Bengtström *et al. Fire Science Reviews* (2016) 5:4
DOI 10.1186/s40038-016-0013-2

Fire Science Reviews

REVIEW Open Access

The role of isocyanates in fire toxicity

Linda Bengtström, Mariëlle Salden and Anna A. Stec*

Abstract

Isocyanates are a group of low molecular weight, highly reactive compounds with a functional isocyanate group. The main human exposure route is via inhalation of airborne isocyanates, although dermal exposure has also been reported. The inhalation of isocyanates is associated with severely adverse health effects such as asthma, inflammation in the respiratory tract and cancer. During thermal degradation of polyurethane materials, airborne isocyanates can be sampled in the fire effluent. This paper discusses the reactivity and commercial applications of isocyanates and the generation of airborne isocyanates during thermal degradation, the human health effects as well as the environmental fate of some of the most commercially important isocyanates. This is followed by a review of the generation of isocyanates from large-scale fire testing and bench-scale test methods as well as sampling techniques and derivatisation agents necessary to stabilise the isocyanates and analysis.

Keywords: Isocyanate, Fire, Toxicity, Thermal degradation, Analysis, Sampling, Derivatisation

Introduction

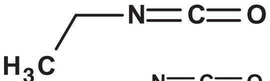
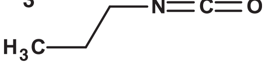
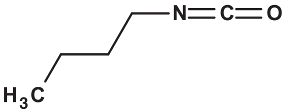
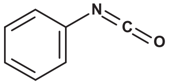
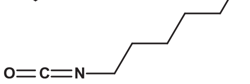
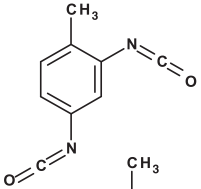
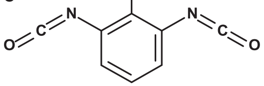
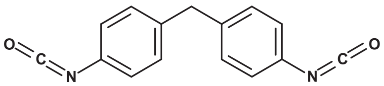
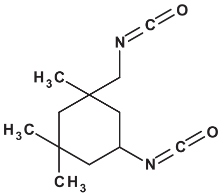
Isocyanates are a family of highly reactive and relatively low molecular weight aromatic and aliphatic compounds. The family is defined by the isocyanate functional group ($-N=C=O$). Most commercial isocyanates contains one isocyanate group (mono-isocyanates) or two isocyanate groups (di-isocyanates), attached to an aliphatic or an aromatic moiety (Avar et al. 2012). Inhalation of isocyanates is the most important human exposure route and may result in respiratory sensitisation (Kimber & Dearman 2002). There is also limited evidence that dermal contact may result in human respiratory sensitisation (Pronk 2006). The high chemical reactivity of isocyanates are reflected in their toxicity, as exposure to isocyanates is one of the most common causes of occupational asthma in developed countries (Redlich & Karol 2002; Lockey et al. 2015). Additionally, low concentrations of airborne isocyanates are acutely toxic following inhalation, and the production of isocyanates and products containing isocyanates is therefore heavily regulated from a health and safety at work perspective (Mishra et al. 2009), particularly polyurethane (PU) based foams, fillers and coatings. However, airborne isocyanates have also been sampled in fire effluent from building materials during the early stages of fire development (Blomqvist et al. 2003).

Isocyanates are widely used in the manufacturing of flexible and rigid PU foams (PUF and PUR respectively), soft furniture and insulation in buildings as well as fridges and freezers respectively (Avar et al. 2012). In addition isocyanates are used in the manufacturing of fibres, paint and varnish formulation, and are increasingly used in the automobile and aerospace industry as co-monomers for paints and lacquers (Avar et al. 2012; Boutin et al. 2004; No et al. 2014). Due to their versatility and wide range of applications, isocyanate-containing products can be found in most homes as well as office and public buildings. The two main products in the isocyanate market, with an approximate market share of 90 %, are both di-isocyanates: isomers of toluene-di-isocyanate (TDI) and diphenylmethane-di-isocyanate (MDI), see Table 1 (Twitchett 1974; Market and Markets 2014). The global production of di-isocyanates was estimated at six billion metric tonnes in 2007, which is 35 % higher than in 2000 (Markets 2014). It is estimated that the annual increase in production for isocyanates in the next years will be approximately 7 %, mainly due to an increased demand for TDI and aromatic isocyanates as well as 1,5-naphthalene di-isocyanate (NDI) in paint and coating industry (Market and Markets 2014). In 2019, the global annual production of isocyanates is estimated to be worth around $39 billion (Market and Markets 2014).

---

* Correspondence: AAStec@uclan.ac.uk
Centre for Fire and Hazards Science, School of Physical Sciences and Computing, University of Central Lancashire, PR1 2HE Preston, UK

Table 1 Structures for the most commercially important isocyanates. Also presented is CAS number, molecular weight and other physico-chemical properties, such as melting point, boiling point and vapour pressure as well as solubility and main commercial uses

Compound	CAS number	Molecular weight ($g \cdot mol^{-1}$)	Structure	Melting point (℃)	Boiling point (℃ at 760 mmHg)	Vapour pressure (mmHg at 25 ℃)	Solubility	Commercial use
Isocyanic acid (ICA)	75-13-8	43.03		−86	17	6752.5	Water, benzene, toluene, ether	
Methyl isocyanate (MIC)	624-83-9	57.05		−45	39	348	Water	Chemical intermediate
Ethyl isocyanate (EIC)	109-90-0	71.08		−50	60	209.5	Soluble in ethanol, ether, chlorinated and aromatic hydrocarbons as well as water	Chemical intermediate
Propyl isocyanate (PIC)	110-78-1	85.10		−30	83	83.9	Insoluble in water	
Phenyl isocyanate (PHI)	103-71-9	119.12		−30	163	2.1	Water, alcohol; very soluble in ether	Chemical intermediate
Hexamethylene di-isocyanate (HDI)	822-06-0	168.19		−67	255	0.0	Water	Coatings
Toluene di-isocyanate (2,4-TDI)	584-84-9	174.16		20	251	0.0	Very soluble in ether. acetone, and other organic solvents	PUF, PUR
Toluene di-isocyanate (2,6-TDI)	91-08-7	174.16		18	248	0.0	Soluble in acetone, benzene, decomposes in water	PUF, PUR
Methylene bisphenyl di-isocyanate (MDI)	101-68-8	250.25		38	373	0.1	Soluble in acetone, benzene, kerosene, and nitrobenzene, decomposes in water	PUR, PIR
Isophorone di-isocyanate (IPDI)	4098-71-9	222.28		−60	158	0.0	Soluble in esters, ketones, ethers, and aromatic and aliphatic hydrocarbons. Decomposes in water	Crosslinking agent, coatings

One of the main end-product categories for isocyanates are PUF and PUR foams as well as polyisocyanurate (PIR) foams (Markets and Markets 2011). TDI is mainly used for the production of flexible foam but can also be used in lacquers. MDI is used to produce rigid foam, as a base for glues or as a binder in sand moulds for iron casting (Dahlin 2007). Isocyanates such as hexamethylene di-isocyanate (HDI) and isophorone di-isocyanate (IPDI), are used in applications such as coatings as these compounds are UV-resistant (Karlsson et al. 1998). Aromatic isocyanates like TDI and MDI oxidize when exposed to UV-light and are therefore not suitable to be used in outdoor coatings (Rogers & Long 2003). Besides insulation foams, PU sprays containing isocyanates have been developed for a wide range of applications to protect concrete, wood, steel and aluminium constructions and fibreglass (Avar et al. 2012).

This article is a review of isocyanates present in common material found in buildings such as PU insulation and upholstery furniture foam as well as the generation of isocyanates during thermal degradation of these materials. The first part of this review discusses the reactivity and commercial applications of isocyanates and the thermal degradation of materials generating airborne isocyanates. The second part summarizes toxicological findings from both high, acute doses as well as chronic low doses after exposure to airborne isocyanates. This part also includes a comprehensive overview of legislation for airborne isocyanates and a discussion of human exposure. The third part of this review discusses the generation of isocyanates in fire effluents by bench-scale and large-scale fire tests, different sampling techniques and agents for derivatisation airborne isocyanates and detection techniques. This is to the authors' knowledge the first time a review about the sampling, analysis and toxicity of isocyanates generated from fires have been made.

Isocyanates: reactivity and generation during thermal degradation

Reactivity and commercial applications of isocyanates

The most common, industrially used isocyanates are presented in Table 1. In general, mono-isocyanates have a lower molecular weight than di-isocyanate and are in comparison more volatile. Due to the adjacent double bonds in the NCO group, isocyanates are very reactive (Krol 2007). Within the isocyanate family, aromatic isocyanates are the most reactive, due to the negative charge shift towards the direction of the aromatic ring structure (Ulrich 1967). This in turn causes the carbon atom of the isocyanate group to have a greater delta positive charge in aromatic isocyanates (Ulrich 1967). Additionally, di-isocyanates such as MDI are generally more reactive than mono-isocyanates and initially exhibit the same reactivity in both NCO-groups (Pascault et al. 2002). However, substantial differences in isocyanate reactivity can be observed depending on the double bond position within the isocyanate chain, i.e. primary group or secondary group, as well as potential intramolecular forces, such as covalent or ionic bonds holding together the atoms in the compound, and the substitution effect for some of the di-isocyanates or urethane–isocyanates (Krol 2007). The substitution effect is a decrease in reactivity of the second NCO-group after the first NCO-group has reacted (Pascault et al. 2002).

Isocyanates are widely used in the production of PU foams. To synthesise PU, an isocyanate is combined with a polyol and a urethane bond is formed. PU is very versatile polymer with its texture ranging from soft to rigid, and the production involves isocyanates with two or more functional groups reacting with polyols (Avar et al. 2012). The first PU foam to be synthesised was PUR 1937 (Bayer 1947), exploiting the reaction of aliphatic isocyanates with a diamine formed a polymer which had a high melting point as well as hydrophilic properties (Chattopadhyay & Raju 2007). For the production of flexible foams, such as PUF, TDI is mostly used as an 80/20 mixture of the 2,4- and 2,6-isomers (TDI 80) (Saunders 1973). However, to meet the demand of particular applications and more specialised products, the composition and ratio of isocyanates and polyols are varied during synthesis of PUR products (Saunders 1973). PIR foams can theoretically be created with no polyol, using only isocyanates reacting with other isocyanates (Avar et al. 2012). However, commercially available PIR foams are usually PUR foam with polyisocyanurate added (Avar et al. 2012).

During the polymerisation step isocyanates can form dimers as well as trimers (Levchik & Weil 2004). Whereas the dimer formation is readily reversible, the isocyanurate ring formed by the trimerisation is extremely stable (Levchik & Weil 2004). The thermal stability of PUR materials, and in particular rigid foams at high temperatures, is affected by the ratio of these isocyanurate cross-links distributed in the material (Levchik & Weil 2004).

Isocyanate generation during thermal degradation

Isocyanates are generated during the thermal degradation of any PU based material (Blomqvist et al. 2003). Overall, nitrogen-containing compounds, such as isocyanates and organo-nitriles, will be generated during thermal degradation of PU foams heated to about 400 °C (Hull & Paul 2007). The most studied materials for the generation of isocyanates during thermal degradation are PUR and PIR foams. The thermal degradation of isocyanate-based PUR foams has been described as a two- or three-stage process (Jiao et al. 2013; Allan et al. 2014; Sui et al. 2014; Lefebvre et al. 2004; Woolley 1972), see Fig. 1.

When the temperature during an initial heating of PUR foam materials were increased to 200 °C, the blowing agent, such as CH_3CCl_2F, and other small molecules were released (Jiao et al. 2013). The observed weight loss in this initial stage was approximately 3 %, suggesting that the chemical bonds in the polymer were unbroken and that no isocyanates were released (Jiao et al. 2013). In the first step of the thermal degradation process, starting from around 200 °C, the urethane bonds in the polymer are broken (Allan et al. 2014). In this stage, a high amount of isocyanates and polyols are released as a yellow smoke (Levchik & Weil 2004; Jiao et al. 2013; Woolley 1972). The other studies also discussed a volatile yellow smoke which was assigned to the tolylene diisocyanate unit released at low temperatures (200–300 °C) (Woolley 1972). According to Woolley, the free TDI released during thermal decomposition, which is very reactive, polymerizes with itself to form the particulate yellow smoke, which is thus a TDI polymer. Studies of the yellow smoke show a similar elemental composition to TDI, but with slightly higher hydrogen and carbon content. It is proposed that yellow smoke involves the loss of C and O from the TDI, and that the most likely structure is a polymeric isocyanurate. Another possibility is carbodiimide formation. (Woolley 1972; Woolley & Fardell 1977).

As the temperature increases the polyol segments start to decompose into aliphatic ether alcohols (Allan et al. 2014). Above 300–500 °C the remaining residues decompose into volatiles such as CO, CO_2, benzene alkyls and aliphatic alcohols with branched chains (Allan et al. 2014; Jiao et al. 2013). The rate of the thermal degradation of isocyanate-based materials is increased in the presence of oxygen (Jiao et al. 2013; Levchik & Weil 2004). At higher temperatures, from 800 to 1000 °C, the isocyanates in the yellow smoke degrades into low molecular weight nitrogen containing compounds, mainly hydrogen cyanide (Woolley 1972).

The initial degradation temperature of the urethane bond in PUR foams is dependent on the structure of the isocyanate and the alcohol used (Chattopadhyay & Webster 2009). Easily formed PU polymers, containing the more reactive aromatic and/or di-isocyanates, generally decomposes rapidly, at low to moderate temperatures (120–180 °C), to release isocyanates. PU polymers formed by alkyl and/or mono-isocyanates decomposes at a higher temperature, (200–250 °C) to release isocyanates (Chattopadhyay & Webster 2009; Song et al. 1996).

Isocyanates and human health issues

Impact on human health

Most isocyanates can be absorbed into the body by inhalation, ingestion and through the skin, although the main exposure route is inhalation of isocyanate vapours or aerosols (Pronk 2007; Pronk 2006; Hulst et al. 2015; Fisseler-Eckhoff et al. 2011). In fire effluents, isocyanates are classified as an organic irritant gas, i.e. they are not asphyxiants, but they exhibit an adverse effect on the respiratory system (Stec & Hull 2011). However, it is difficult to determine the health impact of isocyanates in fire gases because they are masked by effects of many other irritant gases, such as nitric oxide and aldehydes present after the combustion of PUs (Stec & Hull 2010). A summary of the toxicological effects of isocyanates for different endpoints is presented in Table 2.

Published literature from both animal and clinical studies evidently demonstrates uptake of isocyanates via the respiratory tract or dermal exposure and excretion after metabolism via the urine (Cocker 2011; Bernstein et al. 2006). In general, the metabolism and toxicokinetics of isocyanates are not well understood (Cocker 2011). Studies have shown that rapidly after exposure the isocyanates are hydrolysed to isocyanate-derived amines and eventually excreted through the urine (Brorson & Skarping 1990; Austin 2007). For instance, TDI is transformed to toluene-2,6-diamine (TDA), a

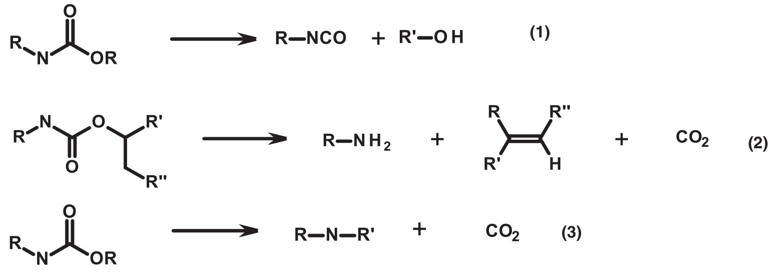


Fig. 1 Main reaction steps for the thermal decomposition of rigid PU foams (PUR). 1) First step is the break of the urethane bonds. 2) and 3) further decomposition of the materials to primary amines, secondary amines, vinyl esters and carbon dioxide. Adapted from Jiao et al. (2013) (Jiao et al. 2013)

Table 2 Summary of toxicological endpoints for isocyanates. The endpoints include carcinogenicity, genotoxicity, effects on reproductive systems and teratogenic properties for the most commercially important isocyanates. Target organs for short term and long term exposure as well as sensitization are also summarised

Compound	Carcinogenicity	Genotoxicity	Reproductive	Teratogenetic	Neurotoxic	Target organ – single exposure	Target organ – repeated dose	Skin sensitization	Respiratory sensitization	Eye irritation	Dermal irritation
Isocyanic acid (ICA)	No	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Severe (rabbit)	Severe (rabbit)
Methyl isocyanate (MIC)	Possible	Yes (Goswami et al. 1990)	Yes	Yes	Yes (Gupta & Prabha 1996)	Liver	Chronic obstructive lung disease	Yes (ACIGH 1986)	Yes (human)	Severe (human)	Severe (human)
Ethyl isocyanate (EIC)	N/A	Yes[a]	Yes[a]	Yes[a]	Cholinesterase Inhibitor	Liver[a]	Chronic obstructive lung disease [e]	Yes[a]	Yes[a]	Severe[a]	Severe[a]
Phenyl isocyanate (PHI)	Possible IARC rating: 2B[b]	Yes (Bureau 2000)	No (Nehez et al. 1989)	No (Nehez et al. 1989)	N/A	N/A	Irreversible decline in pulmonary function (NIOSH 2004)	Yes (Karol & Kramarik 1996)	Yes (Pauluhn et al. 1995)	Severe (O'Neil 2006; Berufsgenossenschaft der chemischen Industrie 1997)	Yes (Berufsgenossenschaft der chemischen Industrie 1997)
Hexamethylene di-isocyanate (HDI)	Possible IARC rating: 2B[b]	Yes[b] (Marczynski et al. 2005; Bilban 2004; Bolognesi et al. 2001)	No (Sids OECD 2001)	N/A	Cholinesterase Inhibitor	Lungs (Montelius & Sant 2009)	Lesions in the nasal cavity (Sids OECD 2001)	Yes (Centers for Disease Cotrol and Prevention 2015b)	Yes (Centers for Disease Cotrol and Prevention 2015b)	Severe (Vernot et al. 1977)	Severe (Vernot et al. 1977)
Toluene-2,4-di-isocyanate (2,4-TDI)	Possible IARC rating: 2B	Contradictory (Mäki-Paakkanen & Norppa 1987; Lindberg et al. 2011)	N/A	N/A	Cholinesterase Inhibitor	Lungs (Lindberg et al. 2011)	Irreversible decline in pulmonary function (The National Institute for Occupational Safety and Health (NIOSH) 2004)	Yes (Centers for Disease Cotrol and Prevention 2015c)	Yes (Centers for Disease Cotrol and Prevention 2015c)	Yes (Centers for Disease Cotrol and Prevention 2015c)	Yes (Centers for Disease Cotrol and Prevention 2015c)
Toluene-2,6-di-isocyanate (2,6-TDI)	Possible IARC rating: 2B	Yes (Mäki-Paakkanen & Norppa 1987)	No[c], (Le Quesne et al. 1976)	N/A	Yes	Lungs (Fabbri et al. 1987)	Irreversible decline in pulmonary function (NIOSH 2004)	Yes (Centers for Disease Cotrol and Prevention 2015c)	Yes (Centers for Disease Cotrol and Prevention 2015c)	Yes (Centers for Disease Cotrol and Prevention 2015c)	Yes (Centers for Disease Cotrol and Prevention 2015c)
Methylenebis (phenylisocyanate) (MDI)	Possible IARC rating: 2B[b]	Contradictory (Bolognesi et al. 2001)	No (Zocca et al. 1990)	Yes (Buschmann 1990)	Insufficient evidence (Hughes et al. 2014)	Lungs (Hughes et al. 2014)	Irreversible decline in pulmonary function (Centers for Disease Cotrol and Prevention 2015e)	Yes (Zocca et al. 1990)	Yes (Zocca et al. 1990)	Yes (Zocca et al. 1990)	Yes (Zocca et al. 1990)
Isophorone di-isocyanate (IPDI)	N/A	No (European Aliphatic Isocyanate Producer Association 2013)	N/A	N/A	N/A	Lungs (NIOSH 2004)	Irreversible decline in pulmonary function (Centers for Disease Cotrol and Prevention 2015d)	Yes (Centers for Disease Cotrol and Prevention 2015d)	Yes (Centers for Disease Cotrol and Prevention 2015d)	Yes (Centers for Disease Cotrol and Prevention 2015d)	Yes (Centers for Disease Cotrol and Prevention 2015d)

[a] Data extrapolated from toxic effects of MIC

[b] Data extrapolated from toxic effects of TDI

[c] Impotence has been reported in fire fighters, though thought to be due to an indirect neurological effect rather than direct effect on the male genitals

N/A indicates level not available/not applicable potential carcinogen (Austin 2007; Cocker 2011; Centers for Disease Cotrol and Prevention 2015a).

Primates exposed to the yellow particulate smoke from PU foams pyrolysed under nitrogen at 300 °C in an early version of the ISO 97000 tube furnace, demonstrated the smoke as a potent respiratory tract and deep lung irritant (Purser & Woolley 1983). Immediate signs of bronchoconstriction, respiratory tract and deep lung irritation were observed during exposure, followed by the development of pneumonia and oedema a few hours after exposure (Purser & Woolley 1983; Purser & Grimshaw 1984; Purser & Buckley 1983). In one case, the exposure to the yellow smoke proved to be fatal (Purser & Woolley 1983; Purser & Grimshaw 1984; Purser & Buckley 1983). Based on these findings, it is likely that the yellow smoke containing partially polymerised TDI is a major contributor to the overall irritancy observed when exposed to fire effluent from PU foams, affecting both escape capability as well as post-exposure morbidity and mortality resulting from lung inflammation.

The first recording of asthma from exposure to isocyanates in a PU factory was made by Fuchs and Valade 1951 (Fuchs & Valade 1951). In general, exposure to isocyanates are irritating to the skin, mucous membranes, respiratory tract as well as the eyes (NIOSH 2004). The most common adverse health effect associated with the exposure to isocyanates is asthma due to sensitisation (NIOSH 2004; Piirilä et al. 2008), where the isocyanates readily conjugates with proteins in the epithelial cells in the lungs (Wisnewski et al. 1999). These conjugates have been suggested to be the major antigens to trigger airway inflammation (Wisnewski et al. 2005). The correlation between dermal exposure to isocyanates and the development of asthma in humans is not well defined (Rom & Markowitz 2007). Furthermore, methyl isocyanate (MIC), although associated with other severe acute health effects such as pulmonary oedema and bronchoconstriction, is not described as a sensitizer (Rom & Markowitz 2007).

Studies on both animals and humans have demonstrated general inflammation in the respiratory tract, a non-immune response, as well as immune mechanisms such as di-isocyanate specific antibody production and T cell response after exposure to di-isocyanates, (Redlich & Karol 2002; Lockey et al. 2015). It has been suggested that the conjugates of isocyanates and epithelial cells can trigger responses in the immune system, and could be the cause of sensitisation upon repeated exposure (Wisnewski et al. 1999). Patients diagnosed with occupation asthma from HDI generally produce specific immunoglobulin E (IgE) antibodies (Dykewicz 2009). IgE antibodies are associated with hypersensitivity and allergic asthma (Rhoades & Pflanzer 2003). In contrast, only a minority of patients with occupational asthma caused by TDI produce specific IgE antibodies (Dykewicz 2009).

It usually requires months to years of exposure for an individual to develop asthma after isocyanate exposure, however, there are reports of development of asthmatic condition after exposure to a single high dose (Bernstein et al. 2006; Centers for Disease Cotrol and Prevention 2015b; Centers for Disease Cotrol and Prevention 2015c; Centers for Disease Cotrol and Prevention 2015e). An asthmatic attack may occur immediately after exposure, or several hours after exposure or a combination of both immediate and later reactions (NIOSH 2004). In addition, only approximately one third of patients diagnosed with isocyanate-induced asthma will recover fully despite a complete avoidance of exposure to isocyanates (Rachiotis et al. 2007). This ratio does not seem to be related to the duration of avoidance (Rachiotis et al. 2007). In order to avoid any exposure resulting in occupational, isocyanate-induced asthma, a major effort has been made to identify occupational risks as well as early physiological signs (Piirilä et al. 2008; Pisati et al. 2007).

Other, less prevailing adverse health effects are irritant and allergic forms of contact dermatitis, with symptoms as rashes, itching, hives and swelling of extremities (NIOSH 2004; Streicher et al. 2000). Another less common effect from isocyanate exposure is hypersensitivity pneumonitis, an inflammation of the alveoli caused by inhaled isocyanate particles (Lockey et al. 2015; Vandenplas et al. 1992). In terms of low-dose and chronic exposure, it has been suggested that isocyanates, together with carbon monoxide, cyanide, nitrogen dioxide as well as a low oxygen concentration can cause irreversible damage to the bronchi and alveoli and acute respiratory function (Choi et al. 2014). A summary of human health effects for individual isocyanates are presented in Table 1.

Isocyanates are also of interest in the field of genetic toxicology because they may act as electrophilic agents and react with DNA to produce genetic damage. Di-isocyanates have been found to form adducts with haemoglobin, in particular in long lived cells such as peripheral blood lymphocytes, in relatively high concentrations after cumulative doses (Lindberg et al. 2011). It has recently been demonstrated that isocyanates are capable of undergoing bio-transformation reactions, such as DNA damage, apoptosis, oxidative stress, and inflammation in cultured human lymphocytes and lung fibroblasts (Mishra et al. 2008). These effects are closely linked with cancer initiation (Simone Reuter 2011; Jindal & Singh 2014; Lindberg et al. 2011).

Five of the isocyanates, PHI, HDI, 2,4-TDI, 2,6-TDI and MDI have been classified by the International Agency for Research on Cancer (IARC) as potential carcinogens, see Table 1. However, only 2,4-TDI and 2,6-TDI have been evaluated for their potential carcinogenicity, for the other isocyanates the data has been extrapolated from data obtained on studies with TDI. Isocyanates are not considered human carcinogens, although TDI is classified as an animal carcinogen and MDI as a suggested animal carcinogen (Rom & Markowitz 2007). Additionally, epidemiologic studies on mainly TDI and MDI foam production workers have not shown a higher prevalence for any cancer (Bolognesi et al. 2001).

Furthermore, EIC, HDI and TDI have been described as potent acetylcholinesterase inhibitors (Brown et al. 1982), with similar effects as nerve gasses such as sarin. This enzyme is essential for the breakdown of the nervous transmitter acetylcholine in the synapses (Rhoades & Pflanzer 2003). The symptoms after exposure to an airborne acetylcholinesterase inhibitor vary from pupil constriction (myosis), bronchoconstriction and chest tightness for a minor exposure, through coughing and shortness of breath for moderate exposures, to severe bronchorrhea and bronchospasms and potential coma and rapid death for individuals exposed to a high dose (Rhoades & Pflanzer 2003).

Hazard classification and legislation of isocyanates

Due to their toxicity, isocyanates are among the compound groups with the lowest occupational exposure limits (OEL). In the UK, the general requirements for controlling exposure to hazardous compounds, including isocyanates, are regulated in the Control of Substances Hazardous to Health (COSHH) Regulations 2002 (Health and Safety Executive HSE 2014). As the effect from isocyanate exposure is mainly respiratory sensitisation, the Health, Safety, and Environment (HSE) have assigned two maximum exposure limit (MEL) values for this class of compounds: a time-weighted average (TWA) for an eight- hour working day, assuming 40 h of work per week, of 0.02 mg m^{-3} and 0.07 mg m^{-3} for a short-term exposure of 15 min (Health and Safety Executive HSE 2014). In the US, levels set by the Occupational Safety and Health Administration (OSHA), TWA are 0.05 mg m^{-3} and 0.2 mg m^{-3} for an 8 h and a 10 min exposure respectively (Centers for Disease Cotrol and Prevention 2015c; Centers for Disease Cotrol and Prevention 2015e; Centers for Disease Cotrol and Prevention 2015b; Health and Safety Executive 2011).

A summary of different exposure levels for isocyanates from different agencies is presented in Table 3. It should be noted that the levels stated by the OSHA and HSE are part of regulations, and that the levels stated by US Environmental Protection Agency (US EPA), The National Institute for Occupational Safety and Health (NIOSH), American Conference of Governmental Industrial Hygienists (ACGIH) and American Industrial Hygiene Association (AIHA) are guidelines. Furthermore, the UK HSE combines all isocyanate monomers and polyisocyanates into one single total value, using the NCO-group as the measurement for exposure, in comparison to the United States legislative and guideline levels, from agencies such as OSHA, US EPA and NIOSH, that concerns individual isocyanates (Rom & Markowitz 2007).

As of March 2013, none of the isocyanates were included in the European Commission initiated Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Annex XIV, a list of substances that require authorisation for continuous use in the EU (Agency 2015). However, there are ongoing REACH substance evaluations for the most commercially important isomers of TDI and MDI that in the future may lead to further action such as restrictions in usage or authorisation (No et al. 2014).

Human exposure to isocyanates

There are data gaps in the health effects of mono-isocyanates in comparison to di-isocyanates due to lower industrial production of mono-isocyanates. However, during one of the worst industrial disasters in the history of mankind, the Bhopal gas tragedy in India 1984, approximately half a million people were exposed to MIC (Eckerman 2005; Mishra et al. 2009). It is estimated that at least 3800 people were killed during or in the immediate aftermath of the accident and another 200 000 people were debilitated (Broughton 2005; Mishra et al. 2009). It has been reported that a majority, around 75 %, of all deaths occurred within the first 72 h of the accident (Mishra et al. 2009). At the time, no information was available about the toxic effects of MIC, meaning that there were no action taken as to how to minimise the impact (Mishra et al. 2009). The acute symptoms after exposure to MIC in Bhopal were respiratory distress such as pulmonary oedema and bronchoconstriction, irritation of the skin, profuse eyelid oedema and superficial corneal ulcerations (Eckerman 2005). The subsequent long-term studies from the Bhopal accident reported pulmonary, ophthalmic, reproductive, immunologic, neurological, and hematologic toxicity among the survivors of the accident (Varma & Guest 1993). However, most current studies are not focussed on the acute toxic effects after a single high dose of isocyanates, but on the occupational hazards of long-term exposure in lower doses and risks.

Human exposure to low doses of airborne isocyanates can for instance occur during spray painting cars using paints containing isocyanates. Reeb-Whitaker et al.

Table 3 Summary of exposure regulation and guideline levels for TDI, MDI and HDI. This table includes the lethal dose 50 (LC$_{50}$) for rats in ppm as well as the short term and long term levels for the respective airborne isocyanate from regulating organs

Compound	Agency	LC50[a] (ppm)	Short term exposure									Long term exposure	
			STEL (ppm)	AEGL1 (ppm)		AEGL2 (ppm)		AEGL3 (ppm)		ERPG2 (ppm)	ERPG3 (ppm)	TWA (ppm)	REL (ppm)
TDI (Both isomers)		14		10 min	30 min	10 min	30 min	10 min	30 min				
	OSHA		0.2									0.005	
	UK HSE		0.041[b]									0.0116[b]	
	US EPA			0.02	0.02	0.24	0.17		0.65				
	NIOSH												0.005 (TWA), 0.02[c]
	ACGIH		0.02									0.005	
	AIHA									0.15	0.6		
MDI		36											
	OSHA		0.2									0.005	
	UK HSE		0.04[b]									0.0116[b]	
	US EPA			N/A	N/A	N/A	N/A	N/A	N/A			0.65	
	NIOSH												0.005 (TWA), 0.02[c]
	ACGIH		0.02									0.005	
	AIHA									0.5	5.4		
HDI		22											
	OSHA		N/A										
	UK HSE		0.04[b]									0.0116[b]	
	US EPA			N/A	N/A	N/A	N/A	N/A	N/A				
	NIOSH												0.005 (TWA), 0.02[c]
	ACGIH											0.005	
	AIHA									N/A	N/A		

[a] Rat inhalation (4 h)

[b] As NCO-group

[c] Ten minute exposure

STEL Short-term exposure limit (15 min unless otherwise stated), *AEGL1* Acute Exposure Guideline Level 1 "Notable discomfort, irritation, or certain asymptomatic non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure", *AEGL2* Acute Exposure Guideline Level 2 "Irreversible or other serious, long lasting adverse health effects or an impaired ability to escape", *AEGL3* Acute Exposure Guideline Level 3 "Life threatening health effects or death", *ERPG2* Emergency Response Planning Guidelines level 2 "is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms which could impair an individual's ability to take protective action", *ERPG3* Emergency Response Planning Guidelines level 3 "the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects", *TWA* Time weighted average (8 h per day during 40 h week unless otherwise stated), *REL* Recommended exposure limits

N/A indicates level not available/not applicable

(Reeb-Whitaker et al. 2012) reports of sampling of the airborne isocyanates HDI and IPDI in auto body shops in the US using two PTFE filters in series impregnated with 1-(2-pyridyl)piperazine (2-PP) and 9-(methyl- aminomethyl)anthracene (MAMA) respectively. The results from the study indicates a high occupational exposure for the two isocyanates, as eighty per cent of the samples contained concentrations above the OSHA STEL value (Reeb-Whitaker et al. 2012). As a comparison, 98 % of the samples were above the UK HSE STEL (Reeb-Whitaker et al. 2012). When analysing urine samples from workers in in vehicle repair shops, Williams et al. (Williams et al. 1999) found the metabolite of HDI, hexamethylene diamine (HDA), in four out of 22 spray workers and one by-stander, even with the use of personal protective equipment among the workers. HDA was not found in individuals not exposed to HDI (Williams et al. 1999). Although the metabolism of HDI and oligomers of HDI is not well understood, there is seemingly a good correlation between the amount of airborne HDI and the amount of HDA excreted via urine (Brorson & Skarping 1990). Several other studies have reported a similar correlation between TDI (Rosenberg & Savolainen 1986; Brorson et al. 1991; Persson et al. 1993) and IPDI (Tinnerberg et al. 1995) with their respective amines after human exposure and excretion via the urine.

There are further studies reporting the analysis of isocyanates in urine from exposed individuals. In a study from Brorson and Skarping (Brorson & Skarping 1990), urine samples from exposed volunteers were collected and analysed for HDA. Additionally, Blomqvist et al. (Blomqvist et al. 2003) found traces of 2,4-TDA and 2,6-TDA, the amine derivatives from the TDI isomers, in individuals exposed to isocyanates during large-scale fire tests even though the exposed individuals wore protective masks. However, there are some issues with using the corresponding amine derivative of an isocyanate as a biomarker for isocyanate exposure; the analysis of biomarkers in urine is complicated due to the high reactivity of the analytes, as well as uncertainty regarding the toxicokinetics and metabolism of individual isocyanates or mixtures of isocyanates (Rom & Markowitz 2007).

In a study by Mirmohammadi et al. (Mirmohammadi et al. 2010) the concentration of airborne HDI in PUR factories as well as the HDA concentration in urine samples from workers in the factories were investigated. The airborne isocyanates were sampled by impingers containing tryptamine (Mirmohammadi et al. 2010). High concentrations of HDI, 88 μg m^{-3}, was found in the air samples from the factories and all 50 urine samples from the workers contained HDA. Moreover, Creely et al. (Creely et al. 2006) investigated the exposure of airborne isocyanates in PU industry sectors using a single glass fibre filter impregnated with the 1, 2-MP reagent. Out of 70 samples taken from different steps during the PU manufacturing process, such as moulding, storage sawing and spraying, only three samples exceeded the UK HSE TWA limit (Creely et al. 2006). However, when analysing urine sampled from the same workers included in the air sampling survey for HDA, TDA and the amine derivate for IPDI, isophorone diamine (IPDA), 37 samples were found to contain concentrations of at least one of the amine derivatives investigated (Creely et al. 2006). The main conclusion from the study therefore that biological uptake might occur in workers despite low ambient concentrations of airborne isocyanates (Creely et al. 2006).

In one of the few studies investigating fire related exposure to isocyanates, Axford et al. (1976) suggested that permanent or long-term damages to the respiratory tract among a group of fire fighters could be caused by TDI, however the results were inconclusive (Axford et al. 1976). Out of the 31 firefighters exposed to a single, high dose of TDI and investigated for effects on the respiratory system, 14 had persistent symptoms, mainly cough and/or chest tightness (Axford et al. 1976). Four years after exposure there were some evidence that 43 %, 15 out of the 35 firefighters exposed, had sustained permanent damage to their respiratory tract (Axford et al. 1976).

Sampling and analysis of isocyanates in fire effluents

Generation of isocyanates in fires and fire tests

Isocyanates are generally produced during the early stages of fire (Woolley 1972). Some of the PU based insulation materials are highly flammable and can spread the flame fast when ignited (Marlair et al. 1993). The flammability of PUR, and in particular PUR foams, is strongly dependant on the structure of the polyol as well as the isocyanate used and their ratio (Levchik & Weil 2004). Another highly important factor for the flammability and flame spread is the density of the foam, where highly porous, lightweight materials tend to have a fast combustion and flame propagation rate as well as a high thermal radiation (Levchik & Weil 2004; Lefebvre et al. 2004). One approach to reducing the flammability of PUR foams is to add more isocyanate to the formulation before polymerisation, in order to allow the isocyanate to trimerise, forming an isocyanurate ring, of higher thermal stability than the urethane or other linkages (Dominguez-Rosado et al. 2002; Ashida et al. 1997).

Large-scale fire tests have historically been essential in advancing the understanding of fire behaviour and the generation of toxic products. Real large fires and tests are designed to replicate several different stages of the fire as well as the change over time (Stec et al. 2010). However, these experiments are complex in their set-up, with combustion conditions varying over both time and space, resulting in poor repeatability. Moreover, the measurements are dependent on the positioning or mounting of the material to be analysed, making the results difficult to interpret and to reproduce (Stec et al. 2009). Other disadvantages of large-scale fire tests are the time-consuming preparations as well as the high cost associated (Stec et al. 2009). In addition, there are currently very few standardised fire scenarios or procedures available for large-scale fire toxicity studies. It is therefore beneficial to study the generation of isocyanates by bench-scale testing methods as a complement to large-scale fire testing. A summary of the studies reporting generation of isocyanates in bench-scale testing and in large-scale fire testing are presented in Table 4.

One of the standardised large-scale fire tests used for generation of isocyanates is the standardised room test (ISO 9705) (Hertzberg et al. 2003), The ISO 9705 test is a large-scale fire test method for assessing fire properties of surface materials (Hansen & Hovde 2002).

Fent et al. (Fent & Evans 2011) used a denuder system with dibutyl amine (DBA) coated filters attached to fire

Table 4 Summary of studies generating and analysing isocyanates in fire effluents. Summary of the large-scale fire test and bench-scale methods for generating isocyanates and the materials used, as well as sampling methods, temperature, the isocyanates detected and concentration

Study	Test method and materials	Sampling method	Temperature (°C)	Isocyanates detected	Isocyanate concentration	Comments
Boutin et al (2004)	DIN 53436 furnace Car paint	Impinger 1,2-MP	Sample temperature:473 Oven temperature: 600	ICA, HDI, all linear isocyanates ranging from MIC to n-hexyl isocyanate, alkenyl isocyanates ranging from propylene to octylene isocyanate and structural isomers of these isocyanates	N/A	The most abundant isocyanates detected were MDI, HDI, TDI and IPDI.
Hertzberg et al (2003)	Room test (ISO19705) Sofa (containing PUR)	Impinger-filter DBA	N/A	ICA, PHI, MDI, 2,4-TDI and 2,6-TDI	The average isocyanate concentration measured was approximately 0.5 ppm	The highest concentrations were found in the rigid foams, with PIR, an improved form of PUR, giving the highest yield. In all foams ICA was the main product and was considered the final breakdown product. The ratio of ICA to TDI was much higher in full- scale experiments in comparison to the combustion of flexible PUR in the cone calorimeter
	Cone calorimeter (ISO5660) Insulation materials	Impinger-filter DBA	N/A	ICA, MIC	~800-1000 μg m^{-3}	Glass fibre insulation gave the highest isocyanate concentration of all materials tested. ICA and MIC were the most abundant isocyanates.
Karlsson (2001)	Urea-based resins and PUR coated sheets	Impinger-filter DBA	N/A	ICA, MIC	In Bakelite up to 14 % of its weight was emitted as ICA and 0.1 % as MIC	These amounts dependant on temperature and the duration of the heating. The composition of the released isocyanates differs between coatings.
Blomqvist et al (2003)	PUR mattresses were used a fire source to trigger a sprinkler system, according to IMO resolution A.800	Impinger-filter DBA	N/A	ICA and smaller amounts of 2,4-TDI and 2,6-TDI	First test: close to 10 ppb. Second test; 50 ppb.	Comparing the potential health hazard between isocyanates and other major fire gases revealed isocyanates as the greatest hazard.
Lönnermark and Blomqvist (2006)	ISO 5659, large-scale car fires	Impinger-filter DBA	N/A	ICA, EIC, MIC, PHI, 2,4-TDI, 2,6-TDI, HDI	Total yield of airborne isocyanates: 240 g/kg	Significant amounts of isocyanates were found in the smoke from the vehicle fires
Blomqvist et al. (2007)	Identical setup to BS 7990:2003 PUR mattresses and insulation material, wood	Impinger-filter DBA	650 °C and 825 °C	ICA, TDI, EIC	PUR mattress:~ 2 mg/g PUR insulation: :~ 2.5 mg/g Wood: 0.0035 mg/g	Two different fire scenarios were investigated; well-ventilated and under-ventilated No significant differences in isocyanate generation were detected for the two fire scenarios
	ISO/TS 19700	Denuder		ICA, MIC, EIC, PHI, MDI		

Table 4 Summary of studies generating and analysing isocyanates in fire effluents. Summary of the large-scale fire test and bench-scale methods for generating isocyanates and the materials used, as well as sampling methods, temperature, the isocyanates detected and concentration *(Continued)*

Blomqvist et al. (2014)	PVC carpet, wood board	DBA	350 °C, 650 °C and 825 °C			Distribution of isocyanates in gas phase and particle phase were investigated Mono-isocyanates were found almost exclusively in the gas phase Only small amounts of di-isocyanates were found
(Fent and Evans (2011))	Vehicle fire	Denuder DBA impregnated filter	N/A	TDI, MDI, HDI, PHI, MIC, EIC, PIC, IPDI, ICA	5.9-66.8 µg m^{-3} TRIG (total reactive isocyanate groups)	Isocyanates were only found in passenger compartment fires and not in engine fires. Isocyanates are present in foam in the passenger compartment and not used in engines.
HSL 2007	Simulated workplace samples (welding of PU painted car parts)	MP impregnated filter	200 °C	TDI, MDI, HDI, PHI, MIC, EIC, PIC, IPDI, ICA, butyl isocyanate, diisopropylphenyl isocyanate, hydrogenated MDI	High levels of ICA (167 mg NCO/m$^{3)}$) and traces of other isocyanates	
		MP impregnated filter	400 °C	TDI, MDI, HDI, PHI, MIC, EIC, PIC, IPDI, ICA, butyl isocyanate, diisopropylphenyl isocyanate, hydrogenated MDI	High levels of ICA (167 mg NCO/m$^{3)}$) and traces of other isocyanates	

N/A indicates level not available/not applicable fighters to sample isocyanates generated from vehicle fires. The main conclusion from this study was that passenger compartment fires produced detectable levels of airborne isocyanates originating for the foams used for the seats (Fent & Evans 2011). No isocyanates were detected in samples from engine fires where foams were absent (Fent & Evans 2011).

Bench-scale testing methods can be subdivided into those developed to replicate a single stage in the fire or a small fire from beginning to end, the latter preventing isolation of individual fire stages. There arebench-scale testing methods with constant combustion, such as the DIN 53436 furnace and the smoke chamber (ISO 5659–2) (Stec & Hull 2010). The DIN 53436 furnace offers a wide range of well-controlled combustion conditions, and both well-ventilated as well as under-ventilated combustion conditions can be simulated (Gann & Bryner 2008). Another bench-scale method for generating fire effluents is the cone calorimeter (ISO 5660). The cone calorimeter is a small scale fire test where the material have an unlimited access to oxygen, meaning that the combustion condition for this test is inevitably well-ventilated (Blomqvist et al. 2014).

The smoke chamber (ISO 5659–2) was originally designed to evaluate the smoke development from burning materials, in order to assess the visual obscuration during a fire, in a closed passenger compartment (Stec & Hull 2010). It can give a good indication of visual obscuration because the light source and photocell are mounted vertically from top to bottom of the chamber. It has also been used in attempts to quantify the toxic smoke yield for materials burning during well-ventilated conditions, but the flaming is extinguished before the fire develops into the later, under-ventilated conditions (Stec & Hull 2010). Therefore, the smoke chamber gives no information about the variation of yield during different stages during the fire (Stec & Hull 2010). Another disadvantage with the smoke chamber is the poor reproducibility because the fire plume must be sampled at fixed position(s) in the chamber (Stec et al. 2014).

The steady state tube furnace (ISO TS 19700) was developed to replicate different stages of fires on a bench-scale (Stec et al. 2008a). The principle of the ISO TS 19700 tube furnace is a fixed rate feeding of the sample into a furnace under a fixed air supply (Stec et al. 2008b ; Stec & Hull 2010). A good correlation between the yields for several of the major acute toxicants from fires such as CO and hydrogen cyanide (HCN) generated from large-scale tests and the steady state tube furnace has been shown (Hull et al. 2008).

Boutin et al. (Boutin et al. 2004) reported of the analysis of airborne isocyanates sampled from the effluent of car paint thermally degraded by the DIN 53436 furnace. The car paint in this study was thermally degraded under conditions thought to represent flaming combustion, or oxidative degradation (Boutin et al. 2004; Boutin et al. 2006). The airborne isocyanates generated were sample using impinger flasks and 1-(2-methoxyphenyl)piperazine (1,2-MP) as derivatisation agent. Results from the study revealed a non-negligible generation of airborne alkenyl as well as aliphatic isocyanates from the thermal degradation of PU car paint (Boutin et al. 2004).

In a study by Hertzberg et al. (Hertzberg et al. 2003) airborne isocyanates from 23 common materials found in buildings were sampled after being generated by a cone calorimeter. The airborne isocyanates were collected by impinger-filter and were derivatised by DBA (Hertzberg et al. 2003). The main findings from these initial small scale tests were that all nitrogen-containing materials included in the study produced isocyanates upon thermal degradation (Hertzberg et al. 2003). Airborne isocyanates were also sampled from a ISO 9705 using a sofa containing PUF (Hertzberg et al. 2003). The experiment went to flash over, meaning that the combustion occurred during under-ventilated conditions (Hertzberg et al. 2003). The relatively high amounts of isocyanates measured, mainly ICA, but also MIC, PHI and 2,4-TDI, from this test were considered a potential health hazard (Hertzberg et al. 2003).

Additionally, significant concentrations of airborne isocyanates generated from the large-fire scale tests conducted by Hertzberg et al. (Hertzberg et al. 2003), Blomqvist et al. (Blomqvist et al. 2003), from the same set of tests, also reports a large-scale fire test conducted by burning mattresses containing PUF. The mattresses were burnt to produce enough heat and smoke to activate a sprinkler system according to the IMO Resolution A.800 (Blomqvist et al. 2003). The isocyanate sampling, by impinger-filter using DBA as the derivatisation reagent, were positioned to simulate normal breathing height for people (Blomqvist et al. 2003). The main isocyanate measured in this test was ICA, followed by lower concentrations 2,4-TDI and 2,6-TDI (Blomqvist et al. 2003).

Using the steady state tube furnace, Blomqvist et al. (Blomqvist et al. 2007; Blomqvist et al. 2014) analysed the generation of isocyanates from materials such as PUR mattresses and insulation materials as well as PVC carpets and wood board. A correlation between the magnitude of the obtained yields for isocyanates from the PUR materials from the well-ventilated stage and yields from PUR from the cone calorimeter was reported (Blomqvist et al. 2007). Additionally, no significant difference between the yield of isocyanates from the PUR materials burnt at well-ventilated and under-ventilated conditions were observed (Blomqvist et al. 2007). Moreover, it was reported that the smaller and more volatile mono-isocyanates were found almost exclusively in the gas phase, whereas the non-volatile MDI never was found in the vapour phase but only in the particle phase of the fire effluent (Blomqvist et al. 2014).

In a study by Lönnermark and Blomqvist (Lönnermark & Blomqvist 2006) significant concentrations of airborne isocyanates (ICA, MIC, EIC, PHI, 2,4 and 2,6-TDI, HDI and 2,4- and 2,6-TAI) from an automobile fire were also identified. The airborne isocyanates were sampled by impinger-filter and derivatised by DBA (Lönnermark & Blomqvist 2006).

The Health and Safety Laboratory (HSL) studied the generation of low-molecular weight airborne isocyanates by heating a variety of isocyanate-based materials on a hotplate at 200 and 400 °C alongside air samples taken during spot welding of PU coated car parts (Health and Safety Laboratory (HSL) 2007). The isocyanates were sampled by an MP impregnated filter (Health and Safety Laboratory (HSL) 2007). The main result reported for this study was that high concentrations of ICA were produced during the thermal degradation of insulation materials, upholstery materials and packaging materials (Health and Safety Laboratory (HSL) 2007). In addition, high concentrations of IPDI were detected in samples taken during the spot welding (Health and Safety Laboratory (HSL) 2007).

Sampling of isocyanates

The sampling and analysis of airborne isocyanates in fire effluents are a challenging task as the functional group can occur as a range of chemical species, such as monomers, dimers, oligomers or polymeric form. Moreover, airborne isocyanates may be present as vapours, aerosols and absorbed on particulate matter or in the form of particulate polymerised isocyanate (Henneken et al. 2007; Woolley 1972). Fire effluents are complex matrices containing a variety of substances, such as gases, vapours, particulates and aerosols of liquid droplets, that all have ability to interfere with the sampling and analysis of isocyanates. There are several methods for sampling and derivatisation of vaporised isocyanates in air described in the literature, such as impingers filled with derivatisation solution, or denuder with impregnated filters, see Table 5. However, it should be noted that there is no generic sampling method suitable for all applications, meaning that the selection of the sampling method will affect the outcome of the study. Generally, the selection of sampling and analysis method for isocyanates in fire effluent depends on several factors; the chemical nature and physical state of the isocyanates, required sampling time, sampling set-up (personal or area), matrix and the required sensitivity of the entire method (Streicher et al. 2002). However, all isocyanate sampling and analytical methods have limitations that will affect the results obtained (Streicher et al. 2002), stressing the importance of making the correct choice of sampling method to meet the aim of the study.

The major advantage of collecting airborne isocyanates by impingers is the large sampling capacity (Henneken

Table 5 Overview of sampling methods and derivatisation agents used by these sampling methods. This table summarizes the sampling method and derivatisation agent as well as the advantages and disadvantages of respective sampling method

Sampling method	Derivatisation agent	Advantages	Disadvantages
Impinger	Nitro reagent MAMA 1-2PP 2-MP Tryptamine DBA MAP Acid Alkaline ethanol	Simple set-up Large sampling capacity	Smaller particles and gas phase molecules could be drawn out from the impinger flask Poor collection efficiency of particles (range 0.01-1.5 μm)
Impinger-filter	DBA 2-MP MAP	No pre-impregnation of filter (DBA) High reagent concentrations can be used Collection of particles (range 0.01-1.5 μm)	Limited sampling time due to evaporation of the solvent Not convenient for exposure measurements on workers
Diffusive sampling (incl. ISO-CHEK)	2-MP DBA		Difficulty of discriminating between particles and droplets Sensitive to wind, humidity and temperature fluctuations
Impregnated filter/solid sorbent samplers	MAMA 1-2MP 2-PP Tryptamine DBA	High capacity (compared to exposure levels) User-friendly handling	Limited amount of reagent can be used Risk of particle depletion
Annular denuder system	DBA	Higher sampling capacity and efficiency for the vapour phase compared to the cylindrical type	Simultaneous sampling of gaseous and aerosol concentrations

et al. 2007). The method utilizes a large excess of the derivatisation agent, generating favourable kinetics for the derivatisation reaction and virtually quantitative recovery (Henneken et al. 2007). However, airborne particles could be pass through the impinger in air bubbles, and escape from the trapping solution. In particular, the impinger method does not efficiently wash all the particles between 0.01 and 1.5 μm. For the collection of airborne particles, in-line chemically treated filters coupled in series after the impinger, as an impinger-filter system, are usually used (Karlsson et al. 2000; BSI Standards Publication 2013; Health and Safety Executive HSE 2014; Creely et al. 2006). The advantages of sampling airborne isocyanates by impinger is the simple set-up as well as the large sampling capacity and efficiency. However, the impinger sampling is impractical for personal air sampling, i.e. when investigating the exposure of workers by attaching a sampling device on their person. Additionally, during prolonged sampling with an impinger, the solvent containing the derivatisation agent could evaporate.

Denuder or dry sampling methods, such as the ISO-CHECK® three stage filter system, as well as passive sampling methods where the isocyanates are absorbed onto a filter without using any pumps or other assistance, have been developed for personal sampling and/or prolonged sampling times (Marand et al. 2005; Gylestam et al. 2014; Henneken et al. 2006; Henneken et al. 2003; von Zweigbergk et al. 2002; Nordqvist et al. 2005). Furthermore, these solvent-free, filter-based methods do not need any field preparation or fragile glassware, such as an impinger (Gylestam et al. 2014). The stability of the collected isocyanates by a denuder system have also been described as superior to the impinger-filter method (Gylestam et al. 2014). However, due to the limited amount of derivatisation agent that can be used to impregnate the filters used for solvent-free sampling of isocyanates, such as denuder systems, the amount of isocyanates that can be sampled is lower than when sampling by the impinger-filter method (Gylestam et al. 2014). Moreover, there is also a greater chance of carry-over when larger quantities of analytes are present. These methods are therefore not suitable for quantitative purposes (Henneken et al. 2006).

All in all, the impinger-filter method is the most suitable method for sampling the potentially high concentrations of isocyanates found in fire effluents, although there is need for immediate sample work-up after collection.

Derivatisation of isocyanates

As isocyanates are highly reactive compounds, there is need for rapid stabilisation after sampling (Henneken et al. 2006). Some studies reports of sampling of isocyanates without derivatisation, either by collecting them on a modified polyphenylene oxide (MPPO) resin followed by thermal desorption (Bianchi et al. 1997), or by direct injection via headspace (Harden & Shoff 1997). However, these methods result in unnecessarily high limits of detection (Henneken et al. 2007). Several different derivatisation agents have been described, such as 2-PP (EPA 1997; Occupational Safety and Health Administration (OSHA) 1989a; Occupational Safety and Health Administration (OSHA) 1989b; British Standard Institution 2012), MAMA (Reeb-Whitaker et al. 2012; Persson et al. 1993), 1-(9- anthracenylmethyl) piperazine (MAP) (Woskie 2004; NIOSH 1998; NIOSH 2003), 1-(2- methoxyphenyl)piperazine (1-2MP) (NIOSH 8/15/94 1994; Molander et al. 2000; Thomasen et al. 2011; Boutin et al. 2006), tryptamine (Wu et al. 1987), 9-anthracenylmethyl-1-piperazinecarboxylate (PAC) (Roh et al. 2000), and DBA (Spanne et al. 1996; Karlsson et al. 2000; BSI Standards Publication 2013).

When comparing the different derivatisation agents, Henneken et al. (Henneken et al. 2006) established that even though some of the established methods endorsed by agencies, such as the OSHA (Occupational Safety and Health Administration (OSHA) 1989a; Occupational Safety and Health Administration (OSHA) 1989b) uses 2-PP; derivatisation by MAMA and MPP achieves greater stability and sensitivity. Moreover, 2-PP also demonstrates stability problems if not properly stored before sampling (Streicher et al. 1996).

The two derivatisation reagents MAMA and MAP share an anthracene moiety, used for sensitive UV and fluorescence detection. However, the response by fluorescence detection is heavily dependent on the structure of the isocyanate when analysing isocyanate-MAMA derivatives (Rando et al. 1995). Studies evaluating the reactivity, analytical sensitivity as well as the applicability for different isocyanates species reported that MAP was superior in comparison to MPP, 2-PP and MAMA (Streicher et al. 2002; Bello et al. 2002). The properties of MAP enables a more structure independent response when analysed by fluorescence detection in comparison to MAMA (Henneken et al. 2007). However, non-isocyanate compounds that reacts with MAP may potentially interfere with the quantification when analysed by liquid chromatography coupled to a UV-detector (LC-UV) (NIOSH 2003).

1,2-MP is probably the reagent most commonly used for the derivatisation of airborne isocyanates (Henneken et al. 2007). However, studies have reported that the variability of UV detection for the isocyanate derivatives formed by 1,2-MP can sometimes render in unreliable results (Streicher et al. 1995).

When using tryptamine as derivatisation reagent, the response for individual isocyanates by fluorescence and electrochemical detectors was found to be fairly structure-independent (Henneken et al. 2007). The disadvantages of using tryptamine are interferences from matrix components in the lower wavelength ranges (λ 275 nm) during UV detection as well as a reduced reactivity towards isocyanates as tryptamine is a primary amine, rather than a secondary amine (Henneken et al. 2007), such as DBA. Furthermore, PAC has more recently been introduced as another derivative reagent to form isocyanate-urea derivatives, and although the reaction is seemingly less structure dependant, the reaction rate is also slower than for other listed reagents (Roh et al. 2000).

The reaction rate for DBA with isocyanates to form a urea-derivative was found to be rapid as well as selective towards isocyanate species, thus eliminating the issues with interfering compounds (Spanne et al. 1996; Karlsson et al. 1998). However, when using DBA as derivatisation agent for filters in dry samplers, the amine in itself is too volatile for adequate derivatisation of the analytes (Gylestam et al. 2014). Studies have therefore described mixing DBA with acetic acid to form a less volatile ion-pair (Gylestam et al. 2014). A comprehensive summary of the derivatisation agents and the suitable detection method are presented in Table 6.

Detection of isocyanates

High-performance liquid chromatography (HPLC) as a separation technique coupled to either a UV/Fluorescence (UV-FL) detector or a mass spectrometer (MS) is the preferred method for the detection of isocyanates from a range of different matrices, see Table 6. Analyte separation in HPLC occurs when a pressurised solvent, the mobile phase, containing the analyte in a mixture with other compounds passes through a column filled with a solid adsorbent material, also called stationary phase. Each compound in the mixture will retain on the stationary phase slightly different, causing a separation of the compounds as they elute from the column.

Many compounds in solution absorbs visible light and/or UV light. A UV detector coupled to an HPLC continuously measures the intensity of light with a specific wavelength passing through the mobile phase containing the target analyte, and compares it to the intensity of the light before it was passed through the sample (Lough & Wainer 1996). Since compounds will absorb specific wavelengths, they can be identified according to the absorbance. In addition, some compounds absorbs light at one specific wavelength and emits light in another wavelength (Lough & Wainer 1996). This is utilised in FL detectors. UV detection and FL detection are often combined into one detector in modern instruments.

MS is a detection technique based on the measurement of the mass-to-charge (*m/z*) ratio of ionised analyte molecules. The obtained *m/z* ratio from an analytes can then be identified by correlating the mass with that of a specific molecule and/or by identifying characteristic fragmentation patterns that may occur during ionisation (de Hoffman & Stroobant 2007). In order to ionise the analytes in a solution there is need to transfer the molecules in to gas phase. One of the most widely used ionisation techniques is electrospray ionisation (ESI), which applies a high voltage to the mobile phase to create an aerosol within the ionisation chamber (de Hoffman & Stroobant 2007). The droplets of solvent are then vaporised by heating up the ionisation chamber situated prior to the MS inlet.

HPLC-MS has the advantage of a wide mass range in combination with high sensitivity and high selectivity, which is essential for the analysis of low concentration analytes in a complex matrix such as fire effluent. With matrices with a lower expectancy of interfering compounds, such as air samples, some studies use HPLC-UV or HPLC-UV/FL detectors such as diode array detection (DAD), see Table 6. The selectivity of UV-FL absorbance detection for isocyanates is described as good for air samples (Ceballos et al. 2011). However, this detection method generally suffers from slightly lower limit of detection (LOD) than MS, and a lower selectivity, especially in complex matrices (Corradini et al. 1998). In addition, fire effluents are also likely contain polyaromatic species that can interfere with the UV/FL detection.

When analysing derivatised airborne isocyanates by HPLC coupled to tandem MS (HPLC-MS/MS), a majority of the studies reports use of a ESI in positive as an ionisation source (Pronk 2006; Sennbro et al. 2004; Dahlin et al. 2008a; Boutin et al. 2006; Thomasen et al. 2011). ESI as ionisation technique has the advantage of very little in-source fragmentation, meaning that the molecular ion can always be observed (de Hoffman & Stroobant 2007). When combining the ESI with MS/MS, the possibility to quantify analytes by collision induced disassociation (CID) methods can be used to further enhance selectivity (de Hoffman & Stroobant 2007). This selected reaction mode (SRM), also known as multiple reaction monitoring (MRM) depending on instrument vendor, requires a selected intact analyte molecular ion after the ionisation to pass through the first analyser, in order to be fragmented in a collision cell to allow the second analyser to detect its specific product ions (de Hoffman & Stroobant 2007). Although SRM methods in general are widely used for the quantitative analysis of airborne isocyanates, some of the drawbacks are laborious method development in comparison to other techniques discussed, the lack of post-acquisition re-interrogation of the data other than the ion transitions already programmed in the method and the dependence on analytical standards.

Table 6 Summary of the derivatisation reagents and suitable detections methods used for sampling isocyanates. The advantages and disadvantages with respective reaction are also summarised together with the matrices used for sampling airborne isocyanates and sampling method used in respective study

Derivatisation reagent	Advantages	Disadvantages	Sample	Sampling method	Analytical detection	Isocyanates	Ref
9-(N-Methylaminomethyl) anthracen (MAMA)	Structure independent (UV)	Light sensitive Interference with amines and alcohols during derivatisation Slow reaction rate	Air (breathing zone)	In-house made, identical to ISO-CHEK (three stage filter cassette)	HPLC-DAD-FL	IPDI monomer, HDI monomer, IPDI polyisocyanate, 3 polyisocyanate forms of HDI	(Reeb-Whitaker et al. 2012)
			Air	Impinger	HPLC-UV	TDI, 2,4-TDA, 2,6-TDA	(Persson et al. 1993)
1-(2-methoxyphenyl)-piperazine (1-2MP)	Signal independent for electrochemical detection (EC) Commercially available internal standards	Underestimation of air-levels during long time sampling Interference with amines and alcohols during derivatisation	Air	Impinger	HPLC-EC and UV	Monomeric	(NIOSH 8/15/94 1994)
			Air	Glass fibre filters	TPMLC	2,4-TDI, 2,6-TDI, MDI	(Molander et al. 2000)
			Air	Impinger, ISO-CHECK, IOM samplers (filter based sampling mainly for particles)	LC-MS, HPLC-UV-FL, HPLC-PDA UV, HPLC-DAD	Mono- and polymeric HDI	(Thomasen et al. 2011)
			Air	Impinger	HPLC/MS/MS	ICA, aliphatic isocyanates, alkenyl isocyantes, structural isomers	(Boutin et al. 2004)
			Air (breathing zone)	In-house made, identical to ISO-CHEK	HPLC	IPDI monomer, HDI monomer, IPDI polyisocyanate, 3 polyisocyanate forms of HDI	(Reeb-Whitaker et al. 2012)
			Personal air, urine	Inhalable dust sampling heads, polystyrene containers	HPLC, negative ion CI MS	MDI, HDI, TDI, IPDI, urinary metabolites of HDI, TDI, MDI, IPDI	(Creely et al. 2006)
			Air	Glass fibre filters, bubblers	LC-MS/MS	ICA, linear aliphatic isocyanates, alkenyl isocyanates, HDI, IPDI, 2,4-TDI, 2,6-TDI, MDI, PHI	(Boutin et al. 2006)
			Air	Impregnated filters	LC-MS/MS	2,4-TDI, 2,6-TDI, NDI, MDI, IPDI, PHI, MIC, ICA	(Sennbro et al. 2004)
			Air	Glass fibre filter in IOM sampler	LC-MS/MS	HDI based isocyanates	(White 2012)
			Air	IOM sampler, impregnated filter	LC/UV/MS	MDI	(Vangronsveld et al. 2010)
			Air	Impregnated filters	LC/ESI/MS	TDI	(Mattsson et al. 2008)

Table 6 Summary of the derivatisation reagents and suitable detections methods used for sampling isocyanates. The advantages and disadvantages with respective reaction are also summarised together with the matrices used for sampling airborne isocyanates and sampling method used in respective study *(Continued)*

1-(9-Antracenylmethyl) piperazine (MAP)	Increased chromatographic performance Quantifies polyisocyanates Near universal UV response factor Sensitive UV detection Compatible with Ph gradient solution	Variable fluorescent yield per NCO Stability of derivatives uncertain Not commercially available MAP artefact peaks	Air	Impregnated filters, impinger, or both	HPLC-UV-FL	Total	(NIOSH 2003)
			Air	Impregnated filters, impinger, or both	HPLC-UV-FL	Monomeric and oligomeric HDI	(Woskie 2004)
Di-n-butylamine (DBA)	No interference with amines and alcohols during derivatisation Can be used in higher concentrations to avoid underestimation Quantifies isocyanates and amines Faster reaction times Commercially available internal standards	Non-routine, expensive analysis Quantifying polyisocyanates requires standards	Air	Impinger and filter	LC-MS/MS	-	(Marand et al. 2005)
			Air	Impinger	HPLC-ESI-MS/MS	HDI and its oligomers	(Pronk 2006)
			Air	Impinger	LC-MS/MS	2,4-TDI, 2,6-TDI. NDI, MDI, IPDI, PHI, MIC, ICA	(Sennbro et al. 2004)
			Air	Denuder-impactor	LC-MS/MS	ICA, MIC, EIC, PIC, PHI, HDI, 2,4-TDI, 2,6-TDI, IPDI, MDI	(Dahlin et al. 2008b)
1-(2-pyridyl)piperazine (2-PP)	Separation of isocyanates (mainly monomers)	Polyisocyanates difficult to separate	Gaseous and/or aerosol samples drawn from a emission source	Multicomponent sampling train	HPLC-UV	2,4-TDI, HDI, MDI, MIC	(EPA 1997)
			Air	Glass fibre filters	HPLC-UV/FL	HDI, 2,4-TDI, 2,6-TDI	(Occupational Safety and Health Administration (OSHA) 1989a)
			Air	Glass fibre filters	HPLC-UV/FL	MDI	(Occupational Safety and Health Administration (OSHA) 1989b)
			Air	Glass fibre filters	HPLC-UV/FL	2,4-TDI, 2,6-TDI	(British Standard Institution 2012)
			Extracts from solids, soils, filters, foams, collected in impinger solutions		HPLC-DAD/MS	2,4-TDI, 2,6-TDI, HDI, HDI biuret, HDI trimer, 2,4-MDI, 4,4-MDI	(US EPA 2004)
			Air	Filter	HPLC-UV/FL	Di-isocyanates	(Sigma-Aldrich 1994)

Table 6 Summary of the derivatisation reagents and suitable detections methods used for sampling isocyanates. The advantages and disadvantages with respective reaction are also summarised together with the matrices used for sampling airborne isocyanates and sampling method used in respective study *(Continued)*

Tryptamine	Structure independent reaction	Slow reaction rate Matrix interference when using UV detectors	Air	Impinger	HPLC-FL/EC	-	(NIOSH 1998)
			Air, urine	Impinger	HPLC-EC/UV	HDI	(Mirmohammadi et al. 2010)
9-anthracenylmethyl-1-piperazinecarboxylate (PAC)	No chromatographic losses of isocyanate species No response factor variability between isocyanates	Impurities may give high blank of cleavage product Slow reaction rate	Air	Impinger	HPLC-UV-FL	HDI, PHI, MDI, 2,4-TDI	(Roh et al. 2000)
Ferrocenoyl piperazide (FP)	Sensitivity	No data on reactivity or stability	Air	Impingers	LC-EC/MS	-	(Seiwert et al. 2004)

Some studies have reported on the use of proton transfer mass spectrometry (PTR-MS) for the analysis of isocyanate-DBA urea derivatives (Gylestam et al. 2011). The method described by Gustavsson et al. (Gustavsson et al. 2010) and Gylestam et al. (Gylestam et al. 2011) offered a continuous and real-time analysis of airborne isocyanates as well as very little in-source fragmentation (Gylestam et al. 2011). However, one drawback of using the PTR-MS is the severe fragmentation of some alkenes, rendering in complex spectra without the presence of the molecular ion (Hewitt et al. 2003), making the method more suitable for applications in analysing aromatic isocyanates.

Internal standards

When considering derivatisation reagents for quantitative studies, the use of internal standards are important, as they compensate for variations in the sample work-up procedure as well as in detector response (Remane et al. 2010). Studies have reported the use of deuterium labelled isocyanates, generated from thermal degradation of carbamate ester derivatives of the corresponding deuterium labelled amines, as internal standards (Karlsson et al. 1998; Karlsson et al. 2000; Karlsson et al. 2002). However, this process is time consuming and laborious (Karlsson et al. 2005). Therefore, the use of internal standards with deuterium labelled reagents, such as d_9-DBA or d_{18}-DBA as well as d_3-1-2MP, have been developed (Marand et al. 2004; Henriks-Eckerman et al. 2002; Sennbro et al. 2004). An increase of instrumental precision for HPLC-MS/MS with the increase of the number of deuterium in the molecule has also been reported (Karlsson et al. 2005).

Conclusions

Isocyanates are used in the production of flexible and rigid foams for insulation in buildings as well as in paints, varnishes and as hardener for paints and lacquers. In addition, the global demand of isocyanates is predicted to increase in the coming years. Isocyanates are highly reactive compounds, with associated with several adverse health effects after exposure, such as respiratory sensitisation causing lifelong asthma, inflammations to the respiratory tract, hypersensitivity pneumonitis and potentially cancer, associated with exposure. Although there are studies on the acute toxicological effects of isocyanates, such as investigations on MIC after the Bhopal disaster, most toxicological studies are nowadays focused on occupational risks after chronic, low-dose exposure. Several studies report a good correlation between isocyanate exposure and measurements of amine derivatives of isocyanates in urine. However, further research on the toxicokinetics and metabolism of isocyanates is needed in order to select the most suitable biomarkers as well as establish a definitive correlation between exposure concentration and biomarker concentration.

The most well studied materials for the generation of isocyanates during thermal degradation of materials are PUR and PIR foams. There are currently significant data gaps in the knowledge of how to sample and quantitate isocyanates from fire effluents. Despite the complexity of determining isocyanates in fire effluents, recent advances in both sampling as well as analytical techniques have contributed significantly to optimising these methods. The most common sampling method for isocyanates generated from fires is an impinger-filter sampling technique using DBA as derivatisation agent. Due to the favourable reaction kinetics, this method is suitable for quantitative analysis. Sampled isocyanates are generally analysed by HPLC coupled to either UV/FL or MS detectors. Although the selectivity is described as good for isocyanates sampled in air by HPLC-UV/FL, MS/MS detectors are to prefer when analysing more complex matrices, such as fire effluents, due to better selectivity and sensitivity, especially when internal standards are used. Continuous improvements in investigating the generation of isocyanates from thermal degradation of materials as well as sampling and analysis are expected in the future.

Abbreviations

ACGIH: American Conference of Governmental Industrial Hygienists; AEGL1: Acute Exposure Guideline Level 1; AEGL2: Acute Exposure Guideline Level 2; AEGL3: Acute Exposure Guideline Level 3; AIHA: American Industrial Hygiene Association; CID: Collision induced disassociation; COSHH: Control of Substances Hazardous to Health; DAD: Diode-array detector; DBA: Dibutyl amine; EC: Electrochemical detection; ERPG2: Emergency Response Planning Guidelines level 2; ERPG3: Emergency Response Planning Guidelines level 3; ESI: Electrospray ionisation; FP: Ferrocenoyl piperazide; HDA: Hexamethylene diamine; HDI: Hexamethylene di-isocyanate; HPLC: High-performance liquid chromatography; HPLC-MS/MS: High-performance liquid chromatography with tandem mass spectrometer detector; HSE: Health and Safety Executive; HSL: Health and Safety Laboratory; IARC: International Agency for Research on Cancer; ICA: Isocyanic acid; IgE: Immunoglobulin E; IPDA: Isophorone diamine; IPDI: Isophorone di-isocyanate; LC-UV: Liquid chromatography with UV detector; LOD: Limit of detection; MDI: Diphenylmethane-di-isocyanate; MIC: Methyl isocyanate; MRM: Multiple reaction monitoring; MS: Mass spectrometer; NDI: 1,5-naphthalene di-isocyanate; NIOSH: National Institute of Occupational Safety and Health; OEL: Occupational exposure limits; OSHA: Occupational Safety and Health Administration; PAC: 9-anthracenylmethyl-1-piperazinecarboxylate; PHI: Phenyl isocyanate; PIC: Propyl isocyanate; PIR: Polyisocyanurate foam; PTR-MS: Proton transfer mass spectrometry; PU: Polyurethane; PUF: Flexible polyurethane foam; PUR: Rigid polyurethane foam; REACH: Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals; REL: Recommended exposure limits; SRM: Selective reaction monitoring; STEL: Short-term exposure limit (15 min unless otherwise stated); TDA: Toluene-2,6-diamine; TDI: Toluene-di-isocyanate; TWA: Time weighted average; UV-FL: UV/Fluorescence detector.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LB, MS and AA all contributed equally to the writing of this manuscript. All authors read and approved the final manuscript.

Received: 5 February 2016 Accepted: 25 April 2016

References

Agency EC (2015) Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) - Annex XIV of REACH ("Authorisation List")., Available at: http://echa.europa.eu/addressing-chemicals-of-concern/authorisation/recommendation-for-inclusion-in-the-authorisation-list/authorisation-list

Allan D, Daly JH, Liggat JJ (2014) Thermal volatilisation analysis of a TDI-based flexible polyurethane foam containing ammonium polyphosphate. Polym Degrad Stab 102(1):170–179, Available at: http://dx.doi.org/10.1016/j.polymdegradstab.2012.12.002

American Conference of Governmental Industrial Hygienists (1986) American Conference of Governmental Industrial Hygienists. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th edn. American Conference of Governmental Industrial Hygienists, Cincinnati, OH

Ashida K et al (1997) Polyisocyanurate foams modified by thermally stable linkages. In: ACS Symp Series., p 669, 81–100

Austin S (2007) Biological monitoring of TDI-derived amines in polyurethane foam production. Occup Med Oxford England 57(6):444–448

Avar G et al (2012) Polyurethanes., Available at: http://linkinghub.elsevier.com/retrieve/pii/B9780444533494002752

Axford AT et al (1976) Accidental exposure to isocyanate fumes in a group of firemen. Br J Ind Med 33(2):65–71

Bayer O (1947) Das Di-Isocyanat-Polyadditionsverfahren (Polyurethane). Angew Chem 59(9):257–272, Available at: http://doi.wiley.com/10.1002/ange.19470590901 [Accessed November 4, 2015]

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(3):351–360, Available at: http://pubs.rsc.org/en/content/articlehtml/2002/em/b110613a

Bernstein LI, Chan-Yeung M, Malo J-L, Bernstein DI (eds) (2006). Asthma in the Workplace, 3rd edn. CRC Press, Boca Raton, FL, USA

Berufsgenossenschaft der chemischen Industrie (1997) Toxikologische Bewertungen, Diphenyl-2-ethylhexylphosphat

Bianchi AP, Trevor K, Joyner B (1997) Determination of toluene-2, 4-diisocyanate in environmental and workplace air by sampling onto Tenax-TA followed by thermal desorption and capillary gas chromatography using flame ionisation and ion-trap detection. Journal of Chromatography A 771:233–239

Bilban M (2004) Mutagenic testing of workers exposed to toluene-diisocyanates during plastics production process. Am J Ind Med 45(5):468–474, Available at: http://dx.doi.org/10.1002/ajim.10365

Blomqvist P et al (2007) Detailed determination of smoke gas contents using a small-scale controlled equivalence ratio tube furnace method. Fire Materials 31:495–521

Blomqvist P et al (2014) Detailed study of distribution patterns of polycyclic aromatic hydrocarbons and isocyanates under different fire conditions. Fire Materials 38:125–144

Blomqvist P et al (2003) Isocyanates, aminoisocyanates and amines from fires - a screening of common materials found in buildings. Fire Mater 27(6):275–294, Available at: http://doi.wiley.com/10.1002/fam.836

Bolognesi C et al (2001) Carcinogenic risk of toluene diisocyanate and 4,4′-methylenediphenyl diisocyanate: epidemiological and experimental evidence., Available at: http://www.ncbi.nlm.nih.gov/pubmed/11763481

Boutin M et al (2006) Determination of Airborne Isocyanates Generated During the Thermal Degradation of Car Paint in Body Repair Shops. Ann Occup Hyg 50(4):385–393, Available at: http://annhyg.oxfordjournals.org/cgi/doi/10.1093/annhyg/mei075

Boutin M et al (2004) Identification of the isocyanates generated during the thermal degradation of a polyurethane car paint. J Anal Appl Pyrolysis 71(2):791–802

British Standard Institution (2012) BS ISO 14382:2012 Workplace atmospheres. Determination of toluene diisocyanate vapours using 1-(2-pyridyl) piperazine-coated glass fibre filters and analysis by high performance liquid chromatography with ultraviolet and fluorescence detectors

Brorson T, Skarping G (1990) Biological monitoring of isocyanates and related amines., pp 385–389

Brorson T, Skarping G, Sangö C (1991) Biological monitoring of isocyanates and related amines. Int Arch Occup Environ Health 63(4):253–259

Broughton E (2005) The Bhopal disaster and its aftermath: a review. Environ Health 4(1):6

Brown WE et al (1982) Inhibition of cholinesterase activity by isocyanates. Toxicol Appl Pharmacol 63(1):45–52

BSI Standards Publication (2013) BSI Standards Publication Determination of organonitrogen compounds in air using liquid chromatography and mass spectrometry Part 1 : Isocyanates using dibutylamine derivatives

Bureau EC (2000) IUCLID Dataset, phenyl isocyanate (103-71-9) (2000 CD-ROM edition)., Available at: doi:10.1039/c1ay05225j

Buschmann J (1990) Teratoge nicitv studv of monomeric 4.4′-methvlenediohenvl diisocvanate (MDI) aerosol after inhalation exuosure in Wistar rats. Teratology 50(5):40A

Ceballos DM et al (2011) A laboratory comparison of analytical methods used for isocyanates. Anal Methods 3(11):2478, Available at: http://pubs.rsc.org/en/content/articlehtml/2011/ay/c1ay05225j

Centers for Disease Cotrol and Prevention (2015a) NIOSH Pocket Guide to Chemical Hazards - Toluenediamine., Available at: http://www.cdc.gov/niosh/npg/npgd0620.html [Accessed December 11, 2015]

Centers for Disease Cotrol and Prevention (2015b) NIOSH Pocket Guide to Chemical Hazards - Hexamethylene diisocyanate., Available at: http://www.cdc.gov/niosh/npg/npgd0320.html [Accessed December 11, 2015]

Centers for Disease Cotrol and Prevention (2015c) NIOSH Pocket Guide to Chemical Hazards - Toluene-2,4-diisocyanate., Available at: http://www.cdc.gov/niosh/npg/npgd0621.html [Accessed December 11, 2015]

Centers for Disease Cotrol and Prevention, 2015d. NIOSH Pocket Guide to Chemical Hazards: Isophorone diisocyanate. *2015*. Available at: http://www.cdc.gov/niosh/npg/npgd0356.html.

Centers for Disease Cotrol and Prevention (2015e) NIOSH Pocket Guide to Chemical Hazards: Methylene bisphenyl isocyanate., Available at: http://www.cdc.gov/niosh/npg/npgd0413.html [Accessed December 11, 2015]

Chattopadhyay DK, Raju KVSN (2007) Structural engineering of polyurethane coatings for high performance applications. Prog Polym Sci 32(3):352–418

Chattopadhyay DK, Webster DC (2009) Thermal stability and flame retardancy of polyurethanes. Progress in Polymer Science (Oxford) 34(10):1068–1133

Choi J-H et al (2014) Pulmonary function decline in firefighters and non-firefighters in South Korea. Ann Occup Environ Med 26(1):9, Available at: http://www.aoemj.com/content/26/1/9

Cocker J (2011) Biological monitoring for isocyanates. Ann Occup Hyg 55(2):127–131, Available at: http://www.ncbi.nlm.nih.gov/pubmed/21252056

Corradini D, Eksteen (Katz) E, Eksteen R, Schoenmakers P, Miller N (1998) Handbook of HPLC, vol 78. Marcel Dekker, Basel, Switzerland

Creely K et al (2006) Assessing Isocyanate Exposures in Polyurethane Industry Sectors Using Biological and Air Monitoring Methods. Ann Occup Hyg 50(6):609–621, Available at: http://annhyg.oxfordjournals.org/cgi/doi/10.1093/annhyg/mel024

Dahlin J (2007) Aerosols of Isocyanates, Amines and Anhydrides Sampling and Analysis

Dahlin J, Spanne M, Dalene M et al (2008a) Size-separated sampling and analysis of isocyanates in workplace aerosols - Part II: Aging of aerosols from thermal degradation of polyurethane. Ann Occup Hyg 52(5):375–383

Dahlin J, Spanne M, Karlsson D et al (2008b) Size-separated sampling and analysis of isocyanates in workplace aerosols. Part I. Denuder - Cascade impactor sampler. Ann Occup Hyg 52(5):361–374

Dominguez-Rosado E et al (2002) Thermal degradation of urethane modified polyisocyanurate foams based on aliphatic and aromatic polyester polyol. Polym Degrad Stab 78(1):1–5

Dykewicz MS (2009) Occupational asthma: Current concepts in pathogenesis, diagnosis, and management. J Allergy Clin Immunol 123(3):519–528, Available at: http://linkinghub.elsevier.com/retrieve/pii/S0091674909002140

Eckerman I (2005) The Bhopal Saga: Causes and Consequences of the World's Largest Industrial Disaster. Environ Health Perspect 113:A344

EPA, U. (1997) METHOD 207-A Method for Measuring Isocyanates in Stationary Source Emissions

European Aliphatic Isocyanate Producer Association (2013) Properties, Hazards and Safety Information for IPDI * Product : IPDI (Isophorone diisocyanate ; CAS No . 4098-71-9) Physical and chemical data Toxicological Information., Available at: http://www.alipa.org/index.php?page=monomeric-diisocyanates

Fabbri LM et al (1987) Bronchoalveolar Neutrophilia during Late Asthmatic Reactions Induced by Toluene Diisocyanate. Am Rev Respir Dis 136(1):36–42

Fent KW, Evans DE (2011) Assessing the risk to firefighters from chemical vapors and gases during vehicle fire suppression. J Environ Monit 13(3):536–543, Available at: http://www.ncbi.nlm.nih.gov/pubmed/21274476

Fisseler-Eckhoff A et al (2011) Environmental isocyanate-induced asthma: Morphologic and pathogenetic aspects of an increasing occupational disease. Int J Environ Res Public Health 8(9):3672–3687

Fuchs S, Valade P (1951) Clinical and Experimental Study of Intoxication by Desmodur T (Di-isoeyanate of Toluylène 1-2-4 and 1-2-6). Archives des Maladies Professionnelles de Medecine du Travail et de Securite Sociale 12(2):191–196

Gann RG, Bryner NP (2008) Combustion Products and Their Effects on Life Safety. In: National Institute of Standards and Technology., p Capter 2 (11–34)

Goswami H et al (1990) Search for chromosomal variations among gas-exposed persons in Bhopal. Hum Genet 84(2):172–176

Gupta M, Prabha V (1996) Changes in Brain and Plasma Amino Acids of Mice Intoxicated with Methyl Isocyanate. J Appl Toxicol 16(6):1–5

Gustavsson M et al (2010) Adsorption efficiency of respirator filter cartridges for isocyanates. Ann Occup Hyg 54(4):377–390, Available at: http://www.ncbi.nlm.nih.gov/pubmed/20215336

Gylestam D et al (2011) Determination of Gas Phase Isocyanates Using Proton Transfer Reaction Mass Spectrometry. Anal Chem Lett 1(4):261–271, Available at: http://www.tandfonline.com/doi/abs/10.1080/22297928.2011.10648228

Gylestam D et al (2014) Dry sampling of gas-phase isocyanates and isocyanate aerosols from thermal degradation of polyurethane. Ann Occup Hyg 58(1):28–49

Hansen AS, Hovde PJ (2002) Prediction of time to flashover in the ISO 9705 room corner test based on cone calorimeter test results. Fire Mater 26(2):77–86, Available at: http://onlinelibrary.wiley.com/doi/10.1002/fam.788/abstract\npapers3://publication/doi/10.1002/fam.788

Harden CS, Shoff DB (1997) Detection of methyl isocyanate in air with the use of hand-held ion mobility spectrometers. Field Anal Chem Technol 1(Issue 5):285–294

Health and Safety Executive (2011) EH4O / 2005 Workplace exposure limits EH4O / 2005 Workplace exposure limits. (March 2013)., pp 1–74

Health and Safety Executive HSE (2014) Organic isocyanates in air: Laboratory method with derivatisation in situ either on treated glass fibre filters or in solution using impingers with a treated back up filter in series, followed by high-performance liquid chromatography analysis MDHS25., Available at: www.hse.gov.uk/pubns/mdhs

Health and Safety Laboratory (HSL) (2007) Analytical Methods for Low Molecular Weight Isocyanates. Available at: www.hse.gov.uk/research/hsl_pdf/2007/hsl0747.pdf

Henneken H et al (2003) Diffusive sampling of methyl isocyanate using 4-nitro-7-piperazinobenzo-2-oxa-1,3-diazole (NBDPZ) as derivatizing agent. J Environ Monit 5(1):100–105, Available at: http://www.ncbi.nlm.nih.gov/pubmed/12619763

Henneken H et al (2006) Validation of a diffusive sampling method for airborne low-molecular isocyanates using 4-nitro-7-piperazinobenzo-2-oxa-1,3-diazole-impregnated filters and liquid chromatography-tandem mass spectrometry. J Chromatogr A 1134(1–2):112–121, Available at: http://www.ncbi.nlm.nih.gov/pubmed/16996529

Henneken H, Vogel M, Karst U (2007) Determination of airborne isocyanates. Anal Bioanal Chem 387(1):219–236, Available at: http://www.ncbi.nlm.nih.gov/pubmed/17103147

Henriks-Eckerman M-L et al (2002) Exposure to airborne isocyanates and other thermal degradation products at polyurethane-processing workplaces. J Environ Monit 4(5):717–721, Available at: http://xlink.rsc.org/?DOI=b206339p

Hertzberg T, Blomqvist P, Dalene M, Skarping G (2003) SP Report 2003:5 Particles and isocyanates from fires Brandforsk project 324–021, SP Swedish National Testing and Research Institute, Borås, Sweden, p 0-50

Hewitt CN, Hayward S, Tani A (2003) The application of proton transfer reaction-mass spectrometry (PTR-MS) to the monitoring and analysis of volatile organic compounds in the atmosphere. J Environ Monit 5(1):1–7, Available at: http://xlink.rsc.org/?DOI=b204712h

de Hoffman E, Stroobant V (2007) Mass Spectrometry: Principles and Applications Third Edit. John Wiley & Sons Ltd., Chichester, UK

Hughes M a et al (2014) Does diisocyanate exposure result in neurotoxicity? Clin Toxicol 52(4):242–257, Available at: http://informahealthcare.com/doi/abs/10.3109/15563650.2014.898769

Hull TR et al (2008) Comparison of toxic product yields of burning cables in bench and large-scale experiments. Fire Safety Journal 43(2):140–150

Hull TR, Paul KT (2007) Bench-scale assessment of combustion toxicity-A critical analysis of current protocols. Fire Safety Journal 42(5):340–365

Hulst AG et al (2015) Mass spectrometric identification of isocyanate-induced modifications of keratins in human skin. Chem Biol Interact 237:141–150, Available at: http://www.sciencedirect.com/science/article/pii/S0009279715002367

Jiao L et al (2013) Thermal degradation characteristics of rigid polyurethane foam and the volatile products analysis with TG-FTIR-MS. Polym Degrad Stab 98(12):2687–2696, Available at: http://linkinghub.elsevier.com/retrieve/pii/S0141391013003200

Jindal A, Singh N (2014) Oxidative Stress and Lung Cancer. In: Studies on Respiratory Disorders. Springer, New York, pp 245–257

Karlsson D et al (2000) Airborne thermal degradation products of polyurethane coatings in car repair shops. J Environ Monit 2(5):462–469, Available at: http://xlink.rsc.org/?DOI=b004562o

Karlsson D et al (2005) Determination of airborne isocyanates as di-n-butylamine derivatives using liquid chromatography and tandem mass spectrometry. Anal Chim Acta 534:263–269

Karlsson D et al (1998a) Determination of complex mixtures of airborne isocyanates and amines Part 4. Determination of aliphatic isocyanates as dibutylamine derivatives using liquid chromatography and mass spectrometry. Analyst 123(January):117–123

Karlsson D et al (2002) Determination of isocyanates, aminoisocyanates and amines in air formed during the thermal degradation of polyurethane. J Environ Monit 4(2):216–222, Available at: http://xlink.rsc.org/?DOI=b110593k

Karlsson D, Dalene M, Skarping G (1998b) Determination of complex mixtures of airborne isocyanates and amines. Part 5. Determination of low molecular weight aliphatic isocyanates as dibutylamine derivatives. Analyst 123(7):1507–1512

Karlsson D, Dalene M, Skarping G, and Marand Å (2001), Determination of isocyanic acid in air. J Environ Monit 3:432–436.

Karol MH, Kramarik JA (1996) Phenyl isocyanate is a potent chemical sensitizer. Toxicol Lett 4274:96

Kimber I, Dearman RJ (2002) Chemical respiratory allergy: role of IgE antibody and relevance of route of exposure. Toxicology 181–182:311–315

Krol P (2007) Synthesis methods, chemical structures and phase structures of linear polyurethanes. Properties and applications of linear polyurethanes in polyurethane elastomers, copolymers and ionomers. Prog Mater Sci 52(6):915–1015, Available at: http://linkinghub.elsevier.com/retrieve/pii/S007964250600079X

Lefebvre J et al (2004) Flame spread of flexible polyurethane foam: Comprehensive study. Polym Test 23:281–290

Levchik SV, Weil ED (2004) Thermal decomposition, combustion and fire-retardancy of polyurethanes - A review of the recent literature. Polym Int 53(11):1585–1610

Lindberg HK et al (2011) Micronuclei, hemoglobin adducts and respiratory tract irritation in mice after inhalation of toluene diisocyanate (TDI) and 4,4′-methylenediphenyl diisocyanate (MDI). Mutat Res 723(1):1–10, Available at: http://www.ncbi.nlm.nih.gov/pubmed/21453781

Lockey JE et al (2015) Isocyanates and Human Health. J Occup Environ Med 57(1):44–51, Available at: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00043764-201501000-00006

Lönnermark A, Blomqvist P (2006) Emissions from an automobile fire. Chemosphere 62(7):1043–1056, Available at: http://www.sciencedirect.com/science/article/pii/S0045653505006351 [Accessed July 20, 2015]

Lough WJ, Wainer IW (1996) High Performance Liquid Chromatography: Fundamental Principles and Practice. Blackie Academic & Professional, Bodmin, Cornwall, UK

Mäki-Paakkanen J, Norppa H (1987) Chromosome aberrations and sister-chromatid exchanges induced by technical grade toluene diisocyanate and methylenediphenyl diisocyanate in cultured human lymphocytes. Toxicol Lett 36(1):37–43

Marand A et al (2004) Determination of technical grade isocyanates used in the production of polyurethane plastics. J Environ Monit 6(7):606–614, Available at: http://www.ncbi.nlm.nih.gov/pubmed/15237291

Marand A et al (2005) Solvent-free sampling with di-n-butylamine for monitoring of isocyanates in air. J Environ Monit 7:335–343

Marczynski B et al (2005) DNA strand breaks in the lymphocytes of workers exposed to diisocyanates : indications of individual differences in susceptibility after low-dose and short-term exposure. Arch Toxicol 79:355–362

Market and Markets (2014) Isocyanate Market by Type (MDI, TDI, Aliphatic, Others) & Application (Rigid Foam, Flexible Foam, Paints & Coatings, Adhesive & Sealants, and Elastomers & Binders) - Global Trends & Forecast to 2019. Available at: http://www.marketsandmarkets.com/Market-Reports/isocyanate-market-174077042.html.

Markets and Markets (2011) Methylene Diphenyl Diisocyanate (MDI), Toluene Diisocyanate (TDI) and Polyurethane Market (2011 – 2016)., Available at: http://www.marketsandmarkets.com/Market-Reports/mdi-tdi-polyurethane-market-381.html

Marlair G, Prager FH, Sand H (1993) Behaviour of commercially important di-isocyanates in fire conditions. Part 1: Toluene di-isocyanate (TDI). Cell Polym 12(5):349–372, Available at: http://doi.wiley.com/10.1002/fam.810170206

Mattsson C, Lindh CH, Tinnerberg H (2008) Underestimation of toluene diisocyanate concentration using long-term sampling with 1-(2-methoxyphenyl) piperazine impregnated filters. Int J Hyg Environ Health 211:458–462, Available at: http://dx.doi.org/10.1016/j.ijheh.2007.08.003

Mirmohammadi M et al (2010) Indoor air pollution evaluation with emphasize on HDI and biological assessment of HDA in the polyurethane factories. Environ Monit Assess 165(1–4):341–347, Available at: http://www.ncbi.nlm.nih.gov/pubmed/19444630

Mishra PK et al (2009) Bhopal Gas Tragedy: review of clinical and experimental findings after 25 years. Int J Occup Med Environ Health 22(3):193–202

Mishra PK et al (2008) Isocyanates induces DNA damage, apoptosis, oxidative stress, and inflammation in cultured human lymphocytes. J Biochem Mol Toxicol 22(6):429–440, Available at: http://www.ncbi.nlm.nih.gov/pubmed/19111005\nhttp://onlinelibrary.wiley.com/doi/10.1002/jbt.20260/abstract

Molander P et al (2000) Determination of 1-(2-methoxyphenyl)piperazine derivatives of isocyanates at low concentrations by temperature-programmed miniaturized liquid chromatography. J Chromatogr A 892(1–2): 67–74, Available at: http://www.sciencedirect.com/science/article/pii/S0021967399013515 [Accessed November 2, 2015]

Montelius EJ, Sant FV (2009) Scientific Basic for Swedish Occupational Standards XXIX

Nehez M et al (1989) Investigations on the Acute Toxic, Cytogenetic, and Embryotoxic Activity of Phenyl Isocyanate and Diethoxyphosphoryl Isocyanate. Ecotoxicol Environ Saf 17:258–263

NIOSH, 2003. ISOCYANATES, TOTAL (MAP): METHOD 5525, Issue 1, dated 15 March 2003., (1), pp.1–18.

NIOSH, 1998. ISOCYANATES: METHOD 5522, Issue 2

NIOSH 8/15/94, 1994. Isocyanates, monomeric. NIOSH Manual of Analytical Methods (NMAM), Fourth Edition, 8/15/94, pp.4–9.

No LEP et al (2014) Survey of certain isocyanates (MDI and TDI)

Nordqvist Y et al (2005) A chemosorptive cylindrical denuder designed for personal exposure measurements of isocyanates – evaluation on generated. J Environ Monit 7:469–474

O'Neil MJ (ed) (2006) The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals, 14th edn. Merck Manuals, Rahway, NJ, USA, p 1259

Occupational Safety and Health Administration (OSHA) (1989a) Method 42 - Chemical Sampling - 1,6-Hexamethylene Diisocyanate, Toluene-2,6-Diisocyanate, Toluene-2,4-DiisocyanateChemical Sampling - 1,6-Hexamethylene Diisocyanate, Toluene-2,6-Diisocyanate, Toluene-2,4-Diisocyanate., Available at: https://www.osha.gov/dts/sltc/methods/organic/org042/org042.html

Occupational Safety and Health Administration (OSHA), 1989b. Methylene Bisphenyl Isocyanate (MDI) Occupational Safety and Health Administration (OSHA) Method No. 47. No 47. Available at: https://www.osha.gov/dts/sltc/methods/organic/org047/org047.html.

Pascault J-P et al. (2002) Thermosetting Polymers. CRC Press.

Pauluhn J, Rüngeler W, Mohr U (1995) Phenyl Isocyanate induced asthma in Rats Following a 2-week Exposure Period. Fundemental Appl Toxicol 24:217–228

Persson P et al (1993) Biological monitoring of occupational exposure to toluene diisocyanate: measurement of toluenediamine in hydrolysed urine and plasma by gas chromatography–mass spectrometry. Br J Ind Med 50(12):1111–1118, Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1061334&tool=pmcentrez&rendertype=abstract

Piirilä PL et al (2008) Inflammation and functional outcome in diisocyanate-induced asthma after cessation of exposure. Allergy 63(5):583–591, Available at: http://www.ncbi.nlm.nih.gov/pubmed/18394133

Pisati G et al (2007) Rechallenging subjects with occupational asthma due to toluene diisocyanate (TDI), after long-term removal from exposure. Int Arch Occup Environ Health 80(4):298–305, Available at: http://www.ncbi.nlm.nih.gov/pubmed/16957957

Pronk A (2006) Dermal, inhalation, and internal exposure to 1,6-HDI and its oligomers in car body repair shop workers and industrial spray painters. Occup Environ Med 63(9):624–631

Pronk A (2007) Isocyanate exposure and respiratory health effects in the spray painting industry

Purser DA, Grimshaw P (1984) The incapacitative effects of exposure to the thermal decomposition products of polyurethane foams. Fire Mater 8(1):10–16, Available at: http://doi.wiley.com/10.1002/fam.810080104

Purser DA, Buckley P (1983) Lung Irritance and Inflammation during and after Exposures to Thermal Decomposition Products from Polymeric Materials. Med Sci Law 23(2):142–150

Purser DA, Woolley WD (1983) Biological Studies of Combustion Atmospheres. J Fire Sci 1(2):118–144

Le Quesne PM et al (1976) Neurological complications after a single severe exposure to toluene di-isocyanate. Br J Ind Med 33(2):72–78, Available at: http://www.ncbi.nlm.nih.gov/pubmed/179562

Rachiotis G et al (2007) Outcome of occupational asthma after cessation of exposure: a systematic review. Thorax 62(2):147–152, Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2111252&tool=pmcentrez&rendertype=abstract

Rando RJ, Poovey HG, Gibson RA (1995) Evaluation of 9-Methylamino-Methylanthracene as a Chemical Label for Total Reactive Isocyanate Group: Application to Isocyanate Oligomers, Polyurethane Precursors, and Phosgene. J Liq Chromatogr 18(14):2743–2763

Redlich CA, Karol MH (2002) Diisocyanate asthma: clinical aspects and immunopathogenesis. Int Immunopharmacol 2(2–3):213–224, Available at: http://www.ncbi.nlm.nih.gov/pubmed/11811926

Reeb-Whitaker C et al (2012) Airborne Isocyanate Exposures in the Collision Repair Industry and a Comparison to Occupational Exposure Limits. J Occup Environ Hyg 9(5):329–339

Remane D et al (2010) Systematic investigation of ion suppression and enhancement effects of fourteen stable-isotope-labeled internal standards by their native analogues using atmospheric-pressure chemical ionization and electrospray ionization and the relevance for multi-anal. Rapid Commun Mass Spectrom 24(7):859–867, Available at: http://www.ncbi.nlm.nih.gov/pubmed/20196193

Rhoades R, Pflanzer R (2003) Human Physiology, 4th edn. Thomson Learning, Inc, Stamford, CT, USA

Rogers ME, Long TE (2003) Synthetic Methods in Step-Growth Polymers. John Wiley & Sons Inc., Hoboken, New Jersey

Roh Y-M, Streicher RP, Ernst MK (2000) Development of a new approach for total isocyanate determination using the reagent 9-anthracenylmethyl1-piperazinecarboxylate. Analyst 125(9):1691–1696, Available at: http://xlink.rsc.org/?DOI=b003655m

Rom WN, Markowitz SB (2007) Environmental and Occupational Medicine Fourth Edi. Lippincott Williams and Wilkins, Philadelphia, PA, USA

Rosenberg C, Savolainen H (1986) Determination of occupational exposure to toluene diisocyanate by biological monitoring. J Chromatogr A 367:385–392

Saunders KJ (1973) Organic Polymer Chemistry: An Introduction to the Organic Chemistry of Adhesives, Fibres, Paints, Plastics and Rubbers First. Chapman and Hall Ltd., Salisbury, Wiltshire, Uk

Seiwert B, Henneken H, Karst U (2004) Ferrocenoyl piperazide as derivatizing agent for the analysis of isocyanates and related compounds using liquid chromatography/electrochemistry/mass spectrometry (LC/EC/MS). J Am Soc Mass Spectrom 15(12):1727–1736, Available at: http://www.ncbi.nlm.nih.gov/pubmed/15589750

Sennbro CJ et al (2004) Determination of Isocyanates in Air Using 1-(2-Methoxyphenyl)piperazine-impregnated Filters: Long-term Sampling Performance and Field Comparison with Impingers with Dibutylamine. Ann Occup Hyg 48(5):415–424, Available at: http://annhyg.oupjournals.org/cgi/doi/10.1093/annhyg/meh035

Sids OECD (2001) Hexamethylene Diisocyanate CAS N°:822-06-0

Sigma-Aldrich (1994). Monitor Airborne Diisocyanates Using ORBOTM-80 Coated Filters. Application note 31.

Simone Reuter BBA (2011) Oxidative stress, inflammation, and cancer: How are they linked? Free Radic Biol Med 49(11):1603–1616

Song YM et al (1996) Effect of isocyanates on the crystallinity and thermal stability of polyurethanes. J Appl Polym Sci 62(5):827–834, Available at: <Go to ISI>://A1996VL34600015

Spanne M et al (1996) Determination of complex mixtures of airborne isocyanates and amines. Part 1. Liquid chromatography with ultraviolet detection of monomeric and polymeric isocyanates as their dibutylamine derivatives. Analyst 121(8):1095

Stec AA et al (2008a) The effect of temperature and ventilation condition on the toxic product yields from burning polymers. Fire Mater 32(1):49–60, Available at: 10.1002/fam.955

Stec AA et al (2008b) Characterisation of the steady state tube furnace (ISO TS 19700) for fire toxicity assessment. Polym Degrad Stab 93(11):2058–2065, Available at: 10.1016/j.polymdegradstab.2008.02.020

Stec AA et al (2009) Comparison of toxic product yields from bench-scale to ISO room. Fire Saf J 44(1):62–70, Available at: doi:10.1016/j.firesaf.2008.03.005

Stec AA, Hull TR (2010) Fire toxicity. Woodhead Publishing Limited, Cambridge, England

Stec AA, Hull TR (2011) Assessment of the fire toxicity of building insulation materials. Energy Buildings 43(2–3):498–506, Available at: doi:10.1016/j.enbuild.2010.10.015

Stec AA et al (2014) Fire Toxicity Assessment: Comparison of Asphyxiant Yields from Laboratory and Large Scale Flaming Fires. In: 11th International Symposium on Fire Safety Science. University of Canterbury, New Zealand

Streicher RP et al (2000) Determination of airborne isocyanate exposure: considerations in method selection. AIHAJ-American Industrial Hygiene Association 61(4):544–556

Streicher RP et al (1996) Development of a Novel Derivatization Reagent for the Sampling and Analysis of Total Isocyanate Group in Air and Comparison of its Performance with that of Several Established Reagents. Am Ind Hyg Assoc J 57(10):905–913

Streicher RP et al (1995) Investigation of the Ability of MDHS Method 25 to Determine Urethane-Bound Isocyanate Groups. Am Ind Hyg Assoc J 56:5

Streicher RP et al (2002) Selecting isocyanate sampling and analytical methods. Appl Occup Environ Hyg 17(3):157–162, Available at: http://dx.doi.org/10.1080/104732202753438234

Sui H et al (2014) Primary thermal degradation effects on the polyurethane film. Polym Degrad Stab 101(1):109–113, Available at: http://www.sciencedirect.com/science/article/pii/S0141391013004023

The National Institute for Occupational Safety and Health (NIOSH) (2004) A Summary of Health Hazard Evaluations : Isocyanates, 1989 to 2002

Thomasen J et al (2011) Field Comparison of Air Sampling Methods for Monomeric and Polymeric 1,6-Hexamethylene Diisocyanate. J Occup Environ Hyg 8(3):161–178, Available at: http://www.tandfonline.com/doi/full/10.1080/15459624.2011.555711

Tinnerberg H et al (1995) Test chamber exposure of humans to 1, 6-hexamethylene diisocyanate and isophorone diisocyanate. Int Arch Occup Environ Health 67:367–374

Twitchett HJ (1974) Chemistry of the production of organic isocyanates. Chem Soc Rev 3(2):209, Available at: http://xlink.rsc.org/?DOI=cs9740300209

Ulrich H (1967) Cycloaddition Reactions of Heterocumulenes. Academic, New York, NY

US EPA (2004) Analysis of Isocyanates Liquid Chromatography - Diode Array / MSD., p 11

Vandenplas O et al (1992) Occupational asthma caused by a prepolymer but not the monomer of toluene diisocyanate (TDI). J Allergy Clin Immunol 89(6):1183–1188

Vangronsveld E et al (2010) Isocyanate and total inhalable particulate air measurements in the European wood panel industry. Int J Hyg Environ Health 213(6):475–488, Available at: http://www.ncbi.nlm.nih.gov/pubmed/20851674

Varma DR, Guest I (1993) The Bhopal accident and methyl isocyanate toxicity. J Toxicol Environ Health 40(4):513–529

Vernot EH, MacEwen JD, Haun CC, Kinkead ER (1977) Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol Appl Pharmacol 42(2):417–423

White J (2012) MDHS 25 Revisited: Part 2, Modified Sampling and Analytical Procedures Applied to HDI-Based Isocyanates. Ann Occup Hyg 56(4):466–480

Williams NR, Jones K, Cocker J (1999) Biological monitoring to assess exposure from use of isocyanates in motor vehicle repair. Occup Environ Med 56:598–601

Wisnewski AV et al (2005) Glutathione protects human airway proteins and epithelial cells from isocyanates. Clin Exp Allergy 35:352–357, Available at: <Go to ISI>://WOS:000227837300018

Wisnewski AV et al (1999) Isocyanate-conjugated human lung epithelial cell proteins: A link between exposure and asthma? J Allergy Clin Immunol 104(2 Pt 1):341–347

Woolley WD (1972) Nitrogen-containing products from the thermal decomposition of flexible polyurethane foams. Br Polym J 4(1):27–43

Woolley WD, Fardell PJ (1977) The prediction of combustion products. Fire Saf J 1(1):11–21

Woskie SR (2004) Determinants of Isocyanate Exposures in Auto Body Repair and Refinishing Shops. Ann Occup Hyg 48(5):393–403, Available at: http://annhyg.oupjournals.org/cgi/doi/10.1093/annhyg/meh021

Wu WS et al (1987) Application of tryptamine as a derivatizing agent for airborne isocyanates determination. Part 1. Model of derivatisation of methyl isocyanate characterised by fluorescence and amperometric detection in high-performance liquid chromatography. Analyst 112(6):863–866

Zocca E et al (1990) Leukotriene B4 and late asthmatic reactions induced by toluene diisocyanate. J Appl Physiol 68(4):1576–1580

von Zweigbergk P et al (2002) Development of a diffusive sampling method for determination of methyl isocyanate in air. J Environ Monit 4(5):663–666, Available at: http://xlink.rsc.org/?DOI=b203384b. Presented at AIRMON 2002, Lillehammer, Norway, 3???7 February 2002