

Polyisocyanates in Occupational Environments: A Critical Review of Exposure Limits and Metrics

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Background Determination of polyisocyanates is important because they are a major contributor of exposure to the isocyanate functional group in many workplace environments and are capable of inducing sensitization and asthma. However, with multiple different measurement metrics in use, comparison of isocyanate exposure data between studies and development of occupational exposure limits (OELs) for polyisocyanates is difficult.

Methods An analysis of existing problems in the measurement and regulation of isocyanates is presented based on the published analytical, toxicological, and regulatory literature, and the authors' own analytical data and experience with isocyanates.

Results This analysis supports a need for standardization of isocyanate measurement metrics and provides a framework for the development of an OEL for polyisocyanates.

Conclusions The total isocyanate group ($\mu\text{g NCO}/\text{m}^3$) is recommended as the most feasible and practical metric (unit) by which to express polyisocyanate exposures for research, control, and regulatory purposes. The establishment of a comprehensive isocyanate OEL that simplifies the current agent-by-agent approach and expands coverage to polyisocyanates is also recommended. Am. J. Ind. Med. 46:480–491, 2004. © 2004 Wiley-Liss, Inc.

KEY WORDS: isocyanate standards; exposure metric; polyisocyanates; regulatory toxicology; occupational asthma; exposure limits

INTRODUCTION

The main objective of this paper is to evaluate whether assessment of isocyanate exposure for epidemiological research, clinical studies, and the development of isocyanate

regulations, is best achieved by using the total isocyanate group as a common exposure metric for commercially used polyisocyanates and diisocyanate monomers. The term exposure metric has a broad meaning and can include a number of parameters such as sampling strategy (species measured, units of measurement, sampling type and duration), analytical methodology (accuracy and precision), and the relevance to health effects of interest. The primary interest here is on the measured isocyanate species, polyisocyanates, and the unit of measurement. We focus primarily on polyisocyanates for several important reasons. Polyisocyanates are the major contributor of exposure to isocyanate groups in many work environments and like the diisocyanate monomers from which they are derived, such as toluene diisocyanate (TDI), diphenylmethane diisocyanate (MDI), and hexamethylene diisocyanate (HDI), they are capable of inducing sensitization and asthma. In addition, polyisocyanates currently are inadequately regulated in most occupational settings.

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Contract grant sponsor: National Institute for Occupational Safety and Health (NIOSH); Contract grant number: R01OH03457; Contract grant sponsor: National Institutes of Health NIH/NIHES; Contract grant number: K24-ES00355.

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Accepted 23 June 2004

DOI 10.1002/ajim.20076. Published online in Wiley InterScience (www.interscience.wiley.com)

Isocyanate Uses

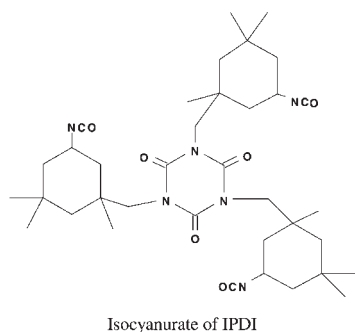
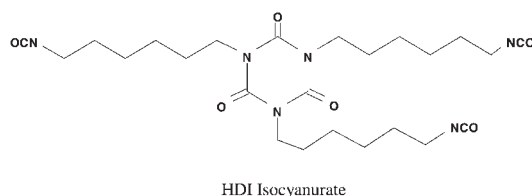
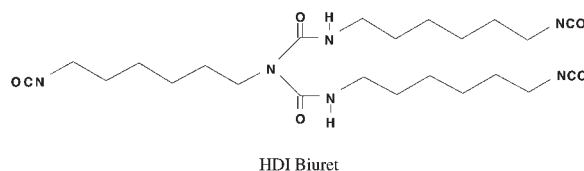
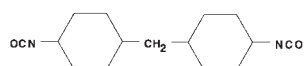
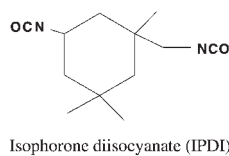
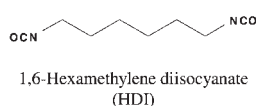
Isocyanates are highly reactive chemicals of low-molecular weight containing the functional group $\text{N}=\text{C}=\text{O}$. Isocyanates are classified based on the number of $\text{N}=\text{C}=\text{O}$ groups in the molecule into monoisocyanates (one NCO), diisocyanate monomers (two NCO), or polyisocyanates (multiple NCOs). The diisocyanate monomers are important because the two NCO groups allow them to undergo direct polymerization reactions with alcohols to form polyurethanes, in addition to enabling prepolymerization reactions to form commercially important polyisocyanates. Polyisocyanates formed by the condensation of up to ~ 10 monomeric isocyanates are also called oligomers. Polyisocyanates still contain multiple free NCO groups and can further react

with other active hydrogen compounds, such as polyfunctional alcohols (polyols) or amines, to form polymeric products of even greater complexity.

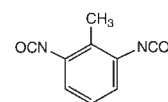
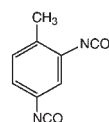
Isocyanates are also classified as either aromatic (one or more aromatic rings) or saturated (aliphatic and alicyclic), the term aliphatic isocyanate referring to saturated isocyanates. 2,4-/2,6-TDI, 4,4'-MDI, and their higher polymers are commercially the most important aromatic isocyanates, whereas 1,6-HDI, isophorone diisocyanate (IPDI), methylenedicyclohexyl diisocyanate (HMDI), and their higher polymers are the most important aliphatic isocyanates.

Figure 1 lists the chemical structures of some major isocyanates of commercial importance [Bayer Corporation, 1997]. Aliphatic isocyanates such as those based on HDI are used mostly in external paints and coatings due to their

A Aliphatic isocyanates

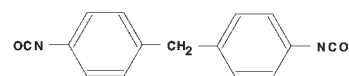


B Aromatic isocyanates

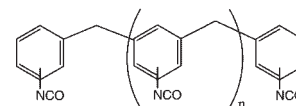
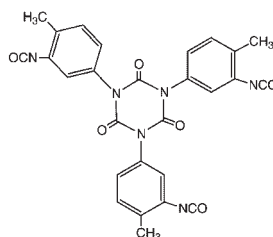


2,4-Toluene diisocyanate (2,4-TDI)

2,6-Toluene diisocyanate (2,6-TDI)

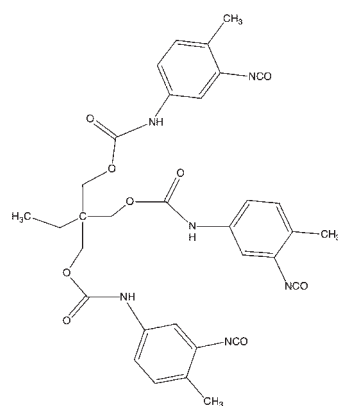


4,4'-Diphenylmethane diisocyanate (4,4'-MDI)



$n = 0 \text{ to } 4$

Polymeric MDI



TDI-trimethylolpropane adduct

FIGURE 1. Chemical structures of selected isocyanates of major commercial value.

excellent resistance to chemicals and abrasion, and superior weathering characteristics such as gloss and color retention. Aromatic isocyanates such as MDI are used in a diverse number of applications such as foams, adhesives, sealants, elastomers, and binders, which require fast curing rates and have less stringent requirements on their chemical and mechanical stability. Polyurethane foams are a major end-use of aromatic isocyanates.

Health Effects of Isocyanate Exposure

Exposure to diisocyanates can cause contact dermatitis, skin and respiratory tract irritation, immune sensitization and asthma, and less commonly hypersensitivity pneumonitis [NIOSH (National Institute for Occupational Safety and Health), 1996]. NIOSH considers 2,4-/2,6-TDI a potential occupational carcinogen [NIOSH (National Institute for Occupational Safety and Health), 1989, 1996]. However, sensitization and asthma are the primary health concerns, and their estimated prevalence in the exposed workforce is 1–20% [Vandenplas et al., 1993a; Bernstein, 1996; Petsonk et al., 2000; Wisnewski and Redlich, 2001; Diller, 2002]. Despite substantial research on isocyanates the pathogenic mechanisms, host susceptibility factors, and dose–response relationships remain unclear [Deschamps et al., 1998; Redlich et al., 1999; Liu and Wisnewski, 2003]. The influence of exposure characteristics such as duration, peak versus average exposures, chemical composition, and route of exposure on health outcomes is still poorly defined [Torling et al., 1990, 1997; Meredith et al., 2000; Conner, 2001; Peck, 2001; Ott et al., 2003].

There is growing evidence that skin exposure can be an important route of isocyanate sensitization in animal models [Karol et al., 1981; White et al., 1983; Rattray et al., 1994; Zissu et al., 1998; Le Coz et al., 1999; Herrick et al., 2002]. Although the evidence in humans regarding dermal exposure is more limited it is likely that skin exposure can induce isocyanate sensitization [Bernstein et al., 1993; Kimber, 1996; Petsonk et al., 2000; Redlich and Karol, 2002]. Skin exposure may be especially important with less volatile diisocyanates such as polyisocyanates and MDI, where skin contact may be the major route of exposure.

Despite uncertainties in understanding the mechanisms of isocyanate sensitization, the high reactivity of the NCO functional group is believed to be key in this process. Models seeking to predict chemical structure–biological activity relationships have found reactivity to be the major physico-chemical property that discriminates sensitizing chemicals from non-sensitizers [Karol et al., 2001]. Isocyanates, due to their high reactivity, can bind to carrier proteins, via the reaction of the NCO group with nucleophiles such as SH, NH₂, NH, and OH groups present in these proteins. Several peptides and proteins found in airway epithelial cells, serum and skin have been observed to bind diisocyanates, including

glutathione (tripeptide) [Day et al., 1997; Lange et al., 1999a], albumin [Sepai et al., 1995; Wisnewski et al., 1999], tubulin [Lange et al., 1999b], and keratin [Wisnewski et al., 1999, 2000]. Covalent binding of isocyanate groups to carrier proteins is likely an important step in the chain of events leading to sensitization and asthma.

The importance of NCO reactivity in determining isocyanate toxicity is also supported by the fact that different diisocyanate monomers and polyisocyanates cause the same health outcomes, primarily immune sensitization and asthma. Immunologic cross-reactivity between different isocyanates [Baur, 1983; Thorne et al., 1987; Baur, 1996] also suggests some commonality in the pathomechanisms of sensitization, possibly related to NCO binding carrier proteins. Together these factors suggest that the total NCO group content is an important determinant of the adverse effects of isocyanates, and therefore, its direct measurement might produce a relevant exposure metric.

Animal studies have also contributed to our understanding of the health effects of isocyanate exposure and potential differences in toxicity between different species. However, in evaluating animal toxicology data related to isocyanate asthma it is important to recognize that dose–response relationships with immune-mediated processes such as isocyanate asthma can be more variable and complex than with direct toxic effects. In addition, the dose that induces sensitization and the dose that induces subsequent responses and progressive disease can be quite variable. Concentration, route (respiratory vs. skin), and timing of antigenic exposures can modify immune responses, such that the same antigenic exposure can cause disease or immune tolerance, and lower doses can be more immunogenic and pathogenic than higher doses, which can even be protective. For example, in our mouse model of HDI asthma [Herrick et al., 2002], skin sensitization with a lower dose of HDI resulted in substantially greater airway inflammation following HDI airway challenge than mice sensitized with a higher skin dose of HDI (followed by the same HDI airway challenge). Also of note, there was discordance between the lung inflammatory response and the serum HDI-specific antibody response, with the higher skin sensitization dose of HDI causing substantially greater HDI-specific antibody production but minimal airway inflammation following airway challenge. Thus extrapolation from animal models to human health effects can be particularly challenging with immune-mediated processes, especially when many of the animal models have focused on direct toxic effects.

Toxicity Differences Within Diisocyanates or Polyisocyanates

Isocyanates likely differ in toxicity due to factors beyond inherent reactivity of the NCO functional group, such as properties (electrophilic, lipophilic, three-dimensional struc-

ture, etc.) of the moiety attached to the NCO group, deposition site in the lungs, or concomitant exposures such as solvents. Such properties likely determine a molecule's permeability through biological barriers and ability to get to a target reaction site. The moiety attached to the NCO group appears to be responsible in part for variations in biochemical reactivity and toxicity within the isocyanate class. For example, aromatic isocyanates react orders of magnitude faster than aliphatic isocyanates in reactions with active hydrogen compounds as a result of the electrophilic effect of the aromatic ring on the $\text{N}=\text{C}=\text{O}$ bond. It has been suggested that the more lipophilic isocyanates such as MDI and polymeric MDI (pMDI) may penetrate biological barriers easier, thus reaching biologically susceptible sites faster than less lipophilic isocyanates such as isocyanurate [Pauluhn, 2002]. Based on the interplay of such factors (reactivity, lipid solubility, and deposition site) one would expect a range of toxicities for different isocyanates.

Animal data suggests that there are some differences in toxicity between various isocyanates [Pauluhn et al., 1990, 1995, 2002; Pauluhn and Eben, 1992; Pauluhn, 2000a, 2000b, 2002; Pauluhn and Mohr, 2001]. With regard to diisocyanate monomers, the largest reported differences are for HDI versus MDI. When the no-observed-adverse-effect-levels (NOAEL) of the volatile aliphatic HDI (5 ppb or $17 \mu\text{g NCO}/\text{m}^3$) [Fourman et al., 1994] is compared to the non-volatile aromatic MDI (NOAEL $0.5 \text{ mg}/\text{m}^3$ or $\sim 160 \mu\text{g NCO}/\text{m}^3$) [Pauluhn, 2002], toxicity differences between the two monomers are approximately an order of magnitude. However, these NOAELs represent levels for different outcomes using different exposure protocols; hence, they are not strictly comparable.

The exposure-response information in most epidemiological and clinical studies to date is too limited and the exposure settings and uses too variable to make any conclusions regarding relative toxicity differences between monomeric isocyanates, TDI, MDI, and HDI [Jang et al., 2000; Meredith et al., 2000; Ott et al., 2003]. However, all three likely cause isocyanate sensitization and asthma at approximately similar doses and specific challenge studies with TDI, MDI, and HDI use similar challenge protocols (typically 5–20 ppb for up to 2 hr) to induce an asthmatic response [Vandenplas et al., 1992a; Malo et al., 1999].

Although animal studies comparing different polymeric isocyanates are limited, they suggest that toxicity differences between different polymeric isocyanates are not likely to vary by much more than the diisocyanate monomers. For example, the NOEL of pMDI ($0.16 \text{ mg NCO}/\text{m}^3$) is similar to that for polymeric HDI (pHDI, biuret, and isocyanurate; NOAEL $\sim 0.65 \text{ mg NCO}/\text{m}^3$) [Pauluhn and Mohr, 2001; Pauluhn, 2002]. Animal toxicity data for other polyisocyanates, such as polymeric IPDI (pIPDI) and polymeric TDI (pTDI), are limited and it is difficult to draw any general conclusions for the whole class of polyisocyanates based on

toxicity data of pMDI and pHDI. We are not aware of any human studies that compare the relative toxicity of different polyisocyanates.

Toxicity Differences Between the Monomer and its Polyisocyanate

In contrast to diisocyanate monomers, for which there is a significant body of animal and human literature, the data on polyisocyanates is more limited but demonstrates that polyisocyanates can cause the same adverse health effects as diisocyanate monomers. Studies of workers exposed to polyisocyanates have demonstrated isocyanate asthma in these settings [Welinder et al., 1988; Simpson et al., 1996; Ulvestad et al., 1999; Petsonk et al., 2000] and specific inhalation challenge testing of individual patients has confirmed that prepolymers can cause asthma [Vandenplas et al., 1992b, 1993b]. Cases of hypersensitivity pneumonitis have also been reported in workers exposed to polyisocyanates [Vandenplas et al., 1993; Baur, 1995]. The more limited clinical and epidemiologic literature on polyisocyanates is likely related to several factors and should not be interpreted as indicating lesser toxicity. Having gained commercial popularity more recently than the diisocyanate monomers, polyisocyanates have received less investigative attention. Polyisocyanates, typically complex mixtures of different isocyanate species that also contain variable amounts of the monomer, are therefore, more complex to quantitate than monomers [Streicher et al., 2000; Bello et al., 2002]. In addition, current exposure settings of concern are frequently small end-use applications, where use can be sporadic, and which can be more difficult to study than large isocyanate production facilities.

Analysis of toxicity differences between diisocyanate monomers and their respective polyisocyanates is, in addition to mixed monomer/polyisocyanate exposures, further complicated by a poor understanding of the relationship between the physical form of isocyanates and their deposition site in the respiratory tract. Monomers tend to occur mostly in the vapor phase and tend to be more chemically reactive than polymers; however, the partitioning value for isocyanate vapors in the upper and lower airways is unknown. Polyisocyanates have substantially lower vapor pressures and generally occur as an aerosol, the particle size distribution of which is determined primarily by its mode of generation rather than the isocyanate itself. Yet, particle size will determine where the isocyanate aerosol deposits in the respiratory tract, which may influence its biological effects.

An example is HDI monomer/polyisocyanate exposure. Animal studies suggest that HDI monomer may be more capable of inducing allergic airway inflammation than its polyisocyanate forms (pHDI) HDI-biuret and HDI-isocyanurate. However, with intradermal sensitization both HDI

monomer and its polyisocyanate forms (pHDI) produce high specific antibody titres [Pauluhn, 2002; Pauluhn et al., 2002]. The HDI monomer differs from its polyisocyanate forms with regard to its higher volatility ($>10^5\times$) and its tendency to partition between both the vapor and aerosol phases, which could result in different deposition sites in the lungs.

In contrast to HDI/pHDI, a study that evaluated findings from two different chronic aerosol inhalation studies concluded that the pulmonary effects of MDI and pMDI aerosols were almost identical and had equivalent NOAELs [Feron et al., 2001]. However, the two studies were designed as relatively high-dose carcinogenicity studies rather than models of immune-mediated asthma, used different exposure protocols, and used lung pathologic endpoints unrelated to asthma. Due to their low-vapor pressure, both MDI and pMDI occur primarily in aerosol form which makes their likely deposition sites more equivalent than that found with the vapor/aerosol combination present with HDI/pHDI. In addition, the pMDI product used in these studies also contained about 50% monomeric MDI. So, although these studies suggest no major differences between MDI and pMDI exposures, the caveats regarding the exposure scenarios used in these studies demonstrate the need to carefully evaluate the relevance of animal toxicity studies to human health effects.

Current Exposure Assessment

Monomers

Currently methods for analyzing a sample of a diisocyanate monomer use standards of the pure monomer as the reference material to quantify exposure levels in the form of a urea derivative, usually achieved through reaction with a primary or secondary amine. The result of these analyses is an estimate of the mass of that specific monomer present in the sample. Since the chemical structure of the monomers is well characterized, it is fairly easy to express the concentration in whichever unit one wishes. The two most common units used to express a monomer concentration are ppm or mg/m^3 of that specific monomer. The major problem with the conversion of ppm to/from mg/m^3 units for monomer concentrations is that the underlying assumption that all monomer exists in the vapor form is often not true. In many applications, monomers will partition between the aerosol phase and vapor phase, and the partitioning value will depend largely on the particular circumstances under investigation (monomer species, environmental conditions, application method, and sampling time with regard to the equilibrium point). For example, one study found that the HDI monomer was partitioned approximately 80% in the vapor phase and 20% as aerosol [Rando and Poovey, 1999]. Thus, use of mass/air volume units (e.g., mg/m^3) would better reflect the multi-phase nature of many of the monomers.

Polyisocyanates

Quantifying polyisocyanates is much more complex. There are currently three potential approaches used to quantify and express concentrations of polyisocyanates; the pure product mass, the NCO group concentration or mass, and the monomer equivalent mass. These approaches originate from the analytical method employed for their determination and may not be suitable as exposure metrics for studying health effects.

Pure product mass. This approach has been widely used to quantify isocyanate exposures. The pure bulk isocyanate products from the chemical manufacturer are used to create a calibration curve for the analytical instrument, typically high-performance liquid chromatograph (HPLC) with an ultraviolet, fluorescent, or electrochemical detector. The portion of the sample assumed to be the polyisocyanate is quantified as the mass of the pure bulk product [Rudzinski et al., 1995, 1996; Bayer CIHL (Corporate Industrial Hygiene Laboratory), 1996; Maître et al., 1996]. Although appealing due to its simplicity, this pure product mass approach has several disadvantages including an inability to handle complex exposures of mixed bulk composition, or to account for changes in the chemical composition of the aerosol as a result of ongoing curing reactions with polyols.

NCO count or mass. The NCO count or mass approach directly measures the NCO content of a sample, which is expressed as the NCO group concentration (moles of NCO group) or mass of total NCO groups and expressed as $\mu\text{g NCO}/\text{m}^3$. The NCO content of a sample can be measured directly by several analytical methods, which use a diisocyanate monomer standard to quantify the NCO content of a sample (MDHS-25/3 [HSE (Health and Safety Executive), 1999b] NIOSH method 5525 [NIOSH (National Institute for Occupational Safety and Health), 2004], and the 9-(methylaminomethyl)anthracene (MAMA) method [Lesage et al., 1992; Rando et al., 1993; Rando et al., 1995]). This NCO metric is used by the British, Australian and Swedish to regulate isocyanates, as discussed below [HSE (Health and Safety Executive), 1999a].

Monomer equivalent mass. The monomer equivalency unit of measurement is a variation of the NCO metric. It expresses the amount of polyisocyanate as the concentration of monomer that would have the equivalent number of NCO groups. The NCO content of the sample is converted to the monomer mass equivalent using a monomer dependent factor. For example, if HDI monomer is used as the reference standard, the HDI monomer mass equivalent concentration is two times the NCO mass concentration. This is because the molecular weight of HDI monomer (168) is twice that of

the two NCO groups (2×42) found in the molecule. This approach is used as a bridge between the NCO group count and the more common pure product mass concentration approach.

Our on-going studies of the autobody industry demonstrate the complexity of quantifying polyisocyanate exposures [Bello et al., 2002; Sparer et al., 2004; Woskie et al., 2004]. Two thirds of 68 bulk products collected from manufacturers' containers [Bello et al., 2002; Sparer et al., 2004] were mixtures of different polymeric products, the most frequent being pHDI isocyanurate premixed with polymeric IPDI (pIPDI) and pHDI biuret premixed with pHDI isocyanurate. The remaining third of the products contained only one type of polyisocyanate either pHDI biuret, pHDI isocyanurate, pIPDI, and/or other products. The NCO content of each isocyanate product type also varied widely (range 3.9–26.9%, mean 10.0%). Over 85% of Material Safety Data Sheets described these different HDI-based polymeric isocyanates nonspecifically with the same CAS number 28182-81-2 as 'homopolymer of HDI.' This lack of specificity coupled with the fact that many commercial products are of mixed isocyanate composition makes the choice of pure product for the basis of exposure quantification problematic.

Interconversion of Isocyanate Exposure Metrics

The typical exposure unit used to report polymeric isocyanate exposures is either mass pure product (e.g., mass of HDI biuret (N100)/m³) [Purnell and Walker, 1985; Alexandersson et al., 1987; Myer et al., 1993], or, less commonly, total NCO mass/m³ [Pisaniello and Muriale, 1989]. This dual system of units for field exposure data has caused confusion in comparing exposure data from different studies.

To facilitate comparison of exposure data for different isocyanate products, conversion factors to convert from pure product mass concentration to NCO mass concentration, where both are expressed in the same units, for example, mg/m³ are provided in Table I. For example, NCO mass concentration can be converted to Bayer N100 (HDI biuret) pure product mass by multiplying it with 4.55. Inversely, the Bayer N100 pure product mass concentration can be converted to NCO mass by dividing it by the same factor. The following formula can be used for conversion from NCO mass concentration to any isocyanate product mass concentration:

$$C_{IP_mass} = C_{NCO_mass} \times \frac{EW_{IP}}{42} = \frac{C_{NCO_mass}}{f_{NCO}} \quad (1)$$

where, C_{IP_mass} is mass concentration of the isocyanate product; C_{NCO_mass} is NCO mass concentration; EW_{IP} is the equivalent weight of the isocyanate product, calculated as $EW_{IP} = (\text{average}) \text{ MW product} / (\text{average}) \text{ number of NCO groups in the molecule}$; 42 is the equivalent weight of one NCO, EW_{NCO} ; f_{NCO} is the fraction of NCO in the product.

EW_{IP} and % NCO can be obtained from the product manufacturer or determined by titration.

Advantages of the NCO Mass Metric

The NCO mass unit offers a number of advantages for measuring isocyanate exposure over the pure product mass unit. For one, this exposure metric is explicit. There is no confusion about what it represents, and how it is calculated. Second, because NCO content is a common denominator of all isocyanates, comparisons between published data become straightforward and unambiguous. Because of its universality, this NCO metric is insensitive to rapid market changes in product formulations. For example, one study [Janko et al., 1992] reported HDI polyisocyanate concentration in mass/m³ using Bayer N75 (HDI biuret diluted with 25% solvent) and Bayer N3390 (HDI isocyanurate diluted with 10% solvent) as analytical standards. It is unclear how the solvent dilution factor relates to these exposure data. Another study [Myer et al., 1993] reports polyisocyanate mass concentrations based on Bayer HDI-based Desmodur[®] N products, which include biuret (N100, N3200, N75) and isocyanurate products (N3300, N3390).

TABLE I. Conversion Factors Between NCO mass/m³ and Various Isocyanate Products mass/m³ Units

Isocyanate ^a	Equivalent weight (EW _{IP}) ^b	Multiply NCO concentration by this factor to convert it to a specific product mass concentration ^c
1,6-HDI	84.1	2.00
IPDI	111.1	2.64
HDI biuret	191	4.55
HDI isocyanurate	195	4.64
2,4-/2,6-TDI	87.1	2.07
4,4'-MDI	125.2	2.98
HMDI	131.2	3.12
TDI prepolymer	Variable ^b	
MDI prepolymer	135.5 ^b	3.23
General formula for another product	EW _{IP}	EW _{IP} /42.0

To convert from NCO mass concentration to product mass concentration multiply by the given factor. To make the reverse conversion divide by the same factor. Both concentrations should be expressed in the same unit, for example, mg/m³.

^aHDI, 1,6-hexamethylene diisocyanate; IPDI, isophorone diisocyanate; TDI, 2,4- and/or 2,6-toluene diisocyanate; MDI, 4,4'-diphenylmethane diisocyanate; HMDI, 4,4'-methylenedicyclohexyl diisocyanate. Conversion factors for monomers apply also to exposure values expressed as monomer equivalent, namely, the amount of monomer having the same NCO content as the pre/polymeric product.

^bEW_{IP}, equivalent weight of the isocyanate product. EW_{IP} for prepolymeric TDI and MDI is very product dependent. Value shown for the MDI prepolymeric product is typical.

^cConversion factor = EW_{IP}/42, where EW_{1,6-HDI} = 84, EW_{IPDI} = 111.1, etc. and EW_{NCO} = 42.

Another advantage of using total NCO mass rather than pure product mass is that it enables the NCO content of bulk products comprised of a mixture of different isocyanate products to be expressed with a single unit. Although, if desired, each isocyanate type can also be expressed separately using this metric. Adding up the NCO contribution from different isocyanate products is more meaningful than adding up several different pure product masses to describe the total exposure in a mixed isocyanate exposure scenario. Finally, as previously discussed, measurement of the NCO content provides a more toxicologically relevant exposure metric. Thus we recommend that quantitative isocyanate exposure data be reported as NCO mass concentration. Information on the specific isocyanate products and diluents used should also be provided.

Current Isocyanate Occupational Exposure Limits (OELs)

A summary of existing airborne OELs for isocyanates is presented in Table II [Streicher et al., 2000]. The majority of these OELs are for diisocyanate monomers and only a few exist for polyisocyanates, despite the known human adverse health effects of polyisocyanate exposure. The Occupational Safety and Health Administration (OSHA) has ceiling Permissible Exposure Limits (PELs) for TDI and MDI monomers, but no 8-hr-time weighted average (TWA) standard for diisocyanates or polyisocyanates. NIOSH has ceiling and full-shift TWA recommended exposure limits (RELs) for several diisocyanate monomers, but none for polyisocyanates. The American Conference of Governmental Industrial Hygienists (ACGIH) has primarily full-shift TWA threshold limit values (TLVs) for a variety of monomers with a short-term exposure limit (STEL) set only for TDI monomer. ACGIH has no polyisocyanate TLVs. The OSHA, ACGIH, and NIOSH OELs for diisocyanate monomers are all based on the monomer mass concentration. The Bayer Corporation [Myer et al., 1993] has established Manufacturer's Guideline Limits (MGL), which were later adopted by the Oregon State OSHA [Janko et al., 1992] as an 8-hr PEL of 0.5 mg/m³ and a ceiling limit of 1 mg/m³ for the HDI-based polyisocyanates biuret and isocyanurate only (HDI monomer excluded), expressed as pure product mass concentration.

The United Kingdom Health and Safety Executive (UK-HSE) has taken a very different approach to regulating isocyanates using total NCO mass as the exposure metric. This approach combines all monomers and polyisocyanates into a single total isocyanate standard which is expressed as micrograms NCO group/m³. The UK-HSE sets the maximum exposure limits at 20 µg NCO/m³ for the full shift and 70 µg NCO/m³ for a 15-min short-term exposure limit (STEL) [HSE (Health and Safety Executive), 1999a]. The Australian National Occupational Safety and Health Com-

TABLE II. Current USA (OSHA, NIOSH, ACGIH), UK-HSE, and Swedish Occupational Exposure Limits (OEL) (µg/m³ air) for Isocyanates

Isocyanate species ^a	OSHA PEL			NIOSH REL			ACGIH [®] TLV [®]			Bayer Corporation OEL			UK-HSE OEL ^c			Swedish OEL		
	TWA 8-hr	Ceiling		TWA 10-hr	Ceiling 10 min		TWA 8-hr	STEL 15 min		TWA 8-hr	STEL 15 min		TWA 8-hr	Ceiling 10 min		TWA 8-hr	STEL 5 min	
Aromatic diisocyanates	—	140 (68)		CA-LFC ^b	—		36 (17)	140 (68)		—	—		—	—		—	—	
	—	200 (67)		50 (17)	200 (67)		51 (17)	—		—	—		—	—		—	—	
	—	—		40 (16)	170 (68)		—	—		—	—		—	—		—	—	
Aliphatic diisocyanates	—	—		35 (18)	140 (70)		34 (17)	—		—	—		—	—		—	—	
	—	—		45 (17)	180 (68)		45 (17)	—		—	—		—	—		—	—	
	—	—		—	110 (35)		54 (17)	—		—	—		—	—		—	—	
Polyisocyanate	—	—		—	—		—	—		500 (110)	1,000 (220)		—	—		—	—	
Universal std ^d	—	—		—	—		—	—		—	—		(20)	(70)		(20) ^e	(44) ^e	

Bracketed values represent the equivalent standard in µg NCO/m³.

^aProduct names are provided in the footnote "a" of Table I. NDI, naphthalene diisocyanate.

^bNIOSH considers TDI to be an occupational carcinogen (CA) and recommends that exposures be reduced to the lowest feasible concentration (LFC).

^cBayer's OEL, called manufacturer guideline limits (MGL), applies only to HDI-based polyisocyanates biuret and isocyanurate expressed as bulk product, excluding the HDI monomer. The State of Oregon OSHA has promulgated the same standards as Bayer's MGL.

^dTotal reactive isocyanate group in µg NCO group/m³. The standard applies to all isocyanate species (monomers, polyisocyanates, and their mixtures) regardless of their origin.

^eThe Swedish OEL is based on 5 ppb (TWA), which equals 90 µg HDI-biuret/m³ (20 µg NCO/m³), and 5-min STEL of ~13 ppb, which equals 200 µg HDI-biuret/m³ (44 µg NCO/m³).

mission has also adopted the UK-HSE maximum exposure limits for isocyanates [NOHSC (Australian National Occupational Health and Safety Commission), 1995]. The Swedish standard is set at 20 (TWA) and 44 (5-min STEL) $\mu\text{g NCO}/\text{m}^3$ (equal to 90 and 200 μg pure HDI-biuret mass/ m^3 , respectively) [Alexandersson et al., 1987; Torling et al., 1990].

All of these standards are expressed either as the pure product mass concentration for isocyanate-specific OELs (USA), or as a non-specific NCO mass concentration (UK and Sweden). Unlike isocyanate-specific OELs for monomers and HDI polyisocyanate, the UK and Swedish total NCO standards are a sum of monomer and prepolymeric isocyanate group content.

Origin of the Current Isocyanate OELs

Although the monomer mass OELs appear to be quite different from each other, in fact when reported as ppb or NCO mass concentration they are essentially the same ($17 \mu\text{g NCO}/\text{m}^3 = 5 \text{ ppb}$, 8 hr TWA) [Streicher et al., 2002]. The only exception is HMDI (Table II), for which NIOSH specifies a ceiling value equivalent to $35 \mu\text{g NCO}/\text{m}^3$. The diisocyanate monomer OELs were all (except HMDI) based on the airborne exposure levels for TDI [NIOSH (National Institute for Occupational Safety and Health), 1978]. The rationale for the TDI TWA OEL (5 ppb) is based primarily on the epidemiological study of Elkins et al. [1962] and the 10-min TDI ceiling (20 ppb) on the study of Hama [1957], discussed in detail in the NIOSH Criteria Document of 1973 [NIOSH (National Institute for Occupational Safety and Health), 1973]. The UK-HSE total NCO standards were extrapolated from the corresponding exposure limits for monomeric TDI under the assumption of equal toxicity for the monomeric and polymeric isocyanates [Silk and Hardy, 1983]. The Bayer Corporation guidelines for HDI-based polyisocyanates biuret and isocyanurate, adopted by Oregon State OSHA, were based on animal pulmonary irritation studies [Weyel et al., 1982; Ferguson et al., 1987]. The Swedish standard appears to be based on human epidemiologic studies using an approach similar to that of the UK-HSE total NCO standard, namely, an extrapolation of the monomer OEL's. The British standards are 5.5 (TWA) and 3.1 (STEL) times more protective than Bayer's MGL, but about 1.6 times less protective than the Swedish STEL standard. On an NCO basis, the 8 hr TWA OELs for monomers in the USA and for total NCO in Sweden and the UK are practically identical.

Basis for Future Standards

There has been considerable controversy in the literature whether the diisocyanate monomer OELs are sufficiently protective [Wegman et al., 1982; Gee and Morgan, 1985;

Woods, 1987; Banks et al., 1990; Bernstein et al., 1993; Clark et al., 1998; Meredith et al., 2000; Pauluhn, 2000a; Conner, 2001; Pauluhn and Mohr, 2001]. This is not surprising for an immune-mediated disease such as isocyanate asthma. Although fewer cases of isocyanate asthma are reported in settings with reduced exposures [Bernstein et al., 1993; Ott et al., 2003], dose-response relationships with isocyanate asthma remain poorly defined, as noted above, and the minimum dose necessary for immune sensitization remains unclear. Interest has shifted to regulating polyisocyanates because of their extensive use, their ability to cause sensitization and asthma, and the limited workplace regulations.

Occupational exposure standards typically cover a range of issues including requirements for medical and exposure monitoring and the use of personal protective equipment. Regulation of a whole class of chemicals, such as isocyanates, requires knowing that it is "more likely than not" that a significant risk of material impairment exists and that regulation will reduce that risk. Based on these criteria, identified toxicity of representative members of a chemical class would be adequate justification to regulate the whole class.

The main sources of toxicity data on polyisocyanates, namely, animal experiments and clinical and epidemiological studies, have their own limitations. Historically, clinical and epidemiological studies have focused on workers exposed to diisocyanate monomers (TDI, MDI, and HDI). When polyisocyanates have been studied, they tend to include mixed monomer and polyisocyanate exposures as noted. Finally, few human studies have included quantitative exposure-response analyses.

Although a number of animal isocyanate toxicology studies have been performed, animals provide only an approximation of the human health effects [Persson, 2002; Redlich et al., 2002] and such data cannot be applied to humans without incorporating a substantial uncertainty factor [Greenberg and Foureman, 1995]. Limitations of animal studies have included (1) use of acute high concentrations that cause respiratory tract irritation rather than immune sensitization and asthma, (2) the use of exposure protocols which may not reflect more complex and chronic human exposures, and (3) measurement of different endpoints. Thus, animal experiments, though important in furthering our understanding of isocyanates, do not provide data that can be easily extrapolated for standard setting.

Options for Future Isocyanate Exposure Limits

The call for regulation of polyisocyanates in occupational settings began two decades ago [Silk and Hardy, 1983; Janko et al., 1992] and has become more urgent as polyisocyanates increasingly compose the major form of isocyanate

exposure in many workplace environments. For example, HDI monomer levels during spray painting in autobody shops were so low that no personal samples exceeded the NIOSH 10 min ceiling REL while 79% of HDI polyisocyanate levels exceeded the UK STEL OEL of $70 \mu\text{g NCO}/\text{m}^3$ [Woskie et al., 2004]. Many agree that the question is not whether or not we should have a polyisocyanate OEL, but what kind of OEL it should be. A critical step in establishing such an OEL is developing a consensus regarding what exposure metric to use.

In principle, there are three major options for developing exposure limits for isocyanates: (i) Individual OELs based on isocyanate-specific toxicity data. This option would be reasonable if toxicity differences between and within isocyanate classes were excessively large. (ii) A single universal total NCO exposure limit of the type now in place in the UK, Sweden and Australia. This second option would be attractive if toxicological differences between isocyanates were relatively small. Since the majority of workplace environments present mixed isocyanate exposures, a single total NCO OEL would also be the simplest choice. (iii) A hybrid of the two, multiple total NCO OELs for which a mixture OEL formula could be applied. Using the multiple total NCO OELs approach, all isocyanate monomers could, for example, have a separate total NCO OEL, whereas all polyisocyanates could have another total NCO OEL. This alternative represents a compromise between the two prior options.

Of the three regulatory options presented, the first, individual OELs for each isocyanate species is undesirable for several reasons: (1) individual regulation is impractical, given the considerable number of isocyanates in use and a very innovative isocyanate market; (2) the current diisocyanate monomer OELs are in essence a single standard; (3) in addition, di- and poly-isocyanates cause similar adverse health effects in humans.

The second regulatory option would be to assign a single total NCO OEL for all forms of isocyanates, as is currently done, for example, in the UK, Sweden, and Australia. This approach has the advantage of simplicity for analysis and interpretation in light of the fact that most isocyanate workplace scenarios consist of a combination of monomer and polyisocyanate exposures, involving more than one type of isocyanate, and that isocyanate products and workplace processes are constantly changing. However, it ignores the possibility that some isocyanate forms may be less harmful than others. The argument has been made that polyisocyanates appear to be less toxic than monomers based on animal studies. However, as noted above the significance of these findings is lessened by concerns regarding the relevance of these animal studies to humans. In addition, some toxicity differences may be attributable to differences in the physical rather than chemical form of the isocyanate, i.e., an aerosol versus a vapor, which can vary as the isocyanate products and production processes change. Thus focusing on the

biologically reactive functional group presents a simple, practical, and conservative approach to standard setting. However, this option could result in over regulation of less toxic isocyanates.

The third option would be to develop dual total NCO OELs; one for all monomers and one for all polyisocyanates. This approach would allow for the possibility that monomeric isocyanates and polyisocyanates may have different toxicities. The single monomer OEL would be retained and expressed as NCO concentration (current equivalent would be $17 \mu\text{g NCO}/\text{m}^3$ TWA and $70 \mu\text{g NCO}/\text{m}^3$ ceiling) and a new polyisocyanate standard would be set. To accommodate the many complex exposure environments with mixed monomeric and polyisocyanate exposures that are present in workplaces, a mixture OEL approach could be used. In mixed exposure environments, the mixture OEL would be exceeded if the concentration/OEL for polyisocyanates plus the concentration/OEL for monomers exceeded 1. Although this approach assumes the toxicity of the two isocyanate forms is additive, until research discovers another relationship this approach would address the mixed exposure environment. Besides the issues previously raised concerning the underpinning of this approach, a dual OEL would be more cumbersome and costly since it requires separate quantification for monomer and polyisocyanate for each sample. Since most workplace environments with substantial polyisocyanate use will also have monomer exposures the mixture OEL will have to be applied. However, in many cases the majority of the NCO exposure will come from the polyisocyanate fraction, making the effort to differentiate the forms a marginal contribution to evaluating worker risk.

Adoption of either the single or dual total NCO exposure limits would present a vast improvement over the current situation in the United States, where only a handful of monomer standards using the mass pure product metric are in place, and there are no standards that apply to polyisocyanates. The switch to a total NCO metric is favored on practical and toxicological grounds. It would be easier to implement analytically, would cover both monomer and polyisocyanate exposure scenarios, and would simplify comparison of toxicological and epidemiological studies. Consensus on standardization of an NCO exposure metric could facilitate the development of polyisocyanate OELs. However, it is not our goal to recommend specific OELs. In addition, it should be noted that the isocyanate OELs do not address protection from skin exposure, which may prove to be another important component of disease prevention.

CONCLUSIONS

Polyisocyanate exposures are common in today's workplace and often represent the major exposure source to isocyanates. Polyisocyanates, similar to diisocyanate

monomers, can cause sensitization and asthma and represent an important health risk to workers. This demands accurate determination, regulation, and exposure control. Mixed exposure scenarios impose major challenges to the occupational hygienists and physicians who have to sort through different and often confusing exposure units and standards. We have argued that the NCO mass concentration metric offers advantages to the metric based on the pure product mass concentration and have recommended that future analytic samples and OELs be expressed as mass NCO/m³. We have further argued that the adoption of either a single total NCO or dual total monomer/total polyisocyanate NCO OEL approach is justified. A polyisocyanate OEL would be a substantial improvement over the current situation in the United States and would facilitate the control of the entire class of isocyanates. Further clinical, epidemiologic, and animal research is needed to better understand isocyanate exposure risk factors and elucidate disease mechanisms. In the interim, isocyanate regulation will benefit from constructive debate and discussion among isocyanate researchers, users and producers, and policy makers.

ACKNOWLEDGMENTS

The authors acknowledge contribution of Greg Lotz, Heinz Ahlers, and Lisa Delaney at NIOSH for their insights and comments of the manuscript.

REFERENCES

- Alexandersson R, Plato N, Kolmodin-Hedman B, Hedenstierna G. 1987. Exposure, lung function, and symptoms in car painters exposed to hexamethylene diisocyanate and biuret modified hexamethylene diisocyanate. *Arch Environ Health* 42:367–373.
- Banks DE, Rando RJ, Barkman HW, Jr., 1990. Persistence of toluene diisocyanate-induced asthma despite negligible workplace exposures. *Chest* 97:121–125.
- Baur X. 1983. Immunologic cross-reactivity between different albumin-bound isocyanates. *J Allergy Clin Immunol* 71:197–205.
- Baur X. 1995. Hypersensitivity pneumonitis (extrinsic allergic alveolitis) induced by isocyanates. *J Allergy Clin Immunol* 95(5 Pt 1): 1004–1010.
- Baur X. 1996. Occupational asthma due to isocyanates. *Lung* 174(1): 23–30.
- Bayer CIHL (Corporate Industrial Hygiene Laboratory). 1996. Determination of isocyanates in spray mist environments by sampling with an impinger containing *N*-(4-nitrobenzyl)-propylamine in toluene and analysis by high performance liquid chromatography. (Method No. Bayer CIHL 1.4.4.) Pittsburgh, PA.
- Bayer Corporation. 1997. The chemistry of polyurethane coatings: A general reference manual. Pittsburgh, PA: Bayer Corporation.
- Bello D, Streicher RP, Woskie SR. 2002. Evaluation of the NIOSH draft method 5525 for determination of the total reactive isocyanate group (TRIG) for aliphatic isocyanates in autobody repair shops. *J Environ Monit* 4:351–360.
- Bernstein JA. 1996. Overview of diisocyanate occupational asthma. *Toxicology* 111(1–3):181–189.
- Bernstein DI, Korbee I, Stauder T, Bernstein JA, Scinto J, Herd ZL, Bernstein IL. 1993. The low prevalence of occupational asthma and antibody-dependent sensitization to diphenylmethane diisocyanate in a plant engineered for minimal exposure to diisocyanates. *J Allergy Clin Immunol* 92:387–396.
- Clark RL, Bugler J, McDermott M, Hill ID, Allport DC, Chamberlain JD. 1998. An epidemiology study of lung function changes of toluene diisocyanate foam workers in the United Kingdom. *Int Arch Occup Environ Health* 71:169–179.
- Conner P. 2001. Occupational asthma: Can this disease be controlled? Based on AIHCE 1999 roundtable 247. Fairfax, VA: AIHA Press. p 36–43.
- Day B, Jin R, Basalyga D, Kramarik JA, Karol MH. 1997. Formation, solvolysis, and transcarbamoylation reactions of bis(*S*-glutathionyl) adducts of 2,4- and 2,6-diisocyanatotoluene. *Chem Res Toxicol* 10: 424–431.
- Deschamps F, Prevost A, Lavaud F, Kochman S. 1998. Mechanisms of occupational asthma induced by isocyanates. *Ann Occup Hyg* 42: 33–36.
- Diller WF. 2002. Frequency and trends of occupational asthma due to toluene diisocyanate: A critical review. *Appl Occup Environ Hyg* 17: 872–877.
- Elkins HB, McCarl GW, Brugsch HG, Fahy JP. 1962. Massachusetts experience with toluene di-isocyanate. *Am Ind Hyg Assoc J* 23:265–272.
- Ferguson JS, Schaper M, Alarie Y. 1987. Pulmonary effects of a polyisocyanate aerosol: Hexamethylene diisocyanate trimer (HDI₃) or Desmodur N (Des-N). *Toxicol Appl Pharmacol* 89:332–346.
- Feron VJ, Kittel B, Kuper CF, Ernst H, Rittinghausen S, Muhle H, Koch W, Gamer A, Mallett AK, Hoffmann HD. 2001. Chronic pulmonary effects of respirable methylene diphenyl diisocyanate (MDI) aerosol in rats: Combination of findings from two bioassays. *Arch Toxicol* 75: 159–175.
- Foureman GL, Greenberg MM, Sangha GK, Stuart BP, Shiotsuka RN, Thyssen JH. 1994. Evaluation of nasal tract lesions in derivation of the inhalation reference concentration for hexamethylene diisocyanate. *Inhal Toxicol* 6(Suppl):341–355.
- Gee JB, Morgan WK. 1985. A 10-year follow-up study of a group of workers exposed to isocyanates. *J Occup Med* 27(1):15–18.
- Greenberg MM, Foureman GL. 1995. Derivation of the inhalation reference concentration for hexamethylene diisocyanate. *Toxic Sub Mech* 14:151–167.
- Hama GM. 1957. Symptoms in workers exposed to isocyanates—suggested exposure concentrations. *AMA Arch Ind Health* 16:232–233.
- Herrick CA, Xu L, Wisniewski AV, Das J, Redlich CA, Bottomly K. 2002. A novel mouse model of diisocyanate-induced asthma showing allergic-type inflammation in the lung after inhaled antigen challenge. *J Allergy Clin Immunol* 109:873–878.
- HSE (Health and Safety Executive). 1999a. EH 40/98, occupational exposure limits 1998. Sudbury, England: HSE Books.
- HSE (Health and Safety Executive). 1999b. MDHS 25/3, methods for the determination of hazardous substances: Organic isocyanates in air. London: Health and Safety Executive/Occupational Safety and Hygiene Laboratory.
- Jang AS, Choi IS, Koh YI, Moon JD, Lee KJ. 2000. Increase in airway hyperresponsiveness among workers exposed to methylene diphenyl-diisocyanate compared to workers exposed to toluene diisocyanate at a petrochemical plant in Korea. *Am J Ind Med* 37:663–667.

- Janko M, McCarthy K, Fajer M, van Raalte J. 1992. Occupational exposure to 1,6-hexamethylene diisocyanate-based polyisocyanates in the state of Oregon, 1980–1990. *Am Ind Hyg Assoc J* 53:331–338.
- Karol MH, Hauth BA, Riley EJ, Magreni CM. 1981. Dermal contact with toluene diisocyanate (TDI) produces respiratory tract sensitivity in guinea pigs. *Toxicol Appl Pharmacol* 58:221–230.
- Karol MH, Macina DT, Cunningham AC. 2001. Cell and molecular biology of chemical asthma. *Ann Allergy Asthma Immunol* 87:28–32.
- Kimber I. 1996. The role of skin in the development of chemical respiratory hypersensitivity. *Toxicol Lett* 86:89–92.
- Lange RW, Day BW, Lemus R, Tyurin VA, Kagan VE, Karol MH. 1999a. Intracellular S-glutathionyl adducts in murine lung and human bronchoepithelial cells after exposure to diisocyanatotoluene. *Chem Res Toxicol* 12:931–936.
- Lange RW, Lantz RC, Slotz DB, Watkins SC, Sundaresan P, Lemus R, Karol MH. 1999b. Toluene diisocyanate colocalizes with tubulin on cilia of differentiated human airway epithelial cells. *Toxicol Sci* 50:64–71.
- Le Coz C-J, El Aboubi S, Ball C. 1999. Active sensitization to toluene di-isocyanate. *Contact Dermatitis* 41:104–105.
- Lesage J, Goyer N, Desjardins F, Vincent J-Y, Perrault G. 1992. Workers' exposure to isocyanates. *Am Ind Hyg Assoc J* 53:146–153.
- Liu Q, Wisniewski AV. 2003. Recent developments in diisocyanate asthma. *Ann Allergy Asthma Immunol* 90(5 Suppl 2):35–41.
- Malo JL, Ghezzi H, Elie R. 1999. Occupational asthma caused by isocyanates: Patterns of asthmatic reactions to increasing day-to-day doses. *Am J Respir Crit Care Med* 159(6):1879–1883.
- Maitre A, Leplay A, Perdrix A, Ohl G, Boinay P, Romazini S, Aubrun JC. 1996. Comparison between solid sampler and impinger for evaluation of occupational exposure to 1,6 hexamethylene diisocyanate polyisocyanates during spray painting. *Am Ind Hyg Assoc J* 57:153–160.
- Meredith SK, Bugler J, Clark RL. 2000. Isocyanate exposure and occupational asthma: A case-referent study. *Occup Environ Med* 57:830–836.
- Myer HE, O'Block ST, Dharmarajan V. 1993. A survey of airborne HDI, HDI-based polyisocyanate and solvent concentrations in the manufacture and application of polyurethane coatings. *Am Ind Hyg Assoc J* 54:663–670.
- NIOSH (National Institute for Occupational Safety and Health). 1973. Criteria for a recommended standard: Occupational exposure to toluene diisocyanate. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, HSM 73-11022.
- NIOSH (National Institute for Occupational Safety and Health). 1978. Criteria for a recommended standard: Occupational exposure to diisocyanates. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, NIOSH Publication No. 78–215.
- NIOSH (National Institute for Occupational Safety and Health). 1989. Current Intelligence Bulletin 53, Toluene Diisocyanate (TDI) and Toluenediamine (TDA): Evidence of Carcinogenicity, U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.
- NIOSH (National Institute for Occupational Safety and Health). 1996. Preventing asthma and death from diisocyanate exposure. DHHS (NIOSH) publication No. 96-111, U.S. Department of Health and Human Services, Public Health Services, Centers for Disease Control and Prevention.
- NIOSH (National Institute for Occupational Safety and Health). 2004. NIOSH manual of analytical methods. 4th edition. In: Schlecht PC, O'Connor PF, editors. Cincinnati, OH: NIOSH. Method 5525, isocyanates, total (MAP), issue 1.
- NOHSC (Australian National Occupational Health and Safety Commission). 1995. Adopted national exposure standards for atmospheric contaminants in the occupational environment. NOHSC: 1003.
- Ott MG, Diller WF, Jolly AT. 2003. Respiratory effects of toluene diisocyanate in the workplace: A discussion of exposure–response relationships. *Crit Rev Toxicol* 33(1):1–59.
- Pauluhn J. 2000a. Inhalation toxicity of 1,6-hexamethylene diisocyanate homopolymer (HDI-IC) aerosol: Results of a single inhalation exposure studies. *Toxicol Sci* 58:173–181.
- Pauluhn J. 2000b. Acute inhalation toxicity of polymeric diphenylmethane 4,4'-diisocyanate in rats: Time course of changes in bronchoalveolar lavage. *Arch Toxicol* 74:257–269.
- Pauluhn J. 2002. Short-term inhalation toxicity of polyisocyanate aerosols in rats: Comparative assessment of irritant-threshold concentrations by bronchoalveolar lavage. *Inhal Toxicol* 14:287–301.
- Pauluhn J, Eben A. 1992. Altered lung function in rats after subacute exposure to *n*-butyl isocyanate. *Arch Toxicol* 66:118–125.
- Pauluhn J, Mohr U. 2001. Inhalation toxicity of 1,6-hexamethylene diisocyanate homopolymers (HDI-IC and HDI-BT): Results of subacute and subchronic repeated inhalation exposure studies. *Inhal Toxicol* 13:513–532.
- Pauluhn J, Eben A, Kimmerle G. 1990. Functional, biochemical, and histopathological evidence of airway obstruction in rats following a four-hour acute inhalation exposure to *n*-butyl isocyanate. *Exp Pathol* 40:197–202.
- Pauluhn J, Rungeler W, Mohr U. 1995. Phenyl isocyanate-induced asthma in rats following a 2-week exposure period. *Fundam Appl Toxicol* 24:217–228.
- Pauluhn J, Eidmann P, Mohr U. 2002. Respiratory hypersensitivity in guinea pigs sensitized to hexamethylene diisocyanate (HDI): Comparison of results obtained with the monomer and homopolymers of HDI. *Toxicology* 171:147–160.
- Peck J. 2001. In: Occupational asthma: Can this disease be controlled? Based on AIHCE 1999 roundtable 247. Fairfax, VA: AIHA Press. p 1–6.
- Persson CG. 2002. Con: Mice are not a good model of human airway disease. *Am J Respir Crit Care Med* 166:6–7.
- Petsonk EL, Wang ML, Lewis DM, Siegel PD, Husberg BJ. 2000. Asthma-like symptoms in wood product plant workers exposed to methylene diphenyl diisocyanate. *Chest* 118:1183–1193.
- Pisaniello DL, Muriale L. 1989. The use of isocyanate paints in auto refinishing—a survey of isocyanate exposures and related work practices in South Australia. *Ann Occup Hyg* 33:563–572.
- Purnell CJ, Walker RF. 1985. Methods for the determination of atmospheric organic isocyanates: A review. *Analyst* 110:893–905.
- Rando R, Poovey HG. 1999. Development and application of a dichotomous vapor/aerosol sampler for HDI-derived total reactive isocyanate group. *Am Ind Hyg Assoc J* 60:737–746.
- Rando RJ, Poovey HG, Lefante RR, Esmundo FR. 1993. Evaluation of 9-methylaminomethyl-anthracene as a chemical label for total reactive isocyanate group: A comparison of mono- and di-isocyanate monomers. *J Liquid Chromatogr* 16:3977–3996.
- Rando RJ, Poovey HG, Gibson RA. 1995. Evaluation of 9-methylaminomethyl-anthracene as a chemical label for total reactive isocyanate group: Application to isocyanate oligomers, polyurethane precursors, and phosgene. *J Liquid Chromatogr* 17:2743–2763.
- Rattray NJ, Botham PA, Hext PM, Woodcock DR, Fielding I, Dearman RJ, Kimber I. 1994. Induction of respiratory hypersensitivity to

- diphenylmethane-4,4'-diisocyanate (MDI) in guinea pigs. Influence of route of exposure. *Toxicology* 88:15–30.
- Redlich CA, Karol MH. 2002. Diisocyanate asthma: Clinical aspects and immunopathogenesis. *Int Immunopharmacol* 2:213–214.
- Redlich CA, Cain H, Wisnewski AV. 1999. The immunology and prevention of isocyanate asthma: A model for low molecular weight asthma. *Semin Resp Crit Care Med* 20:591–599.
- Redlich CA, Wisnewski AV, Gordon T. 2002. Mouse model of diisocyanate asthma. *Am J Respir Cell Mol Biol* 27:385–390.
- Rudzinski WE, Dahlquist B, Svejda SA, Richardson A, Thomas T. 1995. Sampling and analysis of isocyanates in spray-painting operations. *Am Ind Hyg Assoc J* 56:284–289.
- Rudzinski WE, Norman S, Dahlquist B, Greebon KW, Richardson A, Locke K, Thomas T. 1996. Evaluation of 1-(9-anthracenylmethyl) piperazine for the analysis of isocyanates in spray-painting operations. *Am Ind Hyg Assoc J* 57:914–917.
- Sepai O, Henschler D, Sabbioni G. 1995. Albumin adducts, hemoglobin adducts, and urinary metabolites in workers exposed to 4,4'-methylene-diphenyl diisocyanate. *Carcinogenesis* 16:2583–2587.
- Silk SJ, Hardy HL. 1983. Control limits for isocyanates. *Ann Occup Hyg* 27:333–339.
- Simpson C, Garabrant D, Torrey S, Robins T, Franzblau A. 1996. Hypersensitivity pneumonitis-like reaction and occupational asthma associated with 1,3-bis(isocyanatomethyl) cyclohexane pre-polymer. *Am J Ind Med* 30:48–55.
- Sparer J, Stowe M, Bello D, Liu Y, Gore RJ, Youngs F, Cullen MR, Redlich CA, Woskie SR. 2004. Isocyanate exposure in autobody shops work: The Spray study. *J Occup Environ Hyg* 1:1–12.
- Streicher RP, Reh CM, Key-Schwartz RJ, Schlecht P, Cassinelli ME, O'Connor PF. 2000. Determination of airborne isocyanate exposure: Considerations in method selection. *Am Ind Hyg Assoc J* 61:544–556.
- Streicher RP, Reh CM, Key-Schwartz R, Schlecht PC, Cassinelli ME, O'Connor PF. 2002. Selecting isocyanate sampling and analytical methods. *Appl Occup Environ Hyg* 17:157–162.
- Tarlo SM, Liss GM, Dias C, Banks DE. 1997. Assessment of the relationship between isocyanate exposure levels and occupational asthma. *Am J Ind Med* 32:517–521.
- Thorne PS, Hillebrand JA, Lewis GR, Karol MH. 1987. Contact sensitivity by diisocyanates: Potencies and cross-reactivities. *Toxicol Appl Pharmacol* 87:155–165.
- Torling G, Alexandersson R, Hedenstierna G, Plato N. 1990. Decreased lung function and exposure to diisocyanates (HDI and HDI-BT) in car repair painters: Observations on re-examination 6 years after initial study. *Am J Ind Med* 17:299–310.
- Ulvestad B, Melbostad E, Fuglerud P. 1999. Asthma in tunnel workers exposed to synthetic resins. *Scand J Work Environ Health* 25:335–341.
- Vandenplas O, Malo JL, Cartier A, Perreault G, Cloutier Y. 1992a. Closed-circuit methodology for inhalation challenge tests with isocyanates. *Am Rev Respir Dis* 145:582–587.
- Vandenplas O, Cartier A, Lesage J, Perreault G, Grammer LC, Malo JL. 1992b. Occupational asthma caused by a prepolymer but not the monomer of toluene diisocyanate (TDI). *J Allergy Clin Immunol* 89:1183–1188.
- Vandenplas O, Malo JL, Saetta M, Mapp CE, Fabbri LM. 1993a. Occupational asthma and extrinsic alveolitis due to isocyanates: current status and perspectives. *Br J Ind Med* 50:213–228.
- Vandenplas O, Cartier A, Lesage J, Cloutier Y, Perreault G, Grammer LC, Shaughnessy MA, Malo JL. 1993b. Prepolymers of hexamethylene diisocyanate as a cause of occupational asthma. *J Allergy Clin Immunol* 91:850–861.
- Wegman DH, Musk AW, Main DM, Pagnotto LD. 1982. Accelerated loss of FEV-1 in polyurethane production workers: A four year prospective study. *Am J Ind Med* 3:209–215.
- Welinder H, Nielsen J, Bensryd I, Skerfving S. 1988. IgG antibodies against polyisocyanates in car painters. *Clin Allergy* 18:85–93.
- Weyel DA, Rodney BS, Alari Y. 1982. Sensory irritation, pulmonary irritation, and acute lethality of a polymeric isocyanate and sensory irritation of 2,6-toluene diisocyanate. *Toxicol Appl Pharmacol* 64:423–430.
- White IR, Stewart JR, Rycroft RJG. 1983. Allergic contact dermatitis from an organic diisocyanate. *Contact Dermatitis* 9:300–303.
- Wisnewski AV, Redlich CA. 2001. Recent developments in diisocyanate asthma. *Curr Opin Allergy Clin Immunol* 1:169–175.
- Wisnewski AV, Lemus R, Carol MH, Redlich CA. 1999. Isocyanate-conjugated human lung epithelial cell proteins: A link between exposure and asthma? *J Allergy Clin Immunol* 104:341–347.
- Wisnewski AV, Srivastava R, Herick C, Xu L, Lemus R, Cain H, Magoski NM, Karol MH, Bottomly K, Redlich CA. 2000. Identification of human lung and skin proteins conjugated with hexamethylene diisocyanate in vitro and in vivo. *Am J Resp Crit Care Med* 162:2330–2336.
- Woods G. 1987. The ICI polyurethanes book. New York: ICI Polyurethanes. John Wiley & Sons. p 222–223.
- Woskie SR, Sparer J, Gore R, Stowe M, Bello D, Liu Y, Youngs F, Redlich CA, Eisen EA, Cullen MR. 2004. Determinants of exposure to isocyanates in auto body shops. Determinants of isocyanate exposures in autobody repair and refinishing shops annals. *Occup Hyg* 48(3):211–221.
- Zissu D, Binet S, Limasset JC. 1998. Cutaneous sensitization to some polyisocyanate prepolymers in guinea pigs. *Contact Dermatitis* 39:248–251.