Scand J Work Environ Health 2003;29(2):152-158

<https://doi.org/10.5271/sjweh.717>

Issue date: Apr 2003

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Key terms: [aerosol](#); [diphenylmethane diisocyanate](#); [guinea pig](#); [isolated lung](#); [methyl isocyanate](#); [mineral wool](#); [perfused lung](#); [phenyl isocyanate](#); [polyurethane foam](#); [thermal degradation product](#); [toluene diisocyanate](#)

This article in PubMed: www.ncbi.nlm.nih.gov/pubmed/12718501

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Effects of thermal degradation products from polyurethane foams based on toluene diisocyanate and diphenylmethane diisocyanate on isolated, perfused lung of guinea pig

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Låstbom L, Colmsjö A, Johansson R, Karlsson D, Melin J, Nordqvist Y, Skarping G. Effects of thermal degradation products from polyurethane foams based on toluene diisocyanate and diphenylmethane diisocyanate on isolated, perfused lung of guinea pig. *Scand J Work Environ Health* 2003;29(2):152–158.

Objectives The composition of thermal degradation products from two types of polyurethane foams, one based on toluene diisocyanate (TDI) and the other on diphenylmethane diisocyanate (MDI), was analyzed and their toxic lung effects were compared.

Methods Isolated perfused lungs of guinea pig were subjected to thermal decomposition products of polyurethane foams from an aerosol generator with compartments for diluting, mixing, and sampling.

Results Thermal degradation of MDI-based polyurethane foams released MDI, phenyl isocyanate, and methyl isocyanate. The emitted particulate fraction was 75% for MDI, whereas that for TDI from TDI-based polyurethane foam was 3%. Thermal degradation products from MDI-based foam caused a pronounced dose-dependent decrease in the measured lung function parameters (conductance and compliance). In contrast, the thermal degradation products from TDI-based foam did not cause any decrease in lung function.

Conclusions Thermal degradation products generated from MDI-based polyurethane foam were more toxic to the lung than those generated from TDI-based polyurethane foam. This difference was probable due to MDI in the particle phase.

Key terms aerosol, methyl isocyanate, mineral wool, phenyl isocyanate.

Today, enormous quantities of monomer and oligomer diisocyanates are used in industry to produce polyurethanes. Products containing isocyanates (eg, adhesives, paints, plastics, synthetic rubber, and rigid and elastic foams) can be found everywhere in the environment. When polyurethanes are heated, isocyanates and other thermal degradation products are released (1–5). Isocyanates are irritating to the respiratory tract (6–10) and are known as the most common cause of occupational asthma (11). They can sensitize workers and can cause severe asthma attacks even when workers are exposed to concentrations far below the occupational exposure limits (1, 12). Due to the extensive use of poly-

urethanes, and therefore the extensive exposure of workers (eg, firemen, pipelayers, people working with the shaping of plastics containing polyurethane, and welders working with painted metal sheeting), there is much interest in the composition and toxicity of their thermal degradation products.

Using a perfused lung system, we had earlier performed several toxicology and mechanistic studies with pure isocyanates, such as toluene diisocyanate (TDI) and hexamethylene diisocyanate (HDI) (13–15). Since our results during a study with radioactive TDI were analogous to those obtained in vivo, we concluded that the isolated perfused lung model was a very useful tool

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for studying the effects of isocyanates (16). Therefore, in order to evaluate the acute toxic effect of the thermal degradation products of polyurethanes, we generated aerosols similar to those found in workplaces and exposed an isolated lung system from a guinea pig to their degradation products. We chose to work with two kinds of polyurethane foams, one based on TDI and the other on diphenylmethane diisocyanate (MDI). Unifying these two rather complex systems, the aerosol generator and the isolated perfused lung setup made it possible to study the composition of the aerosols formed during the thermal degradation of TDI- and MDI-based polyurethane foams and to compare the acute lung effects caused by the degradation products.

Subjects and methods

Materials

The TDI-based polyurethane foam consisted of 1-mm thick dishclothes cut in strips (240×10 mm). The MDI-based polyurethane foam was obtained from materials intended for car seats. It was likewise cut in strips of suitable sizes.

Mineral wool was used to generate test atmospheres containing methyl isocyanate (MIC). In this study we used the following three kinds of mineral wool: type A with 7% binder and a density of 35 kg/m³, type B with 1.8% binder and a density of 130 kg/m³, and type C with 2.9 % binder and a density of 30 kg/m³.

Generation of the test atmosphere

To generate the thermal degradation aerosols, we used a system developed by Melin et al (figure 1) (2). The TDI-based foam strips were burned at 300°C, whereas, 350°C or 450°C was used for the MDI-based strips. A stream of preheated combustion air (0.5 l/min) was passed through the furnace, and it transported the combustion products to a heated manifold into which diluting air (25 l/min) was added. Thereafter the air and its components were directed to a mixing compartment. Only a small part of the total air stream was directed to the perfused guinea pig lung. The air was room temperature by the time it reached the lung. All the tubes were made of Teflon™.

Phenyl isocyanate (PhI) vapor was generated by directing a stream of air through a nozzle against the surface of liquid PhI in a vial placed in a cooling block. The vapor outflow through a tube in the glass vial was then diluted and mixed in a mixing tower. Lungs were exposed as in the polyurethane experiments. The conditions for the experiments were a generator airflow of

0.1 l/min and a diluting airflow of 25 l/min; 1 ml of PhI was kept at 0.5°C in the vial.

Mineral wool often contains a urea-based binder, which, upon heating, releases MIC. In order to obtain the degradation products of the binder components of the mineral wool, we used the same equipment that generated the thermal degradation products of the polyurethane foam. The temperature chosen for these experiments was 300°C, except for one experiment with sample B, which was conducted at 350°C. The content of the urea-based binder in the mineral wool is important with respect to the MIC concentrations generated. The densities of mineral wool cannot generally be correlated with its binder content.

Sampling of isocyanates in the generated test atmospheres

Two simultaneous air samples were taken in periods that varied between 2 and 5 minutes, starting at the beginning of the lung exposure. New samples were taken periodically every 15 minutes until the end of the exposure. The sampling flow rate was set to 1.0 l/min. The samples were collected in impinger flasks containing 10 ml of 0.01 M dibutylamine (DBA) in toluene (17). In two experiments the particles escaping the impinger flasks, smaller than 1.5 µm (18), were collected on

Figure 1. Schematic drawing of the aerosol generator system. (1= geared electric motor, 2 = flushing port for nitrogen, 3 = holder tube for quartz sample, 4 = suspended magnets, 5 = sample strip, 6 = diluting air, 7 = furnace, 8 = combustion gas, 9 = thermocouple, 10 = mixing compartment, 11 = equilibrium compartment, 12 = sampling tower, 13 = exhaust, 14 = outlet for exposure)

13-mm glass-fiber filters in polypropylene filter holders. Immediately after the exposure, the glass-fiber filters were transferred to vials containing 10 ml of toluene.

Determination of toluene diisocyanate in air samples

The TDI-DBA derivatives were analyzed with a high-performance liquid chromatographic (HPLC) system equipped with an ultraviolet detector with the wavelength set at 240 nm. The mobile phase was 80% acetonitrile and 20% water. The column was 10-cm C-18 with 5- μ m particles, and the flow rate was 1.0 ml/min.

Determination of diphenylmethane diisocyanate, phenyl isocyanate and methyl isocyanate in the air samples

The sampling solutions and standard solutions were spiked with deuterium-labeled isocyanate-DBA derivatives (internal standards). The solutions were evaporated to dryness and dissolved in 0.5 ml of acetonitrile. The solutions were then injected into a liquid chromatograph-mass spectrometer. The mass spectrometer was working in the electrospray mode, monitoring positive ions, and was connected to a Phoenix 40 micro-LC pump. Injections were made with a CMA/200 autosampler. The isocyanate-DBA derivatives were analyzed using linear gradient elution for 30 minutes with a mobile phase of acetonitrile:water (from 50:50% to 95:5% volume/volume) and 0.05% formic acid with a flow rate of 40 μ l/min. The used liquid chromatographic column was Hypersil C18 (150 $\times$ 1.0 mm, with 5 μ m particles).

Isolated perfused lungs of guinea pigs

Lung preparations from guinea pigs of the Dunkin-Hartley strain and weighing 400–600 grams were used. The animals were anesthetized with pentobarbital (Mebumalum Vet, Nord Vacc, Sweden), 120 mg/kg being injected intraperitoneally. The lungs were then surgically removed as described by Kröll et al (19) and perfused with the same buffer and under the same conditions as described by Låstbom et al (20). Once suspended in the thoracic chamber, the lungs were ventilated at 60 breaths/minute by creating an alternating negative pressure (–0.32 to –0.58 kPa) inside the thoracic chamber using an animal respirator (model 7025, Ugo Basile, Biological Research Apparatus, Varese, Italy) and a vacuum source connected to the thoracic chamber. The tracheal airflow was measured with a heated pneumotachograph (Hans Rudolf Inc, Kansas City, MO, USA). Via laboratory instrument system architecture (LISA, AstraZeneca, Lund, Sweden), pulmonary pressure, together with tracheal airflow, was monitored and recorded

directly on a computer, on which calculations of lung conductance (G_{aw}) and dynamic compliance (C_{dyn}) were performed (21). Lung conductance is a measurement of how easy the air moves in the upper airways, and lung compliance is a measurement of the elasticity of the lower part of the lung. The perfusion flow was measured manually.

The lungs were allowed to stabilize for 20 minutes with single-pass perfusion buffer containing albumin before the experiment was started. Only lung preparations with stable baseline values for perfusion flow, conductance, and compliance were used. The values for conductance and compliance were 72.8 (SD 16.9) ml/(s·kPa) and 8.2 (SD 2.7) ml/kPa, respectively, and the perfusion flow was 30 (SD 5.0) ml/min (N=28). Before the exposure the lungs were allowed to equilibrate for 10 minutes in 150 milliliters of recirculating Krebs-Ringer buffer containing 2% albumin.

The lung preparation was exposed to normal air for 10 minutes and then exposed via the air passage for up to 30 minutes to PhI or thermal degradation products. The pneumotachograph was taken away during the exposure and put back every 15 minutes in order to obtain the conductance and compliance values.

Results

When the MDI-based polyurethane foam was heated, not only was MDI released, but also PhI and MIC. As seen in table 1, there was an increasing formation of the three isocyanates, of which MDI and MIC correlated significantly with the increasing mass feeding rate of the polyurethane foam (MDI: $F=11.6$, $r=0.75$; MIC: $F=24.4$, $r=0.93$; F and r denotes goodness of fit and the correlation coefficient, respectively). In experiments 10 and 11, in which the temperature was 350°C, both gaseous and particulate isocyanates were sampled in contrast to the experiments conducted at 450°C, when only gaseous isocyanates were sampled.

The particulate MDI measured at 350°C amounted to about 75% of the total MDI content. The gaseous isocyanate content did not differ between the experiments conducted at 350°C and 450°C.

From the TDI-based foam, degraded at 300°C, both 2,4-TDI and 2,6-TDI were formed; the total values are presented in table 2.

We compared the acute toxic lung effects of the thermal degradation products from the two types of polyurethane foams, one based on TDI and the other on MDI. Thermal degradation products from MDI-based polyurethane foam caused a dose-dependent decrease in such lung function parameters as conductance and compliance (table 1 and figure 2). There were no clear signs

Table 1. Concentrations of isocyanates in the air samples taken during lung exposure to the thermal degradation products of MDI-based polyurethane foam (N=11). (PUF = polyurethane foam, MDI = diphenylmethane diisocyanate, PhI = phenyl isocyanate, MIC = methyl isocyanate, CV = coefficient of variation, Temp = temperature, Conc = concentration, - = not applicable, .. = not analyzed)

Experiment	Temp (°C)	Mass feeding rate of PUF (mg/min)	MDI						PhI						MIC	
			Particle phase (N=4)		Gas phase (N=6)		Total (N=4)		Particle phase (N=4)		Gas phase (N=6)		Total (N=4)		Total (N=6)	
			Conc (ppb)	CV (%)	Conc (ppb)	CV (%)	Conc (ppb)	CV (%)	Conc (ppb)	CV (%)	Conc (ppb)	CV (%)	Conc (ppb)	CV (%)	Conc (ppb)	CV (%)
1	450	4.5	..	..	2.0	38.1	.	.	..	..	16.7	32.8	.	.	..	..
2	450	5.1	..	..	1.7	60.5	.	.	..	..	23.0	91.7	.	.	..	..
3	450	5.1	..	..	8.9	38.2	.	.	..	..	75.8	32.6	.	.	0.0	0.0
4	450	5.5	..	..	4.6	132	.	.	..	..	45.1	62.8	.	.	0.6	245
5	450	16.9	..	..	7.6	35.2	.	.	..	..	56.5	38.9	.	.	..	..
6	450	17.7	..	..	9.5	70.5	.	.	..	..	68.9	78.1	.	.	16.2	51
7	450	19.3	..	..	10.2	60.4	.	.	..	..	65.2	103	.	.	..	..
8	450	19.7	..	..	12.0	93.7	.	.	..	..	70.9	65.7	.	.	25.2	100
9	450	20.4	..	..	10.7	56.9	.	.	..	..	83.4	42.0	.	.	..	..
10	350	16.2	33.8	8.2	14.2	45.1	48.0	18.5	4.8	40.4	231.0	45.6	235.8	46.3	28.3	27.4
11	350	18.8	34.7	4.2	7.9	47.5	42.6	12.4	5.8	41.1	52.5	16.7	58.3	18.6	24.1	27.4

of edema in the lungs exposed to MDI-based polyurethane foam (data not shown).

In figure 3, the concentration of MDI is four times higher at 350°C than at 450°C because both particulate and gaseous isocyanates were sampled in the former case, whereas only gaseous isocyanates were determined in the latter. Consequently, the same bronchoconstriction was obtained at both 350°C and 450°C. The thermal degradation products from TDI-based polyurethane foam did not cause any decrease in lung function.

Table 2. Concentrations of isocyanates in the air samples taken during lung exposure to TDI-based polyurethane foam (N=6). (TDI = toluene diisocyanate, PUF = polyurethane foam, CV = coefficient of variation)

Experiment	N	Mass feeding rate of PUF (mg/min)	TDI (ppb)	CV (%)
1	8	6.2	1100	8.0
2	6	6.3	996	4.2
3	8	6.5	812	25.7
4	8	6.6	765	28.5
5	8	9.7	1130	17.8
6	6	10.0	1240	34.8

Figure 2. Reduction in the conductance and compliance of the lung function parameters after 30 minutes of exposure to air containing thermal degradation products from MDI-based polyurethane foam (N=9), TDI-based polyurethane foam (N=6), or pure phenyl isocyanate (PhI) (N=2). Every point represents values of conductance or compliance from one experiment after 30 minutes of exposure. (MDI = diphenylmethane diisocyanate, TDI = toluene diisocyanate)

Figure 3. Reduction in the conductance and compliance of the lung function parameters after 30 minutes of exposure to air containing thermal degradation products from MDI-based polyurethane foam heated to 350°C (N=2) or 450°C (N=7). The experiments conducted at 350°C show the total MDI concentrations, including both particulate and gaseous MDI, whereas the experiments at 450°C show only the gaseous MDI. (MDI = diphenylmethane diisocyanate)

Table 3. Generation of phenyl isocyanate (PhI) from evaporation (N=3). (CV = coefficient of variation)

Experiment	N	PhI (ppb)	CV (%)
1	4	2360	11.4
2	4	2170	5.3
3	4	2250	6.5

Lungs were exposed to plain PhI vapor in order to determine whether PhI was the cause of lung function impairment during exposure to degradation products from MDI-based polyurethane foam. The generated PhI concentrations are presented in table 3. However, PhI did not decrease conductance and compliance to the same degree as the thermal degradation products from MDI-based polyurethane foam, even if 10 times higher concentrations of pure PhI were used than the PhI

Table 4. Concentrations of methyl isocyanate (MIC) in the air samples taken during lung exposure to thermal degradation products from mineral wool and the resulting reduction in lung conductance (N=7). (Temp = temperature, CV = coefficient of variation)

Mineral wool	Samples (N)	Binder mass feeding rate (mg/min)	Temp (°C)	MIC (ppb)	CV (%)	Reduction in conductance (%)
Type A	5	0.91	300	332	22.4	1
Type A	5	1.0	300	226	17.9	7
Type A	5	1.7	300	480	22.7	5
Type B	5	1.2	300	293	14.2	3
Type B	5	1.0	350	443	19.8	0
Type C	5	0.53	300	145	66.9	20
Type C	5	0.37	300	107	23.3	0

released during the heating of MDI-based polyurethane foam (figure 2).

During the heating of MDI-based polyurethane foam, MIC was formed along with MDI and PhI. Therefore we made some additional and comparative experiments. Thus three different types of mineral wool were used to generate MIC. The results in table 4 show that MIC, in concentrations up to about 500 ppb, had no acute effect on lung conductance.

Discussion

In this study we used a system for generating isocyanate aerosols that are similar in composition to those found in workplaces (2). The system was connected to an isolated perfused lung model that allowed us to measure lung function at different concentrations of isocyanates in air. When the chemical bonds of polyurethane foam break up during heating, several isocyanates, carbon monoxide, hydrogen cyanide, and particles are formed. We measured the concentration of some of the important isocyanates released during the heating of polyurethane foams.

The thermal degradation products from MDI-based polyurethane foam, including MDI, PhI, and MIC, caused a dose-dependent decrease in lung function. In contrast, the thermal degradation products from TDI-based polyurethane foam did not seem to affect lung function. Despite a TDI concentration that was up to 150 times higher than that of released MDI, the degradation products from TDI-based polyurethane foam had no acute effect on lung function. When isolated perfused lungs from guinea pigs were exposed to PhI in our experiments, we observed no effect on lung function. Pauluhn et al (22) reported chronic airway inflammation in rats exposed to PhI. The concentrations used were similar to ours although the rats were exposed for 2 weeks (6 hours/day), whereas our study of acute effects used

only 30 minutes of exposure. Because neither exposure to pure PhI concentrations of up to 2400 ppb nor MIC exposures at levels up to 500 ppb caused an acute effect on lung function in experiments with mineral wool, we propose that the bronchoconstriction determined during exposure to thermal degradation products from MDI-based polyurethane foam is caused primarily by MDI. When the effects of different isocyanates are compared, their relative distribution in the gas and particle phases may be important. We found that 75% of the total MDI concentration emitted during the degradation of MDI-based polyurethane foam was in the particulate phase. Because of their small size, these particles must be sampled on filters connected after an impinger flask. For example, Spanne et al (18) have shown that impingers have low sampling efficiencies for particles with diameters of less than 1.5 μm . With a likely size range typical of condensation aerosols, the particulate MDI generated in our study had diameters less than about 1.5 μm and should have been deposited in both the alveolar and bronchial region (23).

Isocyanates in the form of small particles may be more toxic than gaseous isocyanates because of the deeper penetration of the particles into the lungs. Melin et al (3) previously showed that only about 3% of total TDI is emitted as particles when TDI-based polyurethane foam is thermally degraded at 300°C. Thus TDI emitted from TDI-based polyurethane foam is associated with particles to a much lower degree (3) than the 75% particulate fraction of MDI. With the higher total TDI concentration of 1000 ppb, compared with 40 ppb for MDI in our study, it is reasonable to assume that the particle concentration of the two isocyanates was similar. However, the much more pronounced effect on lung function during exposure to MDI indicates that particles generated during the thermal degradation of MDI-based polyurethane foam are more toxic per se than those of TDI-polyurethane foam. A recent study by Pauluhn et al (24) showed that guinea pigs experience an increase in respiratory rate when challenged with an MDI aerosol and that a 15-minute inhalation exposure to MDI at 135 mg/m³, as either a 1.7- μm or a 3.8- μm aerosol (mass median aerodynamic diameter), can sensitize guinea pig lungs. Together with our results, this finding indicates that the inhalation of thermal degradation products is a real occupational hazard, as it can both induce an acute reduction in lung function and lead to sensitization.

We conclude that the inhalation of thermal degradation products from MDI-polyurethane foam is likely to be more hazardous than the inhalation of such products produced by heated TDI-polyurethane foam. This finding is especially relevant because TDI is being replaced by other isocyanates, including MDI, in in-

dustrial. We suspect that the higher toxic response to degradation products from heated MDI-based polyurethane foam may be caused by MDI in particulate form.

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Received of publication: 13 October 2001