TLV® ADJUSTMENTS FOR SENSITIZATION

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ABSTRACT

The possibilities of having a sensitized worker in the workplace are significant given that 40-45 % of the population can become sensitized. At the same time, TLVs® are based on the reaction of "normal healthy workers" to workplace chemicals. Sensitized workers, such as those with allergies or asthma do not fall into the category of "normal healthy workers" and the TLVs may not protect them. If the chemical has a sensitization notation (DSEN or RSEN) it is identified as having the potential to cause sensitization, and the TLV may be based on other effects but may be low enough not to cause sensitization. When the basis for the TLV includes sensitization, the TLV should be low enough to prevent sensitization, but neither will protect workers who are already sensitized. It is the duty of the occupational hygienist to identify potentially hazardous situations and ensure that sensitized or potentially sensitized workers have their exposures maintained as low as reasonably practicable, and not just to meet the minimum requirements of the TLV. This presentation provides some guidance in the identification and protection of susceptible workers.

INTRODUCTION

The TLVs® "represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse effects."[(1)] The TLVs are written as guidelines to be interpreted by occupational hygienists relative to the workplace and the workers within it. Because of individual differences, heredity and environment, some workers will react to a chemical at much lower exposure levels than expected even when these individual differences are taken into consideration. These workers may have become sensitized to the presence of the chemical through previous exposures. As shown in Table 1, these sensitized workers can react to sensitizing materials at much lower levels than will the "normal" worker.

Table 1: Comparison of TLVs for selected sensitizers and the exposure levels that may cause an effect in sensitized workers.

Sensitizing Material	TLV	Reaction Level for Sensitized Workers
TDI and HDI[(2)]	0.005 ppm	<0.00001 ppm
Ethylenediamine[(3)]	10 ppm	0.3 ppm
MDI*	0.005 ppm	0.0014 ppm

*From MSDS

Our main interest here is not with primary irritant dermatitis such as by acids, alkalis, detergents, or solvents where cell damage occurs. Our interest is with allergic contact dermatitis which affects only specifically sensitized individuals where the skin has been sensitized by previous exposure.

Sensitization occurs when a material capable of producing an antigen **–** antibody complex gets past the body's defense by injection, inhalation, ingestion, or absorption and produces an allergic **–** type reaction. For most people allergens are normally harmless substances, such as pollen, food, and house dust mites. In susceptible individuals the allergen provokes an exaggerated immune response to materials that are inhaled, ingested or that come in contact with skin.

This response can explain why a small number of workers can have adverse reactions to workplace environments when all other workers show no reaction. The simple comparison of exposure limits to air samples will lead one to conclude that there is no workplace problem but a worker problem. This can be wrong; the professional must look deeper to find the truth of the situation.

The potential for having a sensitized worker in the workplace is not trivial. About 15 % of the white population in the United States is easily sensitized to many things. Another 25 – 30 % are less easily sensitized, while the majority, 55 – 60 % does not appear to become sensitized[(4)]. What this means is that there is a real possibility that any workplace can already employ sensitized or sensitizable workers.

WHAT ARE SENSITIZERS?

Health Canada defines sensitizers or allergens as materials that can cause severe skin and/or respiratory responses in a sensitized worker after exposure to a very small amount of the material. Sensitization develops over time. When a worker is first exposed to a sensitizer, there may be no obvious reaction. However, future exposures can lead to increasingly severe reactions in sensitized workers. Not all exposed workers will react to sensitizing materials. As mentioned above, some workers will never become sensitized.

Allergens are usually large molecules (high-molecular-weight (HMW) substances) such as proteins from plants, bacteria, or animal origin. However, allergens can also be small reactive molecules (low-molecular-weight (LMW) substances) such as isocyanates, acid anhydrides, platinum, nickel, or other metallic salts, persulfates, and reactive dyes, any substance that, after absorption, attach themselves to proteins within the host's body creating a new protein that is foreign to the host. Examples of different sensitizers/allergens are shown in Table 2 with examples of occupations where they can be found.

Table 1: **Some occupations that may lead to sensitization, and the related sensitizing agents[5, 6, 7].**

Occupation	Agent
Animal breeding /Handling	Animal dander, urine, bird products, crustaceans, egg protein
Baking	Flour, insects mite debris
Hairdresser	Sodium/ potassium persulfate
Coffee processor	Green coffee beans
Detergent enzyme worker	Proteases
Farm worker	Animal antigens, vegetable dusts, moldy hay, herbicides, insecticides, antibiotics
Food additive worker	Tartrazine
Grain handler	Grain dust, insect debris
Laboratory worker	Animal antigens
Leather worker	Formalin, chromium salts,
Lumber & woodworking	Wood dusts
Milling	Flour, insects, mite debris
Paper product manufacture	Natural glues
Pharmaceutical worker	Penicillin, ampicillin, tetracycline
Plastics industry	Diisocyanates, anhydrides
Platinum refiner	Platinum salts
Plating, welding	Nickel, chromium, platinum
Printer	Vegetable gums
Veterinarian	Animal antigens
Vegetable oil production	Flaxseed, cottonseed, castor bean

The most common occupational reaction to a sensitizer is contact dermatitis, with allergic rhinitis and asthma being less common. Table 3 shows routes of entry, conditions that can affect the reaction, and examples of sensitizers/allergens. Episodes occur after exposure; however, the symptoms may occur several hours after exposure, and they usually disappear during weekends. The symptoms can resemble a cold or mild hay fever and include difficulty in breathing, chest tightness, wheezing and coughing, fever, and general feelings of bodily discomfort.

Table 3: Routes of entry for sensitizers, some of the conditions that affect that reaction, and Examples of sensitizers.

Route of Entry	Conditions	Examples
Skin	Wet skin, local effect	Flour, detergents, vegetables, nickel, chrome, rubber, azo dyes,

		formaldehyde
Digestive tract	The effect is reduced through the cooking and digestive processes An inflammation of the mucosa allows more of the allergen to pass Affects organs elsewhere in the body	Raw foods
Respiratory tract	Infections increase effect Increased exposure increases effect Affects organs elsewhere in the body	pollens, animal hair, dust, isocyanates, metal salts, plant products, microbial agents, organic dusts
Injection		Insect stings

Once a person has become sensitized to one material, they may also react to other similar materials as shown in Table 4.

Table 4: **Examples of cross-sensitivity as reported in material safety data sheets**

Group Showing Cross-Sensitivity	Examples
Isocyanates	TDI, HDI, MDI, PMPPI
Aliphatic polyamines	Ethylenediamine, triethylenetetramine, 2,2'-diaminodiethyl amine
Aromatic diols	Resorcinol, resorcinol monoacitate, hexylresorcinol, hydroquinone, catechol, phenol, pyrogallol, hydroxyhydroqinone, orcinol
Chemical/physical (light)	Chromium salts
Azo dyes	Derivatives of paraphenylenediamine (PPD)
Metal salts	Chromium, nickel, cadmium

THE ROLE OF HEREDITY

Heredity helps determine the likelihood that an individual will develop an allergic reaction to materials in their environment[5, 7, 8]. Heredity does not determine what they will become sensitive to, but rather whether they will become sensitized at all.

About 10-15 % of the population in the United States is easily sensitized to many things. Another 25-30 % are less easily sensitized, while the majority, 55-60% do not appear to become sensitized[2]. 15-30 % of the European countries are readily sensitized and 9-20 % in Turkey[4, 9].

A family history of allergies is strongly associated with the easily sensitized group, and

decreases with the other two groups. If both parents were allergic, 60-80 % percent of the offspring were allergic; the rate decreases to 30-50 % percent if one parent was allergic, and 6-10 % percent if neither were allergic[10, 11]. Thus, knowledge of a positive family history of allergies would be useful in determining if sensitization is, or could be a problem in the workplace. Unfortunately, this may be considered confidential medical information and therefore may not be available to the occupational hygienist.

THE ROLE OF THE ENVIRONMENT

Just as heredity determines the probability that a worker will become sensitized, environmental conditions determine to what the worker will become sensitized. These environmental conditions include both the pattern of exposures as well as the chemicals in the workplace.

A non-workplace exposure that seems to predispose workers to allergic sensitization is smoking. Perhaps this is due to the injury to the bronchial epithelium which enhances permeability of the bronchial epithelium[5].

The worker is normally repeatedly exposed to a sensitizing material before sensitization occurs. In most cases, there is a latent period of weeks or years between first exposure to the occupational allergen and the onset of symptoms. The likelihood of becoming sensitized to a material is dose dependant. Intermittent high-level exposures have been reported as being important in the development of asthma. Workers exposed more frequently to spills or who maintain equipment report more asthma like symptoms. But once the worker is exposed, very low levels of the substance can provoke an asthmatic reaction.

Exposure to most allergens is not a problem unless you have been exposed to it previously and are sensitized to it. As mentioned, it may take months or years of repeated exposure before full-blown allergic symptoms develop.

However, some materials can cause sensitization after a single high exposure and a short latent period (as little as four days). Examples of this include plant toxins as found in poison ivy, poison oak, cashew nut, oils from mango fruit, lacquers from the Japanese lacquer tree and Cedar wood.

ALLERGIC CONTACT DERMATITIS

Although the prevalence of contact dermatitis due to environmental agents is unknown, it is felt to be a major public health concern. In 1975, about 45 percent of occupational diseases were work-related skin conditions, most of which were contact dermatitis. In 2011 the incidence of occupational skin diseases in western industrial countries was

estimated at 0.5 – 1.9 cases/1,000/year, but it is assumed that the prevalence of occupational contact dermatitis was underestimated by a factor of 30–50 %[12].

It should be noted that except from the worker's medical history, there are usually no distinguishing features between occupational and nonoccupational contact dermatitis. A history of allergic episodes occurring after exposure, ending when exposure stops, and recurring on re-exposure, suggests an occupational dermatitis.

There is a minimum interval between first contact and the development of sensitization of between 6 and 25 days; sometimes it does not occur until after months or years of repeated exposures. After sensitization, further contact will usually cause a reaction within 1 to 2 days and sometimes within a few hours.

A delayed allergic reaction is responsible for 20 % of all cases of contact dermatitis. This type of reaction requires active participation of the immune system and very low concentrations of the causative agent. Many allergens are also irritants, but the threshold for irritation is usually much higher than that required for sensitization[13].

The usual sites for occupationally related contact dermatitis are the back of the hands, the inner wrists, and forearms, but it can occur anywhere on the skin. When the forehead, eyelids, ears, face, or neck is involved, dusts, fumes, or vapors should be suspected. Generalized contact dermatitis comes from a massive exposure such as wearing contaminated clothing or a sensitization from preexisting dermatitis.

Reactions may be exacerbated when the skin has been damaged by chapping, friction, or other trauma so the rate of the absorption of the allergen is increased. These reactions are decreased when there are immunological deficiencies, such as those caused by lymphomas, metastatic diseases, malnutrition, immunosuppressant drugs, or glucocorticosteroids.

Table 5: Common skin allergens [13].

Metals	**Rubber additives**	**Dyes**
Nickel Chrome Cobalt Mercury	Mercaptobenzothiazole Thiurams Carbamates Thioureas	Paraphenylene diamine Photographic colour developers Disperse textile dyes
Plants	**Plastics**	**Biocides**
Urushiol (*Toxicodendron*) Sesquiterpene lactones (*Compositae*) Primin (*Primula obconica*) Tulipalin A (*Tulipa*, *Alstroemeria*)	Epoxy monomer Acrylic monomer Phenolic resins Amine catalysts	Formaldehyde Kathon CG Thimerosal

Once a worker has become sensitized to one material such as poison ivy, they can become sensitized to similar materials such as poison oak, and can have a reaction to the first exposure without the latent period.

Sex-related differences to allergic contact dermatitis usually represent differences in occupational or environmental exposures to various allergens rather than actual gender differences. Other genetic factors, however, do play a role; for example, a worker with a light-complexion or redheaded workers are less resistant to skin damage when working with irritant dusts and solvents.

PHOTOALLERGIC CONTACT DERMATITIS

Photosensitivity occurs when there is a chemical substance on the skin surface that can be activated by ultraviolet radiation in the 290 – 400 nm wavelengths. These are frequently chemicals with aromatic rings. If the material cannot absorb UV radiation, a reaction is unlikely.

Phototoxic reactions
Phototoxic reactions are the most common of the photosensitivity reactions. They can be produced in all workers when there is sufficient light and photosensitizer present. There is an immediate burning, stinging, or smarting of the skin shortly after exposure to the sun. The appearance is that of an extreme sunburn. Workers exposed to coal tar products are susceptible to this reaction. Factors affecting phototoxicity include:

- Skin pigmentation
- Skin thickness
- The dose received of the photosensitizing chemical
- The dose of the UV light
- Skin covering (clothing, hair)

Photoallergic reactions
Photoallergic contact dermatitis is slightly different and has a much lower incidence[(14)]. Since the means of action is different than phototoxicity, photoallergenic reactions do not occur on the first exposure to an agent.

The light alters the chemical structure of either a normal metabolite or a foreign substance such as a drug which then becomes a true allergen. In photoallergenic contact dermatitis, the epidermal changes resemble those of a typical allergic contact dermatitis and are limited to sun-exposed skin where the allergen has been in contact. It becomes evident immediately as a type of skin rash notable for dark red, raised, itchy bumps (hives). It can also appear as a delayed hypersensitivity reaction 24 to 48 hours later.

The following list contains examples of chemicals with phototoxic and photoallergenic properties. It should be noted that ingredients for sunscreens are included in the list. Since sunscreens are a control method, care should be taken in selecting an

appropriate sunscreen.

Coal Tar Products	**Dyes**
Crude coal tar	Acridine
Pitch	Eosin
Creosote	Fluoroscein
	Rhodamine
	Rose bangal
	Methylene blue
Plants	Mustard
Carrots	Parsley
Celery	Parsnip
Bergamot	Rue
Buttercup	Gas plant
Klamath Weed	Angelica
Dill	Goose foot
Figs	Scurfy pea
Lemons	St. John's wort
Limes	
Essential Oils and Fragrances	Rue oil
Angelica root oil	Cedarwood oil
Bergamot oil	Sandalwood oil
Lemon oil	Lavender oil
Lime oil	Musk ambrette
Orange oil (bitter)	6-methyl coumarin
Drugs	Ibuprofin
P-aminobenzoic acid and esters	Nonsteroidal antiinflammatories
Chlorothiazides	Benzophenones
Diphenhydramine	Nalidixic acid
Enoxacin	Quinine
Estrogens	Tetracyclines
Fenofibrate	Sulfonamides
Phenothiazines	Sulfisoxazole
Griseofulvin	Thoridazine
Antimicrobials	Dapsone
Halogenated salicylanilides	Isoniazid
Bithinal	Mupirocin
Hexachlorophene	Pyrazinamide
Flucytosine	Sulfonamide derivatives
Griscofluvin	Chloroquine
Terconazole	Proguanil
Ceftazidime	Pyrmethamine
Miscellaneous	Cyclamates
Sunscreens (PABA, cinnamates, benzophenones)	Optical whiteners
Saccharin	Epoxy resin

OCCUPATIONAL ASTHMA

The US National Heart, Lung, and Blood Institute defined asthma as*'… a chronic inflammatory disorder of the airways…. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment."*

The symptoms of occupational asthma usually improve during weekends and vacations, and become more severe during the weekday. The symptoms must be accompanied by exposure to a material that can cause asthma.

There are two types of occupational asthma: allergic or non-allergic. Here we are addressing allergic occupational asthma, or sensitizer-induced asthma which includes 65-80 % of asthma cases. Occupational asthma is asthma that is caused by exposures to agents in the workplace. As with other allergic type of reactions, individuals at high risk for developing this disease include those with a family history of asthma, previous sensitization to one or more allergens, exposure to tobacco smoke, and, most importantly, employed at high-risk workplace[(7)].

Asthma can develop at any time in life but it has been estimated that about 50–60% of all cases develop in adulthood[(15)]. With adult-onset cases, clear causal relationships can sometimes be established between the disease onset and exposure to agents in the workplace. About 9–15 % of adult-onset asthma cases can be attributed to exposures at work. These can be prevented if exposure to known occupational allergens can be avoided. People with occupational asthma often have to change jobs or careers to relieve their symptoms; hence, work disruption and economic hardship are common consequences of the disease.

Risk factors include tobacco smoking, previous allergic sensitization and a genetic predisposition[(5)]. However, the level of exposure (dose, duration, etc.) to workplace sensitizers and irritants is most important in the development of occupational asthma.

There is evidence that tobacco smoking aggravates work related asthma. There is also some evidence that tobacco smoking contributes to the risk of developing occupational asthma by increasing the likelihood of sensitization to some causal agents. When combined with smoking, exposure to isocyanates, platinum salts, salmon and snow crab increases the risk of occupational asthma compared to exposure alone. But the relationship between smoking and the risk of developing occupational asthma is unclear when the causal agents are laboratory animals, enzymes, or acid anhydrides.

Irritant-Induced Occupational asthma

Irritant-induced occupational asthma should be suspected if the symptoms begin within 24 hours after accidental exposure to a high inhaled concentration of a workplace irritant, whereas sensitizer-induced occupational asthma should be suspected if the symptoms begin during a work shift or is worse at work or in the evenings after work,

and diminishes during weekends or holidays.

Irritant-induced occupational asthma occurs shortly after single or multiple high level exposures to respiratory irritants. Examples of such irritants reported in medical literature are listed below. The Documentation® identifies other respiratory irritants.

Accidental mixtures or reactions of chemicals (*eg*, bleach and ammonia)
Acetic acid
Anhydrous ammonia
Bleaching agents
Burnt paint fumes
Calcium oxide
Chlorine
2-Diethylaminoethanolamine
Diisocyanates
Floor sealant
Glutaraldehyde
High-level irritant dust (*eg*, from the World Trade Center collapse)
Hydrochloric acid
Hydrogen sulfide
Locomotive/diesel exhaust
Phosgene
Phosphoric acid
Sulfuric acid
Silicon
Silo gas
Smoke (from fires)
Smoke (inhaled)
Sodium hydroxide
Spray paint without isocyanates
Sulfur dioxide
Tear gas
Trichlorosilane
Welding fume
Zinc chloride

Work-aggravated asthma

Work-aggravated asthma is different from occupational asthma in that it does not result in new cases of asthma. Persons with work-aggravated asthma have a history of preexisting asthma. They have recurrent asthmatic episodes that are triggered by a nonspecific mechanism such as cold temperatures, excessive exertion, or exposure to

irritant aerosols including dusts, fumes, vapors, and gases. In other words, the worker already has asthma, and workplace exposures trigger the symptoms.

SENSITIZERS AND SHIFTWORK

Allergic responses increase at night with the greatest decrease in FEV_1 (volume that has been exhaled at the end of the first second of forced expiration) occurring after a late-evening exposure to a potential allergen. There is also a greater potential for the symptoms to begin several hours after exposure and may continue for many hours or days. This response is called late asthmatic response (LAR). 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 a non-work related evening exposure[16].

Cutaneous allergy response can also vary significantly depending on the time of day the exposure occurs.

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