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The spectrum of allergic disease in the chemical industry

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Abstract ***Objectives***: To describe the types of allergic responses which can be seen among employees working in the chemical industry. ***Methods***: This is a review of current literature. ***Results***: Although allergic reactions are more frequently attributed to protein exposure, there is increasing evidence that certain chemicals can produce allergic disease for each of the four types of allergic reactions described by Gell and Coombs. Type I hypersensitivity reactions are seen with certain low-molecular-weight chemicals. Type II hypersensitivity reactions, exemplified by Goodpasture's syndrome, have been associated with certain metal exposures. Low-molecular-weight chemicals have been reported to cause type III hypersensitivity reactions such as those seen in hypersensitivity pneumonitis. Finally, the majority of type IV reactions are characterized by allergic contact dermatitis, although some hard metals have produced type IV pulmonary disease. Several predictive tests are now available to screen chemicals for pulmonary and skin sensitizing capability. ***Conclusions***: Chemicals have been implicated in producing a wide variety of hypersensitivity reactions. Screening tests can be of use in managing the risks of these chemicals.

Keywords Allergy · Hypersensitivity · Screening tests · Allergens

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Introduction

Allergic disease initiated by chemicals is becoming better understood, as evidenced by the increasing number of reports in the medical literature of agents capable of inducing allergic asthma as well as allergic dermatitis. Allergic disease is a large economic and disease burden to industry and society. This was recognized by the United States' National Occupational Research Agenda (NORA), which, in 1996 by consensus, established 21 topic areas for research. These topic areas were felt to have the highest likelihood of reducing morbidity and mortality. Two of these areas dealt with allergic disease: (1) allergic and irritant dermatitis, and (2) asthma and chronic obstructive pulmonary disease.

Allergic and irritant dermatitis together account for 12% to 15% of all reported occupational diseases and are likely very under-reported. Estimated total annual cost to US industry is estimated to be $1 billion, just in workday and productivity losses. Most of these diseases are considered to be preventable. About 3,000 chemicals are felt to be capable of inducing allergic contact dermatitis and approximately four times as many chemicals can produce irritant contact dermatitis. Some chemicals can cause both allergic and irritant disease. Nearly all individuals can develop irritant dermatitis from these chemicals but only a minority will develop allergic contact dermatitis, largely because of genetic predisposition. Atopic individuals with dermatitis are more susceptible to irritant damage. Additionally, it is often difficult to distinguish allergic and irritant dermatitis in individuals with chronic dermatitis.

Occupational asthma is the most frequent occupational respiratory disease diagnosis. An estimated 9 million US workers are exposed to known sensitizers or irritants associated with asthma. One of NORA's research agenda items is to develop models for identifying occupational asthmagens prior to workplace introduction.

This article is intended to present a broad overview of allergy in the chemical industry. It is hoped that this discussion will assist medical practitioners to better recognize allergic disease as it arises.

Immunotoxicology

Immunotoxicology is defined as the study of the effects of toxins on the immune mechanism. In this regard, there are three possible recognized types of responses: immunosuppressive, immunostimulatory, and autoimmune. Immunosuppressive responses can be seen with PCBs, heavy metals and certain pesticides. The focus of this discussion will be primarily about immunostimulatory responses, although some examples of autoimmune response will be addressed.

Normally, immunostimulatory responses are termed 'hypersensitivity' or 'allergy'. Hypersensitivity can be thought of as an exaggerated response to a recalled antigen. An estimated 13% of most populations are felt to be 'hypersensitive'. Hypersensitivity problems account for 9% of all medical visits. Most affected individuals have a genetic predisposition to develop allergic diseases.

Classification of immune reactions

Allergic reactions are characterized by a very complex set of interactions involving the body's lymphoid, myeloid, immunoglobulin and complement systems. Cytokines, particularly interleukins, have a major role in effecting these reactions.

Gell and Coombs devised a classification system for these reactions. Table 1 depicts the four types of immune responses as characterized by the types of cells, immunoglobulin and complement involved.

The first three types are commonly referred to as the humoral system. Type I is also referred to as 'IgE-mediated'. In this reaction, B lymphocytes are initially presented antigen. In conjunction with T-helper cells, these B cells are stimulated to produce antigen-specific IgE. This phase is known as 'induction' The IgE is then bound to the surface of mast cells. Subsequent exposure to antigen results in the cross-linking of IgE with the subsequent release of mediators, predominately histamine. This phase is known as 'elicitation'. These reactions typically occur within minutes to hours after re-exposure to the antigen.

Type II reactions are also known as 'antibody-dependent cytotoxicity'. In this immune reaction, antibody is directed against a person's own cellular surface antigens – 'auto-antibodies'. Complement, in conjunction with effector cells, then arrives and causes the damage. An example of this is Goodpasture's disease, where basement-membrane damage from organic solvents and other agents can lead to antibodies being directed against the lung or kidney membrane, and which results in pulmonary hemorrhage or nephritis.

Type III reactions are known as 'immune complex diseases'. In this reaction, immune complexes formed in the blood by the combining of antigen and antibody are deposited in tissue, complement is activated, and polymorphonuclear cells are attracted, all resulting in inflammation and tissue damage. These complexes are usually deposited in areas of high blood pressure and turbulence such as the lung, kidney and at blood-vessel bifurcations.

Type IV reactions are known as 'delayed hypersensitivity responses'. Typically, these reactions are heavily dependent on T-cell interaction with antigen and result in erythema and induration 1 to 2 days after re-exposure.

Both the skin and lung are the primary sites of occupational chemical-induced allergy, because of the typical inhalation and dermal routes of exposure. Although both the skin and lung can experience all four types of reactions (examples of which are seen in Table 2), the skin experiences predominately type IV reactions, and the lung, type I.

Table 1. Gell and Coombs classification. Source: *Clinical environmental health and toxic exposures*

Type	Cells	Immunoglobulin	Complement	Examples
I	Mast cells Basophils	IgE	No	Anaphylaxis Asthma
II		IgG IgM	Yes	Transfusion reaction Goodpasture's syndrome
III	Neutrophils	IgG	Yes	Serum sickness Farmer's Lung
IV	T cells Macrophage	IgM	Yes	Contact allergic dermatitis

Table 2. Examples of allergic diseases in target organs by type of immune response. Source: *Allergic hypersensitivities induced by chemicals*

Organ	Type I	Type II	Type III	Type IV
Skin	Contact urticaria	Skin purpura, bullous pemphigus	Allergic vasculitis	Allergic contact dermatitis
Lung	Allergic asthma	Goodpasture's syndrome	Allergic alveolitis	Hard-metal lung disease

Type I hypersensitivity reactions

Type I hypersensitivity responses can be induced by high-molecular-weight (HMW) and low-molecular-weight (LMW) chemicals. HMW compounds are more frequently proteins and typically produce immediate-response reactions in seconds to minutes after exposure, through IgE involvement. LMW chemicals usually cannot mount hypersensitivity responses by themselves, but rather serve as a hapten by binding to body proteins or the major histocompatibility complex (MHC) molecule, a limited number of these existing on the surface of the body's antigen-presenting cells. The complex of the antigen and MHC molecules is then recognized by specific T cells, which initiate the reaction. There is some evidence for IgE mediation with some LMW chemicals. Typically, these LMW chemicals produce delayed reactions, such as bronchospasm, 6 to 10 h after exposure. Some chemicals can induce both immediate and/or late-onset responses. The mechanism of these late-onset responses is still unclear, although there is a role for Th2 and possibly Th1 cells, mononuclear cells, and leukocytes.

An important feature of both HMW and LMW chemical-induced hypersensitivity reactions is the dose–response relationship. There appear to be thresholds for both the induction and elicitation phases. Typically, the threshold to induce hypersensitivity is higher than that seen for elicitation. This has been seen with toluene diisocyanate.

As noted above, HMW allergens are typically proteins, usually derived from animal, plant and microbial sources, such as enzymes that are produced by bacteria and molds. Table 3 depicts some commonly known HMW allergens.

LMW respiratory allergens are shown in Table 4. The chemicals here have been recognized as causing disease in both humans and animals. Many irritants are also sensitizers, which sometimes causes questions about whether the bronchospasm elicited is perhaps an irritant response (through a non-specific bronchial hyper-reactivity mechanism), or is a true allergic response. Sometimes, both irritant and allergic responses may be involved. Chemicals such as the diisocyanates and acid anhydrides are electrophiles that seek electrons and are thought to react covalently with nucleophylic sulfhydryl, hydroxyl, or amino groups of protein components of macromolecules. This covalent bonding is felt to be necessary to confer immunogenicity. However, being electrophilic is not reason enough for a substance to cause these changes. Another isocyanate, HMDI, is electrophilic, but is not a respiratory sensitizer. It is, however, a skin contact allergen.

Table 3. Examples of HMW respiratory allergens. Source: *Asthma in the workplace*

HMW Respiratory allergen			
Laboratory animals	Egg protein	Snow crab	Grain mite
Locust	Silkworm larva	Molds	Grain dust
Wheat, rye, soya flour	Coffee bean	Latex	Enzymes

Type II hypersensitivity reactions

Type II hypersensitivity reactions are autoimmune diseases in which antibody formation is a necessary step in eventually leading to cytotoxicity. This reaction can be caused by an interaction of genes, hormones and environmental agents. There may not be a clear dose-related response. This is seen in the glomerulonephritis of gold-salt therapy for rheumatoid arthritis, in which only approximately 10% of recipients will demonstrate signs of disease. Antibody binds to membrane or cell surface antigen, which activates complement (C3), leading to cytotoxicity. A good example is autoimmune hemolytic anemia.

Hypersensitivity reactions in the skin are skin purpura and bullous pemphigus, and Goodpasture's syndrome in the lung and kidney. Skin purpura is actually caused by an autoimmune reaction against circulating platelets, leading to thrombocytopenia and easy bleeding in the skin. For Goodpasture's syndrome, examples of compounds which can initiate antibody deposition of anti-glomerular basement membrane IgG1 and IgG4 are inorganic lead, mercury and cadmium.

Type III hypersensitivity reactions

Type III hypersensitivity reactions are caused by the deposition of immune complexes in blood-vessel walls and tissues. Repeated antigen exposure leads to sensitization, with the production of an insoluble antigen and antibody complex. As these complexes are deposited in tissues, the complement system is activated, polymorphonuclear cells are attracted, and immune-mediated damage occurs. These reactions typically peak between 3 and 10 h after antigen provocation. Diagnosis of these

Table 4. Examples of LMW respiratory allergens. Source: *Allergic hypersensitivities induced by chemicals*

LMW respiratory allergen			
2-Hydroxy-1,4-naphthalone	Abietic acid	Cyanuric chloride	Hexamethylene diisocyanate
Diphenyl methane-4,4'-diisocyanate	Phthalic anhydride	Piperazine	Pliatic acid
Toluene 2,4-diisocyanate	Toluene 2,6- diisocyanate	Trimellitic anhydride	Platinum salts
Reactive dyes	Welding flux	Chromium, cobalt and nickel fume	

reactions is assisted by specific hemagglutinin and precipitin tests.

The most common skin conditions in this reaction category are allergic vasculitis and erythema nodosum. Pulmonary reactions include hypersensitivity pneumonitis (HP), characterized best by Farmer's Lung, which is a reaction to microbic thermophilic actinomycetes organisms found in moldy hay. Other organic dusts and some LMW chemicals can cause HP. In the right setting, it is possible for some HMW compounds to cause HP.

HP is characterized by a variety of granulomatous, interstitial, and alveolar diseases. Typically, in bronchial lavage fluid analysis, activated lymphocytes are seen. An interstitial mononuclear infiltrate is seen in tissue biopsy. Mast cells are seen in granulomas. The hallmark symptoms and signs of HP are dyspnea, cough, temperature elevation and a decrease in oxygen saturation. Wheezing is not a common symptom.

Although HP is typically thought of as being caused by exposure to proteins and micro-organisms, certain occupational lung conditions have been ascribed to LMW chemicals. Bathtub Refinisher's Lung is caused by toluene diisocyanate exposure, Epoxy Resin Lung from phthalic anhydride, and Plastic Worker's Lung from trimellitic anhydride.

Type IV hypersensitivity reactions

Type IV hypersensitivity reactions are primarily T-cell mediated, with erythema and induration occurring in a previously sensitized individual, usually within one or two days after contact with the allergen.

The hallmark of occupational type IV hypersensitivity is allergic contact dermatitis. This is often difficult to distinguish from irritant dermatitis, especially if the reaction is chronic. Confounding this distinction is that many skin allergens are also irritants. At high exposures, irritant contact dermatitis may predominate, whereas at sub-irritant levels, allergic contact dermatitis could be seen. Often, only diagnostic patch testing can resolve the diagnostic dilemma. Prognosis is generally poor once occupational allergic contact dermatitis is established, severe dermatitis persisting in some individuals even after removal from exposure.

Table 5 depicts some of the general categories of type IV skin reactions. Many of the examples depicted are included in a standard battery in patch testing kits available commercially. Table 6 shows some LMW contact allergens seen in the chemical industry.

Type IV pulmonary hypersensitivity reactions have traditionally been described for a variety of inorganic dusts. Recently, hard metal and beryllium exposures have been included in this hypersensitivity reaction category. Hard-metal exposure actually involves cobalt from the grinding of steel. Cobalt exposure produces a pattern of interstitial pneumonia, but also demonstrates multinucleated giant cells in the interstitium and alveoli. Beryllium exposure also demonstrates lung granuloma formation. For both cobalt and beryllium, there appears to be a strong genetic predisposition.

Table 5. General categories of exposures and examples producing allergic contact dermatitis. Sources: *Allergic hypersensitivities induced by chemicals*, and *Contact and occupational dermatology*

General category (example)			
Rubber chemicals (thioureas)	Anti-microbials and preservatives (glutaraldehyde, triclosan)	Resins (epoxy)	Metals (nickel, mercury, copper)
Dyes (potassium dichromate)	Formaldehyde	Medicaments (bacitracin, chloramphenicol, benzoyl peroxide)	Plastic, glues (formaldehyde-linked resins, phthalates, isocyanates)
Sunscreen agents	Disinfectants	Flavors, perfumes, and fragrances	Pesticides

Table 6. LMW contact allergens. Source: *Allergic hypersensitivities induced by chemicals*

LMW contact allergen				
Benzocaine	1-Chloromethyl pyrene	1-Chloro, 2,4,5-trinitrobenzene	Cinnamic aldehyde	1,4-Dichloro-2,5-dinitro-benzene
1,3-Dichloro-4,5-dinitro-benzene	Diethanolamine	Diethyl fumurate	Diethyl triamine	Dimethylbenzanthracene
2,4-dinitro-chloro-benzene	Ethanolamine	Eugenol	Fluorescein	Furacin
Geraniol	Hydroquinone mono-benzylether	2-Hydroxy-1,4-napthaquinone	Isoeugenol	*N*-nitroso-dimethylaniline
p-Nitroso-*N*,*N*-dimethylaniline	Oxazolone	Penicillin G	3-Pentadecyl orthoquinone	*p*-Phenylene-diamine
Picryl chloride	Streptomycin	Tetrachloro-salicylanalide	Turpentine	4-Vinylpyridine

Identifying respiratory sensitizing chemicals

Because the number of recognized respiratory sensitizers is expanding, much work has gone into the development of predictive models which could be used as screening tests prior to chemical development.

A variety of in-vivo methods has been described, using different species. Most of these models are more effective in screening for HMW rather than LMW compounds.

The mouse IgE test has been used successfully to screen for LMW chemicals. In this test, the chemical is applied to the mouse skin, followed by challenging testing of the mouse's ear and a search for IgE. This test is based on an assumption that IgE is stimulated by chemicals with respiratory sensitizing capability when applied dermally to mice, whereas contact sensitizers do not. Although fairly low in cost, this technique still requires additional validation.

The guinea pig inhalation test (GPIT) involves intratracheal injection of allergen followed by observation for immediate and late respiratory responses, as well as IgG, which is a marker for type I sensitization in this species. This test has been validated with toluene diisocyanate across several laboratories. More data are derived than with the mouse IgE Test, but the cost is also greater.

A variety of in-vitro methods has been used as a screen for respiratory sensitizers. Many of these can be used in a tier approach prior to subjecting animals to testing. Most are based on the binding reactivity of chemicals to peptides. For instance, step one of a tiered evaluation could be to conduct structure analysis to determine whether the chemical has the potential to link covalently to proteins. If so, then in-vitro testing of this ability can be conducted. This could be followed by the in-vivo subcutaneous injection of the chemical–protein hapten into guinea pigs to assess antibody titer production and respiratory activity. Finally, if results of this test look positive, an in-vivo GPIT could be performed. This tier approach has been used against phthalic anhydride, toluene diisocyanate, and reactive B dye, with all tiers being positive, and also supporting the known human respiratory sensitizing ability of these chemicals. Additionally, a chemical thought *not* to be a human sensitizer, phthalic acid, was also *not* identified as such through this approach.

Identifying skin-sensitizing chemicals

In-vivo methods have been much more commonly used as predictive tests for skin contact allergens than for respiratory sensitizers. Most of these methods are based on the guinea pig model and many have been codified under regulation, especially in Western Europe.

The European Economic Commission (EEC) in 1992 required the Buehler and adjuvant (maximization) guinea pig tests to screen for newly produced chemicals. The Buehler test is more commonly used in the US and involves an occluded patch test using the chemical in question, followed by observation for erythema and edema 24 to 48 h later. The maximization test is similar to the Buehler test except that Freund's adjuvant is used to maximize the reaction of moderate-to-weak sensitizers. The Office for Economic Co-operation and Development (OECD) has adopted the Buehler and maximization tests, but does permit some variance in protocols for special reasons and also allows some mouse screening tests prior to guinea pig testing. Current regulatory guidelines do not endorse any specific test methodologies for assessing the potential of chemicals to induce photoallergy.

Recently, the local lymph node assay (LLNA) has gained favor as an alternative to the established guinea pig tests mentioned above. Both the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the European Centre for the Validation of Alternative Methods (ECVAM) have approved the LLNA as a stand-alone test and equivalent test for predicting the risk of human allergic contact dermatitis. In this test, the chemical is applied to the ear for 3 consecutive days followed by an intravenous injection of radioactive thymidine. The radioactive thymidine uptake in the excised local lymph node is used as an indication that sensitization and lymphocyte proliferation has occurred. The OECD has reviewed the LLNA and it is expected that a formal OECD test guideline, no. 429, will soon be approved.

Summary

Although proteins derived from animals, plant products, and microbial agents have been traditionally recognized as the most common etiological factors in the development of allergy, increasingly, chemicals are recognized to have this potential. Chemicals are now acknowledged as having a role in all the traditional Gell and Coombs' categories of hypersensitivity reactions. Predictive tests continue to be developed to allow adequate screening for allergic sensitivity prior to workplace introduction.

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