, notably at level 4 (preparation method = 4.54 ppm, GC method = 3.23 ppm). There is reason to believe that the preparation method value for this sample is anomalous because the FTIR value for the same sample was close to the GC result (FTIR = 3.67 ppm). Given this excellent agreement for the m-xylene validation experiment, this was taken as acceptable confirmation of the spiked breath concentrations for the other three compounds.

Three sets of LOD results for the selected compounds are shown in Table II. $LOD_1$ values were determined by performing least squares regressions on predicted versus actual concentrations of the reference spectra and using the upper 95% confidence limit of the intercept as the $LOD_1$. Using the standard errors of the intercept, Student's t-test's were performed and confidence limits were calculated to determine whether the intercepts significantly differed from zero. Highly significant t-tests (p-values < 0.05) indicate that the intercept is indeed different from zero, namely above zero. The results of the t-tests are reflected in the confidence limits about the intercept. To be conservative, the upper confidence limit of the intercept was reported as the LOD. Concentrations in FTIR spectroscopy are normally reported in ppm-meters, which standardizes concentrations for spectra collected on different instruments with varying pathlengths. The path-dependent concentration of a sample is then calculated by dividing the ppm-m value by the pathlength, which for the cell used here is 4.8 meters. The LOD in Table II were taken as the upper 95% confidence limit of the intercept (and divided by 4.8 meters).

*Table II. Three sets of FTIR-determined LOD for 10 VOC.*

| Compound | LOD1 Upper 95% (ppm)[B] | P-value[A] | LOD2 Upper 95% (ppm)[B] | P-value[A] | LOD3 Average (ppm) | Coefficient of Variation |
|---|---|---|---|---|---|---|
| Ethanol | 1.3421 (1.1580) | 0.0001 | | | 11.1901 | 0.2527 |
| Ethylbenzene | 0.3817 | 0.1510 | | | 1.6492 | 0.9647 |
| n-Hexane | 1.3017 | 0.5794 | 0.5181 | 0.9425 | 0.1709 | 0.8496 |
| Methyl Ethyl Ketone | 2.4742 | 0.7004 | 0.9098 (0.5460) | 0.0104 | 0.4445 | 1.6426 |
| Methyl tert-Butyl Ether | 0.0594 | 0.8252 | | | -0.3434 | -1.2812 |
| m-Xylene | -0.0002 (-0.0003) | 0.0000 | 1.1582 (0.3080) | <0.01 | 1.6935 | 0.7273 |
| Tetrachloroethylene | 0.0657 (0.0470) | 0.0022 | | | 0.9862 | 0.2988 |
| Toluene | 0.4803 | 0.7790 | | | 1.2783 | 0.8499 |
| 1,1,1-Trichloroethane | 1.9501 | 0.7814 | 1.2104 | <0.19 | 0.4392 | 0.0968 |
| Trichloroethylene | 0.4799 | 0.9663 | | | 1.4310 | 0.3210 |

[A]P-value > 0.05 signifies intercept is not different from zero, using $t = \frac{x - \mu}{s/\sqrt{n}}$, $\mu = 0$.

[B]Parenthetical values reflect mean intercept where p-value < 0.05.

The $LOD_1$ for the selected VOC ranged beyond four orders of magnitude. The extremely low LOD for m-xylene, for example, may be erroneous. In the quantitation method, the training data set (calibration spectra) that were used to construct the calibration curve were also used as the validation set (cross-validation). So, there is reasonable potential for near-perfect agreement between the prediction method and the validation spectra (which *are* the training spectra).

For this reason, spiked breath samples were used to determine a second set of LOD values to assess each method's accuracy. Table II depicts the $LOD_2$ calculated for each of the four compounds used for validation by the injection method. These $LOD_2$ were obtained by performing a least squares regression at four concentration levels between the FTIR-determined concentrations and those calculated from the spiking method. As shown, the $LOD_2$ are in much closer agreement with each other than the $LOD_1$.

The $LOD_2$ ranged from 0.5181 ppm for hexane to 1.2104 ppm for m-xylene. Negative LOD values are a result of the regression line not passing through the origin. This could be due to nonlinearity with respect to Beer's law. When calibration methods contain standards that span several orders of magnitude, IR spectra have been shown to deviate from Beer's law.(6) The spectrum of this particular sample could have deviated significantly from the rest of the breath samples, and subsequently, the quantitation method was not able to recognize and accurately predict a non-zero quantity. Alternatively, because the quantitation method is attempting to quantify absorbance levels near the baseline, noise associated with the baseline fluctuates above and below zero. Therefore, some of the time a slightly negative absorbance registered during the measurement of a blank sample produces a slightly "negative" concentration value in the analysis.

Finally, FTIR-determined LOD ($LOD_3$) were generated on blank breath samples. These values are the average FTIR predicted concentrations of two blank mixed expired breath samples from each of the four subjects. This analysis perhaps gives the best measure of the FTIR instrument's minimum detection ability because it is synonymous with the general definition of the LOD--the measurement of an analytical blank. As can be seen fromTable II, ethanol has a high $LOD_3$ (11.1901 ppm) compared to the other 9 VOC. This is not consistent with the previous two LOD procedures, where all ten VOC LOD were in closer agreement. There was also no general pattern within functional groups, as the chlorinated compounds $LOD_3$ ranged from 0.4-1.4 ppm, although the aromatic compounds were in good agreement (1.6492 ppm, 1.6935 ppm, and 1.2783 ppm, for ethylbenzene, m-xylene, and toluene respectively). The negative $LOD_3$ associated with

MTBE (-0.3434 ppm) must have again been attributable to the FTIR method registering negative absorbances in the region of used for quantitation in the blank breath samples.

A separate quantitation method was constructed to quantify carbon dioxide because of its poor accuracy when incorporated into the VOC's quantitation methods. This resulted in a comparison between FTIR-determined $CO_2$ concentrations and those by the Ametek $CO_2$ Analyzer for all breath samples. A very close correlation between FTIR and the Ametek $CO_2$ values is depicted in Figure 2. The mean end-tidal carbon dioxide measurements for subjects 1-4 were 5.28%, 4.67%, 4.75%, and 4.55% respectively. In a study where mixed expired breath samples were obtained from truly exposed individuals, the mean end-tidal $CO_2$ values would have been used to adjust mixed expired breath levels to alveolar levels. When these values are applied to this study's data, they suggest that the FTIR could detect a slightly lower level of body burden if the same analyses were performed directly on alveolar air.

*Figure 2. Scatter Plot of FTIR vs. Ametek Carbon Dioxide Measurements*

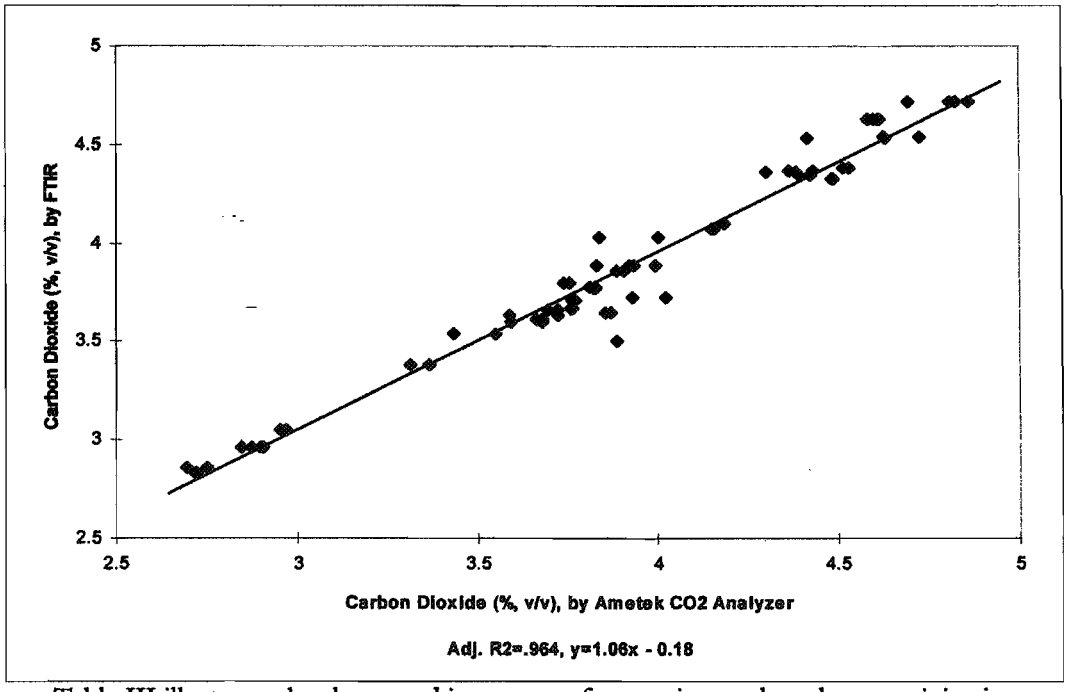



Table III illustrates the slopes and intercepts of regression analyses between injection method values and those determined by the FTIR quantitation methods, across all four validation compounds. As shown, quantitation methods for m-xylene and MEK had good accuracy (slope ~ 1) over their concentration ranges. However, the methods for hexane and TCA consistently underpredicted the higher concentration levels.

*Table III. Intercepts and slopes from regression lines between FTIR and injection method concentrations.*

| Compound | Subject | Intercept (ppm) | P-value | Slope (unitless) | P-value[A] |
|---|---|---|---|---|---|
| n-Hexane | 1 | 0.02 | 0.94 | 0.69 | <0.005 |
| Methyl Ethyl Ketone | 2 | 0.55 | 0.01 | 0.93 | <0.10 |
| m-Xylene | 3 | -1.14 | 0.01 | 1.19 | <0.05 |
| m-Xylene | 4 | 1.76 | 0.00 | 1.21 | <0.10 |
| 1,1,1-Trichloroethane | 1 | 0.97 | 0.00 | 0.58 | <0.001 |
| 1,1,1-Trichloroethane | 2 | 0.57 | 0.01 | 0.64 | <0.001 |
| 1,1,1-Trichloroethane | 3 | 0.47 | 0.05 | 0.62 | <0.001 |
| 1,1,1-Trichloroethane | 4 | 0.53 | 0.19 | 0.66 | <0.001 |

[A]P-value > 0.05 signifies slope is not different from one, using. $t = \frac{x - \mu}{s/\sqrt{n}}, \ \mu = 1$

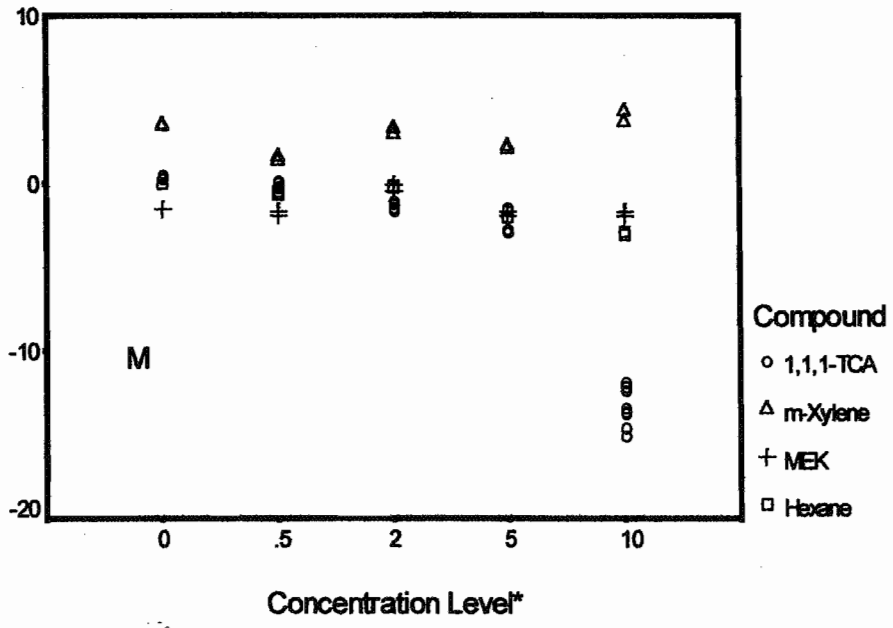
Table IV is a summary of FTIR-determined concentrations performed on all spiked breath samples. A paired t-test was performed to test whether the mean difference in concentration (between FTIR and injection method) was different from zero. The test revealed that indeed the mean difference was significantly different from zero ($p < .01$), indicating an overall FTIR underestimation of all concentration levels across all four compounds. This underprediction is heavily weighted by the large underestimates at the highest concentration level (for all compounds). Furthermore, as Table V depicts, the greatest difference is -15.0865 ppm, a large underestimate, compared to the highest overestimate, +4.2829 ppm.

*Table IV. Summary Table of Differences Between FTIR and Injection Method Concentrations.*

| | ppm | Paired t-test | P-value |
|---|---|---|---|
| Maximum | 4.2829 | | |
| Minimum | -15.0865 | | |
| Mean | -1.4578 | 26.4974 | < .01 |
| Median | -0.223 | | |
| Standard Deviation | 4.2912 | | |

Figure 3 depicts the variation in measured differences over increasing concentration levels for all subjects. As shown, the largest underestimate of TCA is at the highest concentration level (Level 5 for TCA = 40 ppm), and this is also the case for hexane (Level 5 for hexane = 10 ppm). The m-xylene quantitation method consistently overestimated concentrations at all levels, and slightly more so at the highest level (Level 5 for m-xylene = 10 ppm). The highest concentration level for all compounds was invariably the most underestimated for all subjects. Analyses of variance (ANOVA) of the measured difference between FTIR-determined and injection methods were run for three factors: compound, concentration level, and subject. These revealed that when the measured differences between the FTIR and injection methods were grouped by compound and concentration level, there was significant variation within each group (p-values < 0.01 each). Additionally, it revealed a two-way interaction between compound and concentration level that accounts for a large percentage (36%) of the total variation in the data (p-value < 0.01). Thus, there was no consistency in the variation of measured differences between compounds as the concentration level changed. In contrast, the second ANOVA of FTIR and injection method differences run by subject revealed that, as hoped, there is little between-subject variability in these measured differences, and as such, the subject factor contributes little to the total variation in the data (p-value = 0.424).

*Figure 3. Measured Difference between FTIR and Injection Method Values versus Concentration Level, by Compound.*




To further assess the accuracy of the FTIR quantitation methods, the results for mixed expired breath samples containing m-xylene were compared to results obtained by charcoal tube desorption with GC/FID. Both analyses were conducted on the same set of breath samples. The m-xylene method had good accuracy for subject 3 (slope 1.09, adjusted $r^2 = 0.960$), but tended to overestimate values for subject 4 (slope 1.13, adjusted $r^2 = 0.957$).

### 3.4 DISCUSSION

This study has determined three sets of LOD using FTIR for a variety of volatile organic solvents in breath that span different functional groups. The LOD values determined from the quantitation method alone, and from spiked samples, were comparable to the LOD values determined from blank breath samples. Compared to similar published data, the FTIR-determined LOD for ethanol (~11 ppm) differed by over an order of magnitude from the FTIR-determined LOD for methanol (0.5 ppm) by Franzblau *et al.*[6] Li-Shi and Levine found FTIR-determined LOD *in ambient air* that ranged from 0.007-0.067 ppm for seven of the same compounds used in this study.[7] Clearly, the sensitivity of FTIR to organic solvents is diminished when sampling expired breath in comparison to ambient air.

In addition, because mixed expired air is a dilution of alveolar air, if true alveolar air were sampled using FTIR, the same LOD would permit detection of a lower level of body burden than if the analysis were performed on mixed expired air.

The FTIR quantitation methods were accurate at determining concentration levels in breath samples for $CO_2$, MEK, and m-xylene (subject 3). The methods tended to greatly underestimate hexane and TCA, while slightly overestimating m-xylene for subject 4. Regarding the latter, interference from harmonic overtones due to water vapor probably added to the variability in its quantitation method. Although the quantitation methods were able to determine concentrations for a mixture of analytes, no mixtures of VOC were quantified. It has been noted that the effects of spectral overlap on LOD and FTIR accuracy are not consistent.[23] Li-Shi and Levine found a 2-50 fold decrease in LOD when solvents were mixed.[26]

In general, further optimization of FTIR quantitation methods, such as continued modification of PLS factors and critical review of reference spectra prior to inclusion, might improve accuracy. Perhaps better

homogeneity in composition between reference spectra and sample spectra would also help improve performance of calibration methods. Ideally, calibration spectra used for mixed expired breath analysis should be from mixed expired breath that contain differing levels of the compound in question.

Also, it has been recommended that FTIR spectral quantitation methods only be constructed using calibration spectra collected on the same instrument.[21] Indeed, the generation of FTIR quantitation methods using spectra from external libraries might be unjustified. Discrepancies such as differences in environmental conditions, detector response, interferogram Fast Fourier Transform algorithm computations (phase correction or apodization), data file production, and spectral file conversion can all contribute to errors in the quantitation methods.

Prior to the completion of this study, several attempts were made to separate water and carbon dioxide from the breath samples before measurement by FTIR. Columns of Drierite and non-hygroscopic soda lime granules, respectively, were used to remove each of these components. Although substantial fractions of both water and carbon dioxide were removed from breath samples, large amounts of VOC were also removed. Other breath analyses have used cryogenic methods to separate components prior to analysis, but these methods are obviously not compatible with direct-reading nor applicable to field use, and are beyond the scope of this paper.

Because it is often not advisable to operate analytical instruments near their LOD, more work needs to be done to determine limits of detection and quantitation for FTIR and organic solvents in breath samples. It has been shown that these FTIR methods can probably detect these VOC at levels anticipated for end-of-shift sampling, but may be questionable for end-of-work-week or beginning-of-work-week sampling, depending on the toxicokinetics specific to each compound.

### 3.5 REFERENCES FOR SECTION 3


1. Wilson H.K.: Breath analysis. Physiological basis and sampling techniques. Scand. J. Work Environ. Health 12:174-192 (1986).

2. Andrews, L.S.; Snyder, R.: Toxic Effects of Solvents and Vapors. *In* Klaassen CD, Amdur MO, Doull J, eds.: Casarett and Doull's Toxicology. The Basic Science of Poisons. Third Edition. (New York:Macmillian Publishing Company, 1986).

3. American Conference of Governmental Industrial Hygienists: Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices for 1995-1996. ACGIH, Cincinnati, OH (1995).

4. Mflhave, L.; Pederson, O.F.: Measurements of alveolar concentrations of toluene. Int. Arch. Occup. Environ. Health 54:65-71 (1984).

5. Stewart, R.D.; Gay, J.J.; Erley, D.S.; Hake, C.L.; Peterson, J.E.: Observations on the concentrations of trichloroethylene in blood and expired air following exposure of humans. Am. Ind. Hyg. Assoc. J. 23(2):167-170 (1962).

6. Franzblau, A.; Levine, S.P.; Burgess, L.A.; Qu, Q.S.; Schreck, R.M.; D'Arcy, J.B.: The use of a transportable Fourier Transform Infrared (FTIR) spectrometer for the direct measurement of solvents in breath and ambient air--I: Methanol. Am. Ind. Hyg. Assoc. J. 53:221-227 (1992).

7. Xiao, H.; Levine, S.P.; Nowak, J.; Puskar, M.; Spear, R.C.: Analysis of organic vapors in the workplace by Remote Sensing Fourier Transform Infrared spectrscopy. Am. Ind. Hyg. Assoc. J. 54(9):545-556 (1993).

8. Li-Shi, Y.; Levine, S.P.: Evaluation of the applicability of Fourier Transform Infrared (FTIR) spectroscopy for quantitation of the components of airborne solvent vapors in air. Am. Ind. Hyg. Assoc J. 50(7):360-365 (1989).

9. Astrand, I.: Uptake of solvents in the blood and tissues of man. Scand. J. Work Environ. Health 1:199 (1975).

10. Cotes, J.E.: Lung function: Assessment and application in medicine. Blackwell Scientific Publications, Oxford, (1979).

11. Kelman, G.R.: Theoretical basis of alveolar sampling. Br. J. Ind. Med. 39:259-264 (1982).

12. Sato, A.; Nakajima, T.: Pharmacokinetics of organic solvent vapors in relation to their toxicity. Scand. J. Work Environ. Health 13:81-93 (1987).

13. Whitney, G.E.: Evaluation of the use of carbon dioxide as a normalizing factor when measuring organic solvents in the expired breath of humans. (Masters Thesis). University of Washington School of Public Health and Community Medicine, Department of Environmental Health, (1992).

14. Niu, H.C.; Schoeller, D.A.; Klein, P.D.: Improved gas chromatographic quantitation of breath hydrogen by normalization to respiratory carbon dioxide. J. Lab. Clin. Med. 95(5):755-763 (1979).

15. Strocchi, A.; Ellis, C.; Levitt, M.: Reproducibility of measurements of trace gas concentrations in expired air. Gastroenterology 101:175-179 (1991).

16. Guillemin, M.; Guberan, E.: Value of the simultaneous determination of $PCO_2$ in monitoring exposure to 1,1,1-trichloroethane by breath analysis. Brit. J. Ind. Med. 39:161-168 (1982).

17. Droz, P.O.; Guillemin, M.P.: Occupational exposure monitoring using breath analysis. J. Occup. Med. 28:593-602 (1986).

18. Engstrom, K.; Husman, K.; Pfaffli, P.; Riihimaki, V.: Evaluation of occupational exposure to xylene by blood, exhaled air and urine analysis. Scand. J. Work Environ. Health 4:114-121 (1978).

19. Glaser, R.A.; Arnold, J.E.; Shulman, S.A.: Comparison of three sampling and analytical methods for measuring m-xylene in expired air of exposed humans. Am. Ind. Hyg. Assoc. J. 51:139-150 (1990).

20. Jones, A.W.: Role of rebreathing in determination of the blood-breath ratio of expired ethanol. J. Appl. Physiol. 55:1247-1241 (1983).

21. Smith, B.C.: Fundamentals of Fourier Transform Infrared Spectroscopy. CRC Press, Inc., Boca Raton, FL 1996.

22. Strang, C.R.; Levine, S.P.; Herget, W.F.: A preliminary evaluation of the Fourier Transform Infrared (FTIR) spectrometer as a quantitative air monitor for semi-conductor manufacturing process emissions. Am. Ind. Hyg. Assoc. J. 50:70-77 (1989).

23. Strang, C.R.; Levine, S.P.: The limits of detection for the monitoring of semiconductor manufacturing gas and vapor emissions by Fourier Transform Infrared (FTIR) spectroscopy. Am. Ind. Hyg. Assoc. J. 50 (2):78-84 (1989).

24. Taylor, J.K., Ed.: Sampling and Calibration for Atmospheric Measurements, p. 16. ASTM Pub. #STP-957. ASTM, Philadelphia, PA. 1987,.

25. Galactic Industries Co. PLSplus/IQ™ User's Guide. Galactic Industries Corporation, Salem, NH, (C) 1991-1996.

26. Li-Shi, Y.; Levine, S.P.; Strang, C.R.; Herget, W.F.: Fourier Transform Infrared (FTIR) spectroscopy for monitoring airborne gases and vapors of industrial hygiene concern. Am. Ind. Hyg. Assoc. J. 50(7):354-359 (1989).

# 4 FIELD STUDIES

## 4.1 FIELD EVALUATION OF THE PHYSIOLOGIC SAMPLING PUMP

The physiologic sampling pump (PSP) was designed to be used in the field under real world conditions without interfering with a worker's daily routine. In order to validate that it functions as intended, a small pilot field study was performed. The Indirect HR Method described in above was used to estimate minute ventilation in this study. While the primary goal of this pilot field study was to assess the performance of the PSP in the field, this was also an opportunity to explore (non-statistically) some other questions of interest:

(1) Do the subjects' 15-second heart rate averages appear to be normally distributed?

(2) Do the subjects' 15-second minute ventilation averages appear to be normally distributed?

(3) Do the 15-second air concentration averages appear to be lognormally distributed?

(4) How do the TWAs compare to the PVWAs for each subject?

(5) Does there seems to be any correlation between the minute ventilation estimates and the air concentration for any of the subjects?

(6) Do the charcoal tube results for the samples collected on the TSP and PSP suggest that samples collected on a PSP in the field are valid?

In order to explore these questions, two additional instruments were used in the field. The first instrument was a traditional sampling pump (TSP); by pairing the PSP with a TSP, the first three questions listed above were explored. The second instrument was a Miran (Foxboro, , East Bridgewater, MA); by recording real-time air concentrations of toluene or xylene, the last two questions were examined. The answers to these questions may serve as guidance for further studies.

The methods used for this study will be presented first, followed by the results. The results will include: (1) descriptions of the workers and their tasks, (2) the PSP performance in the field, (3) histograms of heart rate, minute ventilation, and air concentration averages (3) the charcoal tube analysis results for six analytes (m-xylene, o-xylene, p-xylene, toluene, ethyl benzene, and benzene), (4) the sampling time and volume for each charcoal tube, (5) the calculated air concentrations, (5) the TWAs and PVWAs, and (6) a graph of the air concentration versus minute ventilation.

### 4.1.1 METHODS

The pilot field study consisted of three subjects: a spray painter and two histologists. These subjects were selected by asking people who worked with solvents at the University of Washington if they would volunteer to be a subject. After receiving interest from a worker, as well as a signed Human Consent form, a sampling day was chosen in which their use of solvents was highest.

#### *4.1.1.1 Equipment Calibration*

The PSP, the TSP, and the Miran were calibrated prior to the start of each worker's work shift. The PSP was calibrated using a program loaded into the PSCU via a Pentium laptop computer. A mass flowmeter was placed upstream of a blank charcoal tube; its voltage was fed into the PSCU. The pump flow rate was controlled by the PSCU program entitled PUMPCAL. This program sent five voltages to the pump, holding

each voltage level for 20 seconds; the final mass flow meter voltages were stored by the PSCU. After the last voltage was recorded, PUMPCAL calculated the calibration curve (a polynomial curve) and displayed the coefficients on the screen for the user to record. The calibration coefficients were then entered into the program entitled FIELDPSP and saved, so that this step need not be repeated in the field.

The TSP was set to a flow rate of 0.200 liters per minute by comparing it to a primary standard.

The Miran was calibrated by laboratory personnel working in the University of Washington's Environmental Health Analytical Laboratory. They followed closed-loop the calibration method outlined in the Miran 2B manual. A chemically inert, bellows pump was placed in a closed circuit with a septum port and the Miran. A quantity of the toluene or xylene was injected through the septum in the fixed volume of the closed-loop so that atmospheres of 1, 5, 10, 15, and 20 ppm would be produced. The corresponding responses were entered into the Miran's memory and a calibration curve was created by the Miran. The Miran was used in the background subtraction mode.

#### *4.1.1.2 Experiment Preparations*

The following equipment was brought to each work site:

- a fanny pack with the PSCU in the pouch and two sampling pumps (a modified GilAir5 for the PSP and a Gilian Low Flow Sampler for the TSP) attached to the waist band on either side of the pouch. Tubing of approximately two feet in length was attached to their inlets.
- a Pentium laptop computer loaded with Txtools and the FIELDPSP program (which used the Indirect HR Method to estimate minute ventilation)
- a Polar® Vantage XL heart rate monitor
- a Miran 2B and a Rustrak Ranger datalogger (Gultan, East Greenwich, RI)
- pre-labeled charcoal tubes

At the work site, subjects were asked their age, height, weight, health status, and the number of days a week they usually exercised. In addition, they were asked if they were taking any medication. Resting heart rate was measured by having each subject sit at rest for five minutes while wearing the Polar Monitor chest band and wristwatch. At the end of five minutes, the heart rate value displayed on the wristwatch was recorded.

The Miran instrument and the attached datalogger were started upon arrival to the site. For the first field session, a long hose was attached to the intake of the Miran; the Miran remained stationary while the intake location was moved in conjunction with the worker; this ensured that the toluene measurements would approximate the worker's personal toluene concentration values. For the second and third field sessions, however, this arrangement was not possible; the Miran's intake location remained stationary, thereby providing area measurements.

#### *4.1.1.3 Sample Collection*

Charcoal tubes were inserted into the ends of the tubing opposite their connection to the TSP and PSP inlets. The PSCU was connected to the laptop computer and the Txtools program named FIELDPSP was downloaded and initiated. This program was designed to pause two minutes before the PSP starts sampling. During this pause, the PSCU was disconnected from the computer, the fanny pack (with PSP and TSP) was placed on the worker, and the charcoal tubes were attached to the lapel of the worker (one charcoal tube on each side). When the PSP commenced sampling, the TSP was manually turned on.

Each charcoal tube was sampled for approximately two hours. During Subject #1's shift, three sets of charcoal tubes were sampled. For Subjects #2 and #3, only one set of charcoal tubes was sampled. The charcoal tubes were analyzed by the University of Washington's Environmental Health Analytical Laboratory for the following analytes: p-xylene, m-xylene, o-xylene, toluene, ethyl benzene, and benzene. Results were reported as mass of each analyte on each charcoal tube.

### 4.1.2 RESULTS

The three field subjects' characteristics are displayed in Table 4-1. The table includes the following data: sample date, the subjects' job descriptions, the main task they performed the day of sampling, their age (in years), their sex, their weight (in kilograms), their height (in centimeters), their resting heart rate (in beats per minute), the average number of times they exercise per week, their current health status, and if they were taking any medication which could affect their heart rate.

The histologist identified as Subject #3 actually refused to wear the PSP soon after the experiment had started. In order to try to collect some potentially useful data, one of the researchers volunteered to wear the PSP equipment as a surrogate subject. The characteristics for Subject #3 below, other than job description and main task, apply to the researcher who wore the equipment, not to the intended subject (the histologist).

*Table 4-1: Field subject characteristics. Note that Subject #3's characteristics that are in italics apply to the surrogate subject, not to the histologist.*

| **Subject#** | **1** | **2** | **3** |
|---|---|---|---|
| **Date** | 3/18/97 | 4/10/97 | 4/24/97 |
| **Job** | Painter | Histologist | Histologist |
| **Main task** | Spray booth | Coverslipping | Slide staining |
| **Age (yrs)** | 54 | 41 | *41* |
| **Sex** | M | F | *M* |
| **Wt (kg)** | 73 | 91 | *79* |
| **Ht (cm)** | 173 | 180 | *188* |
| **Rest HR** | 93 | 78 | *69* |
| **Fitness** | 0 | 0 | *3-4x/wk* |
| **Health** | Normal | Normal | *Normal* |

#### *4.1.2.1 Subject #1*

Subject #1 worked in the Carpentry Shop at the University of Washington as a painter. He worked primarily in a spray paint booth that was well ventilated. His main task for that day included spray painting chairs and doors with lacquer in the spray paint booth (with the fan on and while wearing a respirator). Other tasks include sanding, applying lacquer by hand, applying stain by hand, and cleaning brushes.

The PSP system worked well in the field with Subject #1. The PSP operating tasks such as pump calibration, loading the PSCU with the FIELDPSP program for Subject #1, and downloading the data were easily performed. The main complaint from the subject was that the fanny pack unit (which carried the PSCU and two sampling pumps) kept sliding down over his hips. Since he essentially stood all day, it did not get in his way due to its size or location. However, the subject refused to wear the PSP during his lunch break due to embarrassment over its appearance and size.

Histograms of Subject #1's 15-second heart rate and minute ventilation averages are displayed in Figures 4-1 and 4-2. Note that the heart rate values extended below Subject #1's measured resting heart rate of 93

beats per minute. In addition, at times it seemed the PSCU failed to pick up the heart rate signal, as indicated by the low 15-second averages. It was decided that for the purpose of looking at the distributions of these values, heart rate averages less than 80 beats per minute would be eliminated. In addition, since the 15-second minute ventilation averages were based on the heart rate values, the minute ventilation estimates corresponding to these heart rate values were removed as well. A total of 88 sets of data points were removed, out of a total of 1816; therefore, approximately 5% of the heart rate averages were considered invalid. A histogram of the toluene concentrations, recorded on the Miran datalogger, is shown in Figure 4-3. A timeline of Subject #1's minute ventilation averages and toluene concentrations are displayed in Figure 4-4. Subject #1 had a lunch break from 12:20 P.M. until 1:08 P.M.; this portion is not included in the graph.

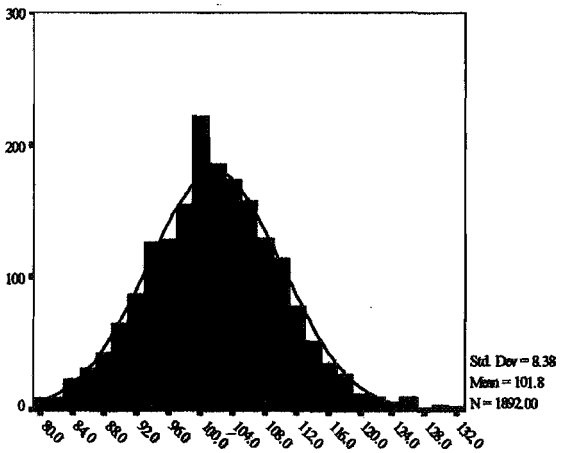



*Figure 4-1: Histogram of 15-second heart rate for Subject #1.*

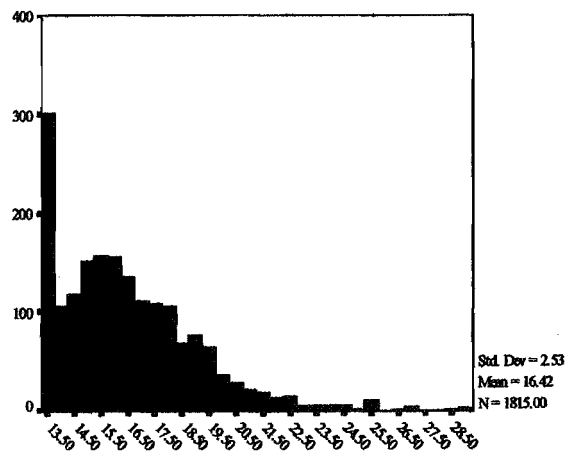



*Figure 4-2: Histogram of 15-second minute ventilation.*

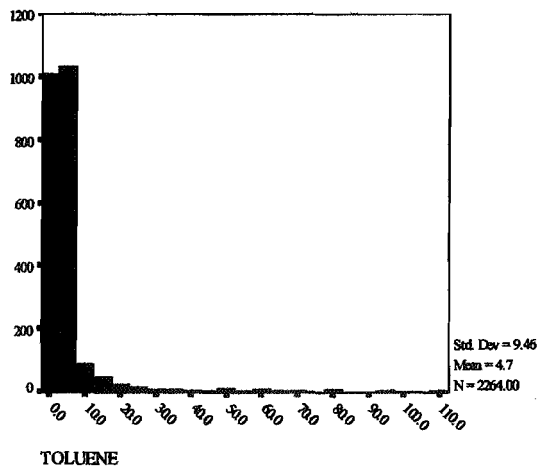



*Figure 4-3: Histogram of 30-second averages of toluene concentration for Subject #1.*

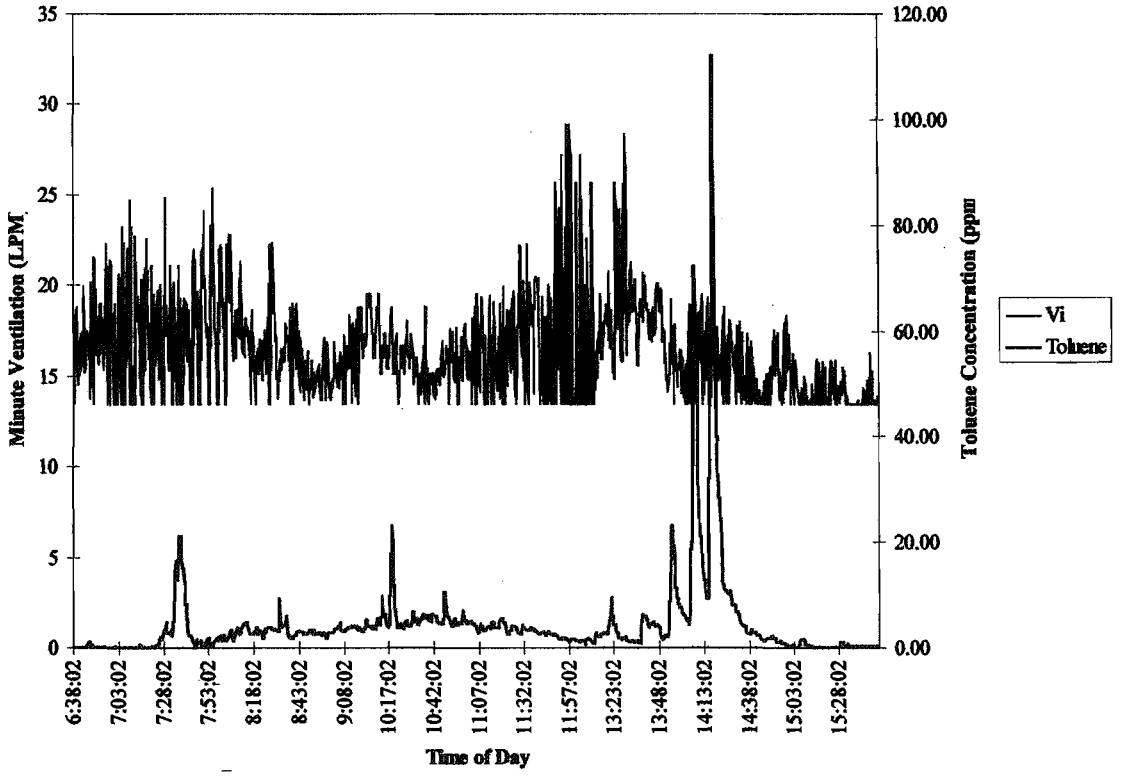



*Figure 4-4: Minute ventilation and toluene concentration over time.*

The charcoal tube laboratory results were reported as the mass of each analyte per charcoal tube (Table 4-2). The sample identification reflects both the pump type on which the sample was collected (TSP or PSP) and the sample collection progression (e.g. sample #1 collected first, followed by sample #2, etc.). The sample collection times and the volume of air sampled per charcoal tube also are listed. The mass for each analyte was divided by the sample volume to calculate the air concentrations listed in Table 4-3.

*Table 4-2: Mass of analyte (in micrograms) on the charcoal tube samples collected on the TSP and PSP for Subject #1. The toluene results for the third PSP sample could not be assessed because the sample exceeded the upper quantitation limit (UQL).*

| Sample | Duration (Min) | Volume (L) | p-xylene (µg) | m-xylene (µg) | o-xylene (µg) | toluene (µg) | ethyl benz (µg) | benzene (µg) |
|---|---|---|---|---|---|---|---|---|
| TSP1 | 138 | 27.6 | 45.69 | 132.60 | 64.54 | 381.74 | 36.31 | 0.43 |
| TSP2 | 156 | 31.2 | 24.52 | 66.16 | 36.75 | 188.99 | 19.38 | 0.36 |
| TSP3 | 167 | 33.4 | 71.49 | 204.36 | 104.93 | 1291.88 | 59.43 | 0.51 |
| PSP1 | 142 | 60.9 | 97.18 | 258.70 | 141.79 | 675.06 | 70.58 | 0.51 |
| PSP2 | 158 | 63.0 | 58.49 | 173.13 | 95.77 | 469.90 | 46.45 | 0.63 |
| PSP3 | 158 | 62.2 | 173.93 | 454.39 | 241.51 | >UQL | 137.16 | 0.73 |

The air concentrations based on the TSP samples are compared to those based on the PSP samples in the following graph (Figure 4-5). Each data point plots the air concentration of one of the analytes from a TSP sampled charcoal tube paired with the air concentration of the same analyte for the corresponding PSP sampled charcoal tube. Therefore, for each analyte (except toluene) there are three data points plotted (one for each charcoal tube sampling period). For toluene, only two points are plotted since the PSP3 sample could not be quantified. Note that the benzene concentrations are all close to zero, and overlap one another on the graph. The line represents a line of unity (i.e. perfect agreement). Based on a paired T-test, these concentration values are not significantly different.

*Table 4-3: Air concentration results (in milligrams per cubic meter) based on charcoal tube samples collected for Subject #1. The toluene results for the third PSP sample could not be assessed because the sample exceeded the upper quantitation limit (UQL).*

| Sample | p-xylene (mg/m³) | m-xylene (mg/m³) | o-xylene (mg/m³) | toluene (mg/m³) | ethyl benzene (mg/m³) | benzene (mg/m³) |
|---|---|---|---|---|---|---|
| TSP1 | 1.66 | 4.80 | 2.34 | 13.83 | 1.32 | 0.02 |
| TSP2 | 0.79 | 2.12 | 1.18 | 6.06 | 0.62 | 0.01 |
| TSP3 | 2.14 | 6.12 | 3.14 | 38.68 | 1.78 | 0.02 |
| PSP1 | 1.60 | 4.25 | 2.33 | 11.09 | 1.16 | 0.01 |
| PSP2 | 0.93 | 2.75 | 1.52 | 7.46 | 0.74 | 0.01 |
| PSP3 | 2.80 | 7.30 | 3.88 | >UQL | 2.20 | 0.01 |

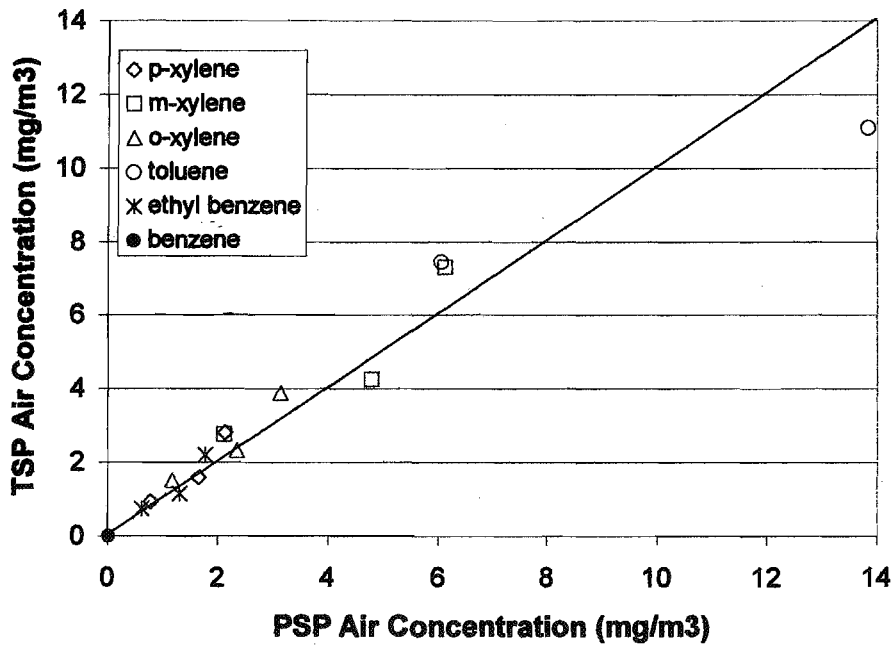



*Figure 4-5: Comparison of analysis results between the three charcoal tubes sampled using the TSP versus the three sampled via the PSP. Estimated air concentrations are expressed in milligrams per cubic meter or air.*

The TWAs and PWAs for each analyte were calculated by dividing the sum of the concentrations by the total time (to arrive at the TWA) or the total volume (for the PWA). To compute the values for toluene, the sum of the concentrations and sample times were restricted to samples #1 and #2. The values are shown in Table 4-4, and a paired T-test revealed that the PVWAs were not significantly different from the TWAs.

*Table 4-4: TWA and PVWA results for Subject #1's work shift on 3/18/97. The toluene values are based on the first two charcoal tube results only.*

| Sample | p-xylene (mg/m³) | m-xylene (mg/m³) | o-xylene (mg/m³) | toluene (mg/m³) | ethyl benzene (mg/m³) | benzene (mg/m³) |
|---|---|---|---|---|---|---|
| TWA | 1.54 | 4.37 | 2.24 | 9.71 | 1.25 | 0.01 |
| PVWA | 1.77 | 4.76 | 2.57 | 9.25 | 1.37 | 0.01 |

The relationship between minute ventilation and toluene concentration is displayed in Figure 4-6. The correlation coefficient between these two variables is -0.02.

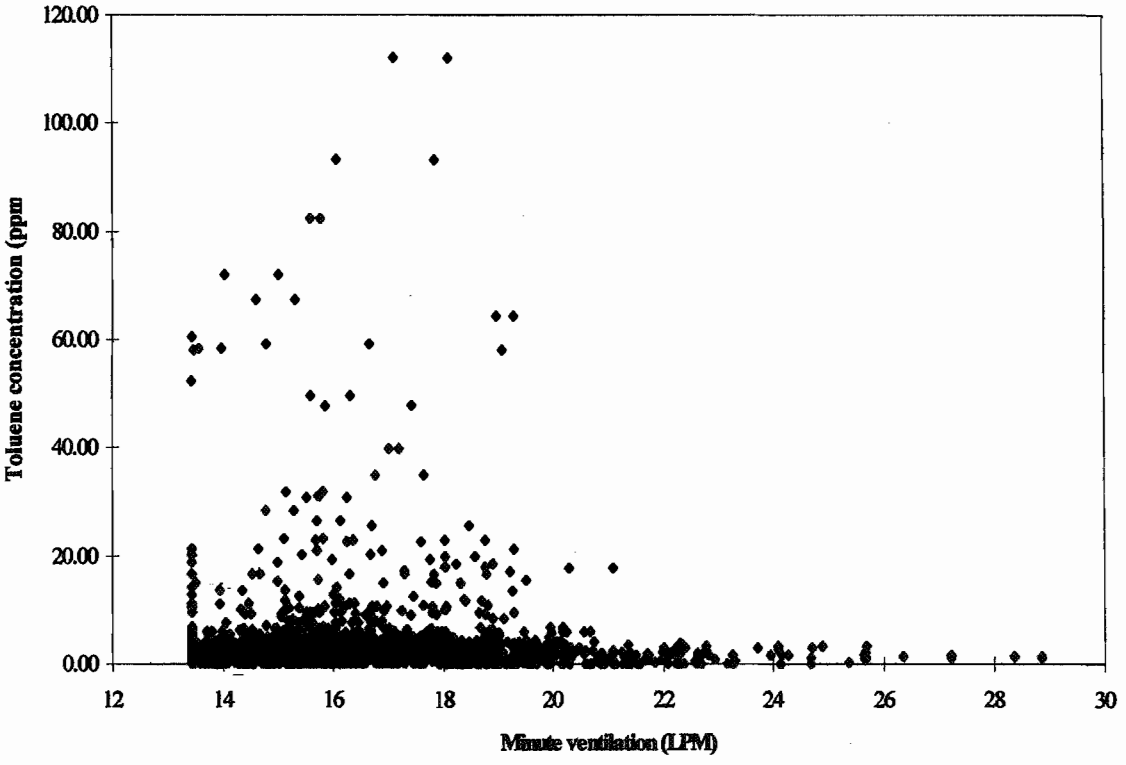



*Figure 4-6: Relationship between air concentration of toluene (ppm) and minute ventilation (LPM) for Subject #1.*

### *4.1.2.2 Subject #2*

Subject #2 worked in the Zoology Department at the University of Washington as a histologist. On the day of sampling her main task was to coverslip slides. In addition to coverslipping, she performed microscope work and cleaned dishes at a sink. She only worked two hours the day of sampling, so only one sample per pump was collected. As in the experience with Subject #1, the use of the PSP from an industrial hygienist's perspective was very straightforward and easy. The subject did complain, however, that it was not easy to sit comfortably; she was not able to lean back properly and the bulk of the equipment pushed her too far forward on her chair. Suspenders were used to hold up the fanny pack, to avoid the slippage problem encountered with Subject #2; this solution was effective. Figures 4-7 and 4-8 display the histograms of heart rate and minute ventilation for Subject #2. Data points below 60 beats per minute (11 values) were removed from these graphs as invalid data, which amounts to about two percent of the 15-second heart rate averages.

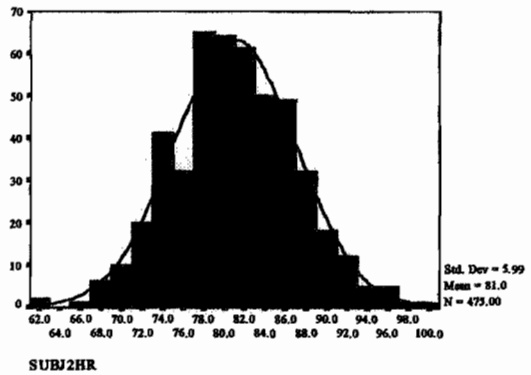



*Figure 4-7: Histogram of Subject #2's 15-second heart rate.*

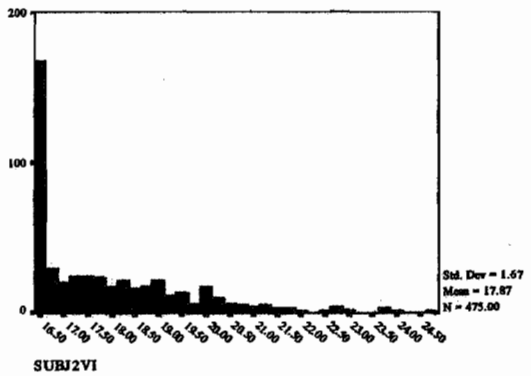



*Figure 4-8: Histogram of 15-second minute ventilation*

The Miran data for Subject #2 was not reliable due to an instrument drift problem. Therefore, the relationship of xylene concentration to the subject's minute ventilation can not be determined. A timeline of the subject's minute ventilation is displayed in Figure 4-9. The charcoal tube analysis results are summarized in Table 4-5. The air concentrations based on the two charcoal tube analyses are displayed in Table 21.

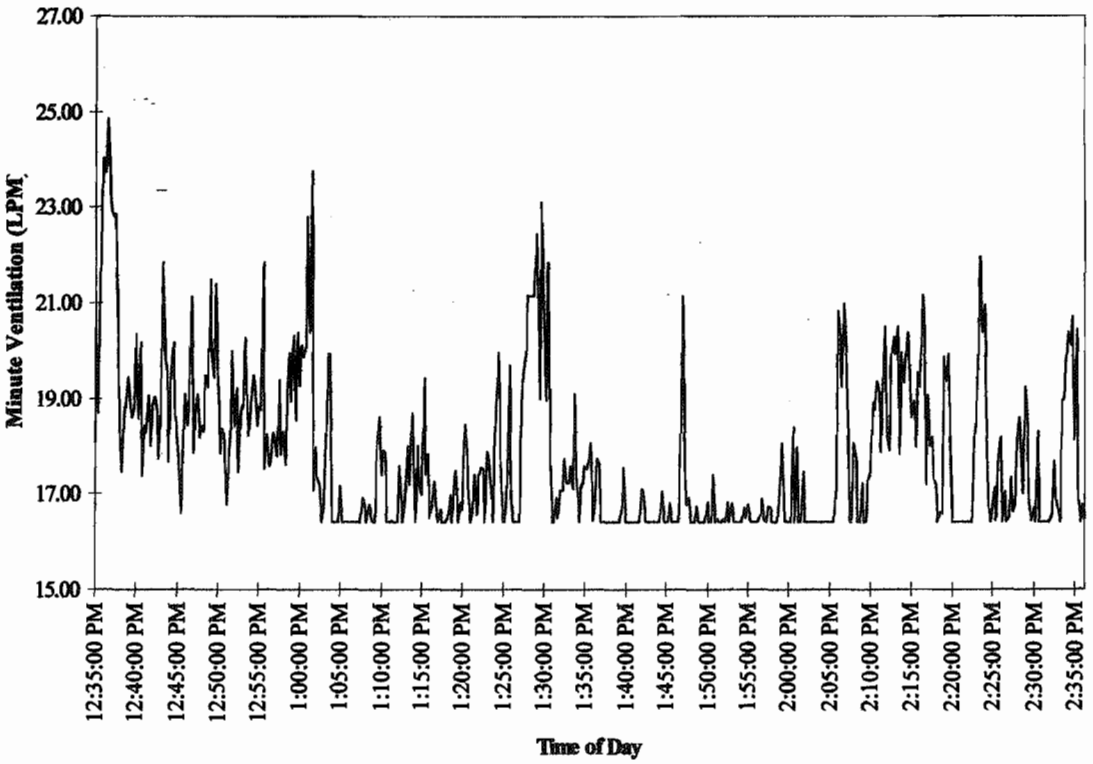



*Figure 4-9: Minute ventilation over time.*

*Table 4-5: Mass of analyte (in micrograms) on the charcoal tube samples collected on the TSP and PSP for Subject #2.*

| Sample | Duration | Volume | p-xylene (µg) | m-xylene (µg) | o-xylene (µg) | toluene (µg) | ethyl benzene (µg) | benzen (µg) |
|---|---|---|---|---|---|---|---|---|
| TSP1 | 120 | 24.0 | 3.14 | 7.94 | 3.40 | 2.01 | 2.25 | 0.52 |
| PSP1 | 120 | 54.2 | 7.49 | 18.47 | 7.96 | 3.56 | 5.20 | 0.89 |

*Table 4-6: Air concentration results based on charcoal tube samples collected on the TSP and PSP for Subject #2.*

| Sample | p-xylene ($mg/m^3$) | m-xylene ($mg/m^3$) | o-xylene ($mg/m^3$) | toluene ($mg/m^3$) | ethyl benz ($mg/m^3$) | benzene ($mg/m^3$) |
|---|---|---|---|---|---|---|
| TSP1 | 0.13 | 0.33 | 0.14 | 0.08 | 0.09 | 0.02 |
| PSP1 | 0.14 | 0.34 | 0.15 | 0.07 | 0.10 | 0.02 |

The relationship of the PSP results to the TSP results is demonstrated in Figure 4-10. The correlation coefficient was 0.997 and a paired T-test showed no significant difference between the calculated air concentrations.

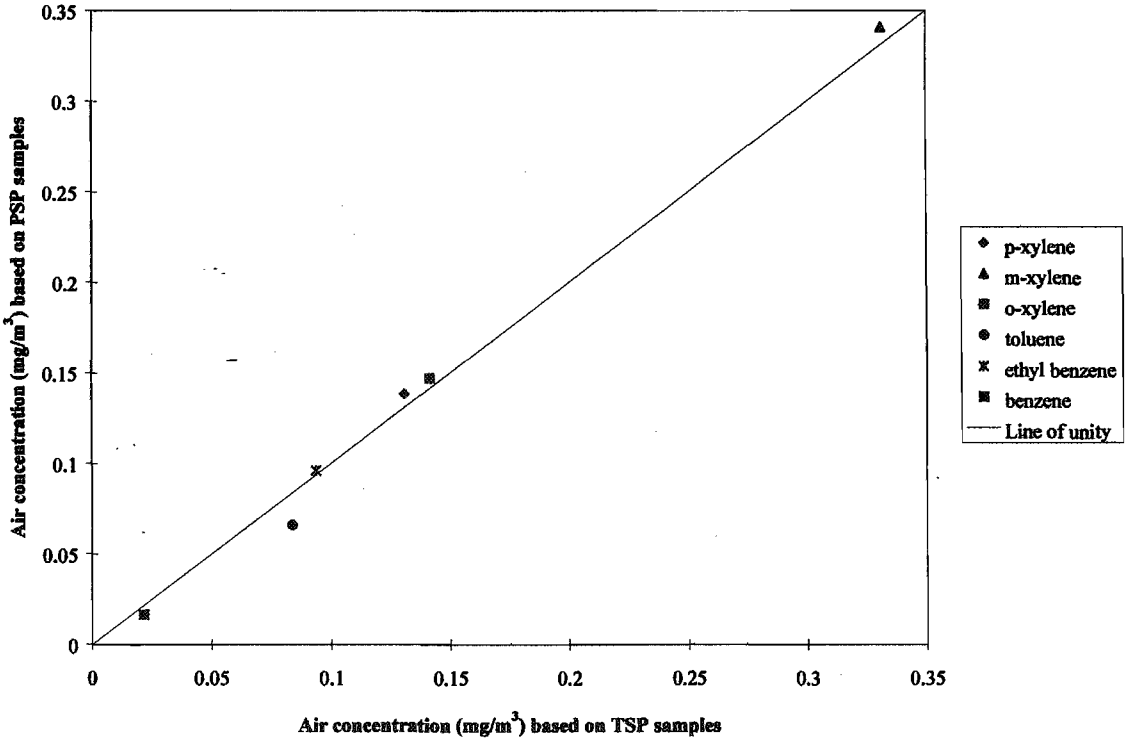
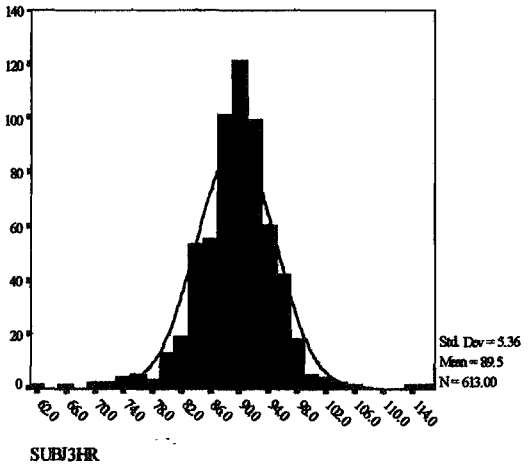



*Figure 4-10: Comparison of analysis results between the charcoal tube sampled using the TSP versus the one sampled via the PSP. Estimated air concentrations of six analytes (p-xylene, m-xylene, o-xylene, toluene, ethyl benzene, and benzene) are expressed in milligrams per cubic meter or air.*

### *4.1.2.3 Subject #3*

Subject #3 was a histologist at the University of Washington Medical Center. As mentioned previously, this worker refused to wear the PSP equipment after she was fitted with it (note: she had been shown the equipment prior to setting up the sampling appointment). She claimed that the equipment was too heavy and would look too embarrassing. None of the other workers in the laboratory would volunteer to wear it, so one of the researchers decided to wear it as a last resort. While the researcher was in the same room as the histologist, the room was too small to enable the researcher to mimic the histologist's movements. The main task performed the day of sampling was slide staining. This task was only performed during the morning shift, however, so only one charcoal tube sample per pump was collected. The researcher who wore the sampling equipment did have any complaints, and the system continued to operate flawlessly.

Figures 4-11 and 4-12 display the histograms of heart rate and minute ventilation for Subject #3. In this experiment, the critical heart rate value, below which data points were removed from these graphs, was 60 beats per minute. There were 2 values less than 60 beats per minute, out of a total of 614; therefore, about 0.3 percent of the 15-second heart rate averages were deemed invalid. A histogram of the xylene concentrations for Subject #3 is displayed below, in Figure 4-13. A timeline of Subject #3's minute ventilation averages and the xylene concentration in the laboratory are displayed in Figure 4-14.



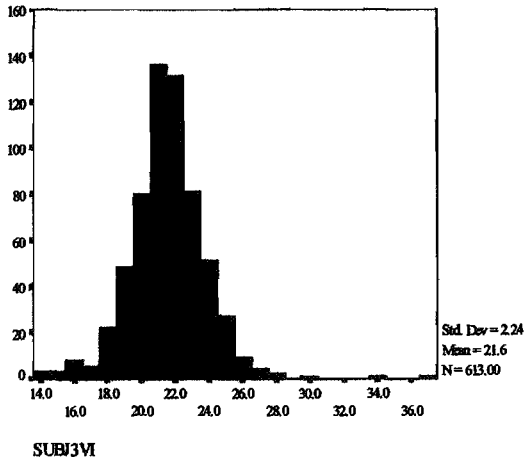




*Figure 4-11: Histogram of Subject #3's 15-second heart rate averages.* *Figure 4-12: Histogram of 15-second minute ventilation.*

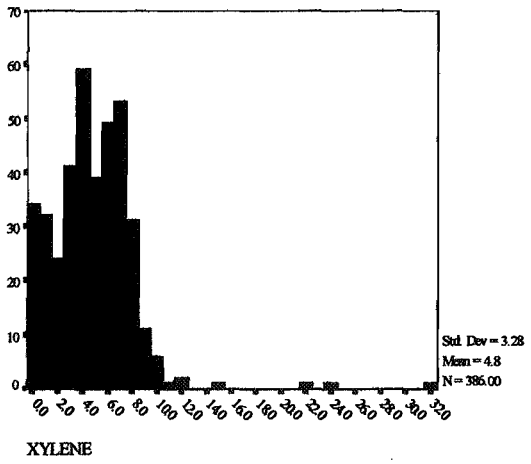



*Figure 4-13: Histogram of 30-second xylene concentration averages.*

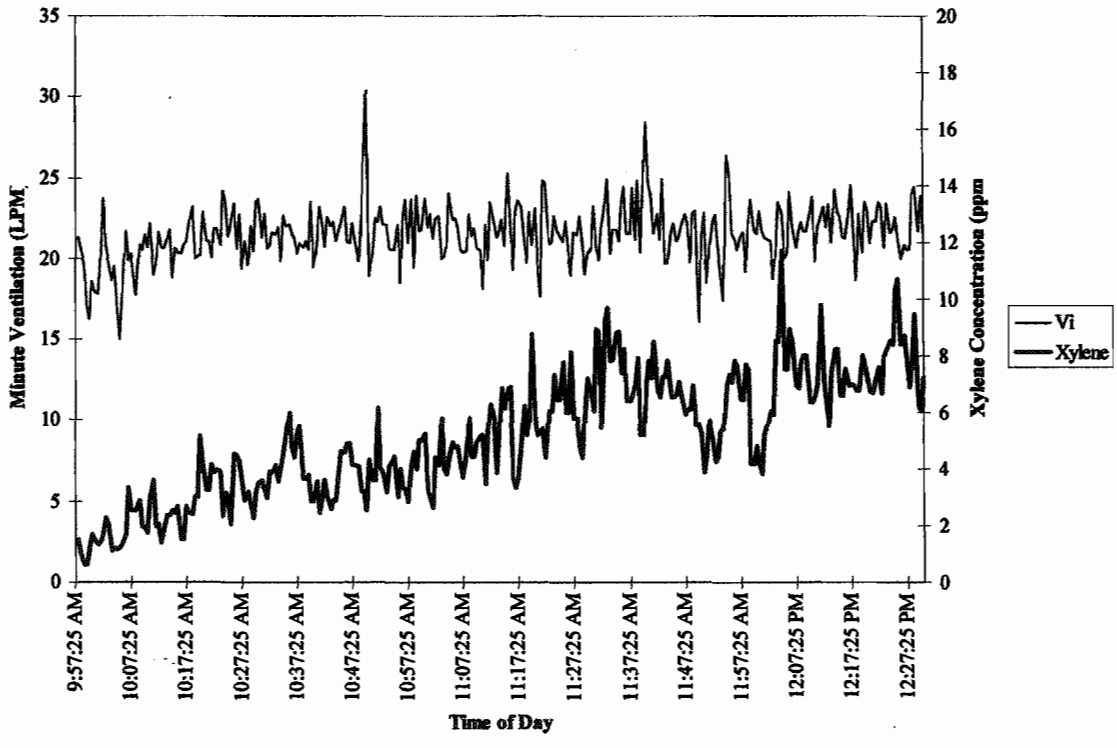



*Figure 4-14: Minute ventilation and xylene concentration over time.*

The masses of the six analytes on each charcoal tube, as reported by the University of Washington's Environmental Health Analytical Laboratory, are shown in Table 4-7. The air concentrations based on the two charcoal tube analyses are displayed in Table 4-8.

*Table 4-7: Mass of analyte (in micrograms) on the charcoal tube samples collected on the TSP and PSP for Subject #3. The benzene results for the PSP sample could not be assessed because it was less than the lower quantitation limit (LQL).*

| Sample | Duratio (Min.) | Volume (L) | p-xylene | m-xylene | o-xylene | toluene | ethyl benz | benzene |
|---|---|---|---|---|---|---|---|---|
| TSP1 | 164 | 32.8 | 1.31 | 3.01 | 1.51 | 3.70 | 0.89 | 0.11 |
| PSP1 | 164 | 82.7 | 3.38 | 8.76 | 4.59 | 8.69 | 2.52 | <LQL |

*Table 4-8: Air concentration results (in milligrams per cubic meter) based on charcoal tube samples collected on the TSP and PSP for Subject #3.*

| Sample | p-xylene ($mg/m^3$) | m-xylene ($mg/m^3$) | o-xylene ($mg/m^3$) | toluene ($mg/m^3$) | ethyl benzene ($mg/m^3$) | benzene ($mg/m^3$) |
|---|---|---|---|---|---|---|
| TSP1 | 0.034 | 0.092 | 0.046 | 0.113 | 0.027 | 0.003 |
| PSP1 | 0.041 | 0.106 | 0.055 | 0.105 | 0.031 | <LQL |

The relationship of the PSP results to the TSP results is demonstrated in Figure 4-15. The correlation coefficient was 0.976 and a paired T-test showed no significant difference between the calculated air concentrations.

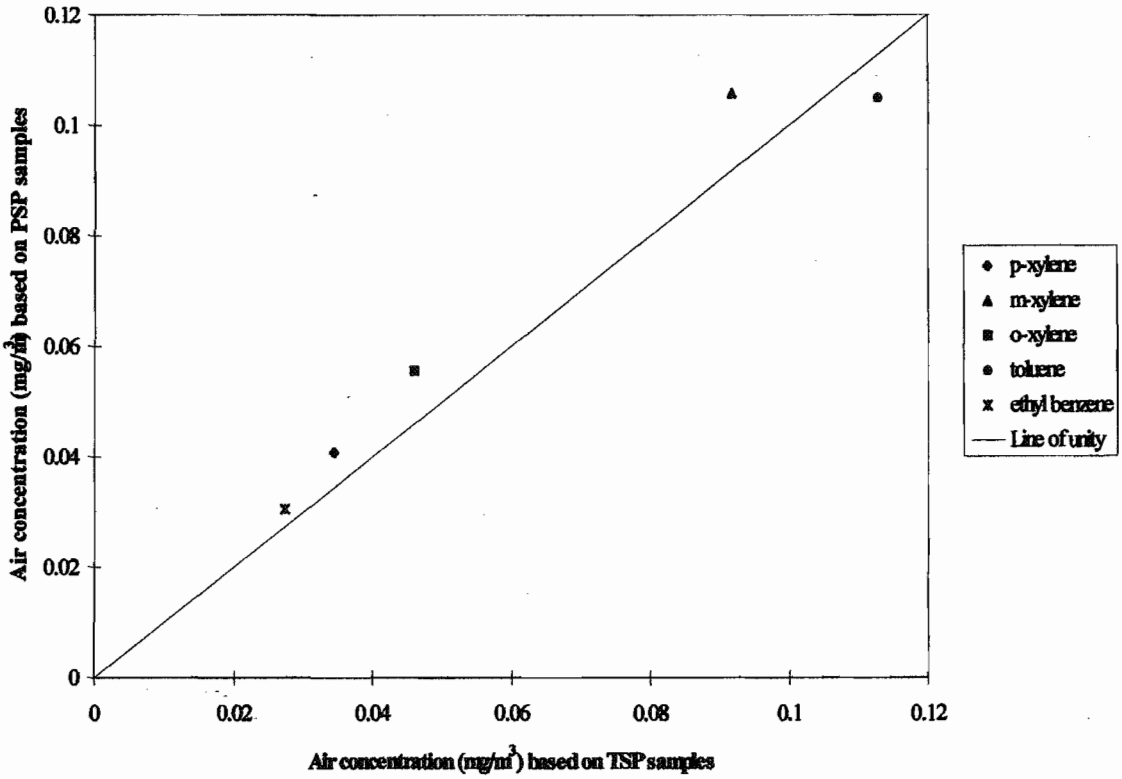



*Figure 4-15: Comparison of analysis results between the charcoal tube sampled using the TSP versus the one sampled via the PSP. Estimated air concentrations of six analytes (p-xylene, m-xylene, o-xylene, toluene, ethyl benzene, and benzene) are expressed in milligrams per cubic meter or air.*

A graph of xylene concentration versus minute ventilation for Subject #3 is presented in Figure 4-16. While there was a correlation coefficient of 0.27 between these two variables, conclusions regarding this relationship cannot be made since the xylene concentrations were measured from a stationary instrument and the minute ventilation values were from the surrogate subject, not the histologist.

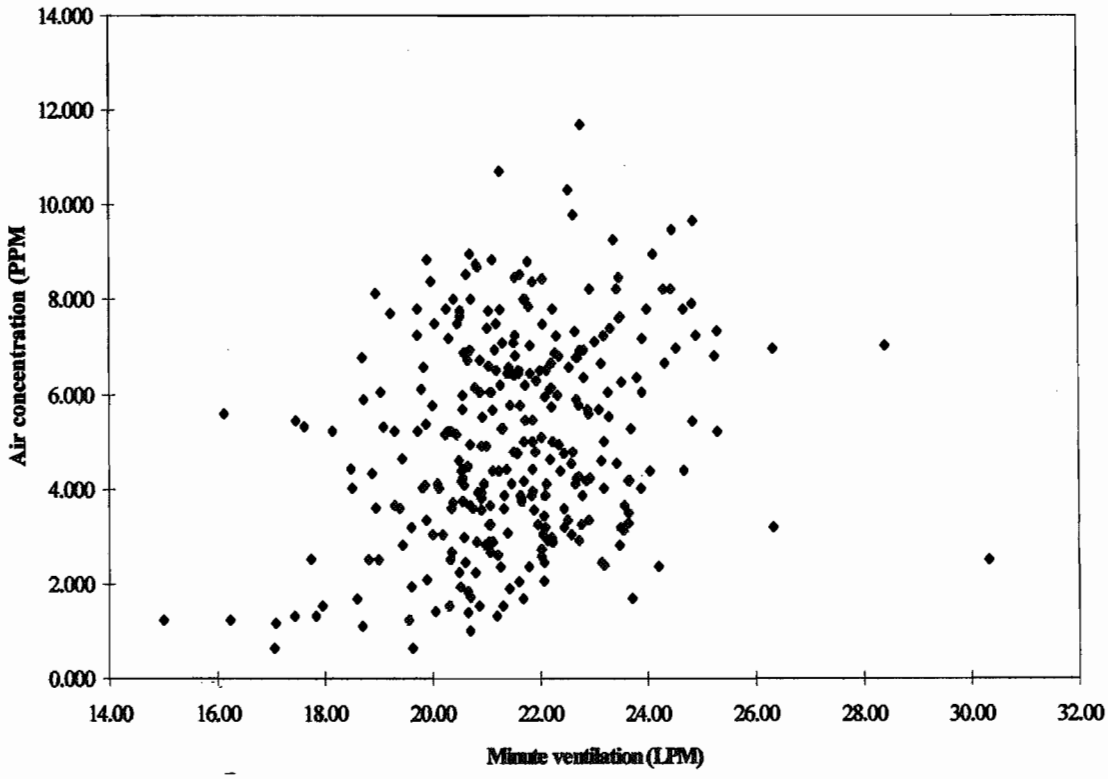



*Figure 4-16: Relationship between air concentration of xylene (ppm) and minute ventilation (LPM) for Subject #3.*

### 4.1.3 DISCUSSION

The overall usability of the PSP in the field was well within acceptable limits for industrial hygiene use. It was easy to calibrate, setup, collect samples with, and download data. The complaints from the subjects concerned the size, weight, and appearance of the equipment. It is important to remember that all of these factors would be much more agreeable on a manufactured device, rather than a prototype; it would be smaller, lighter, and more refined. In addition, the weight and size burden during this experiment was magnified by attaching the TSP to the same fanny pack that carried the PSP equipment

According to the Kolmogorov-Smirnov test for normality (using the Lilliefors significance correction), Subject #2 had the only heart rate average distribution that was normal. The distribution for Subject #1 was positively skewed, probably because the cut-off point was set a little bit too high. Subject #3's heart rate average distribution was negatively skewed and had a kurtosis value of 3.7. Because of the exponential relationship between heart rate and minute ventilation (Equation 2-12), if the heart rate averages were normally distributed, then the minute ventilation average should be lognormally distributed.

The peaks seen at the lowest x-axis values in Figures 4-2 and 4-8 are artifact; the minute ventilation equation (Equation 2-13) uses delta heart rate (HR-HR0) rather than the actual heart rate value. In order to incorporate this into the equation, the FIELDPSP program must be instructed to subtract the subject's resting heart rate from the calculated heart rate averages. When the heart rate averages fall below the resting heart rate, the delta heart rate value is set to zero. Therefore, if the resting heart rate value entered into the FIELDPSP program is higher than the subject's true resting heart rate, any heart rate average less than the entered resting heart rate will result in a constant (and elevated) minute ventilation estimate. This phenomenon resulting in "clipped" minute ventilation estimates. Since Figure 4-12 does not contain a similar peak, it is likely that the resting heart rate for Subject #3 was more accurate.

The existence of these peaks suggest that the method used to estimate resting heart rate in the field was not adequate. While five minutes is more than enough time for a person's heart rate to stabilize, it is likely that the anticipation of the experiment raised the subject's heart rate. One possible solution to this problem would be to have the intended subject wear the heart rate monitor (the chest band and watch) for a prior to the sampling. During this time they would likely become relaxed and forget about the monitoring equipment. The obvious problem with this solution is that the resting heart rates in the predictive equation database were not acquired in such a manner. This logic would suggest that this would lower the estimated minute ventilation estimates for any given heart rate. Since the predictive equation seems to be over-estimating the true minute ventilation in general, this could be an advantageous by-product of this solution.

The real-time air concentration values from the Miran for Subjects #1 and #3 (for toluene and xylene, respectively) were not lognormally distributed (see Figures 4-3 and 4-13). They are both more positively skewed than would be expected in even a lognormal distribution. Figures 4-4, 4-9, and 4-14, show the minute ventilation averages and Miran data over time for each of the subjects. The clipping of the minute ventilation data is apparent in Figures 4-4 and 4-9. Figure 4-14 does not exhibit a similar clipping pattern, again reflecting the fact that the resting heart rate was more accurate for Subject #3.

Subject #1's heart rate data contained a higher percentage of invalid values than for Subject #2 or #3 This indicates that either the Polar transmitter unit or the signal receiver in the PSCU was malfunctioning in an indeterminate manner. After this problem was noted, the system was tested vigorously in the laboratory in order to try to re-create it; this attempt was not successful. While the problem remains a unexplained, the fact that invalid values for Subject #2 and #3 were so much lower (2% and 0.3% versus 5% for Subject #1) suggests that it not a consistent problem. Based on the fact that a high percentage of heart rate values were invalid for Subject #1, the data that was not thrown out is also put into question. If the PSCU was missing heartbeats, then some of the minute ventilation averages could have been erroneously low, but not low enough to be considered "invalid" (which was defined as below 80 beats per minute). The extensive change in heart rate values for Subject #1, seen in particular before 8:10 A.M. and between 11:15 A.M. and 12:15 P.M. (see Figure 18), might be due to missed heartbeats.

One point of interest to note about Subject #2's minute ventilation timeline is that the first half an hour (12:05 P.M. to 12:35 P.M.) is elevated compared to the rest of the shift, the same period of time in which the subject was performing the coverslipping task. It is unfortunate that the Miran data was not valid, because it is very plausible that the subject was exposed to higher xylene concentrations during the coverslipping task.

Subject #3's minute ventilation timeline reflects the fact that he was not performing any tasks other than sitting or standing quietly; it is very flat.

The air concentration timelines are interesting for the following reason: the toluene timeline (see Figure 4-4) shows peaks that were task-related while the xylene timeline (see Figure 4-14) shows a general background build-up of xylene over the work shift. The spray painter, for example, was applying lacquer by hand when the large toluene peaks were measured. This is worth mentioning because task-related contaminant generation could lead to a positive correlation between minute ventilation and air concentration of a contaminant. The fact that the xylene timeline is much smoother does not necessarily signify that the inhaled xylene levels were not task-related; recall that the Miran was stationary during data collection for Subject #3, so it would not capture localized xylene peak concentrations around the histologist.

The fact that the air concentrations based on the TSP samples were not significantly different from the air concentrations based on the PSP samples indicates the following:

1. There was no significant correlation between minute ventilation and air concentration for any of the subjects. The lack of correlation suggested by the similar air concentration results is confirmed for Subject #1 by examining Figure 4-6.

2. The PSP samples are valid. No breakthrough problems were found related to the higher (and variable) flow rate of the PSP.

Based on the fact that (1) the pump flow rate averages for all three subjects ranged from 0.4 to 0.5 liters per minute (less than the lowest flow rate tested in the laboratory breakthrough study), and (2) the highest air concentration of toluene that was sampled was 10 parts per million (Subject #1, sample #3), the following conclusion can be drawn: a single charcoal tube sample would have been adequate to sample Subject #1's entire 8-hour shift (with very low probability of breakthrough occurring).

### 4.1.4 SUMMARY

With the exception of the anomaly regarding missed heartbeats for Subject #1, the PSP performed exceptionally in the field. However, based on the small size and protocol limitations of this pilot field study, conclusions regarding a possible correlation between air concentration and minute ventilation of a worker cannot be drawn. The PSP fulfilled all of the following criteria necessary for an ideal device to be actively used to assess worker exposures in a real-world environment:

- the pump must be easy to use (e.g. no additional training other than reading a simple manual)
- the pump must be easily calibrated in the field (e.g. not technically challenging)
- the time necessary to calibrate the worker must be minimal (e.g. less than 15 minutes, preferably less than 5)

## 4.2 HEART RATE AND METABOLIC WORKLOAD ESTIMATES OF CONSTRUCTION DRYWALLERS

### 4.2.1 INTRODUCTION

The construction industry experiences a very high incidence of cumulative trauma and overexertion injuries. Prolonged awkward postures and high physical workload have been offered as contributing causes to the problem (Iowa Construction Alliance, 1991; Cook and Zimmerman, 1992). Many constantly demanding activities exist in trades, such as drywalling, which place significant metabolic stress on the workers. In a recent study, working in construction was significantly correlated with sudden cardiac-related deaths in Germany (Brettel and Drewnick, 1994). However, very little research has described the level of heart rates and metabolic loads within the industry.

Drywallers perform two essential tasks: 1) stocking material and preparing the work area, and 2) hanging board. The stocking and preparation tasks are done largely by apprentices and less senior workers on larger union worksites. These activities include unloading and stacking sheetrock, moving sheetrock and framing, setting up scaffolds, and cleaning the work area. Hanging board is done primarily by the journey-level drywallers. This activity consists of measuring the sheetrock, cutting, and drilling in place. Depending on the site and area of the building, journey-level workers may also frequently prepare framing and install insulation.

Previous work by Spielholz and Narayan (1995) described the major work activities and postures of union drywallers by observational work sampling. The sampling showed that the workers drywalling spent almost 80% of the day in an upright posture. The most frequently performed activity was drilling at about 16% of the day. This is true for metal stud construction, but may not hold true for other types of drywalling. Lifting and carrying comprised about 20% of the day. Over half of this time involved manipulating drywall weighing over 20 lbs. The workers were observed lifting or carrying drywall weighing more than 50 lbs. approximately 6% of the day.

As part of an on-going project in Washington state, a joint labor-management focus group consisting of union carpenters, contractor health and safety representatives, carpentry apprenticeship school instructors, and local state government representatives was formed. This group meets on a monthly basis and assists in identifying high risk jobs within the trade and developing potential interventions. At the start of the project, an eight-hour training on basic ergonomic principles was provided to this group. Following training, they rated the various carpentry tasks for ergonomic risk factors on a questionnaire. On a scale of perceived exertion level (RPE) the members rated concrete formwork as the most demanding with a score of 16.5 (on a scale of 6-20) and drywalling was rated as the second most demanding with an average score of 16.

These findings pointed to drywalling as a good area for describing metabolic loads. Previous characterization of concrete formwork construction by Spielholz et al. (1995) showed risk factors in that activity to be related more to static postures and localized body movements than aerobic activity. The subsequent study of drywalling identified risk factors, such as lifting and carrying, which are more related to high aerobic energy demands.

Worker interviews have identified airborne exposures as a potential health risk in the construction industry. Data from this research will be used in the development of a physiologically-based air sampler, which can have applications in drywalling and construction trades. Information on metabolic workload demands will also be used for the development of ergonomics and safety training programs for drywallers.

### 4.2.2 METHODS

Five male union drywallers volunteered to participate in the study. The average age of the subjects was 29 (Range 23-45). Four of the subjects were apprentices and one was a journey-level drywaller. The participants had worked an average of 5.2 years as a drywaller and 6.4 total years in construction. No subjects reported having any abnormalities in cardio-pulmonary function, or taking any medication. Table 4-9, below, summarizes the vital information of the subjects.

*Table 4-9: Summary of Participants*

| | Subject 1 | Subject 2 | Subject 3 | Subject 4 | Subject 5 |
|---|---|---|---|---|---|
| Age | 25 | 27 | 23 | 24 | 45 |
| Height | 6' 3" | 5' 10" | 5' 9" | 6' 5" | 6' 0" |
| Weight | 175 lbs | 190 lbs | 160 lbs | 265 lbs | 195 lbs |
| Years Drywalling | 2.0 | 0.5 | 0.1 | 1.5 | 22 |
| Yrs in Construction | 5.0 | 0.5 | 1.0 | 3.5 | 22 |
| Smoker? | Yes | No | No | Yes | No |
| Exercise Regularly? | No | No | No | No | Yes |
| Condition Rating | Average | Average | Average | Average | Above Avg. |

### 4.2.3 PROCEDURE

A consent form approved by the University of Washington Human Subjects Review Committee was used explaining the purpose of the study, procedures, physical risk and discomfort, and confidentiality. A subject data sheet was also prepared to obtain descriptive information from the subjects before the study. Two questions were developed for administration at the end of the day: a Likert Scale question asking the subjects to estimate their relative workload for the day, and a Borg's Scale question to compare the subjects' estimates of metabolic workload (Konz, 1987).

A Polar Vantage XL heart monitor/datalogger was used to record the heart rate. A transmitter attached to an elastic band around the chest sent information to a watch-datalogger worn on the wrist. The data was downloaded through a serial port into a Macintosh 7500 computer using the Polar Computer Interface and Vantage XL Software Version 4.00.

Measurements were collected at a multi-use public building site over three days during a one-week period. Subjects were recruited before the shift at the worksite. Each volunteer was informed of the study purpose and procedures verbally by the researcher, and in writing. Subjects signed the consent form and completed the pre-work questionnaire.

The Polar heart monitor/datalogger was attached to the wrist and the elastic band with transmitter was attached around the chest of the subject. The monitor/datalogger was set to record the heart rate every 15 seconds and measurement was initiated. Some subjects were videotaped for a period of 30 to 60 minutes to record daily job activities.

The heart monitor/datalogger was removed at the end of the shift. Subjects were asked to complete the two post-work questions rating the relative workload and their level of work for the day. Once completed, the subjects were thanked for their time and participation in the study. The heart rate data were downloaded off-site for analysis.

### 4.2.4 RESULTS

The data were filtered through a bandpass filter with the high end set at 90% of the maximum heart rate and the low end set at 10 beats/min below the baseline standing rate for each subject. The data from subject three was incomplete due to an equipment failure during measurement. The results from this subject were included, as analysis of heart rates from the other four subjects showed that the incomplete dataset sampling over approximately the first two hours still provides a reasonable estimate of the average exertion level over the workday (± 3%).

A summary of the heart rate measurements and subject responses are presented in Table 4-10. The mean measurement across the subjects was 102 beats/min (std. dev. = 14.5). The overall range of measurements among the subjects was 58 to 155 beats/min. The subjects rated their workload during the study as being about average. The average rating of perceived exertion (RPE) was 13.4 for work demands over the day, which corresponds to a subjective description of "somewhat hard".

*Table 4-10: Summary of Heart Rate Measurement and Perceived Exertion Ratings*

| | Subject 1 | Subject 2 | Subject 3 | Subject 4 | Subject 5 | Mean |
|---|---|---|---|---|---|---|
| Base Standing HR | 75 | 65 | 75 | 83 | 65 | 73.6 |
| Avg. HR (StDev) | 108.2(10.5) | 101.1(14.5) | 112.5(14.6) | 108.3(10.5) | 86.8(10.5) | 102.0(14.5) |
| Min - Max HR | 83-146 | 58-155 | 77-155 | 78-145 | 62-132 | 58-155 |
| Relative Workload | 3 | 4 | 3 | 3 | 3 | 3.2 |
| RPE Borg's Scale | 13 | 14 | 10 | 15 | 15 | 13.4 |
| Estimated Fitness | Fair | Fair/Good | Fair | Poor/Fair | Good | |
| Major Job Task | Stocking | Stocking | Stocking | Hanging | Hanging | |

The energy expenditure in kcal/min was calculated using the method detailed in Konz (1987). The standing metabolic activity was calculated using the following equation:

Total Metabolism = Basal Metabolism + Activity Metabolism + Spec. Dynamic Action Metabolism 1)

The components of the total metabolism estimate were calculated using the following equations:

Basal Metabolism = [64.95 - .8875(Age) + .0078(Age$^2$)] * [.208 + .945(Dubois Surface Area)] 2)

Activity Metabolism = .6 (W/kg) * Weight (kg) (Standing Relaxed) 3)

Specific Dynamic Action Metabolism = .1(Basal metabolism + Activity Metabolism) 4)

The maximum heart rate was calculated at 220 - age for each of the subjects. No direct oxygen consumption was measured, so the maximum oxygen consumption was obtained using table 12.3 from Konz (1987) based on estimated cardiovascular fitness and age. Cardiovascular fitness was estimated based on subject ratings of fitness, reported regular exercise, resting heart rate, and status as a smoker. These values for aerobic capacity in liters/kg-min were multiplied by the subject weight to obtain $VO_2Max$ in liters/min for each subject.

A linear slope relationship between heart rate and oxygen consumption was calculated using the values for standing relaxed and the estimated maximum measures. The average heart rate over the day was multiplied by the calculated slope for each subject to obtain the average oxygen consumption. The metabolic load was found using the following relationship from McArdle et al. (1991):

Metabolic Energy Expenditure = 4.9(Oxygen Consumption) 5)

The mean oxygen consumption over the workday across subjects was 1.04 liters/minute, with a maximum variation during the day of 0.20-2.55. The mean percentage of $VO_2Max$ over the day ranged between 25-40%, with an average of 30%. The mean energy expenditure over the workday was calculated as 5.10 kcal/minute, with a maximum variation over the day of 1.00-12.48. Table 3 summarizes these results.

*Table 4-11: Summary of Energy Expenditure and Oxygen Consumption Calculations*

| | Subject 1 | Subject 2 | Subject 3 | Subject 4 | Subject 5 | Mean |
|---|---|---|---|---|---|---|
| Average Kcal/min | 5.04 | 5.52 | 5.02 | 5.05 | 4.88 | 5.10 |
| Average $O_2$ l/min | 1.03 | 1.13 | 1.02 | 1.03 | 1.00 | 1.04 |
| Range Kcal/min | 1.00-10.34 | 1.05-12.18 | 1.15-9.67 | 1.40-10.35 | 1.04-12.48 | 1.00-12.48 |
| Range of $O_2$ l/min | 0.20-2.11 | 0.21-2.49 | 0.23-1.97 | 0.29-2.11 | 0.21-2.55 | 0.20-2.55 |
| $VO_2Max$ l/min | 3.18 | 3.67 | 2.55 | 4.06 | 3.99 | 3.49 |
| % $VO_2Max$ | 32 | 31 | 40 | 25 | 25 | 30 |

Heart rate time series plots were analyzed for each subject to identify trends in activity. The baseline heart rate was subtracted from the subject's data series to standardize the data. The mean of the values was computed for each point in the series over all subjects. Figure 4-17 shows a time series over the workday of the mean difference above the baseline heart rate across the subjects.

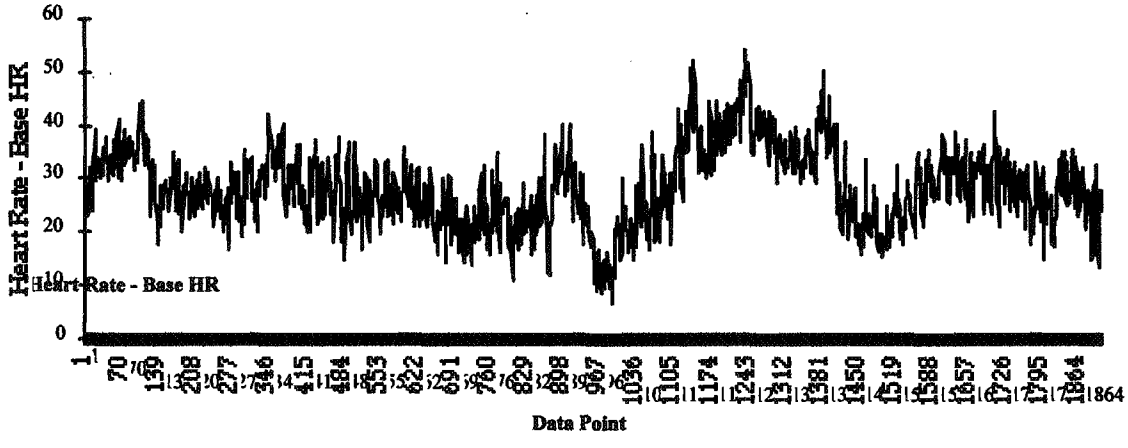



*Figure 4-17: Time series of the mean difference above baseline heart rate across subjects over the workday .*

4.2.5 DISCUSSION

The heart rate measurements and metabolic workload estimates were very close to maximum recommended limits for work. Aerobic work lasting over 4 hours can be maintained by most people at approximately 33% of the individual's oxygen consumption rate, $VO_2Max$ (Astrand and Rodahl, 1986). Workers in this study showed a mean oxygen consumption rate at 30% of maximum.

A work level at 33% of aerobic capacity corresponds to approximately 5.1 kcal/min in males and a heart rate of 100-120 beats/min (Konz, 1987; McArdle et al., 1991). The mean calculated energy expenditure was

exactly at the recommended work design limit. These results appear to show that the drywallers work at approximately the maximum sustainable level for aerobic work over the day.

Several characteristics of the work level during the day may be inferred from analysis of the heart rate time series plots. The workload appears to be slightly higher during the first half-hour while the work area and tools are set up. After dropping to a lower level, the workload rises slightly before lunch, and then drops to near the resting level during lunch. There is a characteristic bell-shaped appearance to the heart rate response after lunch, when the workload level rises to its highest point during the day. The heart rate then drops to near the mean level for the last two hours of the work shift.

Stocking activities are possibly represented more frequently in the metabolic measurements than occurs during drywalling job overall. However, these tasks well represent many of the most demanding job components. Another source of possible variation is in the estimation of maximal aerobic capacity. Significant error is possible in the indirect estimation of VO2Max, though relatively high confidence was achieved with the given physical measurements and subject responses. The mean measures of metabolic load represent a best estimate of the more demanding regular tasks experienced by union drywallers.

The results from this study support subjective estimates of drywalling as one of the most physically demanding construction crafts. Workers were found to work at near their estimated maximum metabolic load for aerobic work. Measurements also show a significant range of metabolic load during the day, from resting during the work break to the generally higher level of work after lunch. The high workload demonstrated by this research indicate that both workers and contractors may benefit by regular scheduling of shorter rest breaks. Regular, shorter rest breaks can effectively lower mean heart rates in workers over the day and increase productivity (Eastman Kodak, 1986).

Training programs and instructional material relating information to drywallers and carpenters regarding safety and health should address aerobic workload demands. Workloads for these trades, found to be at or above recommended limits for many people, constitute a possible health risk, which should be related to and discussed with the workers. Further research should concentrate on the development and assessment of interventions to reduce metabolic load and increase productivity in the drywalling and carpentry trades.

### 4.2.6 REFERENCES FOR SECTION 4.2


Astrand PO and Rodahl K, (1986), Textbook of Work Physiology: Physiological Bases of Exercise, McGraw-Hill Book Company.

Brettel HF, and Drewniok K, (1994), "Sudden Death and Occupational Activity", Versicherungsmedizin, 46(1), pp. 15-17.

Chaffin D, and Anderssen BJ, (1987), Occupational Biomechanics, 2nd Edition, Harcourt, Brace, and Jovanovich.

Cook TM, and Zimmerman CL, (1992), A symptom and job factor survey of unionized construction workers. Kumar, S., ed., Advances in Industrial Ergonomics and Safety IV, Taylor and Francis.

Eastern Iowa Construction Alliance/University of Iowa Joint Project on Reduction of Work-Related Injuries and Illnesses Through Ergonomic Intervention,(1991), Final Report, Phase I, (unpublished).

Eastman Kodak Company, Ergonomics Group, (1986), Ergonomic Design for People at Work: Volume 2, New York: Van Nostrand Reinhold.

Konz S, (1987), Work Design: Industrial Ergonomics, John Wiley and Sons.

Louhevaara V, Tuomi T, Smolander J, Korhonen O, Tossavainen A, and Jaakkola J, (1985), "Cardiorespiratory Strain in Jobs That Require Respiratory Protection", International Archives of Occupational and Environmental Health, 55(3), pp. 195-206.

McArdle W, Katch F, and Katch V, (1991), Exercise Physiology: Energy, Nutrition, and Human Performance, Philadelphia: Lea and Febiger.

Polar Electro Oy, (1993), Polar Heart Rate Analysis Software Manual, Version 4.00 for Macintosh, Finland.

Polar Electro Oy, (1992), Polar Vantage XL Heart Rate Monitor User's Instruction Manual, Finland.

Spielholz P, Narayan MS, (1995), An Ergonomic Characterization of Hazards in Drywalling, Report for the United Brotherhood of Carpenters Health and Safety Fund, June 15, 1995.

Spielholz P, Narayan MS, Wiker S, (1995), "Assessment of Ergonomic Hazards in Unstructured Work: An Application in the Construction of Concrete Formwork", Advances in Industrial Ergonomics and Safety VII, Taylor and Francis.