

ISOCYANATE-INDUCED ASTHMA IN MICHIGAN

Asthma caused by isocyanates is the most common cause of work-related asthma in Michigan. Table I shows the total number of work-related reports in Michigan per year and the number and percent caused by isocyanates. Isocyanates are responsible for 21% of the cases of work-related asthma in Michigan. There are three main types of isocyanates used; HDI, MDI and TDI. Figure I illustrates their chemical structure. Isocyanates are typically mixed with a second chemical in a two part system to manufacture flexible and rigid foam, fibers, paints, varnishes and elastomers. They are widely used in automobile manufacturing, autobody repairs and construction. Although MDI is less volatile than TDI, because of widespread use MDI is as common a cause of work-related asthma as TDI in Michigan. Of the 218 reports of isocyanate-induced asthma in Michigan, 81 were from exposure to TDI, 64 were from exposure to MDI, 6 were from exposure to NDI, 14 were from exposure to HDI, and 53 were from exposure to an unknown type or combination of isocyanates. An additional 5 confirmed asthma cases had a primary exposure to a substance other than an isocyanate, and a secondary exposure to an isocyanate (one was from exposure to MDI and 4 were from exposure to an unknown type of isocyanate).

Health effects from inhalation of isocyanates are: (1) irritation of eyes and respiratory tract; (2) asthma, either from sensitization or an acute exposure causing Reactive Airways Dysfunction Syndrome (RADS); (3) hypersensitivity pneumonitis; and (4) animal evidence that TDI is carcinogenic (the International Agency for Research on Cancer classified TDI as a possible human carcinogen).

It is estimated that 5-10% of workers exposed to isocyanates will become sensitized and develop work-related asthma. Only the level of exposure has been identified as a risk factor; neither atopy, cigarette smoking, pre-existing asthma nor gender have been found to be risk factors. The mechanism of sensitization from isocyanate-induced asthma is not totally understood. Less than 30% of individuals with work-related asthma from isocyanates have specific IgE antibodies. T-lymphocyte involvement with positive patch tests and lymphocyte blast transformation have been described. Also, the release of cytokines such as the leukotriene LTE_4 have been described after exposure to TDI.

Investigations of workplaces in Michigan where workers with isocyanate exposure have developed their work-related asthma have found air levels to be within allowable limits. Of the 80 companies inspected, 50 had air levels tested; all of which had air levels within the Michigan OSHA standard.

In 59 companies where questionnaires were administered to the workers in the isocyanate-using areas, 310 (22.1%) had daily or weekly symptoms of shortness of breath, wheezing or chest tightness made worse by exposures at work (Table II). Additionally there were another 107 workers in medical records at these companies who had never been reported to the state but for whom the company had evidence of isocyanate-related asthma. Among the individuals reported 54.1% had used the emergency room for medical care for their asthma an average of 4.7 times with a range of 1 to 50 and 25.8% had been hospitalized for their asthma an average of 1.3 times with a range of 1 to 40.

Generally, exposures occur before the isocyanates are mixed with a second chemical and react. Some reports, however, are of workers who are exposed to large quantities of recently-made isocyanate foam; it is possible that there is some off-gassing of unreacted isocyanates. Why individuals become symptomatic even though no companies are in violation of the allowable air standards has been attributed to the lack of a comprehensive standard which would cover clean up procedures after spills and leaks. Also, previous to 1993 there is some concern about whether the methodology used to analyze the air samples was appropriate. However, although the numbers are smaller we continue to find similar percentages of symptomatic individuals if we limit the questionnaire responses to after 1993. In addition, no companies have been in violation of the allowable air standard since the new methodology for analyzing the air samples has been used.

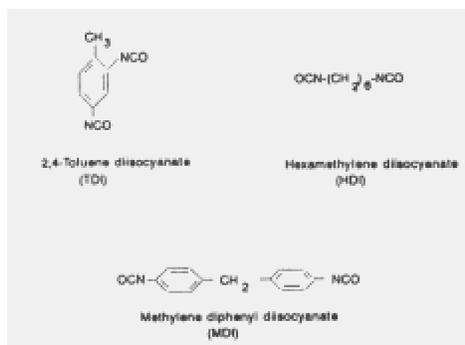


Figure I. Chemical Structures of Diisocyanates.

From: Bernstein, JA. *Overview of diisocyanate occupational asthma Toxicology* 1996; 111:184.

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Table I. Total and Isocyanate-Related Confirmed Cases of Work-Related Asthma by Year Reported

Year	Total Asthma Cases Reported	Isocyanate-Related Asthma Cases Reported	
		#	(%)
1988	31	12	(39)
1989	63	17	(27)
1990	144	38	(26)
1991	114	23	(20)
1992	150	32	(21)
1993	176	22	(13)
1994	152	31	(20)
1995	103*	27	(26)
1996	114*	21	(18)
Total	1,047	223	(21)

*Data from 1995 and 1996 are incomplete at this time.

ABSTRACTS

The first paper describes an outbreak of work-related asthma in a Michigan factory from exposure to a new type of isocyanate. The second paper is a case report of RADS in an isocyanate-exposed machinist.

1. Simpson C, Garabrant D, Torrey S, Robins T, and Franzblau A. *Hypersensitivity Pneumonitis-Like*

Reaction and Occupational Asthma Associated With 1,3-Bis(Isocyanatomethyl) Cyclohexane Pre-Polymer. Am J Indust Med 1996; 30:48-55.

Twenty-three of 34 workers who had worked in the injection molding operation making polyurethane foam parts at an automobile parts manufacturing plant developed respiratory symptoms and/or systemic symptoms over a 2-month period following the full production use of a new diisocyanate paint that contained 1,3-bis (isocyanatomethyl) cyclohexane pre-polymer (BIC) (CAS #75138-76-0, 38661-72-2). At 3 months, all subjects underwent an interview, physical examination, pre- and post-shift pulmonary function tests, and either methacholine challenge test or bronchodilator challenge at an occupational health clinic. The most frequently cited symptoms were dyspnea (65%), cough (61%), chest tightness (57%), chills (57%), wheezing (30%), and myalgias, arthralgias, and nausea (26%). Thirteen subjects had either a positive methacholine challenge test or a positive response to bronchodilator challenge, making the overall prevalence of airway hyperresponsiveness 38%. The overall prevalence of hypersensitivity pneumonitis-like reactions among line operators in the injection molding process was 27%. This disease outbreak suggests that 1,3-bis (isocyanatomethyl) cyclohexane pre-polymer may cause asthma and hypersensitivity pneumonitis-like reactions. The use of BIC was discontinued 6 months after the first workers developed symptoms (author's abstract).

2. Lemiere C, Malo J-L, Boulet L-P, and Boutet M. *Reactive Airways Dysfunction Syndrome Induced By Exposure To A Mixture Containing Isocyanate: Functional And Histopathologic Behavior* Allergy 1996; 51:262-265.

A 31-year-old machinist experienced acute symptoms of rhinoconjunctivitis, coughing, shortness of breath, and wheezing after sudden exposure to fumes containing isocyanates and solvents. Lung function tests carried out 11 days after the event showed reduced flow rates. Forty days after the acute inhalational injury, expiratory flows improved, and the PG_{20} was 0.8 mg/ml, showing moderate bronchial hyperresponsiveness. Six days later, the subject underwent bronchoscopy. Bronchial biopsies showed a marked loss of epithelial cells, severe subepithelial oedema, and inflammatory cells infiltrate (mainly lymphocytes). The subject was given inhaled steroids. The PG_{20} was back to normal 42 days later. Bronchial biopsies then showed incomplete regeneration of the epithelial layer with few ciliated cells and persistence of inflammation (lymphocyte infiltrate) in epithelia and connective tissue. We conclude that irritant exposure to a mixture of isocyanates and solvents can cause occupational asthma without a latency period, i.e., reactive airways dysfunction syndrome (author's abstract).

Table II. Symptoms Consistent with Work-Related Asthma Among Fellow Workers of the 223 Isocyanate-Related Confirmed Cases of Asthma

	AI # (%)	Unspecified Isocyanates # (%)	TDI # (%)	MDI # (%)
New Onset Asthma and/or Daily or Weekly SOB, Wheezing, or Chest Tightness*	313 (22.1)	126 (24.7)	84 (21.5)	100 (20.0)
OSHA Log**	107	12	48	47
No. Interviewed	1,400	511	390	499

*Interviews were performed at 59 of the 107 facilities where isocyanate-related asthma cases worked.

**OSHA Log was reviewed at 79 of the 107 facilities where isocyanate-related asthma cases worked.

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