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A Proposed Approach for Setting Occupational Exposure Limits for Sensory Irritants Based on Chemosensory Models

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Objectives: Setting occupational exposure limits (OELs) for odorous or irritating chemicals is a global occupational health challenge. However, often there is inadequate knowledge about the toxicology of these chemicals to set an OEL and their irritation potencies are usually not recognized until they are manufactured or used in large quantities.

Methods: In this paper, the importance of accounting for risk perception and communication; conditioned responses; and interindividual variability in tolerance, detection and susceptibility with respect to setting an OEL are discussed in relation to three chemosensory models. These parameters and models were then used to construct a flowchart-style methodology that can be used to set an OEL for a specific chemical.

Results: The OEL identified for a chemical odorant or irritant will depend on the type of chemosensory effect that the chemical is likely to exhibit. For example, experience has shown that chemicals with a low odor threshold often require low OELs even though many are not toxic or do not cause irritation at those air concentrations.

Conclusion: In order to establish the appropriate OEL, organizations need to agree upon the percentage of the workforce that they are attempting to protect and the types of toxicological end points that are sufficiently important to protect against (e.g. transient eye irritation, enzyme induction or other reversible effects). This is particularly true for sensory irritants. The method described in this paper could also be extended to setting limits for ambient air contaminants where risk perception plays a dominant role in whether the public views the exposure as being reasonable or safe.

Keywords: occupational exposure limits; odorants; sensory irritants

INTRODUCTION

It is increasingly clear that well-accepted occupational exposure limits (OELs) are the backbone of industrial health programs directed at minimizing diseases due to exposure to airborne chemicals. Of the ~600 substances for which an OEL has already been established, ~66% are sensory irritants (Kurtz, 1987). Furthermore, of the numerous chemicals that are in need of OELs, the odorous or irritating chemicals are a substantial portion. For example, it has been estimated that as many as 40% of the current OELs have prevention of irritation or odor as their primary goal (Paustenbach, 2000).

Currently, none of the scientific or regulatory bodies around the globe attempt to set OELs at concentrations that are so low as to not to be detectable by the senses. Rather, most attempt to identify a concentration that nearly every worker will find tolerable and that will not cause persistent irritation (or any type of measurable pathology). To identify such concentrations is difficult for odors and sensory irritants because some chemicals have odors that warn of their presence before irritation is produced. For other chemicals, their odor may only be detected after severe irritation occurs. The issue is more complicated when the odor is pleasant or, conversely, someone has a preconceived notion that the odor is associated with some type of significant or severe adverse response (e.g. nausea or shortness of breath) (Dalton, 1996; Dalton *et al.*, 1997a,b; Dalton, 1999). Lastly, there are some workers who, due to prior exposure experiences, have a heightened sensitivity to the presence of chemicals.

There have been several proposed methods of estimating OELs for sensory irritants. The use of animal

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bioassays to evaluate sensory irritation of airborne chemicals, which in turn can be used to predict sensory irritation in humans, has been extensively studied by Yves Alarie and colleagues (Alarie, 1966, 1981; Nielsen and Alarie, 1982; Alarie *et al.*, 2001). These values have been used to successfully predict OELs, specifically American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs) and more recently, Polish Maximum Allowable Concentration (MAC) values (Schaper, 1993; Kupczewska-Dobecka *et al.*, 2006). The importance of using data from human exposure studies to determine sensory irritation in order to better set OELs has also been explored by Dalton (2001). Although there has been much written on this topic, there is still not a consistent approach to set OELs for sensory irritants. This paper presents a review of the current literature, as well as a simple and novel method for setting OELs based on chemosensory models, taking into account odor and irritation thresholds.

BACKGROUND

Physiology of detection

Sensory irritants are substances that stimulate trigeminal nerve endings upon inhalation and may evoke an undesirable burning sensation (Arts *et al.*, 2006). The olfactory, trigeminal and laryngeal nerve systems all aid in detecting sensory irritants. As chemicals are inhaled, their odor and pungent properties are detected by olfactory and trigeminal nerves, respectively, in the nasal tissue (Shusterman, 1992; Kendal-Reed, 2001; Paustenbach, 2001; Doty *et al.*, 2004). When odors are present, the olfactory nerves are stimulated and the first cranial nerve relays the message to the brain. The detection of irritation or pungency is relayed to the brain via the fifth cranial nerve. Throat irritation is detected by the superior laryngeal system (Shusterman, 1992; Kendal-Reed, 2001; Paustenbach, 2001; Doty *et al.*, 2004). Together, these pathways help the exposed to distinguish and characterize the inspired air.

In addition to detecting pungency, often referred to as sensory irritation, the trigeminal system along with the tenth, or vagus, cranial nerve (detecting pulmonary irritation) is responsible for stimulating protective responses to potentially dangerous irritants in the respiratory tract (Alarie, 1973b; Shusterman, 1992; Anderson and Anderson, 1999; Alarie *et al.*, 2001). Exposures to irritants in the upper respiratory tract may cause slower breathing or even breath holding, while lower respiratory tract exposure may cause an increase in respiratory rate, thus forcing shallower breaths. These responses act to warn the exposed individual of the presence of the irritant and may prompt them to escape (Alarie, 1973b; Shusterman, 1992; Anderson and Anderson, 1999).

Greater detail of the physiological aspects of odor and irritant detection can be found elsewhere (Alarie, 1973a,b; Shusterman, 1992; Kendal-Reed *et al.*, 2001). In theory, the physiology of odor and irritant detection and reaction appears to be relatively straightforward. However, the large degree of interindividual variation makes attempting to characterize the physiology of a large population (in order to protect it) difficult.

Chemosensory models

Shusterman (2001) published three chemosensory models that can be used to classify irritants based on the concentrations at which they are odorous and at which they act as irritants. Figure 1 depicts these chemosensory models. Because chemicals in each of these models have different odor and irritation thresholds (the lowest concentration at which odor or irritation occurs, respectively), these models also serve as a way to distinguish irritants in the proposed process of setting OELs (as will be discussed later).

Model I. A chemical that does not have a detectable odor at its irritation threshold is described by Model I (Fig. 1). Model I chemicals are potent irritants and weak odorants, such as methyl isothiocyanate (Shusterman, 2001). This chemical was responsible for the incident in Bhopal where several thousand people were affected by an accidental release from a chemical process. Although volatile Model I chemicals are rare, they can be extremely dangerous since, without an odor preceding irritation as the concentration rises, an individual may experience severe irritation or health effects without even knowing of the chemical's presence.

Model II. Most sensory irritants may be classified as a chemosensory Model II chemical (Fig. 1). These chemicals have an odor threshold slightly below the irritation threshold (Shusterman, 2001). In this instance, there is a range of concentrations at which the chemical odor is detected, but irritation does not occur. For example, methylene chloride has a sweet odor like chloroform at concentrations as low as 160 parts per million (p.p.m.). However, at concentrations upwards of 500 p.p.m., it can be a potent irritant (ATSDR, 2000). Many of these chemicals will have their OEL based on systemic toxicity rather than odor or irritation as is the case for methylene chloride and most of the chlorinated solvents.

Model III. Chemosensory Model III represents chemicals that are potent odorants, but weak irritants such as hydrogen sulfide (Fig. 1) (Mackie *et al.*, 1998). In these cases, the chemical has an irritation threshold more than one order of magnitude higher than the odor threshold. In other words, there is an even larger range of concentrations at which the chemical odor may be detected but no irritating symptoms occur.

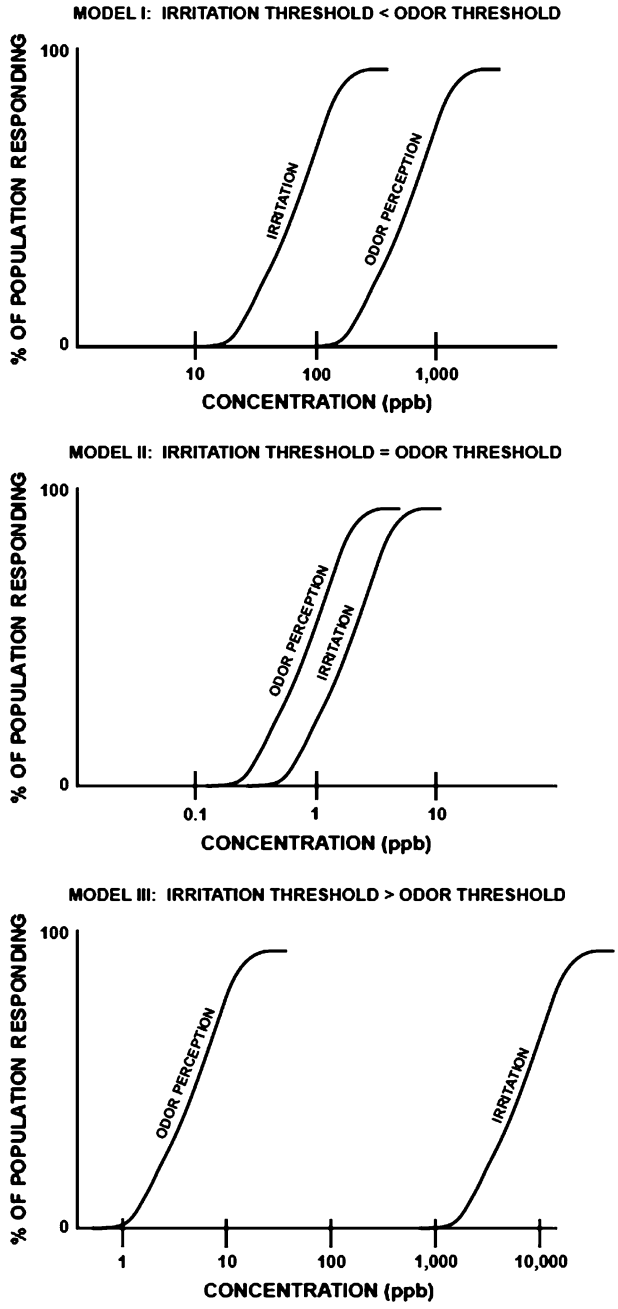

Fig. 1. Chemosensory models reproduced from Shusterman (2001). Model I represents potent chemicals that may cause irritation at levels below which their odor can be detected. Model II represents chemicals that have an odor threshold below the irritation threshold. Model III describes odorous chemicals that have detectable odors at concentration levels several orders of magnitude below the levels at which they are irritants.

METHODS: PROPOSED APPROACH TO SETTING OELS

Figure 2 depicts a simplified flowchart methodology for setting OELs based on the chemosensory models described above. In addition to odor and irritation thresholds, perception of odor, severity of irritation and risk perception are considered.

Model I chemicals

Setting OELs for Model I chemicals will be dependent on the severity of the adverse effects and at what concentration they occur (Fig. 2). If the effects are severe, or even life threatening at low concentrations, exposure to even the lowest concentration that is irritating should not be tolerated, and an OEL should

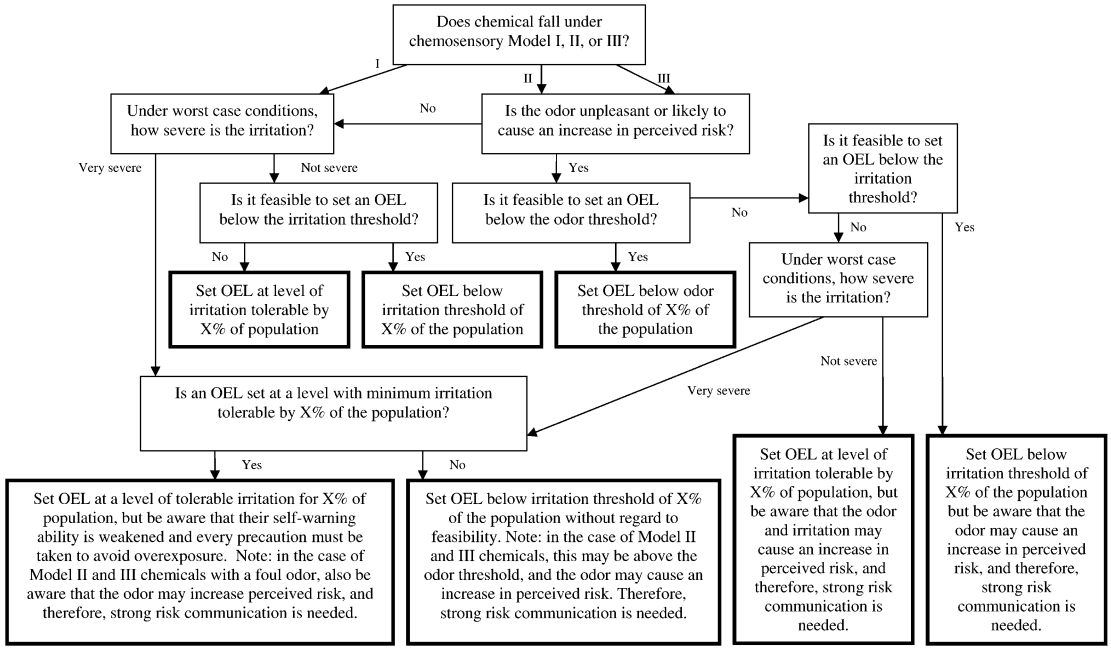

Fig. 2. Simplified flowchart for setting OELs for odors or irritants based on chemosensory model.

be set below the irritation threshold regardless of concern over technological or economic feasibility. However, if at a low concentration, it is known that irritation does not progress to toxicity or pathology, an OEL may be set at a level of irritation tolerable by a certain percentage of the population.

If an OEL is set based on the fact that a low level of irritation is acceptable in a workplace, employers and their health professionals should be aware that for certain chemicals, workers may adapt to this level of irritation. Sometimes, adaptation to low levels of irritation will not put the worker at harm while for some chemicals this is a genuine hazard. For example, with repeated exposure, their body's natural warning signs no longer respond as well and this can put them at some degree of risk from overexposure.

In the case of Model I chemicals that do not cause severe irritation (i.e. watery eyes or slightly scratchy throat) the OEL should be set at a level of irritation tolerable by the vast majority of the workforce if it is not feasible to set the OEL below the irritation threshold, but the consequences of adaptation need to be considered.

Model II chemicals

Setting an OEL for a Model II chemical depends not only on the severity of irritation and how the irritation changes with concentration but also on the properties of the odor associated with the chemical (Fig. 2). For example, if the odor of the chemical is pleasant or does not cause a perceived risk or worry, setting the OEL for the chemical will be similar to that of a Model I chemical without regard to the odor threshold. However, if the chemical has a foul odor or increases risk perception by the means discussed in the next section and it is not feasible to set the OEL below the odor threshold, setting an appropriate OEL is a greater challenge. Not only will severity of the irritation have to be assessed as with Model I chemicals but also effective risk communication will have to be implemented in the workplace.

Setting the OEL at a level above the odor threshold may cause the workforce to feel uncomfortable or sense some degree of risk of an adverse health effect. Normally, this is not acceptable; however, for some chemicals it is necessary. In these cases, an effective employee education program regarding the properties of the chemical needs to be implemented (e.g. risk communication) so that the likelihood of promoting a psychological, rather than physiological, response to the agent is minimized. These are sometimes called conditioned responses as discussed below.

Although setting an OEL at a concentration above the odor threshold but below the irritation threshold may seem practical, a potential problem of this approach is that of unconditioned and conditioned responses (Siegel, 1999; Shusterman, 2001). For example, Shusterman (2001) reported a case where an electronics worker was accidentally overexposed to phosphine gas on the job. She suffered severe irritation and her unconditioned psychological response was to panic. Although she was physically healthy after the incident, she eventually had to quit her job because simply smelling phosphine gas was enough to trigger symptoms. She had developed a conditioned response to the odor of phosphine gas and could

not tolerate even low levels of exposure (Shusterman, 2001). Conditioned responses are also reported to occur in chemotherapy patients as they often develop nausea before treatment even begins (Siegel, 1999). The only way to avoid the development of conditioned responses is to take every precaution possible to ensure no workers are ever overexposed to the irritant.

Another issue that should be addressed in setting OELs for Model II chemicals is odor adaptation. Odor often serves as a warning signal to notify the worker of the chemical's presence. If an OEL is set at a level above which workers are able to detect odor, some workers may adapt to that odor such that they no longer recognize the chemical's presence, although this may not be true for all chemicals (Schwartz *et al.*, 1989; Walker *et al.*, 2003). Adaptation is often seen as a positive trait because it increases the worker's comfort in the workplace. However, adaptation should be considered an adverse effect in situations where a chemical is a severe irritant and the worker no longer relies on odor perception as a warning signal to escape a situation of potential overexposure to the irritant. Therefore, in setting OELs for Model II chemicals, the likelihood of adaptation should be monitored through field studies and the severity of the irritation following adaptation should be understood.

Model III chemicals

The same considerations and precautions taken into account while setting an OEL for a Model II chemical are applicable to Model III chemicals (Fig. 2). If the chemical has a strong odor, the odor may simply annoy workers or it could overwhelm the worker's ability to sense irritation (Seeber *et al.*, 2002; van Thriel *et al.*, 2003). Therefore, if severe irritation does not occur, working in an odorous environment may be tolerated as long as exposure is well controlled and there is little chance that workers could become overexposed.

While setting OELs for Model II and III compounds, it is important to keep in mind that malodorous chemicals may promote a perception of increased risk. This can then lead to increased reporting of irritation symptoms by employees even though the concentration of the chemical is well below the irritation threshold. At that point, employees will often question the reasonableness or acceptability of the OEL (Dalton, 2001).

RESULTS: APPLICATIONS OF THE PROPOSED APPROACH

Three sensory irritants were chosen to evaluate the model presented in Fig. 2: ammonia, methyl mercaptan and phenol.

Ammonia is a colorless gas with a very distinct odor many people associate with cleaning products. According to Shusterman's chemosensory models, ammonia is a Model II chemical with a geometric mean odor threshold value of 17 p.p.m. (recommended value by the American Industrial Hygiene Association) but reported as low as 3.6 p.p.m. in the literature and a reported irritation threshold of 20–25 p.p.m. (American Industrial Hygiene Association, 1989; Mackie *et al.*, 1998; McGinn *et al.*, 2003). Following Fig. 2, one would answer 'yes' to whether or not the odor associated with ammonia is unpleasant since it is a pungent odor and then 'no' to whether it is feasible to set an OEL below the odor threshold or irritation threshold. Because exposure to high concentrations of ammonia can cause lung damage or may even prove fatal, the response to the question in Fig. 2 regarding the severity of irritation would be 'very severe' (Agency for Toxic Substances and Disease Registry, 2004), which leads to the question, 'Is an OEL set at a level with minimum irritation tolerable by X% of the population'. The answer to this question would be 'yes', as the current ACGIH TLV time-weighted average (TWA) for ammonia is 25 p.p.m., which falls very close to the irritation threshold, indicating that it may pose minor irritation to some people, but not all. ACGIH has set a short-term exposure limit for ammonia at 35 p.p.m., which should protect workers from more severe irritation (American Industrial Hygiene Association, 1989) but one can expect that some portion of the worker population exposed for >15–30 minutes will report some level of discomfort.

Methyl mercaptan is a naturally occurring colorless gas with a foul odor similar to rotten cabbage and decaying mattter (Agency for Toxic Substances and Disease Registry, 1992). Methyl mercaptan's low odor threshold of 0.00054 p.p.m. for detection and reported irritation threshold of 1500 p.p.m. make it a chemosensory Model III chemical (American Industrial Hygiene Association, 1989; Young, 2005). According to Fig. 2, the first response regarding an unpleasant odor would be 'yes' and because the odor threshold is so low, it would not be feasible to set an OEL below the odor threshold. However, because the irritation threshold for methyl mercaptan is so high, it is possible to set an OEL below the irritation threshold. In fact, the ACGIH TLV TWA for methyl mercaptan is 0.5 p.p.m. (1000-fold above the detection level).

Phenol is a liquid with a sweet odor that is mainly used in the production of phenolic resins and synthetic fibers but also has many other industrial and consumer uses (Agency for Toxic Substances and Disease Registry, 1998). It has a recommended odor threshold value for detection of 0.06 p.p.m. and a reported irritation threshold of 5 p.p.m., making it also a Model III chemical (American Industrial Hygiene Association, 1989; Mackie *et al.*, 1998; McGinn *et al.*, 2003). The phenol odor, although it can be

sickly sweet at high concentrations, is not as unpleasant as ammonia or methyl mercaptan and, therefore, one could answer 'no' to the first question in Fig. 2. The dose–response curve for severity of irritation in humans from inhalation has not been well documented, but it is known that severe lung irritation and even death has occurred in animals exposed to phenol via inhalation so one would respond 'very severe' to the question regarding severity of irritation (Agency for Toxic Substances and Disease Registry, 1998). This leads us to the final question as to whether or not an OEL with minimum irritation will be tolerable by a certain percentage of the population and the answer would be 'yes' since the ACGIH TLV TWA is set at the reported irritation threshold of 5 p.p.m. (American Industrial Hygiene Association, 1989).

These three sensory irritants demonstrate the utility of the simplified model for setting OELs as presented in Fig. 2. In each case, the OEL set by ACGIH matched the recommendation provided in the figure. Therefore, we believe that it is a useful tool for evaluating chemicals for which OELs have not yet been set or that are being reevaluated. Alas, the approach described in Fig. 2 does not address the issue of risk perception nor the percentage of the population to be protected against the undesirable effects of irritants.

Risk perception

Risk perception plays a key role in each individual's ability to tolerate a workplace where a sensory irritant is present. Workers who believe they may be at an increased health risk may tend to report symptoms of adverse health (when none objectively exist) as opposed to those who feel they are not at risk. In a study by Shusterman *et al.* (1991) modeling symptom prevalence of people residing near hazardous waste sites, odor perception and environmental worry exhibited positive interaction (Shusterman *et al.*, 1991). Although this model was developed to address environmental odor concerns, it could be easily transferred to the workplace setting. For example, this could potentially occur if an OEL was set above the odor threshold for a malodorous Model II or III chemical. Decreased employee morale in addition to increased symptom reporting may result if there is a perceived increase in risk from exposure to odorous or irritating chemicals.

In addition to perceived risk, personal expectations of and prior experience with an odor or irritant may affect the ability of a worker to adapt to the exposure (Dalton, 1996; Dalton *et al.*, 1997b; Dalton, 1999). For instance, in a study by Dalton *et al.* (1997b), subjects adapted to odors more easily if they had a positive impression of the odor (i.e. the odor was good for them or smelled pleasant) than if they believed the odor was harmful. Those subjects who had a negative impression of the odor reported higher odor intensities, irritation and significantly more adverse health effects than those with the positive impression. It is interesting to note that both the subject groups were exposed to the same concentration of the same odor but were told different stories about the nature of the odor by investigators (Dalton *et al.*, 1997b). Therefore, if a Model II or III chemical in a workplace has a pleasant odor or workers have a positive belief about the odor, an OEL set above the odor threshold would be better tolerated than a malodorous compound.

Where tolerance is merely a matter of preference and not health, it may be unreasonable to expect an OEL to be set below both the odor and irritation threshold to accommodate the pickiest of the population. In these instances, strong risk communication with the workforce is necessary. The workforce should know that they are not at an increased health risk, despite what they may believe. They should also be made aware of each and every odor or irritant they may be exposed to on the job before they accept employment.

Populations to be protected

In setting an OEL, no matter what chemosensory model fits the chemical or what the population believes about the chemical based on its odor or potential risk, the issue of what percentage of the working population to protect needs to be considered. This question has not been directly addressed by the ACGIH TLV committee in the 60 years they have been setting OELs. Their goal has been to 'protect nearly all workers' without specifically stating the percentage of the exposed population that they hope to protect. Obviously, the goal of all OELs is to insure that the health of all employees be protected. However, each OEL-setting organization seems to interpret this charge in a different manner. For instance, subjecting workers to malodors without health consequence is keeping them healthy, but if an OEL is set at a level that may cause slight irritation, organizations may disagree as to whether or not such symptoms as watery eyes falls in the category of healthy or unhealthy. The definition of healthy and what constitutes a safe level is currently unresolved for those chemicals that are odorous or irritating.

Most OELs set in the US by the Occupational Safety and Health Administration (OSHA) and ACGIH strive to protect all workers from chronic irritation and acute toxic effects, but are set above the odor threshold, allowing odor detection. Some organizations may set limits that protect only 60% of the workforce from reversible adverse effects that do not produce an objective pathologic response. Yet, there are other organizations that may attempt to

Table 1. Selected OELs for substances with irritation potency

Substance	ACGIH TLV[a] (p.p.m.)	OSHA PEL[a] (p.p.m.)	German MAK[b] (p.p.m.)
Acrolein	0.1 (ceiling)	0.1	—
Allyl alcohol	0.5	2	—
Chlorine	0.5	1 (ceiling)	0.5
Chloropicrin	0.1	0.1	0.1
Chrotonaldehyde	0.3 (ceiling)	2	—
Formaldehyde	0.3 (ceiling)	0.75	0.3
Methyl isocyanate	0.02	0.02	0.01
Nicotine	0.5 (mg/m^3)	0.5 (mg/m^3)	—
Sulfur dioxide	2	5	0.5
2,4-Toluene diisocyanate	0.005	0.02 (ceiling)	—

All values are 8-h TWAs unless noted otherwise. PEL, Permissible Exposure Limit; MAK, *Maximale Arbeitsplatz Konzentrationen*.
[a]2006 values.
[b]2004 values.

completely minimize worker detection of odors and irritants. Table 1 lists selected ACGIH TLVs, OSHA Permissible Exposure Limits and German *Maximale Arbeitsplatz Konzentrationen* values. Although it is difficult to identify a specific percentage of the population that should be protected, for potent irritants with the potential to cause irreversible damage, perhaps protecting >90% of the population would be appropriate. This would depend, however, on the societal expectations of the nation where the OEL has been set. Figure 2 outlines a simplified recommended method of setting OELs, but it would be beneficial and productive if all organizations could come to agreement as to what end points to protect against and what percentage of the workforce should be protected.

Using human data to set an OEL

In order to set OELs based on the proposed method (Fig. 2), the odor and irritation thresholds of the chemical of interest need to be defined and the degree of irritation at varying concentrations need to be understood. Odor thresholds for Model II and III chemicals can be safely measured with human volunteers by subjecting them to increasing concentrations of the chemical until it is detected (Doty *et al.*, 2003a; Walker *et al.*, 2003; Wysocki *et al.*, 2003; Doty *et al.*, 2004).

There are both subjective and objective methods for determining the irritation one senses as a result of exposure to an irritant. Subjective means, such as in a questionnaire rating the level of irritation based on a scale, is subject to bias from risk perception and preconceived impressions of the chemical as previously discussed. In a recent article by Arts *et al.* (2006) following a conference on the subject, it was concluded that subjective methods for measuring irritation thresholds may be an unsuitable method upon which to base the establishment of OELs.

Many scientists have studied objective ways to measure irritation to avoid such bias. The following methods are reported in the literature to have been used to objectively measure irritation: respiration volumes and rates, eye blink rates, tear film breakage, epithelium damage, foam formation in the canthus and nasal cross-sectional area and volume (Kjaergaard, 1992; Kjaergaard *et al.*, 1992; Hempel-Jorgensen *et al.*, 1997; Kendal-Reed *et al.*, 1998; Kendal-Reed, 2001; Kendal-Reed *et al.*, 2001; Walker *et al.*, 2001a,b, 2003; Doty *et al.*, 2004; Kjaergaard *et al.*, 2004; Suarez *et al.*, 2005). For example, Walker *et al.* (2001a) compared the responses of normosmic (able to sense odors) and anosmic (lacking olfactory nerve input) individuals to propionic acid. They found that the greater the concentration the population was exposed to, the greater the percentage in decreased volume of inspired air and the quicker this decrease occurred after the initial exposure. The anosmic population only experienced a decline in inspired volume at the highest exposure concentration (Walker *et al.*, 2001a). Furthermore, in another study looking at entire body exposure to environmental tobacco smoke, Walker *et al.* (2001b) found that respiration changes as well as eye blinking rates are useful indicators of irritation. These methods of measuring odor perception and sensory irritation could be used to determine odor and irritation thresholds for airborne chemicals often found in the workplace. When human odor and irritation threshold data on chemicals are available, OELs can be set based on these thresholds in accordance with Fig. 2.

Using animal data to set an OEL

When human data are not available, as is the case with many of the new chemicals in the workplace, the results of relatively quick and inexpensive animal studies may be used to set preliminary OELs (Alarie,

1998; Alarie *et al.*, 2001). For example, Schaper (1993) published a database of RD_{50} values for 154 chemicals of which 89 had published ACGIH TLVs. An RD_{50} is defined as the concentration at which a 50% decrease in respiratory rate has been observed in male Swiss-Webster mice or other strains of mice of comparable sensitivity. Schaper found that the TLVs were very close to 3% of the corresponding RD_{50} values (TLV = 0.03 × RD_{50}) (Schaper, 1993). Using this method to set OELs assumes that the human irritation threshold is somewhere between 1% and 10% of the RD_{50}, and setting an OEL at 3% will be sufficiently protective. Furthermore, Kupczewska-Dobecka *et al.* (2006) evaluated the Polish MAC values of 17 irritants set based on the RD_{50}. They found that the mean value of the ratio between the MAC value and the RD_{50} for these chemicals was equal to 0.03 and concluded that using 3% of the RD_{50} value was a suitable quick method for determining acceptable exposure levels (Kupczewska-Dobecka *et al.*, 2006).

Using chemical properties to set an OEL

When neither human nor animal studies on the odorant or irritant of interest are available, there are still other methods for estimating OELs based on the chemical properties of the substance. For instance, if the chemical is an organic acid or base, Leung and Paustenbach (1988) found that preliminary OELs may be developed based on the chemical's equilibrium dissociation constant (pK_a). To set OELs for organic acids, Leung and Paustenbach came up with the model: log OEL ($\mu mol/m^3$) = 0.43 pK_a + 0.53. The OEL-setting model for organic bases is as follows: OEL ($\mu mol/m^3$ = −200 pK_a + 2453 (Leung and Paustenbach, 1988).

More recently, sophisticated methods of predicting irritation potency (log RD_{50}) have been developed based on physiochemical properties, chemical reactivity descriptors and quantitative structure–activity relationship (QSAR) models (Alarie *et al.*, 1995, 2001; Luan *et al.*, 2006; Schultz *et al.*, 2006). For example, Alarie *et al.* (1995) found that vapor pressure and the Otswald solubility coefficient were the best estimators of log RD_{50} values. Furthermore, QSAR models have successfully been developed for many reactive and nonreactive chemicals to predict irritation potency as a method of chemical screening (Luan *et al.*, 2006; Schultz *et al.*, 2006) These represent alternative means of setting an OEL when human and animal data are unavailable.

DISCUSSION

A simplified method for setting OELs for sensory irritants is presented. Although this approach may not be as straightforward for all chemicals as it was for ammonia, methyl mercaptan and phenol simply because data on odor and irritation thresholds and health effects may not be available for all compounds, the approach is feasible for those chemicals for which this information is known. The strengths of this model lie in its flexibility such that it can easily be adopted by any OEL-setting organization. It can be tailored to the organization's goal of what toxicological end point (e.g. odor perception, transient eye irritation, etc.) is important to protect against and what percentage of the workforce the OEL intends to protect. However, this may also be the greatest weakness of the method. Determining the toxicological end point of interest and the percentage of the workforce to be protected is subjective and controversial. The proposed method would be greatly strengthened if OEL-setting organizations would come to agreement in these matters.

Perhaps the biggest challenge in setting an OEL for a sensory irritant, and therefore, the greatest inherent weakness in the proposed method is interindividual variability in both tolerance and odor and irritation thresholds. There is a great amount of variability in what people consider tolerable and therefore, an OEL will never satisfy everyone. Some people may not mind a mild odor, while others may find the same odor terribly offensive and would not even consider working in such conditions. Likewise, there are workers who do not mind slightly watery eyes or may find it easy to adapt to a slight irritant while others will not tolerate it. Both risk perception and odor/irritation thresholds help determine what a person will tolerate.

Interindividual variability with respect to when odors and irritants are detected is another major issue to take into consideration while setting OELs for sensory irritants. Some people may smell a chemical at a concentration where a majority of the population cannot detect it. Or, there may be a few people who do not sense irritation when exposed to an irritant at the same concentration that the majority of the population finds intolerable. A wide range (up to 1000-fold differences) of individual variability in odor and irritation threshold ranges have been observed in controlled human studies (Dalton *et al.*, 1997a; Wysocki *et al.*, 1997). However, the extent of this variability is unknown and appears to be nonrandom. For example, Shusterman *et al.* (2003) found that irritant sensitivity variability can be predicted by age, gender and allergic rhinitis status.

Studies in the literature have suggested that certain medications such as antihypertensive and antihyperlipidemic drugs; disorders such as schizophrenia, multiple sclerosis, Huntington's disease, Alzheimer's disease, Parkinson's disease, sinus or nasal disorders and seasonal affective disorder; depression; ingestion of ethanol; trauma; smoking; gender and even age may impact a persons ability to detect odors and/or irritation (Doty, 1979; Doty *et al.*, 1984; Doty,

1989; Frye *et al.*, 1990; Deems *et al.*, 1991; Doty *et al.*, 1991, 1995; Bylsma *et al.*, 1997; Doty *et al.*, 1997; Moberg *et al.*, 1997a,b; Doty *et al.*, 1998; Mesholam *et al.*, 1998; Doty *et al.*, 1999; Postolache *et al.*, 1999; Yousem *et al.*, 1999a,b; Postolache *et al.*, 2002; Doty *et al.*, 2003b; Doty and Bromley, 2004; Patel *et al.*, 2004). Even attempting to control for possible health conditions that may cause dysosmia, or a impairment in the sense of smell, Walker *et al.* (2003) still found odor thresholds to vary by >20-fold. Furthermore, in studying anosmic and normosmic individuals, Kendal-Reed *et al.* (2001) have found that a great deal of individual variability could be the result of the way the olfactory and trigeminal messages combine in the brain. This is a challenging issue, as it means that those responsible for setting OELs need to have some level of experience in interacting with persons who routinely work with the chemical and understand the range of airborne concentrations to which they are exposed. Then, with this knowledge, a decision regarding the percentage of the population to protect needs to made.

Even if determining a plausible range of odor and irritation thresholds in humans is achievable, the challenge of setting an OEL that satisfies people in the working population who are hypersensitive to odors or irritants still remains. Hypersensitive individuals such as those with multiple chemical sensitivity (MCS) or sick building syndrome (SBS) often report the same symptoms associated with sensory and pulmonary irritation, just at much lower levels than the normal population. Gibson *et al.* (2003) reported that people with MCS may spend up to one-third of their incomes on health care. Entire communities are being formed for those people sensitive to chemicals. This has encouraged many scientists to study hypersensitive populations in hopes of finding a cause (Doty *et al.*, 1988; Doty, 1994; Anderson and Anderson, 1999; Siegel, 1999; Haumann *et al.*, 2002; van Thriel *et al.*, 2002; Wiesmuller *et al.*, 2002; Haumann *et al.*, 2003).

Using mice, Anderson and Anderson (1999) studied sensory and pulmonary irritation from everyday chemicals and found that the mice became more sensitive to some chemicals over multiple exposures, leading them to postulate that this type of sensitization may be what occurs in MCS or SBS individuals. Siegel (1999) suggests that many MCS symptoms may be due to conditioned responses learned from previous overexposure. Doty *et al.* (1988) and Doty (1994) found that MCS may be associated with nasal airflow resistance, respiration rate, heart rate and possible depression, but not with more sensitive odor detection thresholds (Doty *et al.*, 1988; Doty, 1994). Researching SBS, several studies have assessed the adverse health effects associated with exposure to nonindustrial office dust and have found slight irritating effects after exposure in healthy individuals (Pan *et al.*, 2000; Molhave *et al.*, 2002, 2004). Pejtersen *et al.* (2001) found that renovating a building by replacing the ventilation system and carpeted interior significantly reduced symptom reporting in a population complaining of severe indoor air pollution. It has been reported that improvements in air quality could save between $12 and $125 billion in worker productivity alone (Fisk and Rosenfeld, 1997). Despite the cause or reasoning behind these disorders, protecting hypersensitive individuals in the workplace is a real challenge. Unless we are able to develop feasible means of controlling the source of these chemicals, setting OELs to meet the needs of this hypersensitive population may not be possible.

In general, risk communication in the workplace is key to a content, productive workforce, regardless of whether or not there is a real or perceived health risk due to irritant exposure. Proper communication has the power to dispel any myths the worker might have regarding the odor or irritant. Dalton (2001) reported that workers exposed to a solvent odor who were told positive or neutral cues about the odor were much less likely to report irritation or health symptoms than those given negative cues. The more a worker knows about the source, the potential health effects (or lack of), what concentrations health effects may occur and what they can do to adequately protect themselves, the more comfortable they will feel working in an environment exposed to odors and irritants whether considered harmful or not. Working in an odorous or irritating environment is not ideal, so any action on the part of the employer to make the job more comfortable for the workers not only will be greatly appreciated but will also help to increase workplace morale and productivity.

CONCLUSIONS

The occupational health community is currently challenged with the need to set OELs for the numerous chemicals that are being introduced to the workplace for the first time, and for which we do not know the extent of their ability to cause adverse health effects in those occupationally exposed. This need is even more evident today as irritants such as diacetyl are making the news, implicated in cases of rare and disabling disease (Kanwal *et al.*, 2006). This paper presents a simplified method of suggesting how to set OELs based on chemosensory models and also discusses the issues that must be addressed in setting OELs such as risk perception and individual variability. Using animal data and chemical property data in the absence of available human data is also discussed. However, to use the methods presented in this paper, OEL-setting organizations need to identify what level of irritation or toxicological end point (if any) is acceptable in the workplace and what

percentage of the population the OEL should aim to protect. To date, there has not been an occupational guideline addressing these needs. After these issues have been addressed and perhaps agreed upon, the methods addressed in this paper may be built upon to develop an even better, more detailed, method for establishing OELs for sensory irritants.

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