A GUIDE FOR THE PRIMARY CARE PHYSICIAN IN EVALUATING DIISOCYANATE EXPOSED WORKERS FOR OCCUPATIONAL ASTHMA

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Invitation to Participate in the Diisocyanate Registry

Health care providers currently evaluating workers exposed to diisocyanate chemicals for possible Occupational Asthma: are invited to participate in a surveillance project for diisocyanate-exposed workers, who are presenting with asthma symptoms. The project will include hands on training for using *The Guide for the Primary Care Physician in evaluating Diisocyanate Exposed Workers.*

This guidance for evaluating diisocyanate-exposed workers presenting with lower respiratory symptoms was designed to assist the primary care physician to diagnose diisocyanate-induced occupational asthma. By participating, you will learn how to accurately assess respiratory complaints and choose appropriate treatment interventions to manage work-related asthma. You will also be able to download fillable forms for taking a history and recording pulmonary function data.

Who is eligible to participate? Physicians responsible for evaluating and managing diisocyanate-exposed workers presenting with work-associated respiratory symptoms.

What is involved? The program will begin with a live web training session conducted by a group of medical experts. During the online session, each participant will be instructed on the step-by-step diagnostic approach for the evaluation of work related asthma described in the *Guide,* as well as possible treatment interventions. The program participants will then be able to directly evaluate diisocyanate-exposed symptomatic worker while still at work.

If you choose to participate, you will learn how to:

1. Use the *Guide* to evaluate and diagnose workers who are suspected of Diisocyanate Asthma while still at work.
2. Report de-identified clinical data on one diisocyanate-exposed worker undergoing *Guide*-directed evaluation using a HIPPA[1] compliant web-based data collection system.
3. Evaluate clinical outcomes of workers diagnosed with work-related asthma after implementing specific *Guide*-directed treatment interventions.

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1 HIPPA: US Health Insurance Portability and Accountability Act of 1996

Introduction

Occupational asthma (OA) is a disease characterized by variable airway obstruction due to causes or conditions attributable to a particular occupational environment. Work exposures may account for 16% of all new cases of adult onset asthma (Bernstein et al., 2013; Tarlo, 2014). The diisocyanates, an essential group of reactive compounds (see **Table 2**), are widely used for a variety of applications in many industries and are known respiratory sensitizers and exposure to these chemicals has been a common cause of occupational asthma (Meyer et al., 1999). In spite of increasing use, an overall decrease in the total number of cases of diisocyanate-related occupational asthma (DA) has been reported over the past 10 years. Several explanations have been offered including medical surveillance, product stewardship efforts to minimize exposures via increased ventilation and use of personal protective equipment (Buyantseva et al., 2011). This Guide can assist in accurately diagnosing occupational asthma related to diisocyanates and documenting actual cases.

Much has been learned about clinical characteristics of DA. Asthmatic symptoms begin after variable durations of exposure ranging from weeks to years. Clinical asthma is most likely to improve or even be cured in workers diagnosed early after symptoms begin, provided they are restricted from further exposure to diisocyanates (Bernstein et al., 1993; Tarlo and Liss, 2002). If the diagnosis and appropriate intervention (*i.e.* cessation of diisocyanate exposure) is delayed, chronic asthma can persist for many years after leaving work. Thus, the key to prevention of impairment and disability due to DA is early identification of new cases.

To achieve this goal, the following Guide has been designed to assist the primary care physician in diagnosing DA. Because this protocol relies on the serial measurement of lung function during active exposure to diisocyanates, this approach is applicable only for workers who can remain at work during the evaluation (Tarlo et al., 2008). It should not be used for those who have already left the workplace. If possible, measurement of personal diisocyanate exposure should be performed concurrent with evaluation of the worker using reliable analytical methods. This could allow comparison of days when there is documented diisocyanate exposure with work-related symptoms and changes in lung function.

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Purpose

The main goal of this Guide is to provide clinical guidance for the physician asked to evaluate a worker exposed to diisocyanate chemicals who is reporting lower respiratory symptoms at work. In such a scenario, *occupational asthma (OA)* due to respiratory sensitization to diisocyanates (diisocyanate-related asthma or DA) is one of several potential causes of work-related lower respiratory symptoms. A medical history of work-related lower respiratory symptoms of cough, dyspnea, chest tightness and/or wheezing alone has insufficient specificity for establishing a diagnosis of OA (Tarlo et al., 2008). Ideally, the diagnosis of DA should be confirmed objectively by demonstrating reduced lung function associated with diisocyanate exposure at work and improvement away from work. The main objective of this document, therefore, is to serve as resource to the physician in identifying those workers with a probable diagnosis of DA by using accessible clinical tools. The involvement of the non-specialist in this process will enable early identification of DA, a potentially serious asthmatic condition. If DA is recognized early in its course, prompt cessation of exposure to diisocyanates is effective in reducing and preventing future work-related asthma symptoms.

This Guide for evaluating workers suspected of DA has been designed for those situations in which consultation with a medical specialist experienced in the evaluation of occupational lung disorders is not possible. Adherence to the steps detailed in this stepwise algorithm will greatly increase the likelihood of an accurate diagnosis. The ability to adhere strictly to this protocol may depend on available resources for performing lung function testing both at work and home. Deviation from this protocol could result in an erroneous diagnosis.

If the following Guide is unsuccessful in establishing or excluding DA via monitoring of lung function in the workplace, controlled specific inhalation challenge (SIC) testing (if available) with diisocyanates can be considered on a case by case basis. Although not available in many countries, SIC protocols are well described and conducted routinely and safely in specialized clinics under the supervision of experienced physician specialists (Tarlo, 2015). Briefly, ambient diisocyanates are generated in a chamber where chemical levels can be controlled and monitored. After obtaining informed consent, the worker is briefly exposed by inhalation to sub-irritant doses of diisocyanate and FEV_1 (forced expiratory volume in 1 second) is monitored for up to 24 hours. A decrease in FEV_1 of $\geq$20% from pre-challenge baseline, not observed on a separate placebo challenge day, confirms the diagnosis of DA.

Background

Causes of Lower Respiratory Symptoms

Accurate diagnosis of DA is greatly facilitated by the understanding that, in addition to asthma, there are several causes of work-related as well non work-related lower respiratory symptoms that need to be considered. In evaluating the worker suspected of DA, one must also be aware of a variety of potential other causes of work-related lower respiratory symptoms that may not be

attributable to asthma. Cough and lower respiratory symptoms are commonly triggered by nonspecific irritants at work in: current smokers; persons with chronic obstructive pulmonary disease (COPD); and workers with preexisting allergy to seasonal pollens or indoor inhalant aeroallergens (*e.g.* animal proteins, house dust mite). Workers with seasonal allergic rhinitis, for example, often have "twitchy" or hyperreactive airways during peak pollen seasons and, during those times, are more likely to develop lower respiratory symptoms (cough or wheezing) triggered by nonspecific workplace irritants or physical factors (*e.g.* cold air, nuisance dust, fumes, etc.). Chronic post-nasal drainage caused by upper respiratory disorders such as allergic or non-allergic rhinitis is the most common source of chronic cough. Finally, any patient with chronic unexplained lower respiratory symptoms should also receive a medical evaluation and chest imaging procedures to exclude underlying cardiopulmonary disorders (*e.g.* cardiac failure, lung tumor).

Definitions of Work-Related Asthma

When using this Guide, it is useful to be familiar with the following definitions of various work-related asthma conditions (Bernstein et al., 2006):

Work-related asthma is a general non-specific term used to describe asthmatic symptoms identified to increase during or after work exposure, that usually improve after leaving. Work-related asthma encompasses: 1) pre-existing asthma conditions exacerbated at work, referred to as **Work-aggravated Asthma or WAA** and; 2) *de novo* **Occupational Asthma** caused by ambient exposures unique to the work environment such as chemical respiratory sensitizers (diisocyanates as well as other chemicals) or high levels of respiratory irritants, which can result in Irritant Induced Occupational Asthma (also referred to as the Reactive Airways Dysfunction Syndrome or RADS). Diagnostic criteria for RADS include: 1) acute high level exposure to a respiratory irritant; 2) onset of lower respiratory symptoms within 24 hours after irritant exposure; and 3) a positive methacholine test demonstrating airway hyperresponsiveness (Brooks et al., 1985). This classification scheme is illustrated in **Figure 1.**

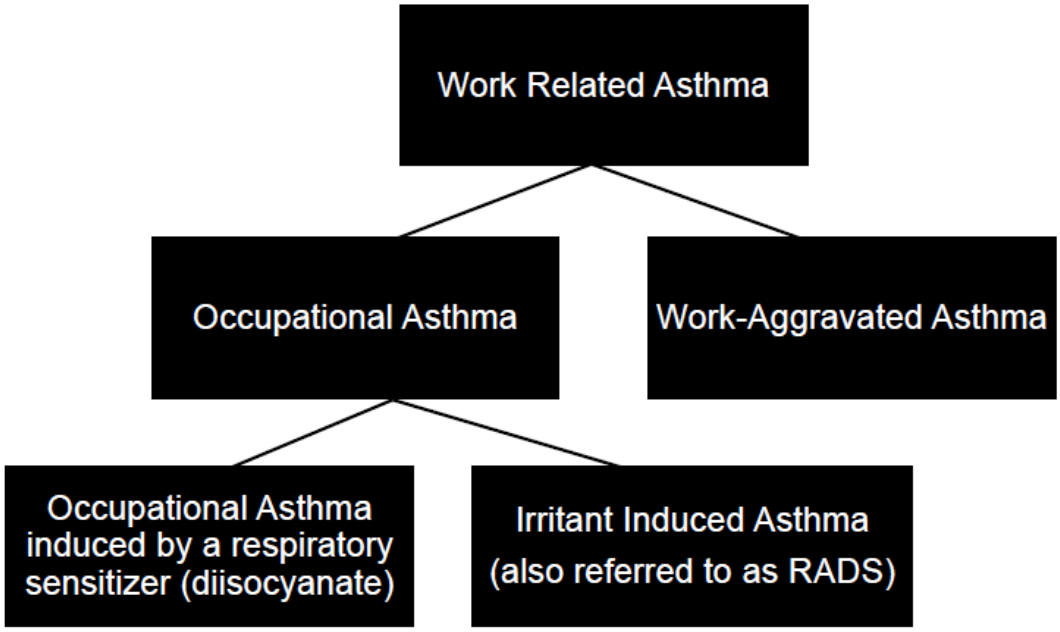

Figure 1. Classification scheme of work-related asthma

Work-aggravated asthma (WAA) is worsening of preexisting asthma due to workplace triggers such as a nonspecific irritant (environmental tobacco smoke, chemical irritants, etc.) or physical stimulus (*e.g.* exercise or cold air). WAA can be manifested by increase in frequency or severity of asthma symptoms or reduced control of asthmatic symptoms while at work, often requiring increase in use of rescue bronchodilators (*e.g.* inhaled albuterol) (Tarlo et al., 2008). Common clinical examples are patients with longstanding allergic asthma caused by seasonal outdoor pollen exposure whose asthma symptoms are coincidentally triggered at work by exertion or exposure to workplace irritants. WAA can often be prevented by avoiding workplace triggers or adjusting asthma medications, and may not require relocation or a job change.

Occupational asthma can be defined as asthma caused by some exposure unique to the workplace (Bernstein et al., 2006). This broad definition encompasses: 1) ***OA caused by respiratory sensitization*** to a workplace allergen (*e.g.* natural rubber latex) or chemical (methylene diphenyl diisocyanate or MDI) characterized by a preceding asymptomatic period of exposure (*i.e.* latency period) for months or years prior to onset of asthma at work; and 2) ***Irritant induced asthma*** (also referred to as the Reactive Airways Dysfunction Syndrome or RADS) in which OA is caused by single or multiple inhalational exposures to high levels of respiratory irritants. Either category of OA is almost always recognized in workers with no pre-existing history of asthma. Thus, it is essential for the evaluating physician to differentiate OA from WAA, which, as described, is recognized primarily in workers with pre-existing asthma conditions whose asthma symptoms are triggered at work.

Evaluation of a diisocyanate exposed worker with work-associated respiratory symptoms is particularly challenging because diisocyanates can be associated with a variety of work-related respiratory syndromes including: 1) Diisocyanate-induced occupational asthma (DA); 2) sudden

onset irritant induced asthma (RADS); 3) irritant cough symptoms without asthma; and 4) WAA. Distinguishing features of various forms of diisocyanate WRA are presented in **Table 1.**

Table 1. Types of diisocyanate work-related asthma

Term	Definition	Diisocyanate Exposure Scenarios	Clinical Features
Diisocyanate-induced occupational asthma (DA)	Asthma triggered by exposure to sub-irritant levels of diisocyanate; onset is preceded by asymptomatic period of exposure (months to years)	Induction of respiratory sensitization often requires repeated short term exposures above the OEL* but can be induced after a single high-level diisocyanate exposure. Dermal exposure may contribute to development of sensitization to diisocyanates.	Probable immune basis, not necessarily IgE-related, onset after repeated exposures
Irritant- induced occupational asthma or RADS	Sudden Onset asthma	Single high level (often accidental) exposure to diisocyanates	Immediate onset (see definition of RADS in text).
Irritant-induced Lower Respiratory (non-asthmatic) symptoms	Non-asthmatic symptoms especially cough triggered by irritants encountered at work	Diisocyanates and other chemicals at work are irritants and can trigger cough symptoms	Cough symptoms, often in smokers, are triggered at work. Asthma is excluded by negative methacholine test and absence of reversibility in lung function.
Work-aggravated asthma (WAA)	Worsening of previously diagnosed asthma or bronchial hyperresponsiveness	"Non-massive" non-isocyanate exposure (*e.g.* cold, exercise, non-sensitizing dust, chemical fumes, or sprays that generally would irritate susceptible populations)	Elicitation of transient asthma symptoms by a variety of non-specific triggers at work including dust, smells, vapors fumes, cold, exercise

* Occupational Exposure Limit

Objectives of this Guide

Occupational asthma may account for 2-15% of all new cases of adult-onset asthma (Bernstein et al., 2006). The diisocyanates, an essential group of reactive compounds (see **Table 2**) widely used for a variety of applications in many industries, is a relatively common cause of occupational asthma (Klees and Ott, 1999). The aim or intent of this Guide is to provide direction to primary care physicians who are asked to perform the initial evaluation of workers with suspected occupational asthma caused by exposure to diisocyanate chemicals. **This step-wise approach to the evaluation of work-related asthma can be applied only to those symptomatic workers who are able to remain at work long enough for the lung function monitoring evaluation (described below) to be completed.** This Guide does not apply to the worker no longer at work and not actively exposed to diisocyanates who may require consultation with a specialist experienced in the evaluation of occupational lung disorders. Where available, such an evaluation might include a specific inhalation test at a specialized center to the diisocyanate chemical encountered at work. This diagnostic Guide has been designed for those situations in which such consultants are not available.

Table 2. Diisocyanate chemicals and common applications in industry

Chemical	***Industries or applications***
Toluene diisocyanate (TDI)	flexible foam, coatings, elastomers
Diphenylmethane Diisocyanate (MDI)	flexible and rigid foam, binder in foundries and forest product composites, adhesives, elastomers
Hexamethylene diisocyanate (HDI)	hardeners for spray paint, coatings
Naphthylene diisocyanate (NDI)	rubber manufacturing, elastomers
Prepolymers (diisocyanates partially reacted with polyols)	elastomers, one component coatings

This Guide may help identify workers with OA (caused by the workplace) as well as those with non-occupational asthma (possibly aggravated at work, *i.e.* WAA). In essence, this Guide describes a workplace monitoring test. Adherence to the steps detailed below will increase the likelihood of an accurate diagnosis. The ability to adhere strictly to this protocol may depend on medical supervisory staff available for oversight of lung function testing (such as instructions on the correct performance of peak flow maneuvers) in the work setting. However, it should be emphasized that omissions of key evaluation steps in this protocol could result in erroneous conclusions.

A limitation of this workplace monitoring approach is that, although it can be very useful in demonstrating work-related asthma; it does not definitively prove causation by diisocyanates vs. other substances encountered in the work environment. An expert assessment by an industrial hygienist can help identify the relevant causative exposure and assist in differentiating between occupational and work aggravated asthma (de Olim et al., 2015).

This Guide does not recommend immune testing because specific IgE antibodies for diisocyanate –human serum albumin (HSA) conjugated test antigens are not sensitive enough to be a diagnostic or a screening tool for identifying workers with diisocyanate related OA. Specific IgE was found in less than half of clinically confirmed cases diisocyanate related OA (Tee et al., 1998). The role of specific IgG is also unclear. Several studies have found that specific IgG responses to diisocyanate –human serum albumin (HSA) conjugates are also generally associated with exposure and not disease (Lushniak et al., 1998). In conclusion, immunologic testing does not replace physiologic methods for the diagnosis of Diisocyanate Asthma (Tarlo et al., 2008). Consequently, it is not routinely recommended for investigating workers with possible diisocyanate-related asthma.

Diagnostic Algorithm

This Guide for evaluating and confirming diisocyanate-related asthma is presented as a stepwise diagnostic algorithm in **Figures 3 and 4.** The annotations explaining the steps in the figures are described in detail below:

Step 1: Obtain a Medical and Occupational History of Work-related asthma

Although a history consistent with occupational asthma alone is not enough to confirm and establish a diagnosis of occupational asthma, it is an essential first step. An occupational respiratory questionnaire is provided in ***Appendix I***, which can be used by the physician to capture relevant information pertaining to work-related asthmatic symptoms. Any worker who is employed in a facility where a diisocyanate is being used and reports reporting cough, shortness of breath, wheezing or chest tightness during or after the work shift should undergo further testing as outlined in the following steps.

The physician obtaining the occupational history should be aware of the following different patterns of work-related asthmatic reactions following sensitization that can be elicited by sub-irritant levels of ambient diisocyanate exposure: 1) early onset of asthmatic symptoms that begin within 1-2 hours after arriving at work that may last for 3-4 hours or may persist through the entire duration of the work shift; 2) late onset asthmatic symptoms that begin 4-12 hours after beginning the work shift (Note: occasionally respiratory symptoms are noticed to begin after leaving work). These patterns of asthmatic reactions have been demonstrated after controlled inhalation challenge with diisocyanates (Perrin et al., 1991). As with common outdoor and indoor aeroallergens such as molds, pollens and house dust mite, respiratory exposure to occupational sensitizers may cause early, late, and dual (immediate and late) responses. Low molecular weight chemical occupational sensitizers are unique by virtue of their ability to cause isolated late responses without immediate asthmatic responses. This should be considered when assessing the temporal history between work exposure and development of respiratory symptoms in symptomatic diisocyanate exposed workers (Perrin et al., 1991).

Using this knowledge, the examining doctor should be aware that some workers with occupational asthma might report that lower respiratory symptoms begin at work whereas others might not experience symptoms until many hours at work or even after completion of the workshift. Although unusual, asthmatic symptoms associated with late onset asthma can persist for days or even weeks away from work following a single diisocyanate exposure. However, most workers with occupational asthma report symptomatic improvement on the weekend or vacation.

Step 2: Spirometry testing- Confirm the presence of asthma

Before assessing a symptomatic worker for work-related asthma, it is essential to first demonstrate that the worker has asthma defined as reversible variable airway obstruction. Ideally, during a period when the worker is experiencing asthmatic symptoms, simple spirometry testing should be performed before and after 2-4 inhalations of a short acting β_2-agonist (SABA; *e.g.* albuterol) delivered by a metered dose inhaler or nebulizer device. It is important to instruct patients to withhold short acting inhaled bronchodilators for at least 4 hours and long acting β_2-agonist bronchodilators (LABA) for at least 12 hours prior to the spirometry test. An increase in FEV_1 of at least 12% after bronchodilator treatment from the pre-treatment baseline FEV_1 establishes reversible airway obstruction, confirming a diagnosis of asthma. **Failure to demonstrate reversible airway obstruction on a single test day does not exclude asthma.** The test for reversibility in FEV_1 can be repeated on a different day when the patient is actively symptomatic. **Regardless of whether there is demonstrable reversibility in FEV_1, all workers reporting lower respiratory symptoms must proceed to Step 3 for serial monitoring of lung function both at and away from work combined with methacholine inhalation testing (Step 4).**

Step 3: Workplace Monitoring by Serial Monitoring of Lung Function (Tarlo et al., 2008)

When carefully supervised, serial monitoring of lung function (*i.e.* FEV_1 and/or peak expiratory flow rate [PEFR]) while on the job is considered a **workplace monitoring test**. Because there is potential risk in exposing a worker to a substance capable of triggering acute bronchoconstriction, baseline lung function must be adequate and asthma must be clinically stable for at least 1 week prior to initiating the workplace monitoring testing. Serial monitoring of PEFR at work should be performed only in workers who have a baseline FEV_1 of $\geq$70% of predicted. Those workers who report previous severe work-related bronchospastic episodes and/or have an FEV_1 <70% of predicted should be referred to a medical consultant experienced in the evaluation of occupational asthma. Workers with concomitant medical conditions (*e.g.* congestive heart failure) who are medically unstable should not be considered for the workplace monitoring test.

Measurement of intrashift decrements in FEV_1 is an alternative to serial PEFRs for confirming work-related airway obstruction. However, lung function tests (*e.g.* FEV_1) performed before and after the workshift on several days is less sensitive than serial measurement of PEFR performed every 2-4 hours or a minimum of four times daily (Anees, 2003; Anees et al., 2004; Nicholson et al., 2005). An intra-shift or cross-shift decrease on FEV1 of ≥10% measured during weeks at work (*i.e.* 2-3 times/week) but not during weeks away from work signifies the presence of work-

related airway obstruction. Failure to demonstrated intrashift or cross-shift changes in FEV_1 does not exclude occupational asthma nor does it preclude the need to perform more frequent serial measurements of PEFR.

To obtain quality PEFR data, workers must be properly trained in the use of a portable peak flow rate meter, emphasizing the necessity to obtain a maximal forced expiratory effort. Three efforts are required for each measurement and they must be close to each other; all three efforts should be recorded. Worker instructions and PEFR diaries are provided in ***Appendix II*** and ***Appendix III.*** PEFR measurements should be performed by symptomatic workers for 1-2 weeks at work (in a work area where a diisocyanate is being used) and during 1-2 weeks completely removed from exposure. Peak flows rates are to be recorded in diaries every 2-4 hours during waking hours and if awakened. At least 4 daily readings are required (Anees et al., 2004). Once peak flow recordings have been collected, the highest value in each reading (L/min) may be plotted on the Y-axis versus time on the X axis **(see Figure 2)**.

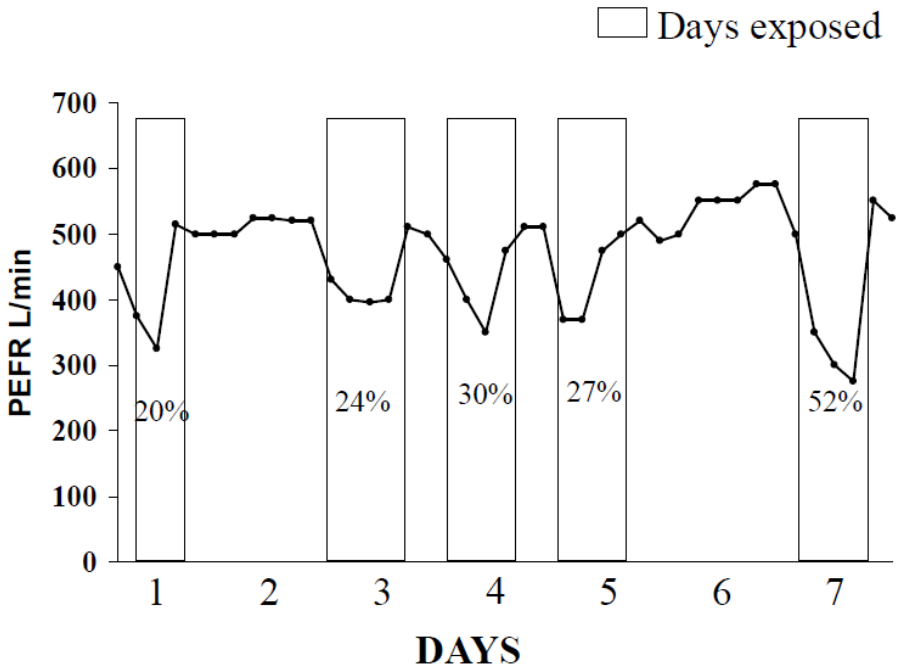

Figure 2. Plot of a PEFR record obtained from a worker with occupational asthma shown as time in days versus the peak expiratory flow rate (L/min) (Nicholson et al., 2005)

Maintenance non-bronchodilator asthma medications including inhaled corticosteroids should not be withdrawn during PEFR monitoring. If deemed safe by the physician, workers should withhold long-acting beta agonist (*e.g.* formoterol) or long-acting anti-muscarinic agents (*e.g.* tiotropium) during this testing period, which can potentially inhibit changes in lung function. Short acting β_2-agonists (*e.g.* albuterol) bronchodilators should be used for "as needed" rescue treatment for acute asthma symptoms. Lung function records obtained during acute asthma exacerbations or viral infections, which can cause decrements in lung function, should not be

included in the PEFR data analysis.

Ideally, two experienced physicians blinded to the medical history of the worker should interpret by visual inspection the PEFR graphs obtained during weeks at and away from the workplace. As shown in **Figure 2**, consistent daily variability (maximum-minimum/maximum PEFR value x 100) in PEFR of $\geq$20% compared to measurements obtained on days (or weeks) away from work are characteristic of occupational asthma (Tarlo et al., 2008). The absence of increased daily variability in PEFR of $\geq$20% on work days with concurrent isocyanate exposure makes occupational asthma unlikely. Significant decreases in PEFR both during weeks while at work and during weeks away from work are likely attributable to non-occupational asthma or work-aggravated asthma. Rarely, failure to improve away from work can be seen in patients with persistent OA.

Step 4: Methacholine Testing (Pralong et al., 2016)

A methacholine inhalation challenge test defines the presence or absence of "hyperactive airways" or nonspecific bronchial hyperresponsiveness (NSBH). Methacholine (Provocholine™) testing is performed routinely in many physicians' offices and in pulmonary function laboratories. Nonspecific bronchial hyperresponsiveness, defined by a positive methacholine test, is a universal feature of persistent asthma with airway inflammation but can also be detected in a variety of non-asthmatic conditions such as chronic bronchitis, congestive heart failure and in atopic individuals and chronic smokers.

The methacholine test is performed by having the patient inhale nebulized saline which is followed by inhalation of incremental doses of methacholine (range of concentrations: 0.125-25 mg/mL) every 5-10 minutes until a 20% decline from the post-saline FEV_1 is observed or until all challenge doses have been delivered without any decrease in the FEV_1. A positive response is defined as a 20% decrease in FEV_1 after inhalation of a provocative concentration (PC_{20}) of $\leq$16 mg/mL of methacholine (Cockcroft, 2003).

It is expected that not all physicians using this Guide will have access to methacholine testing. This test is unnecessary in a worker in whom reversible airway obstruction has already been detected in Step 3, unless there is need to validate inconclusive PEFR records.

For the purpose of confirming or excluding occupational asthma, it is essential to perform methacholine testing:

1) During work hours or within 1 hour after leaving the workplace because airway reactivity can normalize within 2-3 hours after leaving work (Durham et al., 1987);
2) After the individual's normal workplace exposure to diisocyanates for at least 2 weeks; and if possible,
3) On the last day of the work week.

A methacholine test is positive if the provocative concentration that elicits a 20% decrease in FEV_1 (PC_{20}) from the saline baseline challenge is $\leq$ 16 mg/mL of methacholine chloride. A positive test will validate abnormal PEFR studies. In addition, normalization of the

methacholine PC_{20} associated with normalization of the PEFR weeks after leaving the workplace further supports a diagnosis of OA (Tarlo et al., 2008). On the other hand, a normal methacholine test (PC_{20} >16 mg/mL) would likely exclude occupational asthma and validate normal PEFR studies, or invalidate abnormal PEFR measurements collected by the worker (Pralong et al., 2016). If the methacholine test is normal and the PEFR results abnormal, poor technique or falsification of PEFR data must be suspected. When PEFR results are discordant or inconclusive, referral to a specialist with expertise in evaluation of OA is recommended.

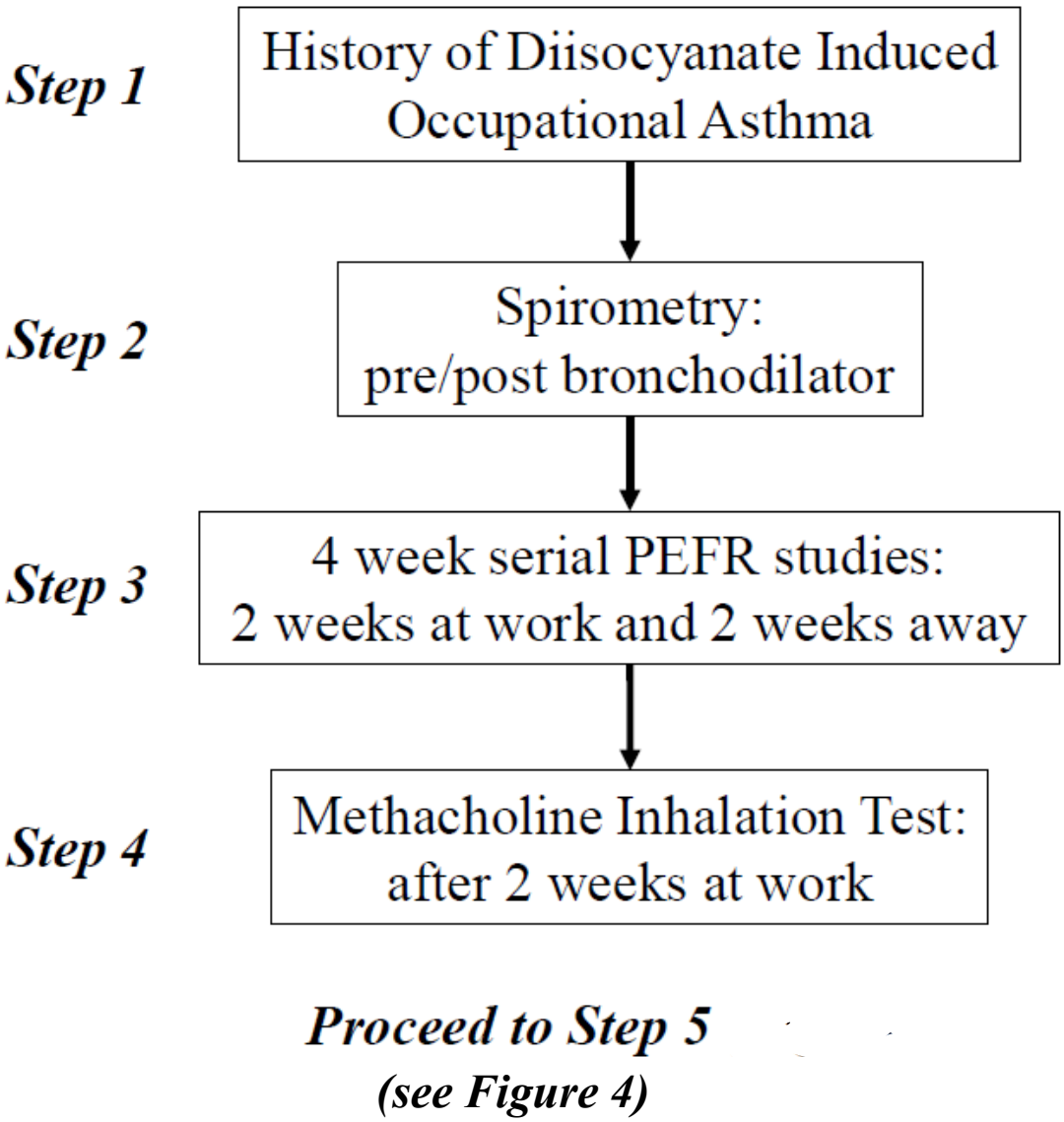

Figure 3. *Diagnostic algorithm for occupational asthma associated with diisocyanate exposure*

Step 5: Diagnosis and Intervention

As shown in **Figure 3**, Steps 1, 2 and 3 lead to five possible combinations of test results among symptomatic workers. Suggested interventions for diagnoses derived from results of methacholine and PEFR tests are shown in **Figure 4** and are described below:

a. ***Normal PEFR studies and a negative methacholine test at work.*** Such workers do not have clinical asthma and can continue to work but should be re-evaluated every 6 months for as long as they continue to work with diisocyanates and experience respiratory symptoms.

b. ***Normal PEFR studies and a positive methacholine test***. It is likely that this worker has increased airway responsiveness and no work-related asthma, although he/she could have non-occupational asthma. If such workers are allowed to return to work, monthly spirometry should be conducted by trained personnel before, during and after several work shifts during which diisocyanates are being used in order to confirm absence of work-related asthma. The absence of intrashift decreases in FEV_1 (≥15%) likely excludes work-related asthma.

c. **Abnormal *PEFR studies and a negative methacholine test***. It is unlikely that the worker has asthma. As already mentioned, poor technique in performance of the PEFR maneuver or poor reporting of PEFR data could account for these anomalous results. Such workers can be cautiously sent back to work. However, careful monthly follow up should be performed with cross-shift and intrashift determinations of FEV_1 every 2-4 hours (see Step 5b) and assessment of asthma symptoms and asthma medications for as long as it is clinically indicated.

d. ***Abnormal PEFRs that decrease at work and improve away from work combined with a positive methacholine test.*** These results suggest that the worker has occupational asthma. Such individuals should be restricted completely from future exposure to all diisocyanates. Following cessation of diisocyanate exposure, periodic assessment of FEV_1 and of asthma symptoms, is recommended in order to determine long term treatment requirements and overall improvement in asthma.

e. ***Abnormal PEFR changes both at work and away from work and a positive methacholine test.*** This presentation presents a unique clinical challenge. Such individuals with continuous asthma may have either non-occupational asthma (that may be aggravated by work; *i.e.* WAA) or chronic occupational asthma. Because, in rare cases, improvement in occupational asthma and lung function may not be determined for months following cessation of exposure to diisocyanates, it is recommended that these workers be totally restricted from exposure to diisocyanates for 6 months. Monthly evaluations for clinical symptoms, asthma medication requirements and FEV_1 are recommended. Gradual improvement in lung function and symptoms confirms occupational asthma and such workers should not be re-introduced to workplaces where exposure to diisocyanates is possible. Failure to show improvement after a prolonged absence from work exposure may be more consistent with non-occupational asthma. However, such a worker should be referred to a physician knowledgeable in occupational lung disease for further evaluation and management.

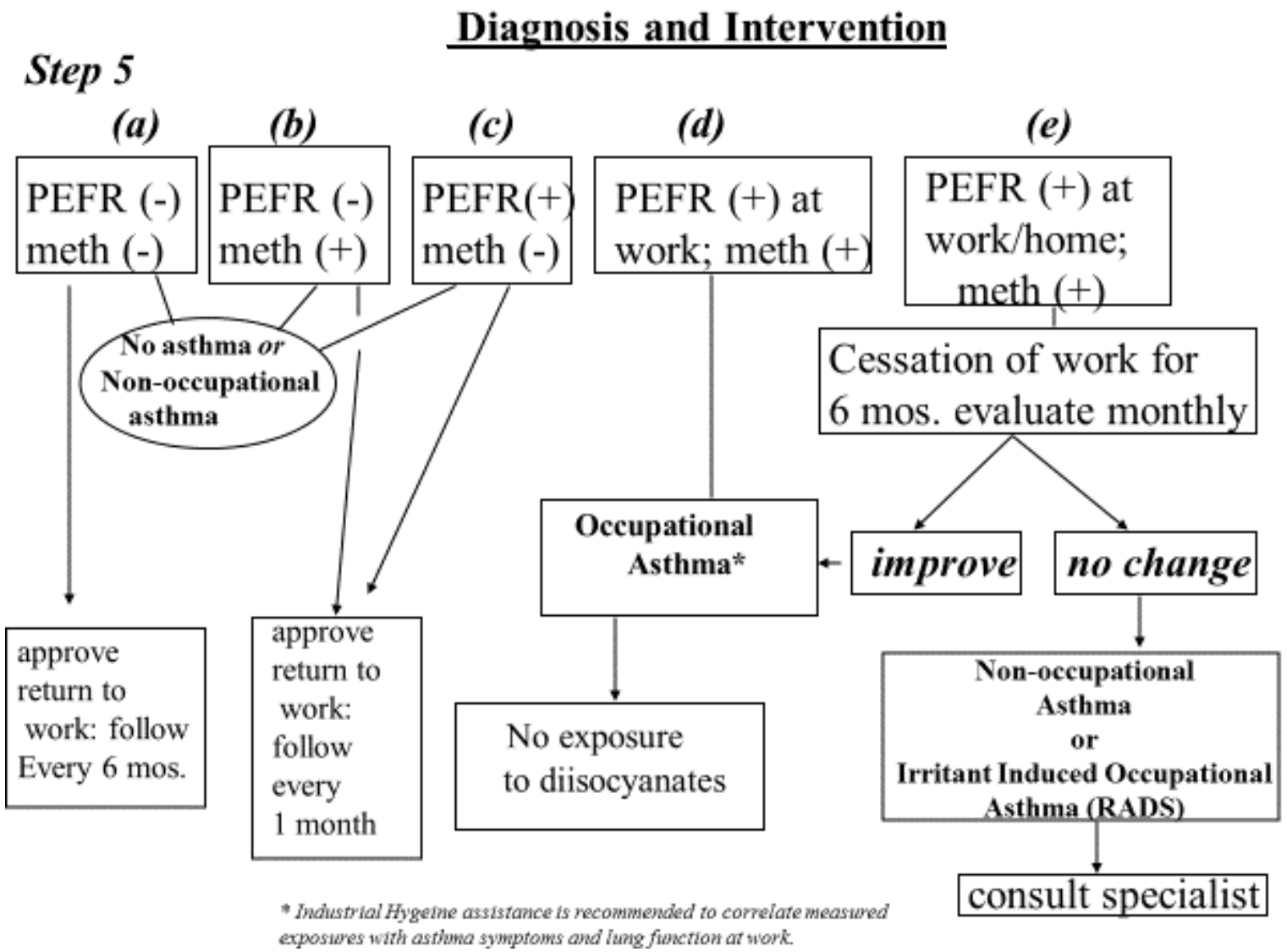

Figure 4. Diagnostic confirmation and interventions following evaluation for diisocyanate related asthma

APPENDIX I: MEDICAL SURVEY FORM

(Please Print)

Today's date:						
Associate identification						
Last name:		First:		Middle:		Marital status (circle one) Single / Mar / Div / Sep / Wid
Birth date: / /	Height:	Weight:	Age:	Sex: ❑ M ❑ F		If female, are you pregnant? ❑ Yes ❑ No
Home Street address:				Home phone: ( )		Alternate phone: ( )
Ethnic Background: European: ____ Asian: ____ African ____	City:			State:	ZIP Code:	
Occupation:	Employer:			Employer phone: ( )		

OCCUPATIONAL HISTORY (CURRENT COMPANY)			
Have ever you been transferred from a job for a health reason? YES NO			
If YES, give details:			
When did you start your current job?	/ /		
What is your current job description?			
What is your usual shift?			
What shift are you working presently?			
What is your current work area?			
What percent of the time are you in your work area?			
List chemicals or other substances which may be used in your work area during a typical work week.			
Substance	How are you exposed? (dermal, air)	Month/Year Started	Month/Year Ended

Describe previous jobs at your **current** place of employment.
(*Please begin with your most recent job and end with your first job, and do not list current job.)*

Department	Job Title/Description	Dates (Start/Stop)	Total Years

PREVIOUS EMPLOYMENT HISTORY

Describe previous jobs at **other** places of employment.

Department	Job Title/Description	Dates (Start/Stop)	Total Years

List chemicals or other substances which you may have been exposed to in previous jobs.

Substance	How were you exposed? (dermal, air)

MEDICAL INTERVIEW

Have ever you been transferred from a job for a health reason?	YES	NO	
If YES, give details:			

While at your current job, have you had:

Chest Tightness	YES	NO
Wheezing	YES	NO
Cough	YES	NO
Shortness of breath	YES	NO

If **YES**, then answer the following….

Do these symptoms begin *immediately* after starting work (less than 1 hour)?	YES	NO
Do these symptoms begin only after starting work?	YES	NO
If so, approximately how many hours after starting work?		
How many hours do these symptoms last while at work?		
Do these symptoms continue after coming home from work? *(ex. Cough while sleeping)*	YES	NO
If so, for how many hours?		
How many days?		
What time of day to they stop?		
Are these symptoms better on weekends?	YES	NO
Are these symptoms better on vacation?	YES	NO
How many months were you on the job before symptoms started?		
IMPRESSION: Are work-related symptoms present?	YES	NO
Are symptoms associated with exposure to a substance at work?	YES	NO
If yes, what process or substance?		

SMOKING HISTORY			
Do you smoke cigarettes?	Now	Former	Never
If so, how many packs per day?			
How many years have you smoked?			
Do you use e-cigarettes?	Now	Former	Never
If so, how many milliliters per day?			
For how many years?			

CHRONIC BRONCHITIS		
Do you cough on most days, for at least 3 months out of the year?	YES	NO
If YES, how many years have you had this cough?		

OTHER RESPIRATORY		
Have you ever been told by a physician you have COPD, emphysema or chronic bronchitis?	YES	NO
Have you ever been diagnosed or treated for asthma by a physician?	YES	NO
If yes, what year were you diagnosed with asthma?		
If yes, what medications have you been prescribed for asthma?		

ATOPIC HISTORY		
Do you have itchy eyes, runny and congested nose during spring, summer or fall on a yearly basis?	YES	NO
If YES, what year did these symptoms start?		

DISOCYANATE EXPOSURE		
Have you been present for a MDI or TDI spill?	YES	NO
If YES, give details: (dates, number of incidents etc.)		

HOBBIES AT HOME		
Have you ever done urethane spray painting on your car or on other metal surfaces at home?	YES	NO
If YES, explain		
Did you use expanding PU foam to seal gaps, windows, doors or use it as hobby material?	YES	NO
If YES, explain		
Have you personally used very strong glues or polyurethane-based coatings at home?	YES	NO
If YES, explain		
Have you ever had respiratory symptoms while using these products at home?	YES	NO
If YES, explain		

FOR PHYSICIANS USE ONLY (circle one):	
Impression:	No Asthma
	Non-occupational Asthma
	Occupational Asthma
	Bronchitis
Physician Signature:	Date:

APPENDIX II

INSTRUCTIONS FOR PEAK FLOW MEASUREMENT

You have been supplied with a **portable peak flow meter device** in order to do serial recordings of your pulmonary function by measuring your own peak flow rates. This will help us evaluate any potential breathing problems related to your exposures at work. It is very important that you follow these instructions very carefully to minimize errors. Ideally you should take peak flow measurements for a total of four weeks to include 2 weeks at work and 2 weeks away from work exposure to suspect chemical. While doing your regular job, follow normal work routines and make sure you handle chemicals as you normally would. For the next phase, completely eliminate exposure to the suspect chemical at work for 7-10 days. You may consider arranging to take vacation time away from work during that period

1. Hold the Peak Flow Meter device level, be sure the air holes in back and the arrow on top are not covered. Stand up. Take as deep a breath as possible. Put your mouth around the mouthpiece, sealing your lips around the mouthpiece. Blow out as hard and as fast as you can. No need for a long exhalation. A short hard huff is okay.

2. Reset the arrow on top. Do the procedure 3 times and record all three readings in the boxes of the supplied Peak Flow recording form. Take a measurement (3 repeat readings) every 3-4 hours while awake. Take a minimum of 4 sets of measurements per day for four weeks. Weeks one and two should be while exposed to diisocyanate, using pages 1 and 2 for the first week (Days 1-7), pages 3 and 4 for the second week of recordings (Days 8-14). Weeks three and four should be away from exposure, using pages 5 and 6 for the third week, and pages 7 and 8 for the 4^{th} week of monitoring

3. All peak flow measurements should be done BEFORE taking any asthma medication. If an asthma inhaler has been used in the past two hours, please note this in the box supplied on the form.

4. Record any symptoms of wheezing, shortness of breath, chest tightness at the time of the peak flow recording by checking all the boxes that apply.

APPENDIX II

PEAK FLOW METER DIARY (14/28 DAYS)

NAME:________________________________ WORK SHIFT (e.g. 7AM-3PM) ______________DATE DISPENSED:______________

INSTRUCTIONS:

1. **Hold the Peak Flow Meter level, be sure the air holes in back are not covered. Stand up. Take as deep a breath as possible. Put your mouth around the mouthpiece, sealing your lips around the mouthpiece. Blow out as hard and as fast as you can. No need for a long exhalation. A short hard huff is okay.**
2. **Reset the arrow. Do procedure 3 times and record all three readings in box (see example Day 1) every 3-4 hours while awake.**
3. **Evening peak flows and morning peak flows should be done BEFORE taking any asthma medication. If an asthma inhaler has been used in the past two hours please note this on the diary by putting an M (for medication) next to the time of the reading.**
4. **Record symptoms of wheezing, shortness of breath, cough or chest tightness at the time of the peak flow recording by circling (S) (for symptoms) in the left corner of each box.**

Time (Circle AM or PM)	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14
AM PM	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S
AM PM	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S
AM PM	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S
AM PM	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S
AM PM	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S
AM PM	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S	- - - - - - S
Work Day? Y or N														

APPENDIX III

SAMPLE PEAK FLOW METER 14 DAY DIARY

NAME: John Doe WORK SHIFT (e.g. 7AM-3PM) 7am – 3pm DATE DISPENSED: Feb 2016

Time (Circle AM or PM)	DAY 1 Mon	DAY 2 Tues	DAY 3 Wed	DAY 4 Thurs	DAY 5 Fri	DAY 6 Sat	DAY 7 Sun	DAY 8 Mon	DAY 9 Tues	DAY 10 Wed	DAY 11 Thurs	DAY 12 Fri	DAY 13 Sat	DAY 14 Sun
06:00 AM	540 550 530 Avg 540 S	600 580 550 Avg 577 S	530 530 480 Avg 513 S	420 500 410 MED Avg 443 S	450 450 490 Avg 463 S	600 600 600 Avg 600 S	570 560 600 Avg 577 S	420 450 500 Avg 45 S	420 440 450 Avg 437 S	520 540 540 Avg 533 S	550 520 550 Avg 540 S	500 50 490 Avg 500 S	620 510 620 Avg 617 S	640 600 650 Avg 630 S
12:00 PM	550 535 565 Avg 550 S	520 450 550 Avg 507 (S)	560 590 600 Avg 583 S	550 550 500 Avg 533 S	550 550 570 Avg 557 S	500 520 550 MED Avg 523 S	550 570 580 Avg 567 S	420 450 440 Avg 437 (S)	440 440 450 Avg 447 (S) M	580 560 510 Avg 550 S	560 560 480 Avg 533 S	540 540 550 Avg 543 S	660 660 656 MED Avg 655 S	640 620 650 Avg. 637 S
20:00 PM	540 540 515 Avg 532 S	590 520 590 Avg 567 S	520 550 540 Avg 536 S	550 545 480 MED Avg 525 S	540 550 600 Avg 563 S	550 560 580 Avg 563 S	560 580 580 Avg 573 S	460 490 450 Avg 467 S	400 450 450 Avg 433 (S) M	600 420 400 Avg 473 (S)	450 480 510 Avg 517 S	480 470 500 Avg 483 S	650 650 620 Avg 640 S	640 600 600 Avg 613 S
AM PM	--- --- S	--- --- S	--- --- S	--- --- S	--- --- S	--- --- S	--- --- S	--- --- S	--- --- S	--- --- S	--- --- S	--- --- S	--- --- S	--- --- S
AM PM	--- --- **S**	--- --- **S**	--- --- **S**	--- --- **S**	--- --- **S**	--- --- **S**	--- --- **S**	--- --- **S**	--- --- **S**	--- --- **S**	--- --- **S**	--- --- **S**	--- --- **S**	--- --- **S**
AM PM	--- --- **S**	--- --- **S**	--- --- **S**	--- --- **S**	--- --- **S**	--- --- **S**	--- --- **S**	--- --- **S**	--- --- **S**	--- --- **S**	--- --- **S**	--- --- **S**	--- --- **S**	--- --- **S**
Work Day? Y or N	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	No

Mon: Monday; Tue: Tuesday; Wed: Wednesday; Thurs: Thursday; Fri: Friday; Sat: Saturday; Sun: Sunday; Avg: Average of 3 readings

(**S**): Indicates symptoms observed at time of PEFR. **M**: Medicine administered within 2 hours of PEFR

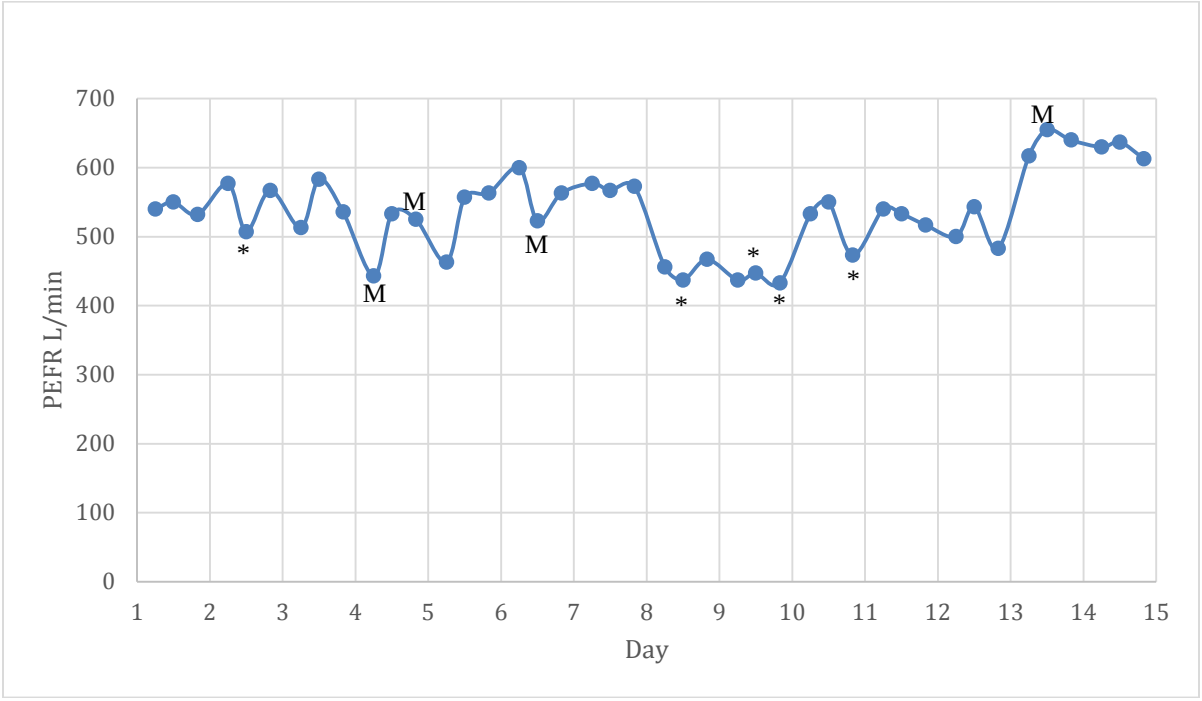

*Figure 5. Plot of the PEFR record in APPENDIX III for a fictitious worker. Shown as time in days (14) versus the peak expiratory flow rate (L/min). *: Indicates when symptoms were observed. M: Indicates when medicine was administered within 2 hours of PEFR measurement.*

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