

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO TDI AND MDI IN THE UNITED STATES

Diisocyanates have widespread commercial use due to their reactivity and versatility. These compounds are predominantly used in the production of polyurethane materials. Two diisocyanates, TDI and MDI, and their related polyisocyanates make up >90% of the commercial market. Commercial-grade TDI comprises an 80:20 mixture of isomers 2,4- and 2,6-TDI and represents >95% of TDI industrial use. There are several isomers of MDI, including 4,4'-, 2,4'-, and 2,2'-MDI, as well as oligomers and polymeric compounds. The principal commercial product of MDI is made up of a mixture of all of these components, with a typical composition in the range of 40–50% 4,4'-MDI, 2.5–4.0% 2,4'-MDI, and 0.1–0.2% 2,2'-MDI; the remainder is oligomers. 4,4'-MDI is the most commercially common isomer and is referred to as pure MDI.

The dominant process affecting the overall environmental fate, transport, and bioaccumulation potential of TDI and MDI is hydrolysis. Diisocyanates react with water forming the respective amines, which in turn may react with more diisocyanates to produce inert, insoluble polyureas. Hydrolysis half-lives of MDI and TDI have been measured to be on the order of a few minutes to a few hours. Due to the rapid hydrolysis of these compounds, they are not expected to persist or bioaccumulate in the environment.

Almost all of the potential exposures to these compounds are associated with the production, handling, use, and disposal of diisocyanates and products containing unreacted diisocyanates. TDI and MDI are most frequently detected in occupational settings, mainly by inhalation of aerosol and vapor (TDI only). Diisocyanates are used in the production of polyurethane foam during foaming, casting, spraying, and other processes. Exposure may also occur after production when the polymer is processed. Thermal degradation of polyurethane foam during processes such as heat cutting of foam blocks, flame lamination with textiles, and welding, cutting, or grinding of polyurethane-coated metal, can also release diisocyanates into the air. Another route is through dermal exposure by contact with uncured polyurethane foams.

Exposure of the general population to diisocyanates could potentially result from industrial exposures, as well as the use of consumer products containing uncured TDI and MDI. There has been an increase in the number of uncured diisocyanate-containing products used by consumers. TDI emissions were not

2. RELEVANCE TO PUBLIC HEALTH

detected in a study of polyurethane products such as carpet padding, furniture cushions, and varnishes. However, application of a concrete water solvent did result in elevated TDI levels.

2.2 SUMMARY OF HEALTH EFFECTS

TDI. Epidemiology studies and laboratory animal studies have investigated the toxicity of TDI and identified the respiratory tract as the most sensitive target of toxicity. A 6-hour exposure of healthy adults to 0.005 ppm did not result in respiratory symptoms, but did result in slight declines in lung function (specific airway conductance and maximal expiratory flow [MEF]). A shorter duration exposure to a higher concentration (0.02 ppm for 20 minutes) did not result in alterations in specific airway resistance in healthy or asthmatic subjects. Occupational exposure studies primarily report three types of respiratory effects: occupational asthma, asthma-like symptoms, and declines in lung function. Occupational asthma, which is characterized by airflow limitations and/or airway hyperresponsiveness, is seen in individuals who become hypersensitive to TDI. In sensitized individuals, exposure to low, non-irritating concentrations of TDI can result in wheezing and dyspnea, a marked decrease in lung function, and nonspecific airway hyperresponsiveness. In some workers, removal from TDI exposure can result in improvement in symptoms and a lack of response to a TDI challenge (a brief exposure to a non-irritating concentration); however, a fair percentage of workers still reported asthma symptoms. One study of TDI-sensitized subjects reported an improvement in respiratory symptoms 11 years after removal from TDI exposure; however, 60% of the workers still complained of asthmatic symptoms. Subjects who are diagnosed with occupational asthma shortly after the onset of symptoms, immediately discontinue TDI exposure after diagnosis, and have a milder degree of airway hyperresponsiveness are more likely to recover from the respiratory symptoms. Recovery has not been reported in workers who continue to be exposed to TDI; continued exposure may result in further declines in lung function. TDI concentrations resulting in sensitization are not known, but the sensitization is believed to be due to a brief exposure to a very high concentration or prolonged exposure to lower concentrations. Prior to 1970 when occupational exposure levels were higher, the prevalence of TDI-induced asthma was 5–6%; after the mid-1970s when the occupational limit was typically maintained at 0.005 ppm, rates of <1% have been reported. Some workers report asthma-like symptoms such as wheezing, dyspnea, and chest tightness but do not respond to a TDI challenge; several studies have found that approximately half of the subjects with asthma-like symptoms will have a positive response to a TDI challenge.

The primary health effect observed in nonsensitized workers exposed to TDI is a decline in lung function, particularly the forced expiratory volume in 1 second (FEV₁). Two longitudinal studies provide

2. RELEVANCE TO PUBLIC HEALTH

suggestive evidence that the greatest declines in lung function occur within the first couple of years of exposure to lower TDI concentrations. A decline in FEV₁ and forced vital capacity (FVC) was found in workers with no previous history of occupational exposure to TDI who were exposed to an 8-hour time-weighted average (TWA) TDI level of 0.0012 ppm. However, no declines in lung function were found in the cohort, which mostly consisted of workers with prior TDI exposure. Additionally, when the naïve workers were followed for another several years, no additional declines in lung function were found. Declines in lung function were observed in workers with an 8-hour TWA TDI exposure level of 0.0082 ppm, but no effects were observed in workers with an 8-hour TWA TDI level of 0.0017 ppm.

Animal studies have reported histological lesions in the nasal cavity and lungs after acute, intermediate, or chronic TDI exposure. The nasal lesions typically consisted of rhinitis, necrosis, ulceration, and metaplasia; the severity of the lesions and location within the nasal cavity appear to be concentration- and duration-related. Rhinitis was reported at 0.02 ppm in intermediate-duration studies; chronic or necrotic rhinitis was reported at 0.05 ppm in a chronic mouse study. Interstitial pneumonitis and catarrhal bronchitis was observed at slightly higher concentrations in the chronic mouse study. In addition to the histological alterations, airway hyperresponsiveness and increases in respiratory rates have been observed in laboratory animal studies exposed for acute or intermediate durations.

A limited number of other adverse health effects have been reported in humans and animals. A chronic study in rats and mice examined major tissues and organs and only reported adverse effects in the respiratory tract. Dermal irritation and ocular irritation have also been reported in TDI workers. Reproductive and developmental toxicity of TDI has been investigated in rats. No evidence of reproductive toxicity was observed in a 2-generation study in which rats were exposed to concentrations as high as 0.3 ppm. An increase in litters with poorly ossified cervical centrum was observed in the offspring of rats exposed to 0.5 ppm on gestation days (GDs) 6–15; this concentration was also associated with significant maternal toxicity, including a 45% decrease in maternal weight gain and labored breathing.

Although the carcinogenicity of TDI specifically has not been investigated in occupational exposure studies, three studies have examined workers at polyurethane foam manufacturing facilities and found associations between work in the polyurethane foam manufacturing facility and lung cancer in female workers; none of the studies examined associations specifically with TDI exposure. A chronic-duration study in rats and mice did not find significant increases in neoplastic tumors. HHS has classified TDI as reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from

2. RELEVANCE TO PUBLIC HEALTH

studies in experimental animals. The International Agency for Research on Cancer (IARC) has classified TDI as a Group 2B carcinogen (possibly carcinogenic to humans) based on inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. EPA has not classified the carcinogenicity of TDI.

TDI is rapidly hydrolyzed in water and is not likely to be detected in aquatic environments; thus, it is unlikely that the general population will be exposed via this route. The oral toxicity of commercial-grade TDI has been investigated in a series of gavage studies in rats and mice; there is some question regarding the relevance of these data to humans due to likely pharmacokinetic differences between ingestion of TDI and gavage administration directly into the acidic environment of the stomach, which could result in the formation of 2,4-toluene diamine (TDA). Muroid bronchopneumonia was observed in rats following intermediate exposure to 240 mg/kg/day, 5 days/week for 13 weeks or following chronic exposure 30 or 60 mg/kg/day, 5 days/week for 2 years; decreases in survival were also observed at these doses. Bronchopneumonia was not observed in mice; however, an increased incidence of cytomegaly in the renal tubules was observed in male mice administered 120 mg/kg/day, 5 days/week for 2 years. Decreases in survival were also observed in mice chronically exposed to 240 mg/kg/day. The chronic study also found clear evidence of carcinogenicity in rats and female mice. In rats, there were increases in the incidence of subcutaneous fibromas and fibrosarcomas, pancreatic acinar cell adenomas and islet cell adenomas, mammary gland fibroadenomas, and neoplastic nodules of the liver. In the female mice, the incidences of hemangiomas or hemangiosarcomas and hepatocellular adenomas were increased.

MDI. Similar to TDI, the respiratory tract is the primary target of toxicity for MDI. Occupational exposure can result in occupational asthma, asthma-like symptoms, and decreases in lung function. Although a number of studies have reported MDI-induced asthma or asthma-like symptoms, no reliable concentration-response data or prevalence data are available. As with TDI, occupational asthma likely results from exposure to very high concentrations of MDI or prolonged exposure to high levels that result in sensitization. Approximately half of workers reporting asthma-like symptoms such as wheezing, dyspnea, and chest tightness have a positive response to a short MDI-challenge. Many MDI-sensitized workers also respond to nonspecific irritants; the prevalence of subjects with asthma-like symptoms exhibiting bronchial hyperresponsiveness following exposure to methacholine was significantly higher than in non-exposed subjects or other MDI workers. Unlike TDI, a small number of workers with asthma-like symptoms also reported chills, fever, and malaise, which are considered symptoms of hypersensitivity pneumonitis.

2. RELEVANCE TO PUBLIC HEALTH

Decreases in lung function were observed in MDI workers. Other studies have not found decreases in lung function when pre-shift levels were compared to post-shift levels; one of these studies that examined 27 workers noted that the MDI levels at the facility ranged from 0.0005 to 0.001 ppm.

A limited number of studies have been conducted in laboratory animals. A study measuring respiratory rates in mice reported increases in respiratory rates at 7 mg/m³, which were followed by a gradual decline in respiratory rate; the investigators suggested that this pattern was indicative of pulmonary irritation rather than sensory irritation. Airway hyperresponsiveness to acetylcholine was observed in guinea pigs exposed to 0.01 ppm MDI 6 hours/day for 5 days or 6 hours/day, 5 days/week for 4 weeks. A chronic-duration study with polymeric MDI containing about 50% monomeric MDI found increases in nasal lesions (basal cell hyperplasia and Bowman's gland hyperplasia) and lung lesions (localized fibrosis and alveolar duct epithelialization in rats exposed to 1.0 mg/m³ polymeric MDI 6 hours/day, 5 days/week for 2 years. Many of these lesions were observed after 1 year of exposure to 6.0 mg/m³. An unpublished study reported similar lung effects in female rats exposed to 0.23 mg/m³ monomeric MDI 18 hours/day, 5 days/week for 2 years.

The chronic study in rats did not find any other systemic effects. In a rat developmental toxicity study, an increased incidence of litters with fetuses displaying asymmetric sternebrae was observed at 9 mg/m³ MDI administered on GDs 6–15; a decrease in maternal food consumption was also observed at that exposure level.

No occupational exposure studies have examined the possible association between MDI exposure and cancer risk. As discussed in the TDI section, a possible association between lung cancer and employment at polyurethane foam manufacturing facilities was reported in female workers. The chronic inhalation rat study found increases in lung adenomas in male rats exposed to 6.0 mg/m³ polymeric MDI; one incident of lung adenocarcinoma was also found. IARC has classified 4,4'-MDI as a Group 3 carcinogen (not classifiable as to its carcinogenicity to humans) based on inadequate evidence of carcinogenicity in humans and inadequate or limited evidence in experimental animals. EPA has characterized the carcinogenicity of MDI/polymeric MDI as "cannot be determined, but for which there is suggestive evidence that raises concern for carcinogenic effects".

2. RELEVANCE TO PUBLIC HEALTH

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been established for TDI and MDI. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs for TDI***Acute Duration***

- An MRL of 1×10^{-5} ppm has been derived for acute-duration inhalation exposure (≤ 14 days) to TDI.

A limited number of human studies have evaluated the acute toxicity of TDI. No respiratory symptoms were reported in healthy subjects exposed to 0.005 ppm TDI for 6 hours followed by a 20-minute exposure to 0.02 ppm TDI; however, slight, but statistically significant, decreases in specific airway conductance and MEF at 25% of FVC were observed (Vandenplas et al. 1999). No alterations in specific airway resistance were observed in healthy or asthmatic subjects exposed to 0.02 ppm for 20 minutes (Chester et al. 1979). Acute-duration animal inhalation studies have reported rhinitis, lung damage, and airway hyperresponsiveness. The severity of rhinitis was concentration-related; moderate rhinitis was observed in mice exposed to 0.07 ppm 6 hours/day for 4 days (Zissu 1995), moderate-to-severe rhinitis was observed in mice exposed to 0.4 ppm 6 hours/day for 5 days (Buckley et al. 1984), and severe nasal

2. RELEVANCE TO PUBLIC HEALTH

1 lesions were observed in mice exposed to 1 ppm 6 hours/day for 3 days (Arts et al. 2008). Interstitial
2 inflammation, pleural thickening, and goblet cell hyperplasia were observed in the lungs of guinea pigs
3 exposed to 1.4 ppm TDI 3 hours/day for 3 days (Wong et al. 1985). Airway hyperresponsiveness to
4 methacholine or acetylcholine was also observed in guinea pigs and mice exposed to ≥ 0.01 ppm
5 (Gagnaire et al. 1996; Gordon et al. 1985; Marek et al. 1999); a no-observed-adverse-effect level
6 (NOAEL) of 0.005 ppm for airway hyperresponsiveness was identified in guinea pigs exposed to TDI
7 6 hours/day for 5 days (Marek et al. 1999). An increase in the incidence of litters with poorly ossified
8 cervical centrum was observed in the offspring of rats exposed to 0.5 ppm commercial-grade TDI
9 6 hours/day on GDs 6–15 (Tyl et al. 1999a); this concentration was also associated with maternal toxicity
10 including a marked decrease in body weight gain and signs of nasal irritation and audible respiration.

11
12 The Vandenas et al. (1999) human study identified the lowest lowest-observed-adverse-effect level
13 (LOAEL) (0.005 ppm) for respiratory effects caused by acute inhalation exposure to TDI; the lowest
14 LOAEL in animals is approximately 10-fold higher. The Vandenas et al. (1999) study was considered
15 suitable for derivation of an MRL. The LOAEL of 0.005 ppm was adjusted to continuous 24-hour
16 exposure; the resulting LOAEL_{ADJ} was 0.00125 ppm. The MRL of 0.00001 ppm (1×10^{-5} ppm) was
17 calculated by dividing the LOAEL_{ADJ} by an uncertainty factor of 100 (10 for the use of a LOAEL and
18 10 for human variability). There is some uncertainty whether the acute-duration MRL based on the
19 Vandenas et al. (1999) single exposure study would be protective of continuous exposure to TDI for
20 14 days. Chronic-duration occupational exposure studies provide some support for this MRL. The
21 lowest LOAEL values identified in longitudinal studies of workers exposed to TDI are 0.0012 and
22 0.0019 ppm (Clark et al. 1998; Diem et al. 1982); the effects observed at these concentrations included
23 decreases in lung function (FEV₁ and/or FVC). These LOAELs are roughly 2–4 times lower than the
24 LOAEL from the Vandenas et al. (1999) study. However, since there is uncertainty that the MRL
25 would be protective for continuous exposure for 14 days, it is recommended that measured air
26 concentrations should not exceed the MRL of 1×10^{-5} ppm during a 24-hour period.

27
28 ***Intermediate Duration.*** No human studies have examined the intermediate-toxicity of TDI; several
29 animal studies have examined the respiratory tract following intermediate-duration exposure. Nasal and
30 lung inflammation were observed in mice exposed to 0.02 ppm commercial-grade TDI 4 hours/day,
31 5 days/week for 6 weeks (Matheson et al. 2005); increased airway hyperresponsiveness was also observed
32 at this concentration. At a slightly higher concentration (0.07 ppm), severe rhinitis with metaplasia and
33 necrosis of the nasal respiratory epithelium was observed (Zissu 1995). The LOAELs in the animal
34 studies are >10 times higher than the LOAELs identified in occupational exposure studies (see Chronic

2. RELEVANCE TO PUBLIC HEALTH

Duration section) and may not be protective for declines in lung function. In a study by Clark et al. (1998), lung function declines were observed within the first couple of months of exposure. Thus, the data were not considered suitable for an intermediate-duration inhalation MRL for TDI.

Chronic Duration

- An MRL of 3×10^{-6} ppm has been derived for chronic-duration inhalation exposure (≥ 1 year) to TDI.

A number of studies of workers at TDI production facilities and polyurethane foam manufacturing facilities have reported respiratory effects consisting of asthma, asthma-like symptoms, and declines in lung function. TDI-induced asthma is a type of occupational asthma characterized as bronchial inflammation and/or airway hyperresponsiveness. The wheezing, dyspnea, and chest tightness observed in individuals with asthma often persists for years after exposure termination (Mapp et al. 1988; Moller et al. 1986; Moscato et al. 1991; Padoan et al. 2003; Paggiaro et al. 1984). Individuals with TDI-induced asthma are considered to be sensitized to TDI, in that brief exposures to nonirritating concentrations can result in a worsening of symptoms and a decline in lung function. Other workers reported asthma-like symptoms of wheezing and dyspnea, but do not respond to a TDI inhalation challenge; although the workers may not have asthma, the observed respiratory effects may still be indicative of TDI sensitization. The exposure level resulting in TDI sensitization is not known; TDI sensitization may result from a brief exposure to very high TDI concentrations or prolonged exposure to lower concentrations. It is believed that $<10\%$ of workers become sensitized to TDI; lower rates of sensitization ($<1\%$) have been found since the occupational exposure limit has been lowered to 0.005 ppm (Ott et al. 2003).

The available data suggest that the primary effect in non-sensitized workers is a decline in lung function. Several longitudinal studies have evaluated the effect of TDI exposure on the annual decline in lung function (Adams 1975; Bodner et al. 2001; Butcher et al. 1977; Clark et al. 1998, 2003; Diem et al. 1982; Jones et al. 1992; Omae et al. 1992; Ott et al. 2000; Peters et al. 1970; Wegman et al. 1977, 1982). Although the results across studies are not consistent, several factors may contribute to this inconsistency, including differences in peak exposure levels, difference in the length of exposure, exposure to higher TDI levels prior to the start of the study, and inclusion of sensitized workers. A 5-year study of a new TDI manufacturing facility found greater annual declines in FEV₁ and forced expiratory flow at 25–50% of FVC (FEF_{25–50%}) among nonsmoking workers with a cumulative TDI exposure of ≥ 0.0682 ppm-months (Diem et al. 1982). Another study that examined workers at a polyurethane foam manufacturing

2. RELEVANCE TO PUBLIC HEALTH

facility with no prior TDI exposure found significant annual declines in FEV₁ and FVC; however, no significant alterations in lung function were observed in the entire cohort. The mean 8-hour TWA TDI concentration for the entire cohort (naïve workers and workers with prior TDI exposure) was 0.0012 ppm (Clark et al. 1998). When the naïve worker subcohort was examined several years later, the declines in lung function did not significantly vary from predicted levels (Clark et al. 2003). Clark et al. (1998) suggested that the decline in lung function observed in the naïve subcohort may have been due to respiratory irritation. Another study found greater-than-expected declines in maximal midexpiratory flow (MMF), ratio of FEV₁ to FVC, and peak expiratory flow (PEF) in polyurethane foam manufacturing workers with an 8-hour TWA TDI level of 0.0082 ppm, with peak levels of 0.02–0.03 ppm (Omae et al. 1992). No alterations were found in workers with a TWA level of 0.0017 ppm with peak levels of 0.0003–0.004 ppm. A fourth study found significant declines in FEV₁ levels in workers with TDI exposure levels \geq 0.0035 ppm (Wegman et al. 1977, 1982). No alterations in lung function were observed in other longitudinal studies with TDI levels of 0.0015–0.015 ppm (Bodner et al. 2001; Butcher et al. 1977; Jones et al. 1992; Ott et al. 2000).

Only one study examined the chronic toxicity of airborne TDI in laboratory animals; significant increases in the incidence and severity of chronic or necrotic rhinitis with epithelial atrophy and mucous and squamous metaplasia were observed in mice exposed to \geq 0.05 ppm TDI 6 hours/day, 5 days/week for 2 years (Loeser 1983). Interstitial pneumonitis and catarrhal bronchitis was also noted in mice exposed to 0.15 ppm; however, the incidence was not reported.

The adverse effect levels for declines in lung function in TDI workers were about 5 times lower than the LOAEL for nasal effects in mice; thus, the occupational exposure studies were selected as the basis of the MRL. The results of the Diem et al. (1982) and Clark et al. (1998) studies suggest that the greatest declines in lung function occur during the first several years of exposure to TDI; thereafter, the declines are not significantly different from predicted levels. Thus, these studies were considered as the basis of the MRL. The Clark et al. (1998) study was selected over the Diem et al. (1982) because it identified a slightly lower adverse effect level (0.0012 versus 0.0019 ppm) and did not rely on unpublished monitoring data. The mean daily exposure level of the exposed group of 0.0012 ppm was adjusted for intermittent exposure (8 hours/day, 5 days/week). This adjusted adverse effect level of 0.00029 ppm was divided by a total uncertainty factor of 100 (10 for use of an adverse effect level and 10 for human variability) resulting in an MRL 0.000003 ppm (3×10^{-6} ppm or 0.003 ppb).

2. RELEVANCE TO PUBLIC HEALTH

Oral MRLs for TDI

TDI is rapidly hydrolyzed in water and is not likely to be detected in aquatic environments. Thus, oral exposure to TDI in humans is unlikely, thereby lessening the need for oral MRLs.

Inhalation MRLs for MDI

Acute Duration. Several case reports of acute-duration inhalation exposure to MDI have been identified (Banks et al. 1986; Chang and Karol 1984; Stingeni et al. 2008; Suojalehto et al. 2011). The reports described breathing difficulties (Stingeni et al. 2008), asthma (Chang and Karol 1984; Suojalehto et al. 2011), and asthma-like respiratory symptoms (Banks et al. 1986). Although the exposure levels were not reported, they were likely to be relatively high based on the severity of the observed effects. In guinea pigs, exposure to 0.01 ppm MDI 6 hours/day for 5 days resulted in increased airway hyperresponsiveness; a NOAEL of 0.005 ppm was identified for this effect (Marek et al. 1999). The Marek et al. (1999) study was not considered a suitable basis for an MRL because the study did not include a histological examination of the respiratory tract and it is possible that histological alterations, particularly in the nasal cavity, may occur at lower concentrations than airway hyperresponsiveness.

Intermediate Duration. Bascom et al. (1985) reported a case of a male who exhibited dyspnea, fever, malaise, and hypoxemia, effects characteristic of hypersensitivity pneumonitis, 2 months after beginning a job involving the use of a polyurethane foam containing MDI. Malo and Zeiss (1982) also described a case of a foundry worker who developed dyspnea and restrictive breathing 1 month after beginning work. Neither case included information on exposure levels. Exposure of guinea pigs to 0.01 ppm MDI 6 hours/day, 5 days/week for 4 weeks resulted in increased airway hyperresponsiveness to acetylcholine (Marek et al. 1999). This study did not include a histological examination of the respiratory tract. As noted in the discussion for the acute-duration MRL, the lack of a histological examination precludes using the Marek et al. (1999) study as the basis for deriving an MRL.

Chronic Duration

- An MRL of 0.001 mg/m³ has been derived for chronic-duration inhalation exposure (≥1 year) to polymeric MDI.

The primary effects of MDI observed in occupational exposure studies include occupational asthma in sensitized individuals and decreases in lung function. Asthma and/or asthma-like symptoms were

2. RELEVANCE TO PUBLIC HEALTH

reported by several investigators (Hur et al. 2008; Wang and Petsonk 2004; Woellner et al. 1997; Zammit-Tabona et al. 1983); none of these studies provided exposure information. Symptoms of hypersensitivity pneumonitis (e.g., chills, fever, malaise) have also been reported in a study of workers with asthma-like symptoms (Baur 1995). Liss et al. (1988) found a significant decrease in FEV₁ levels when pre-shift levels were compared to post-shift levels in workers at a steel foundry using MDI; the study did not provide monitoring data. Comparison of pre- and post-shift lung function levels did not reveal significant differences in a study of 27 polyurethane foam workers (Sulotto et al. 1990); the MDI levels ranged from 0.0005 to 0.001 ppm. Musk et al. (1982) also found no differences in lung function when pre- and post-shift values were compared in workers at two polyurethane plastic manufacturing facilities. Monitoring data were provided by the facilities and were measured by the investigators; however, there was a large discrepancy between the values.

The chronic toxicity of inhaled MDI has been investigated in rats exposed to an aerosol of polymeric MDI, which contained 44.8–50.2% monomeric MDI 6 hours/day, 5 days/week for 2 years (Reuzel et al. 1994). Exposure to 1.0 mg/m³ resulted in significant increases in the incidence of basal cell hyperplasia and Bowman's gland hyperplasia in the nasal cavity and mild to moderate localized fibrosis in the lungs and alveolar duct epithelialization. Localized alveolar bronchiolization was also observed at 6.0 mg/m³. The study identified a NOAEL of 0.2 mg/m³. An unpublished study conducted by Hoyemann and associates and reviewed by Feron et al. (2001) found similar results in female rats exposed to monomeric MDI 18 hours/day, 5 days/week for 2 years. In this study, an increased incidence of bronchiolo-alveolar hyperplasia and fibrosis were observed at ≥ 0.23 mg/m³. After adjusting for intermittent exposure, the LOAEL value identified in the Reuzel et al. (1994) study (0.178 mg/m³) is very similar to the LOAEL from the Hoyemann study (0.123 mg/m³).

The NOAELs from the Sulotto et al. (1990) occupational exposure study and the Reuzel et al. (1994) rat study were both considered as possible points of departure for the chronic-duration inhalation MRL (the Hoyemann study was not considered as the basis of the MRL because the study was not available to ATSDR for review). Two TDI studies (Clark et al. 1998; Diem et al. 1982) showed that the greatest declines in lung function occurred within the first year of exposure to TDI. Sulotto et al. (1990) is not a prospective study, so it is possible that exposure to 0.005–0.001 ppm might have resulted in a decline in lung function in naïve workers that would have gone undetected. Due to this uncertainty, the Reuzel et al. (1994) study was selected as the basis of the MRL. The incidence data for basal cell hyperplasia in the nasal cavity, Bowman's duct hyperplasia in the nasal cavity, and lung fibrosis were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS, version 2.4.0) using the extra risk

2. RELEVANCE TO PUBLIC HEALTH

option. The $BMCL_{10}$ values predicted from the selected models for basal cell hyperplasia and lung fibrosis were 0.48 and 0.70 mg/m^3 , respectively; none of the models provided an adequate fit to the incidence data for Bowman's gland hyperplasia. The $BMCL_{10}$ of 0.48 mg/m^3 was selected as the point of departure for the MRL and was adjusted for intermittent exposure (6 hours/day, 5 days/week) resulting in a $BMCL_{ADJ}$ of 0.086 mg/m^3 . A human equivalent concentration ($BMCL_{HEC}$) was calculated by multiplying the $BMCL_{ADJ}$ by a regional deposited dose ratio (RDDR) of 0.453. The chronic-duration inhalation MRL of 0.001 mg/m^3 for polymeric MDI was derived by dividing the $BMCL_{HEC}$ of 0.039 mg/m^3 by a total uncertainty factor of 30 (3 for extrapolation from animals to human with dosimetric adjustments and 10 for human variability).

Oral MRLs for MDI

MDI is rapidly hydrolyzed in water and is not likely to be detected in aquatic environments. Thus, oral exposure to MDI in humans is unlikely, thereby lessening the need for oral MRLs.