

Review Article

Isocyanates, polyurethane and childhood asthma

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Isocyanates are the most prominent and well-studied cause of occupational asthma. Over the decades, airborne isocyanates have been regulated to extremely low levels in the workplace, some of the lowest for any organic compound. Yet the incidence of isocyanate-induced occupational asthma remains high and the role of dermal exposure in disease etiology is only slowly being recognized. Almost completely overlooked is the potential relationship between isocyanates in consumer products and increasing prevalence of asthma in the general population, especially children. The steady rise in asthma over the past decades points strongly to a potential role of environmental exposures in its development. Imbalances in the immune system favoring respiratory diseases have been linked to biological and chemical stressor exposures early in life. Evidence for the presence of isocyanates in many polyurethane-containing materials, especially polyurethane foams, is presented as a possible contributor to the increase in asthma. Polyurethane foam is ubiquitous in western societies and used in bedding, furniture, automobile seats, footwear, etc., and numerous medical materials. Theoretical, epidemiologic, experimental and clinical evidence of a role for isocyanates and polyurethanes in the genesis of non-occupational allergy and respiratory disease are reviewed. These data all point to the urgent need for additional research on the links between isocyanates, polyurethanes and the role of the skin in non-occupational asthma.

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Even at extremely low exposures, isocyanates are notable because of their capacity to produce disease, especially respiratory disorders including asthma (1). Dermatitis with symptoms such as rash, itching, hives, and swelling of the extremities can occur with dermal contact (2). The respiratory diseases linked to occupational exposure to isocyanates have been studied and reviewed extensively (3–5). These will be summarized only briefly herein. Almost completely overlooked is the possibility of adverse health effects from residual isocyanates in consumer products, in particular polyurethane-containing products. The analysis and occurrence of isocyanates in such products, and the relationship to respiratory diseases, especially in children, will be highlighted in this review.

Worldwide annual production of isocyanates is in excess of 4 million tons (6). The largest use

of isocyanates is in the production of polyurethanes (PU), especially polyurethane foams (PUF). The global PU business is now well over 8.5 million tons. The isocyanates utilized in the manufacture of PUF are generally aromatic, low molecular weight, volatile and possess high chemical reactivity. Prior to 1980, most PUF was produced using toluene diisocyanate (TDI). Post-1980, there was a shift to the use of methylenediphenyl diisocyanate (MDI) and pre-polymers of TDI (pre-reacted TDI polymer). The low volatility of these isocyanates resulted in much lower air exposures in the workplace but, remarkably, produced little of the expected reduction in occupational asthma. Fig. 1 shows the general structure of an isocyanate and the reaction involved in production of polyurethane; generally, a poly-isocyanate plus a poly-alcohol. Herein, we will use the term NCO to refer

An isocyanate



Reaction of a polyol with a diisocyanate to form a polyurethane

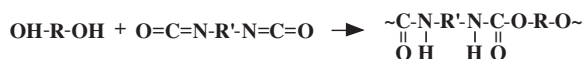


Fig. 1. General structure of an isocyanate and reaction with an alcohol to form polyurethane.

collectively to both unreacted isocyanates and diisocyanates. TDI, MDI, and hexamethylene diisocyanate (HDI) are the most common NCOs used in PU; these isocyanates are liquids at room temperature. In the manufacture of PUF, for example, different NCOs and varying proportions of them are used to produce PU with diverse physical properties (e.g., flexibility, rigidity, elasticity, etc.) (7, 8). The amount of NCO used in PUF manufacture is almost always added in excess. This can result in PUF with varying levels of unreacted residual NCO content that has been shown to be surprisingly persistent over many years.

Occupational diseases and isocyanates

In the US alone, there are an estimated 280,000 workers exposed to NCO annually (6). A significant portion (e.g., 5–20%) of TDI-exposed workers has shown to become sensitized to this NCO (1). NCO exposure in the PU manufacturing arena is the leading cause of occupational asthma. The prevalence of NCO-asthma in exposed workers ranges from about 3–13%. Even non-workers living near PUF factories are reported to experience NCO-associated symptoms and exhibit antibodies to NCO (9). In addition to the direct exposure to NCO during manufacture, other industrial processes can lead to disease. For example, soldering of PU enamels in the electronics industry can produce asthma (10). The causative agent was reported to be TDI. Workers at an autoseat cover factory experienced wheezing, shortness of breath and asthma when a new PUF-containing fabric was introduced (11). Low concentrations of TDI were measured in the air near the foam. Sprayed and heated PU glues are associated with respiratory symptoms, nasal inflammation and the presence of biomarkers of NCO exposure in workers (12). Nurses applying an MDI-containing cast material for immobilizing broken bones developed respiratory symptoms and asthma (13). The vapor pressure of MDI is very low and no

airborne MDI could be detected using the most sensitive methods. This study concluded that dermal contact was capable of producing asthma in the nurses. Fortunately, the patients' skin was covered with a protective gauze barrier that prevented contact with the cast material.

The role of dermal exposure in the occupational setting

In the 1950s, exposure to NCO was observed to elicit asthma. Yet, there is still no consensus on the primary mechanism by which NCO causes asthma, or on a threshold-sensitizing inhalation dose in adults. At first, it was logical to assume that airborne exposure must be causal because the most commonly used isocyanate, TDI, is volatile and the respiratory tract was the target of the disease process. 'The association of respiratory distress with TDI-workers may have contributed to the current assumption that respiratory sensitization of workers is a result of *inhalation exposure* to TDI' (14, *italics original authors*). Based on this assumption, regulations limiting inhalation exposure in the workplace were adopted as legal requirements to protect workers during the 1970s.

Development of an animal model in 1980 partially validated this theory by inducing pulmonary hypersensitivity in guinea pigs via a head-only inhalation exposure (15). However, the authors were troubled by the observation that prolonged exposures to high levels of TDI were necessary to induce low rates (15%) of sensitization. Furthermore, inhalation exposure to NCO levels reflective of actual workplace levels produced no sensitization or asthma. The reports that 'some TDI-sensitized workers experienced spills or splashes with TDI' raised doubt that inhalation of TDI was necessary for inducing TDI respiratory hypersensitivity (14). In a follow-up study, a single TDI dermal exposure in guinea pigs resulted in prolonged antibody production, skin sensitivity and pulmonary sensitization in 30–40% of the animals (14). More recent studies have consistently confirmed the capacity of dermal TDI exposure to induce airway hyper-reactivity (16).

TDI and other isocyanates are known skin sensitizers. It had been demonstrated earlier that administration of simple chemical hapten skin sensitizers by routes other than cutaneous application (oral, intra-tracheal, etc.) suppressed rather than induced hypersensitivity responses. Doe et al. (17) investigated the effects of prior inhalation exposure on the skin reaction to TDI. Prior inhalation inhibited the skin's reaction to TDI. The inhibition lasted up to 9 wk, and

suggested involvement of immune suppressor cells. These authors concluded, 'It must be asked whether inhalation of haptens by humans might not normally induce unresponsiveness rather than respiratory sensitivity, thus, accounting for the majority of members of hapten-exposed workforces who do not become sensitized to inhaled chemicals' (17). In 1990, a further study of the respiratory sensitizers trimellitic anhydride and MDI demonstrated IgE-specific down-regulation of immune response after inhalation exposure (18). In contrast to allergen exposure by the dermal route, prior inhalation also markedly reduced the capacity of the animals to undergo a bronchial constriction response. This suggested to the authors 'the initial route of exposure may have profound effects on the development of occupational respiratory allergy' (18).

The influence of the route of exposure on the induction of respiratory hypersensitivity to MDI in animals has been further investigated (19, 20). Attempts to sensitize guinea pigs via inhalation were unsuccessful and antibody response was infrequent and low grade. In contrast, sensitization by a single topical application induced antibody responses in the majority of the animals and a portion of those exhibited a pulmonary response on inhalation challenge (19). The route of exposure markedly influenced the effectiveness of sensitization. Thus, skin contact with respiratory allergens may represent an important cause of occupational respiratory asthma (19, 20).

Several other insights from the occupational setting deserve mention. MDI was introduced as a safer substitute for TDI in the manufacture of PU due to MDIs exceedingly low volatility and correspondingly low inhalation potential (less than 1 ppb on average). However, in South Korea, workers exposed to MDI were found to be at higher risk of asthma in comparison to TDI-exposed workers even though the mean air concentration of exposures for the TDI workers was over 10-fold higher than MDI concentrations (21).

Petsonk et al. (22) evaluated respiratory health at a new wood products manufacturing plant. The plant was designed and operated to control worker inhalation exposure to NCO, and thus asthma, by using MDI. However, during the first 2 yr of operation, a relatively high proportion of the employees who worked with liquid MDI were found to have developed asthma-like symptoms. Fifty-two percent of workers who reported asthma-like symptoms exhibited MDI-skin staining. Asthma symptoms were slightly more associated with skin stains than clothing stains

suggesting that skin contact may be a potential site for sensitization. No symptoms of asthma were detected among the 50% of plant workers who had no direct contact with liquid MDI yet had inhalation exposure similar to that of the affected workers.

MDI is now reported as the leading cause of isocyanate sensitization in the PU industry (23). As of June 1995, Dow Chemical Company has stated on its material safety data sheet for MDI that 'Skin contact may result in allergic skin reaction or respiratory sensitization.' Currently, however, no regulatory health and safety-standards organization has assigned a 'skin' warning to NCO to alert users regarding precautions to reduce skin exposure.

Polyurethane-containing products: ubiquitous in modern society

It is nearly impossible to avoid contact with PU in the developed nations or any urbanized area worldwide (7, 8). Nearly all furniture, bedding (mattresses, mattress covers, and pillows), carpet underlay or padding, automobile seats and child autosafety seats contain PUF. Foam insulation in homes is widespread. Food packaging, sports footwear and other sporting gear are commonly constructed with PU (e.g., golf balls, skis, surfboards, tennis rackets, non-submersible boats, canoes, etc.).

In the medical field, catheters, feeding tubes and chest drains are often constructed of PU (24). PUF is found in adhesive oximetry sensors, foam-backed electrodes, and wound dressings. Adhesive PU-containing dressings for wound care have become increasingly common. Many such products include a non-adherent PU net for contact with the wound, a PUF pad to absorb wound exudate and an adhesive transparent PU film to fix the dressing in place. Other wound dressings incorporate traditional non-woven pads with the PU films. Adhesive PU films alone are also used to protect fragile skin and for the fixation of catheters, sensors, etc. Breast implants have been constructed with PUF coverings.

Isocyanates in polyurethane-containing consumer products

Despite the extensive literature on the hazards of NCO, little has been published on their analysis in PU-containing consumer products. Of the published methods, most are intended for NCO determination in the air of industrial environments. These methods generally are not suitable for evaluation of NCO in the PU-containing

materials to which the general population is exposed. Gas chromatography with various detection methods (flame-ionization and mass spectrometry) has been applied to NCO (and their chemical derivatives (e.g., 9-*N*-methylamino-methylanthracene (MAMA)) from consumer products (25–27). Generally, analyses of PUF have been limited to examination of small-scale laboratory-produced or factory samples for the purpose of method validation (e.g., Refs 26–28). The amounts of NCO detected in these studies were variable and depended on time, humidity, and other conditions. For example, concentrations of TDI present in freshly made foams varied from 2.4 µg/g (27) to 300 µg/g (26). Much lower amounts were found after a 24 h ‘curing’ process.

Because of the high reactivity of NCO, it has been assumed that no residual NCO would remain in products by the time they reached the consumer. This assumption rarely has been questioned, especially in the case of PUF products. In the manufacture of PUF, an additional 5–10% of isocyanate is always added over and above the amount required for stoichiometric reaction with the hydroxyl groups of polyols and water (7, 29). In 1990, data on residual TDI content of eight PUF formulations typical of consumer products were submitted to the State of California, US, to comply with consumer safety regulations enacted in 1986 (i.e., Proposition 65) (30). Proposition 65 requires reasonable warnings of products that may contain toxic chemicals, especially suspected carcinogens such as TDI. This research, sponsored by TDI manufacturers, indicated that the average levels of residual TDI in these test formulations ranged from 0.07 to 1.1 µg/g, although levels as high as 2.1 µg/g were reported (30).

Recently developed high-performance liquid chromatographic (HPLC) methods with fluorescence detection of MAMA derivatives have been used to measure NCO in PU of food packaging (31) and in PUF (32). Polyurethane sheets and adhesives intended for food contact use contained extractable NCO in concentrations up to circa 1 µg/g (30).

The only published surveys of retail consumer PUF products used both an HPLC method and a semi-quantitative colorimetric indicator wipe test (called ‘Swype’ (Colormetric Laboratories Inc., Des Plaines, IL, USA)) to detect and quantify NCO in consumer PUF products (33). Selected representative PU-containing medical products have also been tested using the colorimetric test (33). Comparable results were obtained using this

Table 1. Presence of isocyanate (NCO) in polyurethane consumer products* tested with Swype pads

Sample	Form of polyurethane†	Bound NCO‡	Free NCO§
Mattress pad A	Foam	+	+
Mattress pad B	Foam	+	+
Mattress	Foam	+	+
Autoseat	Foam	+	+
Sofa padding	Foam	+	+
Carpet pad	Foam	+	+
Pillow	Foam	+	+
Ironing board pad	Foam	+	+
Child autosafety seat	Foam	+	+
Child toy	Foam	+	+
Clear adhesive dressing	Film	+	+/-
Wound dressing (pad)	Foam	+	+
Wound dressing (adhesive)	Film	+	+/-
Oximetry sensor	Foam	+	+
Electrodes (foam-backed)	Foam	+	+
Eye protector (phototherapy)	Foam	+	+

*Adapted from data in Krone et al. (24, 33).

†Physical form of polyurethane material.

‡Visible(+) or no visible (–) color on tested material at 60 min.

§Visible(+), faint (+/-) or no visible (–) color on Swype pad at 60 min.

colorimetric method in the previously mentioned study of orthopedic casts (13).

Table 1 summarizes the results for NCO in PU-containing products using the colorimetric test. Generally, all PUF-containing products demonstrated bound NCO, with varying intensity of un-bound ‘free’ NCO. The presence of the ‘free’ NCO was confirmed by extraction and HPLC analysis of selected PUF samples (33). TDI monomer, which is widely used in the manufacture of flexible foams, comprised between 25% and 100% of the total soluble ‘free’ NCO found. A general trend toward lower concentration in older samples was observed.

Adhesive PU-containing films used as part of complete wound dressings or as separate strips or sheets used for affixing sensors, dressings, catheters, etc., also showed color development with a Swype indicator (both the adhesive skin-side and the back-side of the film). However, reaction times were longer prior to color development (e.g., > 60 min) than with PUF. The longer time suggests several-fold lower concentration of NCO than in the PUF materials (24). The finding of bound and ‘free’ NCO in these medical products suggests human skin exposure to NCO can occur whenever such materials are applied. In all these applications, the PU products are intended to be in contact with the skin for hours to days. This could provide ample time for some NCO to penetrate the skin.

In addition to studies that extracted and analyzed the NCO, two other reports suggest

that the NCO could be found in PUF long after manufacturing and, thus, potentially serve as a route of human exposure. One hundred days after preparation, laboratory-produced PUF still contained unreacted NCO groups (28). This study did not distinguish between bound and free NCO, but showed there was a rapid decline of NCO in the first 10–15 days after PUF production, followed by a slow and gradual reduction. The data produced a rate-of-decline curve, which described the disappearance of NCO groups over time. In our studies, we reported that even a 30-year-old PUF contained measurable NCO (33). In fact, setting the time at 30 yr in the formula of Gheluwe et al. (28) resulted in an estimate of 5% of initial NCO groups remaining at this time point. Therefore, it is not surprising to find NCO in PUF, even in 30-year-old foam.

A more recent study was intended to evaluate the potential for consumer inhalation exposure to NCO from PUF (29). In this study, TDI-containing air was passed through PUF in a closed system and >99% of the introduced amount was retained in the foam. After a 3-day 'aging' period in the a closed system, no detectable levels (less than 0.5%) of this TDI load could be removed by passing TDI-free air through the PUF for 72 h. At the detection limit of their system, this seemingly small amount of released NCO could, however, produce some measurable level of TDI in room air if the PUF were part of a typical size PUF mattress. Likely more important from a human exposure perspective, no attempt was made to use solvents or extract 'trapped' TDI from the 'loaded' PUF nor to determine the fate of the trapped TDI (29). The distinct possibility is raised that the 99% retained NCO remained trapped in the PUF matrix and could be available to dissolve in lipophilic skin oils upon dermal contact.

In spite of the prospect of finding free NCO in consumer products and the ubiquitous nature of these items, it is surprising that so little analytical work has been done. The limited data that are currently available and the high potential for producing disease strongly suggest that additional study of NCO in consumer products and additional research into the potential health effects of exposure are a high priority.

Polyurethane and non-occupational allergy and asthma

By far, the most common cause of occupational asthma is NCO. Despite the use of excess NCO in manufacture of PU products and the findings of NCO in finished consumer products, several

compendia, covering the chemistry, manufacturing and uses of PUF, state 'PUF is non-toxic' (e.g., Ref. 7). These statements are made with little or no supporting references cited. However, there are reports of allergy-like responses to PU-containing products. For example, contact dermatitis from the PU in athletic shoes has been reported (6), and childhood asthma and wheezing attacks have been associated with the use of PUF bedding (34).

Polyurethane-coated breast implants may contribute to autoimmune responses in breast implant patients. These devices can produce a highly vascular inflammatory response (35), very thick capsules around them post-implantation, and associated biomarkers of delayed hypersensitivity (36). Fluid surrounding the capsule of implants show a predominance of T lymphocytes, specifically those associated with an up-regulation of immune response with the potential for stimulating antigen-specific antibody production (37). Thus, it appears that both cell-mediated (delayed hypersensitivity) and humoral (antibody) immune responses can be influenced by the PU in these devices. Recent animal model studies of NCO asthma have also found indicators (i.e., cytokines, IgE, etc.) representative of both types of immune response (38).

Acute hypersensitivity-like reactions were reported in close association with insertion of catheters made from Aquavene (39, 40). The catheters are constructed of an inner layer of PU and an outer layer of the biomaterial Aquavene, a blend of PU and polyethylene oxide. Investigations of some possible catheter residual chemicals have been carried out, but analyses of NCO were not done (41). The mechanism of the potentially life-threatening adverse reactions remains unknown (40). It is possible that persons previously sensitized to NCO or immuno-compromised due to illness could experience these severe reactions from exposure to NCO residues diffusing from the catheter.

The home environment and its relationship to allergic diseases has been examined by several groups. Strachan and Carey (34) found positive associations between the use of PUF pillows, childhood asthma and a significant increase in childhood wheezing attacks. Further studies confirmed these results and also demonstrated that the association of foam pillows with current wheezing was of similar strength among children with and without skin prick reactions to Der p I, the major allergen of the house dust mite *Dermatophagoides pteronyssinus* (42). This refuted the idea that dust mites were the causative factor in the asthma symptoms. Moreover, a

study in adults found evidence that the use of foam pillows increases the risk of perennial or seasonal rhinitis (43). It has been suggested (34) that some unknown volatile chemical associated with synthetic pillows may be a causal agent and if so, could account for 53% of the severe asthma in the study population. The findings of bound and free isocyanates in PUF domestic products, including pillows and bedding (33), are concordant with a chemical-causation link between PUF and asthma/rhinitis.

In urban and rural Ethiopia, a possible link between use of PUF mattresses and pillows, and increased allergic symptoms and sensitivity was reported (44). A somewhat unexpected prevalence of asthma had been observed in an urbanized area, even though the adoption of 'westernized' life style was in its early stages. A risk of wheeze was positively associated with foam bedding (44) that was used by 15% of the urban population but less than 1% of the rural residents. A number of other potentially confounding life style factors were also considered and not found to be linked to symptoms (e.g., housing size and type, pesticides use, vaccinations, family size, cigarette smoking, environmental air pollution, diet, etc.). However, additional studies will be needed to confirm the asthma-PUF relationship in this population.

More than a dozen studies since 1995 have associated synthetic bedding with an increase in asthma, wheeze and other allergic symptoms. However, many of these reports do not specifically state the materials constituting the bedding. For example, in New Zealand, polyester is the most common synthetic filling material for pillows and quilts. Whereas, in the US and UK, PUF is more typical in synthetic pillows. Siebers et al. (45) summarized the findings of recent studies and discussed possible explanations for the positive associations. An increase in childhood wheeze over the 13-year period from 1978 to 1991 was largely attributed to increasing use of synthetic non-feather pillows (46). Use of these items was the only indoor domestic exposure that could explain the results. Because higher levels of allergens (e.g., dust mite, cat, and dog allergens) have been measured in synthetic compared to feather bedding, Ponsonby et al. (47) examined whether the association between synthetic bedding and respiratory symptoms was more manifest among skin prick test positive (i.e., sensitized) children. A positive link between synthetic quilt/pillow use and asthma, recent wheeze and allergic rhinoconjunctivitis among skin prick test positive children was found (47). This suggested that higher allergen load in

synthetic bedding could bring about the respiratory symptoms. However, avoidance of these 'allergen risks' does not appear to confer significant benefit. Indeed, the results of Karaman et al. (48) seem to indicate that allergen avoidance merely delays appearance of symptoms rather than prevents them. Furthermore, the results of Ponsonby et al. are also not inconsistent with the hypothesis (34) regarding volatile chemicals (and we might suggest NCO) in synthetic bedding as an enhancer of allergenicity.

Isocyanates and the role of the skin in childhood asthma

From 1980 to 1994, the prevalence of asthma in the United States increased 75% (49). Asthma is the most common chronic childhood disease. Atopy is a genetic predisposition to develop hypersensitivity reactions in response to allergens. Atopic diseases include asthma, dermatitis, rhinitis, food allergy, etc. These disorders represent a complex gene-environment interaction that, for full expression, involves exposure not only to antigens, but also environmental stressors. Environmental and life style factors that have been associated with prevalence of allergy and asthma include early infections (e.g., viral and bacterial), bacterial endotoxins, diet (e.g., antioxidant nutrients, omega-3 fatty acids, etc.), air pollution, environmental tobacco smoke (ETS) (50) and 'western' life style (51, 52). The view that naturally occurring infections (e.g., bacterial, viral, parasitic, etc.) can exert a protective effect on atopy and allergic diseases was proposed by Strachan in 1989 (53). This concept is often referred to as the 'hygiene hypothesis.' Although research into aspects of the hygiene hypothesis continues to provide support for this theory, there are many lines of evidence that do not mesh. It is very possible that other currently unrecognized factors, such as chemical stressors, including NCO in PU-containing consumer products, are responsible for increases in childhood atopy and asthma.

Among all of the chemical and biological stressors, a common feature may be their ability to modulate various components of the immune system, particularly the T-helper cells type 1 (TH₁) and T-helper cells type 2 (TH₂). A dysregulation of the TH₁/TH₂ balance in early life has been related to the risk of developing asthma (54). At birth, humans exhibit a dominant humoral, TH₂, responsiveness (i.e., an atopic state). This state generally converts to a cellular immune response (TH₁) during the first few years of life. A shift of the allergen-specific T-cell

immunity into adult-equivalent TH₁ patterns rather than the fetal TH₂ patterns occur in most children before age 5 yr (55). This suggests that research should focus on the immediate post-natal period.

Atopy is a recognized risk factor for childhood asthma (55). Atopic children tend to exhibit a delayed transition from the predominant TH₂ immune response to a more balanced TH₁/TH₂ response. This allows a TH₂-type pattern to persist longer and extends the period of vulnerability to environmental allergens and stressors, and increases the likelihood of subsequent disease expression, including asthma (54, 56). In the developing immune system of animals, if TH₁-stimulating factors are lacking, maturation of the TH₁-dependent mechanisms are inhibited and life long TH₂ response dysregulation may result (57). Moreover, it has been suggested that the presence of TH₂-stimulating substances (e.g., food allergens, air pollutants, etc.) in early life could increase allergic sensitization and also promote the persistence of atopy (52, 58, 59). Chemical stressors, including diesel exhaust particles and ETS, and especially some of the polycyclic aromatic hydrocarbons they contain, have the potential to alter the immune response toward a TH₂ pattern (52) and are strongly associated with asthma.

The skin is acknowledged to be an effective antigen-presenting organ. Primary sensitization to protein allergens can occur through the skin of mice (60). Recently, dermal application of diaper rash ointments containing peanut oil was shown to be associated with development of peanut allergy in childhood (odds ratio 6.8) (59). Refined peanut oil contains a protein that produces, in patients with peanut allergy, typical allergic responses (e.g., positive skin prick tests). The 'epidemic' of systemic latex allergy within the medical industry can be attributed to initial dermal sensitization to latex proteins latent in the medical exam gloves (61). Medical professionals, in particular nurses, who were directed to wash hands frequently with extremely harsh (80% alcohol) disinfectant skin cleansers became latex sensitized when directed to wear latex gloves. These examples suggest that skin exposures may play a primary role in the provocation of the TH₂ immune system response. Thus, skin exposures could be important for the early sensitization of neonates and children through contact with PU products and the NCO they contain.

A primary biological function of the skin's immune system is to prevent systemic infection by environmental microorganisms when the

dermal barrier is damaged or cut. The skin of human neonates is thin, delicate and susceptible to alterations in integrity; it is a much poorer barrier than the skin of older children or adults. Damage to the skin barrier properties by physical (e.g., by tape stripping) or chemical (e.g., acetone or ethanol) assault up-regulates the dermal immune system and initiates a range of responses (62). These include increased cytokine and DNA production. The palliative use of ointments containing peanut oils or the contact of latex with chemically abused skin can induce a systemic sensitization. It is plausible that the use of PU products such as wound dressings containing unreacted NCO functional groups could put NCO in direct contact with a hyper-stimulated immune system and also induce sensitization.

As described in an earlier section, NCO (monomers and pre-polymers) has demonstrated ability to provoke skin sensitization and subsequent respiratory disorders in experimental animals and humans (e.g., Refs 16, 20, 38, 63, 64). Because of the relatively low molecular weight of NCO used in PU manufacture compared to typical high molecular weight allergens (e.g., pollen, food allergens, pet allergens, etc.), a variety of non-allergenic mechanisms have been proposed to explain NCO asthma. However, these theories do not account for the typical immunologic features of the condition. T-cell responses characteristic of atopic allergy are seen in NCO asthma (e.g., asthma-associated cytokines, specific IgE, etc.) (22, 65). A recently developed mouse model of isocyanate-induced asthma demonstrated a mixed TH₁/TH₂ response to dermal exposure of isocyanates (38).

This mouse model of NCO-induced asthma exhibits the lung inflammation and other characteristics of human disease (specific antibody responses, high numbers of eosinophiles and mucous hypersecretion) (38). In the model, dermal sensitization to HDI, two applications 1 wk apart, led to contact hypersensitivity, HDI-specific antibodies, strong inflammatory lung response and eosinophilia. In the sensitized animals, the serum antibody and cytokine profiles were representative of a mixed TH₁/TH₂ response. The airway eosinophilia was mediated by TH₂ cytokines (IL-4 and IL-13) and other TH₂ responses. TH₂ activation has been observed in many patients with NCO-induced asthma (e.g., Refs 22, 65–67). TH₂ cytokines (IL-4 and IL-5) are produced in TDI-challenged patients with TDI asthma (66). Thus, neonatal and young childhood contact with PU-containing materials could initiate sensitization and a TH₂-type response, prolonging the window of

vulnerability to other chemical stressors and allergens.

An important finding in the Herrick et al. (38) mouse model was that the optimum skin exposure dose of NCO for either lung inflammation or contact hypersensitivity was 10 times lower than the optimum dose for antibody response. This suggests that low dosage and small numbers of exposures can produce sensitization and lead to typical NCO-induced cytokine and asthmatic responses without producing IgE. This finding also may help explain why only a proportion of patients with NCO asthma exhibit elevated NCO-specific IgE (22, 68).

Mapp et al. (67, 69) reported on genetic markers of susceptibility to NCO asthma. Certain allelic variants in the 1 type glutathione-S-transferase locus (GSTP1) can apparently protect against or pre-dispose to TDI induced asthma. The GSTP1 location on the chromosome is close to other genetic markers associated with asthma. Also, the gene product of this locus, glutathione-S-transferase, is an enzyme that is protective of cellular oxidative stress. Such stress has been linked to the probability of an increased sensitization by NCO and the likelihood that asthma will persist with continuing exposure. These studies suggest that at least two factors may be involved in development of NCO asthma: a genetic tendency and environmental exposure (67, 69). Almost all neonates and children are exposed to PU. Those with a genetic susceptibility may be at higher risk of becoming sensitized and allowing the TH₂-dominant state to persist.

Chemical stressors, including NCO, can influence the development of immune responses and pre-disposition to atopy and asthma. Isocyanates can elicit asthma symptoms at very low airborne concentrations but the initial immune sensitization is likely primarily through dermal contact. One might speculate that even more important than the direct initiation of respiratory disease, is the possibility of NCO exposure causing a skewing the neonatal TH₁/TH₂ balance. Such imbalances have been suggested as paramount in the increasing incidence of childhood asthma and may be especially true in genetically pre-disposed individuals.

Challenging the 'conventional wisdom' – re-evaluating our assumptions

It has generally been thought that finished PU products are non-toxic, and unreacted and unbound NCO is not present. However, evidence demonstrates that this belief is mistaken. Furthermore, a number of other 'truths' of 'conven-

tional wisdom' regarding factors causing and exacerbating asthma have recently been challenged.

Exposure to cats and dogs in infancy has long been thought to increase the risk of later allergy and asthma (70). However, the opposite relationship has recently been observed (71). Orthodox views regarding associations between allergy/asthma and feather pillows and bedding, fitted carpets and rugs, dust mites, and other environmental factors have also been brought into question (e.g., Refs 34, 42–46, 48). Thus, earlier 'conventional wisdom' regarding causation and prevention of asthma and other respiratory diseases has been contradicted by more recent, well-designed and complete studies.

If long-held beliefs about residual NCO in PU and its capability to produce disease also prove to be incorrect, then several puzzling trends may be explained. It is well documented that the incidence of childhood asthma rapidly increases as a society adopts westernized life styles. Among the first of these life style changes is the introduction of more 'modernized' medical procedures and equipment. Thus, the dramatic rise in asthma in East Germany after reunification with the West (52, 72) may be associated with improved medical care and the incipient use of PU-containing medical products, as well as, the wider availability of PUF consumer products.

Another puzzling observation might also be clarified if it is demonstrated that PU products can be a source of NCO immune-sensitizing exposures. Several long-term follow-up studies of subjects with occupational NCO-asthma have found persistent symptoms, even months or years after work exposure to NCO has ceased. For example, 51% of patients with TDI-asthma who completely avoided occupational exposure to NCO for more than 2 yr and had received appropriate anti-asthma medications still exhibited symptoms (73, 74). Furthermore, many of these sensitized individuals displayed sensitivity to multiple chemicals that had previously provoked no adverse reactions. Might it be that these subjects were the most highly sensitized and the continued, unrecognized, exposure to NCO in consumer products prevented remission from their symptoms?

Conclusions

Isocyanates are the largest cause of occupational asthma and their greatest use is in the production of PU. An excess proportion of NCO is almost always persistent during manufacturing of PU, yet few studies have examined NCO residuals in,

or the potential for causing disease by, the ubiquitous PU-containing consumer products. NCO is highly reactive compound, yet when tested, PUF and PU have been documented to contain remarkably stable unreacted NCO residues (24, 31, 33). PU is considered non-toxic and is widely used by the medical industry in products that come into direct contact with the skin or blood of neonates. Where these products have produced adverse reactions in patients, the cause remains unexplained. In addition, some PU products have been linked to allergy-like hypersensitivity reactions and respiratory disease (34, 40, 42–44, 75).

Even today, the minimum respiratory exposure that will cause sensitization in susceptible individuals and produce occupational asthma is not known (i.e., some believe that there may be no lower limit of exposure below which no workers will be sensitized) (3). No information on the sensitizing inhalation dose in children is available. It is extraordinary that all evidence points to the skin as the primary route of immune sensitization yet; the only regulation of exposure still focuses on inhalation. The understanding of the immunologic mechanisms of respiratory disease development in early childhood is consistent with a potential causal role for NCO from medical and consumer products. We might postulate that the increasing incidence of asthma in developing and developed nations is somehow, in part, linked with NCO/PU exposure.

The etiology of asthma is nevertheless multi-dimensional and appears to involve genetic and other environmental factors. One risk factor alluded to often is a 'westernized' lifestyle. In reality, this factor consists of a collection of exposures, which includes not only the modern environment (e.g., indoor and outdoor air, housing, carpets, furnishings, artificial light, etc.), but also life style habits (e.g., processed foods, exercise, etc.). As populations adopt a 'westernized' life style, people spend more time indoors. In the United States for example, most children spend the majority of each day (average 20 h) inside buildings (76). Thus, exposure to indoor air contaminants is increased and benefits of natural sunlight are decreased.

In the mid-twentieth century, research on and production of plastics and other synthetic macromolecules began a vast expansion. Polyurethanes were initially investigated in the 1940s and the first patent was assigned in 1942 (8). The first flexible PUF products became available in the 1950s and production rose rapidly in the 1960s and beyond. PUF bedding

has penetrated into relatively isolated locations in Africa and respiratory disease has increased in the 'exposed' populations. Is it merely coincidental that the ongoing rise in the UK of allergic skin sensitization, a precursor of asthma, began with those born after the 1940s? (77) Could the unexplained continuation of asthma symptoms in one-fourth of persons with occupational NCO asthma who cease work exposure be exacerbated by everyday contact with NCO in PU-containing consumer products (73, 74)? It is understandable that most researchers in childhood asthma have never heard of NCO as this has been considered an 'industry only' exposure. Greater attention and research is warranted on possible non-occupational links between NCO exposure and asthma. These are ideas, which call for greater attention by industry and medicine.

Suggestions for further research

Retrospective epidemiologic studies could help determine if there is a relationship between medical use of PU-containing products on neonates/infants and an increase in childhood asthma. Are there variations in medical PU usage among regions, in rural vs. urban populations, in westernized vs. third world nations?

A number of animal models have been used to demonstrate the sensitizing properties of NCO. The recent development of the mouse local lymph node assay to screen industrial chemicals for immunological response potential provides a new tool to further investigate NCO. The mouse lymph node assay can determine whether compounds are likely skin or respiratory sensitizers. This method could be employed to screen consumer and medical products that are manufactured using chemicals that are known immune system sensitizers. The murine model could be further enhanced by incorporating a modified Draize test, based on the protocol used to evaluate cosmetics for irritancy. The Draize test requires cosmetics be tested on both healthy intact skin and abraded or compromised skin. Consumer products, and more importantly, medical and cosmetic products intended for use on infant skin should be carefully screened for immunological response.

PU-containing medical products should also be tested in animal models (guinea pig, murine, etc.) in a manner that is representative of their intended human use. For example, adhesives, electrodes, etc., would be tested on healthy intact skin. Wound dressings should be tested on damaged skin. A determination of the extent and immunological response profile would offer

valuable insight into the human immune system's response to these products and guide the regulation of required testing prior to public distribution of products.

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