

## Why the Clerical Application of TLVs May Not Protect Workers – A Case Study

### AUTHORS

John Elias, MPH, CIH, ROH, CRSP. President, Elias Occupational Hygiene Consulting Inc. (jelijas@mts.net)

Alison Reineke, BSc, CRSP. Occupational Hygiene Consultant, Environmental Health and Safety Office, University of Manitoba. (Alison.Reineke@ad.umanitoba.ca)

### ABSTRACT

The problem arose at a sash and door company where the evening shift had low exposure levels ( $<1/100^{\text{th}}$  TLV<sup>®</sup>), less than the day shift, but had all the same health problems: cough, sore throat, respiration difficulties, and sneezing. The investigation showed the work to be similar during both shifts, but much lighter with lower exposures in the evening shift. The main difference appeared to be the time of day the work was done. The shift differences and circadian rhythms appeared to hold the resolution to this problem and lead to the exploration of circadian rhythms and exposure levels.

A literature review suggested that there were several ways that circadian rhythms would modify how toxic materials were metabolized and excreted. The following biological processes vary with the circadian rhythm.

- Plasma adrenaline
- Plasma cortisol
- Plasma histamine
- Liver enzymes
- Glomerular filtration
- Core body temperature
- Blood coagulation
- Blood pressure and heart rate

Since many biological processes that are involved in the metabolism, excretion, or other reaction to workplace chemicals vary with the time of day, the body's reaction to workplace challenges will also vary with the time of day. In some cases, a chemical may be more toxic during the day than at night or vice versa depending on the metabolic pathways. Factors that can vary with time of day include:

- Toxicity of chemicals
- Sensitizers
- Biological monitoring
- General health

The results of the survey pointed to the toxic effects of workplace chemicals modified by circadian rhythms. The lesson learned from this is that the profession of industrial hygiene is more than the clerical function of comparing sample data to TLVs. It is essential to

understand the basis of the individual TLV, the workplace, and the workers to draw correct conclusions to protect workers.

## Background

There are many definitions of shift work, but generally and here, shift work is defined as work performed outside normal daytime hours. Essentially not between 7 am to 6 pm for an 8-hour shift <sup>(1, 2, 7)</sup>.

Shift work is not rare with almost 16% of all fulltime workers being shift workers, with up to 50% of workers in some industries. Since shift work is not a rare or unusual occurrence it must be a consideration in many safety and health programs.

The body reacts to shift work in many ways as described below. There are many differences reported between workers on normal day shifts and those on evening shifts (not between 7 am to 6 pm) <sup>(1, 2, 3, 4, 5, 6, 7)</sup>. These are often reported as causes or effects, and examples are listed below.

- Anxiety
- Addition speed, counting
- Short term and long term memory
- Reaction time
- Handgrip strength
- Neuromuscular control
- Thermal and metabolic responses
- Levels of fatigue
- Digestive problems
- Heart disease
- Manual dexterity
- Muscle strength and speed
- Attention and vigilance or performance speed and accuracy
- Reduced alertness
- Complex high cognitive-load tasks are likely to be performed best during the night shift

Many of the problems associated with shift work can be defined as safety issues. The focus here is on health effects associated with the interaction of shift work and exposure to workplace chemicals. Many jurisdictions base what are considered acceptable levels of exposure on the Threshold Limit Values (TLVs<sup>®</sup>) set by the American Industrial Hygiene Association (ACGIH). The TLVs were developed as guidelines or recommendations to be used by persons trained in the discipline of occupational hygiene. Conditions of the workplace (work schedules, work level, temperature, and humidity) and conditions of the worker (age, gender, ethnicity, genetic, lifestyle, medications, and pre-existing medical conditions) must be taken into account when interpreting workplace exposures <sup>(22)</sup>. The Australian national standards are partly based on the TLVs and employ similar recommendations <sup>(24)</sup>. Some jurisdictions such as the British Health and Safety Executive

(HSE) have developed their own exposure limits called Workplace Exposure Limits (WELs). Similar to the TLVs, the WELs are based on “normal working conditions” and employers must take into account working conditions which impose additional stress on the body and should determine their own working practices and in-house standards for exposure control <sup>(23)</sup>.

One of those things that must be taken into account is shift work. The time of day that an exposure takes place can affect absorption, distribution, metabolism, and elimination of chemical agents due to daily rhythms in biological functions and processes. These daily rhythms are often referred to as circadian rhythms. It is assumed that a specific dose of a chemical will have the same effect on a person regardless of the time of day that the dose is received. Based on experiments with rodents, and experience with medications, this assumption may not be valid <sup>(8, 9)</sup>. The fallacy of this assumption is demonstrated in the practice of chronotherapy where medications are administered according to the time of day to maximize beneficial effects and to minimize potential harmful effects.

Humans, like most organisms have evolved to be active during the day or night and their physiological processes are optimized for nocturnal or diurnal activities. Thus, the time of day that an exposure takes place becomes a factor in humans, as with other living organisms.

In humans the “normal” or active period is during daylight hours, but for many test animals such as rodents, the active period is at night, during darkness. This adaptation takes into account sleep-wake cycles, cardiovascular activity, endocrine system, body temperature, renal activity, kidney, heartbeat, and the gastrointestinal tract. The following are examples of changes in biological processes between active and inactive periods that could affect how a person reacts to workplace exposures. In these examples, the active period is considered “normal” or the basis for comparison.

<b>Biological process</b>	<b>Change during inactive period</b>
Plasma adrenaline	Reduced levels
Plasma cortisol	Reduced levels
Plasma histamine	Reduced levels
Liver enzymes	Increased levels
Glomerular filtration	Reduced levels
Core body temperature	Reduced levels
Blood coagulation	Reduced levels
Blood pressure and heart rate	Reduced levels*

\* A reduced heart rate with reduced blood flow will reduce liver and kidney functions, increasing the half-life of materials in the body.

**TABLE 1:** Examples of differences in the body’s response in test animals during active periods <sup>(7, 16, 18, 19)</sup>.

As mentioned, these findings have been used to determine good drug dosage in the treatment of some diseases (asthma, and arthritis <sup>(7, 13)</sup>). The absorption, distribution,

metabolism, excretion, and action of drugs can vary dramatically as a function of the time of their administration. Circadian rhythms can occur in a target organ such as the skin, the bronchial tree, or any of the internal organs that are directly affected by drug administration (i.e. stomach, heart, and pancreas). The time to achieve the peak blood concentration, the magnitude of the peak plasma concentration, and the half-life of elimination can vary predictably depending on the time of day the drug was administered.

For example long-term oral administration of corticosteroids at 8:00 a.m. and 3:00 p.m. were more effective in controlling nocturnal asthma than the same doses given at 3:00 p.m. and 8:00 p.m. Also, prednisone improved lung function and reduced airway inflammation more effectively when given as a single dose at 3:00 p.m. than in two doses at 8:00 a.m. and 8:00 p.m.<sup>(14)</sup>.

Unfortunately, most research in this area has been carried out to help determine correct drug administration, and very little research has been carried out for workplace chemicals. However, there is no reason to believe that circadian rhythms will not affect a worker's reaction to workplace exposures.

Therefore the potential for different reactions to workplace exposures at unusual times of day should be taken into consideration when evaluating and controlling potential workplace hazards<sup>(1, 4, 5)</sup>. The effects of circadian rhythms may help explain why a person has an adverse reaction to an exposure when the usual evaluation methods suggest that there is no problem. The following is a review of how circadian rhythms affect some aspects of workplace exposures.

## **1) Toxic Materials**

For this discussion toxic materials are defined as non-allergenic compounds that can damage a living organism. Allergenic materials are discussed separately.

As mentioned, absorption, distribution, metabolism, excretion, and the action of chemicals can vary dramatically as a function of the time of their exposure. The time to achieve the peak blood concentration, the magnitude of the peak plasma concentration, and the half-life of elimination can vary depending on the time of day the material was absorbed.

From Table 2, it can be seen that exposures to chemicals which may be tolerated during the normal active period may not be tolerated during the normal inactive period<sup>(20)</sup>. This may be caused by the body's reduced capacity to remove the chemical, or in some cases the liver's ability to transform the chemical into a more toxic form during the inactive period. There were some cases where toxicity during day was more toxic than at night. This would be the "normal" condition, and exposures during the inactive period would have an extra margin of safety.

Chemical	Inactive Mortality Range (%)	Active Mortality Range (%)
Amphetamines (26 mg/kg) <sup>(7)</sup>	10-30	25-80
Strychnine (2 mg/kg) <sup>(7)</sup>	35-55	60-85
Nicotine (0.057 mg/kg) <sup>(7)</sup>	10-25	15-85
Phenobarbitol (190 mg/kg) <sup>(7)</sup>	60-100	0-15
Phenobarbitol Sodium (90 mg/kg) <sup>(7)</sup>	30-40	40-80
Ethanol (NA) <sup>(7)</sup>	10-50	10-60
Urethane (1900 mg/kg) <sup>(7)</sup>	35-60	60-90
Malathion (1800 mg/kg) <sup>(7)</sup>	40-90	35-45
HgCl <sub>2</sub> (5.6 mg/kg) <sup>(7)</sup>	30-80	30-50
Paraquat (21.3 mg/kg) <sup>(7)</sup>	50-70	68-80
X-radiation (NA) <sup>(7)</sup>	40-70	80-85
Cadmium Sulfate <sup>(11)</sup> (2.5 mg/kg)	21.7	3.3
(3 mg/kg)	43.3	16.7
(3.5 mg/kg)	73.3	96.7
	<b>LD50 Inactive Period (mg/kg)</b>	<b>LD50 Active Period (mg/kg)</b>
5-fluorouracil <sup>(12)</sup>	450-500	250-300
HgCl <sub>2</sub> <sup>(10)</sup>	5.54	4.14
	<b>Brain concentration (mg/dl) Inactive period</b>	<b>Brain concentration (mg/dl) Active period</b>
Toluene exposure <sup>(15)</sup> 2000 ppm (4 hours after exposure)	101.5	69.9
Toluene exposure <sup>(15)</sup> 4000 ppm (2 hours after exposure)	146.0	127.6
	<b>Allergic Inactive Response (%)</b>	<b>Allergic Active Response (%)</b>
Late Asthmatic Response (frequency, duration, and severity) <sup>(14)</sup>	90	40
Cutaneous Sensitivity compared to 24 hr average response <sup>(7)</sup>	30-240	15-115

**Table 21:** Effects on subjects when exposed to drugs/chemicals during the active and inactive periods.

### Biological Monitoring

A worker's exposure to toxic materials can be estimated by measuring the concentration of the material or its metabolites in urine, blood, or exhaled air. The values measured are compared to levels observed in healthy workers exposed to known amounts of the material. These levels are related to TLVs and are called Biological Exposure Indices (BEIs<sup>®</sup>). Like the TLVs these are to be used as guidelines.

Since the BEIs measure the amount of the original material or its metabolites in the

worker's body some time after exposure, the rate of metabolism or elimination will affect the amounts measured. Accordingly, biological monitoring should take into account when the samples were collected. Many samples are to be taken at end of shift. If measurements are gathered without respect to the influence of the circadian rhythm, differences in values may represent the variation due to circadian rhythms rather than differences in workplace exposures. There can be false-negative or false-positive results for materials with a short biological half-life<sup>(19, 20)</sup> particularly when samples are collected at the end of shift

## **2) Sensitizers**

Asthma is frequently diagnosed in patients with episodes of wheezy breathlessness interspersed with periods free of symptoms. The patients also show variations in airflow resistance in intrapulmonary airways, often related to specific hypersensitivity reactions. The most common of these are for patients who developed sensitivity to potentially antigenic substances.

Allergic responses increase at night. The greatest decrease in FEV<sub>1</sub> (volume that has been exhaled at the end of the first second of forced expiration) occurs after a late-evening challenge where a person is exposed to an allergen late at night (11:00 p.m.). There is a greater persistence of airway obstruction after the 11:00 p.m. challenge. Dyspnea in asthmatics is more frequent at night and during early morning hours.

An example of circadian susceptibility-resistance is seen in the variance in airway response with the time of day<sup>(14)</sup>. The LD<sub>50</sub> may vary by one or two orders of magnitude depending on the time of day the test animal was exposed to the chemical.

It has been found that there are two ways that asthmatics react when exposed to allergens. In the normal reaction, the airway narrows and wheezing develops within ten minutes, peaks in thirty minutes, and resolves in one to three hours after exposure. In the second reaction, the symptoms do not begin immediately but only several hours after exposure and may continue for many hours or days. This second response is called late asthmatic response (LAR).

The frequency, duration, and severity of the late asthmatic response (LAR) were evaluated in subjects with stable allergic asthma. A 40% LAR was observed following an 8:00 a.m. challenge, whereas an 8:00 p.m. challenge caused a 90% LAR. The duration and severity of the LAR was enhanced after the evening challenge, and an increase in the 20% fall in FEV<sub>1</sub> for a methacholine challenge was greater at 24 h after the evening challenge than at 24 h after the morning challenge. It has also been noted that a person could be exposed to a sensitizer during the day, but the maximum effect may not take place until the evening, leaving the impression that there was an evening exposure.

Cutaneous allergy response can also vary significantly depending on the time of day the challenge is offered. The symptoms of allergic response and inflammatory processes also follow circadian rhythms. These are related to the production of anti-inflammatory

hormones – adrenal corticosteroids and catecholamines which are greatest in the morning, and lowest in the evening<sup>(7, 14)</sup>. Table 3 shows the differences in reaction among workers during day (active period) and night (inactive period) compared with no challenge.

<b>Effect</b>	<b>Active Response (%) Compared to no Challenge</b>	<b>Inactive Response (%) Compared to no Challenge</b>
Late asthmatic response (frequency, duration, and severity) <sup>(14)</sup>	40	90
Cutaneous sensitivity compared to 24 hr average response <sup>(7)</sup>	15-115	30-240

**TABLE 3:** Effects on subjects when exposed to allergens during the active and inactive periods.

Occupational asthma is the same as non-occupational asthma except that it is due partly or totally to exposure to workplace materials such as:

- Natural Products
  - Grain Dusts
  - Animal Dander
  - Detergent Enzymes
- Inorganic Materials
  - Platinum
  - Nickel
  - Chromium
- Organic Materials
  - Diisocyanates
  - Anhydrides
  - Amines
  - Pharmaceuticals

Workers with airway diseases or skin sensitivities involved with shift work that exposes them to irritants or antigenic matter, may experience more reactivity during an evening or night shift. The frequency, severity, and duration of asthmatic reactions to allergen challenges during the normal inactive period are increased and result in further enhancement of bronchial responsiveness. This nocturnal worsening of asthma symptoms for shift workers may help explain problems during evening shifts that do not appear significant during day shifts<sup>(2, 7, 14, 16, 17)</sup>.

### 3) General Health

The health status of workers is one of the items that occupational hygienists must take into account when applying TLVs. Not only will the illness affect how the individual will react to workplace exposures, but the medications taken to control the illness can also affect exposures or even add to them<sup>(25)</sup>. This is not a rare event. Studies in the Netherlands<sup>(26)</sup>

and United States <sup>(27)</sup> have shown that 15 to 30% of workers take prescribed drugs. An additional 8% take nonprescribed drugs.

Unfortunately this effect is exaggerated in shift workers. Shift workers have excessive health related complaints (digestive, chest pains, wheeze, nervous, colds, and fatigue). There is a complex multi-step process associating shift work with increased illness:

- Shift work leads to mismatch of circadian rhythms which can result in sleep disturbances, leading to behavioral changes such as poor diet and smoking.
- Shift work leads to disturbed socio-temporal patterns resulting in social impairment and stress. These also lead to behavioral changes such as poor diet and smoking.
- Behavioral changes such as poor diet and smoking, in addition to affecting workplace exposures, can lead to increased illness.
- A mismatch of circadian rhythms leads to increased susceptibility and internal desynchronization. Both of these are associated with increased illness.
- Increased stress leads to increased illness.

Digestive problems are due to altered eating habits, timing, and food eaten. Males appear to use more medication for stomach and digestive problems. It should be noted that many drugs including over the counter drugs such as antacids contain the same ingredients as workplace chemicals or their metabolites.

Some of the ailments and disorders that shift work has been associated with are:

- Sleep Disorders
- Asthma
- Diabetes Mellitus
- Coronary Artery Disease
- Psychiatric Disorders (Endogenous depression and Bipolar disorders)
- Epilepsy
- GI Disorders
- Long-term Drug Therapy

#### **4) Shift Work as a Hazard**

Although we are primarily interested in how shift work can affect workplace exposures and how the TLVs are interpreted, we should also understand that shift work itself can be a workplace health hazard.

##### **Carcinogenicity**

The International Agency for Research on Cancer (IARC) convened an expert Working Group. This group concluded that “Shiftwork that involves circadian disruption is *probably carcinogenic to humans* (Group 2A).” Group 2A means that there is *limited evidence of*

*carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals.

The Working Group concluded that that long-term night workers have a higher risk of breast cancer risk than women who work during the day. There is evidence from animal studies that show consistent light, dim light at night, or simulated jet lag can increase tumour development. It is suggested that the tumour development is linked to suppressed melatonin development <sup>(28, 29)</sup>.

### **Reproductive Effects**

Studies of shift work have shown reproductive effects such as preterm birth and lower birth weight, pregnancy loss. These may be related to the circadian physiological functions and systems that can be disturbed by shift work. The following are tables showing the number investigations of reported reproductive effects <sup>(30)</sup>.

<b>Effect</b>	<b>Number of reports</b>
Elevated prevalence of menstrual cycle anomalies	2
More spontaneous abortions/stillbirth	5
Intrauterine growth, retardation	1
Preterm birth/low birth weight	4

**Table 4:** Studies reported by Nurminen showing adverse effects with varying work schedules.

<b>Effect</b>	<b>Number of reports</b>
No increase in spontaneous abortions with constant night work	1
No excess orofacial clefts, CNS defects, cardiovascular defects,	1
Preterm birth/low birth weight	1

**Table 5:** Studies reported by Nurminen showing no adverse effects with varying work schedules.

## Discussion

What does all this mean?

Most of the toxicological studies from which workplace exposure limits are based assume that any reaction to a toxic material is going to be constant over time. The potential effects of circadian rhythms are not taken into account, and the assumptions do not cover all cases. Workplace exposure limits protect normal healthy workers under normal working conditions. Most exposure limits carry the caution that they are guidelines intended to be used by qualified persons such as occupational hygienists. Such persons must take into account conditions of the worker and the workplace and make appropriate adjustments to the guidelines so as to protect all workers.

Shift work and circadian rhythms are one factor that should be considered when assessing workplace risks. At the same time there is insufficient data to make a recommendation on how to adjust exposure limits for the effect of circadian rhythms. However, the occupational hygienist should still be aware of the potential for circadian effects. Such effects could help explain why individuals on a night shift react differently to exposures than the day shift. Such effects could also explain why there is a problem when all the usual assessment steps say there is no a problem in the workplace; there are some affected workers on the night shift while there are no significant problems with the day shift.

The following are some effects the occupational hygienist should be aware of:

- 1) Night shifts may react to workplace exposures that have no noticeable effect for day shifts. This applies to both toxic materials and allergens. This is equivalent to being exposed to levels above the TLV. Where little research supports the difference between different shifts for toxic materials, there is ample evidence of an exaggerated effect for allergens.
- 2) It has been shown that allergic responses increase at night. The greatest effects occur after late evening exposures. Thus, exposures that have very little effect or no effect during the day shift may have a significant effect during the night shift. Care should be taken to not blame this on “complainers” and a complete investigation should be carried out. Care should be taken where there is exposure to allergens such as wood dust during evening shifts.
- 3) Late asthmatic response (LAR), where the symptoms do not begin immediately but only after several hours, can cause problems in identifying the cause of the reaction. If the source of the problem was an exposure during the day that is then expressed during the night work shift, there is a potential for wrongly attributing the effect to a workplace exposure. Both previous daily exposures and workplace exposures should be investigated to determine the true cause.

It should be noted that the opposite effect can take place where workplace exposure do not result in a reaction until later at night when the worker is at home. In this case the cause will not be correctly attributed to the workplace.

- 4) Shift workers have excessive health related complaints such as digestive, chest pains, wheeze, nervous, colds, fatigue, and diabetes. It is often assumed that an unhealthy or otherwise atypical target organ may not react the same as a normal organ on exposure to workplace chemicals. With excessive health related issues there will be an increased susceptibility to workplace chemicals among shift workers. The occupational hygienist must be aware of this potential and be prepared to deal with it.

Not only is the increased incidence of illness a potential issue, but the medications that are taken to treat the illness are potential sources of concern. The occupational hygienist must be aware of this potential and be prepared to deal with it as well.

A complicating factor here is that a worker's health status is private information, and the worker may not want to share this information with anyone in the workplace.

## **Conclusion**

Most of the toxicological studies on which workplace exposure limits are based, contain the assumption that any reaction to a toxic material is going to be constant over time. The evidence suggests that this is not always correct and the effects of circadian rhythms are not taken into effect in the development of workplace exposure guidelines.

This lack of data results in insufficient data to make a recommendation on how to adjust TLVs, however, the occupational hygienist should be aware of the potential for circadian effects. Such effects could help explain why individuals on a night shift react differently to exposures than the day shift.

The different reactions between day and night shift workers, to workplace exposures must be explored in each workplace to determine that there is no basis for the difference, and it is not just "complainers" or "malingerers".

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