Government of Canada | Gouvernement du Canada

Screening Assessment for

Methylenediphenyl Diisocyanates and

Methylenediphenyl Diamines

Chemical Abstracts Service Registry Numbers

101-68-8; 2536-05-2, 5873-54-1;

9016-87-9; 26447-40-5; 101-77-9; 25214-70-4

Environment and Climate Change Canada

Health Canada

June 2017

Canada

Cat. No.: En14-273/2017E-PDF
ISBN 978-0-660-08649-1

Synopsis

Pursuant to sections 68 and 74 of the *Canadian Environmental Protection Act, 1999* (CEPA), the Minister of the Environment and the Minister of Health have conducted a screening assessment of seven substances referred to collectively as the Methylenediphenyl Diisocyanate and Diamine (MDI/MDA) Substance Grouping. The MDI/MDA Substance Grouping consists of five MDI substances, which include three monomeric MDI substances (benzene, 1,1′-methylenebis[4-isocyanato-; benzene, 1,1′-methylenebis[2-isocyanato-; and benzene, 1-isocyanato-2-[(4-isocyanatophenyl)methyl]-), one polymeric MDI substance (isocyanic acid, polymethylenepolyphenylene ester) and one mixed MDI substance (benzene, 1,1′-methylenebis[isocyanato-). The MDI/MDA Substance Grouping also includes two MDA substances: one monomeric MDA substance (benzenamine, 4,4′-methylenebis-) and one polymeric MDA substance (formaldehyde, polymer with benzenamine). Their Chemical Abstracts Service Registry Numbers (CAS RNs), *Domestic Substances List* (DSL) names and acronyms are listed in Table 1 below.

Table 1-1. CAS RNs and DSL names for substances in the MDI/MDA Substance Grouping

CAS RN[a]	DSL Name	Acronym
101-68-8	Benzene, 1,1′-methylenebis[4-isocyanato-	4,4′-MDI
2536-05-2[b]	Benzene, 1,1′-methylenebis[2-isocyanato-	2,2′-MDI
5873-54-1[b]	Benzene, 1-isocyanato-2-[(4-isocyanatophenyl)methyl]-	2,4′-MDI
26447-40-5	Benzene, 1,1′-methylenebis[isocyanato-	mixed MDI
9016-87-9	Isocyanic acid, polymethylenepolyphenylene ester	pMDI
101-77-9[b]	Benzenamine, 4,4′-methylenebis-	4,4′-MDA
25214-70-4[c]	Formaldehyde, polymer with benzenamine	pMDA

[a] The Chemical Abstracts Service Registry Number (CAS RN) is the property of the American Chemical Society, and any use or redistribution, except as required in supporting regulatory requirements and/or for reports to the Government of Canada when the information and the reports are required by law or administrative policy, is not permitted without the prior, written permission of the American Chemical Society.
[b] This substance was not identified under subsection 73(1) of CEPA but was included in this assessment as it was considered a priority because of other human health concerns.
[c] This substance was not identified under subsection 73(1) of CEPA but was included in this assessment because of its similarity to 4,4′-MDA.

The five MDI substances and 4,4′-MDA in the MDI/MDA Substance Grouping were identified as priorities for action as they either met categorization criteria under section 73 of CEPA and/or were considered priorities for assessment because of human health concerns. Polymeric MDA (pMDA) did not meet any categorization criteria, but was added to the MDI/MDA Substance Grouping given its similarity to 4,4′-MDA (i.e., its composition largely consisting of 4,4′-MDA).

The MDI and MDA substances are characterized by a similar core structure, but differ in their functional groups, with the presence of isocyanate functional groups for MDI

substances and amino functional groups for MDA substances. MDI substances are very reactive because of the presence of the isocyanate groups.

According to information submitted under section 71 of CEPA, between 10 and 100 million kg each of 4,4′-MDI and pMDI and between 1 and 10 million kg of mixed MDI were imported and used in Canada in 2011. 4,4′-MDA was imported into Canada in quantities of between 1000 and 10 000 kg, and pMDA was imported in a range of 100 to 1000 kg. The major use of 4,4′-MDI, pMDI and mixed MDIs is in the production of polyurethane products, such as adhesives, coatings and insulation foams, flexible packaging laminate and foam slabs used in furniture. MDI substances are also used as adhesives in the production of engineered wood products, such as oriented strand board. The major use of 4,4′-MDA and pMDA is as an intermediate in the production of MDIs.

MDI substances have a potential for release to the environment, primarily to air during industrial use, such as during the production of engineered wood and polyurethane products. Releases of MDI substances to air were reported under the National Pollutant Release Inventory (NPRI) for the years 2008-2013. Oriented strand board facilities are considered to have higher releases than other types of facilities using MDI substances in terms of quantity of substance used and associated proportional release. Quantities of MDI substances released to air may further contribute to deposition to soil and/or surface waters in the surrounding area.

Because of the very reactive nature of the isocyanate groups of MDI substances, when released to the environment, they rapidly hydrolyze in water and in soil, where a degree of moisture is typically present. Hydrolysis reaction of MDI generates inert polyureas and small amounts of MDA as main reaction products. In air, MDI substances will readily react with hydroxyl radicals and/or will condense or be deposited on soil and water surfaces.

Environmental concentrations of 4,4′-MDA and pMDA in Canada were not identified. 4,4′-MDA is on the list of reportable substances under NPRI, but no releases were reported. 4,4′-MDA may be released to the environment from industrial uses, such as polyurethane manufacturing; however, given the low quantities in commerce of this substance in Canada, such releases are expected to be negligible.

Because of its physical and chemical properties, 4,4′-MDA degrades rapidly in air. The substance does not hydrolyze in water, and biodegradation tests using activated sludge suggest that intermediate biodegradation rates would occur under environmental conditions. In soil, 4,4′-MDA covalently binds to humic substances, thereby reducing its bioavailability and bioaccessibility. Faster rates of biodegradation in soil were observed in the presence of degradable organic substances mixed in with the soil substrate. Limited data are available for the degradation potential of MDA in sediments, and it is expected that most 4,4′-MDA in a sediment-water environment will bind to sediments and be unavailable for biodegradation. Degradation of pMDA is expected to be similar to 4,4′-MDA.

Both the MDI and MDA substances are known to have low bioaccumulation potential. They are characterized by low bioconcentration factors in fish. It is expected that very limited amounts of MDI substances would be available for uptake by organisms from environmental media. 4,4′-MDA tends to be readily metabolized and eliminated from the body by mammals and is unlikely to biomagnify in terrestrial food webs.

Results from acute aquatic toxicity studies suggest that neither 4,4′-MDI nor pMDI is appreciably toxic to aquatic species. MDI substances also have low toxicity to the tested soil invertebrate species and plants. Effects of MDI substances on small mammals as a result of inhalation were observed to be moderate. Overall, MDI exposure to organisms in the environment will be below levels expected to cause harm.

4,4’-MDA was observed to be moderately to highly toxic to various aquatic organisms in acute and/or chronic tests, including algae, microorganisms, invertebrates and fish. 4,4′-MDA exhibits low to moderate toxicity to soil organisms and plants and is moderately toxic to sediment-dwelling organisms and birds.

The potential for exposure of aquatic organisms to 4,4′-MDA is likely to result from releases of MDIs to air, their deposition to soil or surface waters, and their subsequent conversion to 4,4′-MDA. The high volumes of MDI substances imported into Canada, along with information on their uses, indicate that MDI substances will be found mainly in air and near point sources of emission. It was determined that harm to aquatic and soil organisms from current exposures to 4,4′-MDA arising from the deposition of MDIs in surface waters and soil is unlikely in Canada. It was also determined that harm to terrestrial mammals from inhalation exposure to MDI substances is unlikely.

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to organisms and the broader integrity of the environment from the substances in the MDI/MDA Substance Grouping. It is concluded that the five MDI substances, 4,4′-MDA and pMDA do not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

Considering the collective information and classifications by other international regulatory agencies critical effects for characterization of the risk to human health from exposure to MDI substances are carcinogenicity, respiratory effects including sensitization, and dermal sensitization. Incidences of lung tumours were observed in rats exposed to high concentrations of MDIs in two-year inhalation studies. The collective evidence from genotoxicity studies suggests that MDI substances are not likely to be mutagenic. Available information from studies with experimental animals, human case studies and epidemiological data were used to establish critical effect levels for risk characterization.

The margins of exposure between upper-bounding estimated environmental concentrations from emissions of MDIs in the vicinity of industrial sites and the critical effect levels for respiratory effects are considered to be adequate to address uncertainties in the health effects and exposure databases. The margins between estimates of exposure resulting from use of certain do-it-yourself (DIY) products, specifically low-pressure two-component spray polyurethane foam (SPF) products, and the critical effect levels for respiratory effects are considered to be inadequate to address uncertainties in the health effects and exposure databases.

Considering primarily assessments by international agencies and the available information, , a critical effect of 4,4′-MDA for characterization of risk to human health is carcinogenicity. No health effects data were identified for pMDA. In consideration of the fact that 4,4′-MDA is the main component of pMDA, the health effects assessment of 4,4′-MDA was used to represent that of pMDA. Exposure of the general population to 4,4′-MDA and pMDA from environmental media is not expected given that they are not manufactured in Canada and their uses are confined to a very limited number of industrial operations. Furthermore, exposure to 4,4′-MDA and pMDA from use of consumer products is not expected. As exposure of the general population to 4,4′-MDA and pMDA is not expected, the risk to human health is expected to be low.

On the basis of the information presented in this screening assessment, it is concluded that MDIs meet the criteria under paragraph 64(*c*) of CEPA as they are entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health. It is also concluded that 4,4′-MDA and pMDA do not meet the criteria under paragraph 64(*c*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Overall conclusion

It is concluded that the five MDI substances (CAS RNs 101-68-8, 2536-05-2, 5873-54-1, 9016-87-9 and 26447-40-5) in the MDI/MDA Substance Grouping meet one or more of the criteria set out in section 64 of CEPA. However, they have been determined not to meet the persistence or bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA. It is also concluded that 4,4′-MDA (CAS RN 101-77-9) and pMDA (CAS RN 25214-70-4) do not meet any of the criteria set out in section 64 of CEPA.

Table of Contents

List of Tables

1. Introduction

Pursuant to sections 68 and 74 of the *Canadian Environmental Protection Act, 1999* (CEPA) (Canada 1999), the Minister of the Environment and the Minister of Health conduct screening assessments of substances to determine whether they present or may present a risk to the environment or to human health.

The Substance Groupings Initiative is a key element of the Government of Canada's Chemicals Management Plan (CMP) (Environment and Climate Change Canada, Health Canada 2007a). The Methylenediphenyl Diisocyanate and Diamine (MDI/MDA) Substance Grouping consists of two MDA substances and five MDI substances. 4,4′-MDA did not meet the categorization criteria under section 73 of CEPA but was considered to be a health priority at the time of categorization on the basis of high hazard classification by other international agencies. Polymeric MDA did not meet categorization criteria but was added to the MDI/MDA Substance Grouping given its similarity to 4,4′-MDA. 4,4′-MDI, polymeric MDI and mixed MDI met the categorization criteria under section 73 of CEPA. 2,2′-MDI and 2,4′-MDI did not meet the categorization criteria but were added to this grouping post-categorization on the basis of new high hazard classifications by other international agencies. None of the substances in the MDI/MDA Substance Grouping met categorization criteria for persistence, bioaccumulation or inherent toxicity to aquatic organisms.

Screening assessments focus on information critical to determining whether a substance meets the criteria for defining a substance as toxic as set out in section 64 of CEPA. Screening assessments examine scientific information and develop conclusions by incorporating a weight-of-evidence approach and precaution.[1]

Evaluation of risk to human health involves consideration of data relevant to estimation of exposure (non-occupational) of the general population, as well as information on health hazards (principally from assessments of other agencies that were used for prioritization of the substance). Decisions for human health are based on the nature of the critical effect and/or margins between conservative effect levels and estimates of exposure, taking into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. The screening assessment presents the critical information and considerations on which the conclusions are based.

[1] A determination of whether one or more of the criteria of section 64 of CEPA are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and products used by consumers. A conclusion under CEPA is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in *the Hazardous Products Regulations*, which are part of the regulatory framework for the Workplace Hazardous Materials Information System for products intended for workplace use. Similarly, a conclusion based on the criteria contained in section 64 of CEPA does not preclude actions being taken under other sections of CEPA or other acts.

This screening assessment includes consideration of information on chemical properties, environmental fate, hazards, uses, and exposure, as well as additional information submitted by stakeholders. Data relevant to the screening assessment of these substances were identified up to February 2015 for ecological sections of the document and up to April 2015 for human health sections. Empirical data from key studies, as well as model results, were used to reach conclusions. When available and relevant, information presented in assessments from other jurisdictions was considered.

This screening assessment was prepared by staff in the Existing Substances Programs at Health Canada and Environment and Climate Change Canada and incorporates input from other programs within these departments. The ecological and human health portions of this assessment have undergone external written peer review/consultation. Comments on the technical portions relevant to the environment were received from Raili Moldov (Department of Chemical Safety, Health Board, Estonia) and Robert J. West (The Dow Chemical Company, United States). Comments on the technical portions relevant to human health were received from scientific experts selected and directed by Toxicology Excellence for Risk Assessment (TERA), including Andrew Maier (TERA), Leena Nylander-French (University of North Carolina at Chapel Hill), Mark Utell (University of Rochester School of Medicine), Paul Siegel (National Institute for Occupational Safety and Health [NIOSH]), Naomi Hudson (NIOSH) and Kathleen Ernst (NIOSH). Additionally, the draft of this screening assessment was subject to a 60-day public comment period. While external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Health Canada and Environment and Climate Change Canada.

The critical information and considerations on which the assessment is based are summarized below.

2. Identity of Substances

This screening assessment focuses on five methylenediphenyl diisocyanate substances (MDIs) and two methylenediphenyl diamine substances (MDAs) within the MDI/MDA Substance Grouping. MDIs and MDAs have similar core structures and differ through presence of functional groups, i.e., MDIs contain isocyanate groups and MDAs are characterized by amino functional groups. MDAs are typically used to make MDIs and are also formed as MDIs degrade.

2.1 MDAs

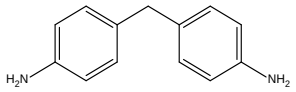
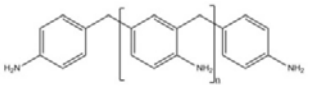
This screening assessment focuses on the assessment of one monomeric MDA substance, 4,4′-MDA (CAS RN 101-77-9), and one polymeric UVCB (unknown or variable composition, complex reaction products, or biological materials) substance , namely pMDA (CAS RN 25214-70-4), which is largely composed of monomeric MDA, likely 4,4′-MDA (Allport et al. 2003).

Production of MDA substances is generally carried out by the acid catalyzed condensation reaction of aniline with formaldehyde to form the polymeric MDA (pMDA), which consists of mixtures of MDA monomers and higher ring homologues (Amini and Lowenkron 2003; Lowenkron 2000). The isomeric composition, along with the relative amount of monomers to higher ring homologues in the pMDA, can be varied depending on the needs of the end user. Therefore, pMDA may show a wide range of compositions; however, the typical composition is 50% 2-ring isomers (the majority of which is 4,4′-MDA), 25% 3-ring isomers, 12% 4-ring isomers, 6% 5-ring isomers and 7% isomers with 6 or more rings or undefined materials (Allport et al. 2003).

Elsewhere, composition of pMDA used in an environmental toxicity study was reported to be of nearly 60% 4,4′-MDA, less than 3% 2,4′-MDA, less than 0.1% 2,2′-MDA, and oligomers at approximate concentrations of 21% for 3-ring isomers, 8% for 4-ring isomers, 3% for 5 ring isomers, and 4% for 6 or more ring isomers (ECHA c2007-2013b). When a higher aniline to formaldehyde ratio is used, the relative proportion of 2-ring structures will increase relative to the higher ring structures (i.e., greater than 2) (Lowenkron 2000). Any unreacted aniline is recycled back to the beginning of the reaction. Also, side reactions which may occur during the production of pMDA typically result in some production of N-methyl and quinazoline derivatives of aniline and MDA; however, processes have been successful in minimizing these side reactions (these would typically make up less than 7% of the pMDA based on the composition presented previously) (Lowenkron 2000).

The structural identities of MDA substances included in the MDI/MDA Substance Grouping are presented in Table 2-1.

Table 2-1. Identity of 4,4′-MDA and pMDA

CAS RN	DSL Name (Acronym)	Chemical structure	Molecular weight (g/mol)	Chemical formula
101-77-9	Benzenamine, 4,4′-methylenebis- (4,4′-MDA)		198.3	$C_{13}H_{14}N_2$
25214-70-4[a]	Formaldehyde, polymer with benzenamine (pMDA)	 Representative structure n = 0–4	198.3-618.8	$C_{13}H_{14}N_2[C_7H_7N]_n$

Abbreviations: CAS RN, Chemical Abstracts Service Registry Number; DSL, Domestic Substance List
[a] This CAS RN is a UVCB (unknown or variable composition, complex reaction products, or biological materials) substance.

2.2 MDIs

The MDI substances in the MDI/MDA Substance Grouping will collectively be referred to as the MDI substances or MDIs. They include three monomeric substances—4,4′-MDI, 2,4′-MDI and 2,2′-MDI (CAS RNs 101-68-8, 2536-05-2, 5873-54-1, respectively)—–a mixture of the monomeric isomers (CAS RN 26447-40-5) and a polymeric UVCB MDI substance (CAS RN 9016-87-9) (see Table 2-2 for structures or representative structures of these substances). It is noted that pMDI (CAS RN 9016-87-9) contains mainly monomeric and oligomeric components, i.e., it is composed of components with a relatively low number of carbon chains (Yakabe et al. 1999). Given the structural similarities of the MDI substances, a read-across approach was taken for assessment of these five substances. For human health and ecological effects assessment, justification for read-across of the MDI substances is available in Appendix A.

Diisocyanates (i.e., MDIs) are produced by reacting pMDA with the chemical reagent phosgene. The resultant polymeric diisocyanates (pMDI) are either sold commercially or are purified to isolate the MDI isomers either individually (i.e., 4,4′-MDI, 2,4′-MDI, or 2,2′-MDI) or as mixed isomers (i.e., a variable composition of 4,4′-MDI, 2,4′-MDI, and 2,2′-MDI isomers) (Amini and Lowenkron 2003). The typical composition of pMDI is usually the same as the corresponding pMDA used to make it. However, all amine groups would be converted to corresponding isocyanates following the phosgenation. Mixed

MDI isomers (CAS RN 26447-40-5) may be composed of predominantly 4,4′-MDI and 2,4′-MDI (Bayer Material Science 2005; Yakabe et al. 2000).

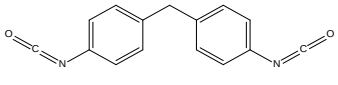
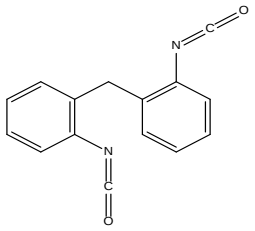
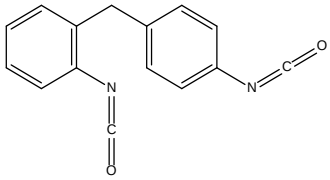
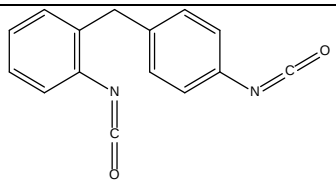
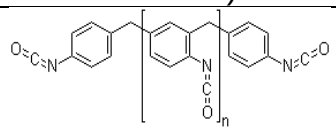
The monomeric MDIs in the grouping are typically composed of a small percentage of residuals or impurities (Allport et al. 2003). Pure 4,4′- MDI typically consists of a minimum of 95% of 4,4′- MDI with the remaining 2% to 5% made up of residuals or impurities of 2,4′-MDI and, to a lesser degree, 2,2′-MDI and higher ring homologues (Allport et al. 2003). It is not expected that minor amounts of isomers with different substitution patterns (i.e., 2,4′- or 2,2′-) will significantly impact on the overall environmental fate, behaviour and toxicological properties of “pure” 4,4′-MDI. Therefore, these residuals/impurities will not be considered further in the assessment of 4,4′-MDI. However, the individual isomers 2,2′-MDI and 2,4′-MDI have been included in this assessment in their “pure” form as there are some reported applications for the use of these specific isomers individually. As in the case of 4,4′-MDI, residual impurities of these substances are not expected to significantly impact the overall environmental fate, behaviour and toxicological properties and therefore will not be considered further in this screening assessment.

As a result of the industrial need for MDI with different viscosity, functionality and reactivity or for special property requirements for the final products, modification of “pure” MDI isomers and polymeric MDI is commonly employed. Modification typically results in the production of MDI “variants” or “pre-polymers” with reduced isocyanate content but improved handling properties (Allport et al. 2003). The most important examples of modified MDIs include MDI dimers (e.g., CAS RN 17589-24-1) and trimers (e.g., CAS RN 31107-36-5) (Dieterich et al. 1993). In addition, the chemical “blocking” of MDIs is typically done using phenols, caprolactam, β-dicarbonyl compounds such as ethyl acetoacetate and ethyl malonate, certain alcohols, oximes, and triazoles to form a thermally weak bond (Dieterich et al. 1993). The isocyanate can be regenerated at elevated temperatures, and thus modified MDIs may become a source of 4,4′-MDI under certain conditions. MDI dimers and trimers are chemically different from 4,4′-MDI and will not form a part of this assessment.

MDI higher (greater than 2) ring homologues (e.g., CAS RN 25686-28-6, 39310-05-9) may be used commercially on their own, and these substances may share some structural similarities to the higher ring homologue fraction found in pMDI. However, as will be discussed later in this screening assessment, the 4,4′-MDI component in pMDI is of greater ecological concern than the higher ring homologue components.

The structural identities of MDI substances included in the MDI/MDA Substance Grouping are presented in Table 2-2.

Table 2-2. Identity of MDI substances in the MDI/MDA Substance Grouping

CAS RN	DSL Name (Acronym)	Chemical structure	Molecular weight (g/mol)	Chemical formula
101-68-8	Benzene, 1,1′-methylenebis[4-isocyanato- (4,4′-MDI)		250.3	$C_{15}H_{10}N_2O_2$
2536-05-2	Benzene, 1,1′-methylenebis[2-isocyanato- (2,2′-MDI)		250.3	$C_{15}H_{10}N_2O_2$
5873-54-1	Benzene, 1-isocyanato-2-[(4-isocyanatophenyl)methyl]- (2,4′-MDI)		250.3	$C_{15}H_{10}N_2O_2$
26447-40-5	Benzene, 1,1′-methylenebis[isocyanato- (mixed MDI)	 (Representative structure)	250.3	$C_{15}H_{10}N_2O_2$
9016-87-9[a]	Isocyanic acid, polymethylenepolyphenylene ester (pMDI)	 Representative structures n = 0–4	250.3–774.8	$C_{15}H_{10}N_2O_2$•$[C_8H_5NO]_n$

Abbreviations: CAS RN, Chemical Abstracts Service Registry Number; DSL, Domestic Substance List

[a] This CAS RN is a UVCB (unknown or variable composition, complex reaction products, or biological materials) substance.

3. Physical and Chemical Properties

The details of experimental and modelled physical and chemical properties of substances in the MDI/MDA Substance Grouping that are relevant to their environmental fate and ecotoxicity are presented in Appendix B, for MDA substances, and Appendix C, for MDI substances.

Models based on quantitative structure-activity relationships (QSARs) were used to generate data for some of the physical and chemical properties of the substances in the MDA and MDI subgroups. These models are mainly based on fragment addition methods, i.e., they sum the contributions of sub-structural fragments of a molecule to make predictions for a property or endpoint. Most of these models rely on the neutral form of a chemical as input. Consequently, except where noted, the modelled values are for the neutral forms of substances.

Purified 4,4′-MDA is a light tan to white crystalline solid with a faint amine-like odour. 4,4′-MDA has a low vapour pressure (less than or equal to 0.01 Pa at room temperature) (MacNab 1999) and a very low Henry's law constant (HLC) (less than 10^{-5} $Pa \cdot m^3/mol$) (HENRYWIN 2008), according to model calculations. The log K_{ow} of 4,4′-MDA was experimentally determined to be low (less than 2). The log K_{oc} has also been experimentally determined in different soil types and was moderate to high at 3.6 to 4.0 (Cowen et al. 1998). A modelled log K_{oc} value of 3.4 based on the molecular connectivity index (MCI) method was similar to the empirically determined values. However, when calculated using log K_{ow}, the modelled log K_{oc} was lower at 1.7 (EPI Suite 2012). This discrepancy in empirical and modelled log K_{oc} values is likely due to molecular hydrophobic interactions of MDA that may not be accounted for by the log K_{ow} method of the KOCWIN (2010) model. Water solubility of 4,4′-MDA was determined to be moderate to high (~1000 mg/L) (Moore 1978; MacNab 1999). Lastly, the pK_a of the phenyl ammonium ion would suggest that 4,4′-MDA would exist primarily in either the 1+ or 2+ ionized form at a pH lower than approximately 5 (MacNab 1999).

Monomeric substances in the MDI subgroup (CAS RNs 101-68-8, 2536-05-2, 5873-54-1, 26447-40-5) are generally solid at room temperature and exist as powders and typically exhibit a low vapour pressure (less than or equal to 0.01 Pa at room temperature). The log K_{ow} of the MDI monomers has been determined experimentally by the HPLC method to be moderate to high (~4.5) (Yakabe et al. 2000). However, since the reactivity of MDI monomers in water is very high, the log K_{ow} may have low environmental relevance for MDI substances. No log K_{oc}, HLC or water solubility values could be determined for the MDI monomers due to the high reactivity of these substances with water. Finally, the MDI monomers have high modelled log K_{oa} values (~9) (KOAWIN 2008). These substances are expected to react quickly in surface waters and with water in soil, and no ionization is expected.

pMDA and pMDI are liquid at room temperature as a result of the higher molecular weight homologues present in these substances. For pMDA, the higher molecular weight homologue components will have lower vapour pressures, lower HLCs and

higher log K_{ow}, K_{oc} and K_{oa} values than the 4,4′-MDA monomer. The water solubility for pMDA was measured to be moderate to high (~360-1500 mg/L), and most components of pMDA would exist primarily in either the 1+ or n+ ionized form at a pH lower than approximately 5. Similarly for pMDI, the higher molecular weight homologue components will have lower vapour pressure and log K_{oa} values than the purified 4,4′-MDI monomer. Other parameters (i.e., HLC, log K_{ow}, log K_{oc}, water solubility, pK_a) were not considered practically measurable or environmentally relevant considering the quick reaction rate of isocyanate groups with water.

4. Sources and Uses

4.1 Sources

4.1.1 MDAs

Methylenediphenyl diamines (MDAs) do not occur naturally in the environment. According to information collected through a survey conducted pursuant to section 71 of CEPA (Environment Canada 2012a), there were no reports of manufacture of 4,4′-MDA (CAS RN 101-77-9) above the reporting threshold of 100 kg in Canada in 2011. However, notifiers indicated that between 1000 and 10 000 kg of 4,4′-MDA were imported into Canada in 2011 (Environment Canada 2012a). pMDA (CAS RN 25214-70-4), which was also included in the survey, was imported in Canada in a range of 100 to 1000 kg for the 2011 reporting year (Environment Canada 2012a).

Releases of MDAs to the environment may result from industrial processes that use these substances. However, MDAs are primarily used in closed systems, leading to minimal releases where manufacturing exists. MDAs could result from the degradation of MDIs released to the environment. Another potential source of MDAs may be the reductive cleavage of azo dyes (ECJRC 2001).

4.1.2 MDIs

Methylenediphenyl diisocyanates do not occur naturally in the environment. According to information collected through a survey conducted pursuant to section 71 of CEPA (Environment Canada 2012a), there were no reports of manufacture above the reporting threshold of 100 kg for 4,4′-MDI (CAS RN 101-68-8), pMDI (CAS RN 9016-87-9) and mixed MDI (CAS RN 26447-40-5) in 2011. The quantity of MDIs imported into Canada in 2011 was determined to be in the range of 10 to 100 million kg (Environment Canada 2012a). The imported quantities of 4,4′-MDI (CAS RN 101-68-8) and pMDI (CAS RN 9016-87-9) were in the range of 10 to 100 million kg each, and the imported quantity of mixed-MDI (CAS RN 26447-40-5) was in the range of 1 to 10 million kg (Environment Canada 2012a). There were reports of lower amounts of 2,4′-MDI (CAS RN 5873-54-1) and 2,2′-MDI (CAS RN 2536-05-2) (ranging from 100 000 to 1 000 000 kg and from 100 to 1000 kg, respectively) imported in Canada, indicating that these isomers may be in commerce both individually and as part of 4,4′- MDI, pMDI or mixed MDI (Environment Canada 2012a).

Elsewhere, MDIs have been identified as high production volume (HPV) chemicals by the HPV programs of the US Environmental Protection Agency and the Organisation for Economic Cooperation and Development (OECD) (OECD 2003, US EPA 2011).

4.2 Uses

4.2.1 MDAs

Methylenediphenyl diamines are used mainly as intermediates in manufacturing processes. Globally, over 98% of all pMDA produced is used as an intermediate in the closed-system production of pMDI and subsequently other MDI isomers (NTP 2011; Amini and Lowenkron 2003; ECJRC 2001). Less than 2% of MDAs are used as other chemical intermediates and curing agents in the production of high-performance polymers and polyurethane elastomers, foams, coatings, adhesives and resins (NTP 2011; ECJRC 2001). MDAs are used as analytical reagents for metal and sulphate analysis, as corrosion inhibitors and antioxidants, as finishing agents for welding and as curative agents in rubber (NTP 2011). They can also be used as intermediates in the production of azo dyes. In the United States, MDAs are used as cross-linking agents in epoxy resins (NTP 2011). The US Food and Drug Administration approved the use of epoxy resins to coat large-capacity containers (greater than 1000 gallons) intended for repeated use of beverages having an alcohol content of 8% (NTP 2011).

In Canada, information on consumer and industrial uses of MDAs was reported in response to a survey under section 71 of CEPA (Environment Canada 2012a). 4,4′-MDA is blended into a product used as a catalyst for industrial processes, and pMDA is blended into a product used for coating machinery. Information identified through this survey does not list uses in consumer products that would result in exposure to the general population (Environment Canada 2012a). In addition, 4,4′-MDA was reported to be used as an intermediate congener in the production of azo dyes, specifically Cartasol Yellow and benzidine-based acid dyes (Environment Canada 2012a).

In Canada, MDAs are not listed in the Drug Products Database (DPD) or the Therapeutic Product Directorate's internal Non-Medicinal Ingredients Database as a medicinal or non-medicinal ingredient in pharmaceutical products or veterinary drugs (DPD 2010; 2011 e-mails from the Therapeutic Products Directorate, Health Canada, to the Risk Management Bureau, Health Canada; unreferenced). Nor are they listed in the Natural Health Products Ingredients Database (NHPID) (NHPID 2013) as ingredients of natural health products or in the Licensed Natural Health Products Database (LNHPD) as being present in currently licensed natural health products (LNHPD 2013). No agricultural products or pesticides containing 4,4′-MDA have been identified by the Pesticide Management Regulatory Agency (PMRA) (2013 emails from PMRA, Health Canada, to the Risk Management Bureau, Health Canada; unreferenced). MDAs are not listed in the Lists of Permitted Food Additives as an approved food additive under the *Food and Drugs Act* (Canada 1978) and associated Marketing Authorizations. On the basis of notifications submitted under the *Cosmetic Regulations* to Health Canada, it is not expected that MDAs are used in cosmetics in Canada (2013 emails from the

Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada; unreferenced).

4.2.2 MDIs

MDIs are generally widely used in the production of polyurethanes and as adhesives in the production of engineered wood products. MDIs are increasingly replacing toluene diisocyanates (TDIs) in the production of flexible and rigid foams, particle board and wood binders, paints and coatings, adhesives, sealants, elastomers, casting materials and spandex fibres (ECJRC 2005; US EPA 2011; Björkner et al. 2001; Methner et al. 2010). MDIs are increasingly being used as a replacement to formaldehyde as a resin binder in the manufacture of oriented strand board products (Environment Canada 2012a).

In the case of flexible foam, MDIs are reacted with polyetherols or polyesterols in industrial settings to form flexible slabstock or moulded parts, which are then used to manufacture furniture, such as sofas and mattresses, automotive foam cushions, flooring underlay, and other packaging foam (ECJRC 2005; Hoffman and Schupp 2009).

Rigid polyurethane foam and polyurethane CASE (coatings, adhesives, sealants and elastomers) are also made from MDIs, which are then used in construction, transportation, machinery, packaging and furniture sectors (ECJRC 2005). Manufactured items represent a large commercial use of MDIs. These types of products also exist in the form of do-it-yourself (DIY) products used by consumers for home improvement projects, i.e., products in which MDIs are reacted with polyols to form rigid foam or CASE upon application, such as sealant around windows or doors, insulation inside walls or floor adhesive (ECJRC 2005).

Textiles and sports tracks are also minor uses of polyurethanes made from MDIs (Booth et al. 2009; Björkner et al. 2001).

In Canada, both industrial and consumer uses of MDIs were reported in a survey conducted under section 71 of CEPA (Environment Canada 2012a). Between 10 and 100 million kg were reported for use in Canada, a fraction of which was available for consumer use (Environment Canada 2012a).

In Canada, MDIs were reported to be used in the manufacturing of polyurethane flexible and rigid foam and CASE, which are then used in other sectors, such as furniture, construction, and automotive (Environment Canada 2012a). Other manufactured items, such as oriented strand board, particle board and other wood products, are produced in Canada for further use in construction (Environment Canada 2012a). Several Canadian industrial sites use pMDI and MDI for engineered wood products, often in conjunction, in combined quantities ranging from 400 000 to close to 6 000 000 kg/year per site (Environment Canada 2012a). MDIs are also used in casting materials by professionals for medical purposes (MSDS 2010, 2011). In addition, manufactured items containing

MDI substances (such as flexible packaging laminate) are imported for use (Environment Canada 2012a).

Information on consumer products collected from the public domain via Canadian retail outlets and websites was also considered in this report. Consumer product uses include several DIY products, such as adhesives, insulating foam and sealants (HPD 2013; HSDB 1983-2003).

The MDIs in this grouping are not listed as approved food additives in the Lists of Permitted Food Additives incorporated by reference into the Marketing Authorizations for food additives, issued under the *Food and Drugs Act* (Canada 1985). A section 71 submission listed MDIs as a component of adhesives used in commercially available food packaging (Environment Canada 2012a), but indicated that migration into food is not expected. MDIs are also used in the manufacture of one polyurethane yarn, which may be used in food packaging applications in Canada (2012 emails from the Food Directorate, Health Canada, to the Risk Management Bureau, Health Canada; unreferenced).

In Canada, the MDIs in this grouping are not listed in the DPD or the Therapeutic Products Directorate's internal Non-Medicinal Ingredients Database as a medicinal or non-medicinal ingredient in pharmaceutical products or veterinary drugs (DPD 2010; 2011 e-mails from the Therapeutic Products Directorate, Health Canada, to the Risk Management Bureau, Health Canada; unreferenced). Nor are they listed in the NHPID as ingredients of natural health products or in the LNHPD as being present in currently licensed natural health products (NHPID 2013; LNHPD 2013). On the basis of notifications submitted under the *Cosmetic Regulations* to Health Canada, it is not expected that MDI substances are used in cosmetics in Canada (2013 emails from the Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada; unreferenced). No agricultural products or pesticides containing MDI substances have been identified by the Pesticide Management Regulatory Agency (PMRA) (2013 emails from PMRA, Health Canada, to Risk Management Bureau, Health Canada; unreferenced).

5. Releases to the Environment

Anthropogenic releases of a substance to the environment depend on various losses that occur during the manufacture, industrial use, consumer/commercial use and disposal of a substance. In order to estimate potential releases to the environment occurring at different stages of the life cycle of a substance, Environment and Climate Change Canada compiles information on the relevant sectors and product lines, as well as emission factors[2] to wastewater, land and air at different life-cycle stages in order to

[2] An emission factor is generally expressed as the fraction of a substance released to a given medium, such as wastewater, land or air, during a life-cycle stage, such as manufacture, processing, industrial application or commercial/consumer use. Sources of emission factors include emission scenario documents developed under the auspices of the Organisation for Economic Co-operation and

identify the life-cycle stages that are the largest contributors to environmental concentrations. Recycling activities and transfer to waste disposal sites (landfill, incineration) were also considered.

This information is used to further develop exposure characterization scenarios to estimate resulting environmental concentrations.

Releases of MDA and MDI substances in the grouping are discussed in the following two sections. Summaries of releases of MDI/MDA substances in the grouping from industrial activities and consumer or commercial uses are also provided. End-of-life disposal is discussed collectively for MDA and MDI substances since conversion of MDI substances to MDA can be expected.

5.1 Releases of MDA Substances

4,4′-MDA is on the list of reportable substances under the National Pollutant Release Inventory (NPRI), but no releases were reported for the years 2008 to 2013 (NPRI 1995a). pMDA is not on the NPRI list (NPRI 1995b). No monitoring data for releases of MDAs in Canada were found.

Given the low quantities of this substance in commerce in Canada (Environment Canada 2012a), releases to the environment as a result of industrial uses are expected to be negligible. One form of 4,4′-MDA is imported into Canada to be formulated into a product for industrial use in Canada. At the end of the life cycle, the consumed formulation is disposed of at a hazardous materials facility because of the presence of other hazardous materials. Information received from the section 71 survey suggests that 4,4′-MDA is not expected to be present in industrial or consumer products (Environment Canada 2012a).

5.2 Releases of MDI Substances

5.2.1 Releases of MDI substances from industrial activities

Releases of pMDI and 4,4′-MDI to air as well as total on-site releases were reported for the years 2008 to 2013 (NPRI 1995c). The NPRI summary of releases of 4,4′-MDI to air from industrial facilities in Canada for 2013 was 3.4 tonnes, with total on-site releases of 6.7 tonnes (NPRI 1995c). Reported releases to air for 4,4′-MDI were 14, 15, 4.8, 1.5,[3] and 1.4 tonnes for the years 2008, 2009, 2010, 2011, and 2012 respectively (NPRI 1995c). Total on-site releases of 4,4′-MDI for those years were the same (no additional release to land or surface water) (NPRI 1995c). The NPRI summary of releases of pMDI to air from industrial facilities in Canada for 2013 was 0.13 tonnes, with total on-site releases of 1.8 tonnes (NPRI 1995c). For previous years, reported pMDI releases to air

Development (OECD), data reported to Environment and Climate Change Canada's National Pollutant Release Inventory, industry-generated data, etc.

[3] This release quantity provided for 2011 is only an estimate because of a potential reporting error that is currently under review.

were 8, 4.6, 1.5, 0.3, and 0.3 tonnes for 2008, 2009, 2010, 2011, and 2012 respectively (NPRI 1995c). Corresponding total on-site releases for pMDI were the same (no additional release to land or surface water). No releases to surface water were reported during any of the NPRI reporting periods for either 4,4′-MDI or pMDI. According to information received from Canadian industry, MDI substances are not manufactured or formulated in Canada (Environment Canada 2012a). Loss estimates indicate that substances in the MDI subgroup have a potential for release to the environment, primarily to air during industrial use, such as the production of engineered wood and polyurethane products.

According to international monitoring data (see section 5.3 Measured Environmental Concentrations) and information submitted to Environment Canada (2012a), oriented strand board (OSB) facilities are considered to have higher releases than any other types of facilities using MDIs in terms of quantity of substance used and associated proportional release.

In OSB facilities, MDIs (formulated in products) are added to wood chips to provide wood adhesion. The blended material is then pressed and heated to make thermoset oriented strand board. The products are then trimmed, sawed and painted (US EPA 2002). Trim and sanderdust from finished OSB panels are often used as fuel for burners (NCASI 2012). According to NCASI (2012), some unreacted MDI may be present in the trim or sanderdust. However, emission factors provided by NCASI (2012) do not indicate significant potential of release when trim is burned. Potential for release of MDI substances can occur between the addition of the resin to wood chips at the mixing stage and thermosetting in the OSB press. Once cured, MDI substances no longer exist as such. Process water is not released from the press, but MDI can be emitted to air. According to NCASI (2012), the highest release from a single facility in Canada is 920 kg MDI/year, resulting from the production of 300 million square feet of OSB per year, which should require 3 450 000 kg (3450 tonnes) of MDI. From that information, an emission factor for MDI releases to air has been estimated at 0.027%; it represents a conservative emission factor.

According to industry information and literature, MDI substances can also be emitted to air during the production of foam or adhesive application. However, this is expected to be in amounts below those emitted from OSB facilities (Environment Canada 2012a; ACC 2012a). Monitoring data and emission reporting guidelines indicate that releases to air from these types of industrial production are an order of magnitude lower than releases from OSB manufacturing (Allport et al. 2003; Acton 2001; ACC 2012a). MDI is also used for the formulation of adhesives and in the application of adhesives by industries or other users. However, according to information received from industry, the typical method of application of adhesives containing MDI is not clearly understood (Environment Canada 2012a). Nonetheless, the potential for releases to air during industrial application of adhesives can be assumed to be negligible given that the vapour pressure of the chemical is less than 0.13 Pa (OECD 2011).

Quantities of MDIs released to air from industrial sources may further contribute to deposition to soil and/or surface waters in the surrounding area.

5.2.2 Releases of MDI substances from consumer / commercial uses

Two major types of products are made with MDI: OSB and flexible or rigid polyurethane (PU) foam products. The known industrial function of MDI is to react as a chemical intermediate to allow the formation of polyurethane. On the basis of industry information (Environment Canada 2012a), it is assumed that MDI substances will react almost entirely during the curing process. Therefore, OSB and polyurethane products should contain no residual MDI or, if any, only very low concentrations.

Theoretically, releases of MDI to air from OSB products are possible, but migration of any residual MDI in the solid matrix of the material is assumed to be difficult. Additionally, many of these products are designed for indoor use or will be protected from weathering agents, so releases to water are not expected (Environment Canada 2012a).

5.2.3 Releases of MDA and MDI substances from end-of-life disposal

Because of the nature of the products and materials containing MDI substances, high quantities of such materials and products that were formed using MDI substances as a starting material are disposed of in landfills. Understanding that polyurethane foam will be largely disposed of in landfills at the end of the life cycle, Brown (unreferenced) (as described by DeGaspari [1999]), assessed the potential degradation of polyurethane foam in landfill conditions. After 700 days in landfill conditions, no evidence of release of MDA or biodegradation from MDI-based foam products was observed. MDA was not detectable in landfill leachate. According to DeGaspari (1999) and Brown (unreferenced), standard polyurethane foams are essentially inert under landfill conditions and would not be expected to release aromatic amine into the environment. A report prepared for Environment Canada also concludes that MDIs and MDA are unlikely to be found in landfill leachate (CRA 2012).

5.2.4 Releases of MDI substances from environmental spills

In Canada, two environmental spills of MDIs have been documented in the past several years, in 1999 and 2001. These spills were minor to moderate in nature. In one case, approximately 200 litres of MDIs spilled onto the ground as a result of a container leak during transportation in Ontario, and the substance was contained onsite. The other spill occurred in British Columbia as a result of improper disposal, into a dumpster, of containers holding approximately 160 litres of 4,4′-MDI, resulting in some of the substance leaking out into the dumpster and onto the ground. In both cases, the spills were contained and did not result in contamination of any aquatic systems.

5.3 Measured Environmental Concentrations

Environmental monitoring data for MDA and MDI substances in the grouping were not available for locations in Canada. However, 4,4′-MDA and certain MDIs have been detected elsewhere. Available environmental concentrations and relevant details of sampling methods in Europe, the United States, and Japan are summarized below. Certain MDIs were measured in air near source locations (Ecoff and Lambach 2012), and MDAs were measured in surface waters (CHRIP 2008; Environment Agency of Japan 2000), wastewater effluent discharged directly to surface waters (OECD 2002), and sediment (CHRIP 2008). Environmental concentrations of neither MDAs nor MDIs in the grouping were available for soil samples. Appendix D provides lists of sampling locations and detected concentrations of MDA and MDI substances.

5.3.1 Air

Atmospheric concentrations of 4,4′-MDA, associated with substance releases in Europe, were reported to be negligible in the OECD Screening Information Data Set (SIDS) for 4,4′-Methylenedianiline (CAS RN 101-77-9) (OECD 2002). Details regarding sampling procedures and geographical locations were not provided.

Monomeric MDIs and 3-ring MDI species have been detected in the air at a variety of near-source locations, including near commercial spray polyurethane foam (SPF) installations and OSB manufacturing facilities. Although filters impregnated with a derivatization reagent or impingers containing derivatization reagents have been used for the collection of MDI species, including the aerosol fraction, aerosol particles of less than 2 µm are not efficiently collected by an impinger, and MDI species present in large particles are not efficiently derivatized when collected on filters impregnated with derivatization reagent (Streicher et al. 1994). Therefore, the use of sampling methods capable of collection in both vapour phase and in aerosol would avoid underestimation of the total concentrations present.

Air concentrations for “free MDI” and, in some cases, higher ring (3+) oligomers from pMDI typically measured using impingers and/or filters from various industrial and commercial sites in the United States and Europe have been reported in peer-reviewed literature, technical reports, and conference proceedings, most of which were summarized in Allport et al. (2003). Concentrations of MDI from foam manufacturing, foam moulding manufacturing, flame lamination, and forest products manufacturers (OSB, fibreboard) ranged from less than 0.1 µg/m^3 to greater than 1000 µg/m^3 in stack/vent emissions with no abatement technologies in place (see Appendix D, Table D-1 for specific values for each type of facility sampled). Area monitoring samples were taken using combined impinger and filter samplers at 25 feet left, right and behind the application and then again at 50 feet downwind of the application at four SPF work sites (Ecoff and Lambach 2012). MDI monomers (2,4′- and 4,4′-MDI only) were detected in 11 of 18 area samples from the four sites at 25 feet at total concentrations of 1.0 to 23.9 µg/m^3 with an average concentration of 9.5 µg/m^3 (higher oligomers were only detected in 4 of 18 samples at 25 feet). At 50 feet downwind of the application site, detectable

MDI monomer concentrations were found at two of three work sites at 1.0 to 3.9 µg/m^3 (no higher oligomers were detected at this distance).

5.3.2 Water

In a survey of several commercially relevant chemical substances by the Environment Agency of Japan, 4,4′-MDA was monitored in samples taken from various surface waters (collected from sea, lake, marsh, and river locations around Japan) between 1985 and 2008, with a general increase in concentration seen with time (CHRIP 2008; Environment Agency Japan 2000). The monitored sampling locations were selected to best investigate persistence of the chemical in the environment, and locations where the surveyed chemical substances would likely be released (e.g., wastewater treatment plant outfall or industrial facilities where import or manufacture was known) were purposely avoided. Therefore, this survey does not consider near field locations, and it is noted that results of the survey do not reflect potential near field MDA concentrations.

4,4′-MDA was not detected in Japanese surface water samples collected in 1985, 1995 or 1998 (CHRIP 2008). In the surface water samples taken from 28 sampling locations around Japan in 2008, 11 sites showed detectable concentrations of 4,4′-MDA, ranging from the detection limit of 0.001 µg/L up to 0.016 µg/L (CHRIP 2008). For 1989, it was reported that 4,4′-MDA was detected in one sampling location out of 24 at a very low concentration of 0.00001 to 0.0001 µg/L (CHRIP 2008). Given that this concentration is about 100 fold lower than the detection limit available in 2008, these measurements are likely not reliable. Available data for surface waters and wastewater are tabulated in Appendix D, Table D-2.

In Europe, industry monitoring data from wastewater treatment plants indicated levels of 4,4′-MDA of less than 500 µg/L (OECD 2002; personal communication, email from German Federal Environment Agency to Environment Canada, dated January 8, 2013; unreferenced). This information was summarized in the OECD SIDS for 4,4′-Methylenedianiline (OECD 2002); however, individual data points as well as sampling locations were not available.

Because of their fast hydrolysis rate, MDI substances in the MDI/MDA Substance Grouping are not expected to be found in the aquatic environment.

5.3.3 Soil

Soil concentrations of 4,4′-MDA were reported to be negligible in the OECD SIDS for 4,4′-Methylenedianiline (OECD 2002). Details regarding sampling procedures and locations were not provided.

Soil concentrations of MDI substances in the MDI/MDA Substance Grouping were not identified. However, it is expected that MDI substances would undergo hydrolysis on contact with any moisture present in soil and consequently would not build up to significant concentrations in this environmental compartment.

5.3.4 Sediments

As with the surface water monitoring mentioned previously, sediments were also monitored for commercially relevant chemicals by the Environment Agency of Japan between 1985 and 1998. Sediment sampling locations were chosen on the basis of the same criteria as for surface waters, i.e., locations where chemicals were known to be released were avoided.

Concentrations of 4,4′-MDA were reported in bottom sediments collected from several locations around Japan (CHRIP 2008). Levels of 4,4′-MDA ranged from the detection limit of 0.02 µg/g dw to 2.1 µg/g dw in 1998 (in 15 out of 33 sampling locations) and from 0.036 to 0.88 µg/g dw in 1995 (in 6 out of 23 sampling locations) (CHRIP 2008). Data available for sediments is listed in Appendix D (Table D-3).

Given that MDIs are unlikely to build up to significant concentrations in water because of their rapid hydrolysis rates, concentrations in sediments are expected to be negligible.

6. Environmental Fate

6.1 Environmental Distribution

6.1.1 MDAs

Level III fugacity modelling (New EQC 2011) simulates the distribution of a substance in a hypothetical, evaluative environment known as the “unit world”. The EQC model simulates the environmental distribution of a chemical at a regional scale (i.e., 100 000 km^2) and outputs the fraction of the total mass in each compartment from an emission into the unit world and the resulting concentration in each compartment. Environment and Climate Change Canada uses only the mass-fraction distribution results for general information on environmental fate of a substance and generally does not use the compartmental concentration results for the predicted environmental concentration (PEC) in a substance assessment. Some exceptions to this may occur, e.g., when a wide dispersive release of a substance suggests that regional scale concentrations are appropriate for the PEC(s).

The mass-fraction distribution of 4,4′-MDA and components of pMDA is given in Table 6-1 using individual steady-state emissions to air, water and soil. The level III EQC

model assumes non-equilibrium conditions between environmental compartments, but equilibrium within compartments. The results in Table 6-1 represent the net effect of chemical partitioning, inter-media transport, and loss by both advection (out of the modelled region) and degradation/transformation processes.

The results of Level III fugacity modelling suggest that 4,4′-MDA is expected to predominantly reside in soil (as a result of deposition from air or because of input directly to soil), water or sediment, while the higher oligomers will predominantly reside in soil or sediment, with only minor amounts in water depending on the compartment of release in each case.

Table 6-1. Summary of the Level III fugacity modelling (New EQC 2011) for 4,4′-MDA and components of pMDA indicating the percentage of substance or substance component partitioning into each compartment

Table 6-1A. 4,4′-MDA

Substance released to:	Air	Water	Soil	Sediment
Air (100%)	0.0	1.7–2.5	96.7–97.7	0.6–0.8
Water (100%)	0.0	71.3–76.7	0.0	23.3–28.7
Soil (100%)	0.0	0.2	99.7-99.8	0.0–0.1

Model inputs: half-lives in water, soil and sediment of 2400-4368, 2400-4368 and 9600-17 472 hours, respectively, and log K_{oc} of 3.7 (average of the range of values presented in Appendix B).

Table 6-1B. 3-ring MDA

Substance released to:	Air	Water	Soil	Sediment
Air (100%)	0.0	0.8	88.0	11.2
Water (100%)	0.0	6.5	0.0	93.5
Soil (100%)	0.0	0.0	99.9	0.1

Model inputs: half-lives in water, soil and sediment of 4368, 4368 and 17 472 hours, respectively, and log K_{oc} of 5.3 (value presented in Appendix B).

Table 6-1C. 4- and 5-ring MDA

Substance released to:	Air	Water	Soil	Sediment
Air (100%)	0.0–0.4	0.3	80.9–81.3	18.4
Water (100%)	0.0	1.6	0.0	98.4
Soil (100%)	0.0	0.0	99.9	0.1

Model inputs: half-lives in water, soil and sediment of 4368, 4368 and 17 472 hours, respectively, and log K_{oc} of 7.4 (4-ring MDA) and log K_{oc} of 9.4 (5-ring MDA) (value presented in Appendix B).

Given the low vapour pressure and relatively high rate of atmospheric degradation expected for 4,4′-MDA and higher pMDA oligomers (3, 4 and 5-ring MDAs), it is expected that neither 4,4′-MDA nor pMDA will be present in significant amounts in the atmosphere (less than 1% predicted by the New EQC model [2011]). In a test atmosphere generated by vaporization of epoxy resin containing 4,4′-MDA hardener, no difference in the sample collection efficiency for 4,4′-MDA was observed when sulphuric acid-coated glass-fibre filters and simple Teflon filters were used, indicating that 4,4′-MDA exists primarily as an aerosol in the atmosphere and would thus likely be removed

from the atmosphere by rain/snow scavenging and dry deposition (Gunderson and Anderson 1988; Bidleman 1988).

Amines including aniline have been determined to form covalent bonds with quinone groups in humic substances (Thorn et al. 1996) typically present in soil and sediment. Furthermore, Cowen et al. (1998) showed that 4,4′-MDA is sorbed to soils slightly more strongly under aerobic than anaerobic conditions. High log K_{oc} values of 3.6 to 3.8 for 4,4′-MDA and very high values of 5.3 to 9.4 for pMDA oligomers suggested that MDA substances would tend to readily partition to organic material in sediment and soil. This trend was also predicted by EQC modelling (New EQC 2011). The environmental monitoring data from Japan described earlier in this report (CHRIP 2008) indicated detection of 4,4′-MDA in both water and sediment samples from several locations. This monitoring data supports the EQC model prediction that releases to water will likely result in some partitioning to sediment, with some 4,4′-MDA remaining in the water. The results from a study on aerobic and anaerobic transformation in aquatic sediment systems (OECD 308) with 4,4′-MDA suggest that most (54 to 90%) 4,4′-MDA will remain bound to sediment (particularly in an aerobic environment where quinone groups are abundant) (Schaefer and Ponizovsky 2013). Covalent binding of 4,4′-MDA to humic substances would not be predicted by EQC modeling, and thus the model results are likely an underprediction of the true partitioning of 4,4′-MDA to sediments.

Given their low vapour pressure and moderate to high K_{oc} values, when released to air, 4,4′-MDA and pMDA are expected to deposit mainly to soil, where they are expected to be immobile and, to a small degree, to partition to water and then to sediment. Similarly, when released directly to soil, MDA substances will predominantly remain in this compartment as predicted by the EQC model (see Table 6-1). The Transport and Persistence Level III Model (TaPL3) (TaPL3 2000) and OECD POPs Screening Tool version 2.2 (OPST) (Scheringer et al. 2009) were used to estimate the characteristic travel distance (CTD) in air of 4,4′-MDA and pMDA (on the basis of its components). The CTD calculated in air for 4,4′-MDA, 3-ring, 4-ring and 5-ring pMDA oligomers ranged from 2 to 110 km using TaPL3, and 5 to 250 km using the OPST model. Therefore, both models suggest that 4,4′-MDA and pMDA are unlikely to be subject to long-range transport in air.

6.1.2 MDIs

Isocyanate groups generally exhibit high reactive rates with active hydrogen compounds such as amines and hydroxyl groups (particularly isocyanate groups in the para position, such as 4,4′-MDI, which are subject to less steric hindrance than those in the ortho position, such as in the 2,2′- and 2,4′- isomers) (Arnold et al. 1956). Thus, the fate and behaviour of substances in the MDI subgroup will be highly affected by their reactivity in environmental media, and properties such as water solubility, water-based partition coefficients (i.e., HLC, K_{ow} and K_{oc}), and pK_a are of no real value and usually cannot be determined accurately. As a result, Level III fugacity modelling (New EQC 2011) was not performed for the MDI subgroup.

MDI isomers, particularly the oligomeric components, are hydrophobic and poorly soluble in water. The heterogeneous reaction with water may therefore be somewhat slower than for the related phenolic isocyanate substances (TDIs) assessed in Batch 1 of the Challenge Initiative (Environment Canada, Health Canada 2008a). However, Sendijarevic et al. (2004) found that although the reaction for pMDI with water appeared to proceed more slowly than that of TDI, after 7 days of stirring (300 rpm) of up to 50 000 mg of TDI and pMDI (in separate containers) per 1 litre of water at room temperature, the isocyanate content was measured as greater than 8% for TDI and only 0.53% for pMDI. Nevertheless, the major product of such a reaction is typically polyurea, which tends to form quickly, starting on the outside and forming a crust that may restrict ingress of water and egress of amines (e.g., MDA) (Gilbert 1988; Heimbach et al. 1996; Brochhagen and Grieveson 1984). Under a very dispersed entry into the environment, it would be expected that polyureas could also be formed, along with residual amounts of corresponding amines (e.g., 4,4′-MDI would yield some residual 4,4′-MDA). Heimbach et al. (1996) added pMDI (consisting of 45% of the monomer 4,4′-MDI) to two small artificial ponds (mesocosms of standing freshwater systems) for over 100 days at high concentrations of 1000 mg/L (1 g/L) and 10 000 mg/L (10 g/L), representative of a spill situation. They found that the pMDI reacted to form polyurea and that no MDI or MDA monomers were detected in pond water (detection limits [DLs] ranged from 4 to 10 μg/L) or fish (DLs were less than 0.5 mg/kg for MDI and less than 1.4 mg/kg for MDA). In a similar study (Heimbach 1993), pMDI was also found to degrade relatively quickly in sediments of the artificial ponds, with a half-life of up to 80 days (ECJRC 2005). Yakabe et al. (1999) determined that hydrolysis of pMDI (comprised of 55% of MDI monomer) resulted in formation of 4,4′-MDA at concentrations of 1.9, 2.0, and 2.5 mg/L for pMDI loadings of 400, 1000, and 10 000 mg/L (0.4, 1.0 and 10 g/L). This suggests that residual amounts of MDA may be formed at a yield of less than 1% at these high concentrations of pMDI. Therefore, in the Heimbach et al. (1996) mesocosm study, residual MDA may have also formed and partitioned to the sediment compartment or was present below the detection limit in water. It is noted that the hydrolysis reaction rates of MDI, as well as the relative proportions of reaction products, may vary with experimental conditions including the MDI starting concentrations. It is possible that lower starting concentrations of MDI might actually result in higher yields of residual MDA because the polymerization reaction to form polyurea would then proceed less efficiently.

Heimbach et al. (1996) also reported that sediment extraction for MDA analysis was conducted, but these results were not provided. It is important to also note that at aquatic temperatures of less than 10^{o}C, pMDI solidifies and forms crystals, and this may significantly affect the dispersion and its subsequent breakdown through the hydrolysis reaction. However, this effect would be more important under relatively high concentration releases.

If released to soil, it is expected that MDI substances will react with moisture present and form polyurea solids. Furthermore, it would be expected that if any residual amines were formed in the reaction they would remain immobile in the soil compartment as discussed in the fate section for MDA. No studies with MDI in soils were found, but the

results of experiments with TDI in undisturbed wet sand showed that this substance is converted to polyureas where, after 24 hours, 5.5% of the original TDI was unreacted, and after 8 days only 3.5% remained, while no toluene diamine (TDA) was found above the detection limit of 0.01 ppm (Gilbert 1988).

In summary, when released to water or soil, it is expected that MDI substances will react to form polyureas with residual amounts of MDA (see previous section for fate of the MDA subgroup substances including 4,4′-MDA and components of pMDA).

Because of their relatively low vapour pressures (less than or equal to 0.01 Pa, see Appendix C), atmospheric emissions of MDI substances may be minimal in the absence of significant thermal sources or aerosol formation during spraying. Airborne MDI substances are usually present (albeit in relatively small amounts) in both vapour and condensation aerosol phases (Karoly et al. 2004). In experiments involving monomeric TDI, which in general hydrolyzes more readily than MDI in water, no evidence of gas-phase reaction with water vapour in a test atmosphere (7% to 70% relative humidity [RH]) was found and no TDA or ureas were detected (Holdren et al. 1984). The detection limit for TDA analysis was approximately 0.1% to 1% of the atmospheric concentration of TDI (0.05 to 0.6 ppm). However, it should be noted that during one series of experiments, TDA was observed at a conversion level of 0.1%. Although this may be an artefact, it cannot be ruled out that this result may suggest that a very low conversion of TDI to TDA may occur in the atmosphere under certain conditions. Duff (1985) ran a series of experiments to assess the importance of various atmospheric degradation mechanisms (i.e., photolytic, OH radical, O_3, other potential catalysts present in TDI emissions) at 28ºC and 60% RH and no TDA was measured in any experiment above the detection limit, which would have measured a $\geq$0.05% conversion rate of TDI to TDA. However, in the presence of condensed phases (e.g., rain drops, fog or clouds), it would be expected that TDI and MDI may react to form polyurea and a TDA and MDA residual, respectively (as in Yakabe et al. 1999), and then may be transported with the condensed phase or be deposited to soil or surface waters.

When MDI substances are released to air, given their relatively short half-life in this medium (13 hours for 4,4′-MDI; Becker et al. 1988), their low vapour pressure, and their tendency to form aerosols, it is expected that they will condense onto adjacent materials, including facility structures/equipment and nearby soil and surface waters. Concentrations of monomeric MDI have been monitored in Europe and the United States in emissions from vents and stacks and in a few cases in ambient outdoor air at certain industrial facilities (e.g., manufacturing facilities of foam, OSB) and commercial locations (e.g., SPF applications) with levels ranging from less than 0.1 to 1320 µg/m^3 (see Appendix D for all data).

6.2 Environmental Persistence

This section summarizes available information separately for MDA and MDI substances. Within these sections, information is presented in subsections on the basis of environmental compartment, addressing reactions that occur in the atmosphere, water

and solid media, including sludge and soil. In particular, the water compartment subsection includes discussion of the hydrolysis reaction and of the available inherent and ready biodegradation studies performed according to the accepted OECD or MITI (Japanese Ministry of International Trade and Industry) protocols and featuring water as the test medium in the experimental design. Modelled data is also presented for MDA substances and provides an additional consideration for the biodegradation potential of these substances.

6.2.1 MDAs

It is noted that degradation tests tend to be conducted using the monomer 4,4′-MDA, which is the major component of pMDA. The composition of pMDA has been reported as a mixture of approximately 50% 4,4′-MDA with a small amount of 2,4′-MDA and the remainder comprising oligomers (Cowen et al. 1998). Generally, the position of amino groups on the carbon rings of the MDA isomers, 4,4′-MDA and 2,4′-MDA may influence the overall reactivity of pMDA because of the steric hindrance and electronic effects. Some differences in reactivity can also be expected between pMDA oligomers and the monomer 4,4′-MDA. Nonetheless, empirical degradation results for 4,4′-MDA can be considered relevant to pMDA. In addition, it is noted that the generic term MDA is often used in literature to refer to the industrial mixture pMDA.

6.2.1.1 In the atmosphere

The reaction of OH radicals with vaporized 4,4′-MDA in simulated atmospheric conditions was studied by Becker et al. (1988). The rate constant of 30 (+/- 10) $x10^{-12}$ cm^3/molecule-second was determined for 4,4′-MDA. Assuming a mean tropospheric hydroxyl radical concentration of 1x $l0^6$ OH·/cm^3, the half-life for 4,4′-MDA was established as 6.4 hours. This half-life suggests a relatively rapid degradation of 4,4′-MDA in air.

6.2.1.2 In water

Hydrolysis

MDA is not expected to undergo hydrolysis reaction under environmental conditions given the characteristics of its molecular structure (see Table 2-1). Studies pertaining to hydrolysis of MDA were not identified in the published literature. Moreover, modelled data for hydrolysis could not be obtained for MDA since the model that was typically used, i.e., EPI Suite (2012), does not generate hydrolysis results for this type of chemical structure.

Ready and inherent biodegradation studies

Ready and inherent biodegradation studies have been conducted for 4,4′-MDA (Study Submission 2012a–d; Kim et al. 2002).

In general, ready biodegradability tests include the modified OECD screening tests, CO_2 evolution test, manometric respirometry test, DOC die-away test, closed bottle test, and the MITI(I) test. They measure mineralization over a 28-day period using a low concentration of activated sludge as an inoculum and a high concentration of the test compound (2 to 100 mg/L). Inherent biodegradability tests include the Zahn-Wellens test, SCAS test, and MITI(II) test and are typically run with high microbial population densities, also using activated sludge inoculum. In general, a substance is considered to be readily biodegradable (i.e., undergo ultimate biodegradation) if at least 60% biodegradation has occurred in 28 days in a ready biodegradation test and to be inherently biodegradable if 70% or more has occurred in 28 days in an inherent test (Aronson and Howard 1999). Biodegradation above 20% may be regarded as evidence of inherent, primary biodegradability (Environment Canada 2009).

Experimental conditions, including concentrations of both the test substance and inoculum, as well as inoculum composition and degree of inoculum acclimation, varied between the available tests. These differences in experimental design and conditions produced a range of biodegradation results. However, overall the results from the available ready and inherent biodegradation tests for 4,4′-MDA indicate that this substance exhibits intermediate biodegradation rates with a large range in degradation results observed in the empirical data. On the basis of the results of a test performed following OECD test guideline 209 (Activated Sludge Respiration Inhibition Test), both the EC_0 and EC_{50} for activated sludge were listed as greater than 100 mg/L of 4,4′-MDA (Caspers et al. 1986). Similarly, in a chronic 10-day study testing the growth rate in *E. coli*, a no observed effect concentration (NOEC) of greater than 100 mg/L was established, and no significant effect on growth of *E. coli* after 10 days of exposure to 4,4′-MDA was observed (ECHA c2007-2013a). These results suggest that 4,4′-MDA concentrations of up to 100 mg/L would be unlikely to have significant inhibitory effects on the microbial populations used in biodegradation tests.

A biodegradability test of 4,4′-MDA at 100 mg/L was carried out in 1994 following OECD guideline for Testing of Chemicals No. 301F (Study Submission 2012a). Study results were inconsistent: two of the three 4,4′-MDA replicates gave 0% biodegradation at 28 days by all of the three methods of estimation. However, in the third replicate, biodegradability of 4,4′-MDA was 19% by BOD, 34% by DOC and 37% at 28 days by residue analysis. Ready biodegradability of 4,4′-MDA at 0.5 mg/L was also tested in 2009 in accordance with OECD guideline 301B (CO_2 Evolution Test) (Study Submission 2012b). Results of the study indicated that 4,4′-MDA biodegraded to some degree; 46% biodegradation was observed following an exposure period of 28 days, and 53% was observed following 63 days. In another study, aerobic biodegradation of 4,4′-MDA at various concentrations was investigated by Kim et al. (2002) using a modified Sturm test (ready biodegradation) with activated sludge following the protocol ASTM D5209-92 (which is similar to OECD Guideline301B). Biodegradation of 4,4′-MDA at a test concentration of 30 mg/L was determined to be approximately 62% and 72% after 28 days and 36 days of incubation, respectively. Biodegradation of 4,4′-MDA by a bacterial strain *Ochrobactarum anthropi* found in sludge was tested at four concentrations. Results indicated a varied level of degradation, depending on the concentration of the

test substance. At the lowest concentration of 30 mg/L, biodegradation of 4,4′-MDA was determined to be approximately 62% and 72% after 28 days and 36 days, respectively, similar to that found in the activated sludge experiment conducted at the same test substance concentration. However, at higher test concentrations of 4,4′-MDA, the level of biodegradation of the substance was observed to be reduced. After 28 days of incubation, about 40% biodegradation was attained at 50 mg/L, 15% at 100 mg/L and less than 5% at 300 mg/L.

Mei et al. (2015) compared results from several different ready biodegradability tests (OECD test guidelines 301A, B, D and F) on the biodegradation of 4,4′-MDA ranging in concentration from 2.0 to 40 mg/L depending on the test guideline followed. The 28-day biodegradation concentrations were found to be 94.8%, 29.5%, 0% and 100% for OECD test guidelines 301A, B, D and F, respectively. Ultimately the authors of this study suggest that 4,4′-MDA exhibits intermediate biodegradation and large variation in replicates are typical of substances which show partial biodegradability. Finally, 4,4′-MDA at 30 mg/L was tested in 1986 using the inherent biodegradability test 302C, Modified MITI Test (II) (Caspers et al. 1986). The biodegradability of the test substance was measured using a respirometer. It was observed that 43% of 4,4′-MDA biodegraded after 28 days. In studies conducted in accordance with OECD guideline 302B (Zahn-Wellens Test) using inoculum from activated sludge from industrial wastewater treatment plants considered to be pre-adapted (Study Submission 2012c and 2012d), the biodegradation of 4,4′-MDA was observed as 95% after 14 days and 97% after 21 days at a test concentration of 389 mg/L.

Overall, empirical evidence from the available ready and inherent biodegradation studies in water indicates that biodegradation rates of 4,4′-MDA vary likely because of the variability in bioavailability of 4,4′-MDA and the capacity of microorganisms to biodegrade the substance. However the results do show that 4,4′-MDA may undergo inherent, primary degradation. In environmental settings, devoid of enhanced conditions such as the presence of pre-adapted inoculum, and considering the tendency of MDA to adsorb to solid particles, biodegradation of the substance may proceed at a moderate to low rate.

Simulation biodegradation test

Schaefer and Carpenter (2013) examined biodegradation of 4,4′-MDA at a nominal concentration of 100 µg/L in surface waters, in accordance with OECD Guideline 309 (Aerobic Mineralization in Surface Water - Simulation Biodegradation Test). The primary objective of the simulation test is to determine the mineralization rate (ultimate biodegradation) of the test substance (as indicated by $^{14}CO_2$ evolution), which takes into account primary and ultimate biodegradation along with any abiotic oxidation/reduction reactions. At the end of the tests (92-days), only 11 to 26% of the radioactivity was associated with evolved $^{14}CO_2$. Furthermore, the test guideline specifies that a reference substance should be used (e.g., aniline or sodium benzoate) to ensure that the microbial activity of the test water is within certain limits, while no reference substance appears to have been used in this study (and thus, this validity criterion is not

met). Simulation biodegradation tests or die-away biodegradation tests may be more environmentally realistic than traditional biodegradation studies but are not commonly used for existing chemicals to date. It is therefore important to benchmark the results against a substance with well characterized biodegradation. Ultimately, what we can conclude from this test is that under fairly environmentally realistic conditions, ultimate biodegradation may proceed to ~20% and primary biodegradation proceeds to <60% (as determined from the surface water trials with the highest recovery rates of 81% to 83%) in a 28-day period (for benchmarking purposes with typical time used in standard ready and inherent biodegradation studies).

6.2.1.3 In soil

Cowen et al. (1998) investigated biodegradation of ^{14}C-labelled 4,4′-MDA in silt loam surface soil and sandy loam soil under aerobic and anaerobic conditions. 4,4′-MDA was tested at six concentrations ranging from 0.5 to 53 mg/L. On the basis of recovery of $^{14}CO_{2,}$ aerobic biodegradation of 4,4′-MDA was calculated to be only 11% after 28 days (Cowen et al. 1998). Under anaerobic conditions, biodegradation of 4,4′-MDA was not observed over the 71-day experimental duration.

In summary, available empirical information regarding the degradation potential of 4,4′-MDA in soil suggests that the substance does not biodegrade quickly in soil and that it binds to humic substances, thereby reducing its bioavailability and bioaccessibility. However, the substance may biodegrade faster in the presence of degradable organic substances mixed in with the soil substrate.

6.2.1.4 In sediments

Schaefer and Ponizovsky (2013) examined transformation of 4,4′-MDA in sediment in a study conducted in accordance with OECD Guideline 308 (Aerobic and Anaerobic Transformation in Aquatic Sediment Systems). The study was performed with ^{14}C-labeled 4,4′-MDA at a concentration of 1.38 to 1.41 mg/kg (dw) in aerobic and anaerobic systems for two sediment types (estuarine and freshwater). Distribution of radioactivity in aerobic sediments after 100 days of incubation was 54% to 90% “non-extractable” from the sediments, 8% to 33% “extractable” from the sediments, 6% to 12% unidentified metabolites in the water (only for aerobic trials), and 3% to 6% $^{14}CO_2$ (mineralization; only for aerobic trials). Ultimately, particle sorption tends to dominate dissipation of MDA in water-sediment systems as indicated by the high proportion of MDA that remained bound to sediment (54% to 90% “non-extractable” plus 8% to 33% “extractable”). Extraction conditions, which included triplicate extractions with acetonitrile (with 1% NH_4OH) with sonication, were considered moderate to severe in the analysis of bound residues (ECETOC 2009). Together with the large proportion of bound residues seen in this study, it is likely that most of the MDA in a water-sediment environment would not be available for degradation or for uptake by organisms.

6.2.1.5 Summary of MDA empirical data for persistence

A summary of the empirical biodegradation data generated from the ready biodegradation tests for 4,4′-MDA over 28 days is provided in Table 6-2 below. Considering evidence of biodegradation of 4,4′-MDA from water, soil and sediment studies, biodegradation of the substance appears to be dependent on its bioavailability. In water, 4,4′-MDA underwent inherent biodegradation only when pre-adapted microbial populations were used. In soil and sediment, where MDA tends to be bound and is less bioavailable, its biodegradation rates were observed to be slow. 4,4′-MDA has a high log K_{oc} value, signifying that it readily adsorbs to particles. Therefore, in the environment, including the water compartment, this tendency to adsorb is considered to be the prevailing process that potentially limits its bioavailability to microorganisms that would aid in its biodegradation. On the basis of the available evidence, it is considered that 4,4′-MDA will biodegrade at a moderate to low rate in the environment.

Table 6-2. Summary of key empirical data for biodegradation of 4,4′-MDA

Medium	Fate process	Test Substance concentration (mg/L)	% Biodegradation[a]	Reference
Activated sludge	Ready biodegradation	100	0	Study Submission 2012a
Activated sludge	Ready biodegradation	100	19	Study Submission 2012a
Activated sludge	Ready biodegradation	0.5	46	Study Submission 2012b
Activated sludge	Ready biodegradation	30	62	Kim et al. 2002
Activated sludge	Ready biodegradation	50	40	Kim et al. 2002
Activated sludge	Ready biodegradation	100	15	Kim et al. 2002
Activated sludge	Ready biodegradation	300	<5	Kim et al. 2002

Medium	Fate process	Test Substance concentration (mg/L)	% Biodegradation[a]	Reference
Activated sludge	Ready biodegradation	40	94.8	Mei et al. 2015
Activated sludge	Ready biodegradation	15.8	29.5	Mei et al. 2015
Activated sludge	Ready biodegradation	2.0	0	Mei et al. 2015
Activated sludge	Ready biodegradation	22.5	100	Mei et al. 2015
Activated sludge	Inherent biodegradation	30	43	Caspers et al. 1986
Activated sludge	Inherent biodegradation	389	> 95–97[b]	Study Submission 2012c, d
Soil	Microbial degradation	0.5–53	11	Cowen et al. 1998

[a] Biodegradation results summarized for the test period of less than or equal to 28 days. [b] Pre-adapted inoculum was used.

6.2.1.6 Modelling of persistence for 4,4′-MDA and pMDA

Although experimental data on the degradation of 4,4′-MDA are available, a QSAR-based weight-of-evidence approach was also applied using the degradation models shown in Table 6-3 below. Modelled data were generated to confirm empirical data for 4,4′-MDA and to generate information on the oligomer components of pMDA. Degradation in air and water was examined using QSARs. MDA substances do not contain functional groups expected to undergo hydrolysis.

Table 6-3. Summary of modelled data for degradation of 4,4′-MDA and oligomer components in pMDA[a]

Fate process	Model and model basis	Substance	Model result and prediction	Extrapolated half-life (days)
Air: Atmospheric oxidation	AOPWIN 2010[b]	4,4′-MDA pMDA (n=3–5)	$t_{1/2}$ =0.05 days	≤ 2
Air: Ozone reaction	AOPWIN 2010[b]	4,4′-MDA pMDA (n=3–5)	NA[c]	NA
Water: Hydrolysis	HYDROWIN 2010[b]	4,4′-MDA pMDA (n=3–5)	NA[c]	NA
Primary aerobic biodegradation: Sub-model 4: Expert Survey (qualitative results)	BIOWIN 2010[b]	4,4′-MDA pMDA (n=3–5)	[2.3–3.3][d] “biodegrades slowly to quickly”	≥ 182
Ultimate aerobic biodegradation: Sub-model 3: Expert Survey (qualitative results)	BIOWIN 2010[b]	4,4′-MDA pMDA (n=3–5)	[1.1–2.4][d] “months and longer”	≥ 182
Ultimate aerobic biodegradation: Sub-model 5: MITI linear probability	BIOWIN 2010[b]	4,4′-MDA pMDA (n=3–5)	[-1.69 to -0.18][e] “biodegrades very slowly”	≥ 182
Ultimate aerobic biodegradation: Sub-model 6: MITI non-linear probability	BIOWIN 2010[b]	4,4′-MDA pMDA (n=3–5)	[0][e] “biodegrades very slowly”	≥ 182

Fate process	Model and model basis	Substance	Model result and prediction	Extrapolated half-life (days)
Ultimate aerobic biodegradation: Probability	DS TOPKAT c2005-2009	4,4′-MDA pMDA (n=3) (pMDA n=4, 5 were outside of the domain of applicability)	[0][e] “biodegrades very slowly”	≥ 182
Ultimate aerobic biodegradation: % BOD (biological oxygen demand)	CATALOGIC 2012	4,4′-MDA pMDA (n=3–5)	% BOD = 0 “biodegrades very slowly”	≥ 182

[a] Substances used in this summary include the following CAS RNs: 101-77-9 and CAS RN 25214-70-4.
[b] EPI Suite (2008).
[c] Model does not provide an estimate for this type of structure.
[d] Output is a numerical score from 0 to 5.
[e] Output is a probability score.

Modelled results presented in Table 6-3 above provide additional and relatively consistent evidence for the degradation potential of MDA as well as oligomeric components of pMDA in air and water.

Modelled degradation results for 4,4′-MDA in air, using the AOPWIN 2010 model, were consistent with the available empirical data for this substance. Overall, modelled results in air indicated a relatively fast degradation, with half-lives of less than 2 days for both 4,4′-MDA and pMDA.

In the water compartment, model results for the ultimate biodegradation, presented in Table 6-3 above, collectively indicated that the substances 4,4′-MDA and pMDA (based on modelling of its oligomers) do not have the potential to biodegrade quickly. A primary aerobic biodegradation model (BIOWIN sub-model 4 [2010]) indicated some variability in the biodegradation potential of 4,4′-MDA and pMDA. Using this model, biodegradation of 4,4′-MDA is predicted to occur relatively rapidly (i.e., in weeks), while biodegradation of pMDA is predicted to be somewhat slower (i.e., months). Nonetheless, examined collectively, the modelled results indicate that 4,4′-MDA and pMDA are likely to biodegrade slowly in water. These results are somewhat consistent with empirical studies available for 4,4′-MDA that show a moderate rate of biodegradation in water.

Input into the EPI Suite (2012) model, composed of information on chemical structures of 4,4′-MDA and pMDA oligomers with 3, 4 and 5 carbon rings, fell within the domain of applicability of the AOPWIN (2010) model and BIOWIN models (2010) featured in Table

6-3. As well, all model inputs were in the domain of applicability of the CATALOGIC (2012) biodegradation model. Finally, the domain of applicability conditions of the DS TOPKAT model (c2005-2009) were not met for pMDA oligomers with 4 and 5 carbon rings. However, the DS TOPKAT model results for these two oligomers indicated no biodegradation potential and were consistent with all other modelled data obtained using both the EPI Suite (2012) and CATALOGIC (2012) models.

6.2.1.7 Conclusion on persistence of MDAs

Overall, empirical data indicated that 4,4′-MDA tends to biodegrade at a moderate or low rate in the water compartment, with a majority of the results demonstrating less than 60% ready biodegradation and less than 70% inherent biodegradation. However, as stated previously, the substance may undergo inherent, primary degradation and has been shown to be inherently biodegradable with pre-adaptation. Given that pMDA is composed of approximately 50% 4,4′-MDA (Cowen et al. 1998), these results are also applicable to pMDA. Modelled ultimate biodegradation results also indicated a very slow biodegradation potential, whereas some variability was observed in the primary model biodegradation results. In soil, slow biodegradation rates were also observed. It can be concluded that 4,4′-MDA and pMDA will likely degrade at a moderate rate in the environment, and covalent binding to sediment or soil will make it less available for biodegradation to proceed. In the air, quick reaction of OH radicals with 4,4′-MDA suggest that it will not be present in air for very long.

6.2.2 MDIs

MDI substances belong to a class of chemicals generally known as aromatic isocyanates. They are highly reactive compounds and react readily with nucleophilic functional groups such as NH_2, NH, OH, SH, and COOH (Mormann et al. 2006). Because of this versatile reactivity of the isocyanate group, MDI substances can be employed to produce a wide variety of materials used in foam cushion and insulation, adhesive, sealant, coating, and elastomer applications. For example, the reaction of an isocyanate with an alcohol yields a urethane; with an amine, a substituted urea; and with water, a carbamic acid, which then readily breaks down into the corresponding primary amine and carbon dioxide (ACC Diisocyanates Panel 2005).

Most studies on chemical reactivity have been devoted to 4,4′-MDI (Mormann et al. 2006), although the hydrolysis reaction has been well characterized using pMDI (Yakabe et al. 1999; Heimbach et al. 1996; Sendijarevic et al. 2004). Overall, the two isocyanate groups of MDI have equal reactivity (Mormann et al. 2006). For 4,4′-MDI, there is no steric hindrance of the isocyanate groups and no electronic effect of one group on the other because of the central methylene group (Mormann et al. 2006). For the other MDI monomers in the MDI/MDA Substance Grouping with isocyanate groups in the ortho position, i.e., 2,2′-MDI and 2,4′-MDI, steric hindrance as well as the electronic effect may influence the reactivity of these substances (Arnold et al. 1956). Nonetheless, data available for 4,4′-MDI are considered relevant and applicable to both 2,2′-MDI and 2,4′-MDI.

6.2.2.1 In the atmosphere

MDI has been reported to be readily degraded by reaction with OH radicals (Carter et al. 1999; Tury et al. 2003). Atmospheric reactivity of 4,4′-MDI was investigated by Carter et al. (1999) through photoreactor studies using a suitable structural analogue substance. Because of the technical difficulty in generating vapour from chemicals of low vapour pressure such as MDI, an analogue, *para* toluene isocyanate (PTI), was used in the study. The suitability of PTI as an analogue for MDI was discussed; the authors rationalized that the MDI molecule can be thought of as two PTI molecules joined at the methylene group, and that it is reasonable to expect that reactions should occur at the aromatic ring and with a similar mechanism for reaction following the OH radical addition. Results of the study indicated that MDI tends to react relatively rapidly in the atmosphere. The second-order rate constant of 5.9×10^{-12} cm^3/molecule-second was established for PTI, which was doubled to estimate the second-order rate constant for the double-ringed MDI to give 1.2×10^{-11} cm^3/molecule-second. The resulting atmospheric half-life for MDI was estimated as 11 hours (ACC Diisocyanates Panel 2005) and 15 hours (Tury et al. 2003), assuming average hydroxyl radical concentrations of 1.1×10^6 molecules/cm^3 and 1.5×10^6 molecules/cm^3, respectively.

In the presence of condensed phases (e.g., rain drops, fog or clouds), it would be expected that atmospheric TDI and MDI may react to form some polyurea with a TDA and MDA residual, respectively (as in Yakabe et al. 1999), and may then be transported with the condensed phase or be deposited to soil or surface waters.

6.2.2.2 In water

Hydrolysis reaction

Aromatic isocyanates are chemically reactive species, known to react with water (Shkapenko et al. 1960; Yakabe et al. 1999). In a simplified description, hydrolysis of an aryl isocyanate with water first forms carbamic acid and then, following a rapid release of carbon dioxide, a primary amine (e.g., MDA). The primary amine can then also react with the isocyanate to form urea (Yakabe et al. 1999).

For diisocyanates such as pMDI—a hydrophobic, dense and viscous substance—the reaction with water tends to occur much slower than the homogenous reaction for simple isocyanates. Because of its physical properties, when poured into water, MDI tends to sink, and hydrolysis occurs heterogeneously at or below the diisocyanate/water interface. In heterogeneous reactions, the rate of hydrolysis may depend on particle size and surface area and on efficiency of mixing (Sendijarevic et al. 2004). When MDI was finely divided and dispersed by vigorous agitation, the hydrolysis reaction rates were observed to be rapid and approaching that predicted for a homogeneous reaction. The oligomeric isocyanate components of the pMDI sample disappeared at approximately the same rate as the monomer 4,4′-MDI. The reaction half-life of 4,4′-MDI was measured to be approximately 25 hours under stirred experimental conditions with a loading rate of 400 mg/L (Yakabe et al. 1999). In contrast, in static experiments,

where diffusion and gas evolution provided the only mixing, pMDI was observed to be present in the mixture for over 20 days, with approximately 25% of unreacted substance remaining (Yakabe et al. 1999). In another study (Study Submission 2012a) investigating the reaction of pMDI with water under unstirred conditions, it was also observed that concentrations of the formed soluble products were lower than those formed in the stirred experiments. Half-lives for 4,4′-MDA formation from pMDI were determined as 3.8, 4.5, and 6.2 days on the basis of surface areas of pMDI of 18.1, 13.2, and 5.7 cm2, respectively. It is noted that with respect to the general reactivity in water, structural differences due to the isocyanate group substitution of the MDI monomers, i.e., 2,2′-MDI, 2,4′-MDI, and 4,4′-MDI, as well as presence of all three monomers (such as in the mixed MDI), are not expected to significantly impact the general chemical pathway or associated reaction rates. Modelled data (EPI Suite 2012) indicated hydrolysis half-lives of less than 10 minutes for all MDI substances in the grouping (i.e., 2,2′-MDI; 2,4, MDI; 4,4′-MDI; representative structure of mixed MDI; and individual components of pMDI [n=2–5]). These results indicated that hydrolysis rates of all MDI substances in the grouping tend to be very similar. However, it is noted that modelled hydrolysis data may underestimate the influence of steric hindrance, physical properties such as viscosity, and impacts of a heterogeneous reaction on the individual hydrolysis rates for MDI substances in the grouping. Therefore, empirical hydrolysis reaction rates for these MDI substances are expected to be somewhat slower than the modelled rates.

The reaction of pMDI in water produced solid, insoluble, unreactive polyurea as a major product, a small yield of 4,4′-methylenedianiline (4,4′-MDA) from 4,4′-MDI present in pMDI, and DOC (Yakabe et al. 1999). The amount of 4,4′-MDA produced was measured at 1% under stirred experimental conditions and at 0.005% under static experimental conditions, indicating that the efficiency of mixing impacted the reaction rate.

Products of the hydrolysis reaction of pMDI were further studied by Sendijarevic et al. (2004). The focus of that study was on the potential for MDA release into the environment as a result of environmental release of pMDI and its subsequent hydrolysis to polyureas. The authors characterized hydrolysis and associated reaction kinetics of polyureas obtained from hydrolysis of pMDI. Polyurea samples were prepared by vigorous agitation of pMDI with water to obtain low-molecular-weight polyureas, which are thought to undergo hydrolysis more readily than the low-molecular-weight polyureas formed under static conditions. The study was conducted using an industrial pMDI sample, commercially known as Lupranate M-205, with a described composition including congeners of polymethylene polyphenyl isocyanate, 39.4% 4,4′-MDI, 3.4% 2,4′-MDI, and 2,4-bis(p-isocyanatobenzyl)phenyl isocyanate. Study results indicated that polyureas formed from contact of pMDI with water can be expected to be essentially unreactive in the environment for millennia. Reaction half-lives for the release of MDA from pMDI-polyurea were determined on a geological time scale indicating that polyureas are extremely stable in the environment (Sendijarevic et al. 2004).

Ready and inherent biodegradation studies

pMDI was tested in an inherent biodegradation study in 1986 in accordance with OECD Guideline 302C (Modified MITI Test [II]) (Caspers et al. 1986). According to the study authors, the inherent test was applied since pMDI was known to be not readily biodegradable. This study also consisted of tests for 4,4′-MDA, and therefore the study protocol is described in more detail in the MDA Persistence section above. In summary, the study protocol for pMDI was also modified with respect to the inoculum source, pMDI was tested at the same concentration of 30 mg/L, and aniline was used as the study reference substance. The test substance pMDI was described to be composed of isomers and oligomers and to consist of approximately 50% monomeric MDI. After 28 days, 0% biodegradation was observed for pMDI. Therefore, pMDI does not inherently biodegrade under the conditions of this test. Using OECD Guideline 209 (Activated Sludge, Respiration Inhibition Test), no inhibition of respiration was reported for any of the pMDI test concentrations used (i.e., 1, 10 or 100 mg/L), indicating that the test substance is not appreciably toxic to the sludge microorganisms.

6.2.2.3 In soil

MDIs are highly reactive substances, especially in contact with water. It is expected that in soil, where a degree of moisture is prevalent, MDI substances will mainly undergo hydrolysis (Martens and Domsch 1981; Allport et al. 2003). Like the hydrolysis reaction in the water compartment, the same heterogeneous reaction is expected in soil, resulting in MDA and polyurea reaction products. During the reaction process, diisocyanate is trapped within a crust of solid, insoluble polyureas (Allport et al. 2003). MDAs tend to be formed in relatively small amounts, and polyureas are the major reaction products.

Degradation of polyureas prepared from ^{14}C-labelled MDI and formed by interaction of MDI with water was investigated in different agricultural soils ranging from sandy to clay (Martens and Domsch 1981). The study aimed to address the fate of a high-content MDA-polyurea after a spillage of monomeric isocyanates. In the study, degradation was not detected after four months, as evidenced by no detectable $^{14}CO_2$ evolution or lack of formation of soluble radiolabeled products, such as diamines and oligoureas (Martens and Domsch 1981).

6.2.2.4 In sediments

Measurements of pMDI concentrations in sediments were conducted in an unpublished study by Heimbach (1993), where high concentrations of the substance (1000 and 10 000 mg/L) were added to artificial ponds to evaluate effects in a spill situation. According to the description of the Heimbach (1993) study in ECJRC (2005), the degradation rate of pMDI was substantial but not constant throughout the study. pMDI concentrations decreased over the course of the study from 7.6 mg/kg to less than or equal to 0.7 mg/kg in the low-dosed pond (1000 mg/L) and from 20 to 0.8 mg/kg in the high-dosed pond (10 000 mg/L). Half-lives of pMDI in the urea residues found in

sediment were found to vary from 7 to 80 days in the low-dosed pond, and from 14 to 28 days in the high-dosed pond. This study suggested that pMDI tends to break down relatively quickly in sediment, but that the reaction rates tend to proceed more rapidly at higher pMDI concentrations.

6.2.2.5 Summary of pMDI empirical data for persistence

MDI substances in the MDI/MDA Substance Grouping belong to a highly reactive class of chemicals. In the atmosphere, MDIs are known to react readily, and relatively rapid half-lives have been established on the basis of the reaction of OH-radicals using an analogue substance (ACC Diisocyanates Panel 2005; Tury et al. 2003) (see Table 6-4 below). MDI substances are also known to rapidly hydrolyze; however, the rate of hydrolysis depends on the mixing conditions (Yakabe et al. 1999). In experiments where MDI was dispersed by vigorous agitation, hydrolysis rates were observed to be fast, whereas in the static conditions, up to 75% of the test substance was reacted after 20 days, but some amounts of the unreacted test substance were observed to remain in solution (Yakabe et al. 1999) (see Table 6-4). An inherent biodegradation test was conducted and results indicated that pMDI does not biodegrade under the conditions of the test. Given that hydrolysis is a major mode of relatively rapid degradation of MDI substances in the environment, they are unlikely to be present in an aquatic/sediment medium for very long. The hydrolysis studies of MDI showed that the half-life in water is very unlikely to be longer than 182 days (6 months) and that the substance is therefore likely to not persist in that environmental compartment. Moreover, since a degree of moisture is typically present in soil, it is expected that hydrolysis will also be the prevailing degradation reaction in this compartment.

Given the abundance of empirical biodegradation data for MDI substances in the grouping in air and water and the fact that these substances are highly reactive in these environmental media, biodegradation modelling in air and water was not performed for these substances.

Table 6-4. Summary of empirical data for environmental degradation of pMDI

CAS RN	Medium	Fate process	Degradation value	Degradation endpoint / units	Reference
Generic MDI	Air	Oxidation	11-15	Half-life (hours)	ACC Diisocyanates Panel 2005; Tury et al. 2003
9016-87-9	Water	Hydrolysis	75[a]	Biodegradation (%)	Yakabe et al. 1999
9016-87-9	Water	Inherent biodegradation	0[b]	Biodegradation (%)	Caspers et al. 1986

[a] after 20 days; [b] after 28 days

6.2.2.6 Conclusion on persistence of MDI substances in the MDI/MDA Substance Grouping

Judging from the available empirical data (Table 6-4), the MDI substances in the MDI/MDA Substance Grouping are not expected to persist in air, water, soil, or sediment.

6.3 Potential for Bioaccumulation

In order to provide multiple lines of evidence for the bioaccumulation potential of substances in the MDI/MDA Substance Grouping, both empirical and modelled data were considered. This section is divided into two subsections, where information available for MDA and MDI substances in discussed separately.

Available experimental and model-generated data including bioconcentration factors (BCF), together with information deduced from the partition coefficients, were additional considerations in the determination of the bioaccumulation potential of MDA and MDI substances.

6.3.1 MDAs

For MDA, experimental and modelled BCFs, together with information deduced from the partition coefficient data as well as read-across data for pMDA, were considered in determining the potential for bioaccumulation. Experimentally determined fish bioconcentration factors (BCFs) are considered as the main line of evidence for the substance's bioaccumulation potential. These empirical findings are also supported by the modelled evidence.

6.3.1.1 Aquatic bioconcentration factor (BCF)

A study testing the potential of 4,4′-MDA to bioaccumulate in fish was conducted in 1992 by the Japanese Ministry of International Trade and Industry (MITI 1992). According to the study report, 4,4′-MDA was tested in carp (*Cyprinus carpio*) at the nominal concentrations of 0.02 and 0.2 mg/L, in accordance with OECD Guideline 305C (Bioaccumulation: Test for Degree of Bioconcentration in Fish). Fish measuring approximately 10 cm in length and weighing 30 grams were used in the study. Fish lipid content was reported as an average of 4.5%. BCF measured was for the substance at equilibrium after a test period of 6 weeks (MITI 1992).

Bioconcentration factors (BCFs) were calculated as less than 3.1 to 15 after exposure to 0.02 mg/L of 4,4′-MDA and as 3 to 14 after exposure to the higher concentration of 0.2 mg/L of the substance. Experimental results indicated that the 10-fold difference in the concentration of the test substance used in the study did not have an impact on the BCF values. Overall, BCF results of less than or equal to 15 indicate a low potential for bioaccumulation. Results from this study are presented in Table 6-5 below.

Table 6-5. Summary of empirical bioconcentration factors (BCF) for 4,4′-MDA

Test organism	BCF value (L/kg)[a]	Reference
Carp (*Cyprinus carpio*)	<3.1–15 (0.02 mg/L) 3–14 (0.2 mg/L)	ECHA c2007-2013a[NARb]

[a] Values in parentheses represent the test concentrations at which the BCFs were derived.
[b] NAR: not available for review.

To corroborate the experimental BCF results, model results were also generated using the BCFBAF model (EPI Suite 2012) and the experimental log K_{ow} value of 1.6 as the model input. Predicted BCF and BAF values for the middle trophic level fish representative of Canadian waters generated using a modification of the mass-balance model from Arnot and Gobas (2003) were both 3.2 L/kg. The predicted values were consistent with the experimental values obtained in the study.

In addition, predicted BCF/BAF values for the 3-ring oligomer of pMDA for the middle trophic level fish, based on the modelled log K_{ow} of 3.29, were both approximately 51 L/kg.

6.3.1.2 Bioaccumulation potential in terrestrial organisms

According to known release patterns, MDA tends to be deposited on soil surfaces, mainly as a result of emissions of MDI substances and their subsequent and rapid conversion to some amounts of MDA (Yakabe et al. 1999). Thus, exposure to terrestrial organisms to MDA and associated amines as a result of conversion of corresponding isocyanates in the environment is theoretically possible.

Experimental log K_{ow} values of 1.55 to 1.64 for 4,4′-MDA and 1.3 to 2.5 for pMDA (see Appendix B, Tables B-1 and B-2) suggest that these chemicals have a low potential to bioaccumulate in biota. However, chemical substances with the combination of moderate log K_{ow} values of greater than or equal to 2 and a high log K_{oa} (log K_{oa} for 4,4'-MDA is 9.5, see Appendix B: Table B1), may have the potential to biomagnify via dietary exposure in terrestrial food webs as suggested by Gobas et al. (2003) and Kelly et al. (2007).

It has been observed that substances with a log K_{ow} less than or equal to 2 are typically metabolized and/or eliminated through routes such as urinary secretion by exposed animals (Kelly et al. 2007). For 4,4′-MDA, studies in rats, mice, guinea pigs, rabbits and monkeys demonstrated that following intraperitoneal/intravenous injection or oral administration of 4,4′-MDA, the substance is largely eliminated in both urine and feces (OECD 2002). Both acetylated 4,4′-MDA metabolites and free 4,4′-MDA have been detected in the urine of exposed animals (OECD 2002). On the basis of this information, it is considered that 4,4′-MDA tends to be readily metabolized and eliminated from the body by small mammals and thus is not likely to biomagnify in terrestrial food webs. Moreover, the modelled biomagnification factor (BMF) calculated from the log K_{ow} and log K_{oa} values for 4,4′-MDA for the top food chain predator, the wolf, indicated no

biomagnification potential (4,4′-MDA BMF_{wolf}=4x10^{-4}) (BMF predictions for wolves were made using a spreadsheet version of Gobas et al. [2003]).

6.3.1.3 Conclusion on bioaccumulation potential of MDAs

Both 4,4′-MDA and pMDA have low to moderate experimental log K_{ow} values and high modelled log K_{oa} values. A low log K_{ow} generally suggests a low potential for bioaccumulation, but since it is only a partition coefficient it does not account for physiological processes such as metabolism. Environment and Climate Change Canada does not consider the use of log K_{ow} in isolation as sufficient evidence to determine the bioaccumulation potential. Low to moderate log K_{ow} together with a high log K_{oa} suggests a potential for biomagnification in terrestrial food webs, given that the route of exposure of the substance is through food sources (Kelly et al. 2007). For 4,4′-MDA, experimental evidence suggests that this substance is readily metabolized and secreted by small mammals (OECD 2002), and it is therefore unlikely that this substance has the potential to biomagnify in terrestrial food webs. This was further confirmed by the very low predicted BMF in the terrestrial top food chain predator (wolf BMF calculations based on Gobas et al. 2003). Experimental BCF in fish was determined to be very low (MITI 1992), indicating that 4,4′-MDA does not bioaccumulate in fish. Empirical fish BCF results were in agreement with model-predicted BCF values (EPI Suite 2012). Finally, modelled BCF for the most prominent 3-ring oligomer in pMDA was also very low (EPI Suite 2012) and thus unlikely to bioaccumulate in biota.

6.3.2 MDIs

MDI substances are highly reactive due to the properties of their isocyanate groups (Yakabe 1999). Consequently, they are not expected to build up to significant concentrations in water or soil, where a degree of moisture is prevalent and would promote the occurrence of hydrolysis. This characteristic was previously described in more detail in the Fate and Persistence sections of this screening assessment. In effect, it is expected that very limited amounts of MDI would be available for uptake by organisms from the environmental media. Moreover, the two main MDI hydrolysis reaction products, polyureas and MDA, bioaccumulate to only very low levels in organisms. Polyureas obtained from MDIs are inert, insoluble and solid and tend to form layers or crusts (Yakabe 1999). They have been observed to cause indirect ecotoxicological effects in populations of benthic organisms (Heimbach et al. 1996). As described above, MDA substances have a low bioaccumulation potential.

The log K_{ow} values determined for the MDI monomers in the MDI/MDA Substance Grouping were approximately 4.5, and the modelled log K_{oa} values were 8.95 (see Appendix C). For pMDI, the log K_{ow} was not determined, whereas the modelled log K_{oa} values ranged from 8.95 (for oligomer with n=2) to 24.8 (n=5) (see Appendix C). For substances with low metabolism potential, such log K_{ow} and log K_{oa} values could indicate probable biomagnification in terrestrial food webs (Kelly et al. 2007). However, given the known reactivity of the MDI substances, it is very unlikely that these substances are available for uptake by organisms from the environment. Therefore,

given the high reactivity, rapid degradation and the lack of persistence of the MDI substances of the MDI/MDA Substance Grouping in environmental media including air and soil, estimation of the bioaccumulation potential in terrestrial food webs is not considered in this screening assessment.

6.3.2.1 Aquatic bioconcentration factor (BCF)

A fish bioconcentration study for 4,4′-MDI was performed in 2002 by the Japanese Chemicals Evaluation and Research Institute using carp (*Cyprinus carpio*) (Study Submission 2012e). The study was conducted according to OECD Guideline 305 (Bioconcentration: Flow-through Fish Test). Since the test substance was observed to rapidly react with water, a carrier solvent was used to stabilize the chemical. It is noted that the use of a carrier solvent is not representative of conditions naturally encountered in the environment but is considered acceptable for the purpose of testing a highly reactive substance. The stock solution was prepared by dissolving ^{14}C-labelled 4,4′-MDI (radio-label positioned at both carbon rings) in acetone, and this preparation was observed to be fairly stable (95% of 4,4′-MDI remained in the acetone solution after 4 days). A 96-hour range finding test in Japanese rice fish (*Oryzias latipes*) indicated a low LC_{50} value of 0.5 mg/L from exposure to 4,4′-MDI in acetone. Therefore, for the 28-day bioconcentration study, carp ranging from 5.8 to 7.4 cm in length were exposed to 4,4′-MDI/acetone at two concentrations: 0.8 µg/L and 0.08 µg/L. Stock solutions of 4,4′-MDI in acetone for both exposures were prepared as 8.0 mg/L and 0.8 mg/L, and the test solutions were renewed every two to three days. Measurements of the test substance in the test solutions were carried out throughout the study, and the measured concentrations did not deviate more than 20% from the nominal concentrations. On the basis of observations of minimal variation (less than 20%) in at least three consecutive measurements of BCF, steady state was judged to be attained in the course of 28 days. Fish lipid content was determined from the control fish only and was reported as 2.8% before the start of the study and as 4.5% at the end. After 28 days of exposure to the test substance, BCFs in the 0.8 µg/L exposure group were determined to be in the range of 61 to 150, while BCFs in the 0.08 µg/L exposure group were determined to be in the range of 120 to 330. Average BCFs were calculated and were reported as 92 from the exposure concentration of 0.08 µg/L and as 200 from the 10-fold lower test concentration of 0.08 µg/L. Average BCFs are summarized in Table 6-6 below.

Table 6-6. Empirical bioconcentration factors (BCF) of 4,4′-MDI

Test organism	Kinetic and/or steady-state value (L/kg)[a]	Reference
Carp *(Cyprinus carpio)*	92 (0.8 µg/L) 200 (0.08 µg/L)	Study Submission 2012e; ECHA c2007-2013c

[a] Values in parentheses represent the test concentrations at which the BCFs were derived.

Results of the study indicate that 4,4′-MDI has a low bioaccumulation potential. It is noted that without the use of a carrier solvent, the test substance would hydrolyze quickly, not allowing for maintenance of the nominal test concentration and would ultimately not be bioavailable to the test organisms. It is uncertain whether the test substance reacted in the water since the measurements of test substance concentrations were not specific to the presence of the isocyanate groups, but rather were based on the radioactive label placed on the carbon rings of 4,4′-MDI. However, since the heterogeneous reaction of MDI in water and formation of polyureas were not acknowledged in the study report, it is concluded that 4,4′-MDI concentrations remained stable in the test solutions.

Results of this study are also considered applicable to the other MDI substances in the Grouping. 4,4′-MDI is structurally very similar to the monomers 2,2′-MDI and 2,4′-MDI, as well as to mixed MDI, which consists of a combination of the three monomers. 4,4′-MDI also constitutes approximately 50% of pMDI, and thus is a major component of this substance (see Identity of Substances section).

With regard to the methodology of the available bioaccumulation study, it is acknowledged that experimental procedures adopted in this study created artificial conditions for MDI exposure. Given that pMDI is a highly reactive substance, it is expected that it would not be available for uptake by aquatic organisms from the surrounding media. Under environmental conditions, where the hydrolysis reaction of MDI would occur readily, organisms would be mainly exposed to polyureas and MDAs, rather that MDI. Like MDIs, both polyureas and MDAs have a low bioaccumulation potential.

Finally, given the availability of reliable empirical bioaccumulation data for MDI substances in the grouping and the fact that these substances are highly reactive in water, bioaccumulation modelling was not performed for these substances.

6.3.2.2 Conclusion on bioaccumulation potential of MDI substances in the MDI/MDA Substance Grouping

MDI substances in the MDI/MDA Substance Grouping belong to a highly reactive class of chemicals. They are known to quickly hydrolyze and, as a result, have only a transient existence in environmental media such as water or soil, where a degree of moisture is typically present (Yakabe 1999). For this reason, it is considered that MDI substances tend not to be present in appreciable concentrations in the environment for prolonged periods of time and therefore are not available for uptake by organisms and are very unlikely to biomagnify in aquatic or terrestrial food webs. Available empirical evidence in fish from exposure to a solvent-stabilized 4,4′-MDI over 28 days suggests that this substance does not bioaccumulate in fish. BCF results from this bioconcentration study are considered as read-across for the remaining monomer MDIs in the MDI/MDA Substance Grouping, 2,2′-MDI and 2,4′-MDI, as well as mixed MDI. Also, since 4,4′-MDI is a major component of pMDI, study results for 4,4′-MDI are considered to be representative of pMDI as well.

Therefore, the available empirical evidence for bioaccumulation potential, physical-chemical properties and environmental fate suggests that MDI substances in the MDI/MDA Substance Grouping are not likely to be very bioaccumulative.

7. Potential to Cause Ecological Harm

7.1 Ecological Effects Assessment

Available environmental toxicity information for MDA and MDI substances in the MDI/MDA Substance Grouping is summarized in the subsections below.

For 4,4′-MDA, the available empirical studies for water-, soil- and sediment-dwelling organisms are summarized in subsections for each environmental compartment and in corresponding Tables 7-1, 7-3 and 7-4. Given that pMDA is composed of over 50% of 4,4′-MDA (Allport et al. 2003), toxicity data available for pMDA are also presented as potential read-across information (Table 7-2). Not surprisingly, toxicity levels in aquatic species, such as algae, water flea, and microorganisms in the activated sludge, established from experimental exposure to pMDA are similar to those determined for 4,4′-MDA (see Tables 7-1 and 7-2).

Similarly, empirical data available for the MDI substances in the MDI/MDA Substance Grouping are summarized in subsections for each environmental compartment and in Tables 7-6, 7-7 and 7-8. Since ecological studies were conducted for only two substances in the subgroup, i.e., 4,4′-MDI and pMDI, results from these studies were considered as read-across to inform ecological effects from potential exposure to 2,4′-MDI, 2,2′-MDI and mixed MDI. 2,4′-MDI and 2,2′-MDI are very similar isomers of 4,4′-MDA, and mixed MDI is a mixture of all three MDI monomers. Therefore, ecological effects resulting from exposure to these MDI substances are expected to be comparable.

7.1.1 MDAs

7.1.1.1 Empirical studies for the aquatic compartment

Given the physical-chemical properties of MDA and its predicted environmental fate (see Environmental Fate section, Table 6-1), it is expected that when released into water, most of the substances, and particularly the monomer 4,4′-MDA, will remain in water and subsequently partition into sediment (up to approximately 30%) (see Table 6-1A, 6-1B and 6-1C). However, soil and sediment are expected to be the main receiving media upon MDA releases to air and soil. Therefore, potential route of exposure of aquatic organisms to MDA would mainly result from the direct releases of MDA substances into water.

Effects of 4,4′-MDA have been extensively studied in aquatic species including microorganisms (marine and fresh water bacteria and activated sludge), algae, invertebrates (*Daphnia magna*) and fish. Similar effects have also been established for pMDA in green algae and invertebrates (*D. magna*), although the number of studies carried out was fewer. Generally, the observed levels of toxicity in different aquatic

species measured through ecological endpoints were comparable between 4,4′-MDA and pMDA.

Ecological effects of 4,4′-MDA were studied in three species of microorganisms: a marine Gram-negative bacterium, *Photobacterium phosphoreum*; a Gram-negative bacterium, *Escherichia coli*; and unidentified microorganisms found in activated sludge.

The luminescent bacterial toxicity assay, known as the Microtox test, was performed using the marine bacterium *P. phosphoreum* to create a toxicity data index for over 1300 chemicals (Kaiser and Palabrica 1991). 4,4′-MDA was one of the chemicals tested in this study. The 30-minute acute EC_{50} value determined for 4,4′-MDA in the Microtox bioassay was 6.6 mg/L (Kaiser and Palabrica 1991), indicating a moderate toxicity potential of the test substance.

In the two other bacterial studies available for 4,4′-MDA, the substance was not observed to be appreciably toxic to the test organisms at both acute and chronic exposures (ECHA c2007-2013a). In a 3-hour acute study conducted in 1986, activated sludge from a laboratory-scale wastewater treatment plant was tested according to OECD Guideline 209 (Activated Sludge, Respiration Inhibition Test) at concentrations of up to 100 mg/L. EC_{50} for respiration inhibition was determined as greater than 100 mg/L following a 3-hour exposure to 4,4′-MDA (Caspers et al. 1986). Similarly, in a chronic 10-day study testing the growth rate in *E. coli*, a NOEC of greater than 100 mg/L was established, and no significant effect on growth of *E. coli* after 10 days of exposure to 4,4′-MDA was observed (ECHA c2007-2013a).

Ecotoxicological effects of 4,4′-MDA and pMDA were also determined in algae. 4,4′-MDA was tested in two species, *Selenastrum capricornutum* and *Desmodesmus subspicatus,* in a 2002 study and 1985 study, respectively. Both studies were performed in accordance with OECD Guideline 201 (Alga, Growth Inhibition Test), and summaries of the study reports are available from the European Chemicals Agency website (ECHA c2007-2013a). In the 2002 study, *S. capricornutum* was exposed to 4,4′-MDA at nominal concentrations ranging from 0.2 to 20 mg/L for 48 and 72 hours. At 72 hours, the EC_{50} for growth rate was 14.4 mg/L, and for calculation of the area under the growth curve, endpoints reported included a NOEC of 0.93 mg/L and a 72-hour EC_{50} of 5.34 mg/L. In the 1985 study, *D. subspicatus* was exposed to 4,4′-MDA at the nominal concentrations ranging from 10 to 160 mg/L for 72 hours. An EC_{50} for the growth rate was reported as 21 mg/L (ECHA c2007-2013a). In summary, both species of algae, *S. capricornutum* and *D. subspicatus,* appear to have similar sensitivities to the exposure of 4,4′-MDA for up to 72 hours, with EC_{50} values for the growth rate inhibition ranging from 13.5 to 21 mg/L.

A summary of a similar study for pMDA performed in 1992 according to the industrial standard test guideline DIN 38 412 Part 9, is also available from the European Chemicals Agency website (ECHA c2007-2013a). In this study, the green algae *D. subspicatus* was exposed to pMDA for 72 hours, and two ecotoxicological endpoints, growth rate inhibition and biomass increase were considered. EC_{10} values were

reported as 0.3 and 2.4 mg/L, and EC_{50} values were reported as 11 and 9.8 mg/L for the growth rate inhibition and increase in biomass, respectively (see Table 7-2). According to the available studies, the ecotoxicological effects of 4,4′-MDA and pMDA on algae appear to be similar. The pMDA used in this study was reported to be composed of nearly 60% 4,4′-MDA, less than 3% 2,4′-MDA, less than 0.1% 2,2′-MDA, and oligomers at approximate concentrations of 21% for n=3, 8% for n=4, 3% for n=5 oligomer, and 4% for n greater than or equal to 6 (ECHA c2007-2013a).

Several short- and long-term ecotoxicological endpoints were established for the water flea *Daphnia magna* as a result of numerous studies testing 4,4′-MDA (ECHA c2007-2013a; Salinas 2011; Mitsubishi Chemical Safety Institute 2002a, 2002b). Also, two acute ecotoxicity studies investigating the effects of pMDA on daphnids were recently conducted (Study Submission 2012f, g; ECHA c2007-2013a). In general, both 4,4′-MDA and pMDA are highly toxic to *D. magna*, with EC_{50} or LC_{50} endpoints reaching less than 1 mg/L as a result of acute and chronic exposures. Available studies are summarized in Tables 7-1 and 7-2.

Ecotoxic effects, including reproduction inhibition, in *D. magna* from a long-term 21-day exposure to 4,4′-MDA were determined in a study by the Mitsubishi Chemical Safety Institute (2002b). The study was conducted according to OECD Guideline 211 (Test for Reproduction of *Daphnia*). Daphnids were exposed to the test substance at concentrations ranging from 0.006 to 0.6 mg/L. The chronic LC_{50} value was reported as 0.0291 mg/L, and the NOEC, lowest observed effect concentration (LOEC) and median effective concentration (EC_{50}) values for growth inhibition were 0.00525, 0.0182, and 0.0149 mg/L, respectively. This study demonstrates the lowest toxicity effects observed from exposure of an aquatic species to 4,4′-MDA.

Two unpublished studies examining acute effects of pMDA exposure to *D. magna* were available for review (Study Submission 2012 f, g; ECHA c2007-2013b) (see Table 7-2). The 48-hour NOEC, EC_{50}, and maximum effective concentration (EC_{100}) values for immobilization, based on the mean measured concentrations, were reported as 0.273, 0.57, and 1.24 mg/L, respectively. Another similar unpublished study conducted in 2010 also investigated the effect of pMDA on the immobilization of *D. magna* after a short-term (48-hour) exposure. The NOEC, EC_{50} and EC_{100} values for *D. magna* immobilization, based on the nominal test concentrations, were reported as 0.1 mg/L, 0.1 to 1 mg/L, and 1 mg/L, respectively. Results from both studies are consistent and show a similar degree of toxicity to the test organisms.

In the fish species, short-term toxicity of 4,4′-MDA was established through a series of unpublished studies conducted between 1985 and 2002. Summaries of these studies are available on the European Chemicals Agency website (ECHA c2007-2013a). Available endpoints from the fish toxicity studies are provided in Table 7-1. The studies were short-term (96-hour) studies conducted in four fish species: Japanese rice fish (*Oryzias latipes*), rainbow trout (*Oncorhynchus mykiss*), golden orfe (*Leuciscus idus*), and zebrafish (*Brachydanio rerio*). Effect levels were comparable among the four species, falling within the same order of magnitude (see Table 7-1) with 96-h LC_{50}s

ranging from 20.6 mg/L for Japanese rice fish to 65 mg/L for zebrafish. Available empirical toxicity data for fish suggests that short-term exposure (up to 96 hours) to 4,4′-MDA results in moderately toxic effects. Lethal concentration values established for the fish species in these studies are similar and fall within the same order of magnitude. Long-term chronic toxicity studies in fish were not identified in either the published literature or through unpublished sources. However, it is expected that ecotoxicological effects of 4,4′-MDA in fish would be more pronounced following longer exposure to the substance than those established in the short-term studies. Fish studies were not identified for pMDA. It is expected, however, that effects of pMDA may be similar to those of 4,4′-MDA, given the structural similarities between both substances.

In conclusion, aquatic organisms are sensitive to both short- and long-term exposure to MDA substances, with the observed toxic effects intensified as a result of chronic exposure, typical of a neutral narcotic chemical. 4,4′-MDA and pMDA were observed to be highly to moderately toxic to various aquatic organisms tested, including algae, microorganisms, the invertebrate *D. magna*, and fish. The water flea *D. magna* exhibited the highest sensitivity to exposure to both MDA and pMDA, with several acute and chronic ecotoxicological endpoints determined to be less than 1 mg/L. In addition, ecotoxicological endpoints determined for 4,4′-MDA and pMDA in algae and *D. magna* were very similar, confirming that the results from studies for pMDA can be used as read-across for 4,4′-MDA.

Table 7-1. Summary of empirical data for aquatic toxicity from studies for 4,4′-MDA

Test organism	Duration of test	Endpoint	Value (mg/L)	Reference
Marine bacterium *(Photobacterium phosphoreum)*	30 minutes	EC_{50} (Microtox test)	6.6	Kaiser and Palabrica 1991
Activated sludge	3 hours	EC_{50} (respiration)	> 100	Caspers et al. 1986
Bacteria *(Escherichia coli)*	10 days	NOEC (growth rate)	> 100	ECHA c2007-2013a[NAR]
Algae *(Selenastrum capricornutum)*	48 hours	EC_{50} [NAR] (growth rate)	13.5	ECHA c2007-2013a

Test organism	Duration of test	Endpoint	Value (mg/L)	Reference
Algae *(Selenastrum capricornutum)*	72 hours	EC_{50} ^{NAR} (growth rate)	14.4	ECHA c2007-2013a
Algae *(Desmodesmus subspicatus)*	72 hours	EC_{50} ^{NAR} (growth rate)	21	ECHA c2007-2013a
Water flea (*Daphnia magna*)	24 hours	EC_{50} (immobilization)	2.3	ECHA c2007-2013a
Water flea (*Daphnia magna*)	24 hours	NOEC (immobilization)	0.41	Salinas 2011
Water flea (*Daphnia magna*)	48 hours	NOEC (immobilization)	0.19	Salinas 2011
Water flea (*Daphnia magna*)	24 hours	EC_{50} (immobilization)	1.5	Salinas 2011
Water flea (*Daphnia magna*)	48 hours	EC_{50} (immobilization)	0.40	Salinas 2011
Water flea (*Daphnia magna*)	24 hours	EC_{100} (immobilization)	> 4.3	Salinas 2011
Water flea (*Daphnia magna*)	48 hours	EC_{100} (immobilization)	2.0	Salinas 2011
Water flea (*Daphnia magna*)	24 hours	NOEC (immobilization)	0.63	Mitsubishi Chemical Safety Institute 2002a
Water flea (*Daphnia magna*)	48 hours	NOEC (immobilization)	0.2	Mitsubishi Chemical Safety Institute 2002a

Test organism	Duration of test	Endpoint	Value (mg/L)	Reference
Water flea (*Daphnia magna*)	24 hours	EC_{50} (immobilization)	8.08	Mitsubishi Chemical Safety Institute 2002a
Water flea (*Daphnia magna*)	48 hours	EC_{50} (immobilization)	2.47	Mitsubishi Chemical Safety Institute 2002a
Water flea (*Daphnia magna*)	48 hours	EC_{100} (immobilization)	200	Mitsubishi Chemical Safety Institute 2002a
Water flea (*Daphnia magna*)	14 days	NOEC (reproduction)	0.15	ECHA c2007-2013a
Water flea (*Daphnia magna*)	21 days	LC_{50} (reproduction inhibition)	0.0291	Mitsubishi Chemical Safety Institute 2002b
Water flea (*Daphnia magna*)	21 days	EC_{50} (reproduction inhibition)	0.0149*	Mitsubishi Chemical Safety Institute 2002b
Water flea (*Daphnia magna*)	21 days	NOEC (reproduction inhibition)	0.00525	Mitsubishi Chemical Safety Institute 2002b
Water flea (*Daphnia magna*)	21 days	LOEC (reproduction inhibition)	0.0182	Mitsubishi Chemical Safety Institute 2002b
Rice fish (*Oryzias latipes*)	48 hours	LC_{50}	321	ECHA c2007-2013a^{NAR}
Rice fish (*Oryzias latipes*)	96 hours	LC_{50}	20.6	ECHA c2007-2013a^{NAR}
Rainbow trout (*Oncorhynchus mykiss*)	96 hours	LC_{50}	39	ECHA c2007-2013a^{NAR}

Test organism	Duration of test	Endpoint	Value (mg/L)	Reference
Golden orfe (*Leuciscus idus*)	96 hours	LC_{50}	53	ECHA c2007-2013a[NAR]
Zebrafish (*Brachydanio rerio*)	96 hours	LC_{50}	42	ECHA c2007-2013a[NAR]
Zebrafish (*Brachydanio rerio*)	96 hours	LC_{50}	65	ECHA c2007-2013a[NAR]

Abbreviations: NAR, not available for review; EC_{50}, the concentration of a substance that is estimated to cause some effect on 50% of the test organisms; LC_{50}, the concentration of a substance that is estimated to be lethal to 50% of the test organisms; NOEC, the no observed effect concentration is the highest concentration in a toxicity test not causing a statistically significant effect in comparison to the controls; LOEC, the low observed effect concentration is the lowest concentration in a toxicity test that caused a statistically significant effect in comparison to the controls.
*This endpoint was chosen as the critical toxicity value (CTV). On the basis of a robust study summary, the study was found to be reliable (Environment Canada 2013).

Table 7-2. Summary of empirical data for aquatic toxicity from studies for pMDA

Test organism	Duration of test	Endpoint	Value (mg/L)	Reference
Green algae (*Desmodesmus subspicatus*)	72 hours	EC_{50} (growth rate)	11	ECHA c2007-2013a[NAR]
Green algae (*Desmodesmus subspicatus*)	72 hours	EC_{50} (biomass increase)	9.8	ECHA c2007-2013a[NAR]
Water flea (*Daphnia magna*)	48 hours	NOEC (immobilization)	0.273	Study Submission 2012f; ECHA c2007-2013b
Water flea (*Daphnia magna*)	48 hours	EC_{50} (immobilization)	0.570	Study Submission 2012f; ECHA c2007-2013b
Water flea (*Daphnia magna*)	48 hours	EC_{100} (immobilization)	1.24	Study Submission 2012f; ECHA c2007-2013b

Test organism	Duration of test	Endpoint	Value (mg/L)	Reference
Water flea (*Daphnia magna*)	48 hours	NOEC (mortality)	0.1	Study Submission 2012g; ECHA c2007-2013b
Water flea (*Daphnia magna*)	48 hours	EC_{50} (mortality)	> 0.1 < 1	Study Submission 2012g; ECHA c2007-2013b
Water flea (*Daphnia magna*)	48 hours	EC_{100} (mortality)	1	Study Submission 2012g; ECHA c2007-2013b

Abbreviations: NAR, not available for review; EC_{50}, the concentration of a substance that is estimated to cause some effect on 50% of the test organisms; EC100, the concentration of a substance that is estimated to cause some effect on 100% of the test organisms; NOEC, the no observed effect concentration is the highest concentration in a toxicity test not causing a statistically significant effect in comparison to the controls.

7.1.1.2 Empirical studies for other environmental compartments

Soil

The soil compartment is a receiving medium for MDA substances. Soil deposition of MDIs and subsequent conversion to polyureas and MDA is considered to be the main source of MDA in this environmental compartment. Given its physical-chemical properties and modelled environmental fate, MDA could be found in soil if released directly into the environment. Modelled EQC results presented in Table 6-1 in the Environmental Fate section show that when MDAs are released to air, most will in turn be deposited in soil. Furthermore, when MDA substances are released to soil, nearly all of the substances are expected to remain in this compartment.

Empirical studies for the monomer 4,4′-MDA have been conducted for soil microorganisms, invertebrates and two plant species. Similar studies assessing ecotoxicological effects in soil organisms were not located for pMDA. Available soil toxicity studies for 4,4′-MDA are summarized in Table 7-3.

Ecotoxic effects of 4,4′-MDA on nitrogen-fixing bacteria were investigated in a 2013 study performed according to OECD Guideline 216 (Soil Microorganisms: Nitrogen Transformation Test) (Schwarz 2013) over 28 days. Soil samples consisted of loamy sand and were collected from a site that had not been cultivated for the previous 4 years and that had not been subject to applications of fertilizers, pesticide or herbicide products during those years. The effect of ammonium reduction was not observed at the 4,4′-MDA concentrations tested and a NOEC value of greater than 1000 mg/kg soil was therefore assigned. It was concluded by the authors that results of this study suggested that nitrificating bacteria were not inhibited by the test substance (Schwarz 2013).

Ecotoxicological effects of 4,4′-MDA were determined in a soil arthropod, the springtail (*Folsomia candida*) (Moser 2011). In a 2011 study performed according to OECD Guideline 232 (Collembolan Reproduction Test in Soil), the effects of long-term exposure of 4,4′-MDA on reproduction were determined. The 28-day NOEC and EC_{50} values for reproductive effects were reported as 562 and 910 mg/kg soil (dw), respectively. The results of this study suggested that 4,4′-MDA exhibited low toxicity to the springtail.

Ecotoxicological effects of 4,4′-MDA were determined in a soil invertebrate, the earthworm *Eisenia fetida,* first in 1992 according to OECD Guideline 207 (Earthworm, Acute Toxicity Tests) (Study Submission 2012h) and more recently in 2012 according to OECD Guideline 222 (Earthworm Reproduction Test) (Hamberger and Moser 2012). In the acute toxicity study, earthworms were exposed to the test substance mixed with artificial soil for a period of 14 days (Study Submission 2012h). Reported results were an LC_{50} value of 444 mg/kg soil and NOEC values for behaviour/appearance, weight increase/decrease, and mortality of 56, 32, and 180 mg/kg soil, respectively. In the long-term 56-day study also using artificial soil, the NOEC and EC_{10} values for effects on reproduction were determined as less than 18 mg/kg soil (dw) and 11.2 mg/kg soil (dw), respectively. The results of these two studies indicated that 4,4′-MDA is moderately toxic to earthworms.

Effects on seedling emergence, growth, and survival were studied in two plant species representative of the monocot and dicot plant groups: oats (*Avena sativa)* and lettuce (*Lactuca sativa)* (van der Hoeven et al. 1992).

In the study with oats, the NOEC for seedling emergence was reported as 320 mg/kg soil (dw) following 17 days of exposure. The 14-day NOEC and EC_{50} values for growth rate were determined as 100 and 353 mg/kg soil (dw), respectively. Lastly, the 14-day NOEC value for survival exceeded the highest concentration tested and was reported as greater than or equal to 1000 mg/kg soil (dw). In the study using lettuce, the NOEC for seedling emergence was reported as 100 mg/kg soil (dw) following 17 days of exposure. The NOEC and EC_{50} values for growth rate were determined as 10 and 128 mg/kg soil (dw), respectively, following 14 days of exposure. As in the oats study, the 14-day NOEC value for survival also exceeded the highest concentration tested and was reported as greater than or equal to 1000 mg/kg soil (dw). Both plant studies suggest that 4,4′-MDA has a moderate soil toxicity following two weeks of exposure.

In summary, 4,4′-MDA appears to exhibit low to moderate toxicity to soil organisms and plants. The earthworm was the most sensitive species to 4,4′-MDA, particularly with from the long-term exposure. In addition, two plant species were tested, oats and lettuce, and results from these studies suggested a similar sensitivity between the two plant species to 4,4′-MDA exposure.

Table 7-3. Summary of empirical data for soil toxicity from studies for 4,4′-MDA

Test organism	Duration of test	Endpoint	Value (mg/kg dry soil)	Reference
Soil inoculum (nitrogen-fixing bacteria)	8 days	NOEC (ammonium reduction)	> 1000	Schwarz 2013
Springtail (*Folsomia candida*)	28 days	NOEC; EC_{50} (reproduction)	562	Moser 2011
Springtail (*Folsomia candida*)	28 days	NOEC; EC_{50} (reproduction)	909.9	Moser 2011
Earthworm *(Eisenia fetida)*	14 days	NOEC (weight increase)	32	Hamberger and Moser 2012
Earthworm *(Eisenia fetida)*	14 days	NOEC (behaviour/appearance)	56	Hamberger and Moser 2012
Earthworm *(Eisenia fetida)*	14 days	NOEC (mortality)	180	Hamberger and Moser 2012
Earthworm *(Eisenia fetida)*	14 days	LC_{50}	444	Hamberger and Moser 2012
Earthworm *(Eisenia fetida)*	56 days	NOEC (reproduction)	<18	Hamberger and Moser 2012
Earthworm *(Eisenia fetida)*	56 days	EC_{10} (reproduction)	11.2*	Hamberger and Moser 2012
Oat *(Avena sativa)*	14 days	NOEC (growth)	100	van der Hoeven et al. 1992
Oat *(Avena sativa)*	14 days	EC_{50} (growth)	353	van der Hoeven et al. 1992

Test organism	Duration of test	Endpoint	Value (mg/kg dry soil)	Reference
Oat *(Avena sativa)*	14 days	NOEC (survival)	> 1000	van der Hoeven et al. 1992
Oat *(Avena sativa)*	17 days	NOEC (seedling emergence)	320	van der Hoeven et al. 1992
Lettuce *(Lactuca sativa)*	14 days	NOEC (growth)	10	van der Hoeven et al. 1992
Lettuce *(Lactuca sativa)*	14 days	EC_{50} (growth)	128	van der Hoeven et al. 1992
Lettuce *(Lactuca sativa)*	14 days	NOEC (survival)	> 1000	van der Hoeven et al. 1992
Lettuce *(Lactuca sativa)*	17 days	NOEC (seedling emergence)	100	van der Hoeven et al. 1992

Abbreviations: EC_{50}, the concentration of a substance that is estimated to cause some effect on 50% of the test organisms; EC_{10}, the concentration of a substance that is estimated to cause some effect on 10% of the test organisms; LC_{50}, the concentration of a substance that is estimated to be lethal to 50% of the test organisms; NOEC, the no observed effect concentration is the highest concentration in a toxicity test not causing a statistically significant effect in comparison to the controls; LOEC, the low observed effect concentration is the lowest concentration in a toxicity test that caused a statistically significant effect in comparison to the controls.

* This endpoint was chosen as the critical toxicity value (CTV).

Sediment

Given the physical-chemical characteristics of MDA and its predicted environmental fate, sediment could be a receiving medium of the substance upon its release to the environment. Oligomeric components of pMDA show a higher affinity for sediments than the monomeric MDA. According to the EQC (2011) modelling (Table 6-1), nearly 30% of 4,4′-MDA and over 90% of the MDA oligomers are expected to partition to sediment upon release of 4,4′-MDA or pMDA to water. Partitioning to sediment from air is also expected, particularly for those pMDA oligomers with increased numbers of carbon rings (n greater than 3).

Toxicity of 4,4′-MDA was established in a number of sediment-dwelling species, including invertebrates and crustaceans. Unpublished ecotoxicological study reports conducted between 2000 and 2005 addressed toxicity of 4,4′-MDA to the non-biting midge (*Chironomus riparius*), the blackworm (*Lumbriculus variegatus*), and a

crustacean (*Hyalella azteca*) (Egeler and Ginzburg 2001; Egeler 2002; Egeler and Gilberg 2005). Key ecotoxicological endpoints for the tested species are summarized in Table 7-4. The sediment toxicity profile of 4,4′-MDA based on the chronic 28-day exposure of different species suggests that this substance is moderately toxic to the organisms tested.

Two studies testing chronic effects of 4,4′-MDA in the blackworm, *L. variegatus*, were carried out in 2001 and 2002 (Egeler and Ginzburg 2001; Egeler 2002). Endpoints studied included mortality, reproduction and biomass. It is noted that the results from the two studies showed variable sensitivity of the blackworm to exposure to 4,4′-MDA, with an approximately 10-fold difference in the toxicity level in the parallel endpoints. This lack of correspondence in the study results could be attributed to the differences in the experimental protocols of each study; both studies relied on the Phipps et al. (1993) method, but the 2002 study also followed OECD Guideline 218 (Sediment-Water Chironomid Toxicity Using Spiked Sediment). Overall, however, *L. variegatus* was observed to be the most sensitive species to 4,4′-MDA exposure, and the most sensitive endpoint was the LOEC of 3.75 mg/kg sediment (dw) for effects on biomass (Egeler 2002). The peat content of sediment used in the Egeler (2002) test was 5% (dry weight). Analysis of the test material was deemed not necessary, and the results are therefore based on nominal concentrations. The biomass, based on worm tissue dry weight and on ash-free dry weight, was significantly reduced in all treatments, compared to the control, as determined by analysis of variance (ANOVA) and subsequent Dunnett's T-test ($p \leq 0.05$).

Table 7-4. Summary of empirical data for sediment toxicity to invertebrates from 4,4′-MDA

Test organism	Duration of test	Endpoint	Value (mg/kg)	Reference
Non-biting midge *(Chironomus riparius)*	28 days	NOEC (emergence ratio)	500	Egeler and Gilberg 2005
Non-biting midge *(Chironomus riparius)*	28 days	LOEC (emergence ratio)	1000	Egeler and Gilberg 2005
Non-biting midge *(Chironomus riparius)*	28 days	EC_{50} (emergence ratio)	849	Egeler and Gilberg 2005
Non-biting midge *(Chironomus riparius)*	28 days	NOEC (development rate)	> 1000	Egeler and Gilberg 2005
Non-biting midge *(Chironomus riparius)*	28 days	LOEC (development rate)	> 1000	Egeler and Gilberg 2005
Blackworm *(Lumbriculus variegatus)*	28 days	NOEC (mortality)	> 60	Egeler 2002
Blackworm *(Lumbriculus variegatus)*	28 days	NOEC (reproduction)	3.75	Egeler 2002
Blackworm *(Lumbriculus variegatus)*	28 days	EC_{50} (reproduction)	14.1	Egeler 2002

Test organism	Duration of test	Endpoint	Value (mg/kg)	Reference
Blackworm *(Lumbriculus variegatus)*	28 days	NOEC (biomass)	<3.75	Egeler 2002
Blackworm *(Lumbriculus variegatus)*	28 days	LOEC (biomass)	3.75*	Egeler 2002
Blackworm *(Lumbriculus variegatus)*	28 days	EC_{50} (biomass)	42.6	Egeler 2002
Blackworm *(Lumbriculus variegatus)*	28 days	NOEC (reproduction)	25.2	Egeler and Ginzburg 2001
Blackworm *(Lumbriculus variegatus)*	28 days	LOEC (reproduction)	50.3	Egeler and Ginzburg 2001
Blackworm *(Lumbriculus variegatus)*	28 days	NOEC (biomass)	50.3	Egeler and Ginzburg 2001
Blackworm *(Lumbriculus variegatus)*	28 days	LOEC (biomass)	100.7	Egeler and Ginzburg 2001
Blackworm *(Lumbriculus variegatus)*	28 days	EC_{50} (biomass)	81	Egeler and Ginzburg 2001
Amphipod crustacean *(Hyalella azteca)*	28 days	NOEC (mortality)	41.3	Egeler and Gilberg 2005

Test organism	Duration of test	Endpoint	Value (mg/kg)	Reference
Amphipod crustacean *(Hyalella azteca)*	28 days	LOEC (mortality)	90.9	Egeler and Gilberg 2005
Amphipod crustacean *(Hyalella azteca)*	28 days	EC_{50} (mortality)	117.9	Egeler and Gilberg 2005
Amphipod crustacean *(Hyalella azteca)*	28 days	NOEC (amphipod length)	90.9	Egeler and Gilberg 2005
Amphipod crustacean *(Hyalella azteca)*	28 days	LOEC (amphipod length)	200	Egeler and Gilberg 2005
Amphipod crustacean *(Hyalella azteca)*	28 days	NOEC (total biomass)	90.9	Egeler and Gilberg 2005
Amphipod crustacean *(Hyalella azteca)*	28 days	LOEC (total biomass)	200	Egeler and Gilberg 2005
Amphipod crustacean *(Hyalella azteca)*	28 days	EC_{50} (total biomass)	134.8	Egeler and Gilberg 2005

Abbreviations: EC_{50}, the concentration of a substance that is estimated to cause some effect on 50% of the test organisms; LC_{50}, the concentration of a substance that is estimated to be lethal to 50% of the test organisms; NOEC, the no observed effect concentration is the highest concentration in a toxicity test not causing a statistically significant effect in comparison to the controls; LOEC, the low observed effect concentration is the lowest concentration in a toxicity test that caused a statistically significant effect in comparison to the controls.

* This endpoint was chosen as the critical toxicity value (CTV).

Wildlife

Mammals

Reports of studies addressing toxicity of MDA or pMDA to wild terrestrial mammals were not located in the published literature or from unpublished sources. However, laboratory-bred species typically used in experimental models addressing human health, such as rats and mice, are relevant to wild species. Numerous studies pertaining to effects of MDAs in mice and rats are described in the Health Effects Assessment section and in Health Canada (2013). These studies and established endpoints are considered applicable to certain wild mammalian species such as shrews, field mice, and other small mammals, as well as to other wildlife species with application of appropriate scaling corrections.

Birds

Toxicity of 4,4′-MDA resulting from a short-term exposure to the substance in food was established in the red-winged blackbird (*Agelaius phoeniceus)*. In the study, wild-trapped birds were preconditioned to captivity for 2 to 6 weeks and were usually dosed by gavage with solutions or suspensions of the test chemical in propylene glycol or occasionally by other oral dosing methods, including pellets or gelatin capsules. Since this publication is a compilation of results for several hundred chemicals, experimental details pertaining to 4,4′-MDA were not provided. Exposure duration was reported as 18 hours (ECHA c2007-2013a). Endpoints determined in the study included the LD_{50} for acute oral toxicity and the avian repellency value R_{50}. In addition, the acute avian hazard index (also known as the repellency/toxicity index) was also calculated for numerous chemicals to indicate the likelihood of acute oral poisoning occurrence in the wild. The LD_{50} for 4,4′-MDA was reported as 148 mg/kg, indicating a moderate toxicity of the test substance. The R_{50} was determined as greater than 1.00%. The hazard factor was not calculated for 4,4′-MDA, since the LD_{50} and R_{50} values were not established in other bird species tested in the study, a key aspect in determining a meaningful value or trend by the index. Key findings from the study for 4,4′-MDA are summarized in Table 7-5 below.

Table 7-5. Empirical data for toxicity for 4,4′-MDA birds

Test organism	Duration of test	Endpoint	Value (mg/kg)	Reference
Red-winged blackbird (*Agelaius phoeniceus*)	18 hours	LD_{50}	148	Schafer et al. 1983; ECHA c2007-2013a

Abbreviations: LD_{50}, the dose, i.e., concentration of a substance that is estimated to be lethal to 50% of the test organisms.

Overall, results from this study indicated that 4,4′-MDA is moderately toxic to birds following short-term exposure through ingestion.

7.1.1.3 Derivation of the predicted no-effect concentration (PNEC)

Given the known sources and uses of MDA, soil is considered to be the main receiving environmental compartment of these substances in Canada. For the soil compartment, the long-term 56-day EC_{10} for reproduction of earthworm (*Eisenia fetida*) of 11.2 mg/kg (dry soil) was the most sensitive valid experimental toxicity value and was therefore selected as the critical toxicity value (CTV). The predicted no-effect concentration (PNEC) was determined by dividing this value by an assessment factor of 10 (to account for interspecies and intraspecies variability in sensitivity), resulting in a value of 1.1 mg/kg (dry soil).

In Canada, given the known use and release patterns of 4,4′-MDA and pMDA, water is not expected to be a significant receiving medium for either substance. As a result, exposure to aquatic organisms is not expected. However, considering the importance of the aquatic compartment in the environment and the observations of high toxicity to certain aquatic organisms from exposure to MDA, an aquatic PNEC value was also derived. The 21-day EC_{50} value of 0.0149 mg/L determined in *D. magna* (Mitsubishi Chemical Safety Institute 2002b) is considered to be the CTV for MDA in the aquatic compartment. An application factor of 10 was applied to this CTV value (to account for interspecies and intraspecies variability in sensitivity), resulting in an aquatic PNEC of 0.0015 mg/L.

Similarly, a PNEC was also derived for the sediment compartment given that MDA exhibits low to moderate toxicity to certain benthic organisms. The CTV for MDA in sediment is considered to be the LOEC value of 3.75 mg/kg (dry sediment) for the blackworm *(Lumbriculus variegatus)* (ECHA c2007-2013a). A PNEC for sediment was derived by dividing this CTV by an application factor of 10 (to account for interspecies and intraspecies variability in sensitivity), resulting in a value of 0.375 mg/kg.

PNECs derived in this section are applicable to both 4,4′-MDA and pMDA.

A PNEC for wildlife was not developed. Typically 4,4′-MDA and pMDA do not distribute to air, and for that reason inhalation is not expected to be an exposure route for wildlife. These substances have low bioaccumulation potential, so wildlife exposure through the diet is also unlikely.

7.1.1.4 Summary of ecological effects of MDA

A moderate to high toxicity was observed for 4,4′-MDA and pMDA in aquatic organisms for both acute and chronic experimental exposures. Low to moderate toxicity to sediment-dwelling invertebrates, terrestrial plants, soil invertebrates, and birds was observed from acute and chronic studies.

7.1.2 MDIs

MDI substances in the MDI/MDA Substance Grouping include three monomers (4,4′-MDI, 2,4′-MDI, and 2,2′-MDI) and two mixtures (mixed MDI and oligomeric MDI (pMDI)). Empirical studies addressing toxicity of MDI substances to aquatic, terrestrial and sediment species were conducted for two substances in the MDI/MDA Substance Grouping: 4,4′-MDI and pMDI. Empirical studies for substances 2,4′-MDI, 2,2′-MDI, and mixed MDA were not identified in the published literature or from unpublished sources. However, given that 2,4′-MDI and 2,2′-MDI are very similar isomers of 4,4′-MDI, differing only in the positioning of either one or two isocyanate groups from the para to ortho position on the carbon rings, empirical data for 4,4′-MDI can be used as read-across for both 2,4′-MDI and 2,2′-MDI. A similar approach can be taken for mixed MDI, since it is a mixture of all three MDI monomers, 2,2′-MDI, 2,4′-MDI, and 4,4′-MDI.

On contact with water, MDI substances hydrolyze readily, forming polyureas, carbon dioxide and small amounts of MDA. In the numerous studies addressing the fate and effects of pMDI in water, polyureas are described as inert and biologically inactive compounds (Sendijarevic et al. 2004). Toxic effects to aquatic and benthic organisms associated with polyureas were indirect and resulted from the formation of polyurea layers that covered the sediment (see Empirical Studies for Other Environmental Compartments section).

Polyureas have high molecular weights and very low water solubilities, and bioavailability to the aquatic organisms is therefore expected to be limited. Ecotoxic effects stemming from exposure to oligomeric components of pMDI or the polymeric hydrolysis reaction products are expected to be less than and not exceed the effects from the monomeric components.

Toxic effects of 4,4′-MDA and pMDA (i.e., residual products of 4,4′-MDI and pMDI hydrolysis), determined through empirical studies on aquatic organisms, are discussed in the MDA section above. Evolution of carbon dioxide stemming from reaction of large quantities of pMDI, presumably in a spill situation, was shown to potentially create toxic microhabitats resulting in ecotoxic effects, especially in immobile benthic species. These effects are discussed in more detail in the Empirical Studies in Other Environmental Compartments section below.

7.1.2.1 Empirical studies for the aquatic compartment

MDI substances are highly reactive on contact with water because of the presence of isocyanate groups. pMDI is known to quickly hydrolyze to form polyureas, small amounts of MDAs, and carbon dioxide. However in laboratory tests, hydrolysis rates were observed to vary depending on the experimental conditions (Yakabe et al. 1999). Overall, it is expected that MDI substances will react rapidly in water, resulting in only a transient presence in the water medium and without building up to significant concentrations in the surrounding medium.

4,4′-MDI and pMDI were tested experimentally using several aquatic species, such as green algae, microorganisms, aquatic invertebrates, and fish. Fewer studies were available for 4,4′-MDI, as pMDI appears to have been tested more readily in ecotoxicological studies (study results for 4,4-MDI and pMDI are summarized in Tables 7-6 and 7-7, respectively). Since pMDI is composed of approximately 50% 4,4′-MDI (see Identity of Substances section), results from studies testing pMDI can also be used as read-across for 4,4′-MDI. Effects of pMDI from a simulated accidental pollution event were also studied using artificial ponds, or mesocosms, that contained organisms from different trophic levels, including phytoplankton, zooplankton, macrobenthos, fish and macrophytes (Heimbach et al. 1996).

Three studies for 4,4′-MDI, conducted in 1977, are summarized on the European Chemicals Agency website (ECHA c2007-2013c). Species tested included two invertebrates (a water flea [*D. magna*] and a snail [*Limnea stagnalis*]), and one fish (zebrafish [*B. rerio*]). Available study summaries lacked experimental details, and neither the test concentrations of 4,4′-MDI nor the experimental protocols were described (ECHA c2007-2013c). In all three studies, the preparations of the test substance were found to undergo a heterogenous reaction, with precipitation of an insoluble hydrolyzed reaction product. 4,4′-MDA was detected in the test water at approximately 4 mg/L after the test. The 24-hour NOEC was the only value reported in all three studies and was the same for the three species tested, i.e., greater than or equal to 500 mg/L (ECHA c2007-2013) (see Table 7-6).

Toxic effects of pMDI were established in green algae (*D. subspicatus*) in a study conducted in 1994 according to OECD Guideline 201 (Alga, Growth Inhibition Test). This study is summarized on the European Chemicals Agency website (ECHA c2007-2013c). pMDI was tested at only a single concentration of 1640 mg/L, and after 3 days of exposure no growth inhibition of algae was observed. The NOEC and EC_{50} were therefore assigned as greater than or equal to 1640 mg/L, and greater than 1640 mg/L, respectively (see Table 7-7). Compositional information of pMDI was not provided in the study summary (ECHA c2007-2013c).

A 1986 unpublished study addressing effects of pMDI in microorganisms (from activated sludge), water flea (*D. magna*) and zebrafish (*B. rerio*) was submitted to Environment Canada (Caspers et al. 1986). In addition to the ecotoxicological effects of pMDI, the influence of pMDI dispersion in the test medium on its toxic behaviour was demonstrated in the study with *D. magna*. Generally, in all tests, pMDI could not be dispersed sufficiently and uniformly in the water, likely due its tendency to hydrolyze and form solid polyurea (Caspers et al. 1986). When dispersed using a high-speed shearing method, pMDI was at least an order of magnitude more toxic to *D. magna* than when dispersed using a magnetic stirrer. Therefore, efficiency of dispersion of pMDI in water appeared to influence its potential to cause adverse effects in the exposed organisms. However, it is noted that high-speed shearing is not representative of typical environmental conditions or practical situations.

Effects on the respiration rate of microorganisms found in activated sludge were determined following exposure to pMDI at concentrations of 1, 10 and 100 mg/L for 3 hours (Caspers et al. 1986). pMDI was found not to be appreciably toxic to microorganisms in activated sludge, as 0% inhibition of the respiration rate was observed at the highest concentration tested. The EC_{50} value for respiration inhibition was therefore assigned as greater than 100 mg/L (Caspers et al. 1986) (see Table 7-7).

Acute and chronic toxic effects to waterflea (*D. magna*) were also determined (Caspers et al. 1986). In the acute toxicity study, pMDI was tested using two methods of dispersion of the test substance in the test medium. In one test, pMDI was dispersed in water by high-speed shearing for 1 minute at concentrations ranging from 0.5 to 500 mg/L. In the second test, pMDI was dispersed in water using a magnetic stirrer for 30 minutes, and at concentrations ranging from 20 to 1000 mg/L. The 96-hour EC_{50} value of 130 mg/L for immobilization was calculated from the first set of data when the test substance was dispersed by the high-speed shearing method. An EC_{50} value could not be determined from the second test as adverse effects were not observed in *D. magna* at the highest concentration tested. As mentioned above, this result suggested that efficiency of pMDI dispersion in the test medium influences its potential to cause adverse effects in the test organism.

In the chronic study, reproductive effects of pMDI were studied in *D. magna* at substance test concentrations of up to 10 mg/L (Caspers et al. 1986). The test substance was dispersed in water by slight stirring with a glass rod and a magnetic stirrer for 1 hour. No negative effects on reproduction were detected following 21 days of exposure at the highest pMDI concentration tested of 10 mg/L. Consequently, the NOEC value for reproduction was assigned as greater than 10 mg/L.

Finally, acute toxic effects of pMDI in the zebrafish were also determined in this study (Caspers et al. 1986). pMDI was tested at concentrations of up to 1000 mg/L and was dispersed in the test media by stirring. Formation of solid droplets, thought by the study authors to be undissolved test material, was observed, and it was noted that they provoked curiosity of the fish. Mortality was not observed at the highest pMDI concentration tested of 1000 mg/L following 96 hours of exposure. Therefore, the NOEC was reported as greater than 1000 mg/L. However, it was generally noted that harmful effects on fish caused by oral ingestion or by mechanical damage of sensitive body tissues (e.g., gills) could not be excluded. Specific examples of such effects and the number of fish affected were not provided in the study report (Caspers et al. 1986).

Acute toxicity of pMDI was also previously determined in a 1982 study using the Japanese rice fish (*O. latipes).* The study is summarized on the European Chemicals Agency website (ECHA c2007-2013c). In this study, pMDI was tested according to a Japanese protocol, Nichi-Nou-Sei B2735, in semi-static conditions. pMDI was tested at 3000 mg/L (reported as ppm). The test substance was dispersed in water by stirring, and precipitation to the bottom of test vessels was observed. It was also noted that 2 hours after addition of pMDI to the test medium, white powder appeared on the water surface and attached to fins of fish. No mortality was observed in the test fish. The

NOEC was reported as greater than 3000 mg/L following 48-, 72- and 96-hour exposure to pMDI (ECHA c2007-2013c).

Overall, results from aquatic toxicity studies presented in Tables 7-6 and 7-7 suggest that neither 4,4′-MDI nor pMDI are appreciably toxic to aquatic species following acute exposure. Toxic effects are increased when pMDI is dispersed efficiently in the test medium, as was demonstrated by the use of different dispersion methods in the acute *D. magna* study (Caspers et al. 1986). Lastly, consistent results for acute toxicity were observed in the two fish species tested, the zebrafish and Japanese rice fish, indicating a similar level of sensitivity to the test substance in the two fish species.

It is expected that these observations would also hold for the other MDI substances in the MDI/MDA Substance Grouping, mixed MDI and monomers 2,2′-MDI and 2,4′-MDI, given the structural similarities of the substances in the grouping.

Table 7-6. Summary of empirical aquatic toxicity data for 4,4′-MDI

Test organism	Duration of test	Endpoint	Value (mg/L)	Reference
Water flea *(Daphnia magna)*	24 hours	NOEC	≥ 500	Caspers et al. 1986
Snail *(Limnea stagnalis)*	24 hours	NOEC	≥ 500	ECHA c2007-2013c[NAR]
Zebrafish (*Brachydanio rerio)*	24 hours	NOEC	≥ 500	Caspers et al. 1986

Abbreviations: NAR, not available for review; NOEC, the no observed effect concentration is the highest concentration in a toxicity test not causing a statistically significant effect in comparison to the controls.

Table 7-7. Summary of empirical aquatic toxicity data for pMDI

Test organism	Duration of test	Endpoint	Value (mg/L)	Reference
Activated sludge	3 hours	EC_{50} (respiration inhibition)	> 100	Caspers et al. 1986, ECHA c2007-2013c
Green algae (*Desmodesmus subspicatus*)	3 days	NOEC; EC_{50} (growth rate)	1640; > 1640	ECHA c2007-2013c[NAR]
Water flea (*Daphnia magna*)	96 hours	EC_{50} (immobilization)	130*	Caspers et al. 1986, ECHA c2007-2013c
Water flea (*Daphnia magna*)	21 days	NOEC (reproduction)	> 10	Caspers et al. 1986
Japanese rice fish (*Oryzias latipes*)	48–96 hours	NOEC (mortality)	> 3000	ECHA c2007-2013c[NAR]
Zebrafish (*Brachydanio rerio)*	96 hours	NOEC (mortality)	> 1000	Caspers et al. 1986

Abbreviations: NAR, not available for review; EC_{50}, the concentration of a substance that is estimated to cause some effect on 50% of the test organisms; NOEC, the no observed effect concentration is the highest concentration in a toxicity test not causing a statistically significant effect in comparison to the controls.

* This endpoint was chosen as the critical toxicity value (CTV).

A series of acute exposure studies to pMDI on mollusks, crustaceans, and fish were briefly described in Brochhagen and Grieveson (1984). Results from these studies are not featured in Table 7-7 because experimental details provided in the publication were sparse. Snails, daphnids, and fish were exposed to pMDI at a single concentration of 500 mg/L for 24 hours. For all three species, LC_{50} values were reported to be greater than 500 mg/L. Carp were also exposed to a lower concentration of pMDI of 10 mg/L (reported as 0.001% pMDI) for 35 days. It was reported that the test fish showed signs of behaviour disturbance, 7 fish died and one was sacrificed throughout the course of the study. Upon histological examination, no systemic effects on the liver or kidney were noted. However, the fish showed evidence of integument irritation, which was thought to favour the entry of pathogens (Brochhagen and Grieveson 1984). It is noted that effects observed in carp following the longer term 35-day exposure to pMDI are more intense than those observed in the short-term studies in fish exposed to much higher pMDI concentrations (see Table 7-7 above).

In addition to the laboratory studies conducted to study pMDI effects on individual aquatic species (see Table 7-7), broader studies investigating the effects of pMDI on aquatic ecosystems have been done. The goal of these studies was to evaluate effects of pMDI stemming from environmental spills (Heimbach et al. 1996; Brochhagen and Grieveson 1984).

According to Brochhagen and Grieveson (1984), experiments were carried out where pMDI (reported to be composed of a mixture of monomeric MDI with oligomers) was added at the concentration of 50 mg/L (reported as 0.005% MDI) to marine and river model systems. MDI was observed to rapidly convert to polyureas. Concentrations of MDI and corresponding amines were monitored over 30 days; MDI concentration fell to 5% of the initial value within one day, and amine concentrations were typically 0.4% less than the theoretical amount of diamine that would be produced by total hydrolysis of diisocyanate. It was reported that all forms of zooplankton and phytoplankton were reduced in number, except the photosynthetic chlorophyta. The maximum reduction in number reached 75% and occurred about 10 days after MDI treatments (Brochhagen and Grieveson 1984).

In a more recent study, effects of a simulated accidental pollution event with pMDI in the aquatic environment were investigated by means of artificial ponds (Heimbach et al. 1996). The artificial ponds were designed to model standing freshwater ecosystems and included natural lake sediment.

Ponds were populated with a number of planktonic and benthic species, a limited number of fish (kept in cages to maintain the prey-predator balance), and macrophytes to establish natural communities with prey and predator conditions. Two ponds were treated with pMDI at concentrations of 1000 and 10 000 mg/L, and the third pond was left untreated to serve as a control. Ponds were investigated for a period of 112 days. pMDA was reported to be composed of approximately 45% of 4,4′-MDI, as well as higher homologs and isomers and appeared as a viscous liquid that, when applied to the ponds, reacted with water to produce polyureas and carbon dioxide and formed a uniform layer on top of the sediment (Heimbach et al. 1996). At the end of the study, measurements of MDI and MDA in pond waters were below the analytical detection level of 0.004 to 0.01 mg/L (4 to 10 µg/L). Effects on the mesocosm organisms, including phytoplankton and zooplankton communities, and on a variety of species of fish and macrophytes were observed. Application of pMDI at rates up to 10 000 mg/L, representative of a spillage scenario, was observed to cause moderate, but transient, biological effects on the exposed aquatic species. Hydrolysis of pMDI resulted in changes in the pond water chemistry, and the new conditions enhanced the growth of certain phytoplankton groups and macrophytes and, in turn, increased oxygen production in the ponds. However, at the highest concentration tested, an imbalance in the ecosystem prey-predator relationships was noted where changes in the water chemistry and phytoplankton populations affected zooplankton, which had detrimental effects on the top predator, the rainbow trout. Overall, it is expected that an affected aquatic system should recover quickly, even though a spillage could result in some alteration of species composition over a limited area (Brochhagen and Grieveson 1984).

Effects in benthic organisms were also observed and these are discussed in the sediment subsection of section 7.1.2.2.

7.1.2.2 Empirical studies for other environmental compartments

Soil

Given that MDI substances are highly reactive in water, it is expected that in soil, where a degree of moisture is prevalent, they will undergo a hydrolysis reaction, forming polyureas, some MDAs and carbon dioxide. Therefore, as with the water compartment, it is expected that MDI substances will have a transient presence in soil, without building up to significant concentrations.

Effects of pMDI were determined for the earthworm *Eisenia fetida* in a 1992 study conducted according to OECD Guideline 207 (Earthworm, Acute Toxicity Test) (Study Submission 2012h). The test substance was reported to consist of 40 to 50% of 4,4′-MDI, 2 to 4% of 2,4′-MDI, and 40 to 60% of the 3-ring isomers, as well as traces of impurities. This study is also summarized on the European Chemicals Agency website (ECHA c2007-2013c) and is associated with CAS RN 9016-87-9. Earthworms were exposed to the test substance at a concentration of 1000 mg/kg (dry soil) for 14 days in artificial soil. The NOEC values were estimated by comparing effects on mortality and weight as well as the visual assessment of the behaviour and appearance of the exposed animals with those of the control animals. No effects on mortality, weight increase, or behaviour and appearance were observed after 14 days of exposure to pMDI. Therefore, the NOEC values for the ecotoxicological endpoints were assigned as greater than or equal to 1000 mg/kg dry soil (See Table 7-8). It was noted in the study that since MDI reacts with water, the absence of effects may have been due to its disappearance from the test medium (Study Submission 2012h).

Ecotoxic effects of pMDI were also studied in two plant species: oats (*Avena sativa)* and lettuce (*Lactuca sativa)* (van der Hoeven et al. 1992). The study was conducted according to OECD Guideline 208 (Terrestrial Plants Test: Seedling Emergence and Seedling Growth Test) and effects on seedling emergence, growth, and survival were examined over 14 days. The pMDA used in the study was reported to be composed of 40 to 50% of 4,4′-MDI, 2 to 4% 2,4′-MDI, and 40 to 60% 3-ring isomers. The test substance was applied at only one concentration of 1000 mg per kg of dry soil. Test samples were prepared in steps, where coarse sand was first coated with pMDI previously mixed with acetone. The acetone was then removed by drying for two days in the fume hood, following which pMDI containing sand was mixed in a 1:1 ratio with agricultural soil to reach the desired sample concentration of 1000 mg/kg dw. Demineralized water was added (ratio 1:1 on weight basis), and the final moisture content was 50%. Soil pH remained at 6.3 to 6.4 throughout the study. Results of the tests indicated that exposure of oats and lettuce to pMDI at the test concentration of 1000 mg/kg dw did not cause significant effects on the parameters studied. The EC_{50} and NOEC values for seedling emergence, growth, and survival were determined to be greater than or equal to 1000 mg/kg (dry soil). Therefore, this study suggests, on the

basis of a sub-chronic exposure of two weeks, that pMDI is likely to be of low toxicity to plants.

Table 7-8. Summary of empirical soil toxicity data for pMDI

Test organism	Duration of test	Endpoint	Value (mg/kg dry soil)	Reference
Earthworm *(Eisenia fetida)*	14 day	NOEC (mortality, weight increase, or behaviour and appearance)	≥ 1000	Study Submission 2012h, ECHA c2007-2013c
Oat *(Avena sativa)*	14 day	NOEC, EC_{50} (growth); NOEC (seedling emergence); NOEC (survival)	≥ 1000	van der Hoeven et al. 1992
Lettuce *(Lactuca sativa)*	14 day	NOEC, EC_{50} (growth); NOEC (seedling emergence); NOEC (survival)	≥ 1000	van der Hoeven et al. 1992

Abbreviations: NOEC, the no observed effect concentration is the highest concentration in a toxicity test not causing a statistically significant effect in comparison to the controls; EC_{50}, the concentration of a substance that is estimated to cause some effect on 50% of the test organisms

In summary, ecotoxicity studies were performed for a soil invertebrate, an earthworm, and two plant species. Very low toxicity was observed in all studies after a short-term exposure time of two weeks. Since pMDI is a very reactive substance, lack of effects in soil could be the result of the rapid degradation and subsequent disappearance of pMDI from the test samples. There was no indication in the available study summaries that the concentration of the test substance was maintained throughout the course of both studies, and test substance concentrations during and at the end of the study were not provided.

Sediment

Effects of pMDI exposure on benthic organisms were studied in the context of an accidental pollution event (Heimbach et al. 1996). In the study, artificial ponds, complete with sediment and populated with aquatic and benthic organisms, were treated with high pMDI concentrations of 1000 mg/L and 10 000 mg/L and studied for 112 days.

Application of pMDI to the artificial ponds, especially at the high dose of 10 000 mg/L, had a severe effect on the populations of benthic organisms and affected both the treated and untreated areas as the test substance continuously moved across the sediment. Ecotoxic effects of pMDI were indirect; an MDI layer that formed over sections of the sediment created microhabitats where organisms either starved as a

result of physical obstruction or died due to the lack of oxygen or toxic levels of carbon dioxide. The reacting pMDI caused the populations of the most abundant benthic organisms—the Oligochaeta (Tubificidae and Naididae), Bivalvia and Diptera—to become nearly eliminated in the high-dosed pond 7 to 14 days after treatment. Some recovery of Tubificidae, Naididae and Diptera populations was observed. However, the population of Bivalvia, whose life cycle is longer than those of other benthic species, did not recover and was not detected anywhere in the high-dosed pond at the end of the study. It was also noted that the mobile Gastropoda were not affected by the pMDI treatment. In the low-dosed pond, benthic organisms in the untreated section of the pond were not affected since only a minor fraction of the test substance and its reaction products reached this area. Potential effects resulting from pMDI exposure in the treated sections of the ponds were not described by Heimbach et al. (1996). However, the MDI layer was larger in the treated section of the pond, covering approximately 30% more of the sediment than in the untreated sections. Therefore, effects observed in the treated sections are expected to be similar and likely more severe that those observed in the untreated sections of the ponds.

In summary, when added to artificial ponds at high concentrations reflecting a spill situation, pMDI was observed to form a hardened inert polyurea layer at the top of the sediment. This had a severe impact on the exposed benthic organisms in the artificial ponds, where the physical obstructions from the polyurea layer, lack of oxygen, and toxic carbon dioxide concentrations created by the hydrolysis reaction of pMDI caused several of the residing benthic populations to plummet. It is noted that in Canada, environmental spills of MDIs occurred infrequently in the past several years (one in 1999 and one in 2001), were minor to moderate in nature, and did not result in contamination of any aquatic systems. Given this information, exposure of benthic organisms to MDIs as a result of an accidental spill is therefore not likely in Canada.

Wildlife

Mammals

Reports of studies addressing toxicity of MDI substances to wild terrestrial organisms including mammals were not located in the published literature or from unpublished sources. However, laboratory-bred species used in experimental models addressing human health, such as rats and mice, are relevant to wild species. These data are considered applicable to certain wild mammalian species, such as shrews, field mice, and other small mammals, as well as to other wildlife species with application of appropriate scaling criteria.

Because of the observed toxicity of MDI from exposure in air, subchronic and chronic inhalation studies carried out in small mammals such as rats are of particular interest. These studies and established effects are summarized in the Health Effects Assessment section and in Health Canada (2013). Specifically, in studies by Reuzel et al. (1990 and 1994a), the lowest observed adverse effect concentration (LOAEC) value of 1 mg/m^3 was established on the basis of a chronic inhalation exposure of rats to pMDI. Observed effects at this exposure concentration included respiratory tract effects

(an increase of hyperplasia) in both the pulmonary and extrathoracic regions (see Health Canada 2013).

7.1.2.3 Derivation of the PNEC

Potential exposure from inhalation of MDI substances in the MDI/MDA Substance Grouping can be presumed given the known use and release patterns of these substances in Canada. Therefore, a PNEC value was derived from the chronic LOAEC value of 1 mg/m^3 (as the most sensitive valid experimental LOAEC for an animal exposed to pMDI [Reuzel et al. 1990, 1994a] for rats) by dividing this value by an assessment factor of 10 (to account for interspecies and intraspecies variability in sensitivity), resulting in a value of 0.1 mg/m^3. In the numerous rat studies, irreversible adverse effects were observed from long-term exposures at the inhalation concentrations of approximately 1 to 10 mg/m^3 (Hoymann et al. 1995; Reuzel et al. 1990, 1994a; Buschmann et al. 1996; Waalkens-Berendsen et al. 1992) (see Health Canada 2013).

Limited toxicity data for pMDI substances in the grouping were available for water and soil compartments. In water, only one acute EC_{50} value of 130 mg/L for daphnids was available (see Table 7-7), and other studies indicated no effects at concentrations tested. A rapid hydrolysis reaction of MDIs is expected on contact with water, resulting in only a transient presence of pMDIs in the aquatic compartment. It is recognized that ecotoxic effects from exposure to MDIs in water may be the result of contribution by MDAs formed through hydrolysis. Nonetheless, considering the EC_{50} of 130 mg/L as the CTV of MDIs for the aquatic compartment and applying an assessment factor of 10 (to extrapolate from short-term median effects to long-term no effects), a PNEC value of 13 mg/L is obtained. In soil, all studies showed no effects at concentrations tested (see Table 7-8). Therefore, a PNEC value was not derived for this compartment.

PNECs derived in this section are applicable to both MDI monomers and pMDI.

7.1.2.4 Summary of ecological effects of MDIs

Overall, results from aquatic toxicity studies presented in Tables 7-6 and 7-7 suggest that neither 4,4′-MDI nor pMDI are appreciably toxic to aquatic species following acute and chronic exposure. Similarly, moderate toxicity from exposure to 4,4′-MDI and pMDI was observed in the mammalian studies (test organisms used in these studies can be considered as surrogates to small terrestrial mammals). Low toxicity of pMDI exposure on the soil organism, the earthworm, was observed. In contrast, pMDI was observed to indirectly impact certain populations of benthic organisms in exposure studies simulating accidental spill conditions. Although the impacts on select groups of organisms, such as the immobile bivalves, were severe, they can be considered transitory, as generally populations showed signs of recovery over time.

It is expected that observations of the level of toxicity would be similar for the other substances in the MDI subgroup (mixed MDI, and monomers 2,2′-MDI and 2,4′-MDI), given the structural similarities of these substances.

7.2 Ecological Exposure Assessment

Environmental monitoring data for MDA and MDI substances in the grouping have not been identified in Canada. Canadian environmental concentrations of MDA and MDI substances in the grouping have therefore been estimated on the basis of available relevant information.

Data concerning the concentrations of some of the substances in the MDI/MDA Substance Grouping in air, water and sediment have been identified for other countries (see Appendix D).

Exposure characterization of MDA and MDI substances in the grouping is focused on key exposure scenarios that stem from main environmental releases of these substances. In general, the magnitude of releases is a direct function of the quantity of a substance manufactured or used and its applicable emission factors. In cases where industrial releases are similar in quantity to consumer and/or commercial releases, the former normally results in higher levels of environmental exposure than the latter. This is because industrial releases are concentrated at a limited number of sites while consumer and/or commercial releases are dispersed across the country.

7.2.1 MDAs

In Canada, a small number of companies are known to blend an industrial product containing 4,4′-MDA or pMDA, which is then sent for use in different industrial sectors. The 4,4′-MDA-containing blend is used only as a catalyst and is not present in the final product. Following the use of the 4,4′-MDA-blended product, the spent solution is recovered and sent for waste treatment (Environment Canada 2012a). Releases of 4,4′-MDA to the environment are therefore considered to be minimal. pMDA-containing blends are used as a coating for machine parts for industrial applications (Environment Canada 2012a). The pMDA-coated machine parts are expected to be used in an industrial setting for many decades, with negligible releases of pMDA to the environment (Environment Canada 2012a). Therefore, the potential for environmental releases of MDA substances or products containing MDAs during their processing and application is minimal. Given this information and the very limited potential for environmental releases in this case, it is considered that a quantitative exposure scenario is not needed.

7.2.2 MDIs

Exposure to MDI substances (and MDA created through conversion of MDI) was estimated in the form of predicted environmental concentrations (PECs) resulting from the use of MDI substances in the engineered wood industry as described in the

following sections. Potential of exposure from the engineered wood industry is representative of a high-release industry. MDI substances can also be emitted to air during the production of foam or adhesive application. Literature and emission reporting guidelines indicate that releases to air from these types of industrial production are less by an order of magnitude compared to releases from the engineered wood industry (Allport et al. 2003; Acton 2001; ACC 2012a).

Facilities that use MDI substances to manufacture OSB are considered to represent a high level of environmental exposure because MDI is used in large quantities at a limited number of facilities. The principal media for release from that industry is to air, with the highest estimated emission factor of 0.027% (NCASI 2012). Concentrations in the environment have been estimated using SCREEN3 (1995); inputs and results are described in the text below.

Although a large number of Canadian companies are involved in the polyurethane industry, this scenario was not selected for determining a quantitative exposure estimate. The quantity of MDI used by a single polyurethane facility varies from a few kilograms to 2 million kilograms. It can be assumed that more than 60 Canadian users of MDI will use between 50 000 and 2 000 000 kg of MDI in one location. However, the quantity of MDI assumed to be released at each polyurethane facility is expected to be below quantities released by large OSB facilities across the country (Environment Canada 2012a).

PECs are based on the available information on use quantities of the MDI/MDA substances in the grouping, sector-specific emission factors, and characteristics of the receiving environment. Therefore, PECs were estimated for the air and soil compartments only. MDI substances are primarily released to the air compartment. In soil, atmospheric deposition of MDI in the vicinity of emitters and subsequent chemical transformation to MDA may result in soil exposure of MDA. Given the known use patterns of both MDA and MDI substances in the grouping, no direct releases are expected to the water compartment. Air deposition of MDI substances into water bodies is also expected to be very limited, and on contact with water, MDIs are expected to break down rapidly.

In Canada, direct consumer or commercial uses of MDA or MDI are expected to result in diffuse releases, and consequently low environmental substance concentrations. For that reason, release scenarios for such uses have not been further investigated.

7.2.2.1 Air

As MDI substances can be used by industrial facilities and are reported to be released to air, the US EPA model SCREEN3 was selected to estimate a generic 1-hour maximum concentration surrounding a hypothetical facility (SCREEN3 1995). SCREEN3 is a screening tool that requires fewer and less refined inputs than other more complex models. However, to ensure the use of SCREEN3 was appropriate for MDI, technical particularities of the industry have been considered in the model entries.

The selected scenario is designed to provide an estimate based on conservative assumptions regarding the amount of substance used and released by the facility, and the facility and environmental setting where the releases occur. The inputs used to calculate the PEC surrounding the facility and the output of the model are presented in Appendix E. Assuming a maximum release rate of 0.31 kg/h (based on NCASI 2012) from a hypothetical OSB facility which uses 10 million kg of MDI substances (the upper range of the reported quantities used at any single facility in Canada; Environment Canada 2012a), the SCREEN3 estimates for the maximum 1-hour concentrations at 100, 200, and 1000 m away from the source were 11.44, 12.76, and 5.618 µg/m^3, respectively. The concentration of 12.76 µg/m^3 at 200 m is used as the PEC in the ecological exposure assessment and is expected to be higher than actual air concentrations resulting from any Canadian facility currently using MDIs. Therefore, this PEC is a highly conservative estimation. Nonetheless, the SCREEN3 model estimates are comparable to the measured MDI concentrations from stack emissions for non-Canadian facilities (listed in Appendix D).

7.2.2.2 Deposition to soil and water

For industrial facilities using substances in the MDI subgroup, releases to air are based on volatilization under conditions of high pressure and temperature. Although all MDIs have low vapour pressures, monomeric MDIs would be the predominant species released to air as they have the highest relative vapour pressures of all the MDI substances and substance components. The deposition rate of MDI monomers surrounding an industrial facility was estimated using the calculation presented in Tury et al. (2003). The ambient air concentration and resulting deposition flux of gaseous and aerosol-bound substance to soil was modelled by Tury et al. (2003) using the Operational Priority Substances (OPS) model of the European Union System for the Evaluation of Substances (EUSES). The model assumes that releases are from a low building with no stack. Standardized exposure estimation based on the Gaussian plume model OPS was used by Tury et al. (2003) to carry out a default calculation of the concentration of MDI and TDI in air and deposition flux to soil near a point source based on a given source strength. They obtained an annual average deposition rate for MDI of 9 µg/m^2/yr over a 1-km^2 area from the emitter, for a plant with a continuous release of MDI of 8.8 kg/yr. The use of this default calculation—linearly scaled to a hypothetical site that uses 10 million kg/yr and has an emission factor to air of 0.027%—results in an estimated annual average deposition rate of 2.8 mg/m^2/yr of MDI monomer. This is assumed to be a worst-case Canadian scenario. The deposition of vapour and aerosol fractions, as accounted for by the model, would occur via wet (e.g., rainwater) and/or dry deposition processes that may be specific to local conditions. The OPS model is based on realistic average atmospheric conditions obtained from a 10-year data set of weather conditions for the Netherlands. In addition, the deposition of MDI, particularly under wet conditions (i.e., presence of condensed phases, such as rain drops, fog or clouds), would likely result in some conversion to corresponding amines (i.e., MDA). However, since the deposition rate is relatively low and confined to the area in the vicinity of the plant, it is not expected that the resulting MDA soil concentrations would be greater than 0.023 mg/kg soil in the top 10 cm of soil, accounting for all normal

losses to degradation and soil diffusion (Soil Model 2005). This estimate of steady-state soil concentration is based on an assumption of a 2.8 mg/m^2/yr deposition rate over 10 000 m^2 of soil. Furthermore, it is meant to represent a worst-case scenario as it assumes that 100% of MDI will convert to MDA upon contact with moisture. It is expected that short-term fluxes to soil may fluctuate from this average because of factors including production cycles, plant stack height, local topography, and weather conditions, such as wind and precipitation, controlling the deposition processes. In addition, it is noted that air concentrations of MDIs estimated by means of OPS modelling based on Tury et al. (2003) are similar and comparable to the estimates obtained from SCREEN3. However, calculations based on Tury et al. (2003) were considered more appropriate than SCREEN3 for estimation of MDI concentrations in air that could deposit to soil because they included deposition rates. SCREEN3 results are not considered in the calculation of resulting soil concentrations and were generated merely to validate OPS modelling.

Deposition of MDIs to water bodies from airborne releases is expected to be limited. However, if the emitter were located near a water source such as a lake or a river, it is possible that MDI released to air may deposit/partition to the surface water. Given that MDIs rapidly hydrolyze, they are short-lived in the aquatic environment and thus are not expected to build up to significant concentrations. On contact with water, MDIs typically convert to polyureas and residual amines. Resulting residual MDA concentrations in surface waters would likely be low considering the high dilution capacity in typical surface waters compared to the deposition rate of a substance. Presently, models that would estimate substance concentrations in water resulting from deposition of MDAs are not available. Therefore, the upper end of the range of concentrations measured in Japanese waters in 2008 of 0.02 µg/L (CHRIP 2008) (see Appendix D, Table D-2) is used as a conservative estimate of a PEC in Canadian waters.

7.2.3 Ecological exposure summary

In summary, there is very limited potential for environmental exposure to MDA through its direct use. Instead, exposure to MDA is more likely to result from conversion of MDI released to the environment. MDI is primarily released to air through industrial use in the manufacture of polyurethane or engineered wood products such as OSB. Exposure analyses were based on OSB mills, as they are expected to have the highest releases of all industrial uses. Using SCREEN3 modelling, a PEC for the concentration of MDI in air at 200 m from an OSB facility was estimated as 0.013 mg/m^3 (12.76 µg/m^3). Deposition of airborne MDI to soil was estimated using the OPS model, and was calculated to occur at a rate of 2.8 mg/m^2/yr. Conservatively assuming a 100% conversion rate of MDI to MDA upon contact with soil moisture, a PEC for MDA in soil of 0.023 mg/kg was determined. A PEC could not be modelled for concentrations of MDA in water or sediment resulting from deposition and conversion of MDI. Instead, the available upper end of the range of concentrations measured in Japanese surface waters of 0.02 µg/L was used as a conservative estimate for a PEC in Canadian waters.

7.3 Characterization of Ecological Risk

7.3.1 Risk quotient analysis

The low volumes of MDA imported into Canada, along with information showing that its uses are generally confined to a small number of industrial operations in Canada, indicate a low potential for widespread releases into the Canadian environment. Given that the known MDA use and release patterns in Canada indicate a low potential for direct releases of MDA into air, soil or water, risk quotients were not calculated for direct releases of MDA into any environmental compartments. However, there may be an indirect source of MDA to the Canadian environment through release and conversion of MDIs.

A risk quotient analysis, integrating realistic worst-case and conservative estimates of exposure with ecotoxicity information, was performed for MDI in air to determine whether there is potential for ecological harm in Canada. The site-specific industrial scenario considered actual emission sources resulting from the manufacture of OSB (presented previously in the Ecological Exposure Assessment section). This yielded a maximum PEC for MDI in air of 0.013 mg/m^3. A PNEC for MDI was derived from the chronic inhalation toxicity value for small mammals of 0.1 mg/m^3 (see the Ecological Effects section). The resulting risk quotient (PEC/PNEC) is 0.13. Therefore, harm to terrestrial mammals from inhalation exposure is unlikely at this industrial site.

MDI released to the air may be deposited onto soils, where it will rapidly undergo hydrolysis, forming polyureas and minor amounts of MDA. Given that MDA can persist in soil for a long period of time, there is the potential for exposure of terrestrial organisms to MDA. A risk quotient analysis, integrating realistic worst-case and conservative estimates of exposure with ecotoxicity information, was performed for the terrestrial/soil compartment to determine whether there is potential for ecological harm in Canada. The site-specific industrial scenario considered actual emission sources of MDIs resulting from the manufacture of OSB (presented previously in the Ecological Exposure Assessment section), and then estimated resulting concentrations of MDA in soil from conversion of deposited MDIs. Calculations for this scenario yielded a maximum PEC for MDA in soil of 0.023 mg/kg. A PNEC for MDA of 1.1 mg/kg dw was derived from the long-term toxicity value for the earthworm (see the Ecological Effects section). The resulting risk quotient (PEC/PNEC) is 0.02. Therefore, harm to terrestrial organisms from soil exposure to MDA is unlikely at this industrial site.

As with soils, there is the potential for indirect release of MDA to surface waters through the deposition of MDI substances released to air and their subsequent hydrolysis. Given that MDA could be present in water for a moderately long time, there is still a potential for exposure to aquatic organisms. Therefore, a risk quotient analysis, integrating realistic worst-case and conservative estimates of exposure with ecotoxicity information, was performed for the aquatic compartment to determine whether there is potential for ecological harm in Canada. The measured MDI concentration in Japanese surface waters of 0.02 µg/L (0.00002 mg/L) (see Appendix D, Table D-2) was considered as a conservative PEC for the Canadian environment. It was conservatively assumed that

the conversion rate of MDI to MDA is 100%. 4,4′-MDA showed low to moderate acute to sub-chronic toxicity in the aquatic organisms tested and exhibited high toxicity in chronic tests with the aquatic invertebrate *D. magna*. A PNEC of 1.5 µg/L (0.0015 mg/L) for MDA was derived from a chronic toxicity value of 0.015 mg/L for daphnids (see the Ecological Effects section). The resulting risk quotient (PEC/PNEC) is 0.01. Therefore, harm to aquatic organisms from exposure to MDA arising from the deposition of MDIs in surface waters is unlikely in Canada.

Table 7-9. Summary of risk quotients obtained for different media and exposure scenarios for MDI and MDA substances in the grouping

Media	Substance	Scenario	PNEC	PEC	RQ
Air	MDI	Site-specific industrial releases of MDIs to air from OSB manufacturing and consideration of exposure of wildlife to MDIs through inhalation	0.1 mg/m^3	0.013 mg/m^3	0.13
Soil	MDA	Site-specific industrial releases of MDIs to air from OSB manufacturing, deposition to soil, and conversion to MDA	1.1 mg/kg (dw)	0.023 mg/kg	0.02
Water	MDA	General scenario considering air deposition of MDIs to surface water, and conversion to MDA	0.0015 mg/L	0.00002 mg/L	0.01

7.3.2 Consideration of lines of evidence and conclusion

The approach taken in this ecological screening assessment was to examine various supporting information and develop conclusions based on a weight-of-evidence approach, using precaution as required under CEPA. Lines of evidence considered include results from a conservative risk quotient calculation, as well as information on persistence, bioaccumulation, toxicity, sources, fate, presence and distribution of the substances in the environment.

On the basis of the available sources and uses information for MDA in Canada, no direct releases of the substance to water, air or soil were identified. Releases of MDIs were identified primarily to air. MDA may be found in water and soil as a result of releases of MDIs into air, their deposition to surface waters and soil, and subsequent conversion to MDA in these environmental compartments. Discussion of ecological risk including a risk quotient analysis for MDA and MDI substances as a result of industrial uses of MDI is presented previously in section 7.3.1 for the air, soil, and water compartments. In all three compartments, the risk quotient analysis was less than 1.

MDIs are highly reactive substances and are expected to quickly transform to inert polyureas and minor amounts of MDA upon contact with water, including water present in soils. MDAs are expected to be present in soil and sediment for a long time and only moderately long in water, but they are expected to have a low bioaccumulation potential. Polyureas are also expected to have a low bioaccumulation potential. The high volumes of MDI substances imported into Canada, along with information on their uses, indicate a significant potential for widespread release into the Canadian environment, primarily to air during industrial use. Once released to the environment, they will be found mainly in vapour and aerosol form in air near point sources of emission, with transformation products including polyureas and possibly also MDAs formed upon contact with water, including condensed phases in air and soils.

Finally, the use of MDI substances in consumer and commercial products is not expected to lead to significant emissions to the environment because of the low magnitude and dispersed nature of any resultant emissions to air. In addition, most uses of MDI substances (e.g., DIY adhesives and sealants and spray polyurethane foam products) would not involve any liquid waste associated with their use. Therefore, risk quotients for air and water compartments were not calculated, as releases of MDIs stemming from consumer uses are considered negligible.

Numerous lines of evidence were considered in the characterization of ecological risk posed by MDA and MDI substances. They included reliable toxicological experimental data, known use and release patterns of MDA and MDI substances in Canada, predicted concentrations in the environment based on general and industrial exposure scenarios, and consideration of the potential conversion of MDIs to MDA in the environmental media. This information suggests that there is low risk of harm to organisms and the broader integrity of the environment in Canada from substances in the MDI and MDA grouping.

Although current use patterns and quantities of MDA in commerce are not of concern at current levels, there may be concerns if quantities were to increase in Canada, given the ecological effects associated with these substances.

7.3.3 Uncertainties in evaluation of ecological risk

There were uncertainties in the amount of conversion of MDI to corresponding MDA species when the substance deposits on soils or water. The concentration of MDI in the atmosphere and resultant concentration on surface soils, along with soil characteristics including moisture and degree of saturation, may impact this conversion. The assumption that 100% MDI converts to MDA is considered to be highly conservative and thus would likely lead to an overestimation of risk.

It is also unknown whether higher proportions of MDA would form from hydrolysis of MDI at lower disperse concentrations (such as from atmospheric deposition of MDI) and when there may not be a high enough concentration of MDI to polymerize into polyurea.

To date, studies addressing the hydrolysis reaction of MDI focus on higher MDI concentrations simulating a spill situation.

There are also uncertainties with regard to reaction rates of the heterogeneous hydrolysis reaction of MDI. The available information suggests that this reaction depends on mixing conditions, and given the natural variation in different aquatic environments (e.g., fast-flowing river versus stagnant marsh), varied rates of MDI hydrolysis or incomplete hydrolysis could be expected under certain conditions.

The use of various types and sources of diols or polyols (e.g., polyester polyol, ethylene glycol, castor oil) for the production of polyurethane foams may change the potential for degradation and resulting by-products, including MDA, thus creating some uncertainty in the amount of MDA that would be ultimately liberated during degradation of polyurethane foam in landfills. However, it is not expected that MDA would be a major degradation product under typical landfill conditions. Mitigating factors, including sorption to organic materials within landfills and removal during settling of organic matter during wastewater treatment, would minimize any potential MDA releases to water from degradation of polyurethane foam in landfills.

MDAs have shown high toxicity in certain aquatic invertebrates (i.e., in chronic toxicity tests with daphnids). Present use patterns of MDAs in Canada indicate no releases to water, and no estimates of water concentrations of MDA resulting from atmospheric deposition to surface waters could be determined. However, due to the large dilution capacity, diffuse input into surface waters from air deposition, along with the low conversation rate to MDA seen in laboratory experiments with MDI, it is expected that any resulting aquatic MDA concentrations would be very low. Monitoring data could be used to confirm this.

No information was available on the potential effects on vegetation of atmospheric emissions of MDI, which may cause the formation of a polymeric film which, in turn, can cause secondary physical effects in plants. Estimates of MDI atmospheric concentrations from the highest emitting facilities were determined to not cause any respiratory effects in sensitive wildlife species, and thus, secondary effects in plants at these concentrations may be unlikely.

8. Potential to Cause Harm to Human Health

8.1 Exposure Assessment

8.1.1 Environmental media and food

8.1.1.1 MDAs

No reports of measured concentrations of 4,4′-MDA or pMDA in environmental media or food in Canada were identified. 4,4′-MDA and pMDA are not reported to be manufactured in Canada, nor are they reported to be used for manufacturing of MDIs in Canada (Environment Canada 2012a). Industrial uses of 4,4′-MDA and pMDA are confined to a small number of operations, indicating a low potential for releases into the

Canadian environment. Given the low vapour pressure and high rate of atmospheric degradation, neither 4,4′-MDA nor pMDA are expected to be present in ambient air. The results of Level III fugacity modelling suggest that MDA substances will not partition to air, and if present, will reside in soil, water and/or sediment. Environmental monitoring in Japan showed 4,4′-MDA in surface water above the detection limit of 0.001 µg/L (i.e., up to 0.02 µg/L) at 11 of 28 sites. 4,4′-MDA was also detected in sediments in Japan, with a geometric mean of 0.015 mg/kg (CHRIP 2008; Environment Agency of Japan 2000).

MDIs released to the environment may be transformed into MDAs. No MDAs are expected in the air from atmospheric release of MDIs given the low rate of transformation in air. The deposition rate of MDIs to soil is relatively low and confined to the vicinity of the release point. A worst-case estimate of soil concentration based on a 100% environmental transformation of deposited MDI into MDA, assuming a source release of a 10 km radius, is not expected to be greater than 0.023 mg/kg soil (see Ecological Exposure Assessment section). Furthermore, there is no manufacturing of MDAs or MDIs in Canada, and the quantity of MDAs directly released to the environment is expected to be minimal. When the Japanese water monitoring data and estimated soil concentration values were used to derive conservative upper bounding daily intakes of MDA, these estimates were less than 1 nanogram per kilogram of body weight (kg-bw) per day. The environment is therefore not likely to be a source of exposure for humans.

On the basis of the above information, exposure of the general population to 4,4′-MDA and pMDA via the environment is not expected.

8.1.1.2 MDIs

There is no natural presence of MDIs in environmental media in Canada. Empirical data on concentrations of MDIs in environmental media in Canada or elsewhere were not identified. The chemistry of MDIs precludes the presence of high concentrations in the environment. MDIs are not persistent in water or soil, with degradation occurring primarily via hydrolysis (EPI Suite 2008). Typically, the half-life of MDIs in water can be as short as less than one minute under moving water. MDIs will form degradation products of solid, insoluble polyurea and, to a lesser extent, MDA (Yakabe et al. 1999). Due to the high reactivity of MDIs, the majority will remain and degrade in the media to which it was emitted.

With low vapour pressures for the isomers, MDIs are not expected to be present in significant amounts as vapour in the air. Air concentrations around point sources, such as facilities that use MDIs in production, were estimated using the SCREEN3 model (SCREEN 3 1995). The SCREEN3 1-hour air concentration estimate for a hypothetical facility discussed in the Ecological Exposure Assessment section (Appendix E) was further refined to include human health considerations (US EPA 2004). A small portion of the general population may be exposed to MDI if residing in the vicinity of OSB facilities. The upper-bound modelled estimate for MDI concentration in air at a realistic

distance from the reporting facility where the nearest populated area is expected to be is 0.543 µg/m^3 over 8 hours. This estimate is considered conservative given that wind speed and direction are not accounted for, a constant emission plume is assumed, and physical-chemical properties of MDIs, such as low vapour pressure, are not taken into consideration by this model.

There may also be the potential for exposure through food from food packaging laminate as reported in the survey conducted under section 71 of CEPA (Environment Canada 2012a). A polyurethane adhesive is used to hold several polymer layers together to form a laminate food packaging material. Because the polymer layers are functional barriers between the adhesive and food, MDI in the adhesive layer is not expected to migrate into food (personal communication, Food Directorate, Health Canada, to Risk Management Bureau, Health Canada, dated 2013; unreferenced). Concentrations of 4,4′-MDI in the polyurethane adhesive used in food packaging are low, ranging from 0.005% to 0.5% (Environment Canada 2012a). The potential for exposure from the adhesive is considered to be negligible. No data suggesting presence of MDIs in food in Canada was identified.

On the basis of the overall information, the potential for exposure of the general population to MDIs through environmental media and food in Canada is expected to be low.

8.1.2 Consumer products

8.1.2.1 MDAs

MDAs are mainly used to produce MDIs in closed-system environments; a small fraction is used as a cross-linking agent for polyurethanes, an antioxidant for lubricating oils, a curative agent in rubber and an intermediate in elastomeric fibres and in the preparation of azo dyes (Mortensen et al. 2005; HSDB 1983-2003). No report of use of 4,4′-MDA or pMDA in consumer products in Canada was identified. Exposure to residual free 4,4′-MDA may occur from products made with polyurethanes. However, MDAs are not known to be present in a free state post production of polyurethanes (NTP 2011; IPCS 2005; ECJRC 2005; ECJRC 2001).

4,4′-MDA is known to be used in the production of azo dyes (Cartasol Yellow), which may be used in inks, paper, leather and other textile products (ECJRC 2001). Under reductive cleavage, 4,4′-MDA may unintentionally become free, but there is no quantitative information on a liberation rate (IPCS 2005; ECJRC 2001). One study showed potential migration of low levels of 4,4,′-MDA into food when cooked from plastic cooking utensils containing azo dyes under realistic food preparation conditions. Of the 11 utensils tested, 6 released 4,4′-MDA into the food simulant at concentrations between 1.4 and 2.5 µg aniline equivalents per kg food simulant, which would result in a very low estimated intake of nanograms per kilogram bodyweight (Mortensen et al. 2005). There are no reported consumer uses of MDA in Canada. On the basis of the overall information, potential exposure of the Canadian general population to MDA from its presence as residual in consumer products is considered negligible.

8.1.2.2 MDIs

MDIs have a widespread commercial and consumer use. 4,4′-MDI, pMDI and mixed MDI are primarily used in the production of flexible or rigid polyurethane (PU) foam. 2,2′-MDI and 2,4′-MDI may also be used as ingredients in polyurethane production.

Polyurethane is produced from a reaction between MDIs and polyetherols or polyesters (Allport et al. 2003; Harper et al. 2001).The polyurethane product is subsequently cured, resulting in hardening of the polyurethane and reduction of free isocyanate (NCO) groups.

Flexible polyurethane foam is produced commercially as foam slabs that are available to consumers, after curing, in the form of various manufactured articles, including furniture, mattresses and flooring underlay. Potential for residual MDIs in flexible polyurethane has been investigated (Hoffmann and Schupp 2009; Krone and Klingner 2005). In an air chamber study by Hoffmann and Schupp (2009), the potential for MDI migration from cured foam was evaluated. In a closed air chamber, continuous air sampling of a new foam mattress material containing 5 ppb extractable MDIs was found not to emit MDIs above the detection limit of 5.4 ng/m^3. Using glassfibre filters between foam layers, continuous migration over 5 days was monitored and found to be very low at 9 ng/m^3 (Hoffmann and Schupp 2009). These data indicate that if residual MDIs remained present in the foam at the time of purchase, residues are likely to remain in the polymer matrix.

Therefore, on the basis of the available information (including MDI substances′ low vapour pressure), inhalation and dermal exposure of the general population to potential residual MDIs present in flexible foam products is considered negligible.

Other MDI-based polyurethane products include particle board and oriented strand board (Harper et al. 2001, ECJRC 2005). MDIs are an ingredient in the resin, which itself is added to the wood particles. Through high temperature and moisture, the resin (containing MDI) cures and hardens the wood particles into particle board or strand board. Einbrodt concludes in a position paper (cited in ECJRC 2005) that the polyureabonded particle boards do not emit “hazardous levels” of MDIs. Furthermore, there was no evidence of the presence of MDAs, a potential decomposition product, in the particle board. Under increased thermal conditions, where one may expect MDI emissions from the wood binder or coating, the particle board emitted no MDIs (ECJRC 2005). This was also observed by Harper et al. (2001), who reported that a maximum cure rate is found to increase with isothermal cure temperature.

MDIs are also used to produce polyurethane foam for sealing, insulation and adhesive purposes. These products can be either two-component products or one-component products. Two-component products are typically packaged as two separate chambers, one in which MDIs are in a free state, unreacted, and separate from polyols in the other chamber. During application, both MDIs and polyols are sprayed or dispensed with a spraying gun or nozzle simultaneously to react and form polyurethane foam at the point

of application (Crespo and Galán 1999; Lesage et al. 2007; Methner et al. 2010). Two-component spray polyurethane foam (SPF) products or kits available for do-it-yourself (DIY) applicators or homeowners typically deliver the foam under low pressure (US EPA 2015). SPF can also be applied using a high-pressure delivery system. However, such systems are only used by professional applicators (US EPA 2015).

The one-component DIY products contain an isocyanate pre-polymer prepared from pre-mixed polyols and diisocyanates. Once dispensed, it reacts with moisture in the air to develop its mechanical strength from cross-linking (Cui et al. 2002; RAPRA 2000). These products can have different functions, including sealant, construction adhesive, floor adhesive, hot-melt adhesive and hobby glue. One-component products that release expandable foam are typically used for sealant purposes, while one-component products that are non-expandable are typically used as adhesives.

Tables 8-1, 8-2 and 8-3 provide a description of cure time and concentration ranges for each MDI substance in different types of DIY products (HPD 2013; HSDB 1983-2003).

Table 8-1. Concentrations of 4,4′-MDI in DIY products

Product	Concentration (%w/w)	Cure time
Spray polyurethane foam (low-pressure two-component kit)	30–60	Tack-free: 0.1–1 min Full cure: 1 hour
One-component foam sealant	5–20	Tack-free: 5–30 min Full cure: 1–24 hour
Polyurethane adhesive/assembly sealant	1–30	Tack-free: 15 min Full cure: 1–24 hour
Floor/wall adhesive	1–5	Tack-free: 60–90 min Full cure: 8–10 hour
Construction adhesive	7–50	Tack-free: 20–30 min Full cure: 1–24 hour
General adhesive/hobby glue	10–56	Full cure: 1–4 hour
Super glue	30–50	Full cure: 1–4 hour
Hot-melt adhesive	2–3	Full cure: 0.5–2 min

Table 8-2. Concentrations of pMDI in DIY products

Product	Concentration (%w/w)	Cure time
Spray polyurethane foam (low-pressure two-component kit)	30–60	Tack-free: 0.1-1 min Full cure: 1 hour
One-component foam sealant	5–55	Tack-free: 5–30 min Full cure: 1–24 hour

Product	Concentration (%w/w)	Cure time
Polyurethane adhesive/assembly sealant	1–10	Tack-free: 15 min Full cure: 1–24 hour
Construction adhesive	10–25	Tack-free: 20–30 min Full cure: 1–24 hour
Generic/hobby glue	30–56	Full cure: 1–4 hour
Super glue	30–50	Full cure: 1–4 hour

Table 8-3. Concentrations of mixed MDI in DIY products

Product	Concentration (%w/w)	Cure time
Spray polyurethane foam (low-pressure two-component kit)	5–10	Tack-free: 0.1-1 min Full cure: 1 hour
Polyurethane adhesive/assembly sealant	1–5	Tack-free: 15 min Full cure: 1–24 hour
Construction adhesive	1–5	Tack-free: 20–30 min Full cure: 1–24 hour
Floor adhesive	1–5	Tack-free: 60–90 min Full cure: 8–10 hour
Generic/hobby glue	32–56	Full cure: 1–4 hour
Hot-melt adhesive	<3	Full cure: 0.5–2 min

Exposure to MDIs from use of these DIY products depends partly on their cure rate and the humidity and temperature of the room in which they are applied. Cure rates are measures of reaction rates for MDIs to form polyurethane with subsequent hardening through cross-linking. Curing typically starts immediately upon application and moves from the outside inwards, forming a “skin” or tack-free film on the surface (Cao et al. 2012; Lesage et al. 2007) before completion of the curing phase. The product results in a hardening of the polyurethane and a reduction of free NCO groups (Allport et al. 2003). In studies measuring the cure rate of diisocyanates, it was found that with higher humidity and temperature, there is a faster reaction time (Wirts et al. 2003; Wirts and Salthammer 2002). Product information provides an expected range for the length of time necessary to expect full cure as well as a tack-free or cut time in some instances (Tables 8-1 to 8-3).

Inhalation and dermal exposure to MDIs were estimated for homeowners using MDI-containing DIY products. Products may contain one main MDI isomer or a mixture of several MDIs. Exposure estimates were based on the known concentration of MDIs overall in each product as reported under section 71 and confirmed from product manufacturers’ technical information. Given the intended use of these products, the oral route of exposure was not considered to be relevant.

While these product labels specify personal protection measures, such as the use of gloves or respiratory protection, exposure estimates derived do not consider that individuals are wearing personal protective equipment, given that such equipment may not be readily accessible to consumers or may not be properly handled by consumers.

Inhalation exposure

Low-pressure two-component SPF products are available for purchase off the shelf from retailers in canisters of varying sizes, with two common sizes being 13 and 20 kg (largest kit size). The concentration of each MDI substance contained in this type of product can range from 5 to 60% w/w prior to mixing with polyol to generate foam (Tables 8-1 to 8-3). Foam from a 20-kg tank is expected to cover 600 boardfeet, or 300 ft^2 (28 m^2), assuming a 2-inch foam thickness (2013 email communication from CUFCA to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced; Lesage et al. 2007).

No studies were identified in which air concentrations of MDIs were measured during use of a low-pressure two-component SPF product by a homeowner. There are several studies available in which air concentration of MDIs were measured during applications of two-component SPF products by professionals using either low-pressure or high-pressure delivery (Lesage et al. 2007; Roberge et al. 2009; Fomo Products 2005, 2010; ACC 2012b; Convenience Products 2012, 2014a, 2014b; Dow Chemical Company 2013).

Studies measuring MDI air concentration during application of low-pressure SPF were used for the purpose of this assessment as they are considered to be most representative of a homeowner scenario.

Several studies were submitted by stakeholders in which levels of MDIs were monitored in air during the application of low-pressure two-component SPF products. In these studies, MDI products were applied by professionals for either sealant purposes (by filling in gaps and cracks in walls or ceilings (e.g., gap between joist and wall) or insulation purposes (by covering or filling in the entire area of a wall between joists). Results are presented in Appendix F and summarized in Tables 8-4 and 8-5 below. Studies submitted were conducted either in homes in the United States (Fomo Products 2005; Dow Chemical 2013; Convenience Products 2014a, 2014b) or in dedicated spray chambers (Fomo Products 2010; ACC 2012b; Convenience Products 2012).

Three studies were submitted by stakeholders in which a two-component SPF was applied with low pressure between joists (i.e., full cavity fill) (Fomo Products 2005; Convenience Products 2012; Dow Chemical 2013). These studies were based on monitoring exposure during 1-hour applications or less. It appears from these studies that it would take approximately 1 hour to apply 20 kg of product. The studies were conducted with varying ventilation regimes, some of which are considered to be less representative of a homeowner scenario (e.g., a homeowner may not invest in the purchase of 2 box fans for a one-time use of an SPF kit). Overall, maximum

concentrations were as follows: 0.16 mg/m^3 (during a 13-minute spray time with ventilation through the use of either a box fan or an industrial grade fan) (Dow Chemical 2013); 0.078 mg/m^3 (during a 60-minute application, with 2 box fans installed in windows but set on "OFF", equivalent to opened windows); 0.053 mg/m^3 (during a 60-minute application, with 2 box fans set on "high") (Convenience Products 2012); and 0.082 mg/m^3 (after a 60-minute application, using natural ventilation, i.e., opened windows and doors) (Fomo Products 2005) (See Appendix F for more details). The Dow study was considered to be associated with uncertainties (air concentrations measured were identical even though they were based on two significantly different ventilation regimes), and the concentration of 0.082 mg/m^3 (Fomo Products 2005) is considered to be representative of a homeowner using a low-pressure two-component SPF product (e.g., kit) for 1 hour.

Table 8-4. Maximum personal concentrations of MDIs for the application of low-pressure two-component SPF between joists (i.e., "full cavity" fill)

Study reference	Ventilation (air changes/hour)	Sampling time (min)	Air [ ] during spray (mg/m^3)
Dow Chemical 2013	44 (industrial grade fan)	13	0.16
Dow Chemical 2013	16 (1 box fan)	13	0.16
Convenience Products 2012	6 (opened windows)	60	Total MDI*: 0.078
Convenience Products 2012	102 (2 box fans)	60	Total MDI*: 0.053
Fomo Products 2005	Opened windows	18–20	0.082

* This value is based on adding concentration of MDI monomer and pMDI; pMDI concentration was below the limit of detection (LOD) of 0.02 mg/m^3, it was assumed the level was at half of the LOD.

Three studies were available from stakeholders in which a two-component SPF was applied with low pressure along joists and corners and in cracks (ACC 2012b; Convenience Products 2014a, 2014b). They were based on monitoring exposure during 30-minute applications. It appears from these studies that it would take approximately 30 minutes to apply 13 kg of SPF. The studies were conducted with a wide range of ventilation rates, some less representative of a typical homeowner situation. The maximum concentrations monitored during application of the SPF were: 0.01 mg/m^3 (using 2 box fans inserted in windows); 0.04 mg/m^3 (natural ventilation); and 0.1 mg/m^3 (10.4 air changes per hour in a test chamber, ventilation perpendicular to the spray) (See Appendix F for more details). There are uncertainties associated with the concentration of 0.1 mg/m^3 since the limit of detection for one of the MDIs measured (pMDI) was high (> 0.1 mg/m^3) and therefore the actual contribution of pMDI to the total MDI concentration is unknown. Therefore a range of maximum concentrations of 0.04 to 0.1 mg/m^3 is considered to be representative of exposure during application of a 13 kg low-pressure two-component SPF kit.

Table 8-5. Maximum personal concentrations of MDIs for the application of low-pressure two-component SPF along joists and corners and in cracks

Study reference	Ventilation (air changes/hour)	Sampling time (min)	Air [ ] during spray (mg/m^3)
Convenience Products 2014a	4.7 (2 box fans)	15	0.01
Convenience Products 2014b	0.2 (natural ventilation)	15	0.04
ACC 2012b	10.4 (test chamber)	24–29	0.1*

* This value is based on adding concentration of 2,4′-MDI, 4,4′-MDI and pMDI; pMDI concentration was below the limit of detection (LOD) of 0.102 mg/m^3, it was assumed the level was at half of the LOD.

These concentrations are associated with uncertainty, given that professionals performing the applications in the various studies are likely to be trained and experienced using these products and perform a “cleaner” application than an untrained homeowner.

Bystanders in the home could also potentially be exposed to airborne MDI from the presence of aerosols in the air during use of the low-pressure two-component SPF product. In the case of a professional application of SPF, homeowners would typically be asked to vacate the home during product application and to return at least 1 hour later to minimize exposure to MDI (NRC 2011). Available data indicate that levels in the air drop rapidly once the foam starts curing. In the studies outlined in Table 8-4, Table 8-5, and Appendix F, all post-spray measurements (taken 30 minutes to 1 hour post-application [ACC 2012b]) resulted in MDI concentrations that were below the study detection limit (Fomo Products 2005; ACC 2012b; Convenience Products 2012, 2014a, 2014b; Dow Chemical Company 2013). Furthermore, for high-pressure two-component SPF scenarios, concentrations were found to decrease below the limit of quantitation both with distance from the spray zone and with time from application (Lesage et al. 2007; Roberge et al. 2009).

In addition to the low-pressure two-component SPF products, MDI-containing DIY products include expandable foam one-component products also used as sealants. These products contain a pre-mix of MDI and polyol, i.e., an isocyanate-terminated pre-polymer, and are typically applied with a can and a straw-like nozzle placed close to the wall surface to seal small cracks. At the point of use of the product when this pre-polymer is released from the can, the isocyanate group in the pre-polymer reacts with moisture in the air forming an amine intermediate that further reacts with the isocyanate pre-polymer, and expanding foam is formed. Table 8-6 outlines the results of the studies submitted by stakeholders in which MDI concentrations in air were measured during application of one-component SPF products.

Table 8-6. Results of air concentration measurements during use of one-component expandable SPF products

Study reference	Amount applied	Ventilation	Application time (min)	Air concentration during application (mg/m^3)	Application scenario
Fomo Products 2010	1.5 cans (can size not specified)	None – ventilation was turned off	15	<LOD (0.001)	Applied to cardboard in humidity spray chamber
Convenience Products 2009	NS	NS	15	<LOD (0.0065)	Applied around fabricated large window backed with particle board
Lars Rosell and Marcus Vestergren 2012	524–550 g	NS	<20	<LOD (0.00025)	Applied around fabricated large window backed with particle board

LOD: Limit of Detection; NS: not stated

MDI concentrations described in Table 8-6 were all below the study limit of detection (the study limits of detection vary from 0.00025 to 0.0065 mg/m^3). The European Union MDI Risk Assessment (ECJRC 2005) also reported data submitted by industry showing MDI concentrations below the detection limit of 0.0061 mg/m^3 during use of one-component spray foam products by consumers. The EU used this value as a worst-case estimate of short-term inhalation, stating that this monitoring data reflects the situation in an occupational environment but was applicable for the use of this product by consumers (ECJRC 2005). On the basis of the collective information, the detection limit of 0.0065 mg/m^3 is considered to be an upper bounding estimate of general population exposure to MDI from use of a one-component foam sealant.

Other DIY products containing MDIs are not expandable but are used to fill gaps or to glue pieces together during the assembly of wood, metal or drywall. Monitoring data for these types of products were not identified, and exposure estimates via inhalation from use of these products were derived using ConsExpo v.4.1 software (ConsExpo 2006).

One product, a polyurethane adhesive/sealant or assembly sealant, is used to both bind and fill the space between wood materials, either for furniture or partitioning wall. This product acts as a caulking and can be applied in a thick layer between two surfaces. Assuming a full cartridge (390 g) of assembly sealant is used for a task that takes 30 minutes, the concentration of airborne MDIs during use of that product is estimated via the ConsExpo model to range from 0.00063 to 0.0010 mg/m^3 (see Table 8-7 or Appendix G for more details).

Exposure during a large- and small-scale project requiring adhesives was estimated using ConsExpo,; estimates were based on three scenarios, the use of a floor adhesive, construction glue and hobby glue. The floor adhesive product can be used for a large-scale project, such as a living room, in which installation would take several hours. Assuming an 8-hour day to lay the floor, the concentration of MDIs during use of this type of product is estimated to range from 0.00013 to 0.00047 mg/m^3 (Table 8-7, Appendix G). Construction glue can be used for a variety of projects in the home. Concentrations of MDIs during use of construction glue, assuming a medium-scale project around the home, were estimated to range from 0.0014 to 0.0021 mg/m^3 , on the basis of a 30-minute application time and 30-minute tack-free time on a 1 m^2 surface area (Table 8-7, Appendix G). Hobby glues are expected to be used for small projects, such as modelling and crafting. During the use of 6 g of product for 20 minutes on a 400-cm^2 surface, air concentrations are estimated to range from 1.0×10^{-5} to 1.2×10^{-5} mg/m^3, given an MDI concentration range of 25 to 56% w/w (Table 8-7) in the product (Table 8-7, Appendix G). These levels are consistent with those reported in a Gorilla Glue study conducted by McCoy et al. (2013). In that study, consumer use of hobby glue was simulated by applying small amounts of glue (1, 2 and 30 g) to flat surfaces before gluing them together; the study reported MDI and pMDI air concentrations of less than 0.0005 mg/m^3.

Other adhesives, super glue and hot-melt adhesives were considered to be associated with low air concentrations of MDIs. For instance, the repair of a broken handle from a mug would require very little super glue (0.5 g), would be completed quickly and would be left to cure for a few hours. Using these assumptions, the concentration of MDIs from super glue was estimated to be less than 4.1×10^{-8}mg/m^3. Concentration of MDIs during use of hot-melt adhesives is estimated to be less than 7.9×10^{-8}mg/m^3 (Table 8-7, Appendix G).

Table 8-7. Upper-bounding estimates of air concentrations of MDIs from use of adhesive/sealant type of DIY products

Modelled consumer product scenario[a]	Exposure + cure time	Range of mean event concentration during application and cure time (mg/m^3)
Polyurethane adhesive/assembly sealant	30 + 15 min	0.00063–0.0010
Floor/wall adhesive	8 h + 1.5 h	0.00013–0.00047
Construction adhesive	30 + 30 min	0.0014–0.0021

Modelled consumer product scenario[a]	Exposure + cure time	Range of mean event concentration during application and cure time (mg/m^3)
General adhesive/hobby glue	4 hour	1.0×10^{-5} to 1.2×10^{-5}
Super glue	4 hour	$<4.1\times 10^{-8}$
Hot-melt adhesive	25 + 2 min	$<7.9 \times 10^{-8}$

[a]Ventilation rates for these scenarios was either 0.5 or 0.6 changes/h (See Appendix G for details).

The exposure estimates based on ConsExpo are considered to be conservative because of the constraints of the model. As DIY products are applied, it is expected that the amount of unreacted MDI would decrease as a result of the production of polyurethane and its curing. However, the ConsExpo model does not account for the physical transformation of a substance, and it was assumed that all of the MDI present in the product before application is volatilized (personal communication, RIVM 2013). The amount of free MDIs released to the air during application would likely be lower than estimated by ConsExpo also given the development of a film on the product surface, potentially reducing migration and release of unreacted MDIs (Lesage et al. 2007). ConsExpo estimates of air concentration are based on the physical-chemical properties of MDIs but not the physical transformation of MDIs to polyurethane when applying the product (personal communication, RIVM 2013). The boundary-layer theory mass transfer rate of 0.18 m/min (Sparks et al. 1996) provided by RIVM was suggested to account for the cured layer between the ambient air and uncured polyurethane. Given that the experimental data were based on an average of volatile substances, Sparks et al. (1996) was not considered. More recently, Wirts and Salthammer (2002) determined an experimental mass flow rate of 0.013 m/min on the basis of the emission rate for pure 4,4′-MDI. The study by Wirts and Salthammer (2002) was used in the modelling estimates of adhesive/sealant-type DIY products.

A DIY application product that contains MDIs is used to coat passenger truck beds (Dominion Sure Seal 2014). This product is available from the hardware retail store and is to be applied using a roll-on applicator, brush, spray can or spray gun. Although instructions on the label indicate that the product may be used for patios, basements or garage floors, it is typically used to coat the inside of truck beds for protection against rust. Truck bed coating can be done either professionally or by truck owners. Use of a truck bed liner product by the general public would likely be outdoors or in an open garage and result in application of a maximum of 1 gallon (3.7 L) of product only (maximum size available from the retail shelf). MDI air concentrations during application of truck bed liners have been reported for occupational indoor settings (Myers and Cummings 2005), which are not considered representative of a truck owner scenario. Although no study is available for this specific scenario, the potential inhalation exposure from use of truck bed liners is expected to be significantly lower than exposure during use of DIY product applied indoors

Dermal exposure

Dermal exposure to MDIs from use of DIY products was calculated as an amount of product per area of skin. A series of human skin sensitization studies indicate that dermal sensitization was dependent on the dose per unit area of skin rather than on the overall amount of substance applied to the skin (Kimber et al. 2008, Robinson et al. 2000). The estimates also assume that any dried product remaining on the skin does not act as a barrier from continued application.

Polyurethane spray foam sealant labels suggest safety precautions as the spray may adhere to large areas of the arms and hands during use. For the low-pressure two-component spray polyurethane foam application scenario, an estimate of dermal exposure to MDIs was calculated assuming spray coverage (0.25 g) (ConsExpo 2006) from a spray gun on the back of both hands and forearms (2185 cm^2) resulting in a dermal load of 0.068 mg/cm^2. Application of one-component foam sealants using a long straw-nozzle from a spray can closer to the body, potentially releasing 0.004 g of product on tips of fingers touching the nozzle (10 cm^2), was estimated to result in a dermal load of 0.02 to 0.22 mg/cm^2 (Table 8-8).

Assembly sealants are typically applied like caulking glue, directly on the working surface. In this scenario, the two surfaces glued together are held in place for the glue to begin to set. It is assumed that during this time, there is the potential for 20% of one hand palm or fingers (46 cm^2) to be exposed to drips of glue, giving an upper-bounding estimate of 4.9 mg/cm^2 to MDIs (Table 8-8).

The potential dermal exposure was estimated for construction adhesives, floor glue and hobby glue. Because of the nature of their hands-on application, it is assumed that hands are in contact with floor adhesives during the entire time of floor installation, with a contact rate of 30 mg/min for 8 hours. It is expected that 50% of the hands would be exposed, resulting in an estimate of dermal load of 3.2 mg/cm^2. During use of construction adhesive, i.e., clamping two components together while the glue sets, it is assumed that up to 20% of both hand palms or all fingers (91 cm^2) would be in contact with the glue, resulting in a potential MDI dermal load of 2.2 mg/cm^2. During the application of 0.08 g of hobby glue containing 56% 4,4′-MDI, it is assumed that fingertips (2 cm^2) would be exposed during smaller detail work, resulting in an estimated MDI dermal load of 22 mg/cm^2 (Table 8-8).

Skin contact during application of hot-melt adhesives and super glues is typically avoided to protect the dermal layer from physical harm of burns or tearing. Similarly, skin contact with spray or roll-on coatings, such as application of the vehicle truck bed liner, would typically be avoided. In the event of incidental contact with super glue, a fingertip may be exposed to 5% of the glue used, resulting in a potential MDI dermal load of 13 mg/cm^2. Handling a hot-melt glue bar while inserting it into a glue gun would not result in exposure as the MDIs are cured in the solid bar. Unlike the other DIY products, which may contain free isocyanates prior to use, hot-melt adhesives require

high temperatures to release MDIs. Skin contact would be avoided during the heated glue application, therefore limiting any dermal exposure to MDIs.

Table 8-8. Upper-bounding estimates of dermal exposure to MDIs from DIY products

Modelled consumer product scenario	Contact area (cm^2)	Dermal load (mg/cm^2)
Spray polyurethane foam (low-pressure, two-component kit)	2185	0.068
Foam sealant (one-component)	10	0.22
Polyurethane adhesives/sealant	46	4.9
Floor/wall adhesive	455	3.2
Construction adhesive	91	2.2
General adhesive/ hobby glue	2	22
Super glue	1	13

8.2 Health Effects Assessment

8.2.1 MDAs

Polymeric MDA (pMDA) is a mixture containing mostly 4,4′-MDA. No adequate health effects information has been identified for pMDA. In the European Union (EU) under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation, 4,4′-MDA and pMDA are subject to authorization as substances of very high concern (SVHC given the nature of health effects associated with 4,4′-MDA, which has been classified as a Category 1B carcinogen by the European Commission (ECHA 2011). In consideration of the fact that 4,4′-MDA is the main component of pMDA and that no health effects data were identified for pMDA, the following assessment of health effects of 4,4′-MDA will also be applied to pMDA.

8.2.1.1 Carcinogenicity and genotoxicity

The International Agency for Research on Cancer (IARC) has classified 4,4′-MDA as a Group 2B carcinogen (“possibly carcinogenic to humans”) (IARC 1986) and the European Commission has classified the chemical as a Category 1B carcinogenic substance (“presumed to have carcinogenic potential for humans”) (European Commission 2015a). In addition, the US National Toxicology Program (NTP) has concluded that 4,4′-MDA is “reasonably anticipated to be a human carcinogen” (NTP 1983). These national and international hazard classifications and conclusions were based principally on observation of increases in tumour incidences in experimental animals.

In a two-year animal study, tumours were observed at multiple sites in rats and mice treated with 4,4′-MDA. F344 rats and B6C3F1 mice were exposed to 4,4′-MDA in drinking water at doses of 0, 150 or 300 ppm (approximately equivalent to 0/0, 9/10 or 16/19 (male/female) mg/kg-bw/day for rats, and 0/0, 25/19 or 57/43 (male/female) mg/kg-bw/day for mice) for 103 weeks. A statistically significant increase in thyroid follicular cell carcinomas was observed in high-dose male rats, and statistically significant increases in thyroid follicular adenomas were observed in high-dose female rats and high-dose mice of both sexes. The increase in thyroid C-cell adenomas was found in female rats in a dose-related manner. Neoplastic nodules were observed in the liver of both low- and high-dose male rats. In addition, uncommon tumours were observed in exposed rats at low incidences, including bile duct adenomas in the males and transitional-cell papillomas of the urinary bladder and granulosa cell tumours of the ovary in the females. The incidence of these tumours may be of toxicological significance because their historical control incidence is very low. In mice, a statistically significant increase in hepatocellular carcinomas was observed in all exposed males and females, and a statistically significant increase in hepatocellular adenomas was observed in high-dose female mice. Other tumours that were increased in exposed mice included adrenal pheochromocytomas in the males, and alveolar/bronchiolar adenomas and malignant lymphomas in the females (NTP 1983).

Studies that evaluated cancer outcomes in humans have been identified. Liss and Chrostek (1983) suggested that there was an association between bladder cancer and work in areas with past or present potential exposure to 4,4′-MDA. This was a follow-up investigation of 179 white male deaths among employees who had worked more than a month in areas with potential exposure to epoxy resins and amine hardeners containing 4,4′-MDA. The mortality ratio of cancer was found to be significantly increased when compared to the whole population. However, proportional cancer mortality ratio analysis showed that only the excess of bladder cancer was significantly elevated. In contrast to the findings of Liss and Chrostek (1983), no evidence of an increase in overall or bladder cancer risk was observed in a retrospective cohort study conducted among 595 workers (550 males and 45 females) who were exposed to 4,4′-MDA in a power generation plant in Sweden between 1963 and 1986. Standardized incidence ratios (SIR) were obtained from the ratio of the observed to the expected number of cases. The overall SIR was 0.52 based on five observed cases. The authors indicated that the results should be interpreted with caution since the majority of the subjects were quite young and had not reached cancer-prone age and since the follow-up period was short and may have not covered the latency period for bladder cancer (Selden et al. 1992).

The European Commission (2015a) has classified 4,4′-MDA as a Category 2 mutagen; “substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans.” The genotoxicity data are briefly summarized below.

4,4′-MDA tested positive in bacterial mutation assays. It also induced gene mutation in L5178Ytk+/- mouse lymphoma cells. In Chinese hamster lung (CHL) cells, 4,4′-MDA induced chromosome aberrations, but the effect was equivocal in Chinese hamster

ovary (CHO) cells. It also induced sister chromatid exchange in CHO cells. In an assay to evaluate DNA damage, 4,4′-MDA showed clear evidence of inducing unscheduled DNA synthesis in rat hepatocytes.

The genotoxic potential of 4,4′-MDA was further tested in a series of *in vivo* assays. The sex-linked recessive lethal mutation was observed in adult male *Drosophila melanogaster* when exposed to 4,4′-MDA by feeding, but the result was negative when exposed to a lower dose by injection. In micronucleus assays, 4,4′-MDA showed positive or equivocal results in the exposed mice, but negative in the exposed rats. A weakly positive effect was observed in the exposed mice in the sister chromatid exchange assay. In the unscheduled DNA synthesis assay, negative results were found both in exposed mice and rats. However, 4,4′-MDA induced DNA fragmentation and DNA adducts formation in exposed rats.

8.2.1.2 Non-cancer effects

Non-cancer effects of 4,4′-MDA have been observed in a range of target organs and tissues, but predominantly the liver and thyroid. In the two-year oral study conducted in rats and mice (NTP 1983), thyroid follicular cysts and follicular cell hyperplasia were observed in the animals which received doses of 9 or 10 mg/kg-bw/day and higher dose groups in male and female rats, respectively. Liver fatty metamorphosis and focal cellular changes were also observed in rats of both sexes at the low and high doses, while unspecified dilatation of the liver was only observed in male rats at low and high doses. In mice, thyroid follicular cell hyperplasia and liver cell degeneration were observed in males in the 25 mg/kg-bw/day and higher dose groups, but in females, these effects were observed only in the high dose (43 mg/kg-bw/day) group (NTP 1983).

Several sub-chronic oral studies have been identified. In a study conducted by Ciba-Geigy (1982), follicular cell hyperplasia/hypertrophy and diffuse glandular hyperplasia with colloid depletion in the thyroid were observed in both male and female rats exposed to 4,4′-MDA in drinking water at a dose of 8 mg/kg-bw/day and higher for 3 months. At the higher dose level (23 mg/kg-bw/day for males and 22 mg/kg-bw/day for females), anemia, elevated enzyme levels, altered organ weight, biliary duct hyperplasia, liver lesions and thyroid lesions were observed in both males and females, but kidney mineralization was observed only in males. In addition, elevated numbers of leukocytes and percentage of neutrophils and prolonged prothrombin time were observed in the highest dose groups of both sexes (31 mg/kg-bw/day for males and 32 mg/kg-bw/day for females). Reduced percentages of lymphocytes were observed in female rats; and focal nodular hyperplasia of the thyroid was observed in male rats (Ciba-Geigy 1982). The US NTP also conducted a 13-week study in rats and mice treated with 4,4′-MDA in drinking water. In rats, a dose-related reduction in water consumption was observed both in males and females at doses of 13 mg/kg-bw/day and higher. In mice, a weight gain reduction was observed in males at doses of 27 mg/kg-bw/day and higher. At the highest dose (55 mg/kg-bw/day for males and 52 mg/kg-bw/day for females), bile duct hyperplasia, thyroid adenomas and weight gain

reduction were observed both in male and in female mice (NTP 1983). Other oral sub-chronic studies resulted in LOAELs ranging from 84 to 97 mg/kg-bw/day (Hiasa et al. 1984, Fukushima et al. 1979 and 1981, Tsuda et al. 1987). No inhalation or dermal sub-chronic studies were identified.

A number of short-term studies in various species, with different routes of exposure, have been conducted. In a 14-day drinking water study in rats and mice, reductions in water consumption and weight gain were observed in rats exposed to 4,4′-MDA at doses of 17 mg/kg-bw/day and higher, and in mice at 102 mg/kg-bw/day for females and at doses of 136 mg/kg-bw/day and higher for males (NTP 1983). The BASF (1977) conducted a 14-day oral study in rats. Reduced serum total lipid levels and increased serum alkaline phosphatase (AP) levels were observed in the low–dose group (25 mg/kg-bw/day) of both sexes, and elevated liver weight was observed in the low-dose females only. At the high dose (50 mg/kg-bw/day), anemia with reduced numbers of red blood cells, decreased levels of hemoglobin and hematocrit, and increased numbers of leukocytes were observed in both males and females. Increased serum enzymes (ALAT, alkaline phosphatase), total proteins (males only), total lipids, and total bilirubin and elevated organ weights of liver, kidney, spleen, and thyroid were also observed in the exposed animals at the high dose. In addition, urinalysis revealed adverse effects in females in both dose groups. Isolated renal cells and protein in the urinary sediment were evident. Histopathology showed dose-related mild to moderate lesions in both dose groups consisting of proliferation of bile ducts with initial fibrosis and inflammatory reactions of the liver, enlargement of the spleen due to extramedullary hematopoiesis, and hyperplasia of the thyroid epithelium (BASF 1977). Two additional oral studies in rats resulted in LOAELs of 84 and 100 mg/kg-bw/day based on adverse effects observed in the liver and thyroid of exposed animals (Miyamoto et al. 1977 and Hagiwara et al. 1993).

A short-term inhalation study in male albino and male pigmented guinea pigs was conducted by Leong et al. (1987). Degeneration of the inner and outer segments of the photoreceptor cells and the pigmented epithelial cell layer of the retinas were observed in both strains of guinea pigs exposed to 4,4′-MDA at 440 mg/m^3 for 2 weeks. Small pulmonary granulomas or mild granulomatous pneumonitis were also observed in the exposed animals (Leong et al. 1987).

4,4′-MDA has also caused systemic effects in animals exposed via dermal application. In a 2-week dermal study in mice, increased liver and spleen weight were observed in males and females at 168 mg/kg-bw/day. Deaths were reported in both males and females (Holland et al. 1987). In another dermal study, rabbits were exposed to 4,4′-MDA at 700 mg/kg-bw/day for 10 days. Bile duct proliferation, portal cirrhosis, focal parenchymal necrosis, mild acute glomerulonephritis, acute necrotizing dermatitis, and reduction in final body weight (15%) were observed (DuPont 1976).

8.2.1.3 Toxicokinetics

The evaluation of available toxicokinetic information shows that 4,4′-MDA is absorbed by oral, dermal, and inhalation routes of exposure in humans and animals. Information from a number of case reports indicated that 4,4′-MDA can distribute to various organs after accidental ingestion of the chemical. There is no evidence for accumulation in the body. N-acetylation of 4,4′-MDA apparently represents the detoxification metabolic pathway. 4,4′-MDA and its metabolites are mainly excreted in the urine.

8.2.2 MDIs

Health effects data on any MDI isomer or mixture of isomers of the MDI subgroup were taken into consideration in this section, and health effect levels established for substances within the subgroup were selected to characterize the overall health effects associated with the MDIs subgroup. The rationale for this read-across is presented in Appendix A.

8.2.2.1 Carcinogenicity and genotoxicity

The European Commission has classified MDIs (CAS No. 101-68-8, 5873-54-1, 2536-05-2, 26447-40-5, 9016-87-9) as Category 2 carcinogens (suspected human carcinogens) (European Commission 2009, 2015b). The IARC has classified MDIs (CAS No. 101-68-8, 26447-40-5) as Group 3 carcinogens (not classifiable as to its carcinogenicity to humans) on the basis of inadequate evidence for its carcinogenicity in humans and limited evidence for carcinogenicity in experimental animals (IARC 1999). The discrepancies between the two classifications could be due to the fact that additional studies were considered by the EU, including a review (Feron et al. 2001) comparing the findings of the Reuzel et al. (1990, 1994a) and Hoymann et al. (1995) studies.

Two chronic animal toxicity studies conducted with MDIs were identified.

In an inhalation study conducted by Reuzel et al. (1990, 1994a), male and female Wistar rats (60/sex/group) were exposed to pMDI at concentrations of 0, 0.2, 1.0 or 6.0 mg/m^3, 6 hours/day, 5 days/week for 2 years. pMDI aerosols generated from pMDI liquid using compressed air were used. Eight pulmonary adenomas (6/60 in males, 2/60 in females) and one pulmonary adenocarcinoma (1/60 in males, 0/60 in females) were observed in the 6.0 mg/m^3 exposure group. Lung tumours were not identified in the other exposure groups. Tumours identified in other organs were not considered to be treatment-related. Non-neoplastic effects of this study are described in the subsection under “Other non-cancer effects”.

Hoymann et al. (1995) conducted an inhalation carcinogenicity study in female Wistar rats. The animals (80/group) were exposed to 4,4′-MDI aerosols at concentrations of 0, 0.23, 0.70 or 2.05 mg/m^3, 17 hours/day, 5 days/week for 2 years. Tumour incidence

data were available for the highest exposure group only. One animal (1/80) in the highest exposure group developed a single bronchio-alveolar adenoma.

A large retrospective cohort study was identified to investigate potential health effects associated with exposure to diisocyanates (Sorahan and Nichols 1993, 2002). The study included monitoring of 5824 male and 2464 female employees from 11 factories manufacturing flexible polyurethane foams. Of the 11 factories, 4 used toluene diisocyanates (TDIs) and 7 used TDIs and MDIs. Exposure levels were not available. Mortality and cancer morbidity data were collected from 1958 to 1998. No significant positive trend between the risk of lung cancer or the risk of non-malignant diseases of the respiratory system (no further details provided) and duration of exposures to diisocyanates was found in men. In women, there was a significant increase in standardized mortality ratio (SMR) for lung cancer, but the authors concluded that the development of lung cancer was not likely due to diisocyanate exposure (no explanation for this conclusion was provided There were limitations of the study; for example, smoking habits and dietary factors were not taken into account. The effects of sensitization were not examined in this study.

In *in vitro* mutation assays, MDIs yielded mixed results depending on the type of solvent used.

In Ames assays, results differed depending on whether MDIs were dissolved in DMSO, in acetone or in ethylene glycol dimethyl ether (EGDE). When MDIs were dissolved in DMSO, positive responses were observed in *Salmonella typhimurium* TA 98 and TA 100 in the presence of metabolic activation (S9). Negative responses were observed in other strains (TA 1535, TA 1537 and TA 1538) in the presence or absence of S9. Negative responses were observed in TA 98 and TA 100 in the absence of S9 (Andersen et al. 1980; Herbold 1980a, 1980b; Woolrich 1982; Shimizu et al. 1985; Herbold et al. 1998; Zeiger et al. 1987; Seel et al. 1999). When MDIs were dissolved in acetone, the results in *Salmonella typhimurium* TA 100 were weakly positive with S9 and negative without S9 (Herbold 1980c). When MDIs were dissolved in EGDE, negative responses were observed in strains TA 1535, TA 1537, TA 1538, TA 100 and TA 98 in the absence or presence of S9 (Herbold 1990a, 1990b; Herbold et al. 1998; Seel et al. 1999). Studies showed that traces of water content in commercial DMSO can hydrolyze the isocyanate groups of MDIs into a number of products including methylenediphenyl diamines (MDAs), ureas, polyureas, and carbon dioxide within a short period of time. Also, DMSO can act as a catalyst in the hydrolysis reaction, shown in IR spectroscopy and HPLC analysis (Herbold et al. 1998; Seel et al. 1999). In contrast, MDIs are more stable in EGDE even if traces of water are present. Herbold et al. (1998) examined the stability of MDIs in DMSO and in EGDE in the presence of traces of water. For MDIs dissolved in DMSO with 0.04% water content, HPLC analysis showed that the MDI content was 86.5% at the beginning, 22.1% after 15 minutes, and 1% after 30 minutes, and MDIs became not detectable after 45 minutes. For MDIs dissolved in EGDE with 0.07% water content, 99.1% of MDIs remained after 4 hours. When the water content increased to 0.47%, 93.3% of MDIs was detected after 1 hour, and 78.9% remained after 4 hours.

In mammalian cells, induction of gene mutation in mouse lymphoma L5178Y TK+/- cells was only observed in DMSO at high concentrations of MDIs in the presence of S9 (McGregor et al. 1981a, 1981b). These results might have been confounded by the stability of MDIs in DMSO. DNA damage was not observed in human cells exposed to 4,4′-MDI dissolved in EGDE (Vock et al. 1998). In a chromosome aberration assay, positive results were observed in human whole-blood lymphocytes treated with 4,4′-MDI dissolved in acetone. However, the presence of "polymer-like fibres" was observed on microscopic slides suggesting that MDIs might not be stable in acetone (Maki-Paakkanen et al. 1987). Positive results were observed in cell transformation assays when hamster cells were treated with MDIs dissolved in DMSO in the presence and absence of S9 (Poole and Harris 1980a, 1980b).

In vivo assays for MDIs included several DNA adduct assays and micronucleus induction assays. Weakly positive results were observed for DNA adducts in rats exposed to 4,4′-MDI either dermally or by inhalation (Vock and Lutz 1995a, 1997; Vock et al. 1995b, 1996). In some cases, the DNA radioactivity was too low for nucleotide analysis and the covalent binding index was very low compared to positive controls. Vock et al. (1995b) stated that in comparison with the genotoxic skin carcinogen 7,12-dimethylbenz[a]anthracene on the other hand, the DNA-binding potency of MDI was more than 1000-fold lower.. Mostly negative results were identified in micronucleus induction assays conducted in mice and rats by intraperitoneal injection or by inhalation (JETOC 1982; Zhong and Siegel 2000; Pauluhn et al. 2001; Lindberg et al. 2011).

Limited and inconclusive genotoxicity studies were identified in MDI-exposed humans. Marczynski et al. (1994a, 1994b, 2005) conducted several studies on the effect of MDIs on DNA damage either in MDI-exposed workers, in healthy volunteers or in mild asthmatic volunteers. The healthy and asthmatic volunteers had not previously been exposed to MDIs. Blood samples were collected before and after MDI inhalation exposure (0.05 to 0.31 mg/m^3 for up to 2 hours). DNA damage was analyzed in lymphocytes. No significant increase in DNA strand break frequency was observed. In the Marczynski et al. (2005) study conducted on healthy and asthmatic volunteers, the authors noted that there was a small and susceptible group (10%) that had higher frequencies of DNA strand breaks, though it did not reach statistical significance. The MDIs used in these studies consisted of a mixture with 60% MDIs, 30% various triisocyanates, and 10% undefined diisocyanates.

The mode of action for the respiratory tract tumours observed in rodents has not been fully elucidated. IARC (1999) noted that the incidence of lung tumours observed in Reuzel et al. (1994a) could not be "attributed confidently either to a non-specific small inhaled particle effect or to the chemical composition of the particles." There are two postulated mechanisms of carcinogenesis described by ECJRC (2005), one pertaining to sustained inflammatory response and another to a genotoxic mechanism via the potential MDA metabolite. However, MDAs were not identified in MDI toxicokinetic studies, and it has been suggested that MDAs are not significant metabolites in rats exposed to MDIs (see section 8.2.2.5).

8.2.2.2 Reproductive and developmental toxicity

No reproductive toxicity studies were identified. In a repeated-dose inhalation toxicity study conducted by Reuzel et al. (1994a), rats were exposed via inhalation to pMDI at concentrations of 0, 0.2, 1.0 or 6.0 mg/m^3, 6 hours/day, 5 days/week for 24 months. Information regarding the gross pathology and histopathology of testes were available and showed no exposure-related toxicity. In female rats, ovary weights were not measured.

In terms of developmental toxicity, Buschmann et al. (1996) reported a developmental NOAEC of 3 mg/m^3. A statistically significant increase in asymmetric sternebrae in rat fetuses was observed at 9 mg/m^3; however, there is uncertainty as to whether this anomaly, considered minor, is a treatment-related effect. Pregnant rats were exposed via inhalation to 4,4′-MDI at concentrations of 0, 1, 3, or 9 mg/m^3, 6 h/day, from gestation day (GD) 6 to 15. The fetuses were examined on GD 20. Maternal effects included a decrease in food consumption in all exposed groups during exposure, which returned to control values after the last exposure on GD 15. Significant increases in absolute and relative lung weights were observed in pregnant rats exposed to 9 mg/m^3. Asymmetric sternebrae is a common variant in this strain and in rats. The observed incidence is within the limits of biological variability of the rat strain used. In addition, the increased incidence occurred at doses that also caused maternal toxicity (i.e., decreased food consumption, increased lung weights). No other reproductive or fetal effects were observed; parameters measured included the number of corpora lutea, implantation sites, pre- and post-implantation loss, fetal and placental weights, gross and visceral anomalies, and degree of ossification.

8.2.2.3 Sensitization

The European Commission has classified MDIs (CAS No. 101-68-8, 5873-54-1, 2536-05-2, 26447-40-5, 9016-87-9) as Category 1 respiratory sensitizers and Category 1 skin sensitizers (European Commission 2015b).

Respiratory sensitization

Currently, there is no internationally harmonized standard or guideline for experimental animal studies for identification of potential respiratory sensitization for human health risk assessment (Health Council of the Netherlands 2008; IPCS 2012). The respiratory tracts of animals and humans are very different (Harkema et al. 2006; Zosky and Sly 2007), and there is limited confidence in the quantitative extrapolation of sensitization effect levels from animals to humans.

Guinea pig hypersensitivity is one of the more common non-standard tests used to examine sensitization potential. For this test, respiratory hypersensitivity was induced in guinea pigs that became sensitized after an acute exposure to a high concentration (135 mg/m^3 or above) of MDIs (Pauluhn and Mohr 1994; Pauluhn 1995). Respiratory hypersensitivity was also induced in guinea pigs that became sensitized after being

exposed to lower concentrations of MDIs for 5 consecutive days (17-22 mg/m^3, 3 h/day for 5 days) (Thorne et al. 1986; Karol and Thorne 1988; Griffith-Johnson et al. 1990). MDI-sensitized animals have been reported to develop cross-sensitization to other isocyanate compounds (McDonnell 1971).

A rodent asthma model based on allergic airway inflammatory responses in Brown Norway rats, measured as levels of eosinophils, neutrophils and lymphocytes in bronchoalveolar lavage, has been proposed (Pauluhn 2008a, Pauluhn and Poole 2011). Pauluhn et al. (2008a, 2011) established an elicitation threshold of 5 mg/m^3 of pMDI on the basis of induction triggered by an exposure to pMDI of 936 mg/m^3 via nose-only inhalation for 10 min/day for 5 days. This model is valuable in demonstrating some critical aspects of asthma and its pathogenesis. However, this elicitation threshold is not recommended as a direct point of departure for risk characterization in accordance with the Guidance for Immunotoxicity Risk Assessment for Chemicals (IPCS 2012).

In humans, the reported health effects associated with MDIs exposure can range from individuals being asymptomatic to severe responses such as hypersensitivity pneumonitis or severe asthma symptoms.

In the workplace, MDI-specific immunoglobulin E and G antibodies (IgE, IgG) have been detected in exposed MDI workers (Zeiss et al. 1980; Pezzini et al. 1984; Tse et al. 1985; Liss et al. 1988; Cartier et al. 1989). However, these specific antibodies are not good predictors of health effect risk (US EPA 1998; IPCS 2000). For example, elevated levels of the MDI-specific IgG can be found in both exposed asymptomatic workers and individuals diagnosed with occupational asthma (Lushniak et al. 1988; Baur et al. 1994).

Fatal asthma cases potentially linked to MDI sensitization as a result of exposure in occupational settings have been reported (NIOSH 1996; Carino et al. 1997; MIFACE 2003; MIOSHA 2004; Chester et al. 2005). Post-incident investigation often identified inadequate exposure controls (e.g., exhaust ventilation) and measured MDI concentrations.

Cases of MDI-related occupational asthma, where there was co-exposure to other substances, have been reported in various occupational settings including, manufacturing facilities, body shops, and hospitals (Liden 1980; Leroyer et al. 1998; Dietemann-Morland et al. 1991; Sommer et al. 2000; Lemière et al. 2002; Perfetti et al. 2003; Bonauto and Lofgren 2004; Chester et al. 2005; Suojalehto et al. 2011). In some of the cases, workers developed both respiratory and dermal sensitization (Kanerva et al. 2001; Donnelly et al. 2003; Valks et al. 2003; Stingeni et al. 2008). Cases of occupational hypersensitivity pneumonitis linked to MDI exposure have also been reported (Malo et al. 1982; Baur et al. 1984; Bascom et al. 1985; Walker et al. 1989; Schreiber et al. 2008). The concentration of MDIs inducing the sensitization effect is not always known. In some cases, spills of MDIs were identified.

A number of epidemiology studies that examined respiratory effects, including occupational asthma in manufacturing plants where workers handled MDIs, were

identified. Similar to the case reports, in most instances, the air concentrations of MDI in the workplace were not reported (Diller and Herbert 1983; Pham et al. 1988; Petsonk et al. 2000; Wang and Petsonk 2004).

The American Conference of Governmental Industrial Hygienists (ACGIH), the US Occupational Safety and Health Administration (OSHA) and NIOSH have identical occupational standard limits for MDI levels in the air: 0.05 mg/m^3 as an 8-h time-weighted average (TWA) and 0.2 mg/m^3 as the 10-minute ceiling limit. (ACGIH 1996; CDC 2012; OSHA 2012). In some plants where MDI levels in the air were monitored, the levels were reported to occasionally exceed the occupational standard limit (Vandenplas et al. 1993a; Pham et al. 1978). However, in plants where air concentrations of MDIs were monitored, the potential for dermal exposures and the degree of compliance with protective measures were not clearly described.

In a longitudinal cohort study, there were no significant changes in respiratory function in workers who were exposed to levels up to 0.01 mg/m^3 of MDIs in the air in a polyurethane foam plant (Sulotto et al. 1990). The exposure level was based on one week of continuous tape monitoring, and the workers had been working in the plant for an average of 14 years. Respiratory functions (forced vital capacity [FVC], forced expiratory volume in 1 second [FEV1], %FEV1/FVC, and FEF25-75) were measured.

In a cross-sectional study, workers were exposed to MDIs during window fixation and window glue processes in an automobile manufacturing company (Kakooei et al. 2006). On the basis of personal sampling measurements taken 3 times, the average MDI exposure level was 0.03453 mg/m^3 during the window fixation process and 0.02727 mg/m^3 during the window glue process. A significant decrease was observed in respiratory functions (decreased lung capacity, %FEV1/FVC and percent of peak expiratory flow [%PEF]) in workers compared to controls. However, the workers may have become sensitized over the years since they had worked in the same plant for an average of 6 years. The study was conducted in the summer, when windows of the plant were opened for ventilation. Workers reported that windows were kept partially or fully closed in the winter, suggesting increased air concentrations of MDI in the winter months.

In a cross-sectional study, MDI levels were monitored 24 h/day every day in a three-year-old urethane mould plant designed to minimize human exposure to MDIs (Bernstein et al. 1993). Area monitors were installed at multiple sites in the plant for continuous monitoring of MDIs. Although specific MDI concentrations in air were not available in the study report, it was indicated that measured levels had always been below the occupational standard limit of 0.05 mg/m^3. The entire workforce (243 workers) was involved in this study, and three cases of occupational asthma were diagnosed by physicians. The diagnosed workers all worked in areas where they could have been exposed accidentally to high levels of MDIs in the form of a liquid or fumes. One of the workers recalled the onset of asthmatic symptoms 2 weeks after an accidental exposure to a large MDI spill. One of the workers was a control subject selected randomly among workers who self-reported to be symptom-free but diagnosed by physicians with

possible occupational asthma on the basis of lung function testing. The three workers were transferred to a diisocyanate-free working environment and re-evaluated after a year. Lung function improved in all three workers. Physicians confirmed that the occupational asthma of these workers became inactive. The control worker who reported to be symptom-free also showed improved lung function after working in an isocyanate-free environment and was therefore confirmed to have had occupational asthma.

In a five-year longitudinal study conducted by Musk et al. (1982, 1985), 94 workers from 2 plants exposed to MDIs and TDIs were followed. TDI levels were measured over 4 years with a maximum level of 0.05 mg/m^3, and MDI levels were measured for 1 to 2 years with a maximum level of 0.04 mg/m^3. Over the 5 years of the study, 2573 environmental samples were collected. Workers were divided into 4 exposure groups (none, TDI-only, MDI-only, TDI and MDI-coexposed) using the collected environmental measurements and occupational history. Smoking status was also considered. No significant changes in pulmonary functions based on FEV1 values were observed in the exposed groups compared to the non-exposed group. The exposed subjects demonstrated a normal age- and smoking-related rate of decline in FEV1, which was not considered to be related to isocyanate exposure (Musk et al. 1982, 1985).

Gee and Morgan (1985) examined the ventilatory capacity of 68 workers exposed to MDIs and TDIs. The study included 42 workers who had been studied in 1971 by Musk et al. (1982, 1985) as a 10-year follow up. The mean annual concentrations of TDIs and MDIs were available for the periods 1973 to 1980 and 1975 to 1981, respectively. The highest mean annual concentrations of TDIs and MDIs were 0.024 mg/m^3 and 0.05 mg/m^3, respectively. No significant changes in the spirometry values (FVC and FEV1) of the exposed groups were observed compared to predicted FVC and FEV1 values.

MDIs were introduced in a woodchip board manufacturing plant that had never used isocyanates previously, as reported in a study by Vandenplas et al. (1993a), and a number of workers started to complain of respiratory symptoms as early as 2 weeks after MDIs were first used. After three months, 8 of the 167 workers employed in the plant were diagnosed with hypersensitivity pneumonitis associated with MDIs. Hypersensitivity pneumonitis was diagnosed using an MDI inhalation challenge. These workers developed immunoglobulin G (IgG) and IgE antibodies specific to MDI human serum albumin conjugates. The exposure level was approximately 0.06 mg/m^3 based on two surveys conducted two months after the initial use of MDIs.

In other epidemiological studies where MDI levels in the air were higher, ranging from 0.1 to 0.87 mg/m^3, cases of occupational asthma, respiratory and pulmonary effects were observed in exposed workers (Pham et al. 1978; Kolmodin-Hedman et al. 1980; Diller and Herbert 1982, 1983; Martin et al. 1982; Meredith et al. 2000).

Considering the overall information available from the epidemiological studies discussed above, it appeared that no significant effects were observed at 0.05 mg/m^3 for healthy individuals exposed to diisocyanates in an occupational setting. Uncertainties exist at

this effect level as limitations exist in the epidemiological database. A summary of epidemiological studies is presented in Table 8-9.

Table 8-9. Summary of epidemiological studies on MDIs

Isocyanate concentration	Exposure duration (average)	No. of subjects exposed (control)	Duration of study/ Health effects	Reference
0.01 mg/m^3 (maximum level of MDIs, measurements conducted over 1 week)	14 years	27 (27)	Followed for 1 week/no significant respiratory effects (FVC, FEV1, FEV1%/FVC, FEF25-75)	Sulotto et al. 1990
Average 0.03 mg/m^3 MDIs (personal sampling in 1 day, N=3/person)	6 years	39 (117)	Decreased respiratory functions compared to controls (lung capacity, %FEV/FVC, %PEF)	Kakooei et al. 2006
Less than occupational standard limit of 0.05 mg/m^3 MDIs (monitored 24 h/day since plant is operating)	18.2 months	243 workers (entire plant)	3/243 confirmed with occupational asthma	Bernstein et al. 1993
0.04 mg/m^3(MDIs) 0.05 mg/m^3 (TDIs) (maximum measured levels)	2 years MDIs) and 4 years (TDIs)	94 (from 2 plants)	Followed for 5 years/no significant changes in pulmonary functions (FEV1)	Musk et al. 1982, 1985

Isocyanate concentration	Exposure duration (average)	No. of subjects exposed (control)	Duration of study/ Health effects	Reference
0.05 mg/m^3 (MDIs) 0.024 mg/m^3 (TDIs) (highest mean annual concentration)	7-8 years (MDIs), 9 years (TDIs)	68 (12) from 2 plants	42 workers were studied in Musk et al. (1982, 1985) and followed for 10 years/no changes in respiratory and pulmonary functions (FVC and FEV1)	Gee and Morgan 1985
0.06 mg/m^3 MDIs (based on 2 surveys)	2 weeks to 3 months	167 workers (entire plant)	8 workers confirmed with hypersensitivity pneumonitis	Vandenplas et al. 1993
0.1–0.87 mg/m^3 of MDIs	1–7 years	various	Occupational asthma, decrease in pulmonary function	Pham et al. 1978; Kolmodin-Hedman et al. 1980; Diller and Herbert 1982; Diller and Herbert 1983; Martin et al. 1982; Meredith et al. 2000

Use of toluene diisocyanate (TDIs) as analogues

Effects of MDIs following acute or short-term exposure have not been examined systematically in human volunteer studies, even though some of the occupational cohorts may have had acute exposures. A level of uncertainty in exposure estimates from the epidemiology studies exists. To facilitate the human health effects assessment, a search was conducted to identify appropriate chemical analogues that are structurally, physicochemically and toxicologically similar for read-across purposes. TDIs were identified as appropriate analogues in this assessment to derive effect levels for respiratory effects, including sensitization, from acute exposure to MDIs. The rationale for this read-across is presented in Appendix H. Key human volunteer studies examining effects of acute or short-term exposure to TDIs are described below and summarized in Table 8-10.

There were several TDI inhalation studies conducted on human volunteers who had not previously been exposed to isocyanates. No respiratory effects were observed when 17 healthy humans were exposed to TDIs at 0.030 mg/m^3 for 6 hours followed by an exposure to 0.14 mg/m^3 of TDIs for 20 minutes (Vandenplas et al. 1999). No respiratory effects were observed when healthy or asthmatic volunteers were exposed to TDIs at 0.14 mg/m^3 for 15 to 30 minutes in 3 independent studies by Fabbri et al. *(*1987), Moller et al. (1986), and Chester et al. (1979). When 10 healthy volunteers were exposed to TDIs at 0.14 mg/m^3 for 2 hours, 1 volunteer responded with a positive airway reaction (Vogelmeier et al. 1991). In asthmatic volunteers, i.e., with airways possibly sensitized to multiple allergens, positive airway reactions were observed at an exposure level as low as 0.071 mg/m^3 for a 1- to 2-hour exposure duration (Vogelmeier et al. 1991; Baur 1985).

Table 8-10. Summary of human volunteer studies with TDIs

Exposure conditions	No. of subjects	Health effects	References
0.030 mg/m^3 for 6 h, followed by 0.140 mg/m^3 for 20 min	17 healthy volunteers (smokers and non-smokers)	No adverse health effects	Vandenplas et al. 1999
0.14 mg/m^3 for 15–30 min	6–10 healthy volunteers in each study; 10 asthmatic volunteers in one study	No adverse health effects	Fabbri et al. 1987; Moller et al. 1986; Chester et al. 1979
0.071 mg/m^3 for 1 h, rest for 45 min, 0.14 mg/m^3 for 1 h	10 healthy volunteers; 15 asthmatic volunteers (13 subjects continued at 0.14 mg/m^3)	**Healthy volunteers:** No asthmatic response (defined as 100% increase of airway resistance) **Asthmatic volunteers:** At 0.071 mg/m^3, 1 subject developed a severe asthmatic reaction; At 0.14 mg/m^3, 1 subject developed an asthmatic reaction	Baur et al. 1994
Healthy volunteers: 0.14 mg/m^3 for 2 h; **Asthmatic**	10 healthy volunteers; 15 asthmatic volunteers	**Healthy volunteers:** An initial increase in airway resistance returned to normal after 30 minutes of exposure, 3 subjects reported eye irritation	Baur 1985

Exposure conditions	No. of subjects	Health effects	References
volunteers: 0.071 mg/m^3 for 1 h, rest for 45 min, 0.14 mg/m^3 for 1 h		and/or cough **Asthmatic volunteers:** No significant effect as a group, 4 subjects developed significant bronchial obstruction, increased specific airway resistance > 50%. The 4 subjects also reported chest tightness, rhinitis, cough, dyspnea, throat irritation and/or headache.	
Healthy volunteers: 0.14 mg/m^3 for 2 h **Asthmatic volunteers:** 0.071 mg/m^3 for 1 h, followed by 0.14 mg/m^3 for 1 h	10 healthy volunteers; 14 asthmatic volunteers	**Healthy volunteers:** 1 subject developed a positive airway reaction. **Asthmatic volunteers:** 1 subject developed positive airway reaction at 0.071 mg/m^3, 2 subjects developed positive airway reaction at 0.14 mg/m^3.	Vogelmeier et al. 1991

On the basis of the information available from controlled human studies conducted with TDIs discussed above, an acute respiratory effect level for asthmatics was established at 0.071 mg/m^3 for asthmatics and at 0.14 mg/m^3 for healthy volunteers.

In sensitized individuals, a very low concentration of MDIs, called the elicitation concentration, can trigger sensitization responses such as respiratory effects and asthma. The lowest identified elicitation concentration documented in the literature is 0.00051 mg/m^3 in a dermally sensitized nurse who occasionally applied orthopedic plaster casts containing MDIs to patients (Suojalehto et al. 2011). Other elicitation concentrations identified in the published literature, ranging from 0.01024 to 0.0026 mg/m^3 (Suojalehto et al. 2011; Lemière et al. 2002), indicated that an elicitation threshold level can be exceptionally low in sensitized individuals. In other individuals, elicitation concentrations ranging from 0.05 to 0.1 mg/m^3 of MDIs were identified (Karol 1986; Talini et al. 2010; Carino et al. 1997). Thus, the concentration that can elicit a response among sensitized individuals is highly variable.

Dermal sensitization

The data are consistent in demonstrating that MDIs are skin sensitizers. Assays for skin sensitization in the mouse local lymph node assay (LLNA) show that MDIs are potent skin sensitizers. Five independent mouse LLNA studies showed positive results (Dearman et al. 1992; Plitnick et al. 2005; Selgrade et al. 2006; US EPA 2006; Study Submission 2012i). An EC3 value (the dose of a chemical that is required to elicit a 3-fold increase in proliferation activity in LLNA assay compared to concurrent vehicle controls) of 0.08% was identified in Selgrade et al. (2006). In two other studies, EC3 values of 0.07% and 0.28% were approximated by Health Canada using the linear regression model described in Basketter et al. (2005) (Dearman et al. 1992; Plitnick et al. 2005). EC3 values cannot be identified or calculated in the other two studies (US EPA 2006; Study Submission 2012i).

A comparison of EC3 values from LLNA and human sensitization tests of large datasets of various chemicals suggests that EC3 values correlate linearly with human sensitization thresholds (Griem et al. 2003; Basketter et al. 2005; Api et al. 2009). Thus, EC3 values have been suggested as adequate values to determine a non-expected sensitization induction level (NESIL) or to serve as a surrogate NOEL in quantitative risk assessment (Api et al. 2008; Loveless et al. 2010; IPCS 2012; Peiser et al. 2012).

According to IPCS (2012), the dose metric recommended for use in dermal sensitization risk assessment is the amount of a chemical applied per area of skin. From the LLNA studies conducted by Plitnick et al. (2005), Selgrade et al. (2006) and Dearman et al. (1992), EC3 values were converted to 0.0175 mg/cm^2, 0.02 mg/cm^2 and 0.070 mg/cm^2, respectively.[4] The EC3 value of 0.02 mg/cm^2 from Selgrade et al. (2006) is considered to be the most appropriate value since the study was conducted according to OECD standard testing guidelines.

In addition to LLNA studies, other experimental models that assess dermal sensitizing potential also showed consistent results. Three mouse ear swelling tests conducted on 2 different strains of mice showed positive results (Thorne et al. 1987; Ishizu and Goto 1980; Tanaka et al. 1987). Mixed results were observed in two guinea pig maximization studies (Duprat et al. 1976; Tanaka et al. 1987).

Two healthy volunteers developed skin sensitization 7 to 10 days after an acute dermal exposure to 4,4′-MDI (Hamada et al. 2012). The volunteers, who had no known history of allergy to isocyanates, were dermally exposed to 4,4′-MDI (surface concentration of 0.800 mg/cm^2), and the exposed area was occluded for 8 hours. The surface concentration of 0.800 mg/cm^2 is based on regular patch testing dose of 20 mg of 2.0% vt/vol commercial available patch test preparation. After a period varying between 7 and 10 days post-exposure, allergic contact dermatitis reactions occurred. Patch testing using serial dilutions with 4,4′-MDI, 4,4′-MDA, p-phenylenediamine (PPD) or

[4] Calculation of the skin area dose is based on the assumption that 25 µl of the dose was applied onto 1 cm^2 of the ear skin on each mouse ear per IPCS (2012).

dicyclohexylmethane-4,4′-diisocyanate (DMDI) was performed. Patch testing indicated that both volunteers were sensitized to 4,4′-MDA. One of the volunteers was sensitized to 4,4′-MDI. Some studies proposed that MDA is a marker for MDI contact sensitization (Estlander et al. 1992; Goossens et al. 2002; Frick-Engfeldt et al. 2007). Patch testing in dermatitis patients who are positive to 4,4′-MDI and pMDI has been shown to have positive reactions to 4,4′-MDA. However, the authors also noted that the results of the study do not fulfil the criteria in the traditional definition of active sensitization. The study was considered limited due to its very small sample size.

There are a number of case studies describing workers who have developed dermal sensitization after occupational exposure to MDIs (Liden 1980; Estlander et al. 1992; Hannu et al. 2005; Engfeldt et al. 2013; Engfeldt and Ponten 2013; Kiec-Swierczynska et al. 2014). Furthermore, cross-reaction with other isocyanates has been observed. Stingeni et al. (2008) reported that a worker exposed to 4,4′-MDI occupationally for a year developed isocyanate-specific IgE positive to MDI, HDI and TDI even though he had never been exposed to either HDI or TDI. In animal studies, mouse ear swelling tests also showed evidence of cross-reactivity with other isocyanates (Thorne et al. 1987).

Some evidence suggests dermal and respiratory sensitization responses are linked, since sensitization is a systematic response, and dermal exposure to MDIs may lead to subsequent respiratory sensitization.

In a study by Rattray et al. (1994), guinea pigs were acutely exposed to concentrations of MDIs ranging from 19.4 to 24.7 mg/m^3. Although respiratory hypersensitivity was not observed following the inhalation challenge, some animals developed dermal hypersensitivity. In another study, when guinea pigs were exposed to MDIs intradermally either once or repeatedly, respiratory hypersensitivity was observed following the inhalation challenge with MDIs (Pauluhn and Mohr 1994). In a mouse asthma model, animals were first sensitized dermally, followed by a resting period and a 30-minute inhalation challenge with MDI-albumin conjugates (Wisnewski et al. 2011b). These mice developed non-specific airway hyperreactivity, which was considered an asthma-like response. Similar effects were demonstrated in rat asthma models by Pauluhn (2008b) and Selgrade et al. (2006). Overall, animal studies showed consistent results in demonstrating that induction by skin exposure can lead to asthma-like responses with subsequent inhalation exposures.

In manufacturing plants where air MDI levels are continually measured and maintained below the occupational exposure limit, new cases of isocyanate-induced respiratory sensitization continue to be identified (Petsonk et al. 2000; Bernstein et al. 1993; Wang and Petsonk 2004). Evidence suggests that skin exposure might be an area that has been overlooked (Bello et al. 2007b; Redlich 2010). Dermal exposure levels in occupational settings have rarely been measured. In one case, a worker developed allergic contact urticaria and asthma following direct extensive hand contact with a large amount of MDI glue for a prolonged period of time (Valks et al. 2003). The dermal exposure level was unknown, and inhalation exposure may have been present. There

are a number of documented cases where workers who applied MDI-based orthopedic casts developed what is thought to be MDI-related sensitization (Donnelly et al. 2003; Sommer et al. 2000; Suojalehto et al. 2011). However, inhalation and dermal exposure levels were unknown. Suojalehto et al. (2011) estimated exposure levels in a hospital setting by measuring diisocyanate concentrations in the air during a casting simulation (the synthetic plaster cast was rolled over a piece of wood) and during normal casting work in two hospitals. Diisocyanate concentrations in the air were measured in the breathing zone, near the casting spot (15 cm above), and near the sawing spot (when removing cast), and levels ranged from 0.02 to 2.5 µg NCO/m^3. The measured levels were below the Finnish occupational exposure limit of 35 µg NCO/m^3, which corresponds to about 100 µg/m^3 monomeric MDI. The sampling period in the breathing zone in the two hospitals included phases with no casting work.

8.2.2.4 Other non-cancer effects

Respiratory effects following inhalation of MDIs, other than sensitization-related effects, have been reported in experimental animals.

Transient changes in the bronchoalveolar lavage (BAL) fluid of rats that were exposed (nose only) to MDIs at 0, 0.7, 2.4, 8 or 20 mg/m^3 for 6 hours (Pauluhn 2000) were observed. Animals were observed and BAL fluid was collected 3 hours, 1 day, 3 days and 7 days after exposure. On the basis of transient changes in BAL fluid at 0.7 mg/m^3 (changes in lactate dehydrogenase, total protein, angiotensin-converting enzyme and phospholipids observed 3 hours and one day post-exposure were restored to control levels on day 3 post-exposure), the author concluded that a transient dysfunction of the pulmonary epithelial barrier was observed, which indicated a dysfunction of pulmonary surfactant. In a subsequent publication by Pauluhn (2002) based on the Pauluhn (2000) study and other studies, an acute irritant threshold concentration of 0.5 mg/m^3 was estimated. Minimal histological changes in the lungs were observed at a concentration of 10 mg/m^3 in rats exposed to pMDI at 0, 10, 30 or 100 mg/m^3 for 6 hours (Kilgour et al. 2002).

In a short-term toxicity study, a LOEC of 1 mg/m^3 was identified. This effect level was based on a transient increase in surfactant levels in the alveolar macrophages and lumina in rats exposed to pMDI at concentrations of 0, 1, 4 or 10 mg/m^3 for 6 hours/day, 5 days/week for 4 weeks (Kilgour et al. 2002). In the same study, minimal histological changes, bronchiolitis and thickening of the central acinar regions were observed at 4 mg/m^3. The effects were recovered by 30 days post-exposure.

For subchronic exposure, a LOEC of 1.0 mg/m^3 was identified on the basis of histopathological changes in the lungs observed in female rats. In the study, animals were exposed to 4,4′-MDI at 0.3, 1.0 or 3.0 mg/m^3 for 18 hours/day, 5 days/week for 90 days (Heinrich et al. 1991). However, only an abstract of the study was available. A more appropriate LOEC for subchronic exposure was 4.1 mg/m^3. It is based on accumulation of alveolar macrophages in the lung, macrophages accumulation in the mediastinal lymph node and histopathological changes in the nasal cavity in rats

exposed to pMDI at 0, 4.1, 8.4 or 12.3 mg/m^3, 6 hours/day, 5 days/week for 13 weeks (Reuzel et al. 1994b).

Reuzel et al. (1990, 1994a) identified a chronic NOAEC of 0.2 mg/m^3 on the basis of a significant increase in basal cell hyperplasia in the olfactory epithelium and a significant increase in Bowman's gland hyperplasia in male rats at the next dose level of 1.0 mg/mg^3. Male and female rats were exposed to pMDI at 0, 0.2, 1.0 or 6.0 mg/m^3, 6 hours/day, 5 days/week for 24 months (Reuzel et al. 1990. 1994a). In both sexes, there was a significant accumulation of macrophages with yellow pigment in the lungs and the mediastinal lymph nodes, where the effect was considered minimal at 1.0 mg/m^3 and moderate at 6.0 mg/m^3. Localized fibrosis surrounding the alveolar duct epithelialization was observed at 1.0 mg/m^3 or higher.

Overall, the respiratory tract was the target organ most affected in the inhalation studies, with initial inflammatory responses followed by an increase in cell proliferation. With prolonged exposure, histological changes appeared and eventually resulted in hyperplasia.

8.2.2.5 Toxicokinetics

In animal inhalation studies, exposure to pMDI results in significant deposition both in the nasal region and in the alveolar region of the lungs (Reuzel et al. 1990; 1994a, 1994b). In an unpublished pharmacokinetic study (Saclay 1977), nose-only exposure of male Sprague-Dawley rats (12) to an aerosol (particle sizes less than 5 µm) of radiolabeled monomeric MDI for 15 minutes resulted in distribution of radioactivity, predominantly to the lungs and a variety of extrarespiratory sites, principally muscle, liver, kidneys, and the digestive tract. Labeling of the digestive tract was considered to be a result of transference of labeled material from the lungs. After 4 days, 70% of the absorbed dose was eliminated, with fecal elimination being predominant (57%). When animals were exposed to MDIs in the air (whole body or head only) (Laboratoire d'Etudes du Métabolisme des Médicaments 1977; Kennedy and Brown 1998; Gledhill et al. 2005), which meant they could be exposed to MDI vapour through the nose (via inhalation) and the mouth (by oral), MDIs were widely distributed in all tissues, with higher distribution in the respiratory and pulmonary tracts, gastrointestinal system and blood, followed by liver and kidneys. Generally, a high proportion of MDI was excreted in feces and a smaller amount was excreted in urine. In the Gledhill et al. (2005) toxicokinetic study tested on rats, 79% of the MDI dose was excreted in feces and 5% was excreted in urine over 168 hours post-exposure, whereas in bile duct cannulated animals, 12, 14 and 34% of the dose was found in urine, bile and feces, respectively, over 48 hours post-exposure. The high proportion of fecal excretion was probably due to oral intake from the mouth during whole-body or head-only exposure to MDIs. Several metabolites identified were N-acetylated and N-acetylated-hydroxylated products, which suggested that metabolism pathways involved acetylation followed by oxidation. Given MDAs were not identified in toxicokinetic study, it has been suggested that MDAs are not a significant metabolites in rats exposed to MDIs.

MDIs can form protein adducts in the body. Typically, MDI-related albumin adducts and hemoglobin adducts were measured from blood or urine samples using a harsh hydrolysis method in the laboratory. After hydrolysis, any MDI will be hydrolyzed to MDA. Thus, the level of protein adducts is measured on the basis of the level of 4,4′-MDA in the samples. This hydrolysis method cannot distinguish MDI adduct or any potential MDA adduct. Although theoretically possible, little evidence is available to that shows that MDIs biotransform to free MDAs in the body. MDIs can possibly form protein adducts via mechanisms without the formation of MDAs. In the case of TDIs, it was found that TDIs can form adducts with glutathione (GSH) in the lower respiratory tract (Wisnewski et al. 2011a). The GSH-bound TDIs can travel to other parts of the body to form more stable adducts.

According to an unpublished study investigating the toxicokinetics of MDIs in pregnant Wistar rats, animals were exposed to MDIs at 20 mg/m^3 for 6 hours by inhalation on GD19. Blood samples were collected from the animals. MDA levels, after acid hydrolysis of MDIs, were measured in the maternal blood, amniotic fluid, fetus and placenta immediately after exposure. The highest level of MDA was found in the maternal blood, followed by the placenta, fetus and amniotic fluid (Bartsch et al. 1996).

In an *in vitro* dermal absorption study with guinea pigs, rats and human skin, approximately 58% to 91% of the dose was retained in the skin (Clowes 1997). In another *in vitro* skin absorption study conducted in guinea pig skin, absorption of MDIs (measured using attenuated total reflectance-Fourier transform infrared (ATR-FTIR) spectrometry) from the skin surface was rapid (85% was absorbed in 30 minutes) (Bello et al. 2006). The MDIs were found to diffuse into deeper layers of the skin.

In *in vivo* studies in rats, the systemic dermal absorption of ^{14}C-4,4′-MDI was low, i.e., at or below 1% of the applied dose (Leibold et al. 1998; Hoffmann et al. 2010). When MDIs were intradermally administered, dermal absorption was 26%. Mild soap and water were found not to be effective in removing MDI from the skin (Wester et al. 1999).

In a pilot dermal uptake study, two female healthy volunteers who had no previous history of contact allergy to isocyanates or any respiratory symptoms that could be related to isocyanates were dermally exposed to 4,4′-MDI (Hamada et al. 2012). Quantities of 10 mg or 25 mg of 4,4′-MDI were dermally applied to the volunteers, corresponding to a surface concentration of 0.8 mg/cm^2, and the treated area was occluded for 8 hours. Seventy percent of the 4,4′-MDI was recovered from the skin surface, suggesting that the maximal possible absorbed portion was 30%. However, the study did not derive a percent dermal absorption.

Liljelind et al. (2010) performed an estimated comparison of body burden from dermal exposure versus inhalation exposure to MDIs using the assumptions of a dermal uptake of 1%, a breath volume of 10 m^3 for 8-hour work shift and 70% uptake from the breathed air. The authors estimated that the contribution to the body burden from dermal exposure would be approximately 20 times less than that for inhalation exposure in an estimated exposure scenario.

8.3 Characterization of Risk to Human Health

8.3.1 MDAs

No reports of measured concentrations of 4,4′-MDA or pMDA in environmental media or food in Canada were identified. Given the low vapour pressure and high rate of atmospheric degradation of 4,4′-MDA and pMDA, neither are expected to be present in ambient air. The MDA substances are not manufactured in Canada and are not used to manufacture MDI. According to the available information, industrial uses of MDA and pMDA substances are limited to a small number of operations in Canada. As such, exposure to the general population from environmental media is not expected. 4,4′-MDA and pMDA are not reported to be used in consumer products in Canada. Exposure of the general population to 4,4′-MDA and pMDA is therefore not expected.

Considering principally assessments by international and other national agencies (IARC, European Commission and OECD) and the available information, a critical effect for characterization of risk to human health for 4,4′-MDA is carcinogenicity. Increased incidences of thyroid and liver tumours were observed in a two-year oral study in rats and mice. There were also some uncommon tumours observed in exposed rats at low incidences, namely adrenal pheochromocytomas in male mice and alveolar/bronchiolar adenoma and malignant lymphomas in female mice. In addition, dermal application of 4,4′-MDA has resulted in an dose-related increase in the incidence of hepatic tumours in female mice. Epidemiological studies have also provided some evidence of bladder cancer in occupationally exposed humans.

As exposure of the general population to 4,4′-MDA and pMDA is not expected, the risk to human health is expected to be low. While exposure of the general population to 4,4′-MDA and pMDA is not of concern at current levels, they might have a potential health effect of concern should exposures increase.

8.3.2 MDIs

Considering the assessments of several international regulatory agencies (US EPA 1998; IPCS 2000; ECJRC 2005) and available information, critical effects associated with exposure to MDIs are carcinogenicity following inhalation exposure and respiratory and dermal sensitization. Lung tumours were observed in rats exposed to high concentrations of MDIs by inhalation for 2 years, but not at lower concentrations. The collective evidence from genotoxicity studies suggests that MDIs are not likely to be mutagenic. Some positive genotoxicity results were observed in *in vitro* studies but were associated with uncertainties in the selection of solvents. DNA adduct formation is characterized as weakly positive *in vivo.*

The European Commission has classified MDIs as Category 1 respiratory sensitizers and Category 1 skin sensitizers. Animal experimental studies, human case reports and epidemiological studies all indicate that MDIs are associated with sensitization of the respiratory tract. Cross-reactivity with other isocyanates was also observed in humans and in animals. Currently, no validated animal testing models are available to

characterize respiratory sensitization. The dose-response relationship extrapolation from animals to humans for the immune-related endpoint is not clear (IPCS 2012). In an EU risk assessment report conducted on MDIs, a number of animal studies were described for characterizing the respiratory sensitization endpoint, but "none are considered as validated assays to assess the potential for respiratory sensitization or asthma in humans" (ECJRC 2005).

In two longitudinal cohort studies where workers occupationally exposed to MDIs and TDIs were followed for 5 or 10 years, no significant changes in respiratory or pulmonary functions were observed when isocyanate concentrations in the air were up to 0.05 mg/m^3 (Musk et al. 1982, 1985; Gee and Morgan 1985). Three cases of occupational asthma (among 243 workers) were observed in a study by Bernstein et al. (1993), where MDI levels in the air had never exceeded 0.05 mg/m^3 when monitored 24 hours per day every day in a three-year-old manufacturing plant. However, this incidence is considered low. It is unclear whether the three workers were previously sensitized, and the asthma became inactive and lung functions improved in the workers after they were transferred to an isocyanates-free environment for a year. Another epidemiological study reported workers developing hypersensitivity pneumonitis after two weeks to three months of exposure to a concentration of MDIs of approximately 0.06 mg/m^3 (Vendenplas et al. 1993a). There is uncertainty around the actual exposure level causing an effect since monitoring took place two months after the initial use of MDIs.

On the basis of the collective data from MDI-related epidemiological studies in occupational settings, and taking into account the limitations of the studies, it was considered reasonable to establish an effect level at 0.050 mg/m^3 below which no significant respiratory effects were observed in humans repeatedly exposed to airborne MDIs. The same effect level was selected in the Chemical Safety Report on 4,4′-MDI submitted to European Chemicals Agency under REACH (MDI Consortium 2012). In that report, a derived no-effect level (DNEL) for acute inhalation of 0.05 mg/m^3 was used to characterize the risk from exposure to MDI for the general population; it was based on the German MAK commission ceiling limit value of 0.1 mg/m^3 adjusted for differences between workers and the general population.

Human studies involving acute duration exposure to isocyanates (TDIs) were identified. TDIs are considered to be appropriate analogues for MDIs given similar chemical substructures and similar respiratory and sensitization effects observed in humans and animals. An acute respiratory effect level was identified at 0.14 mg/m^3 on the basis of possible transient increase in airway resistance in 1 out of 10 healthy volunteers exposed to TDIs for 2 hours (Vogelmeier et al. 1991)). Of note, this level is not significantly different from the occupational 10-minute ceiling limit of 0.2 mg/m^2 for MDIs in the air (ACGIH 1996; CDC 2012; OSHA 2012).

A potential source of exposure to MDIs is via inhalation of ambient air for the general population residing in the vicinity of industrial sites (e.g., wood product manufacturing plant using MDIs). Comparison of the upper-bounding estimate of environmental MDI concentration of 5.4×10^4 mg/m^3 in the air near an industrial site to the effect level of

0.05 mg/m^3, based on no significant respiratory effects observed in humans in MDI-related epidemiological studies, results in a margin of exposure (MOE) of 90. Comparison of this same upper-bounding estimate of air concentration to the level at which no tumour or any adverse effect was observed in a chronic two-year inhalation study conducted on experimental animals (NOAEC of 0.2 mg/m^3, based on a significant increase in basal cell hyperplasia in the olfactory epithelium and a significant increase in Bowman's gland hyperplasia in male rats at the next dose tested) (Reuzel et al. 1990, 1994a) results in a MOE of 400. Comparison of this upper-bounding estimate of air concentration to the level associated with incidences of lung tumours in the same two-year inhalation study (i.e., 6.0 mg/m^3) results in a MOE of 11 000. These MOEs are considered to be adequate to account for uncertainties in the exposure and health effect databases.

Another potential source of exposure to MDIs for the general population of Canada is expected to be from use of DIY products. Exposure to these products would be short-term and may occur through inhalation and dermal routes. Margins of exposure for these scenarios were derived using an effect level of 0.05 mg/m^3 identified from the MDI epidemiological studies. Use of this effect level as a critical endpoint for characterizing the risk from use of DIY products is considered conservative given that it is based on observation of effects in workers exposed over a longer duration (continuously throughout an 8-hour work day over several weeks to several years) than that of DIY product users. Therefore, inhalation MOEs were also estimated using an acute respiratory effect level of 0.14 mg/m^3 identified from studies conducted on healthy volunteers exposed to TDIs for a short duration (up to 2 hours). It should be noted that both critical effect levels are considered in the risk characterization because of uncertainties in the health effect database, the severity of health effects (persistent and long lasting adverse effects after sensitized) and the complexity of the health endpoint (respiratory sensitization), for which a mechanism of action is largely unknown. Table 8-11 presents inhalation MOEs based on both critical effect levels for each DIY product scenario and its associated estimated exposure level.

The inhalation MOEs for DIY products are considered to be adequate to account for uncertainties in the exposure and health effect databases, except for the low-pressure two-component spray polyurethane foam products.

For homeowner application of a low-pressure two-component spray polyurethane foam product, inhalation MOEs range from 0.6 to 1.7 when the product is used for insulation purposes and from 0.5 to 3.5 when the product is used for sealant purposes. These MOEs are considered to be inadequate.

In the MDI risk assessment conducted by the EU, a NOAEC of 0.5 mg/m^3, based on an estimated acute irritant threshold concentration for rats (Pauluhn 2000; 2002), was selected for the characterization of risk of consumers from short-term inhalation exposure to MDIs (ECJRC 2005). Comparison of the EU NOAEC with the exposure concentrations selected in this assessment (Table 8-11) to represent exposure during homeowner application of a two-component spray polyurethane foam product (for either

insulation or sealant purposes) would result in MOEs that would be considered inadequate to account for uncertainties in the exposure and health effect databases. California EPA (2015) proposed a MDI/pMDI acute reference exposure level (REL) of 12 µg/m^3 based on a LOAEC of 0.7 mg/m^3 from rats (Pauluhn 2002). Although the report was a draft, the California EPA considered this REL to be reasonably protective against sensitization under a scenario of infrequent repeated acute exposures. The exposure concentrations representing homeowner application of a low-pressure two-component spray polyurethane foam product (for either insulation or sealant purposes) in this assessment were higher than the California EPA REL. Therefore, the human health risk would not be considered acceptable.

Table 8-11. Margins of inhalation exposure from use of DIY products containing MDIs

Product	Exposure concentration (mg/m^3)	MOE (based on a critical effect level of 0.05 mg/m^3 MDIs from a human study)	MOE (based on a critical effect level of 0.14 mg/m^3 TDIs from a human study)
Low-pressure two-component spray polyurethane foam (between joists for insulation purposes)	0.082[a]	0.6	1.7
Low-pressure two-component spray polyurethane foam (along joists and corners and in cracks for sealant purposes)	0.04–0.1[b]	0.5–1	1.4–3.5
One-component polyurethane foam sealant	0.0065[c]	8	22
Polyurethane sealant	0.00063–0.0010[d]	50–80	140–220

Floor/wall adhesive	0.00013–0.00047[d]	100–400	300–1100
Construction glue	0.0014–0.0021[d]	20–40	67–100
Generic/hobby glue	1.0×10^{-5} –1.2×10^{-4} [d]	400–5000	1200–14 000
Super glue	4.1×10^{-8} [d]	> 10 000	> 10 000
Hot-melt adhesive	7.9×10^{-8} [d]	> 10 000	> 10 000

[a] Measured air concentration (See Table 8-4, Appendix F); [b] Measured air concentration, (See Table 8-5, Appendix F); [c] Measured air concentration, (See Table 8-6); [d] Modelled air concentrations (See Table 8-7, Appendix G).

Collective evidence from experimental animal and human case studies and epidemiological data show that MDIs are strong skin sensitizers. In addition, evidence in experimental animals suggests that dermal exposure prior to inhalation exposure could trigger respiratory hypersensitivity, highlighting the importance of minimizing dermal contact.

8.4 Uncertainties in Evaluation of Risk to Human Health

8.4.1 MDAs

Although there is a lack of Canadian environmental monitoring of MDAs, there is confidence in the information indicating that the presence of MDA substances in the environment is likely to be low. There is moderate to high confidence that 4,4′-MDA presence in food (from the use of cooking utensils containing azo dyes) is minimal.

No adequate health effects data have been identified for pMDA. Therefore, the health effects assessment for 4,4′-MDA has been applied to pMDA. This screening assessment does not include a full analysis of the mode of action of effects, including cancer, associated with exposure to 4,4′-MDA.

8.4.2 MDIs

There are uncertainties associated with the assessment of human exposure to MDIs from environmental media. Although there were no empirical data on the concentration of MDIs in environmental media such as water or soil, the substance is not expected to occur or persist in these media due to its reactivity. With respect to concentrations in air, there are uncertainties associated with the environmental estimates using a single-source Gaussian plume model and exact proximity of facilities to populated areas. However, the estimate of exposure from air was based on conservative assumptions.

With regard to consumer product exposure, there are uncertainties associated with the use of studies measuring MDI air concentrations during application by professionals to derive general population exposure. Training and experience of applicators and ventilation levels may not be representative of a homeowner scenario (may represent an over- or under-estimate of homeowner exposure depending on the parameter). For some of these studies, there is uncertainty in assigning the value of half the limit of detection (LOD) to those MDI concentrations that were reported as being below the LOD. However, there is a moderate to high confidence in the exposure assessment in that empirical data were used, maximum exposure levels measured in the studies were used, and the low-pressure two-component SPF products used in the studies are similar to those typically used for DIY applications.

There are uncertainties associated with the assumptions used in estimating exposure with ConsExpo. However, these assumptions are considered conservative, e.g., modelled dermal estimates do not consider the layer thickness of the skin and assume 100% of MDIs in the product will contact the skin.

The empirical health effects data for MDIs are available both in humans and in animals. Uncertainty exists in human epidemiological studies involving occupational exposure. In studies where sensitization was identified, insufficient information was provided to ascertain that workers were not previously sensitized either from exposure to higher concentrations in the same plant occurring prior to measurements or from exposure to MDIs in settings other than the workplace. The “healthy worker” effect might have biased the results of cross-sectional and longer-term epidemiological studies (Le Moual et al. 2008). There is uncertainty regarding the accuracy of the MDI exposure levels reported in occupational settings. The reported MDI levels in the air vary depending on the methodology used. MDI concentrations measured in the air in occupational settings depend on the locations of the air monitoring devices, the time of day at which measurements are taken, and the type of work being done during measurements. The measured exposure levels might not have taken into account accidental spill or exposure to heated MDI. Workers were likely to have been exposed to MDIs via both the inhalation and dermal routes. However, dermal exposure levels were not measured. In addition, occupational workers tend to be intermittently exposed to higher levels of MDIs and continuously exposed to low levels of MDIs in the workplace, which is a different exposure pattern than that of the general population using consumer products. The use of a critical effect level based on MDI-related epidemiological studies in occupational settings to compare with short-term exposure scenarios of consumer DIY products is considered to be conservative; however, it is considered to be appropriate because of uncertainties in the health effect database, the severity of the adverse health effect and the complexity of the health endpoint. There is some uncertainty associated with the use of a structural analogue to characterize human health effects. However, TDIs and MDIs are all isocyanates and have similar health effects both in humans and in animals. The use of a health effect level based on a TDI study for the MDI risk characterization also presents uncertainty in that it is based on effect resulting from inhalation of vapours, while the use of MDI-containing consumer products may result in exposure to both vapours and aerosols. Incidences of lung tumours were observed in a

two-year inhalation study (Reuzel et al. 1990, 1994a) where animals were exposed to high concentration of pMDI (i.e., 6.0 mg/m^3). This high concentration was generated artificially in experimental studies, and it is uncertain whether this level can be generated normally with the use of consumer products containing MDIs. There is uncertainty associated with the mode of action of tumours. Two postulated mechanisms have been identified but the mechanisms have not been fully elucidated.

9. Conclusion

9.1 MDAs

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to organisms and the broader integrity of the environment from 4,4′-MDA and pMDA. It is concluded that 4,4′-MDA and pMDA do not meet the criteria under paragraph 64(*a*) or (*b*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

On the basis of a negligible exposure of the general population to 4,4′-MDA and pMDA, it is concluded that 4,4′-MDA and pMDA do not meet the criteria under paragraph 64(*c*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore concluded that 4,4′-MDA and pMDA do not meet any of the criteria set out in section 64 of CEPA.

9.2 MDIs

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to organisms and the broader integrity of the environment from the five MDI substances in the MDI/MDA Substance Grouping. It is concluded that the MDI substances do not meet the criteria under paragraph 64(*a*) or (*b*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

On the basis of the potential inadequacy of the margins between the estimate of exposure to MDI substances from use of certain DIY products and critical effect levels, it is concluded that the five MDI substances in the MDI/MDA Substance Grouping meet the criteria under paragraph 64*(c)* of CEPA as they are entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore concluded that the five MDI substances in the MDI/MDA Substance Grouping (CAS RNs 101-68-8; 2536-05-2, 5873-54-1; 9016-87-9 and 26447-40-5) meet one or more of the criteria set out in section 64 of CEPA.

The five MDI substances in the MDI/MDA Substance Grouping do not meet the persistence or bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA.

References

[ACC] American Chemistry Council. 2012a. MDI emissions reporting guidelines for polyurethane industry. Report: AX186. Washington (DC): ACC, Center for the Polyurethanes Industry. http://polyurethane.americanchemistry.com/Resources-and-Document-Library/MDI-Emissions-Reporting-Guidelines-for-the-Polyurethane-Industry.pdf.

[ACC] American Chemistry Council. 2012b. Spray polyurethane foam ventilation research project – phase 2, American Chemistry Council's Center for the Polyurethanes Industry, Report dated December 19, 2012. Report submitted to Environment Canada on October 31, 2014.

[ACC Diisocyanates Panel] American Chemistry Council's Diisocyanates Panel. 2005. An Assessment of persistence, bioaccumulation, and inherent ecotoxicity of aromatic diisocyanate substances on the Canadian Domestic Substances List (DSL). Unpublished report submitted to Environment Canada. 21 p.

ACD/Percepta [Prediction Module]. c1997–2012. Toronto (ON): Advanced Chemistry Development. http://www.acdlabs.com/products/percepta/.

[ACGIH] American Conference of Governmental Industrial Hygienists. 1996. TLVs and BEIs. Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati (OH). [cited in NIOSH 2004].

Acton BC. 2001. Stack emissions from a continuous polyurethane panel production line. Great Britain: International Isocyanate Industry. 33 pages. III Report No. 11441.

Agrup G. 1968. Sensitization induced by patch testing. Br J Dermatol. 80(10):631-4.

Allport DC, Gilbert DS, Outterside SM, editors. 2003. MDI and TDI: Safety, health and the environment: a source book and practical guide. Chichester (GB).

Amini B, Lowenkron S. 2003. Aniline and its derivatives. In: Kirk-Othmer Encyclopedia of Chemical Technology. New York (NY): John Wiley & Sons Inc. p. 783-809.

Andersen M, Binderup ML, Kiel P, Larsen H, Maxild J. 1980. Mutagenic action of isocyanates used in the production of polyurethanes. Scand J Work Environ Health 6:221-226.

Angelini G, Vena GA, Giglo G, Fiordalisi F, Meneghini CL. 1985. Contact dermatitis due to cosmetics. J Appl Cosmetol. 3:223-236.

Api AM, Basketter DA, Cadby PA, Cano MF, Ellis G, Gerberick GF, Griem P, McNamee PM, Ryan CA, Safford R. 2008. Dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients. Regul Toxicol Pharmacol. 52(1):2-23.

Api AM, Lalko J, Politano V. 2009. The use of human data when conducting dermal sensitization quantitative risk assessments for fragrance ingredients; how well does the LLNA predict human NOELs? The Toxicologist, Supplement to Toxicol Sci. 108(1):26 (Abstract #133) [cited in Loveless et al. 2010].

Arnold RG, Nelson JA, Verbanc JJ. 1956. Recent advances in isocyanate chemistry. Chem Rev. 57(1):47-76.

Arnot JA, Gobas FAPC. 2003. A generic QSAR for assessing the bioaccumulation potential of organic chemicals in aquatic food webs. QSAR Comb Sci. 22(3):337-345.

Aronson D, Howard PH. 1999. Evaluating potential POP/PBT compounds for environmental persistence. North Syracuse (NY): Syracuse Research Corporation, Environmental Science Center. Report No. SRC-TR-99-020.

Asakura S. 1986. Report to the International Isocyanate Institute, Project FE-E-39-1 [unpublished report]. Yokohama National University, Department of Safety Engineering, Japan. In: Cowen et al. 1998, European Commission 2000.

[ASTM] American Society for Testing and Materials International. c1996–2012. Standards; ASTM D5209-92. West Conshohocken (PA): ASTM International. [accessed 2012 Dec 6]. http://www.astm.org/Standards/D5209.htm.

[ATSDR] Agency for Toxic Substances and& Disease Registry. 1998. Toxicological profile for methylenedianiline. Atlanta (GA) US Department of Health and Human Services, Public Health Service. [accessed 2012 May1]. https://www.atsdr.cdc.gov/toxprofiles/tp122.pdf

Bartsch W, Buschmann J, Hoymann HG, Heinrich U. 1996. [Chronic toxicity and carcinogenicity study on MDI.] Hannover, Fraunhofer Institute for Toxicology and Aerosol Research (unpublished) (in German) [cited in IPCS 2000].

Bascom R, Kennedy TP, Levitz D, Zeiss CR. 1985. Specific bronchoalveolar lavage IgG antibody in hypersensitivity pneumonitis from diphenylmethane diisocyanate. Am Rev Respir Dis. 131(3):463-465.

BASF AG. 1977. Abt. Toxikologie; unveroffenlichte Untersuchung XXIII/539 (07.01.1977). [cited in ECJRC 2001; OECD 2002].

Basketter DA, Clapp C, Jefferies D, Safford B, Ryan CA, Gerberick F, Dearman RJ, Kimber I. 2005. Predictive identification of human skin sensitization thresholds. Contact Dermatitis 53:260-267.

Baur X, Dewair M, Rommelt H. 1984. Acute airway obstruction followed by hypersensitivity pneumonitis in an isocyanate (MDI) worker. J Occup Med. 26(4):285-287.

Baur X. 1985. Isocyanate hypersensitivity. Final report to the International Isocyanate Institute. III File No. 10349; III Project E-AB-19. [cited in National Research Council of the National Academies 2004]: https://www.nap.edu/read/10902/chapter/7#199

Baur X, Marek W, Ammon J, Czuppon AB, Marczynski B, Raulf-Heimsoth M, Roemmelt H, Fruhmann G. 1994. Respiratory and other hazards of isocyanates. Int Arch Occup Environ Health 66:141-152. [cited in US EPA 1998].

Bayer Material Science. 2005. Material Safety Data Sheet: MONDUR ML Pittsburgh (PA): Bayer Material Science LLC. [accessed Jan 2013]. http://purmindex.net/purmmsds/MondurMLMSDS.pdf.

[BCFBAF] Bioaccumulation Program for Windows [estimation model]. 2000-2010. Ver. 4.10. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. http://www.epa.gov/oppt/exposure/pubs/episuite.htm.

Becker KH, Bastian V, Klein T. 1988. The reactions of OH radicals with toluene diisocyanate, toluenediamine, and methylenedianiline under simulated atmospheric conditions. J Photochem Photobiol A Chem. 45:195-205

Bello D, Smith TJ, Woskie SR, Streicher RP, Boeniger MF, Redlich CA, Liu Y. 2006. An FTIR investigation of isocyanate skin absorption using *in vitro* guinea pig skin. J Environ Monit. 8:523-529.

Bello D, Sparer J, Redlich CA, Ibrahim K, Stowe MH, Liu Y. 2007a. Slow curing of aliphatic polyisocyanate paints in automotive refinishing: a potential source for skin exposure. J Occup Environ Hyg. 4:406-411.

Bello D, Herrick CA, Smith TJ, Woskie SR, Streicher RP, Cullen MR, Liu Y, Redlich CA. 2007b. Skin exposure to isocyanates: reasons for concern. Environ Health Perspect. 115:328-335.

Bernstein DI, Korbee L, Staudee T, Bernstein JA, Scinto J, Herd ZL, Bernstein IL. 1993. The low prevalence of occupational asthma and antibody-dependent sensitization to diphenylmethane diisocyanate in a plant engineered for minimal exposure to diisocyanates. J Allergy Clin Immunol. 92:387-396.

Best DH, Coleman WB. 2007. Bile duct destruction by 4,4′-diaminodiphenylmethane does not block the small hepatocyte-like progenitor cell response in retrorsine-exposed rats. Hepatology 46(5):1611-1619.

Bidleman TF. 1988. Atmospheric processes. Environ Sci Technol. 22(4):361-367.

Björkner B, Frick-Engfeldt M, Pontén A, Zimerson E. 2001. *Plastic materials*. In: Johansen JD, Frosch P, LePoittevin J-P, editors. Contact Dermatitis. p. 696.

Boethling RS, Howard PH, Beauman JA, Larosche ME. 1995. Factors for intermedia extrapolations in biodegradability assessment. Chemosphere 30(4):741-752.

Bonauto D, Lofgren D. 2004. Review of three asthma cases and MDI exposure data associated with the spray-on truck bed lining industry. Olympia (WA): Washington State Department of Labor and Industries, State of Washington, Safety and Health Assessment and Research for Prevention (SHARP) Program, Technical Report No. 42-5-2004. [cited in NIOSH 2006].

Booth K, Cummings B, Karoly WJ, Mullina S, Robert WP, Spence M, Lichtenberg FW, Banta J. 2009. Measurements of airborne methlyene diphenyl diisocyanate (MDI) concentration in the U.S. workplace. J Occup Environ Hyg. 6:228-238.

Boutin M, Dufresne A, Ostiguy C, Lesage J. 2006. Determination of airborne isocyanates generated during the thermal degradation of car paint in body repair shops. Ann Occup Hyg. 50:385-393.

Brochhagen FK, Grieveson BM. 1984. Environmental aspects of isocyanates in water and soil. Cell Polym. 3:11-17.

Brochhagen FK, Schal HP. 1986. Diphenylmethane diisocyanate: the concentration of its saturated vapor. Am Ind Hyg Assoc J. 47(4): 225-228.

Brouwer DH, Semple S, Marquart J, Cherrie JW. 2001. A dermal model for spray painters. Part 1: subjective exposure modelling of spray paint deposition. Ann Occup Hyg. 45:15-23.

Buschmann J, Koch W, Fuhst R, Heinrich U. 1996. Embryotoxicity study of monomeric 4,4′-methylenediphenyl diisocyanate (MDI) aerosol after inhalation exposure in Wistar rats. Fundam Appl Toxicol. 32:96-101.

[California EPA] California Environmental Protection Agency. 2015. Methylene Diphenyl Disocyanate (Monomer and Polymeric Forms) Reference Exposure Levels. Technical support document for the

derivation of noncancer reference exposure levels. Appendix D1. SRP Review Draft. May 2015. Air, Community, and Environmental Research Branch, Office of Environmental Health Hazard Assessment.

Canada. [1978]. *Food and Drug Regulations*, C.R.C., c. 870. http://laws-lois.justice.gc.ca/eng/regulations/c.r.c.,_c._870/index.html

Canada. 1985. *Food and Drugs Act*, R.S.C. 1985, c. F-27. http://laws-lois.justice.gc.ca/eng/acts/f-27/

Canada. 1999. *Canadian Environmental Protection Act, 1999*. S.C., 1999, c. 33, Canada Gazette. Part III, vol. 22, no. 3. http://laws-lois.justice.gc.ca/eng/acts/C-15.31,Canada. 2000. *Canadian Environmental Protection Act, 1999: Persistence and Bioaccumulation Regulations,* P.C. 2000-348, 29 March, 2000, SOR/2000-107.
http://laws-lois.justice.gc.ca/eng/regulations/SOR-2000-107/page-1.html

.

Canada, Dept. of the Environment. 2011. *Canadian Environmental Protection Act, 1999: Notice with respect to certain aromatic amines and aromatic azo- and benzidine-based substances.* Canada Gazette, Part I, vol. 145, no. 51. Suppl. http://gazette.gc.ca/rp-pr/p1/2011/2011-12-17/html/sup-eng.html

Canada, Dept. of the Environment. 2012. *Canadian Environmental Protection Act, 1999: Notice with respect to certain methylenediphenyl diisocyanate and diamine, and phenol, methyl- substances*. Canada Gazette, Part I, vol. 146, no. 24. http://www.gazette.gc.ca/rp-pr/p1/2012/2012-06-16/html/notice-avis-eng.html#d101.

Cangemi JM, Dos Santos AM, Neto SC, Cherice GO. 2008. Biodegradation of polyurethane derived from castor oil. Polimeros 18(3):201-206.

Cao LC, Cheng J, Liu XD, Wang R, Zhang JY, Qu J, Jaeger U. 2012. Study of properties of one-component moisture-curable polyurethane and silane modified polyurethane adhesives. J Adhes Sci Technol. 26(10-11):1395-1405.

Carino M, Aliani M, Licitra C, Sarno N, Ioli F. 1997. Death due to asthma at workplace in a diphenylmethane diisocyanate-sensitized subject. Respiration 64(1):111-113.

Carter WPL, Luo D, Malkina IL. 1999. Investigation of the atmospheric ozone formation potential of para toluene isocyanate and methylene diphenylene diisocyante. Riverside (CA): College of Engineering, Center for Environmental Research and Technology, University of California. Final Report to the Chemical Manufacturers Association Diisocyanates Panel.
http://www.cert.ucr.edu/~carter/pubs/mdirpt.pdf.

Cartier A, Gammer L, Malo J-L, Lagier F, Ghezzo H, Harris K, Patterson R. 1989. Specific serum antibodies against isocyanates: Association with occupational asthma. J Allergy Clin Immunol 84:507-514. [cited in US EPA 1998].

Caspers N, Hamburger B, Kanne R, Klebert W. 1986. Ecotoxicity of toluenediisocyanate (TDI), diphenylmethanediisocyanate (MDI), toluene diamine (TDA), diphyenylmethanediamine (MDA). International Isocyanate Institute Project No. E-CE-41. [restricted access].

Castro EA, Moodie RB, Sansom PJ. 1985. The kinetics of methyl and phenyl isocyanates. J Chem Soc Perkin Trans II. 5:737-742.

[CDC] Centers for Disease Control and Prevention. 2012. NIOSH Pocket Guide to Chemical Hazards. [accessed 2012 Aug 16]. http://www.cdc.gov/niosh/npg/npgd0413.html.

Ceballos DM, Yost MG, Whittaker SG, Reeb-Whitaker C, Camp J, Dills R. 2011. Development of a permeation panel to test dermal protective clothing against sprayed coatings. Ann Occup Hyg. 55(2):214-227.

Chemical Industry Directory. Global Chemical Network. Zhejiang NetSun Co., Ltd. [accessed 2015 Jan 29] http://www.chemnet.com/cas/en/2536-05-2/methylenedi-o-phenylene-diisocyanate.html.

Chester DA, Hanna EA, Pickelman BG, Rosenman KD. 2005. Asthma death after spraying polyurethane truck bedliner. Am J Ind Med. 48(1):78-84.

Chester EH, Martinez-Catinchi FL, Schwartz HJ, Horowitz J, Fleming GM, Gerblich AA, McDonald EW, Brethauer R. 1979. Patterns of airway reactivity to asthma produced by exposure to toluene di-isocyanate. Chest. 75:229-231 (Supplement).

[CHRIP] Chemical Risk Information Platform [database]. 2008. Tokyo (JP): National Institute of Technology and Evaluation, Chemical Management Centre (CMC). 2008. [accessed 2013 Mar 14]. http://www.safe.nite.go.jp/english/db.html.

CIBA-GEIGY. 1982. 3-month toxicity study in rats (drinking water); TK 10504, GU Project No. 791743; GU 2. Toxicology (25.06.1982). [cited in ECJRC 2001; OECD 2002].

Clowes HM. 1997. *In vitro* absorption from various doses of MDI through guinea pig, rat and human skin. Central Toxicology Laboratory, Alderley Park Macclesfield, Cheshire (UK), Report No. CTL/P/5348, III Project 125, 3 November 1997. [cited in ECJRC 2005].

[ConsExpo] Consumer Exposure Model. 2006. Ver. 4.1. Bilthoven (NL): Rijksinstituut voor Volksgezondheid en Milieu [National Institute for Public Health and the Environment]. http://www.rivm.nl/en/healthanddisease/productsafety/ConsExpo.jsp#tcm:13-42840.

Convenience Products. (Clayton Corporation). 2009. MDI emissions study of one component polyurethane foam sealant products. Test report conducted by John A. Jurgiel & Associates and submitted to Center for the Polyurethanes Industry. Report submitted to Environment Canada on October 31, 2014.

Convenience Products (Clayton Corporation). 2012. MDI emissions study of full cavity insulation application using low pressure spray foam. Unpublished test report conducted by Certified Safety Consulting. 23 p. Report submitted to Environment Canada on October 30, 2014.

Convenience Products (Clayton Corporation). 2014a. MDI emissions study of low pressure bead applied polyurethane foam sealant applied in a residential basement with ventilation. Unpublished test report conducted by Certified Safety Consulting. 19 p. Report submitted to Environment Canada on October 30, 2014.

Convenience Products (Clayton Corporation). 2014b. MDI emissions study of low pressure bead applied polyurethane foam sealant applied in a residential basement without ventilation. Unpublished test report conducted by Certified Safety Consulting. 18 p. Report submitted to Environment Canada on October 30, 2014.

Cowen WF, Gastinger AM, Spanier CE, Buckel JR, Bailey RE. 1998. Sorption and microbial degradation of toluenediamines and methylenedianiline in soil under aerobic and anaerobic conditions. Environ Sci Technol. 32 (5):598-603.

[CRA] Conestoga-Rovers & Associates (Waterloo, Ontario). 2012. Potential presence and releases of five substances grouping to the environment from the waster sector. Gatineau (QC): Environment Canada. Report Solicitation No.: K2A82-11-0029. Ref. No.: 077785(2).

[CRA] Conestoga-Rovers & Associates (Waterloo, Ontario). 2012. Potential presence and releases of five substances grouping to the enviornment from the waste sector. Solicitation No.: K2A82-11-0029, Ref No.: 077785(2). Report prepared for Environment Canada. 418 p.

Crespo J, Galán J. 1999. Exposure to MDI during the process of insulating buildings with sprayed polyurethane foam. Ann Occup Hyg. 43:415-419.

Cui Y, Chen D, Wang X, Tang X. 2002. Crystalline structure in isocyanate reactive hot melt adhesives. Int J Adhes Adhes. 22:317-322.

Dalene M, Skarping G, Brunmark P. 1995. Assessment of occupational exposure to 4,4′-methylenedianiline by the analysis of urine and blood samples. Int Arch Occup Environ Health 67(2):67-72.

Dearman RJ, Spence LM, Kimber I. 1992. Characterization of murine immune responses to allergic diisocyanates. Toxicol Appl Pharmacol. 112:190-197.

DeGaspari J. 1999. From trash to cash: a new process reclaims former unrecoverables in residue of scrapped vehicles. Mechanical Engineering-CIME. 121(6):48-51.

[DFG] Deutsch Forschungsgemeinschaft. 1997. 4,4′-Methylene diphenyl isocyanate (MDI) and polymeric MDI (PMDI) [MAK Value Documentation, 1997]: http://onlinelibrary.wiley.com/doi/10.1002/3527600418.mb10168stae0008/full#mb10168stae0008-bib-0028

Dietemann-Molard A, Kopfershmitt-Kubler MC, Meyer PD, Tomb R, Pauli G. 1991. Allergic asthma due to domestic use of insulating polyurethane foam. Lancet 338(8772):953.

Dieterich D, Grigat E, Hahn W, Hespe H, Schmelzer HG. 1993. Principles of polyurethane chemistry and special applications. In: Oertel G, editor. Polyurethane Handbook. 2nd ed. Munich (DE): Hanser Gardner Publications. p. 12-53.

Diller WF, Herbert E. 1982. Lungenfunktion und andere gesundheitliche Parameter bei Beschäftigten in einem Isocyanatbetrieb (MDI-Herstellung), (1982):[cited in DFG 1997]: http://onlinelibrary.wiley.com/doi/10.1002/3527600418.mb10168stae0008/full#mb10168stae0008-bib-0028Diller WF, Herbert E. 1983. Lung function and other health parameters in workers in an isocyanate factory (MDI production). Abstr Hyg Commun Dis. 58(8):524-525. [cited in ECJRC 2005]: https://www.ncbi.nlm.nih.gov/pubmed/7090618

Dominion Sure Seal. 2014. Material Safety Data Sheet. EZ Liner, Part A. https://www.dominionsureseal.com/download/bezlg-part-a-ez-liner-bedliner-eng-sds-usa/.

Dow Chemical Company. [MSDSonline] Material Safety Data Sheets. c1998 − 2011. Chicago (IL): MSDSonline. [accessed 2012 Feb 1]. http://www.msdsonline.com. [restricted access].

Dow Chemical Company. February 2012. Low Pressure Spray Foam Products., http://www.regulations.gov/#!docketDetail;rpp=10;po=0;D=EPA-HQ-OPPT-2011-0182 [cited in US EPA docket EPA-HQ-OPPT-2011-0182].

Dow Chemical Company. 1954. Results of Skin Sensitization Tests with Methylene Dianiline, Biochemical Research Department (17.12.1954) (unpublished). [cited in ECJRC 2001; OECD 2002].

Dow Chemical Company. 2013. Residential Home Re-Occupancy and Ventilation After Crawl Space Sprayed with Low Pressure Polyurethane Foam (unpublished). Originally presented at the American Chemistry Council Polyurethanes Technical Conference, Phoenix, Arizona.

[DPD] Drug Product Database [database].[modified 2015 Jul]. Ottawa (ON): Health Canada. [accessed 2013 Feb 12]. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php

Duff PB. 1985. Fate of Toluene Diisocyanate in Air, Phase II Study, Proceedings of the SPI 29th Annual Technical/Marketing Conference, October 23-25, Reno, Nevada.

Dunn BJ. 1978. Guinea Pig Skin Hypersensitization Test, Methylene Dianiline. Allied Chemical Corporation (18.09.1978). [cited in ECJRC 2001; OECD 2002].

DuPont. 1975. Ten-day subacute exposure of rabbit to methylene dianiline. Dot ID. 878220288. (unpublished). [cited in ATSDR 1998].

DuPont. 1976. Skin absorption studies in rabbits treated with 4,4´-diaminodiphenylmethane (MDA). A. pathological and clinical effects of a lo-day subacute study. Dot ID. 878220289. (unpublished). [cited in ATSDR 1998].

Duprat P, Gradiski D, Marignac B. 1976. The irritant and allergenic action of two isocyanates: toluene diisocyanate (TDI) and diphenylmethane diisocyanate (MDI). Eur J Toxicol Environ Hyg. 9(1):43-53. [cited in ECJRC 2005].

[ECETOC] European Centre for Ecotoxicology and Toxicology of Chemicals. 2003. Contact sensitisation: classification according to potency. Technical Report No. 87. http://www.ecetoc.org/technical-reports.

[ECETOC] European Centre for Ecotoxicology and Toxicology of Chemicals. 2009. Workshop: Significance of Bound Residues in Environmental Risk Assessment 14-15 October 2009, Brussels. Workshop Report No. 17. http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC_WR_17._Significance_of_bound_residues_in_environmental_risk_assessment.pdf.

[ECHA] European Chemicals Agency. c2007-2013a. Registered substances database; search results for CAS RN 101-77-9. Helsinki (FI): ECHA. [accessed 2013 Feb]. http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances.

[ECHA] European Chemicals Agency. c2007-2013b. Registered substances database; search results for CAS RN 25214-70-4. Helsinki (FI): ECHA. [accessed 2013 Feb]. http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances.

[ECHA] European Chemicals Agency. c2007-2013c. Registered substances database; search results for CAS RN 101-68-8. Helsinki (FI): ECHA. [accessed 2013 Jan]. http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances.

[ECHA] European Chemicals Agency. c2007-2013d. Registered substances database; search results for CAS RN 2536-05-2. Helsinki (FI): ECHA. [accessed 2013 Feb]. http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances.

[ECHA] European Chemicals Agency. c2007-2013e. Registered substances database; search results for CAS RN 5873-54-1. Helsinki (Fl): ECHA. [accessed 2013 Feb]. Agency. http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances.

[ECHA] European Chemicals Agency. 2011. SVHC Support Document – Formaldehyde, oligomeric reaction products with aniline. http://echa.europa.eu/documents/10162/63daf768-7e14-4a75-9cd9-d99b3242391a.

[ECJRC] European Commission Joint Research Centre. 2001. Risk Assessment Report: 4-4′-methylenedianiline (CAS No. 101-77-9). Luxembourg: Office for Official Publications of the European Communities. Volume 9. https://echa.europa.eu/documents/10162/84f1091d-2a47-47fa-a094-075de9bef78d.

[ECJRC] European Commission Joint Research Centre. 2005. European Union Risk Assessment Report. Methylenediphenyl diisocyanate (MDI) CAS No. 26447-40-5. Luxembourg: Office for Official Publications of the European Communities. Volume 59. https://echa.europa.eu/documents/10162/9f8ad2fd-9b47-4eb6-9bf9-e0fc898f874d.

Ecoff S, Lambach J. 2012. A proposed methodology for establishing a save work zone around a SPF application to exterior walls of a commercial structure. Paper presented at 2012 Polyurethanes Technical Conference, September 24-26, Atlanta, Georgia.

Egeler P, Ginzburg N. 2001. A study on the toxicity of 4,4′-methylenedianiline to the aquatic oligochaete *Lumbriculus variegatus*. ECT Oekotoxikologie GmbH, Germany, Study No. P1LA. [restricted access].

Egeler P. 2002. A study on the toxicity of 4,4′-methylenedianiline to the aquatic oligochaete *Lumbriculus variegatus*. ECT Oekotoxikologie GmbH, Germany, Study No. P2LA. [restricted access].

Egeler P, Gilberg D. 2005. 4,4′-Methylenedianiline: A study on the toxicity to the sediment dweller *Chironomus riparius*. ECT Oekotoxikologie GmbH, Germany, Study No. AD2ME. [restricted access].

Elmer's. 2012. Material Safety Data Sheet. Elmer's Ultimate Glue. Columbus (OH). [accessed 2013 Feb]. http://www.elmers.ca/msds/MP9411_C.HTM

Emmett EA. 1976. Allergic contact dermatitis in polyurethane plastic moulders. J Occup Med. 18(12):802-804.

Engfeldt M, Isaksson M, Zimerson E, Bruze M. 2013. Several cases of work-related allergic contact dermatitis caused by isocyanates at a company manufacturing heat exchangers. Contact Dermatitis 68(3):175-180.

Engfeldt M, Ponten A. 2013. Contact allergy to isocyanates after accidental spillage. Contact Dermatitis 69(2):122-124.

Environment Agency of Japan. 2000. Chemicals in the Environment: Report on the environmental survey and monitoring of chemicals, FY 2004. Environment Health and Safety Division, Environment Agency (Japan), September, 2000. http://www.env.go.jp/chemi/kurohon/en/http2004e/index.html.

Environment Canada. 2009. Guidance for Conducting Ecological Assessments under CEPA, Science Resource Technical Series, Mini Guidance Module: Determining the persistence of a chemical from biodegradation data. Gatineau (QC): Environment Canada, Ecological Assessment Division.

Environment Canada. 2012a. DSL Inventory Update data collected under the *Canadian Environmental Protection Act, 1999*, section 71: *Notice with respect to certain methylenediphenyl diisocyanate and diamine, and phenol, methyl- substances*. Data prepared by: Environment Canada, Health Canada, Existing Substances Program.

Environment Canada. 2012b. National Pollutant Release Inventory (NPRI) downloadable datasets. Ottawa (ON): Environment Canada. (1) Facility data, Year 1993–2010 (Microsoft Access format, March 27, 2012 version). [accessed 2013 Mar]. http://www.ec.gc.ca/inrp-npri/default.asp?lang=en&n=0EC58C98-1.

Environment Canada. 2013. Robust Study Summary: Aquatic toxicity. Gatineau (QC): Environment Canada. Developed for a daphnid reproduction study by Mitsubishi Chemical Safety Institute (2002b). Available on request from: substances@ec.gc.ca.

Environment Canada, Health Canada. 2008a. Screening Assessment for the Challenge: Toluene diisocyanates (TDIs) Chemical Abstracts Service Registry Numbers 26471-62-5, 584-84-9, 91-08-7. Ottawa (ON): Environment Canada, Health Canada. [accessed 2013 Jan]. http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=69A64ACA-1.

Environment Canada, Health Canada. 2008b. Screening assessment for the Challenge: Toluene diisocyanate, benzene, 2,4,-diisocyanato-1-methyl (2,4′-TDI); CAS RN 584-84-9, benzene, 1,3,-diisocyanato-2-methyl- (2,6′-TDI); CAS RN 91-08-7, benzene, 1,3,-diisocyanatomethyl- (TDI mixed isomers); CAS RN 26471-62-5. Ottawa (ON): Environment Canada, Health Canada. http://www.ec.gc.ca/ese-ees/69A64ACA-7187-40CD-B2A4-D9296E6FC8CA/batch1_TDI_en.pdf.

[ECCC, HC] Environment and Climate Change Canada, Health Canada. [modified 2007 Apr 20]. Categorization. Ottawa (ON): Government of Canada. [accessed 2013 July 31]. http://www.chemicalsubstanceschimiques.gc.ca/approach-approche/categor-eng.php [EPI Suite] Estimation Programs Interface Suite for Microsoft Windows [estimation model]. 2012. Ver. 4.1. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. http://www.epa.gov/oppt/exposure/pubs/episuite.htm.

Estlander T, Keskinen H, Jolanki R, Kanerva L. 1992. Occupational dermatitis from exposure to polyurethane chemicals. Contact Dermatitis 27:161-165.

European Commission. 2000. IUCLID Dataset, 4,4′-methylenedianiline, CAS No. 101-77-9. Year 2000 CD-ROM edition. [place unknown]: European Chemicals Agency, European Commission.

European Commission. 2009. Commission Regulation (EC) No 790/2009 of 10 August 2009 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures. http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2009.235.01.0001.01.ENG&toc=OJ:L:2009:235:TOC.

European Commission. 2015a. Details on Substances Classified in Annex VI to Regulation (EC) No. 1272/2008. Index No. 612-051-00-1. [accessed 2015 Oct 26]. http://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/cl-inventory/view-notification-summary/20502.

European Commission. 2015b. Details on Substances Classified in Annex VI to Regulation (EC) No 1272/2008. Index No. 615-005-00-9. [accessed 2015 Oct 26]. http://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/cl-inventory/view-notification-summary/5150; http://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/cl-inventory/view-notification-summary/135486; http://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/cl-

inventory/view-notification-summary/111384; http://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/cl-inventory/view-notification-summary/73160.

Fabbri LM, Boschetto P, Zocca E, Milani G, Pivirotto F, Plebani M, Burlina A, Licata B, Mapp CE. 1987. Bronchoalveolar neutrophilia during late asthmatic reactions induced by toluene diisocyanate. Am Rev Respir Dis. 136:36-42.

Feron VJ, Kittel B, Kuper CF, Ernst H, Rittinghausen S, Muhle H, Koch W, Gamer A, Mallett AK, Hoffmann HD. 2001. Chronic pulmonary effects of respirable methylene diphenyl diisocyanate (MDI) aerosol in rats: combination of findings from two bioassays. Arch Toxicol. 75(3):159-175.

Fomo Products. 2010. An evaluation of airborne methylene diphenyl diisocyanate. Report dated March 9, 2010. Report submitted to Environment Canada on October 31, 2014.

Fomo Products. 2005. MDI air monitoring report-Fomo products wall stud case study. Report submitted to Environment Canada on October 31, 2014.

Foureman P, Mason JM, Valencia R, Zimmering S. 1994. Chemical mutagenesis testing in Drosophila. X. Results of 70 coded chemicals tested for the National Toxicology Program. Environ Mol Mutagen. 23(3):208-227.

Franklin International. 2010. Material Safety Data Sheet. Titebond 811 Advantage. Columbus (OH) [accessed Feb 2013]. http://galleher.com/wp-content/uploads/2011/11/811-MSDS.pdf.

Frick-Engfeldt M, Isaksson M, Zimerson E, Bruze M. 2007. How to optimize patch testing with diphenylmethane diisocyanate. Contact Dermatitis 57:138-151.

Fukushima S, Hirose M, Hagiwara A, Hasegawa R, Ito N. 1981. Inhibitory effect of 4,4′-diaminodiphenylmethane on liver, kidney and bladder carcinogenesis in rats ingesting N-ethyl-N-hydroxyethylnitrosamine or N-butyl-N-(4-hydroxybutyl) nitros-amine. Carcinogenesis 2(10):1033-1037. [cited in ATSDR 1998].

Fukushima S, Shibata M, Hibino T, Yoshimura T, Hirose M, Ito N. 1979. Intrahepatic bile duct proliferation induced by 4,4′-diaminodiphenylmethane in rats. Toxicol Appl Pharmacol. 48(1 Pt 1):145-55. [cited in ATSDR 1998].

Gailhofer G, Ludvan M. 1987. [Change in the allergen spectrum in contact eczema 1975-1984]. Derm Beruf Umwelt 35(1):12-6.

Gee JB, Morgan WKC. 1985. A 10-year follow-up study of a group of workers exposed to isocyanates. J Occup Med. 27:15-18.

Gilbert DS. 1988. Fate of TDI and MDI in air, soil and water. J Cell Plast. 24 (2):178-192.

Gledhill A, Wake A, Hext P, Leibold E, Shiotsuka R. 2005. Absorption, distribution, metabolism and excretion of an inhalation dose of [14C] 4,4′- methylenediphenyl diisocyanate in the male rat. Xenobiotica 35(3):273-292.

Gobas FAPC, Kelly BC, Arnot JA. 2003. Quantitative structure activity relationships for predicting the bioaccumulation of POPs in terrestrial food-webs. QSAR Comb Sci. 22:346-351.

Goossens A, Detienne T, Bruze M. 2002. Occupational allergic contact dermatitis caused by isocyanates. Contact Dermatitis 47:304-308.

Gorilla Glue Inc. 2012. Material Safety Data Sheet. Gorilla Glue. Columbus (OH). [accessed 2013 Feb]. http://www.gorillatough.com/sds.

Griem P, Goebel C, Scheffler H. 2003. Proposal for a risk assessment methodology for skin sensitization based on sensitization potency data. Regul Toxicol Pharmacol. 38:269-290.

Griffiths-Johnson D, Spear K, Jin R, Karol MH. 1990. Late-onset pulmonary responses in guinea pigs sensitized by inhalation of diphenylmethane 4,4′-diisocyanate (MDI). The Toxicologist 10(1):222 (abstract).

Grimalt R, Vilaplana J, Romaguera C. 2009. Three cases of allergic contact dermatitis to 4,4′-diaminodiphenylmethane. Contact Dermatitis 60(6):346-7.

Gulati DK, Witt K, Anderson B, Zeiger E, Shelby MD. 1989. Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro. III. Results with 27 chemicals. Environ Mol Mutagen. 13(2):133-93.

Gunderson EC, Anderson CC. 1988. A sampling and analytical method for airborne m-phenylenediamine (MPDA) and 4,4′-methylenedianiline (MDA). Am Ind Hyg Assoc J. 49(10):531-538.

Hagiwara A, Tiwawech D, Imaida K, Tamano S, Shibata MA, Fukushima S, Ito N. 1993. Modifying influence of prior treatment with toxic agents on induction of preneoplastic and neoplastic lesions in a medium-term multi-organ carcinogenesis bioassay. Teratog Carcinog Mutagen. 13(6):277-287. [cited in ATSDR 1998].

Hall AJ, Harrington JM, Waterhouse JA. 1992. The Epping jaundice outbreak: a 24 year follow up. J Epidemiol Community Health 46(4):327-328.

Hamada H, Isaksson M, Bruze M, Engfeldt M, Liljelind I, Axelsson S, Jönsson B, Tinnerberg H, Zimerson E. 2012. Dermal uptake study with 4,4′-diphenylmethane diisocyanate led to active sensitization. Contact Dermatitis 66(2):101-5.

Hamberger R, Moser T. 2012. 4,4′-MDA: reproduction toxicity to the earthworm *Eisenia fetida*. ECT Oekotoxikologie GmbH and CIP – Chemisches Institut Pforzheim GmbH. Study No. 1AD1RR. [restricted access].

Hansch C, Leo A, Hoekman D. 1995. Exploring QSAR: Hydrophobic, Electronic, and Steric Constants. Washington (DC): American Chemical Society (ACS).

Hannu T, Estlander T, Jolanki R. 2005. Allergic contact dermatitis due to MDI and MDA from accidental occupational exposure. Contact Dermatitis 52(2):108-109.

Harkema JR, Carey SA, Wagner JG. 2006. The nose revisited: a brief review of the comparative structure, function, and toxicologic pathology of the nasal epithelium. Toxicol Pathol. 34:252-269.

Harper DP, Wolcott MP, Rials TG. 2001. Evaluating cure of a pMDI-wood bondline using spectroscopic calorimetric and mechanical methods. J Adhes. 76:55-74.

Health Canada. 2013. Supporting documentation: Summary tables of health effects information for methylenediphenyl diisocyanates and diamines. Ottawa (ON): Health Canada. Available upon request from: substances@ec.gc.ca.

Health Council of the Netherlands. 2008. Prevention of work-related airway allergies. Recommended occupational exposure limits and periodic screening. The Hague, Health Council of the Netherlands, Publication No. 2008/03. http://www.gezondheidsraad.nl/sites/default/files/200803E_0.pdf.

Heimbach F. 1993. Biological effects and fate of Desmodur 44 V 20 (polymeric MDI) in artificial ponds by simulating an accidental pollution. Project 101-EU-ENV for the International Isocyanate Institute. Unpublished report. [cited in ECJRC 2005].

Heimbach F, Jaeger K, Sporenberg W. 1996. Fate and biological effects of polymeric MDI (4,4′-diphenylmethane diisocyanate and homologs) in small artificial ponds. Ecotoxicol Environ Saf. 33 (2):143-153.

Heinrich U, Koch W, Schüler T, Creutzenberg O, Rittinghausen S, Klingebiel R, Hoymann HG, Bartsch W, Preiss A. 1991. Inhalation exposure of rats to 4′,4-methylenediphenyl-diisocyanate (MDI). In: Proceedings, BOHS VIIIth International Symposium on Inhaled Particles, Edinburgh, 1991, p. 6.8. [cited in ECJRC 2005].

Henkel Corporation. 2010. Material Safety Data Sheet. 1-component-polyurethane adhesive. Rocky Hill (CT). [accessed 2013 Feb]. http://www.osipro.com/msds/TRIMTeQ-TeQ-Mount-Mounting-Adhesive-msds.pdf.

[HENRYWIN] Henry's Law Constant Program for Microsoft Windows [estimation model]. 2008. Ver. 3.20. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. http://www.epa.gov/oppt/exposure/pubs/episuite.htm.

Herbold B. 1980a. Desmodur 44M (MDI), *Salmonella*/Microsomen Test zur Untersuchung auf Punkmutagene Wirkung, Bayer Institute fur Toxikologie, Report No. 9341, 1 August 1980. [cited in ECJRC 2005].

Herbold B. 1980b. Desmodur 44V20 (MDI), *Salmonella*/Micrsomen Test zur Untersuchung auf Punmutagene Wirkung, Bayer Institute fur Toxikologie, Report No. 9341, 1 August 1980. [cited in ECJRC 2005].

Herbold B. 1980c. Desmodur 44M (MDI), Erganzung zum Bericht 9130 vom 9 May 1980, Salmonella/Microsomen Test zur Untersuchung auf punkmutagene Wirkung, Bayer Institute fur Toxikologie, Report No. 9303, 17 July 1980. [cited in ECJRC 2005].

Herbold BA. 1990a. Special study, Salmonella/Microsome Test with Desmodur 44M (4,4′-MDI) using TA100, Bayer AG, Fachbereich Toxicology, Report No. 19570, 27 September 1990 [cited in ECJRC 2005].

Herbold BA. 1990b. Special study, Salmonella/Microsome Test with Desmodur 44M (4,4′-MDI) using TA100, Bayer AG, Fachbereich Toxicology, Report No. 19570, 27 September 1990. [cited in ECJRC 2005].

Herbold B, Haas P, Seel K, Walber U. 1998. Studies on the effect of the solvents dimethylsulfoxide and ethyleneglycoldimethylether on the mutagenicity of four types of diisocyanates in the Salmonella/microsome test. Mutat Res. 412:167-175.

Hiasa Y, Kitahori Y, Enoki N, Konishi N, Shimoyama T. 1984. 4,4′-Diaminodiphenylmethane: promoting effect on the development of thyroid tumors in rats treated with N-bis(2-hydroxypropyl)nitrosamine. J Natl Cancer Inst. 72(2):471-766. [cited in ATSDR 1998].

Hoffmann HD, Leibold E, Ehnes C, Fabian E, Landsiedel R, Gamer A, Poole A. 2010. Dermal uptake and excretion of 14^{C}-toluene diisocyanate (TDI) and 14^{C}-methylene diphenyl diisocyanate (MDI) in male rats. Clinical signs and histopathology following dermal exposure of male rats to TDI. Toxicol Lett. 199:364-371.

Hoffmann HD, Schupp T. 2009. Evaluation of consumer risk resulting from exposure against diphenylmethane-4,4′-diisocyanate (MDI) from polyurethane foam. EXCLI J. 8:58-65.

Holdren MW, Spicer CW, Riggin RM. 1984. Reaction of toluene diisocyanate with water vapour. Am Ind Hyg Assoc J. 45(9): 626-633.

Holland JM, Smith LH, Frome E, et al. 1987. Test of carcinogenicity in mouse skin: Methylenedianiline, gamma glycidyloxytrimethyloxysilane, gamma aminopropyltriethoxysilane and a mixture of M-phenylenediamine, methylenedianiline, and diglycidylether of bisphenol-A. Government Reports Announcements & Index (GRA&I) Issue 23. [cited in ATSDR 1998].

Hoymann HG, Buschmann J, Heinrich U. 1995. Examinations about the chronic toxicity/carcinogenicity of 4,4′-mehtylene diphenyl diisocyanate (MDI). Fraunhofer-Institut fur Toxikologie and Aerosolforschung, Hannover, Germany. Report No. 116-06-084. [cited in US EPA 1998; Feron et al. 2001; ECJRC 2005].

[HPD] Household Products Database [database]. 2013. Methylene bisphenyl diisocyanate. Washington (DC): US National Library of Medicine, National Institutes of Health. [accessed 2012 Jun]. http://hpd.nlm.nih.gov/cgi-bin/household/brands?tbl=chem&id=343&query=101-68-8&searchas=TblChemicals.

[HSDB] Hazardous Substances Data Bank [database]. 1983 –2003. Search results for CAS RN 101-77-9. Bethesda (MD): National Library of Medicine (US). [accessed 2013 Jul].www.toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.

[IARC] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. 1986. Some chemicals used in plastics and elastomers. IARC Monogr Eval Carcinog Risks Hum. Volume 39. https://monographs.iarc.fr/ENG/Monographs/vol1-42/mono39.pdf.

[IARC] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. 1999. Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. IARC Monogr Eval Carcinog Risks Hum. Vol. 71, p. 1049-1058. http://monographs.iarc.fr/ENG/Monographs/vol71/mono71.pdf.

[IBTL] Industrial BIO-TEST Laboratories Inc. 1973. Report to CIBA-GEIGY Corporation. Acute Toxicity Studies with FA-56 and FA-57. Unpublished report No. IBT No. 601-03110 (24.04.1993). [cited in ECJRC 2001; OECD 2002].

International Isocyanate Institute Inc. (III). 1978a. Unpublished report No. MA-12-77-5 (08.09.1978). [cited in ECJRC 2001; OECD 2002].

International Isocyanate Institute Inc. (III). 1978b. Unpublished report No. MA-12-77-6 (14.09.1978). [cited in ECJRC 2001; OECD 2002].

[IPCS] International Programme on Chemical Safety. 1999. Environmental Health Criteria 212: Principles and methods for assessing allergic hypersensitization associated with exposure to chemicals. Geneva (CH): United Nations Environment Programme, International Labour Organization, World Health Organization. http://www.inchem.org/documents/ehc/ehc/ehc212.htm.

[IPCS] International Programme on Chemical Safety. 2000. Concise International Chemical Assessment Document 27: Diphenylmethane diisocyanate (MDI). Geneva (CH): United Nations Environment Programme, International Labour Organization, World Health Organization. http://www.who.int/ipcs/publications/cicad/en/cicad27.pdf.

[IPCS] International Programme on Chemical Safety. 2005. OECD SIDS 4,4′ Methylenedianiline UNEP: World Health Organization. (Environmental Health Criteria 75). Jointly sponsored by the United Nations Environment Programme, the International Labour Organization, and the World Health Organization. http://www.inchem.org/documents/sids/sids/101779.pdf.

[IPCS] International Programme on Chemical Safety. 2012. Harmonization Project Document No. 10: Guidance for immunotoxicity risk assessment for chemicals. http://www.who.int/ipcs/methods/harmonization/areas/guidance_immunotoxicity.pdf.

Ishizu S, Goto T. 1980. Preliminary study on skin sensitisation caused by MDI solution. Report to the International Isocyanate Institute. [cited in ECJRC 2005].

[ISOPA]. European Diisocyanate and Polyol Producers Association. 2013. GPS Safety Summary. Brussels (BE).

[JETOC] Japan Chemical Industry Ecology Toxicology and Information Center. 1982. Micronucleus test. Report of the Japan Chemical Industry Ecology, Toxicology and Information Center. [cited in ECJRC 2005].

Johnson BT. 2005. Microtox®acute toxicity test. In: Blaise C, Férard J-F, editors. Small-scale freshwater toxicity investigations. p. 69-105. Netherlands: Springer Netherlands.

Kaiser KLE, Palabrica VS. 1991. *Photobacterium phosphoreum* toxicity data index.Water Poll Res J. 26(3):361-431.

Kakooei H, Shahtaheri SJ, Karbasi HA. 2006. Evaluation of workers' exposure to methylene diphenyl diisocyanate (MDI) in an automobile manufacturing company, Iran. Int J Occup Saf Ergon. 12(4):443-449.

Kanerva L, Estlander T, Jolanki R, Keskinen H. 2001. Asthma from diisocyanates is not mediated through a Type IV, patch-test-positive mechanism. Contact Dermatitis 44(4):247-248.

Karol MH. 1986. Respiratory effects of inhaled isocyanates. Crit Rev Toxicol. 16(4):349-379.

Karol MH, Thorne PS. 1988. Respiratory hypersensitivity and hyper-reactivity: implications for assessing allergic responses. In: Gardner DE, Carpo JD, MAssaro EJ, editors. Toxicology of the Lung. New York (NY): Raven Press p. 427. [cited in Pauluhn and Mohr 1994].

Karoly WJ, Flatley JJ, Stevenson RD, Bowers JD. 2004. Airborne concentrations of methylene diphenyl diisocyanate (MDI) in North American wood mills during the manufacturing of oriented strand board (OSB). J Occup Environ Hyg. 1:789-798.

Kelly BC, Ikonomou MG, Blair JD, Morin AE, Gobas FAPC. 2007. Food web-specific biomagnification of persistent organic pollutants. Science 317:239-238.

Kennedy AL, Brown WE. 1998. Biochemical and histoautoradiographic characterization of the distribution of radioactivity following exposure to 14C-MDI aerosol. Project 103-AM-MTX. International Isocyanate Institute. [cited in ECJRC 2005].

Kiec-Swierczynska M, Swierczynska-Machura D, Chomiczewska-Skora D, Nowakowska-Swirta E, Krecisz B. 2014. Occupational allergic and irritant contact dermatitis in workers exposed to polyurethane foam. Int J Occup Med Environ Health 27(2):196-205.

Kilgour JD, Rattray NJ, Foster J, Soames A, Hext PM. 2002. Pulmonary responses and recovery following single and repeated inhalation exposure of rats to polymeric methylene diphenyl diisocyanate aerosols. J Appl Toxicol. 22(6):371-385.

Kim M, Jang J, Lee I, Le H, Yoon J. 2002. Toxicity and biodegradation of diamines. J Environ Sci Health B 37(1):53-64.

Kimber I, Dearman RJ, Basketter DA, Ryan CA, Gerberick GF, McNamee P, Lalko J, Api AM. 2008. Dose metrics in the acquisition of skin sensitization: thresholds and importance of dose per unit area. Regul Toxicol Pharmacol. 52:39-45.

[KOAWIN] Octanol Air Partition Coefficient Program for Microsoft Windows [estimation model]. 2008. Ver. 1.10. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. http://www.epa.gov/oppt/exposure/pubs/episuite.htm.

[KOCWIN] Organic Carbon Partition Coefficient Program for Windows [estimation model]. 2010. Vers. 2.00. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. http://www.epa.gov/oppt/exposure/pubs/episuite.htm.

Kolmodin-Hedman B, Alexanderrson R, Hedenstierna G. 1980. Diisocyanater-MDI: Lungfysiolo-giska undersökningar pa personal i plastindustri. [cited in DGF 1997]:http://onlinelibrary.wiley.com/doi/10.1002/3527600418.mb10168stae0008/full#mb10168stae0008-bib-0028

Kopelman H, Robertson MH, Sanders PG, Ash I. 1966a. The Epping jaundice. Br Med J. 1(5486):514-516.

Kopelman H, Schever PJ, Williams R. 1966b. The liver lesion of the Epping Jaundice. Quart J Med. 35:553-564.

[KOWWIN] Octanol-Water Partition Coefficient Program for Microsoft Windows [estimation model]. 2010. Ver. 1.68. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. http://www.epa.gov/oppt/exposure/pubs/episuite.htm.

Krone CA, Ely JTA, Klingner T, Rando RJ. 2003. Isocyanates in flexible polyurethane foams. Bull Environ Contam Toxicol. 70:328-335.

Krone CA, Klingner TD. 2005. Isocyanates, polyurethane and childhood asthma. Pediatr Allergy Immunol. 16:368-379.

Laboratoire d'Etudes du Métabolisme des Médicaments. 1977. Pharmacokinetics of MDI after inhalation exposure of rats to labeled MDI. Report to the International Isocyanate Institute, September 1977. Commissariat à l'Energie Atomique, France. [cited in ECJRC 2005].

Lars Rosell and Marcus Vestergren. 2012. Selena straw foams MDI emission report from one-component foam. EPA-HQ-OPPT-2011-0182. Report was also submitted by American Chemistry Council's Center for the Polyurethanes Industry to Environment Canada on October 31, 2014.

Le Moual N, Kauffmann F, Eisen EA, Kennedy SM. 2008. The healthy worker effect in asthma: work may cause asthma, but asthma may also influence work. Am J Respir Crit Care Med. 177(1):4-10.

Leibold HD, Hoffmann, Hildebrand B. 1998. 14C-Methylenbisphenylisocyanate (14C-MDI) – Study of the absorption after single dermal and intradermal administration in rats. BASF Aktiengesellschaft Toxicology, Ludwigshafen/Rhein, Draft report project No. 01B0431/946010, III project No. 126-EU-MTX, 1998. [cited in ECJRC 2005].

Lemière C, Romeo P, Chaboillez S, Tremblay C, Malo JL. 2002. Airway inflammation and functional changes after exposure to different concentrations of isocyanates. J Allergy Clin Immunol. 110(4):641-646.

Leong BK, Lund JE, Groehn JA, Coombs JK, Sabaitis CP, Weaver RJ, Griffin RL. 1987. Retinopathy from inhaling 4,4′-methylenedianiline aerosols. Fundam Appl Toxicol. 9(4):645-658.

Leroyer C, Perfetti L, Cartier A, Malo JL. 1998. Can reactive airways dysfunction syndrome (RADS) transform into occupational asthma due to “sensitisation” to isocyanates? Thorax 53(2):152-153.

Lesage J, Stanley J, Karoly WJ, Lichtenberg FW. 2007. Airborne methylene diphenyl diisocyanate (MDI) concentrations associated with the application of polyurethane spray foam in residential construction. J Occup Environ Hyg. 4:145-155.

Lide DR, editor. 2003. CRC Handbook of Chemistry and Physics. 84th Edition. Boca Raton (FL): CRC Press.

Liden C. 1980. Allergic contact dermatitis from 4,4′diisocyanato-diphenyl methane (MDI) in a molder. Contact Dermatitis 6(4):301-302.

Lindberg HK, Korpi A, Santonen T, Säkkinen K, Järvelä M, Tornaeus J, Ahonen N, Järventaus H, Pasanen AL, Rosenberg C, Norppa H. 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.

Liss GM, Bernstein DI, Moller DR, Gallagher JS, Stephenson RL, Bernstein IL. 1988. Pulmonary and immunologic evaluation of foundry workers exposed to methylene diphenyldiisocyanate (MDI). J Allergy Clin Immunol. 82(1):55-61. [cited in US EPA 1998].

Liss GM, Chrostek W. 1983. NIOSH Health Hazard Evaluation Report, HETA 82-146-1388, Boeing Vertol Company. [cited in OECD 2002].

Liu Q, Wisnewski AV. 2003. Recent developments in diisocyanate asthma. Ann Allergy Asthma Immunol. 90(5 Suppl 2):35-41.

Liu Y, Sparer J, Woskie S, Cullen M, Chung J, Holm C, Redlich C. 2000. Qualitative assessment of isocyanate skin exposure in auto body shops: a pilot study. Am J Ind Med 37:265-274.

[LNHPD] Licensed Natural Health Product Database [database]. [modified 2014 Feb 27].. Ottawa (ON): Health Canada. [accessed 2013 Feb 12]. http://webprod5.hc-sc.gc.ca/lnhpd-bdpsnh/index-eng.jsp.

Loveless SE, Api AM, Crevel RWR, Debruyne E, Gamer A, Jowsey IR, Kern P, Kimber I, Lea L, Lloyd P, Mehmood Z, Steiling W, Veenstra G, Woolhiser M, Hennes C. 2010. Potency values from the local lymph

node assay: Application to classification, labelling and risk assessment. Regul Toxicol Pharmacol. 56:54-66.

Lowenkron S. 2000. Amines, aromatic, methylenedianiline. In: Kirk-Othmer Encyclopedia of Chemical Technology. New York (NY): John Wiley & Sons, Inc. p. 1-11.

[LSAS] Least-Squares Adjustment Spreadsheet (version 1.1). 2005. Zurich (CH): Safety and Environmental Technology Group. http://www.sust-chem.ethz.ch/downloads.

Lushniak B, Reh C, Bernstein D, Gallagher J. 1998. Indirect assessment of 4,4′-diphenylmethane diisocyanate (MDI) exposure by evaluation of specific humoral immune responses to MDI conjugated human serum albumin. Am J Ind Med. 33(5):471-477.

MacNab JI. 1999. Determination of Physical Properties of 4,4′-MDA. International Isocyanate Institute Inc. Project 146. [restricted access].

Maddison P, Merckx EMB. 1996. Responsible care programmes. Forestry & Forest Prod. Int. p. 107-110.

Maki-Paakkanen J, Norppa H. 1987. Chromosome aberrations and sister-chromatid exchanges induced by technical grade toluene diisocyanate and methlenediphenyl diisocyanate in cultured human lymphocytes. Toxicol Lett. 36:37-43.

Malo JL, Zeiss CR. 1982. Occupational hypersensitivity pneumonitis after exposure to diphenylmethane diisocyanate. Am Rev Respir Dis. 125(1):113-116.

Marczynski B, Ammon J, Seemann U, Zimmermann B, Marek W, Baur X. 1994a. [not in English] Lungen Kr. 20, 456-457. [cited in ECJRC 2005].

Marczynski B, Seemann U, Ammon J, Broding H, Marek W, Baur X. 1994b. Analysis of DNA fragmentation in white blood cell debris of workers exposed to diisocyanates. Book of Abstracts-Eurotox′94. Toxicol Lett. 74 (s1):53.

Marczynski B, Merget R, Mensing T, Rabstein S, Kappler M, Bracht A, Haufs MG, Käfferlein HU, Brüning T. 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(6):355-62.

Martin F, Fichet D, Arsanian G, Leloup MC. 1982. Enquéte épidemiologique sur la toxicité des isocyanates en milieu industriel. [cited in DGF 1997]: http://onlinelibrary.wiley.com/doi/10.1002/3527600418.mb10168stae0008/full#mb10168stae0008-bib-0028Massone L, Anonide A, Borghi S, Isola V. 1990. Significato clinico di test epicutanei positivi al diaminodifenilmetano. Folia Allergol Immunol Clin. 37:259-262.

Matsuoka A, Haishima Y, Hasegawa C, Matsuda Y, Tsuchiya T. 2008. Organic-solvent extraction of model biomaterials for use in the in vitro chromosome aberration test. J Biomed Mater Res A 86(1):13-22.

McCoy M, Anderson K, Boyd C. 2013. Inhalation study of Gorilla Glue. GZA GeoEnvironmental Inc. Study presentation at Isocyanates and Health Conference, Potomac, MD.

McDonnell ME. 1971. Production of skin sensitization by inhalation of isocyanates. Haskell Laboratory Report No. 161-71. Sponsored by E.I. du Pont Nemours and Company. OTS No. 86910000460.

McGill DB, Motto JD. 1974. An industrial outbreak of toxic hepatitis due to methylenedianiline. N Engl J Med. 291(6):278-282. [cited in ATSDR 1998; ECJRC 2001; OECD 2002].

McGregor DB. 1981a. Testing the mutagenic potential of HE1003 in the mouse lymphoma assay. Inveresk Research International Report No. 1906, January 1981, to Bayer AG Institut fur Toxikologie. [cited in ECJRC 2005].

McGregor DB. 1981b. Testing the mutagenic potential of HE1003 in the mouse lymphoma assay, Inveresk Research International Report No. 1883, January 1981, to Bayer AG Institut fur Toxikologie. [cited in ECJRC 2005].

McGregor DB, Brown A, Cattanach P, Edwards I, McBride D, Riach C, Caspary WJ. 1988. Responses of the L5178Y tk+/tk- mouse lymphoma cell forward mutation assay: III. 72 coded chemicals. Environ Mol Mutagen. 12(1):85-154. [cited in ATSDR 1998; ECJRC 2001; OECD 2002].

MDI Consortium. 2012. Chemical Safety Report on 4,4′-methylenediphenyl diisocyanate CAS No. 101-68-8. Report prepared for European Chemicals Agency (ECHA).

Mei CF, Liu YZ, Long WN, Sun GP, Zeng GQ, Xu MY, Luan TG. 2015. A comparative study of biodegradability of carcinogenic aromatic amine (4,4′-Diaminodiphenylmethane) with OECD 301 test methods. Ecotoxicol Environ Saf. 111:123-130.

Meredith SK, Bugler J, Clark RL. 2000. Isocyanate exposure and occupational asthma: a case-referent study. Occup Environ Med. 57:830-836.

Methner MM, McKernan JL, Dennison JL. 2010. Occupational health and safety surveillance task-based exposure assessment of hazards associated with new residential construction. Appl Occup Environ Hyg. 15:811-819.

Michalopoulos GK, Barua L, Bowen WC. 2005. Transdifferentiation of rat hepatocytes into biliary cells after bile duct ligation and toxic biliary injury. Hepatology 41(3):535-44.

[MIFACE] Michigan Fatality and Control Evaluation. 2003. Manager of after-market truck bed liner store dies of asthmatic attack after spraying van with isocyanate-based truck bed liner. Lansing (MI): Michigan State University, Occupational and Environmental Medicine, Michigan Fatality and Control Evaluation, MIFACE Investigation 03M1018. [cited in NIOSH 2006].

[MIOSHA] Michigan Occupational Safety and Health Administration. 2004. MIOSHA isocyanate alert: spray-on truck-bed liner operation proves fatal. Lansing (MI): Michigan Occupational Safety and Health Administration, Department of Labor and Economic Growth. http://www.michigan.gov/miosha. [cited in NIOSH 2006].

Mirsalis J, Tyson K, Beck J, Loh F. Steinmetz K, Contreras C, Austere L, Martin S, Spalding J. 1983. Induction of unscheduled DNA synthesis (UDS) in hepatocytes following in vitro and in vivo treatment. Environ Mutagen. 5:482.

Mirsalis JC, Tyson CK, Steinmetz KL, Loh EK, Hamilton CM, Bakke JP, Spalding JW. 1989. Measurement of unscheduled DNA synthesis and S-phase synthesis in rodent hepatocytes following in vivo treatment: testing of 24 compounds. Environ Mol Mutagen. 14(3):155-164.

[MITI] Ministry of International Trade & Industry Japan. 1992. Biodegradation and bioaccumulation data of existing chemicals based on the CSCL Japan. Japan Chemical Industry Ecology-Toxicology & Information Center, October 1992. [restricted access].

Mitsubishi Chemical Safety Institute. 2002a. Final report of acute immobility test against Daphnia magna by 4,4-methylene bis benzene amine (test number A010459-2). Unpublished report to the Ministry of the

Environment (JP). English translation for the International Isocyanate Institute c2008. 32 p. http://www.epa.gov/oppt/tsca8e/pubs/8emonthlyreports/2011/8emay2011.html.

Mitsubishi Chemical Safety Institute. 2002b. Final report of reproduction inhibition test against Daphnia magna by 4,4-methylene bis benzene amine (test number A010459-3). Unpublished report to the Ministry of the Environment (JP). English translation for the International Isocyanate Institute c2008. 41 p. http://www.epa.gov/oppt/tsca8e/pubs/8emonthlyreports/2008/8emay2008.html.

Miyamoto J, Okuno Y, Kadota T, et al. 1977. Experimental hepatic lesions and drug metabolizing enzymes in rats. J Pestic Sci (Nihon Noyakugaku Kaishi); 2(3):257-270.

Moore WM. 1978. Methylenedianiline. In: Mark HF, Othmer DF, Overberger CG, Seaborg GT, editors. Kirk-Othmer Encyclopedia of Chemical Technology. New York (NY): John Wiley & Sons, p. 338-348.

Mori H, Yoshimi N, Sugie S, Iwata H, Kawai K, Mashizu N, Shimizu H. 1988. Genotoxicity of epoxy resin hardeners in the hepatocyte primary culture/DNA repair test. Mutat Res. 204(4):683-8. [cited in ATSDR 1998; ECJRC 2001; OECD 2002].

Mormann W, Vaquero RL, Seel K. 2006. Interactions of aromatic isocyanates with N-acetyl-L-cysteine under physiological conditions: formation of conjugates, ureas and amines. EXCLI J. 5:191-208.

Mortensen SK, Trier XT, Foverskov A, Peterson JH. 2005. Specific determination of 20 primary aromatic amines in aqueous food simulants by liquid chromatography-electrospray ionization-tandem mass spectrometry. J Chromatogr A 1090:40-50.

[MPBPWIN] Melting Point Boiling Point Program for Microsoft Windows [estimation model]. 2010. Ver. 1.43. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. http://www.epa.gov/oppt/exposure/pubs/episuite.htm.

[MSDS] Material Safety Data Sheet. 2010. Material Safety Data Sheet: 3M Scotchcast Poly Plus. St. Paul (MN): 3M Company. [accessed 2014 Jan]. http://multimedia.3m.com/mws/mediawebserver?mwsId=SSSSSuUn_zu8l00xMx_1Ox2Gnv70k17zHvu9lxtD7SSSSSS--.

[MSDS] Material Safety Data Sheet. 2011. Material Safety Data Sheet: 3M Primacast Splint. St Paul (MN): 3M Company. [accessed 2014 Jan]. http://multimedia.3m.com/mws/mediawebserver?mwsId=SSSSSuUn_zu8l00xlYtvlx2vnv70k17zHvu9lxtD7SSSSSS--.

Moser T, Schott C. 2011. 4,4′-MDA: toxicity to the collembolan species *Folsomia candida*, Chemisches Institut Pforzheim Gmhb ECT Oekotoxikologie GmbH project# 11AD1CR. [restricted access].

Musk AW, Peters JM, DiBerardinis L, Murphy RL. 1982. Absence of respiratory effects in subjects exposed to low concentrations of TDI and MDI. J Occup Med. 24(10):746-750.

Musk AW, Peters JM, Berstein L. 1985. Absence of respiratory effects in subjects exposed to low concentration of TDI and MDI: a reevaluation. J Occup Med. 27-917.

Myer HE, Cummings BJ. 2005. Safety considerations for Application of Spary-On Truck Bed Liners. Available: http://polyurethane.americanchemistry.com/Spray-Truck-Bed-Liner/Safety-Considerations.pdf.

[NCASI] National Council of Air and Stream Improvements. 2012. Draft forest product industry methylene diphenyl diisocyanate (MDI) fact sheet. Draft dated March 19, 2012. Submitted to Environment Canada,

Program Development and Engagement Division by Forest Products Association of Canada (FPAC) and NCASI on October 15, 2012. 5 p.

[New EQC] Equilibrium Criterion Model. 2011. Ver. 1.0 (Beta). Peterborough (ON): Trent University, Canadian Centre for Environmental Modelling and Chemistry. http://www.trentu.ca/academic/aminss/envmodel/models/NewEQCv100.html.

[NHPID] Natural Health Product Ingredients Database [database]. 2013. Ottawa (ON): Health Canada. [accessed 2013 Feb 12]. http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/online-enligne/nhpid-bipsn-eng.php.

[NIOSH] National Institute for Occupational Safety and Health. 1996. Preventing asthma and death from diisocyanate exposure DHHS. DHHS (NIOSH) Publication No. 96-111. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/docs/96-111/.

[NIOSH] National Institute for Occupational Safety and Health. 2006. Preventing asthma and death from MDI exposure during spray-on truck bed liner and related applications. DHHS (NIOSH) Publication No. 2006-149. http://www.cdc.gov/niosh/docs/2006-149/pdfs/2006-149.pdf.

[NPRI] National Pollutant Release Inventory . 1995a. NPRI data search for 4,4′-MDA (CAS RN 101-77-9) for the years 2008–2013. Gatineau (QC): Environment Canada. [accessed 2015 Feb]. http://ec.gc.ca/inrp-npri/donnees-data/index.cfm?lang=En.

[NPRI] National Pollutant Release Inventory . 1995b. NPRI data search for pMDA (CAS RN 25214-70-4) for the years 2008–2013. Gatineau (QC): Environment Canada. [accessed 2015 Feb]. http://ec.gc.ca/inrp-npri/donnees-data/index.cfm?lang=En.

[NPRI] National Pollutant Release Inventory . 1995c. NPRI data search for 4,4′-MDI (CAS RN 101-68-8) and pMDI (CAS RN 9016-87-9). Gatineau (QC): Environment Canada. [accessed 2015 Feb]. http://ec.gc.ca/inrp-npri/donnees-data/index.cfm?lang=En.

[NRS] National Research Council. 2011. Evaluation Listing CCMC13447-L. [accessed 2015 Nov]. http://www.cid.ca/PDFs_Products_MSDS_Brochures/FROTH-PAK_CCMC_Approved_Evaluation_September_2011.pdf.

[NTP] National Toxicology Program. 1983. Technical Report on the Carcinogenesis Studies of 4,4′-Methylenedianiline Dihydrochloride (CAS No. 13552-44-8) in F344/N Rats and B6C3FI Mice (Drinking Water Studies). US Department of Health and Human Services. NTP-81-143, NIH Publication No. 83-2504, NTP TR 248.

[NTP] National Toxicology Program. 2005. 4,4′-Methylenedianiline and its Dihydrochloride Salt. Report on Carcinogens, 11th Edition. Research Triangle Park, NC: US Department of Health and Health Services, Public Health Service, National Toxicology Program.

[NTP] National Toxicology Program. 2011. 4,4′ Methylenedianiline and its dihydrochloride. Report on Carcinogens, 12th Edition. Research Triangle Park, NC: US Department of Health and Human Services, Public Health Service, National Toxicology Program. p. 265.

O'Brien IM, Harries MG, Burge PS, Pepys J. 1979. Toluene di-isocyanate-induced asthma. I. Reactions to TDI, MDI, HDI and histamine. Clin Allergy 9(1):1-6.

[OECD] Organisation for Economic Co-operation and Development. 2002. Summary risk assessment report: 4,4′-Methylenedianiline (MDA): (1st Priority List): CAS no. 101-77-9: EINECS no. 202-974-4. Geneva (CH): United Nations Environment Programme (UNEP) Chemicals. [accessed 2013 Jan]. http://www.inchem.org/documents/sids/sids/101779.pdf

[OECD] Organisation for Economic Co-operation and Development. 2003. SIDS Initial Assessment Profile from SIAM 17, 11-14 November 2003. CAS No. 26447-40-5. Methylenediphenyl diisocyanate [accessed 2012 Aug 15]. http://webnet.oecd.org/Hpv/Ul/handler.axd?id=6c7d2813-0f0e-40b3-9d78-49a95abefc3c.

[OECD] Organization for Economic Co-operation and Development. 2004. The 2004 OECD list of high production volume chemicals. Paris (FR): OECD, Environment Directorate, Environment, Health and Safety Division. 143 p. http://www.oecd.org.

[OECD] Organisation for Economic Co-operation and Development. 2011. Emission scenario document on radiation curable coating, inks and adhesives. Paris (FR): OECD Environmental Directorate (Series on Emission Scenario Documents No. 27; Report No.: ENV/JM/MONO(2011)17, JT03304942. [accessed 2013 Mar]. http://www.oecd.org/chemicalsafety/risk-assessment/publicationsonchemicalsexposureassessment.htm.

O'Neil MJ. 2006. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. Merck. 2564 p.

Oprea S. 2011. Degradation of crosslinked poly(ester-urethanes) elastomers in distilled water: influence of hard segment. J Appl Polym Sci. 124:1059-1066.

[OSHA] Occupational Safety and Health Administration. 2012. Permissible exposure limit: Table Z-1 Limits for Air Contaminants. 29 CFR 1910.1000. [accessed 2012 Aug 16]. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992

Parodi S, Taningher M, Russo P, Pala M, Tamaro M and Monti-Bragadin C. 1981. DNA-damaging activity in vivo and bacterial mutagenicity of 16 aromatic amines and azo derivatives, as related quantitatively to their carcinogenicity. Carcinogenesis 2(12):1317-1326.

Parodi S, Zunino A, Ottagio L, de Ferrari M, Santi L. 1983. Lack of correlation between the capability of inducing sister-chromatid exchanges in vivo and carcinogenic potency, for 16 aromatic amines and azo derivatives. Mutat Res. 108:225-238.

Pauluhn J. 1995. Diphenylmethane-4,4′-diisocyanate (MDI-monomer) Evaluation of respiratory sensitization in guinea-pigs following brief high-level inhalation induction exposure and challenge with ramped MDI concentrations. Bayer Study No. T1058323, III-Project 121-EU-MTX, 30 May 1995. [cited in ECJRC 2005].

Pauluhn J. 2000. Acute inhalation toxicity of polymeric diphenyl-methane 4,4′-diisocyanate in rats: time course of changes in bronchoalveolar lavage. Arch Toxicol. 74:257-269.

Pauluhn J. 2002. Short-term inhalation toxicity of polyisocyanate aerosols in rats: comparative assessment of irritant-threshold concentrations by bronchoalveolar lavage. Inhal Toxicol. 14:287-301.

Pauluhn J. 2008a. Brown-Norway rat asthma model of diphenylmethane-4,4′-diisocyanate (MDI): Analysis of the elicitation dose-response relationship. Toxicol Sci. 104(2):320-331.

Pauluhn J. 2008b. Brown Norway rat asthma model of diphenylmethane-4,4′-diisocyanate (MDI): impact of vehicle for topical induction. Regul Toxicol Pharmacol. 50(1):144-54.

Pauluhn J, Mohr U. 1994. Assessment of respiratory hypersensitivity in guinea-pigs sensitized to diphenylmethane-4,4′-diisocyanate (MDI) and challenged with MDI, acetylcholine or MDI-albumin conjugate. Toxicology 92:53-74.

Pauluhn J, Gollapudi B, Hammond T, Linscombe A, Thiel A, Zischka-Kuhbier D. 2001. Bone marrow micronucleus assay in Brown-Norway rats exposed to diphenyl-methane-4,4′-diisocyanate. Arch Toxicol. 75(4):234-42.

Pauluhn J, Poole A. 2011. Brown Norway rat asthma model of diphenylmethane-4,4′-diisocyanate (MDI): Determination of the elicitation threshold concentration of after inhalation sensitization. Toxicology 281:15-24.

Peiser M, Tralau T, Heidler J, Api AM, Arts JH, Basketter DA, English J, Diepgen TL, Fuhlbrigge RC, Gaspari AA, Johansen JD, Karlberg AT, Kimber I, Lepoittevin JP, Liebsch M, Maibach HI, Martin SF, Merk HF, Platzek T, Rustemeyer T, Schnuch A, Vandebriel RJ, White IR, Luch A. 2012. Allergic contact dermatitis: epidemiology, molecular mechanisms, in vitro methods and regulatory aspects. Current knowledge assembled at an international workshop at BfR, Germany. Cell Mol Life Sci. 69(5):763-81.

Perfetti L, Bramé B, Ferrari M, Moscato G. 2003. Occupational asthma (OA) with sensitization to diphenylmethane diisocyanate (MDI) presenting at the onset like a reactive airways dysfunction syndrome (RADS). Am J Ind Med. 44(3):325-8.

Petsonk EL, Wang ML, Lewis DM, Siegel PD, Husberg BJ. 2000. Asthma-like symptoms in wood product plant workers exposed to methylene diphenyl diisocyanate. Chest 118(4):1183-93.

Pezzini A, Riviera A, Paggiaro P, Spiazzi A, Gerosa F, Filieri M, Toma G, Tridente G. 1984. Specific IgE antibodies in twenty-eight workers with diisocyanate-induced bronchial asthma. Clin Allergy 14:453-461. [cited in US EPA 1998].

Pham QT, Cavelier C, Mereau P, Mur JM, Cicollella A. 1978. Isocyanates and respiratory function: A study of workers producing polyurethane foam moulding. Ann Occup Hyg. 21:121-129.

Pham QT, Teculescu D, Meyer-Bisch C, Mur JM. 1988. Effects of chronic exposure to diisocyanates, Bull Eur Physiopathol Respir. 23:561-564.

Phipps GL, Ankley GT, Benoit DA, Mattson VR. 1993. Use of the aquatic oligochaete *Lumbriculus variegatus* for assessing the toxicity and bioaccumulation of sediment-associated contaminants. Environ Toxicol Chem. 12:269-79.

Plitnick LM, Loveless SE, Ladics GS, Holsapple MP, Smialowicz RJ, Woolhiser MR, Anderson PK, Smith C, Selgrade MJK. 2005. Cytokine mRNA profiles for isocyanates with known and unknown potential to induce respiratory sensitization. Toxicology 207:487-499.

Pludro G, Karlowski K, Mankowska M, Woggon H, Uhde WJ. 1969. [Toxicological and chemical studies of some epoxy resins and hardeners. I. Study of acute and subacute toxicity of phthalic acid anhydride, 4,4′-diaminodiphenylmethane and epoxy resin Epilox EG-34]. Acta Pol Pharm 26(4):353-8. [cited in ATSDR 1998].

Poole A, Harris WJ. 1980a. Testing of the cell transformation activity of HE1002, Inveresk Research International, Report No. 1862, November 1980, to Bayer AG Institut fur Toxicologie. [cited in ECJRC 2005].

Poole A, Harris WJ. 1980b. Testing of the cell transformation activity of HE1003. Inveresk Research International, Report No. 1863, November 1980, to Bayer AG Institut fur Toxicologie. [cited in ECJRC 2005].

Rattray NJ, Botham PA, Hext PM, Woodcock DR, Fielding I, Dearman RJ, Kimber I. 1994. Induction of respiratory hypersensitivity to diphenylmethane-4,4′-diisocyanate (MDI) in guinea pigs. Influence of route of exposure. Toxicology 88:15-30.

Redlich CA. 2010. Skin exposure and asthma. Proc Am Thorac Soc. 7:134-137.

Reuzel PGJ, Arts JHE, Kuijpers MHM, Kuper CF. 1990. Chronic toxicity/carcinogenicity inhalation study of polymeric methylenediphenyl diisocyanate aerosol in rats, TNO-CIVO Institutes Report No. V88.122, March 1990, for the International Isocyanate Institute. [cited in ECJRC 2005].

Reuzel PGJ, Arts JHE, Lomax LG, Kuijpers MHM, Kuper CF, Gembardt C, Feron VJ, Loser E. JP. 1994a. Chronic inhalation and carcinogenicity study of respirable polymeric methylene diphenyl diisocyanate (polymeric MDI) aerosol in rats. Fundam Appl Toxicol. 22:195-210. [cited in US EPA 1998].

Reuzel PGJ, Kuper CF, Feron VJ, Appelman LM, Löser E. 1994b. Acute, subacute and subchronic inhalation toxicity studies of respirable polymeric methylene diphenyl diisocyanate (polymeric MDI) aerosol in rats. Fundam Appl Toxicol. 22: 86-194.

[RIVM] Rijksinstituut voor Volksgezondheid en Milieu. 2007. Do-It-Yourself Products Fact Sheet: To assess the risks for the consumer. Bilthoven (NL): Rijksinstituut voor Volksgezondheid en Milieu [National Institute for Public Health and the Environment]. http://www.rivm.nl/bibliotheek/rapporten/320104007.pdf.

Roberge B, Gravel R, Drolet D. 2009. 4,4′-Diphenylmethane diisocyanate (MDI) safety practices and concentration during polyurethane foam spraying. Report R-629. Institut de recherché Robert-Sauvé en santé et en sécurité de travail (IRSST).

Romaguera C, Garcia-Perez A, Martin-Pascual A, Miranda A. 1981. Diaminodiphenylmethane in standard patch tests. Contact Dermatitis 7(6):347-348.

Saclay R. 1977. Pharmacokinetics of MDI after inhalation exposure of rats to labeled MDI. In: Report by Laboratoire d'Etudes du Métabolisme des Médicaments, Dept. Biologie, to the International Isocyanate Institute [cited in US EPA 1998].

Salinas PE. 2011. Report: 4,4′-MDA-acute toxicity (immobilisation) study in the water flea *Daphnia magna* STRAUS. Unpublished report. Parsippany (NJ): International Isocyanate Institute. http://www.epa.gov/oppt/tsca8e/pubs/8emonthlyreports/2011/8emay2011.html.

Schafer EW Jr, Bowles WA, Hurlbut J. 1983. The acute oral toxicity, repellency, and hazard potential of 998 chemicals to one or more species of wild and domestic birds. Arch Environ Contam Toxicol. 12:355-382.

Schaefer EC, Carpenter K. 2013. [^{14}C] 4,4′-Methylenedianiline: aerobic mineralization in surface water (OECD Guideline 309). Wildlife International Project No. 717E-101. [restricted access].

Schaefer EC, Ponizovsky A. 2013. [^{14}C] 4,4′-Methylenedianiline: aerobic and anaerobic transformation in aquatic sediment systems (OECD Guideline 308). Wildlife International Project No.: 717E-102. [restricted access].

Scheringer M, MacLeod M, Wegmann F. 2009. The OECD POV and LRTP Screening Tool, Version 2.2, A manual for the OECD POV and LRTP Screening Tool 2.2 that is a follow-up version of the Software POPorNot 1.0 distributed at the OECD/UNEP Workshop on Application of Multimedia Models for Identification of Persistent Organic Pollutants, ETH Zurich, April 2009. Version 2.2.

Schmidt P, Burck D, Weigmann HJ. 1974. [Acute toxicity of some for plastic processing industry important amines]. Z Gesamte Hyg 20(7):393-8. [cited in ATSDR 1998].

Schmidt P, Gohlke R, Just A, Rothe R, Burck D, Jager H. 1980. Combined action of hepatotoxic substances and increased environmental temperature on the liver of rats. J Hyg Epidemiol Microbiol Immunol. 24(3):271-6. [cited in ATSDR 1998].

Schreiber J, Knolle J, Sennekamp J, Schulz KT, Hahn JU, Hering KG, Raulf-Heimsoth M, Merget R. 2008. Sub-acute occupational hypersensitivity pneumonitis due to low-level exposure to diisocyanates in a secretary. Eur Respir J. 32:807-811.

Schwarz H. 2013. 4,4′-MDA: effect on nitrification in soil. Experimental Toxicology and Ecology. International Isocyanate Institute Inc. Project # 37G0290/08G264. [restricted access].

SCREEN3 [computer model]. 1995. Vers. 96043. Research Triangle Park (NC): US Environmental Protection Agency, Office of Air Quality Planning and Standards, Emissions, Monitoring, and Analysis Division. http://www.epa.gov/scram001/dispersion_screening.htm.

Selden A, Berg P, Jakobsson R, de Laval J. 1992. Methylene dianiline: assessment of exposure and cancer morbidity in power generator workers. Int Arch Occup Environ Health 63(6):403-408.

Sendijarevic V, Sendijarevic A, Sendijarevic I, Bailey RB, Pemberton D, Reimann KA. 2004. Hydrolytic stability of toluene diisocyanate and polymeric methylenediphenyl diisocyanate based polyureas under environmental conditions. Environ Sci Technol. 38(4):1066-1072.

Shaddock JG, Heflich RH, McMillan DC, Hinson JA, Casciano DA. 1989. Pretreatment with mixed-function oxidase inducers increases the sensitivity of the hepatocyte/DNA repair assay. Environ Mol Mutagen. 13(4):281-288.

Shelby MD, Erexson GL, Hook GJ, Tice RR. 1993. Evaluation of a three-exposure mouse bone marrow micronucleus protocol: results with 49 chemicals. Environ Mol Mutagen. 21(2):160-179.

Shkapenko G, Gmitter GT, Gruber EE. 1960. Mechanism of the water-isocyanate reaction. Ind Eng Chem. 52(7):605-608.

Shimizu H, Suzujki, Takemura N, Goto S, Matsushita H. 1985. The results of microbial mutation test for 43 industrial chemicals. Sangyō Igaku 27(6):400-417.

Seel K, Walber U, Herbold B, Kopp R. 1999. Chemical behaviour of seven aromatic diisocyanates (toluenediisocyanates and diphenylmethanediisocyanates) under in vitro conditions in relationship to their results in the Salmonella/microsome test. Mutat Res. 438(2):109-123.

Selgrade M, Boykin EH, Haykal-Coates N, Woolhiser MR, Wiescinski C, Andrews DL, Farraj AK, Doerfler DL, Gavett SH. 2006. Inconsistencies between cytokine profiles, antibody responses, and respiratory hyperresponsiveness following dermal exposure to isocyanates. Toxicol Sci. 94(1):108-117.

Soil Model. 2005. Ver. 3. Peterborough (ON): Trent University, Canadian Centre for Environmental Modelling and Chemistry. A model to calculate chemical behaviour in a surface soil layer including roots. http://www.trentu.ca/academic/aminss/envmodel/models/Soil3.html.

Sommer B, Sherson D, Kjoller H, Hansen I, Clausen G, Jepsen J. 2000. Asthma caused by methylene-diphenyl-diisocyanate cast in a nurse. Ugeskr Laeger 162(4):505-506. [cited in ECJRC 2005].

Sorahan T, Nichols L. 2002. Mortality and cancer morbidity of production workers in the UK flexible polyurethane foam industry: updated findings, 1958-98. Occup Environ Med. 59:751-758.

Sorahan T, Pope D. 1993. Mortality and cancer morbidity of production workers in the United Kingdom flexible polyurethane foam industry. Br J Ind Med. 50:528-536.

Stingeni L, Bellini V, Lisi P. 2008. Occupational airborne contact urticaria and asthma: simultaneous immediate and delayed allergy to diphenylmethane-4,4′-diisocyanate. Contact Dermatitis 58(2):112-113.

Streicher RP, Kennedy ER, and Lorberau CD. 1994. Strategies for the simultaneous collection of vapors and aerosols with emphasis on isocyanate sampling. Analyst 119 (1):89-97.

Study Submission. 2012a. Unpublished confidential study submitted to Environment Canada under the Chemicals Management Plan initiative. Gatineau (QC): Environment Canada, Program Development and Engagement Division. Internal Reference ID: Other_5_V2, p. 47.

Study Submission. 2012b. Unpublished confidential study submitted to Environment Canada under the Chemicals Management Plan initiative. Gatineau (QC): Environment Canada, Program Development and Engagement Division. Internal reference ID: Other_5_V2, p. 117.

Study Submission. 2012c. Unpublished confidential study submitted to Environment Canada under the Chemicals Management Plan initiative. Gatineau (QC): Environment Canada, Program Development and Engagement Division. Internal reference ID No. 8 (original in German).

Study Submission. 2012d. Unpublished confidential study submitted to Environment Canada under the Chemicals Management Plan initiative. Gatineau (QC): Environment Canada, Program Development and Engagement Division. Internal reference ID No. 11 (original in German).

Study Submission. 2012e. Unpublished confidential study submitted to Environment Canada under the Chemicals Management Plan initiative. Gatineau (QC): Environment Canada, Program Development and Engagement Division. Internal reference ID: Other_5_V2, p. 277.

Study Submission. 2012f. Unpublished confidential study submitted to Environment Canada under the Chemicals Management Plan initiative. Gatineau (QC): Environment Canada, Program Development and Engagement Division. Internal reference ID: Other_5_V2, p. 575.

Study Submission. 2012g. Unpublished confidential study submitted to Environment Canada under the Chemicals Management Plan initiative. Gatineau (QC): Environment Canada, Program Development and Engagement Division. Internal reference ID: Other_5_V2, p. 113.

Study Submission. 2012h. Unpublished confidential study submitted to Environment Canada under the Chemicals Management Plan initiative. Gatineau (QC): Environment Canada, Program Development and Engagement Division. Internal reference ID: Other_5_V2, p. 397.

Study Submission. 2012i. Unpublished confidential studies submitted to Environment Canada under the Chemicals Management Plan initiative. Gatineau (QC): Environment Canada, Program Development and Engagement Division.

Sulotto F, Romano C, Piolatto G, Coggiola M, Polizzi S, Ciacco C, Berra A. 1990. Short-term respiratory changes in polyurethane foam workers exposed to low MDI concentration. Int Arch Occup Environ Health 62:521-524.

Suojalehto H, Linström I, Henriks-Eckerman ML, Jungewelter S, Suuronen K. 2011. Occupational asthma related to low levels of airborne methylene diphenyl diisocyanate (MDI) in orthopedic casting work. Am J Ind Med. 54(12):906-910.

Suzuki H, Ikeda N, Kobayashi K, Terashima Y, Shimada Y, Suzuki T, Hagiwara T, Hatakeyama S, Nagaoka K, Yoshida J, et al. 2005. Evaluation of liver and peripheral blood micronucleus assays with 9 chemicals using young rats. A study by the Collaborative Study Group for the Micronucleus Test (CSGMT)/Japanese Environmental Mutagen Society (JEMS)-Mammalian Mutagenicity Study Group (MMS). Mutat Res. 583(2):133-145.

[TaPL3] Long Range Transport and Persistence Level III model. 2000. Version 2.10. Peterborough (ON): Trent University, Canadian Centre for Environmental Modelling and Chemistry. http://www.trentu.ca/academic/aminss/envmodel/models/TaPL3.html

Talini D, Novelli F, Bacci E, de Santis M, Paggiaro PL. 2010. Sequential sensitization to different occupational compounds in a young woman. Med Lav. 101(1):49-54.

Tanaka KI, Takeoka A, Nishimura F, Hanada S. 1987. Contact sensitivity induced in mice by methylene bisphenyl diisocyanate. Contact Dermatitis 17(4):199-204.

Thorgeirsson A. 1978. Sensitization capacity of epoxy resin hardeners in the guinea pig. Acta Dermatovener (Stockholm) 58:332-336.

Thorn KA, Pettigrew PJ, Goldenberg WS. 1996. Covalent binding of aniline to humic substances. 2. ^{15}N NMR studies of nucleophilic addition reactions. Environ Sci Technol. 30(9):2764-2775.

Thorne PS, Hillebrand JA, Karol MH. 1986. Pulmonary irritation and hypersensitivity in guinea pigs exposed to 4,4′-diphenylmethane diisocyanate (MDI) aerosol. Toxicologist 6(1):15 (abstract).

Thorne PS, Hillebrand JA, Lewis GR, Karol MH. 1987. Contact sensitivity by diisocyanates: Potencies and cross-reactivities. Toxicol Appl Pharmacol. 87(1):155-165.

[TRI] Toxics Release Inventory [database]. 2012. Washington (DC): US Environmental Protection Agency [accessed 2013]. http://www.epa.gov/tri/.

Tillmann HL, van Pelt FN, Martz W, Luecke T, Welp H, Dorries F, Veuskens A, Fischer M, Manns MP. 1997. Accidental intoxication with methylene dianiline p,p′-diaminodiphenylmethane: acute liver damage after presumed ecstasy consumption. J Toxicol Clin Toxicol. 35(1):35-40.

Titebond Inc. 2012. Material Safety Data Sheet. Titebond Polyurethane Glue. Columbus (OH). [accessed 2013 Feb]. http://www.titebond.com/ProductMSDSCO.php.

Tse KS, Johnson A, Chan H, Chan-Yeung M. 1985. A study of serum antibody activity in workers with occupational exposure to diphenyl methane diisocyanate. Allergy 40:314-320. [cited in US EPA 1998].

Tsuda H, Ogiso T, Hasegawa R, Imaida K, Masui T, Ito N. 1987. Inhibition of neoplastic development in rat liver, kidney, oesophagus and forestomach by 4,4′-diaminodiphenylmethane administration. Carcinogenesis 8(5):719-22. [cited in ATSDR 1998].

Tury B, Pemberton D, Bailey RE. 2003. Fate and potential environmental effects of methylenediphenyl diisocyanate and toluene diisocyanate released into the atmosphere. J Air Waste Manage Assoc. 53:61-66.

[US CPSC]. US Consumer Product Safety Commission. 2012. Incident reports. [accessed 2012 Dec 3]. http://www.saferproducts.gov/Search/default.aspx.

[US EPA] US Environmental Protection Agency. 1985. Risk Assessment for 4,4′ Methylenedianiline. Washington (DC): US EPA, Office of Toxic Substances. [accessed 2013 Feb]. http://nepis.epa.gov/Exe/ZyNET.EXE?ZyActionL=Register&User=anonymous&Password=anonymous&Client=EPA&Init=1><title>EPA%20-%20Home%20Page%20for%20the%20Search%20site</title><link%20rel=.

[US EPA] US Environmental Protection Agency. 1998. Toxicological review of methylene diphenyl diisocyanate (MDI): (CAS No. 101-68-8 and 9016-87-9): in support of summary information on the Integrated Risk Information System (IRIS). Washington (DC): US EPA. [accessed 2013]. http://www.epa.gov/iris/toxreviews/0529tr.pdf.

[US EPA] US Environmental Protection Agency. 2002. AP 42, 5th edition, volume 1, Chapter 10: wood products industry. Washington (DC): US EPA. Section 10.6.1, Waferboard oriented strandboard. [accessed 2013 Apr]. http://www.epa.gov/ttnchie1/ap42/ch10/index.html.

[US EPA] US Environmental Protection Agency. 2006. *Toxic Substances Control Act* (TSCA) Section 8(e) submission. [accessed 2012 Dec 6]. http://www.epa.gov/oppt/tsca8e/pubs/8ehq/2008/jul08/8ehq_0708_16946c.pdf from http://www.epa.gov/dfe/pubs/projects/spf/related.html#tsca_section_8e.

[US EPA] US Environmental Protection Agency. 2011. Methylene diphenyl diisocyanate (MDI) and related compounds action plan. Washington (DC): US EPA, Office of Pollution Prevention and Toxics. https://www.epa.gov/sites/production/files/2015-09/documents/mdi.pdf

[US EPA] US Environmental Protection Agency. 2015. Information on the Various Types of Spray Polyurethane Foam Products. Available at http://www2.epa.gov/sites/production/files/2015-08/documents/spf_product_types.pdf [accessed 3 Nov 2015].

Valks R, Conde-Salazar L, Barrantes OL. 2003. Occupational allergic contact urticaria and asthma from diphenylmethane-4,4′-diisocyanatae. Contact Dermatitis 49(3):166-167.

Van der Hoeven N, Roza P, Henzen L. 1992. Determination of the effect of TDI, TDA, MDI, MDA on the emergence and growth of the plant species *Avena sativa* and *Lactuca sativa* according to OECD Guideline no. 208. TNO Institute of Environmental Sciences. Study No. IMW-91-0032/33/34/36-02/03. [restricted access].

Van Gheluwe P, Cole KC, Hebrard MJ, Leroux J. 1987. Attenuated total reflectance infrared spectroscopic analysis of high index foams. J Cell Plast. 23:73.

Van Joost T, Heule F, de Boer J. 1987. Van Joost T, Heule F, de Boer J. 1987. Sensitization to methylenedianiline and para-structures. Contact Dermatitis 16(5):246-248.

Vandenplas O, Malo JL, Dugas M, Cartier A, Desjardins A, Lévesque J, Shaughnessy MA, Grammer LC. 1993a. Hypersensitivity pneumonotis-like reaction among workers exposed to diphenylmethane diisocyanate (MDI). Am Rev Respir Dis. 147:338-346.

Vandenplas O, Delwiche JP, Staquet P, Jamart J, Bernard A, Boulanger J, Delaunois L, Sibille Y. 1999. Pulmonary effects of short-term exposure to low levels of toluene diisocyanate in asymptomatic subjects. Eur Respir J. 13(5):1144-1150.

Vock EH, Lutz WK. 1995a. Investigation of adduct formation of 4,4′-methylenediphenyldiisocyanate (MDI) or 4,4′-methylenedianiline (MDA) with DNA or chromatin protein in dermally-exposed rats, for International Isocyanate Institute, III-Project No. 123-EU-MTX, November 28, 1995. [cited in ECJRC 2005].

Vock EH, Catoreggi S, Fupta RC, Lutz WK. 1995b. ^{32}P-postlabelling analysis of a DNA adducts formed *in vitro* and in rat skin by methylene-4,4′-diisocyanate (MDI). Toxicol Lett. 76:17-26.

Vock EH, Hoymann HG, Heinrich U, Lutz WK. 1996. 32P-postlabeling of a DNA adduct derived from 4,4′-methylenedianiline, in the olfactory epithelium of rats exposed by inhalation to 4,4′-methylenediphenyl diisocyanate. Carcinogenesis 17(5):1069-1073.

Vock EH, Lutz WK. 1997. Distribution and DNA adduct formation of radiolabeled methylenediphenyl-4,4′-diisocyanate (MDI) in the rat after topical treatment. Toxicol Lett. 92:93-100.

Vock EH, Vamvakas S, Gahlman R, Lutz WK. 1998. Investigation of the induction of DNA double strand breaks by methlenediphenyl-4,4′-diisocyanate (MDI) in cultured human lung epithelial cells. Toxicol Sci. 46:83-89.

Vogelmeier C, Baur X, Fruhmann G. 1991. Isocyanate-induced asthma: results of inhalation tests with TDI, MDI and methacholine. Int Arch Occup Environ Health 63:9-13.

Waalkens-Berendsen DH, Arts JHE. 1992. Report of a developmental toxicity range-finding study of inhaled polymeric MDI aerosol in rats, TNO Nutrition and Food Research, TNO report V92.102, April 1992, to the International Isocyanate Institute. [cited in ECJRC 2005].

Walker CL, Grammer LC, Shaughnessy MA, Duffy Michele, Stoltzfu VD, Patterson R. 1989. Diphenylmethane diisocyanate hypersensitivity pneumonitis: a serologic evaluation. J Occup Med. 31(4):315-319.

Wang ML, Petsonk EL. 2004. Symptom onset in the first 2 years of employment at a wood products plant using diisocyanates: some observations relevant to occupational medical screening. Am J Ind Med. 46(3):226-233.

[WATERNT] Water Solubility Program [estimation model]. 2010. Ver. 1.01. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. http://www.epa.gov/oppt/exposure/pubs/episuite.htm.

Wester RC, Hui X, Landry T, Maibach HI. 1999. *In Vivo* skin decontamination of methylene bisphenyl isocyanate (MDI): soap and water ineffective compared to polypropylene glycol, polyglycol-based cleanser and corn oil. Toxicol Sci. 48:1-4.

Wirts M, Salthammer T. 2002. Isocyanate emission from PUR adhesives: influence of temperature, monomer content, and curing mechanism. Environ Sci Technol. 36:1827-1832.

Wirts M, Grunwalk D, Schulze D, Uhde E, Salthammer T. 2003. Time course of isocyanate emission from curing polyurethane adhesives. Atmos Environ. 37:5467-5475.

Wisnewski AV, Hettick JM, Siegel PD. 2011a. Toluene diisocyanate reactivity with glutathione across a vapor/liquid interface and subsequent transcarbamoylation of human albumin. Chem Res Toxicol. 24:1686-1693.

Wisnewski AV, Xu L, Robinson E, Liu J, Redlich CA, Herrick CA. 2011b. Immune sensitization to methylene diphenyl diisocyanate (MDI) resulting from skin exposure: albumin as a carrier protein connecting skin exposure to subsequent respiratory responses. J Occup Med Toxicol. 6:6.

Won D, Nong G, Lusztyk E, Schleibinger H. 2013. Emissions of MDI from Do-It-Yourself Products. National Research Council. Institute for Research in Construction. Ottawa, Canada. Unpublished report.

Woolrich PF. 1982. Toxicology, industrial hygiene and medical control of TDI, MDI and PMPPI. Am Ind Hyg Assoc J. 43:89-97.

Yakabe Y, Henderson K, Thompson W, Pemberton D, Tury B, Bailey R. 1999. Fate of methylenediphenyl diisocyanate and toluene diisocyanate in the aquatic environment. Environ Sci Technol. 33:2579-2583.

Yakabe Y, Hiromatsu K, Kawahara K, Nakahara M. 2000. Determination of 1-octanol/water partition coefficients of isocyanate compounds by an HPLC method. Toxicol Environ Chem. 77(3-4):199-206.

Zeiger E. 1987. *Salmonella* mutagenicity test: III. Results from testing of 255 chemicals, Environ Mutagen. 9 (Suppl 9):1-110.

Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K. 1988. Salmonella mutagenicity tests: IV. Results from the testing of 300 chemicals. Environ Mol Mutagen. 11 Suppl 12:1-157.

Zeiss CR, Kanellakes TM, Bellone JD, Levitz D, Pruzansky JJ, Patterson R. 1980. Immunoglobulin E-mediated asthma and hypersensitivity pneumonitis with precipitating anti-hapten antibodies due to diphenylmethane diisocyanate (MDI) exposure. J Allergy Clin Immunol. 65(5):347-352.

Zhong BZ, Siegel PD. 2000. Induction of micronuclei following exposure to methylene diphenyl diisocyanate: potential genotoxic metabolites. Toxicol Sci. 58:102-108.

Zosky GR, Sly PD. 2007. Animal models of asthma. Clin Exp Allergy 37(7):973-88.

Appendices

Appendix A. Justification for a read-across approach for the human health and ecological effects assessment of MDIs

There are a number of considerations that justify the use of read-across between members of the MDI subgroup. The elements considered for the read-across approach are discussed below.

1) **Structure similarity:** As discussed in the Identity of Substances section, the MDI substances covered under the MDI/MDA Substance Grouping share common structural features. 4,4′-, 2,2′- and 2,4′-MDIs are positional isomers of MDIs. Mixed MDI contains a variable composition of the 4,4′-, 2,2′- and 2,4′-MDI isomers. pMDI contains mainly monomeric of MDIs and oligomeric components (with a relatively low number of carbon chains). It is anticipated that the position variation of the isocyanate functional group of each substance does not greatly change the anticipated toxicity.
2) **Similarity of physicochemical properties:** Identified or modelled physicochemical properties for the MDI substances covered under the MDI/MDA Substance Grouping are presented in the Physical and Chemical Properties section. The positional isomers of MDIs and mixed MDI have identical molecular weights and are generally solid at room temperature existing as powders. These MDIs typically exhibit low vapour pressure, high modelled log K_{oa} values and very high reactivity in water. Due to the higher molecular weight homologue components, pMDI is liquid at room temperature and exhibits lower vapour pressure and log K_{oa} values than the MDI monomer. Other parameters (i.e., HLC, log K_{ow}, log K_{oc}, water solubility, pKa) were not considered practically measurable or environmentally relevant due to the quick reaction rate of isocyanate groups with water.
3) **Similarity in toxicokinetics:** An analysis of the toxicokinetics of the MDI substances is provided in the Toxicokinetics section. Via inhalation, MDI substances predominantly deposit to the lungs, gastrointestinal systems and blood, followed by liver and kidneys. Excretion is predominantly through feces and a smaller amount is excreted in urine. The metabolism pathway is expected to involve acetylation followed by oxidation. MDI substances contain isocyanate functional groups, which can bind to proteins including glutathione and albumin. Animal toxicokinetic studies indicate that systemic dermal absorption of MDIs is low (Leibold et al. 1998; Hoffmann et al. 2010).
4) **Similarity of mammalian toxicity:** Review of existing toxicity data for MDI group members is discussed in the Health Effects Assessment section. Available data indicate that group members behave similarly.

   Genotoxicity. Data from *in vitro* genotoxicity studies (e.g., bacterial mutation assays, mouse lymphoma assay, sister chromatic exchange, chromosome

aberration assay, cell transformation, DNA damage) and *in vivo* genotoxicity studies (e.g., DNA adduct, micronucleus induction) were reviewed. Results from genotoxicity studies of group members were similar.

Critical mammalian toxicities. Evidence indicates that all MDI group members exhibit similar respiratory effects, respiratory sensitization and dermal sensitization. Inhalation carcinogenicity studies in animals result in a few incidences of lung tumours when animals are exposed to high concentrations. MDI-related respiratory sensitization and dermal sensitization have also been reported in humans. The isocyanate functional group is responsible for the sensitization effect and is present in all MDI group members.

5) **Similarity of ecotoxicity:** Empirical ecotoxicity data available for the MDI substances in the MDI/MDA Substance Grouping are summarized in subsections for each environmental compartment and in Tables 7-6 (aquatic), 7-7 (aquatic) and 7-8 (soil). Since ecological studies were conducted for only two substances in the subgroup, i.e., 4,4′-MDI and pMDI, results from these studies were considered as read-across to inform ecological effects from potential exposure to 2,4′-MDI, 2,2′-MDI and mixed MDI. 2,4′-MDI and 2,2′-MDI are structurally similar isomers of 4,4′-MDI, and mixed MDI is a mixture of all three MDI monomers. The ecological effects resulting from exposure to these MDI substances are therefore expected to be comparable.
6) **Additional supporting information:** The European Union published a risk assessment report on MDIs in 2005. The general designation of “MDI” defined by the EU included a number of isomeric compounds with the empirical formula $C_{15}H_{10}N_2O_2$, as well as prepolymers and polymers based on these isomers (ECJRC 2005), which were all assessed as a group. The MDI substances in the CMP grouping were part of the EU “MDI” group.

Appendix B. Physical and chemical properties for the MDA substances within the MDI/MDA Substance Grouping

Table B-1. Properties of 4,4′-MDA

Phys-chem Property	Value	Reference
Melting point (ºC)	91.6–92*	O'Neil 2006
Boiling point (ºC)	389*	HSDB 1983-2003
Density (kg/m^3)	1150* (at 20^{o}C)	MacNab 1999
Vapour pressure (Pa)	2.5 x 10^{-4}*	MacNab 1999
Vapour pressure (Pa)	2.7 x 10^{-5} (at 25^{o}C)	Amini and Lowenkron 2003
Henry's law constant (Pa·m^3/mol)	6.1 x 10^{-6}	HENRYWIN 2008 (bond method)
log K_{ow}	1.55	MacNab 1999;
log K_{ow}	1.59*	Hansch et al. 1995; CHRIP 2008
log K_{oc}	Empirical: 3.6–3.8*	Cowen et al. 1998[a]
log K_{oc}	Modelled: 1.76 (based on log k_{ow} method) and 3.4 (based on MCI method)	EPI Suite 2012
log K_{oa}	9.5	LSAS 2005
Water solubility (mg/L)	1000	Moore 1978
Water solubility (mg/L)	1010* (at 25^{o}C)	MacNab 1999
pK_a	4.96	MacNab 1999
pK_a	5.32; 4.23	ACD/Percepta c1997-2012

Abbreviations: log K_{oc}, organic carbon-water partition coefficient; log K_{ow}, octanol-water partition coefficient; log K_{oa}, organic carbon-waterpartition coefficient; WS, water solubility; pK_a, acid dissociation constant;
[a] Calculated from 8-hour Freundlich isotherms in sandy and silt loams of 1.6 and 1.3% organic carbon, respectively.
* Value used for modelling purposes (mean used if a range of values was available)

Table B-2. Properties of pMDA

Phys-chem Property	Value	Reference
Melting point (ºC)	30–70 (2-ring components)	ECHA c2007-2013b; MPBPWIN 2010 (weighted value)
Melting point (ºC)	215 (3-ring components)	ECHA c2007-2013b; MPBPWIN 2010 (weighted value)
Melting point (ºC)	280 (4-ring components	ECHA c2007-2013b; MPBPWIN 2010 (weighted value)
Melting point (ºC)	345 (5- ring components)	ECHA c2007-2013b; MPBPWIN 2010 (weighted value)
Boiling point (ºC)	411	ECHA c2007-2013b
Boiling point (ºC)	398 at 101 kPa	Amini and Lowenkron 2003
Density (kg/m3)	1150 at 20^{o}C	ECHA c2007-2013b
Density (kg/m3)	1070 at 70^{o}C	Amini and Lowenkron 2003
Vapour pressure (Pa)	<0.0001 at 20^{o}C and 0.0016 at 50^{o}C (2-ring components)	Study Report 2010
Vapour pressure (Pa)	1.3 at 100^{o}C (2-ring components)	Amini and Lowenkron 2003
Vapour pressure (Pa)	1.9 x 10^{-10} (3-ring components)	MPBPWIN 2010 (modified grain method, at 25^{o}C)
Vapour pressure (Pa)	6.02 x 10^{-15} (4-ring components)	MPBPWIN 2010 (modified grain method, at 25^{o}C)

Phys-chem Property	Value	Reference
Vapour pressure (Pa)	1.9 x 10^{-19} (5-ring components)	MPBPWIN 2010 (modified grain method, at 25^{o}C)
Henry's law constant (Pa·m^3/mol)	6.1 x 10^{-6} (2-ring components)	HENRYWIN 2008 (bond method)
Henry's law constant (Pa·m^3/mol)	1.9 x 10^{-10} (3-ring components) out of model domain	HENRYWIN 2008 (bond method)
Henry's law constant (Pa·m^3/mol)	6.02 x 10^{-15} (4-ring components) out of model domain	HENRYWIN 2008 (bond method)
Henry's law constant (Pa·m^3/mol)	1.9 x 10^{-19} (5-ring components) out of model domain	HENRYWIN 2008 (bond method)
log K_{ow}	Empirical: 1.3 – 2.5 (1.5 for 2-ring components) at 25^{o}C and pH 6.2	ECHA c2007-2013b
log K_{ow}	Modelled: 2.61 (3-ring components)	KOWWIN 2010 (using EVA with 4,4′-MDA of 1.6)
log K_{ow}	Modelled: 3.71 4-ring components)	KOWWIN 2010 (using EVA with 4,4′-MDA of 1.6)
log K_{ow}	Modelled 4.82 (5-ring components)	KOWWIN 2010 (using EVA with 4,4′-MDA of 1.6)

Phys-chem Property	Value	Reference
log K_{oc}	3.6–3.8 (2-ring components)	Cowen et al. 1998[a]
log K_{oc}	5.3 (3-ring components)	KOCWIN 2010
log K_{oc}	7.4 (4-ring components)	KOCWIN 2010
log K_{oc}	9.4 (5-ring components)	KOCWIN 2010
log K_{oa}	9.5 (2-ring components)	LSAS 2005
log K_{oa}	16.4 (3- ring components) out of model domain	KOAWIN 2008 (user-defined K_{ow})
log K_{oa}	22.0 (4-ring components) out of model domain	KOAWIN 2008 (user-defined K_{ow})
log K_{oa}	27.6 (5-ring components) out of model domain	KOAWIN 2008 (user-defined K_{ow})
Water solubility (mg/L)	360–1220; 1552 (2-ring components) at 20^{o}C	ECHA c2007-2013b
Water solubility (mg/L)	1.1 (3-ring components)	WATERNT 2010
Water solubility (mg/L)	0.001 (4-ring components)	WATERNT 2010
Water solubility (mg/L)	8.4×10^{-7} (5-ring components)	WATERNT 2010
pK_a	4.96 (2-ring components)	ECHA c2007-2013b; ACD/Percepta c1997-2012
pK_a	4.23; 5.32 (2-ring components)	ECHA c2007-2013b; ACD/Percepta c1997-2012
pK_a	4.52; 4.65; 5.16 (3-ring components)	ECHA c2007-2013b; ACD/Percepta c1997-2012

Phys-chem Property	Value	Reference
pK_a	4.52; 4.65; 4.79; 5.16 (4-ring components)	ECHA c2007-2013b; ACD/Percepta c1997-2012
pK_a	4.52; 4.65; 4.69; 4.92; 5.16 (5-ring components)	ECHA c2007-2013b; ACD/Percepta c1997-2012

Abbreviations: log K_{oc}, organic carbon-water partition coefficient; log K_{ow}, octanol-water partition coefficient; log K_{oa}, organic carbon-water partition coefficient; WS, water solubility; pK_a, acid dissociation constant;
[a] Calculated from 8-hour Freundlich isotherms in sandy and silt loams of 1.6 and 1.3% organic carbon, respectively.
[*] Value used for modelling purposes (mean used if a range of values was available)

Appendix C. Physical and chemical properties for the MDI substances within the MDI/MDA Substance Grouping

Table C-1. Properties of 4,4′-MDI

Phys-chem Property	Value	Reference
Melting point (ºC)	37	Lide 2003
Melting point (ºC)	39–43	ECHA c2007-2013c
Boiling point (ºC)	> 300* at 101 kPa	ECHA c2007-2013c
Boiling point (ºC)	196 at 0.1 kPa	Lide 2003
Density (kg/m3)	1320*at 20°C	ECHA c2007-2013c
Vapour pressure (Pa)	0.0007*; < 0.002	Chakrabarti 1989
Vapour pressure (Pa)	0.00049 at 20°C	Brochhagen and Schal 1986
Henry's law constant (Pa·m3/mol)	n/a	n/a
log Kow	4.51* at 22°C and pH ~7	Yakabe et al. 2000
log Koc	n/a	
log Koa	8.95r	KOAWIN 2008 (user-defined Kow)
Water solubility (mg/L)	n/a	n/a
pKa	n/a	n/a

Abbreviations: log K_{oc}, organic carbon-water partition coefficient; log K_{ow}, octanol-water partition coefficient; log K_{oa}, organic carbon-water partition coefficient; WS, water solubility; pK_a, acid dissociation constant; n/a, not applicable (i.e., the phys-chem parameter was not applicable to the substance)

*Value used for modelling purposes (mean used if a range of values was available)

Table C-2. Properties of 2,2′-MDI

Phys-chem Property	Value	Reference
Melting point (ºC)	42.8	ECHA c2007-2013d
Boiling point (ºC)	> 270 (decomposes)	ECHA c2007-2013d
Density (kg/m3)	1130	Chemical Industry Directory 2015
Vapour pressure (Pa)	0.0081*at 20°C and 0.012* at 25°C	ECHA c2007-2013d
Henry's law constant (Pa·m3/mol)	n/a	n/a
log Kow	4.51*	Yakabe et al. 2000
log Koc	n/a	
log Koa	8.95	KOAWIN 2008 (user-defined Kow)
Water solubility (mg/L)	n/a	n/a
pKa	n/a	n/a

Table C-3. Properties of 2,4-MDI

Phys-chem Property	Value	Reference
Melting point (ºC)	34–38*	ECHA c2007-2013e
Boiling point (ºC)	> 241 (decomposes)	
Density (kg/m3)	1240–1320 at 20°C	ISOPA 2013
Vapour pressure (Pa)	0.0014* at 20°C	ECHA c2007-2013e
Henry's law constant (Pa·m3/mol)	n/a	n/a
log Kow	4.51*	Yakabe et al. 2000
log Koc	n/a	n/a
log Koa	8.95	KOAWIN 2008 (user-defined Kow)
Water solubility (mg/L)	n/a	n/a
pKa	n/a	n/a

Table C-4. Properties of Mixed MDI

Phys-chem Property	Value	Reference
Melting point (ºC)	34–38 (read-across from CAS RN 5873-54-1)	ECHA c2007-2013e
Boiling point (ºC)	> 241 (decomposes) (read-across from CAS RN 5873-54-1)	ECHA c2007-2013e
Density (kg/m3)	1240-1320 at 20°C	ISOPA 2013
Vapour pressure (Pa)	0.04 at 43°C	Dow Chemical Company c1998-2011
Henry's law constant (Pa·m3/mol)	n/a	n/a
log Kow	4.51*	Yakabe et al. 2000
log Koc	n/a	
log Koa	8.95	KOAWIN 2008 (user-defined Kow)
Water solubility (mg/L)	n/a	n/a
pKa	n/a	n/a

Table C-5. Properties of pMDI

Phys-chem Property	Value	Reference
Melting point (ºC)	Modelled: 181 (3-ring components)	MPBPWIN 2010 (weighed value)
Melting point (ºC)	Modelled: 253 (4-ring components);	MPBPWIN 2010 (weighed value)
Melting point (ºC)	Modelled: 311 (5-ring components)	MPBPWIN 2010 (weighed value)

Phys-chem Property	Value	Reference
Melting point (ºC)	forms crystals <10	Dow Chemical Company c1998-2011
Boiling point (ºC)	> 230	Dow Chemical Company c1998-2011
Density (kg/m3)	1240 at 20ºC	Dow Chemical Company c1998-2011
Vapour pressure (Pa)	< 0.0013	Dow Chemical Company c1998-2011
Vapour pressure (Pa)	Modelled: 7.5x10-7 (3-ring components)	MPBPWIN 2010 (modified grain method)
Vapour pressure (Pa)	Modelled: 7.2x10-11 (4-ring components);	MPBPWIN 2010 (modified grain method)
Vapour pressure (Pa)	Modelled: < 10-12 (5-ring components) at 25ºC	MPBPWIN 2010 (modified grain method)
Henry's law constant (Pa·m3/mol)	n/a	n/a
log Kow	n/a	n/a
log Koc	n/a	n/a
log Koa	8.95 (2-ring components)	KOAWIN 2008 (user-defined Kow)
log Koa	14.7 (3-ring components) out of model domain	KOAWIN 2008 (user-defined Kow)
log Koa	19.7 (4-ring components) out of model domain	KOAWIN 2008 (user-defined Kow)
log Koa	24.8 (5-ring components) out of model domain	KOAWIN 2008 (user-defined Kow)
Water solubility	n/a	n/a

Phys-chem Property	Value	Reference
(mg/L)		
pKa	n/a	n/a

Appendix D. Concentrations in the environment of substances in the MDI/MDA Substance Grouping

Table D-1. Concentrations of MDI substances in air

CAS RN	Location	Facility type (sampling point and number)	Concentration (average) μg/m^3	Reference
101-68-8, 2536-05-2, 5873-54-1, 26447-40-5	Europe	Foam manufacturer (5; stack)[1,4]	<0.4–3.7[3]	Allport et al. 2003
101-68-8, 2536-05-2, 5873-54-1, 26447-40-5	n/a	Foam panel manufacturer (1; stack)[2,4']	<10–48[3]	Acton 2001
101-68-8, 2536-05-2, 5873-54-1, 26447-40-5	Europe	Fiberboard manufacturer (4; stack)[5,4]	45–1,320[3]	Maddison and Merckx 1996
101-68-8, 2536-05-2, 5873-54-1, 26447-40-5	North America	OSB manufacturer[4] (1; press vent)	160–380[6,] 150–290[3]	Allport et al. 2003
101-68-8, 2536-05-2, 5873-54-1, 26447-40-5	Europe	Flexible foam moulding (3; stack)[4]	<0.1–12.5[3]	Allport et al. 2003
101-68-8, 2536-05-2, 5873-54-1,	Europe	Flexible foam flame lamination (1; stack)[4]	48[3]	Allport et al. 2003

CAS RN	Location	Facility type (sampling point and number)	Concentration (average) μg/m^3	Reference
26447-40-5				
101-68-8, 5873-54-1	US	SPF Work Site (4; 25 feet left, right and behind)	BDL–23.9[7]	Ecoff and Lambach 2012
101-68-8, 5873-54-1	US	SPF Work Site (4; 50 feet downwind)	BDL–3.9[7]	Ecoff and Lambach 2012

Abbreviations: n/a, not available; dw, dry weight; OC, organic carbon; BDL = below detection limit
[1]Facilities manufacturing boardstock (flexible facings) (3) and rigid foam block (2). [2]Factility which manufactures polyurethane panels with metal facings. [3]Estimated MDI monomer concentration from measurement of free isocyanate groups (NCO). [4]No control equipment was used in these stacks; [5]Samples taken from exhaust air in stacks from three different points in the fibreboard process (dryer, press and wet scrubber); [6]Measured using US-EPA "Method 207" (appears to be USEPA OTM-14) which selectively measures 2,4′-MDI and 4,4′-MDI isomers. [7]BMS Sampling and Analytical Methods 1.20.1 (impinger solution) and 1.7.7 (filter desorption fluid) were used for evaluation of MDI/pMDI according to the conference abstract (further details are not available).

Table D-2. Concentrations of 4,4′-MDA (CAS RN 101-77-9) in surface water and industrial wastewater

Location; year	Sample type (Detects)*	Concentration (detection limit) μg/L	Reference
Japan 1985	Surface water (0/10)	n/d (5)	Environment Agency of Japan 2000; CHRIP 2008
Japan 1989	Surface water (1/24)	$1.2x10^{-4}$ (10^{-5} – 0.1)	CHRIP 2008
Japan 1995	Surface water (0/23)	n/d (<1)	CHRIP 2008
Japan 1998	Surface water (0/36)	(<1)	CHRIP 2008
Japan 2008	Surface water (11/28)	0.001 – 0.02 (0.001)	CHRIP 2008
Europe	Industrial wastewater	<500	EURAR 2001

Abbreviations: n/d, not detected
*Number refers to the number geographically distinct sampling station which had samples with reported values above detection limit.

Table D-3. Concentrations of 4,4′-MDA (CAS RN 101-77-9) in sediment

Location; year	Sample type (Detects)*	Concentration (detection limit) µg/g dw	Reference
Japan 1985	Sediment (0/8)	n/d (1)	CHRIP 2008
Japan 1989	Sediment (1/24)	$2x10^{-4}$ (1×10^{-4}–0.03)	CHRIP 2008
Japan 1995	Bottom sediments (6/23)	0.036–0.88 (0.03)	CHRIP 2008
Japan 1998	Bottom sediments (15/33)	0.02–2.1 (0.02)	CHRIP 2008

Abbreviations: dw, dry weight; n/d, not detected

*Number refers to the number geographically distinct sampling station which had samples with reported values above detection limit.

Appendix E. Inputs and summary outputs of SCREEN3, for ecological assessment of inhalation exposure from ambient air near generic industrial point sources

Parameter	Value	Notes
Emission rate (g/s)	0.0856	This value was provided by NCASI, it is based on the assumption that 3450 metric tons of MDI are used and that operation is continuous.
Stack height (m)	10	Based on US EPA, 2004. Technical Appendix E: Derivation of Stack Parameter Data. RSEI Version 2.1.2. Economics, Exposure, and Technology Division; Office of Pollution Prevention and Toxics; United States Environmental Protection Agency; Washington, DC 20460; August 2004.
Stack diameter (m)	0.6	[RDIS] Residual Discharge Information System. 1995. Environment Canada, Pollution Data Branch, Criteria Air Contaminants Division.
Stack gas exit velocity (m/s)	9	US EPA 2004. Technical Appendix E: Derivation of Stack Parameter Data. RSEI Version 2.1.2. Economics, Exposure, and Technology Division; Office of Pollution Prevention and Toxics; United States Environmental Protection Agency; Washington, DC 20460; August 2004.
Stack gas exit temperature (K)	316	RDIS (Residual Discharge Information System). 1995. Environment Canada, Pollution Data Branch, Criteria Air Contaminants Division.
Ambient air temperature (K)	293	Model default.
Receptor height above ground (m)	2.5	Model default, represents height of small arboreal terrestrial organisms.
Urban/Rural Option	Urban	Model default, based on the assumption that the facility is situated in an urban setting.
Building downwash option	Selected	SCREEN3 model default value selected.
Building height (m)	10	Model default, represents the height of building in which production, processing or use takes place (European Commission 2003).
Minimum horizontal dimension (m)	20	Model default, represents typical low-rise industrial facility (Law et al. 2004).
Maximum horizontal dimension (m)	100	Model default, represents typical low-rise industrial facility (Law et al. 2004).
Simple terrain	Selecte	SCREEN3 model default value selected (provides a

Parameter	Value	Notes
	d	more conservative scenario than using complex terrain).
Full meteorological conditions	Selected	SCREEN3 model default value selected (identifies worst-case conditions).
Terrain height (m)	5	Model default, corresponds to one half of the stack height.
Maximum concentration (g/m^3)	$1.276\ E^{-5}$	Maximum value obtained at 200 m.
Concentration at 100 m (g/m^3)	$1.144\ E^{-5}$	100 m corresponds to the average distance between the emissions source and the border of an industrial site.
Concentration at 1000 m (g/m^3)	$0.5618\ E^{-5}$	Not applicable.

For the purpose of the health exposure assessment, values were refined based on the section 71 survey information concerning industrial facilities in Canada (Environment Canada 2012a). These modifications included the use of exact substance quantities and parameters characteristic of specific Canadian facilities.

Appendix F. Air concentrations measured for the application of low-pressure two-component spray polyurethane foam (SPF).

Table F-1. Air concentrations measured for the application of low-pressure two-component SPF kit between joists

Study reference	Area sprayed (ft)	Amount sprayed	Ventilation (air changes/ hour)	Sampling time (min)	Sample type	Air concentration during spray (mg/m^3)
Dow Chemical 2013	Crawl space of a residence (25 ft x 23 ft x 40 in)	11.8 ft^3	44 (industrial grade fan, used to exhaust air)	13	personal	0.16
Dow Chemical 2013	Crawl space of a residence (25 ft x 23 ft x 40 in)	11.8 ft^3	44 (industrial grade fan, used to exhaust air)	13	area	0.017
Dow Chemical 2013	Crawl space of a residence (25 ft x 23 ft x 40 in)	11.8 ft^3	16 (box fan used to supply air into crawl space)	13	personal	0.16
Dow Chemical 2013	Crawl space of a residence (25 ft x 23 ft x 40 in)	11.8 ft^3	16 (box fan used to supply air into crawl space)	13	area	0.022

Study reference	**Area sprayed (ft)**	**Amount sprayed**	**Ventilation (air changes/ hour)**	**Sampling time (min)**	**Sample type**	**Air concentration during spray (mg/m^3)**
Convenience Products 2012	Simulated room B (10x10x8)	20 kg kit used (unknown number of kits used per room)	6 (box fans installed in window but set on "OFF")	A set of 4 X 15 min samples was collected during 3 x 60-min spraying events	personal	**Applicator 1**: MDI monomer: 0.013, 0.022, 0.03, 0.0099 pMDI: <LOD (0.02) **Total MDI*:**0.0199 –0.04
Convenience Products 2012	Simulated room B (10 x 10 x 8)	20 kg kit used (unknown number of kits used per room)	6 (box fans installed in window but set on "OFF")	A set of 4 X 15 min samples was collected during 3 x 60-min spraying events	personal	**Applicator 2**: MDI monomer: 0.031, 0.024, 0.017, 0.016 pMDI: <LOD (0.02) **Total MDI*:** 0.026–0.041
Convenience Products 2012	Simulated room B (10 x 10 x 8)	20 kg kit used (unknown number of kits used per room)	6 (box fans installed in window but set on "OFF")	A set of 4 X 15 min samples was collected during 3 x 60-min spraying events	personal	**Applicator 3**: MDI monomer: 0.039, 0.043, 0.059, 0.068 pMDI: <LOD (0.02) **Total MDI***: 0.049–0.078

Study reference	**Area sprayed (ft)**	**Amount sprayed**	**Ventilation (air changes/ hour)**	**Sampling time (min)**	**Sample type**	**Air concentration during spray (mg/m^3)**
Convenience Products 2012	Simulated room B (10 x 10 x 8)	20 kg kit used (unknown number of kits used per room)	6 (box fans installed in window but set on "OFF")	A set of 4 X 15 min samples was collected during 3 x 60-min spraying events	area	MDI monomer: <LOD (0.002) pMDI: <LOD (0.02) **Total MDI*:** 0.011
Convenience Products 2012	Simulated room A (10 x 10 x 8)	20 kg kit used (unknown number of kits used per room)	102 (box fans in window set on "HIGH")	A set of 4X 15 min samples were collected during 3 x 60-min spraying events	personal	**Applicator 1**: MDI monomer: 0.015, 0.021, 0.015, 0.023 pMDI: <LOD (0.02) **Total MDI***: 0.025–0.033
Convenience Products 2012	Simulated room A (10 x 10 x 8)	20 kg kit used (unknown number of kits used per room)	102 (box fans in window set on "HIGH")	A set of 4X 15 min samples were collected during 3 x 60-min spraying events	personal	**Applicator 2**: MDI monomer: 0.001, 0.023, 0.022, 0.022 pMDI: <LOD (0.02) **Total MDI*:** 0.011–0.033

Study reference	**Area sprayed (ft)**	**Amount sprayed**	**Ventilation (air changes/ hour)**	**Sampling time (min)**	**Sample type**	**Air concentration during spray (mg/m^3)**
Convenience Products 2012	Simulated room A (10 x 10 x 8)	20 kg kit used (unknown number of kits used per room)	102 (box fans in window set on "HIGH")	A set of 4X 15 min samples were collected during 3 x 60-min spraying events	personal	**Applicator 3**: MDI monomer: 0.038, 0.037, 0.035, 0.043 pMDI: <LOD (0.02) **Total MDI*:** 0.045–0.053
Convenience Products 2012	Simulated room A (10 x 10 x 8)	20 kg kit used (unknown number of kits used per room)	102 (box fans in window set on "HIGH")	A set of 4X 15 min samples were collected during 3 x 60-min spraying events	area	MDI monomer: <LOD (0.002) pMDI: <LOD (0.02) **Total MDI*:** 0.011
Fomo Products 2005	NS	NS	Natural ventilation (opened windows and doors)	6 samples of 18-20 min were taken during a total spraying time of 118 min	personal	0.016, 0.054, 0.082, 0.060, 0.057, 0.017
Fomo Products 2005	NS	NS	Natural ventilation (opened windows and doors)	20-40 min	area	0.0041, <LOD (range from 0.0022–0.0045)

LOD = limit of detection
NS = not stated
*These values are based on adding concentration of MDI monomer and pMDI; when a substance was found to be below the limit of detection (LOD), it was assumed the level was at half the LOD.

Table F-2. Air concentrations measured for the application of low-pressure two-component SPF kit along joists and corners and in cracks

Study reference	Area sprayed (ft)	Amount sprayed	Ventilation (air changes/ hour)	Sampling time (min)	Sample type	Air concentration during spray (mg/m^3)
Convenience Products 2014a	Residential basement (24 x 45 x 7)	2/3 of container (13 kg used)	4.7 (2 box fans inserted in windows)	2 X 15 min samples collected during a 30 min spraying time	personal	0.01, 0.01
Convenience Products 2014a	Residential basement (24 x 45 x 7)	2/3 of container (13 kg used)	4.7 (2 box fans inserted in windows)	2 X 15 min samples collected during a 30 min spraying time	area	<LOD (0.007)
Convenience Products 2014b	Residential basement (8 x 30 x 9 + 8 x 30 x 45)	13 kg kit used (20 lb of product applied)	0.2 (natural ventilation, i.e., windows and sliding door opened at one end of room)	15 min samples collected during a 30 min spraying time	personal	0.04, <LOD (0.007)
Convenience Products 2014b	Residential basement (8 x 30 x 9 + 8 x 30 x 45)	13 kg kit used (20 lb of product applied)	0.2 (natural ventilation, i.e., windows and sliding door opened at one end of room)	15 min samples collected during a 30 min spraying time	area	<LOD (0.007)
ACC 2012b	Test chamber (7.9 x 7.9	19lb	10.4 (ventilation was	24–29 (spray time was	personal	**Applicator 1**:

Study reference	**Area sprayed (ft)**	**Amount sprayed**	**Ventilation (air changes/ hour)**	**Sampling time (min)**	**Sample type**	**Air concentration during spray (mg/m^3)**
	x 8.2)		perpendicular to the spray)	19 min); this is one of 4 repeated applications		2,4′-MDI: 0.008 4,4′-MDI: 0.04 pMDI: <LOD (0.102) **Total MDI***:0.1
ACC 2012b	Test chamber (7.9 x 7.9 x 8.2)	19 lb	10.4 (ventilation was perpendicular to the spray)	24–29 (spray time was 19 mins); this is one of four repeated applications	area	**Applicator 1**: 2,4′-MDI: 0.006 4,4′-MDI: 0.003 pMDI: <LOD (0.088) **Total MDI***:0.053
ACC 2012b	Test chamber (7.9 x 7.9 x 8.2)	19 lb	10.4 (ventilation was perpendicular to the spray)	24–29 (spray time was 15 min); this is one of four repeated applications	personal	**Applicator 2**: no result reported
ACC 2012b	Test chamber (7.9 x 7.9 x 8.2)	19 lb	10.4 (ventilation was perpendicular to the spray)	24–29 (spray time was 15 min); this is one of four	area	**Applicator 2**: 2,4′-MDI: 0.009 4,4′-MDI: <LOD

Study reference	**Area sprayed (ft)**	**Amount sprayed**	**Ventilation (air changes/ hour)**	**Sampling time (min)**	**Sample type**	**Air concentration during spray (mg/m^3)**
				repeated applications		(0.0046) pMDI: <LOD (0.140) **Total MDI***: 0.0813
ACC 2012b	Test chamber (7.9X7.9 X8.2)	19 lb	10.4 (ventilation was perpendicular to the spray)	24–29 (spray time was 18 min); this is one of four repeated applications	personal	**Applicator 3**: 2,4′-MDI: 0.010 4,4′-MDI: 0.03 pMDI: <LOD (0.111) **Total MDI***:0.095
ACC 2012b	Test chamber (7.9 x 7.9 x 8.2)	19 lb	10.4 (ventilation was perpendicular to the spray)	24–29 (spray time was 18 min); this is one of four repeated applications	area	**Applicator 3**: 2,4′-MDI: 0.006 4,4′-MDI: 0.01 pMDI: <LOD (0.112) **Total MDI***: 0.072
ACC 2012b	Test chamber (7.9 x 7.9 x 8.2)	19 lb	10.4 (ventilation was perpendicular to the	24–29 (spray time was 16 min); this is one of four	personal	**Applicator 4**: 2,4′-MDI:

Study reference	Area sprayed (ft)	Amount sprayed	Ventilation (air changes/ hour)	Sampling time (min)	Sample type	Air concentration during spray (mg/m^3)
			spray)	repeated applications		0.005 4,4′-MDI: 0.01 pMDI: <LOD (0.118) **Total MDI***:0.074
ACC 2012b	Test chamber (7.9 x 7.9 x 8.2)	19 lb	10.4 (ventilation was perpendicular to the spray)	24–29 (spray time was 16 min); this is one of four repeated applications	area	**Applicator 4**: 2,4′-MDI: <LOD (0.0046) 4,4′-MDI: 0.01 pMDI: <LOD (0.138) **Total MDI***: 0.0813

LOD = limit of detection

* These values are based on adding concentration of 2,4 MDI, 4,4 MDI and pMDI; when a substance was found to be below the limit of detection (LOD), it was assumed the level was at half the LOD.

Table F-3. Air concentrations measured for the application of low-pressure two-component SPF kit for other application type

Study reference	Application type	Area sprayed (ft)	Amount sprayed	Ventilation (air changes/ hour)	Sampling time (min)	Sample type	Air concentration during spray (mg/m^3)
Fomo Products 2010	An entire kit was dispensed into a cardboard board	NS	Entire kit – size unknown	No ventilation (doors closed)	15	Personal	0.089

Study reference	Application type	Area sprayed (ft)	Amount sprayed	Ventilation (air changes/ hour)	Sampling time (min)	Sample type	Air concentration during spray (mg/m^3)
	placed on the floor of a spraying lab						
Fomo Products 2010	Two 10-second spray separated by 10 min interval	NS	NS	No ventilation (doors closed)	15	Personal	<LOD (0.013)

LOD = limit of detection
NS = not stated

Appendix G. Upper-bounding estimates of exposure to MDIs from use of adhesive/sealant types of DIY products, based on ConsExpo

Consumer Product Type	Model Parameters*	Estimated Exposure
Polyurethane adhesive/ assembly sealant	The scenario assumptions are based on a ConsExpo default scenario for assembly sealant (RIVM 2007). The inhalation scenario based on additive evaporation release from increasing area (VP: 0.00049–0.0013Pa; mass transfer rate: 0.013 m/min [Wirts and Salthammer 2002]): - maximum weight fraction: 30% w/w (4,4′-MDI); 10% (pMDI); 5% (mixed MDI) (Henkel 2010) - frequency of use: 1/yr - room volume: 20 m^3 (generic area) - air exchange rate: 0.6 changes/h - exposure duration: 4 h - tack-free time: 15 min - amount of product used: 390 g (based on full use of product cartridge) - release area: 1 m^2 - application duration: 30 min The dermal scenario based on instant application: - exposed surface area: 46 cm^2 (20% of one hand, from drips onto a palm or fingers) - applied amount: 0.5 g	Mean event concentration (additive 4,4′-MDI, pMDI and mixed MDI): 0.0010 mg/m^3 Dermal load (additive 4,4′-MDI, pMDI and mixed MDI): 4.9 mg/cm^2

Consumer Product Type	**Model Parameters***	**Estimated Exposure**
Floor/wall adhesive	The scenario assumptions are based on a ConsExpo default scenario for adhering wood parquet flooring to surface (RIVM 2007) The inhalation scenario based on additive evaporation release from increasing area (VP: 0.00049 - 0.00066 Pa; mass transfer rate: 0.013 m/min [Wirts and Salthammer 2002]): - maximum weight fraction: 5% w/w (MDI); 5% (mixed MDI) (Franklin International 2010) - frequency of use: 0.125/yr (based on a 8-yr remodel) - room volume: 58 m^3 (living area) - air exchange rate: 0.5 changes/h - exposure duration: 8 h - tack-free time: 60-90 min - amount of product used: 22 kg (product information) - release area: 1 m^2 (based on covering adhesive with floor and applying a new section 1 m^2 at a time) - application duration: 8 h The dermal scenario based on constant application: - exposed surface area: 455 cm^2 (50% of both hands, from application and laying of floor) - contact rate: 30 mg/cm^2 - release duration: 8 h	Mean event concentration (additive 4,4′-MDI and mixed MDI): 0.00047 mg/m^3 Dermal load (additive 4,4′-MDI, pMDI and mixed MDI): 3.16 mg/m^2

Consumer Product Type	**Model Parameters***	**Estimated Exposure**
Construction adhesive	The scenario assumptions are based on a ConsExpo default scenario bottled construction glue (RIVM 2007) The inhalation scenario based on additive evaporation release from increasing area (VP: 0.00049–0.0013 Pa; mass transfer rate: 0.013 m/min [Wirts and Salthammer 2002]): - maximum weight fraction: 50% w/w (MDI); 25% (pMDI); 5% (mixed MDI) (Titebond Inc. 2012) - frequency of use: 2/yr - room volume: 20 m^3 (generic area) - air exchange rate: 0.6 changes/h - exposure duration: 4 h - tack-free time: 20-30 min - amount of product used: 250 g - release area: 1 m^2 - application duration: 30 min The dermal scenario based on instant application: - exposed surface area: 91 cm^2 (20% from each palm from applying and clamping together) - applied amount: 0.25 g	Mean event concentration (additive 4,4′-MDI, pMDI and mixed MDI): 0.0021 mg/m^3 Dermal load (additive 4,4′-MDI, pMDI and mixed MDI): 2.2 mg/cm^2

Consumer Product Type	**Model Parameters***	**Estimated Exposure**
General adhesive/ hobby glue	The scenario assumptions are based on a ConsExpo default scenario for generic bottled glue (RIVM 2007) The inhalation scenario based on evaporation release from a constant area (VP: 0.00066 Pa; mass transfer rate: 0.013 m/min [Wirts and Salthammer 2002]): - maximum weight fraction: 56% w/w (4,4′-MDI) (Gorilla Glue Inc. 2012) - frequency of use: 52/yr (based on a weekly hobby) - room volume: 20 m^3 (generic area) - air exchange rate: 0.6 changes/h - exposure duration: 4 h - cure time: 1-4 h - amount of product used: 6 g (adjusted based on product information) - release area: 400 cm^2 - application duration: 20 min The dermal scenario based on instant application: - exposed surface area: 2 cm^2 (fingertips) - applied amount: 0.08 g	Mean event concentration (for 4,4′-MDI): 1.2×10^{-5} mg/m^3 Dermal load: 22.4 mg/cm^2

Consumer Product Type	**Model Parameters***	**Estimated Exposure**
Super glue	The scenario assumptions are based on a ConsExpo default scenario for super glue (RIVM 2007) The inhalation scenario based on evaporation release from a constant area (VP: 0.0013 Pa; mass transfer rate: 0.013 m/min [Wirts and Salthammer 2002]): - maximum weight fraction: 50% w/w (pMDI) (Elmers. 2012) - frequency of use: 12/yr (based on once a month) - room volume: 20 m^3 (generic area) - air exchange rate: 0.6 changes/h - exposure duration: 4 h - cure time: 1-4 h - amount of product used: 0.5 g (adjusted for product use information) - release area: 2 cm^2 - application duration: 5 min The dermal scenario based on instant application: - exposed surface area: 1 cm^2 (fingertips) - applied amount: 0.025 g	Mean event concentration (for pMDI): 4.1×10^{-8} mg/m^3 Dermal load: 12.5 mg/cm^2

Consumer Product Type	**Model Parameters***	**Estimated Exposure**
Hot-melt adhesive	The scenario assumptions are based on a ConsExpo default scenario for hot-melt adhesive (RIVM 2007) The inhalation scenario based on evaporation release from increasing area (VP: 0.00049–0.00066 Pa; mass transfer rate: 0.013 m/min [Wirts and Salthammer 2002]): - maximum weight fraction: 3% w/w (4,4′-MDI); 3% (mixed MDI) (3M Inc. 2012) - frequency of use: 12/yr (based on once a month) - room volume: 20 m^3 (generic area) - air exchange rate: 0.6 changes/h - exposure duration: 25 min - cure time: 30 to 120 sec - amount of product used: 65 g (full bar of solid uncured hot-melt adhesive) - release area: 8.5 cm^2 - application duration: 25 min The dermal scenario was not modeled given that MDIs would only be released under increased temperatures of the solid adhesive.	Mean event concentration (additive 4,4′-MDI and mixed MDI): 7.9×10^{-8} mg/m^3

*The mass transfer rate calculated from Wirts and Salthammer (2002) emission studies for pure 4,4′-MDI was used in place of the default Langmuir's equation

Appendix H. Justification for using toluene diisocyanates (TDIs) as analogues

There are a number of considerations which justify the use of TDIs as analogues for respiratory effects, including sensitization, in the MDIs health effect assessment. The elements considered are discussed below:

1) **Structure:** TDIs and MDIs are structurally similar, consisting of aromatic rings(s) and isocyanate functional groups.

2) Physicochemical properties: The molecular weights of TDIs are lower than MDIs. TDIs are expected to be more reactive than MDIs due to their higher solubility and vapour pressure.

3) **Mammalian toxicity:** TDIs and MDIs exhibit similar respiratory effects and sensitization effects in both human epidemiology studies and in animal experimental studies. Mechanistically, the isocyanates functional groups in TDIs and MDIs are responsible for protein binding and subsequent potential immune sensitization effect (Liu and Wisnewski 2003). Relative potency of dermal sensitization is similar between TDIs and MDIs. Based on LLNA assays, TDIs have an EC3 value of 0.11% (ECETOC 2003), which is similar to the EC3 value of 0.08% for MDIs (Selgrade et al. 2006).