AUSTRALIAN INSTITUTE OF OCCUPATIONAL HYGIENISTS ® 40 YEARS

CELEBRATING OVER 40 YEARS OF PROTECTING AUSTRALIAN WORKER'S HEALTH

Isocyanate Compounds – Potential for Occupational Health Issues

Position Paper

Draft version for member's comments

Association number: A0017462L

ABN: 50 423 289 752

Approved by Council:

Prepared by: AIOH Exposure Assessment Committee

TABLE OF CONTENTS

AUSTRALIAN INSTITUTE OF OCCUPATIONAL HYGIENISTS INC (AIOH)

The Australian Institute of Occupational Hygienists Inc (AIOH) is the association that represents professional occupational hygienists in Australia. Occupational hygiene is the science and art of anticipation, recognition, evaluation, and control of hazards in the workplace and the environment. Occupational hygienists specialise in the assessment and control of:

- Chemical hazards (including dusts such as silica, carcinogens such as arsenic, fibrous dusts such as asbestos, gases such as chlorine, irritants such as ammonia and organic vapours such as petroleum hydrocarbons);
- Physical hazards (heat and cold, noise, vibration, ionising radiation, lasers, microwave radiation, radiofrequency radiation, ultra-violet light, visible light); and
- Biological hazards (bacteria, endotoxins, fungi, viruses, zoonoses).

Therefore, the AIOH has a keen interest in the potential for workplace exposures to isocyanate compounds, as its members are the professionals most likely to be asked to identify associated hazards and assess any exposure risks.

The Institute was formed in 1979 and incorporated in 1988. An elected governing Council, comprising the President, President Elect, Secretary, Treasurer and three Councillors, manages the affairs of the Institute. The AIOH is a member of the International Occupational Hygiene Association (IOHA).

The overall objective of the Institute is to help ensure that workplace health hazards are eliminated or controlled. It seeks to achieve this by:

- Promoting the profession of occupational hygiene in industry, government and the general community.
- Improving the practice of occupational hygiene and the knowledge, competence and standing of its practitioners.
- Providing a forum for the exchange of occupational hygiene information and ideas.
- Promoting the application of occupational hygiene principles to improve and maintain a safe and healthy working environment for all.
- Representing the profession nationally and internationally.

More information is available at our website – http://www.aioh.org.au.

WORKPLACE EXPOSURE ASSESSMENT COMMITTEE MISSION STATEMENT

The AIOH established the Workplace Exposure Assessment Committee to provide expert guidance and comment to the exposure standards setting process at a State and National level and internationally where appropriate, through development of AIOH Position Papers, AIOH guidance publications or comment on relevant Standards, Regulations and Codes of Practice. The Committee's remit is to confirm that the exposure standards numbers, and Standards and Codes of Practice, are changed for valid occupational hygiene and scientific reasons.

STATEMENT OF POSITION REGARDING AIOH POSITION PAPERS

The AIOH is not a standard setting body. Through its Position Papers, the AIOH seeks to provide relevant information on substances of interest where there is uncertainty about existing Australian exposure standards. This is done primarily through a review of the existing published, peer-reviewed scientific literature but may include anecdotal evidence based on the practical experience of certified AIOH members. The Position Papers attempt to recommend a health-based guidance exposure value that can be measured; that is, it is technically feasible to assess workplace exposures against the derived exposure value. It does not consider economic or engineering feasibility. As far as reasonably possible, the AIOH formulates a recommendation on the level of exposure that the typical worker can experience without significant risk of adverse health effects.

Any recommended guidance exposure value should not be viewed as a fine line between safe and unsafe exposures. They also do not represent quantitative estimates of risk at different exposure levels or by different routes of exposure. Any recommended exposure value should be used as a guideline by professionals trained in the practice of occupational hygiene to assist in the control of health hazards.

CONSULTATION WITH AIOH MEMBERS

AIOH activities are managed through committees drawn from hygienists nationally. This Position Paper has been prepared by the Workplace Exposure Assessment Committee, with comments sought from AIOH members generally and active consultation with particular members selected for their known interest and/or expertise in this area. Various AIOH members were contributors in the development of this Position Paper. Key contributors included: Tim White, Ian Firth, Greg O'Donnell, Robert Golec & Ross Di Corleto.

FORTY-FIRST AIOH COUNCIL

President:	Ross Di Corleto (QLD)
President Elect:	Kate Cole (NSW)
Secretary:	Sharann Johnson (VIC)
Treasurer:	Aleks Todorovic (VIC)
Councillors:	Melanie Windust (VIC), Kelly Johnstone (QLD), Marcus Brooks (ACT)

LIST OF ABBREVIATIONS AND ACRONYMS

AIOH	Australian Institute of Occupational Hygienists
ACGIH	American Conference of Governmental Industrial Hygienists
ASTM	American Society for Testing and Materials
BGV	Biological Guidance Value
BMGV	Biological Monitoring Guidance Value
COH®	Certified Occupational Hygienist
DBA	Dibutyl amine
BEI	Biological Exposure Index
ECD	Electrochemical detection
ECHA	European Chemicals Agency
EU	European Union
FL	Fluorescence detection
HCOTN	Health Council of the Netherlands
HDA	Hexamethylene diamine
HDI	Hexamethylene diisocyanate
HMDI	Dicyclohexylmethane 4,4'-diisocyanate
HSE	Health & Safety Executive, UK
HSIS	Hazardous Substance Information System
HSL	Health & Safety Laboratory, UK (Branch of HSE)
IPDI	Isophorone diisocyanate
ISO	International Standards Organization
LC	Liquid chromatography (including high performance & ultra-high performance liquid chromatography)
LOD	Limit of Detection
LOQ	Limit of Quantitation
L/min	Litres per minute
MDA	Methylene diphenyl diamine
MDHS	Methods for the Determination of Hazardous Substance, Health & Safety Executive, UK
MDI	Methylene diphenyl isocyanate
mg/m^3	milligrams (10^{-3} grams) per cubic metre
$\mu g/m^3$	micrograms (10^{-6} grams) per cubic metre
MS	Mass spectrometry
MSMS	Triple quadrupole mass spectrometry
NATA	National Association of Testing Authorities
NCO	Isocyanate functional group; Nitrogen=Carbon=Oxygen
NIOSH	National Institute for Occupational Safety and Health, Centre for Disease Control, USA
OEL	Occupational Exposure Limit
OSHA	Occupational Safety & Health Agency, USA
SCOEL	Scientific Committee on Occupational Exposure Limits

STEL	Short-term exposure limit
SWA	Safe Work Australia
TDA	Toluene diamine
TDI	Toluene diisocyanate
TLV	Threshold limit value
TWA	Time Weighted Average
UK	United Kingdom
US	United States of America
UV	Ultra-violet
WES	Workplace Exposure Standard

DEFINITIONS

- Hazard: Means potential to cause harm.
- Limit of detection (LOD): The lowest concentration of a substance that can be feasibly determined to be statistically different (e.g. 3 x the standard deviation) from a sample that contains none of the substance (i.e. a blank sample).
- Limit of quantitation (LOQ): The lowest concentration of a substance that can be reliably and consistently detected and measured, considering bias and imprecision – it is the level above which quantitative results may be obtained with a specific degree of confidence.
- Risk: Means the probability of harm actually occurring.

AIOH POSITION ON ISOCYANATE COMPOUNDS - POTENTIAL FOR OCCUPATIONAL HEALTH ISSUES

Key messages

- Isocyanates are a group of organic compounds that contain the functional group –NCO and are highly reactive and unstable compounds.
- Isocyanates are widely used in Australia in the manufacture and use of polyurethane foam, external coatings and spray paints, and in the production of products such as flexible and rigid foams, adhesives, and sealants.
- Isocyanates cause asthma due to sensitisation and also irritation of the skin, mucous membranes, eyes, and respiratory tract.
- There is limited information of actual exposure of workers to be gained from measuring the concentration of isocyanate in air.
- The SWA proposed WES of 0.1 µg/m^3 as -NCO is not measurable by currently available sampling and analysis methods.
- Biological monitoring should be the preferred way to accurately assess worker exposure, particularly when inhalation is not the only route of exposure.
- Biological monitoring is recommended to also check on the efficacy of the respiratory protection, and for skin contamination.
- It is important that medical surveillance is utilised to detect susceptible / sensitised individuals.
- If medical surveillance is adopted, then the current TWA-WES may be sufficiently protective to prevent asthma in non-sensitive people.
- It would be in the best interests of all stakeholders to have an industry-specific guidance / best practice approach with a strong focus on training of workers in the correct use of isocyanates.

Summary

This paper was compiled to give guidance on the assessment, evaluation and control of occupational exposure to isocyanate compounds.

The current Australian WES's for isocyanates (as total NCO) are a TWA value of 20 µg NCO/m^3 and a STEL value of 70 µg NCO/m^3. Safe Work Australia (SWA, 2019) has recommended a health-based time-weighted average (TWA) workplace exposure standard (WES) of 0.1 µg NCO/m^3 measured as total isocyanate functional groups (NCO-groups) for isocyanate compounds, as part of their review of Australia's WES's for airborne contaminants.

The AIOH provided feedback to SWA disagreeing with the proposed WES, suggesting that the WES needs to consider measurability, the skin exposure route and protection against sensitisation.

Isocyanates are a group of organic compounds that contain the functional group –NCO and are highly reactive and unstable compounds. They are categorized depending on the number of isocyanate functional groups as monoisocyanate, diisocyanate, triisocyanate and polyisocyanate. Diisocyanates are the smallest base unit that can allow polymerization.

Isocyanates are used in many industries. In addition to their use in the manufacturing of polyurethane foam, they are present in external coatings and spray paints and are used in the production of products such as flexible and rigid foams, adhesives, and sealants. During the use of the various isocyanate products occupational exposure can occur, particularly in processes involving heating and spraying of isocyanates. Volatility of the individual isocyanates can also influence occupational exposure.

Activities such as hot wire cutting foams, welding through polyurethane pipe lagging, high temperature bonding using polyurethane sealants and hot removal of varnishes are activities that may lead to inhalation exposure to isocyanates. Sanding of isocyanate containing materials such as paints, foams and plastics may also result in inhalation exposure from dust particles.

The toxicology of isocyanate compounds is similar with the critical effects being asthma due to sensitisation and irritation of the skin, mucous membranes, eyes and respiratory tract. There is also the potential for both irritant and allergic contact dermatitis.

SWA (2019) state that the recommended TWA WES of 0.0001 mg/m^3 (0.1 µg/m^3) as NCO is quantifiable through available sampling and analysis techniques. However, NCO is considered by occupational hygienists to be one of the most challenging chemicals to sample and analyse. The highly reactive nature of isocyanate compounds and their low occupational exposure limits put high demands on both

sampling and analytical techniques for monitoring them in air. The limit of quantitation (LOQ) for the determination of organic diisocyanates in air using the best methods available is generally greater than 0.1 µg NCO/m³.

As an alternative approach biological monitoring accounts for all routes of exposure. The most common form of biological monitoring of isocyanates is performed by the analysis of the corresponding diamine metabolites in urine (Scholten *et al*, 2020). Studies (Creely *et al,* 2006; Jones, 2019) have noted that biological monitoring by analysis of metabolites in urine can be a relatively simple and inexpensive way to assess exposure to isocyanates, as well as being a useful way to evaluate the effectiveness of control measures in place.

The AIOH has a number of recommendations which are noted above and provided in more detail in the body of this document.

1. Background

Safe Work Australia (SWA, 2019) has recommended a health-based time-weighted average (TWA) workplace exposure standard (WES) of 0.0001 mg/m³ (0.1 µg/m³) measured as total isocyanate functional groups (NCO-groups) for isocyanate compounds, as part of their review of Australia's WES's for airborne contaminants. However, they also recommend a priority in-depth assessment of the toxicological and epidemiological data for this group of chemicals.

The European Chemicals Agency (ECHA, 2019) reviewed a large range of international evaluations of diisocyanates, including those by the American Conference of Governmental Industrial Hygienists (ACGIH) and the Health Council of the Netherlands (HCOTN). The ECHA report was not included in the SWA documentation and provides a comprehensive scientific report concerning occupational exposure limit (OEL) values for diisocyanates at the workplace.

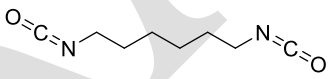
The AIOH provided feedback to SWA disagreeing with the proposed WES, suggesting that the WES needs to consider measurability, the skin exposure route and protection against sensitisation.

2. What are isocyanate compounds?

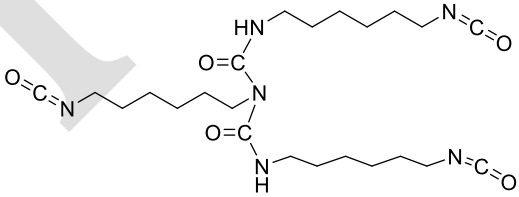
Isocyanates are a group of organic compounds that contain the functional group –NCO and are highly reactive and unstable compounds. They are categorized depending on the number of isocyanate functional groups as monoisocyanate, diisocyanate, triisocyanate and polyisocyanate. Diisocyanates are the smallest base unit that can allow polymerization. Oligomers (also called polyisocyanates) are small polymers composed from only a small number of monomeric units, whereas prepolymers are generally composed of larger polymer chains containing two or more isocyanate groups. The commercial products used in numerous processes are generally made up of diisocyanates and oligomers. Note that in this document, the term "isocyanate" will be used to designate any compound having at least two isocyanate groups.

The main isocyanates used in Australia are:

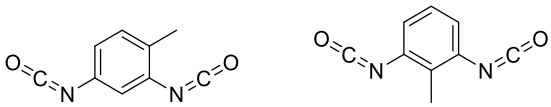
- **HDI:** Hexamethylene diisocyanate; or 1,6-Diisocyanatehexane (CAS number 822-06-0)



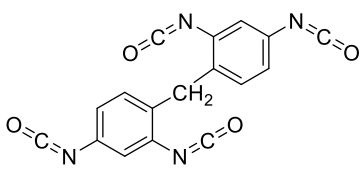
- **HDI Oligomer**: HDI biuret



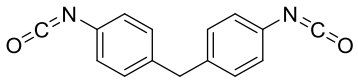
- **2,4-TDI:** Toluene-2,4-diisocyanate; or 2,4-Diisocyanatetoluene; (CAS number 584-84-9)
- **2,6-TDI:** Toluene-2,6-diisocyanate; or 2,6-Diisocyanatetoluene; (CAS number 91-08-7)



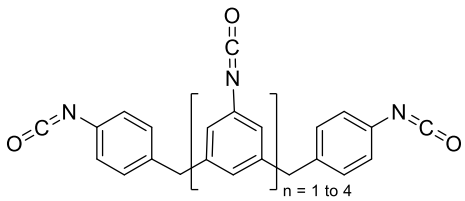
- **TDI Oligomer:** e.g. TDI Tetraisocyanate

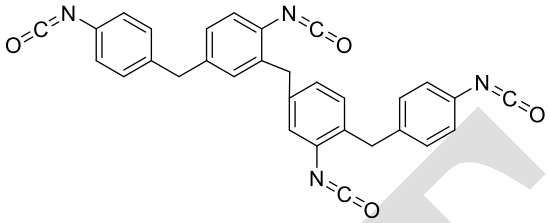


- **MDI:** Methylene diphenyl isocyanate (CAS number 101-68-8)

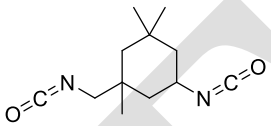


- **MDI Oligomer**: e.g. MDI tetraisocyanate

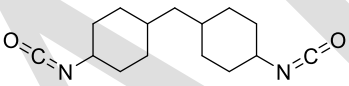




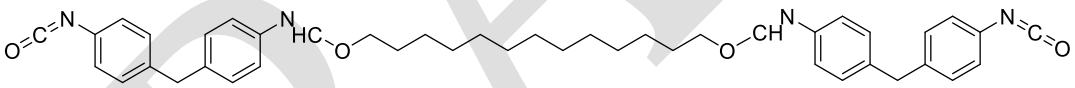
- **IPDI:** Isophorone diisocyanate (CAS number 4098-71-9)



- **HMDI:** Dicyclohexylmethane 4,4'-diisocyanate; 4,4'-methylenedicyclohexyl diisocyanate; or Methylene bis(4-cyclohexylisocyanate) (CAS number 5124-30-1).



- **Pre-polymer :** e.g. 4,4- MDI polyisocyanate



The vapour pressure of isocyanates decreases with increasing molecular weight. HDI and TDI (isomer Mix 80:20) have low vapour pressures of 0.01 and 0.02 mm Hg at 20°C respectively, while MDI, HMDI, polymeric MDI and polymeric HDI have very low vapour pressures of less than 0.0000075 mm Hg at 20°C. Manufacturer's products are therefore designed to have the lowest vapour pressure possible by the inclusion of high percentages of oligomer and pre-polymer compounds. Spray painting formulations for example have a high proportion of polymeric HDI with the monomer component being usually much less than 3%. Foam formulations using MDI usually have a monomer content of around 50% ± 25% with the remainder being made up of polymeric MDI oligomer. Therefore, at room temperature isocyanates are not very volatile. Increased temperature leads to an increase in vapour pressure and in the concentration of these substances in the vapour phase. Spraying promotes the evaporation of isocyanates by significantly increasing contact with air. However, for processes using polymeric MDI and polymeric HDI, these substances will mainly be present in the air as aerosols even if the application process involves spraying of the product or the production of airborne dust. Isocyanates have high odour thresholds above the current ACGIH TLV© of 0.005 ppm, therefore, using smell as an indicator of exposure is impractical.

Isocyanates are highly reactive with amines, alcohols, carboxylic acids and react with water to give off carbon dioxide and heat.

3. How do we measure it?

3.1 Air measurement

SWA (2019) state that the recommended TWA WES of 0.1 µg/m^3 as total NCO is quantifiable through available sampling and analysis techniques. However, NCO is considered by occupational hygienists to be one of the most difficult chemicals to sample and analyse. The highly reactive nature of isocyanate compounds and their low occupational exposure limits put high demands on both sampling and analytical techniques for monitoring them in air.

The analysis of isocyanates is challenging for several reasons. Firstly, the highly reactive character of the isocyanate makes it difficult to capture and stabilise. This is somewhat addressed by capturing the isocyanate with derivatising agents in impingers and on filters and with some methods a combination of both. Secondly, the nature of exposure is both aerosol and vapour phases. This makes sampling demanding as aerosol is not captured completely by a single filter alone, due to not all the NCO functional groups of larger droplets contacting with the derivatising reagent on the filter. An impinger solution does capture aerosol efficiently, however, is prone to under sample the vapour phase that is less than 2 µm in size. The solution to this problem is to use a sampling train of an impinger followed

by a filter. However, the use of impingers filled with derivatising reagent and toluene is clearly undesirable due to the possibility of exposure to solvent vapours during sampling and the risk of solvent spillage, evaporation, glass breakage and the difficulty with shipping.

Reagent impregnated filter devices are safer for the worker to wear, but also can under sample vapour phases due to many active sites inside droplets not coming into contact with the derivatising reagent (Streicher *et al*, 2002; Merck, 2018). Several reagents are used in different methods to stabilise the reactive isocyanates including 1-(9-anthracenylmethyl) piperazine (MAP), 1-(2-methoxyphenyl)piperazine (1-2 MOPP), 1-(2-pyridyl)piperazine (1-2 PP), 1,8-diaminonaphthalene (DAN), di-n-butylamine (DBA), and 9-(N-methylaminomethyl) anthracene (MAMA). Because of compound instability there aren't any commercially available derivatised isocyanate standards. Monomers are purchased by the laboratory with uncertain purity. Standards are then synthesised by derivatisation with the appropriate reagent producing a solid that can be dried and quantified. This is then used for calibration purposes.

Oligomers, polymers, and pre-polymers are usually not available and can vary in chain length and composition in different products and product batches. Therefore, it is necessary for the hygienist to supply a sample of the product isocyanate that is being used in the workplace to the laboratory for characterisation so as the laboratory can identify the oligomer or pre-polymer in that batch of the product being used. Supelco Inc, the original manufacturer of the ASSET™ EZ4-NCO dry sampler (Merck, 2018), has tried to alleviate this problem and has made available some oligomers of HDI, IPDI and MDI. However, they do not cover all oligomers and pre-polymers and are very expensive and not always available.

The current analytical methods employ the following techniques: high performance liquid chromatography or ultra-high performance liquid chromatography (LC) with the following detectors: photo diode array ultra-violet detection (UV) and electrochemical detection (ECD), UV and fluorescence detection (FL), or mass spectrometry (MS) or triple quadrupole mass spectrometry (MSMS). The standard methods are listed in Table 1.

Table 1. Standard methods for determining isocyanates in air

	MDHS 25/4	ASSET	ISO-CHEK	NIOSH 5521	NIOSH 5522	NIOSH 5525	OSHA 42
Analyte	Monomers Polymers	Monomers Polymers	Monomers Polymers	Monomers	Monomers Polymers	Monomers Polymers	Monomers
Quantitation	Total -NCO	Total -NCO	Total -NCO	µg monomer	µg monomer + polymer	Total -NCO	µg monomer
Sampler	Impinger + Filter	13 mm filter + denuder	37 mm closed face double filter cassette	Impinger	Impinger	Filter and/or Impinger	37 mm single filter open-faced cassette
Sample Media	1-2 MOPP Impinger + 1-2 MOPP filter	GFF + denuder with DBA	PTFE filter field derivatized with 1-2 MOPP, GFF with MAMA	1-2 MOPP in toluene impinger	Tryptamine in DMSO	GFF with MAP in 37 mm cassette or IOM, or MAP in butyl benzoate	GFF with 1-2 PP
Sampling Flow Rate	1-2 L/min	0.2 L/min	1 L/min	1 L/min	1-2 L/min	1-2 L/min	1 L/min
Technique	LC UV/ECD	LC MS or LC-MSMS	LC UV	LC UV/ECD	LC FL/ECD	LC UV/FL	LC UV/FL
LOQ (TDI)	0.004 µg NCO	0.002 µg NCO	0.002 µg NCO	0.5 µg monomer	0.2 µg monomer	0.042 µg NCO HDI	0.05 µg monomer
Amt/Sample	0.27 µg NCO/m³ (15L)	0.083 µg NCO/m³ (24L)	0.017 µg NCO/m³ (120L)	5 µg/m³ (100L)	4 µg/m3 (50L)	1.35 µg NCO/m³ (15L)	0.42 µg/m³ (120L)
Air Conc (Recd air volume)							
Validation	HSL 2014	ISO 17734 2006	ASTM 6561 ASTM 6562 2012 ISO 17736 2010	Unrated NIOSH evaluation. 1994	Partial NIOSH evaluation. Recommended for area sampling only. 1998	Partial NIOSH evaluation. 2003 ISO 17735 2019	OSHA evaluation. 1989 ISO 14382 2012

The recommended sampling time for isocyanates in air is 15 minutes to reduce the loss of isocyanate due to the reaction with water vapour, unreacted polyols and amines that may be present (Coleman & Painter, 2013; Ulrich, 1996). The speed of reaction differs with each isocyanate, the aromatic isocyanates (TDI, MDI) being the most reactive with water and the aliphatic isocyanates such as HDI or IPDI tending to be a little slower. Another crucial part of air sampling is to desorb the isocyanate on the filter with a solution containing derivatising reagent immediately after sampling to stabilise the isocyanate and prevent further loss of unreacted components (Schaeffer *et al,* 2013).

The Health & Safety Executive UK Methods for the Determination of Hazardous Substances MDHS 25/4 is the method probably most commonly used worldwide for the determination of organic NCO in air (White, 2006), but it is considered not particularly well suited to workplace conditions and the chemical analysis is complex. It is widely held that the collection and analysis of air samples requires considerable expertise (White, 2006), which tends to make the procedure relatively costly. The qualitative and quantitative limits of detection (LOD / LOQ) for isocyanate using MDHS 25/4, defined as three times and ten times the standard deviation of six blank determinations, have been found to be typically around 0.001 and 0.004 µg NCO per sample respectively (ECD detection). For a 15-litre air sample, these figures correspond to qualitative and quantitative detection limits of 0.07 µg NCO/m^3 and 0.27 µg NCO/m^3 respectively.

The estimated LOQ of NIOSH Analytical Method NIOSH 5522 for the isocyanates 2,4-TDI, 2,6-TDI, MDI and HDI are 0.1, 0.2, 0.3 and 0.2 µg/sample of the monomers, respectively. OSHA Sampling and Analytical Method OSHA 42 samples the monomer of the isocyanates and expresses the test result as the concentration of monomer not as total NCO, for the monomers of HDI, 2,4-TDI, 2,6-TDI and MDI only. The overall OSHA 42 procedure LOD is: 2,6-TDI = 1.6 µg/m^3; HDI = 2.3 µg/m^3; 2,4-TDI = 1.3 µg/m^3; and MDI = 0.8 µg/m^3, with an LOQ of: 2,6-TDI = 2.3 µg/m^3; HDI = 2.9 µg/m^3; 2,4-TDI = 2.5 µg/m^3; and MDI = 2.6 µg/m^3. The LOQ for these methods is around an order of magnitude higher than that for MDHS 25/4.

The ASSET™ EZ4-NCO dry sampler is the more advanced sampling device for measurement of isocyanates in air. It is said to be easy to use and can sample for up to 4 hours at a flow rate of 0.1 L/min for a 24 L maximum sample volume (Merck, 2018). It uses dibutyl amine (DBA) derivatisation of isocyanates according to ISO 17734-1 and the sampler design ensures that both the vapour phase and particulate isocyanates are captured and derivatised during sampling. The analytical method can successfully reach a LOQ of 5 ng NCO/sample for most isocyanates in the final sample when using LC-MSMS analysis and a LOQ of 10 ng NCO/sample when LC-MS instrumentation is used. These numbers translate, respectively, to 0.21 µg NCO/m^3 of isocyanates and 0.42 µg NCO/m^3 in air for a 24-litre air sample.

The LOQ for the determination of organic diisocyanates in air using the best methods available is thus generally greater than 0.1 µg/m^3 and so it is not possible to measure airborne isocyanate levels at the SWA (2019) proposed standard. This LOQ appears to be supported by the LOD/LOQ information for various sampling and analysis methods in Table 15 of the ECHA (2019) document.

When assessing whether accurate sampling and analytical methods are available to measure exposure to assess compliance against a recommended exposure standard, the European Commission (2017) state that 'Measurement techniques should be able to assess exposure at: 0.1 times the OEL for 8-hour TWA'.

3.2 Biological Monitoring

Biological monitoring accounts for all routes of exposure. The most common form of biological monitoring of isocyanates is performed by the analysis of the corresponding diamine metabolites in urine (Scholten *et al*, 2020). These are hexamethylene diamine (HDA) for HDI, toluene diamine (TDA) for TDI and methylene diphenyl diamine (MDA) for MDI. Exposure directly to these amines can be a confounding factor and needs to be accounted for or ruled out. Also, biological monitoring usually only monitors the diamines corresponding to the monomers and not the diamines metabolites of the oligomers or pre-polymers. Creely *et al* (2006), showed in a comprehensive study of isocyanate users in the UK that biological monitoring can show exposures even if the corresponding air measurements were below the detection limit. Both Creely *et al* (2006) and Jones (2019) noted that biological monitoring by analysis of metabolites in urine can be a relatively simple and inexpensive way to assess exposure to isocyanates, as well as being a useful way to evaluate the effectiveness of control measures in place.

4. Hazards associated with isocyanates

The SWA (2015) document "Deemed Diseases in Australia", which reviews the latest scientific evidence on the causal link between diseases and occupational exposures, determined that the key disease caused by isocyanates was occupational asthma. The SWA (2021) Hazardous Substance Information System (HSIS) provides the following classifications in Table 2 as to health effects for the various isocyanates, based primarily on European Commission classifications.

Table 2. Hazard statements for isocyanates in HSIS

Health Hazard Statement	Isocyanate Type
H351 (Suspected of causing cancer)	2,4-TDI, MDI
H330 (Fatal if inhaled)	HDI, 2,4-TDI & MDI
H331 (Toxic if inhaled)	IPDI & HMDI
H334 (May cause allergy or asthma symptoms or breathing difficulties if inhaled)	2,4-TDI

Health Hazard Statement	Isocyanate Type
H335 (May cause respiratory irritation)	2,4-TDI, MDI, IPDI & HMDI
H302 (Harmful if swallowed)	HDI
AUH071 (Corrosive to the respiratory tract)	HDI
H314 (Causes severe skin burns and eye damage)	HDI
H315 (Causes skin irritation)	2,4-TDI, MDI, IPDI & HMDI
H317 (May cause an allergic skin reaction)	2,4-TDI
H319 (Causes serious eye irritation)	2,4-TDI, MDI, IPDI & HMDI
H372 (Causes damage to organs through prolonged or repeated exposure through inhalation)	HDI, MDI
H334 (May cause allergy or asthma symptoms or breathing difficulties if inhaled)	HDI, MDI, IPDI & HMDI
H317 (May cause an allergic skin reaction)	HDI, MDI, IPDI & HMDI

The toxicology of isocyanate compounds is similar with the critical effects being asthma due to sensitisation and irritation of the skin, mucous membranes, eyes, and respiratory tract. There is also the potential for both irritant and allergic contact dermatitis. No difference in potency for the different polyisocyanates has been identified based on the available epidemiological data (ACGIH, 2018; HCOTN, 2018). In addition, while much is unclear about the mechanism(s) by which isocyanates cause allergic reactions, not only inhalation of isocyanates, but also skin contact can contribute to the development of allergic complaints. The reactive -NCO groups, present in all isocyanates, play a role (HCOTN, 2018). Once sensitised, workers will react to very low concentrations (Roberge *et al*, 2013).

Epidemiological studies on more than 4,000 workers in Sweden (1993 and 2004), more than 4,600 in the US (1996) and more than 8,200 in the UK (1993 and 2003) failed to establish any causal link between isocyanates and cancer (Roberge *et al*, 2013).

5. What are isocyanates used for?

SWA (2019) note that isocyanates are used in many industries. In addition to their use in the manufacturing of polyurethane foam, they are present in external coatings and paints and are used in the production of products such as flexible and rigid foams, adhesives, and sealants. In practice, mixtures of different types and different forms of isocyanates are used.

Typical isocyanate-based products include (Rother & Schlüter, 2021):

- Flexible polyurethane
- Rigid polyurethane
- Polyurethane foams (rigid & flexible foams e.g. mattresses)
- Assembly foams (e.g. insulation panels)
- Foundry cores (casting)
- Coating materials (paints, lacquers, varnishes)
- Adhesives and glues
- Elastomers
- Sealants
- Pre-polymers for chemical synthesis
- Engineering plastics
- Polyurethane fibres

The manufacture of polyurethane products is performed by the reaction of an isocyanate with a polyol (a compound with more than one hydroxyl group). The two liquid reactants are separated and are mixed *in-situ*. Commonly referred to as A-Side and B-Side parts are blended to form a solid polyurethane polymer. In polyurethane foam manufacture A-Side contains polymeric MDI and equal amounts of monomeric MDI and higher molecular weight oligomers of MDI. The B-Side is a blend of predominately polyol, catalysts, blowing agents, surfactants and in construction applications possibly fire retardants. In low density foam, water is used as the blowing agent to react with MDI producing carbon dioxide to form an open cell structure. A medium density foam uses a fluorocarbon as the blowing agent. Heat caused by the reaction converts the liquid fluorocarbon into a gas to form the cells. Therefore, a hygienist monitoring a polyurethane operation may also be advised to monitor other agents in the production particularly the catalysts which are usually amine in nature (Wood, 2017).

The main uses of HDI and IPDI include spray paint used on cars, trains, and planes. A mixture of 2,4-TDI and 2,6-TDI in a ratio of 80:20 is used to manufacture polyurethane foam, utilised in bedding, car seats, and furniture. To a lesser extent, TDI is used to manufacture varnish for furniture and floor coverings. The main uses of MDI and its oligomer include elastomers, injection moulding, flexible and rigid foams, paint primers, and sealants. The main uses of HMDI include enamel coatings for floors, roofing, adhesives, and sealants.

6. Potential for exposure in Australia

The potential for occupational exposure to diisocyanates is determined by intrinsic substance properties (e.g. volatility – see Section 2) or to the processes involved in their handling (Rother & Schluter, 2021). During the use of the various isocyanate products occupational exposure can occur particularly for processes involving heating and spraying of isocyanates (HCOTN, 2018).

Activities such as hot wire cutting foams, welding through polyurethane pipe lagging, high temperature bonding using polyurethane sealants and hot removal of varnishes are activities that may lead to inhalation exposure to isocyanates. Very high exposures are found when a process is used where high levels of aerosols are formed (mostly spraying). Sanding of isocyanate containing materials such as paints, foams and plastics may also result in inhalation exposure from dust particles.

The Australian Workplace Exposure Study-Asthma, a national telephone survey, deemed that 2.5% of eligible participants were probably exposed to isocyanates at work in their current job (extrapolated to 3.0% of the Australian working population) (El-Zaemey *et al*, 2018). The most common tasks undertaken that led to these exposures were using expanding foam fillers/sprays and isocyanate and/or polyurethane paints. Exposure occurred mainly among construction workers, wood workers and painters or printers.

While there are few peer-reviewed studies of workplace exposures to isocyanates in Australia, airborne isocyanate concentrations in overseas studies have been found to be generally very low (range 0.5 - 66 µg NCO/m^3). Creely *et al* (2006) found a total of 50 of the 70 samples they collected were less than 1 µg NCO/m^3, their LOQ for MDHS 25/3, hence assigned a value of half the LOQ (0.5 µg NCO/m^3). Of the 70 samples, 67 were below the UK TWA workplace exposure limit of 20 µg NCO/m^3. The highest inhalation exposures occurred during spray painting activities in a truck manufacturing company (66 µg NCO/m^3) and during spray application of polyurethane foam insulation (23 µg NCO/m^3).

Hon *et al* (2016) described historical TDI, MDI and HDI exposures in two of the largest provinces in Canada (Ontario & British Columbia) between 1981–1996. In total, 6,984 isocyanate measurements were analysed, the majority of which were below the LOD (79%). Overall, 8.3% of samples exceeded the ACGIH© TLV-TWA of 0.005 ppm (0.42 µg NCO /m^3 for TDI, 0.61 µg NCO /m^3 for MDI & 0.41 µg NCO /m^3 for HDI). However, most of the samples (95%) were area samples as impinger methods were the only option at that time.

Rother & Schlüter (2021) grouped exposure data for the European Union (EU) in a ranking order according to the reported bandwidths of inhalation exposure levels results as follows:

- HDI and its oligomers in coatings - from 0.003 up to 5,566 µg/m^3 (90th percentile), total range: 0.003–245,000 µg/m^3 (0.001 – 122,354 µg NCO/m^3)
- MDI in spray foam applications - from limit of quantification (LOQ) up to 2,050 µg/m^3 (688 µg NCO/m^3)
- TDI in manufacture of foam - from LOQ up to 203 µg/m^3 (98 µg NCO /m^3)
- TDI in manufacture of polyurethanes and polyurethane composite materials - from LOQ up to 67.3 µg/m^3 (32.5 µg NCO/m^3)
- TDI in adhesives - from LOQ up to 48.2 µg/m^3 (23.2 µg NCO/m^3)
- MDI in adhesives - from LOQ up to 43 µg/m^3 (14 µg NCO/m^3)
- MDI in manufacture of polyurethanes and polyurethane composite materials - from LOQ up to 32.8 µg/m^3 (11.0 µg NCO/m^3)
- TDI in coatings - from LOQ up to 35 µg/m^3 (17 µg NCO/m^3)
- MDI in manufacture of foam - from LOQ up to 29 µg/m^3 (9.7 µg NCO/m^3)
- HDI in adhesives - from LOQ up to 1.0 µg/m^3 (0.50 µg NCO/m^3).

There is further information on workplace airborne exposure concentrations in Table 12 of the ECHA (2019) document and in section 3.1 of the Roberge *et al* (2013) publication.

7. Risk of health effects

Short term exposure to TDI causes eye and nose irritation with a threshold of 170 to 440 µg NCO/m^3, with skin irritation generally arising at higher concentrations. Respiratory sensitisation occurs at much lower exposure levels (ECHA, 2019) and should be the critical health effect upon which the WES is based.

NICNAS (2013) noted a challenge at 0.001 ppm (7 µg/m^3 or 3.4 µg NCO/m^3) TDI induces asthma in previously sensitised subjects, while for participants not suffering from occupational asthma, in controlled experiments, sensitisation occurred at levels of 0.01 ppm (71 µg/m^3 or 34 µg NCO/m^3). ECHA (2019) noted that respiratory sensitisation to diisocyanates can be induced both via the dermal and the inhalation routes and that the risk of asthma from diisocyanates is influenced by both cumulative and peak in-air exposures. They further noted that the epidemiological studies they reviewed do not suggest a definite threshold for induction of respiratory sensitisation and the studies also have limitations for assessing dose response relationships if using strict criteria. Nevertheless, ECHA considers that the most appropriate way to prevent asthma caused by diisocyanates would be to prevent respiratory sensitisation altogether, i.e. to prevent its induction.

Roberge *et al* (2013) noted that it is not possible to determine whether isocyanate sensitisation is caused solely by very high exposure or whether repeated low-dose exposures over a long time can also lead to asthmatic sensitisation. Continuous rather than intermittent exposure to isocyanates seemed to increase the risk of developing occupational asthma. They further noted that current literature suggests that an average exposure of less than 0.005 ppm (34 – 51 µg/m^3 or 17 µg NCO/m^3, depending on type of isocyanate) and peaks of less than 0.020 ppm (137 – 205 µg/m^3 or 69 µg NCO/m^3) lead to an annual occupational asthma incidence of less than 1 percent in non-sensitised workers. This is consistent with the pre-2016 ACGIH finding that since the mid-1970s, annual occupational asthma

incidence rates have been less than 1 percent against measured 8-hour workplace TDI concentrations of less than 0.005 ppm (34 µg/m³ or 17 µg NCO/m³). It is also reflected in the German limits reviewed by SWA (2019).

Plehiers *et al* (2020) reanalysed an epidemiology study on the incidence of TDI-related occupational asthma in three US-based TDI production facilities to identify where to best focus exposure reduction efforts on industrial practice to reduce the risk of sensitisation to TDI. They found that cumulative exposure is not a good indicator of the risk of developing TDI-related occupational asthma. Instead, a statistically significant relationship was determined between asthma incidence and the frequency of exposure to TDI levels indicative of peak events that are expressed as 8-hour TWA values greater than 0.003 ppm (21 µg/m³ or 10 µg NCO/m³) during which no respiratory protection was used. This relationship suggested a threshold for induction of TDI-related asthma.

A critical review of the ACGIH 2016 documentation for reduction of the TDI TLVs™ from a TWA value of 36 µg/m³ to 7 µg/m³ (17 µg NCO/m³ to 3.4 µg NCO/m³), and from a STEL value of 140 µg/m³ to 36 µg/m³ (70 µg NCO/m³ to 17 µg NCO/m³), concluded that they were 'unlikely to result in fewer cases of occupational asthma' and 'not adequately supported' (Lynch *et al*, 2018). Specifically, Lynch *et al* (2018) believe that the ACGIH 2016 documentation does not fully consider or integrate the results of all the available human and animal studies, and the results of the studies published between the 2004 and 2016 ACGIH reviews were similar to previous studies and thus did not indicate that the TDI TLVs should have been changed.

HCOTN (2018) reviewed many epidemiological studies, but only used the data from a select few (Collins *et al*, 2017; Pronk *et al*, 2007 & 2009) to derive their risk value. They established their exposure response relationship using data from two studies in workers exposed to HDI (Pronk *et al*, 2007 & 2009) and one study of workers exposed to TDI (Collins *et al*, 2017). This was used as the basis of deriving a concentration that corresponds with an extra risk of 1 percent for occurrence of adverse effects of the air ways characteristic of occupational asthma. They focussed on the adverse effects on the airways that can occur after sensitisation to isocyanates. HCOTN (2018) notes that the human studies that they used to derive their value had limitations.

Overall, effect levels have been reported in a broad range from 100 (the upper cut-off level of the evaluation) down to less than 1 µg NCO/m³. There were only three studies with an effect at less than 1 µg NCO/m³. Most studies that detected an effect were above 1 µg NCO/m³. In addition, dermal exposure and subsequent sensitisation via the skin could generally not be excluded as a contributing factor.

A closer look at the Pronk *et al* (2007) paper indicates that it does not have any exposure data and notes that data were estimated from previous studies and time estimates of undertaking tasks. It notes "More details are provided in the online supplement." The online supplement contains no data but refers to Pronk *et al* (2006), which has exposure data captured a few years earlier (in their Table 1).

In relation to the LOQ and LOD they note: *"The limit of detection (LOD) for inhalation samples depends on compound and measurement time. The maximum LOD (calculated with the minimum measurement time of 1 min, standard volume of 11.5 ml, and standard flow of 1 l/min) in this study is roughly 0.1 µg NCO/m³ for HDI and 1.4–37.7 µg NCO/m³ for oligomers of HDI. These LODs decrease linearly when measurement time increases."*

Exposure was determined as follows:

$$\text{Exposure} = \sum_{n-1}^{n} (\text{Time})_n \times (\% > \text{LOD})_n \times (\text{Median NCO Concentration})_n$$

"where Exposure = personal exposure expressed in µg NCO x m^{-3} x hour x month^{-1}; n is an arbitrary value from 1 to 6 assigned to the following tasks: (1) spray painting; (2) mixing; (3) cleaning paint equipment; (4) assisting a spray painter; (5) sanding; and (6) welding; (Time)n = time task n was performed expressed in hours per month (on average, 82 h [SD, 89] out of a 161-h [SD, 26] working month was spent on exposed tasks); (% > LOD)$_n$ = percentage of samples above the limit of detection (LOD) for task n; (Median NCO concentration)$_n$ = median inhalatory isocyanate concentration during task n expressed in µg NCO/m³. Separate task-based airborne exposure measurements were available for each combination of industry and task."

It should be noted that the bottom of the range of some of the quoted exposures were less than the 0.1 µg NCO/m³ LOQ value. Additionally, the range covered up to three orders of magnitude suggesting geometric standard deviations well above 5. Hygiene texts suggest that a geometric standard deviation more than three makes statistical assessment of the data unreliable.

The authors also note on page 1093 that *"The use of respiratory protection during spray painting is compulsory and was always observed during the fieldwork. Therefore, the effect of respiratory protection could not be investigated."*

Based on the information available at the time, the authors have used an estimate of the time a task was undertaken and multiplied that by an assessment of exposure taken in different places several years earlier, added in a % > LOD term, and note the mandatory use of respiratory protection. Coupled with no estimate of skin exposure, determination of the actual exposure would have significant limitations.[1]

The issue of using measurements that are less than the LOQ is not limited to just the Pronk *et al* (2007) paper. The ECHA (2019) and HCOTN (2018) publications cite Sennbro *et al* (2004), where the bottom of the range of some of the quoted exposures are also less than the 0.1 µg NCO/m³ LOQ value. Sennbro *et al* (2004), Swierczynska-Machura *et al* (2015), and Middendorf *et al* (2017), cited by the ECHA and HCOTN publications, also used sampling times that were 4 hours or more, longer than recommended (see Section 3.1). Middendorf *et al* (2017) adjusted personal exposure assessments where respiratory protection was worn by dividing the sample result by the assigned protection factor for that type of respirator. This is likely to have underestimated exposures. Caution needs to be taken when drawing any conclusions from these papers.

[1] Note: This is not to criticise the authors, they worked with what they had.

ECHA (2019) consider that it is appropriate to derive an exposure-response based on the concentration of the NCO group and to apply that to all diisocyanates. ECHA however did not propose an OEL for diisocyanates, but recommended risk assessment to further develop the approach to derive an exposure response based on a weight of evidence assessment of three identified key documents presenting exposure responses for respiratory sensitisation. The three identified key documents describe the exposure-response by Daniels (2018) and Collins *et al* (2017) based on TDI exposure, which accounts for 60 percent of current diisocyanate use in Europe, and by Pronk *et al* (2007, 2009) predominantly based on HDI exposure, which accounts for 4 percent of current use in Europe.

Overall, ECHA (2019) notes that none of the dose responses addressed the effect of peak exposures or included dermal exposure. They consider that, when using the exposure responses, they described to establish an exposure limit (8-hour TWA), subsequently, a STEL of not more than 5 times higher than that TWA value should be established.

Another complicating factor is that only a subset of exposed workers develops isocyanate-induced asthma. Taylor *et al* (2021) suggest that some workers' genetics and/or epigenetics may lend them added protection against isocyanate sensitisation.

8. Available controls

Precautionary statements for prevention of exposure or contact with individual isocyanates available from safety data sheets should be followed. Controls should focus on prevention of respiratory and skin exposure. It is considered very important that people using these compounds understand the associated health hazards, especially the risk of sensitisation and are trained in using the controls effectively. Using the hierarchy of controls, occupational exposure to isocyanates can be controlled by:

- Substitution with a safer alternative substance
- Process controls such as automation of handling and processing operations
- Efficient containment and ventilation of processes
- Good housekeeping
- Provision and sensible use of personal protective equipment
- Administrative controls, including inspection and maintenance of engineering controls and restricted access to operations and
- The provision of regular education and training.

The use of isocyanates from 2-pack paints and polyurethane resins in mining has been described in various government publications, such as the Safety Bulletin (74) published in November 2007 by the Queensland Mines Inspectorate. Other useful guidance material is as follows:

- The SWA Guide to Handling Isocyanates
- The UK HSE websites Controlling hazardous substances – Construction isocyanates: Spraying and Solutions from HSE - Isocyanates
- The IRSST Guide for Safe Use of Isocyanates – An Industrial Hygiene Approach.

9. Current exposure standards

9.1 In air

The current Australian WES's for isocyanates (as total NCO) are a TWA value of 20 µg NCO/m^3 and a STEL value of 70 µg NCO/m^3. SWA (2019) recommend reducing the current TWA to 0.1 µg NCO/m^3 as an interim value, removing the STEL value. This revision aims to reduce the risk of occupational asthma and to protect for irritation of the eyes and mucous membranes in exposed workers. No reason is given for not recommending a STEL value. This proposed value appears focussed on adverse effects on airways that can occur after sensitisation to isocyanates and development of asthma, as determined by the Health Council of the Netherlands report (HCOTN, 2018). A chemical induced allergic reaction is preceded by sensitisation: the moment the immune system is triggered, yet no significant complaints occur. A threshold for isocyanate induced sensitisation and development of asthma could not be determined and therefore the Dutch derived the value based on a 1% extra risk of sensitisation due to occupational exposure.

As per the Gestis database for international limit values, there are only four countries with a limit value for isocyanates (all; as total NCO). The TWA value is 20 µg NCO/m^3 , while the STEL ranges from 20 to 70 µg NCO/m^3. There are then limit values for the various types of isocyanates, as follows:

- Toluene diisocyanate (TDI) – 19 countries; TWA = 7 to 100 µg NCO/m^3, with 67 percent at 34 to 35 µg NCO/m^3 (0.005 ppm) and STEL = 3 to 200 µg NCO/m^3, with 61 percent at 140 to 170 µg NCO/m^3 (0.02 ppm)
- Hexamethylene diisocyanate (HDI) – 20 countries; TWA = 20 to 75 µg NCO/m^3, with 67 percent at 35 to 37 µg NCO/m^3 (0.005 ppm) and STEL = 30 to 150 µg NCO/m^3, with 33 percent at 35 µg NCO/m^3 (0.005 ppm)
- Methylene bisphenyl isocyanate (MDI) – 18 countries; TWA = 20 to 100 µg NCO/m^3, with 83 percent at 50 to 52 µg NCO/m^3 (0.005 ppm) and STEL = 50 to 200 µg NCO/m^3, with 38 percent at 200 µg NCO/m^3 (0.02 ppm).

9.2 Biological

The UK HSE (2020) has a Biological Monitoring Guidance Value (BMGV) for isocyanates. It is based on a urine sample taken at the end of exposure and is measured for the corresponding diisocyanate diamine. The BMGV is based on 'good occupational hygiene practice' and was set at the 90th percentile of results (1 µmol/mol creatinine) from a dataset where exposure controls were deemed to be

adequate. The urine test can check exposures for at least the four main isocyanates in use (HDI, IPDI, TDI & MDI) so the test can be helpful in a wide range of industries using isocyanates (polyurethane moulding, foam blowing, use of adhesives etc.) (Jones, 2019).

The ACGIH (2018) has a Biological Exposure Index (BEI) of 5 µg/g creatinine for toluene diamine in urine, collected at the end of shift, applicable to TDI (2,4- & 2,6-isomers) exposures.

ECHA (2020) proposed that a Biological Guidance Value (BGV) be set at the LOQs for relevant diisocyanate metabolites (diamines) in urine.

10. AIOH recommendation

Given the confounding factors associated with the wearing of respiratory protection and skin absorption of isocyanates, there is limited information of actual exposure of the worker to be gained from measuring the concentration of isocyanate in air. The AIOH believes that biological monitoring should be the preferred way to accurately assess worker exposure, particularly when inhalation is not the only route of exposure. Biological monitoring is recommended not only to check on the exposure, but also the efficacy of the respiratory protection, and for skin contamination.

The AIOH considers that a TWA-WES, if adopted, should be based on preventing the sensitisation of workers. Hence the current TWA-WES may be sufficiently protective, particularly where medical surveillance is also required to detect susceptible / sensitised individuals. The AIOH however agrees that further in-depth assessment of this WES is required.

The AIOH strongly recommends the use of a NATA accredited laboratory to conduct isocyanate-related analyses and that the results are reported on NATA endorsed test certificates. Also, health risk relative to guidance values relating to the need for controls and health surveillance should be determined by a Certified Occupational Hygienist (COH®).

The AIOH believes it is important that medical surveillance is utilised to detect susceptible / sensitised individuals. The SWA publication 'Isocyanates health monitoring' should be followed.

Given the complex aspects of isocyanates toxicity and exposure assessment, rather than depend only on an airborne regulatory exposure limit (WES), the AIOH believes it would be in the best interest of all stakeholders to have an industry-specific guidance / best practice approach. Such approaches already exist, including the program described by Gannon *et al* (2005), which has the goals of prevention, early detection and mitigation of effect of key endpoints, especially asthma and to a lesser degree dermatitis, in people who are occupationally exposed, or potentially exposed, to isocyanates and products containing isocyanates. Training of workers in the correct use of isocyanate exposure controls is of paramount importance.

REFERENCES AND SOURCES OF ADDITIONAL INFORMATION

ACGIH (2018). *Documentation of the TLVs® and BEIs® with Other Worldwide Occupational Exposure Values* – CD-ROM version (7th Edition Documentation). American Conference of Governmental Industrial Hygienists Cincinnati, Ohio.

Collins, JJ, S Anteau, PR Conner, LD Cassidy, B Doney, ML Wang, L Kurth, M Carson, D Molenaar, CA Redlich & E Storey (2017). Incidence of Occupational Asthma and Exposure to Toluene Diisocyanate in the United States Toluene Diisocyanate Production Industry. *J Occup Environ Med, 59 Suppl 12*; pp s22-s27.

Coleman, MM & P Painter (2019). *Fundamentals of Polymer Science: An Introductory Text*, Second Edition. CRC Press. ISBN 978-1-351-44639-6.

Creely, KS, GW Hughson, J Cocker & K Jones (2006). Assessing Isocyanate Exposures in Polyurethane Industry Sectors Using Biological and Air Monitoring Methods. *Ann Occup Hyg, 50(6)*; pp 609-621 – see https://academic.oup.com/annweh/article/50/6/609/194288

Daniels, RD (2018). Occupational asthma risk from exposures to toluene diisocyanate: A review and risk assessment. *Am J Ind Med, 61*; pp 282-292.

ECHA (2019). *ECHA Scientific report for evaluation of limit values for diisocyanates at the workplace*. Prepared by the European Chemicals Agency (ECHA), October 2019 – see https://echa.europa.eu/documents/10162/db15bfdf-eec8-c10a-67c4-f65166c5110a

ECHA (2020). *Opinion on scientific evaluation of occupational exposure limits for Diisocyanates*. Prepared by the European Chemicals Agency (ECHA) Committee for Risk Assessment (RAC), 11 June 2020 – see https://echa.europa.eu/documents/10162/30184854/oel_diisocyanates_final_opinion_en.pdf/4c4c70ae-2632-0038-3035-43ea10db554d#:~:text=In%20support%20of%20the%20Commission%E2%80%99s%20request%2C%20ECHA%20prepared,evidence%20on%20the%20subject%20by%2030%20June%202019.

El-Zaemey, S, D Glass, L Fritschi, E Darcey, R Carey, T Driscoll, M Abramson, S Si, G Benke & A Reid (2018). Isocyanates in Australia: Current exposure to an old hazard. *J Occup Environ Hyg, 15(7)*; pp 527-530 – see https://research.monash.edu/en/publications/isocyanates-in-australia-current-exposure-to-an-old-hazard.

European Commission (2017). *Methodology for derivation of occupational exposure limits of chemical agents* - The General Decision-Making Framework of the Scientific Committee on Occupational Exposure Limits (SCOEL), Luxembourg: Scientific Committee on Occupational Exposure Limits – see https://op.europa.eu/en/publication-detail/-/publication/3c8ef3e0-48fc-11e8-be1d-01aa75ed71a1

Gannon, PFG, AS Berg, R Gayosso, B Henderson, SE Sax & HMJ Willems (2005). Occupational asthma prevention and management in industry - an example of a global programme. *Occup Med 55(8)*; pp 600-605.

Health Council of the Netherlands (HCOTN) (2018). *Di and Triisocyanates. Health-based recommendation on occupational exposure limits*. The Hague: Health Council of the Netherlands; publication no. 2018/20 – see https://www.healthcouncil.nl/latest/news/2018/11/28/recommendation-on-occupational-exposure-limit-isocyanates (accessed April 1, 2020).

Hon, C-Y, CE Peters, KJ Jardine &VH Arrandale (2016). Historical occupational isocyanate exposure levels in two Canadian provinces. *J Occup Environ Hyg, 14(1)*; pp 1-8.

ISO 14382 (2012). 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. International Standards Organization (ISO) - see https://www.iso.org/standard/54616.html.

ISO 17734-1 (2013). Determination of organonitrogen compounds in air using liquid chromatography and mass spectrometry — Part 1: Isocyanates using dibutylamine derivatives. International Standards Organization (ISO) - see https://www.iso.org/standard/58006.html.

ISO 17735 (2019). Determination of total isocyanate groups in air using 1-(9-anthracenylmethyl)piperazine (MAP) reagent and liquid chromatography. International Standards Organization (ISO) - see https://www.iso.org/standard/70406.html.

ISO 17736 (2010). Determination of isocyanate in air using a double-filter sampling device and analysis by high pressure liquid chromatography. International Standards Organization (ISO) - see https://www.iso.org/standard/31517.html.

Jones, K (2019). How to do it - Biological monitoring for isocyanates. *Occup Med, 69*; pp 515-517.

Lynch, HN, RL Prueitt & JE Goodman (2018). Critique of the ACGIH 2016 derivation of toluene diisocyanate Threshold Limit Values. *Reg Toxicol Pharm, 97*; pp 189-196 – see https://www.sciencedirect.com/science/article/pii/S0273230018301739?via%3Dihub

Middendorf, PJ, W Miller, T Feeley & B Doney (2017). Toluene Diisocyanate Exposure: Exposure Assessment and Development of Cross-Facility Similar Exposure Groups Among Toluene Diisocyanate Production Plants. *J Occup Environ Med, 59 Suppl 12, S1-s12* – see https://journals.lww.com/joem/Pages/articleviewer.aspx?year=2017&issue=12001&article=00001&type=Fulltext.

Merck (2018). *Analysis of Isocyanates Using the ASSET™ EZ4-NCO Dry Sampler*. Merck KGaA, Darmstadt, Germany (operating as MilliporeSigma in the US & Canada), October 24 2018 – see https://www.envirotech-online.com/article/environmental-laboratory/7/merck-kgaa-darmstadt-germany-the-life-science-business-of-merck-operates-as-milliporesigma-in-the-us-and-canada/analysis-of-isocyanates-using-the-assettrade-ez4-nco-dry-sampler/2446

NICNAS (2013). Toluene diisocyanates: Human health tier II assessment – IMAP Report. National Industrial Chemicals Notification and Assessment Scheme (NICNAS) – see https://www.industrialchemicals.gov.au/sites/default/files/Toluene%20diisocyanates_Human%20health%20tier%20II%20assessment.pdf.

Plehiers, PM, AH Chappelle & MW Spence (2020). Practical learnings from an epidemiology study on TDI-related occupational asthma: Part II-Exposure without respiratory protection to TWA-8 values indicative of peak events is a good indicator of risk. *Toxicol Ind Health, 36(11)*; pp 885-891 – see https://pubmed.ncbi.nlm.nih.gov/32945732/.

Pronk A, F Yu, J Vlaanderen, E Tielemans, L Preller, I Bobeldijk, JA Deddens, U Latza, X Baur & D Heederik (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)*; pp 624-631 – see https://oem.bmj.com/content/63/9/624.

Pronk, A, L Preller, M Raulf-Heimsoth, IC Jonkers, JW Lammers, IM Wouters, G Doekes, AV Wisnewski & D Heederik (2007). Respiratory symptoms, sensitization, and exposure-response relationships in spray painters exposed to isocyanates. *Am J Respir Crit Care Med, 176*; pp 1090-1097 – see https://www.atsjournals.org/doi/full/10.1164/rccm.200702-215OC.

Pronk, A, L Preller, G Doekes, IM Wouters, J Rooijackers, JW Lammers & D Heederik (2009). Different respiratory phenotypes are associated with isocyanate exposure in spray painters. *Eur Respir J, 33*; pp 494-501.

Roberge, B, S Aubin, C Ostiguy & J Lesage (2013). *Guide for Safe Use of Isocyanates – An Industrial Hygiene Approach*. Institut de recherche Robert-Sauvé en santé et en sécurité du travail (IRSST) publication RG-773 – see http://www.irsst.qc.ca/media/documents/PubIRSST/RG-773.pdf.

Rother, D & U Schlüter (2021). Occupational exposure to diisocyanates in the European Union. *Annals of Work Exposures & Health*, advance article preprint. See https://doi.org/10.1093/annweh/wxab021.

Schaeffer, JW, LM Sargent, DR Sandfort, & WJ Brazile, (2013). A comparison of two sampling methods for the detection of airborne methylene bisphenyl diisocyanate. *J of Occup. and Environ. Hyg, 10(4);* pp 213-221. doi:10.1080/15459624.2013.766546

Scholten, B, L Kenny, R Duca, A Pronk, T Santonen, KS Galea, M Loh, K Huumonen, A Sleeuwenhoek, M Creta, L Godderis, K Jones (2020). Biomonitoring for Occupational Exposure to Diisocyanates: A Systematic Review. *Annals of Work Exposures & Health, V64-6* pp 569-585 – see https://academic.oup.com/annweh/article/64/6/569/5822987.

Sennbro, CJ, CH Lindh, A Östin, H Welinder, BAG Jönsson & H Tinnerberg (2004). A Survey of Airborne Isocyanate Exposure in 13 Swedish Polyurethane Industries. *Ann of Occup Hyg, 48(5)*; pp 405-414 – see https://doi.org/10.1093/annhyg/meh034.

Streicher, RP, CM Reh, R Key-Schwartz, PC Schlecht, ME Cassinelli & PF O'Connor (2002). Selecting Isocyanate Sampling and Analytical Methods. *App Occup Environ Hyg, 17(3)*; pp 157-162.

SWA (2015). *Deemed Diseases in Australia*. Prepared for Safe Work Australia by Prof T Driscoll, August 2015 – see https://www.safeworkaustralia.gov.au/doc/deemed-diseases-australia.

SWA (2019). *Isocyanates, (Poly-) (As-NCO)*. Safe Work Australia (SWA) recommended workplace exposure standard (WES) documentation.

SWA (2021). *Hazardous Substance Information System* (HSIS). Safe Work Australia website – see http://hcis.safeworkaustralia.gov.au/.

Swierczynska-Machura, D, S Brzeznicki, E Nowakowska-Swirta, J Walusiak-Skorupa, T Wittczak, W Dudek, M Dbonczarowska, W Wesolowski, S Czerczak & C Palczynski (2015). Occupational exposure to diisocyanates in polyurethane foam factory workers. *Int J Occup Med Environ Health, 28(6);* pp 985–998 – see http://ijomeh.eu/Occupational-exposure-to-diisocyanates-in-polyurethane-foam-factory-workers,58489,0,2.html.

Taylor, LW, JE French, ZG Robbins & LA Nylander-French (2021). Epigenetic Markers Are Associated with Differences in Isocyanate Biomarker Levels in Exposed Spray-Painters. *Front Genet* – see https://www.frontiersin.org/articles/10.3389/fgene.2021.700636/full.

UK HSE (2020). *EH40/2005 Workplace exposure limits* (Fourth Edition 2020).

Ulrich, H (1996). *Chemistry and Technology of Isocyanates*, Wiley. ISBN: 978-0-471-96371-4.

White, J (2006). MDHS 25 Revisited; Development of MDHS 25/3, the Determination of Organic Isocyanates in Air. *Ann Occup Hyg, 50(1)*; pp 15-27 – see https://academic.oup.com/annweh/article/50/1/15/156564.

Wood, RD (2017). Center for the Polyurethanes Industry summary of unpublished industrial hygiene studies related to the evaluation of emissions of spray polyurethane foam insulation. *J. Occup. Environ. Hyg. 14(9);* pp681-693.

APPENDIX

SOME USEFUL CALCULATIONS

V_L = Air volume sampled expressed in litres

Mol Wt = Molecular weight of diisocyanate; HDI = 168.2 g/mol, TDI = 174.2 g/mol, MDI = 250.25 g/mol

42 = Molecular weight of NCO isocyanate group

2 = Number of isocyanate groups per molecule (diisocyanate = 2)

24.46 = Volume (L/mol) of 1 mole of ideal gas at 25° C and 760 mm Hg

1. To convert amount of diisocyanate expressed as µg NCO/sample to µg NCO/m³

$$\text{µg NCO/m}^3 = \text{µg NCO/sample} \times \frac{1000}{V_L}$$

2. To convert amount of diisocyanate expressed as µg/sample to µg NCO/m³

$$\text{µg NCO/m}^3 = \text{µg/sample} \times \frac{2 \times 42}{\text{Mol Wt}} \times \frac{1000}{V_L}$$

3. To convert amount of diisocyanate expressed as µg/m³ to µg NCO/m³

$$\text{µg NCO/m}^3 = \text{µg}/m^3 \times \frac{2 \times 42}{\text{Mol Wt}}$$

4. To convert amount of diisocyanate expressed as ppm to µg NCO/m³

$$\text{µg NCO/m}^3 = \text{ppm} \times 2 \times 42 \times \frac{1000}{24.46}$$