HEALTH EFFECTS OF EXPOSURE TO ISOCYANATES IN A CAR FACTORY

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SUMMARY

Objectives: Isocyanates are known to induce occupational diseases. The aim of this work was to assess the health effects of exposure to isocyanates and to test the sensitivity of selected parameters for early detection of isocyanate-related allergic diseases.

Methods: In total, 35 employees from one factory were tested: 26 workers exposed to isocyanates (exposed group) and nine office workers (control group). All subjects filled in a questionnaire regarding possible health problems. Fractional exhaled nitric oxide (FeNO) and spirometry were measured for each subject at the same time during two consecutive working days. A urine sample was taken for a biological exposure test (BET).

Results: No significant difference was found between the exposed and control groups for spirometry parameters and FeNO. However, in the exposed group, FeNO was highly elevated (> 50 ppb) in five subjects (all reporting health problems at the workplace, all with normal spirometry and non-smokers). The BET revealed a significant difference ($p < 0.001$) between the exposed and control groups for 4,4´-methylenediphenyl diamine (MDA) in the urine.

Conclusions: Our examination showed the usefulness of the BET in monitoring of workplace exposure to isocyanates and the importance of FeNO in monitoring of allergic inflammation of airways in non-smoking employees with normal spirometry.

Key words: isocyanates, methylene diphenyl diisocyanate, fractional exhaled nitric oxide, biological exposure test, occupational asthma

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INTRODUCTION

Isocyanates are reactive chemical substances with the isocyanate functional group (R-N=C=O). The most frequently used ones in industry are diisocyanates, mainly methylene diphenyl diisocyanate (MDI), toluene diisocyanate (TDI), and hexamethylene diisocyanate (HDI). Isocyanates exert irritative and allergic effects in humans. They can cause allergic dermatitis, allergic rhinitis, bronchial asthma (irritative or allergic) and extrinsic allergic alveolitis (1–3).

Isocyanates are reported to be the main occupational allergens causing bronchial asthma worldwide (4). The situation in the Czech Republic was different until 2010, when flour was the main cause of occupational asthma in this country. Probably the boom of the car industry has started the increasing use of glues and colours containing isocyanates and also the production of polyurethanes where isocyanates are reacted with polyols. The worst situation in the Czech Republic was in 2012, when 54.8% of all diagnosed cases of occupational asthma were caused by isocyanates (5).

The aim of our work was to assess the health effects of exposure to isocyanates and to test the sensitivity of selected parameters for early detection of isocyanate-related allergic diseases. The study was done in 2019 in one factory in the Czech Republic where 12 cases of occupational asthma and two cases of occupational rhinitis caused by isocyanates had been diagnosed in 2014–2018 (6). In this factory, various parts of the car's interior (door panels and dashboards) are produced using glue containing 4,4´-MDI. According to the material safety data sheet, the glue can cause a skin allergic reaction and signs of allergy if inhaled, and there is some suspicion of its carcinogenicity. The concentration of 4,4´-MDI in the glue is described to be 1–2.5%.

In the prevention of occupational diseases caused by isocyanates, only spirometry is a mandatory examination used during regular check-ups, which is in agreement with Czech legislation (an X-ray is done only once during the entrance examination). We wanted to test the sensitivity of spirometry as a preventive measure and to learn if fractional exhaled nitric oxide (FeNO) monitoring could be useful in the monitoring of people exposed to isocyanates, who are at a higher risk for the development of allergic diseases, together with the evaluation of symptoms present at the workplace.

MATERIALS AND METHODS

Subjects

In total, 35 employees working in one factory were examined, 26 workers from the production halls exposed to isocyanates and

9 office workers not exposed to isocyanates (Table 1). All subjects were examined on two consecutive days, at the same time of both work shifts. On the first day, a questionnaire was filled in, then FeNO and spirometry measurements were performed in all subjects. The same examination was performed on the second day together with the sampling of urine for biological monitoring using biological exposure test (BET).

Description of the Workplace

The factory is divided into several halls, which are connected. In four halls, various parts of the car's interior are manufactured. Door panels and dashboards are completed from plastic and polyurethane components (artificial leather). The plastic parts are also pressed in the halls. The glue containing 4,4´-MDI is used in production. In the long term, the worst situation regarding isocyanates exposure is at the workplace of lamination, where the glue is applied. The artificial leather is glued to the plastic parts using heat (170 °C) and pressure. At another workplace in the halls, the glue is applied to smaller parts of leather or on leather that is rolled up. The offices are located in another part of the factory distant from the production halls.

In 2016, the concentration of 1,6-HDI, 2,4-TDI and 4,4´-MDI in the air in all production halls was measured. The concentration of all measured diisocyanates was below both the occupational exposure limit (OEL) and short-term exposure limit (STEL) (1,6-HDI: 0.000225–0.000421 mg/m^3, 2,4-TDI: 0.000225–0.000231 mg/m^3 and 4,4´-MDI: 0.000456–0.045265 mg/m^3). The highest concentration was found at the workplace where lamination was done.

The measurement in 2017 revealed the worsening of the situation regarding isocyanates exposure at the workplace. The concentration of 4,4´-MDI ranged from 0.126–2.330 mg/m^3 and exceeded both the OEL and STEL. The highest concentration was again at the lamination workplace. As the measured concentration of 4,4´-MDI was very high, the work in the halls was classified as category 4 according to Czech legislation, which means a high risk of health impairment that cannot be completely excluded despite using personal protective equipment.

Some technical measures were done in the halls, and the repeated measurement in 2018 (11 months before our study was done) showed improvements in the concentrations of 1,6-HDI, 2,4-TDI and 2,6-TDI, which were below the detection limit; the concentration of 4,4´-MDI varied between 0.001 and 0.012 mg/m^3.

In the Czech Republic, the OEL and STEL limits, respectively, are 0.05 mg/m^3 and 0.1 mg/m^3 for 4,4´-MDA, 2,4-TDA and 2,6-TDA, and 0.035 mg/m^3 and 0.07 mg/m^3 for HDA (7).

Questionnaire

All subjects filled in a questionnaire regarding health problems. They were asked about breathing problems (cough, dyspnoea); symptoms such as rhinitis, conjunctivitis, bleeding from the nose, and dermatitis (all at work and outside of work); smoking; treatment; and presence of allergies and other diseases.

Lung Function Testing

Lung function testing was performed with a spirometer (MasterScope, Jaeger). The measurements were carried out according to the standard protocol of the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines (8). The results were expressed as the percentage of the predicted value (%PV). The main examined parameters were forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), peak expiratory flow (PEF), and FEV1/FVC ratio.

FeNO Measurement

Prior to spirometry, the FeNO was measured by the Hypair FeNO analyser (Medisoft, Belgium), according to ATS/ERS recommendations. The FeNO values expressed in parts per billion (ppb) were interpreted as high if > 50 ppb and as low if < 25 ppb (9, 10).

Urine Analysis

The following substances were analysed in the urine: 1,6-hexamethylene diamine (1,6-HDA), 2,6-toluenediamine (2,6-TDA), 2,4-toluenediamine (2,4-TDA), isophorone diamine (IPDA), 1,5-naphthalene diamine (1,5-NDA), and 4,4'-methylenediphenyl diamine (4,4´-MDA). In principle, diamines were extracted from the acid-hydrolysed urine using toluene, derivatized with heptafluorobutyric anhydride (HBFA), and measured by gas chromatography-mass spectrometry (GC-MS). The urine sample (1 ml) spiked with the internal standard 3,3´-methylenediphenyl diamine (3,3´-MDA) was mixed with 3M sulphuric acid (1 ml) and heated at 100 °C for 2 hours. After cooling, the sample was made alkaline with 10M sodium hydroxide (2 ml) and extracted with toluene (1.5 ml). The organic layer was transferred, HFBA (20 µl) was added, and the sample was heated at 50 °C for 1 hour. Afterwards, the reaction mixture was washed with a phosphate buffer of pH 7, and the toluene layer was transferred to another vial and evaporated to a small volume (ca. 100 µl). This was analysed on a DB-5 ms capillary column using a gas chromatograph 7890A coupled to mass spectrometric detector 5975C (both Agilent) operated in the negative chemical ionization mode with m/z values set as follows: 2,4-TDA and 2,6-TDA, 494; 1,6-HDA,

Table 1. *Description of exposed and control group (N = 35)*

Parameter		Exposed group n = 26	Control group n = 9	p-value
Mean age ± CI (years)		36.1 ± 4.0	36.0 ± 7.5	0.977
Sex	Male/female	16/10	4/5	0.441
Smoking	Yes/no	15/11	3/6	0.277

The coverage (confidence) intervals (CI) were calculated on the level of significance α = 0.05.

488; IPDA, 542; 1,5-NDA, 530; and 4,4´-MDA and 3,3´-MDA, 570. The limit of quantitation (LOQ) for 4,4´-MDA was 0.1 μg/l urine. Creatinine was determined by direct analysis of diluted urine using high performance liquid chromatography (HPLC) with the UV detector set at 234 nm (11). Biological limit value for urinary 4,4´-MDA as an indicator of occupational exposure to 4,4´-MDI as defined by German legislation is 10 μg/l (12).

Statistics

Statistical analysis was performed using Excel (Microsoft, USA) and QC Expert software 3.1 (Trilobyte, Czech Republic). For all studied variables, basic descriptive statistics (mean, confidence (coverage) intervals, standard deviations, skewness, and kurtosis, etc.) were calculated and data were tested for normality. We applied independent-sample F-tests and t-tests (two-sample assuming equal variances, two-sample assuming unequal variances, and paired t-test, respectively) for normally distributed data, and Wilcoxon and Mann-Whitney test, respectively, for non-normally distributed data. The bivariate relationship between the variables under study was assessed using correlation coefficients. The coverage (confidence) intervals were calculated on the level of significance $\alpha = 0.05$.

Ethics

The study was conducted according to the Declaration of Helsinki and approved by the Ethical Committee of the First Faculty of Medicine, Charles University, Prague, Czech Republic. All participants were informed of the study aim and signed an informed consent form before the study began.

RESULTS

The main symptoms related to the work in the production halls reported by the subjects from the exposed group were cough (58%), rhinitis (50%), and dyspnoea (42%). A significant difference ($p < 0.05$) was found between the exposed and control groups for cough and dyspnoea prevalence. Cough frequently persisted after work shifts or on weekends (in 42%) but disappeared during the holidays. The subjects from the control group (office workers) reported mainly problems with eyes (itching, burning and watering) mostly during computer work. All results are presented in Table 2.

Spirometry and FeNO measurements were performed on two consecutive days, at the same time in both work shifts. No significant difference was found between the exposed and control groups on each day of the examination (Table 3). When looking

Table 2. *Symptoms present in exposed and control group (N = 35)*

Symptoms	Exposed group (n = 26) n (%)	Control group (n = 9) n (%)	p-value
Cough at work	15 (58)	1 (11)	0.037
Dyspnoea at work	11 (42)	0 (0)	0.042
Rhinitis at work	13 (50)	3 (33)	0.456
Rhinitis out of work	7 (27)	1 (11)	0.401
Bleeding from nose at work	6 (23)	0 (0)	0.172
Dermatitis at work	5 (19)	2 (22)	0.868
Eye itching at work	2 (8)	2 (22)	0.309
Eye burning at work	8 (31)	3 (33)	0.902
Eye watering at work	5 (19)	3 (33)	0.454
Eye symptoms out of work	0 (0)	0 (0)	–

Table 3. *Spirometry and FeNO parameters in exposed group and control group (N = 35)*

Parameter	Unit	Exposed group (n = 26) Mean ± CI	Control group (n = 9) Mean ± CI	p-value
FEV1 day1	%PV	106.2 ± 5.1	108 ± 13	0.689
FEV1 day2	%PV	104.5 ± 4.5	105 ± 12	0.845
PEF day1	%PV	101.5 ± 4.8	111.0 ± 20	0.349
PEF day2	%PV	101.6 ± 5.5	112 ± 19	0.266
FVC day1	%PV	105.5 ± 4.6	103.2 ± 9.0	0.611
FVC day2	%PV	104.5 ± 4.3	100.3 ± 8.0	0.317
FEV1/FVC day1	ratio	0.848 ± 0.028	0.892 ± 0.059	0.137
FEV1/FVC day2	ratio	0.841 ± 0.022	0.894 ± 0.071	0.056
FeNO day1	ppb	23 ± 10	17 ± 11	0.506
FeNO day2	ppb	21 ± 10	16.6 ± 8.5	0.463

%PV – percentage of predicted value; FEV1 – forced expiratory volume in 1 s; FVC – forced vital capacity; PEF – peak expiratory flow; FeNO – fractional exhaled nitric oxide
The coverage (confidence) intervals (CI) were calculated on the level of significance $\alpha = 0.05$.

separately at each group, in the exposed group all spirometry parameters were within normal range, except in one worker with a FEV1 < 80 %PV and in two workers with a FEV1/FVC ratio < 0.75 (all smokers). In the control group, all the followed parameters were within normal range, except in one worker with a FEV1/FVC ratio < 0.75.

FeNO levels were less than 50 ppb in all subjects of the control group but were high (elevated above 50 ppb) in five workers in the exposed group (all currently non-smokers, all with normal spirometry and all with health symptoms at work: cough in four subjects, dyspnoea in two subjects, rhinitis in three subjects, and eye burning and epistaxis in one subject). In these subjects the FeNO was elevated during both measurements on the two consecutive days.

At the end of the second day, spot urine samples collected from the tested subjects (26 from the workers and 8 from the control group, where one person finally denied providing the urine sample) were analysed for diamines, including 1,6-HDA, 2,6-TDA, 2,4-TDA, IPDA, 1,5-NDA and 4,4´-MDA (Table 4). The values of 4,4´-MDA in the exposed group (0.02–2.29 μg/g creatinine) were significantly higher ($p < 0.001$) than in the control group (0.05–0.19 μg/g creatinine). In addition to this, urine samples from another control group (seven research workers) were analysed. Herein, the diamine levels were very similar to those in the control group from the factory, with MDA levels of 0.07 ± 0.05 μg/g creatinine.

DISCUSSION

In the years 2014–2018, 12 occupational allergic asthma cases and two occupational allergic rhinitis cases caused by diisocyanates were acknowledged in the factory where the study was performed (these patients worked and were exposed in the factory when the concentration of isocyanates was high according to the measurements written in the Description of the workplace). That is why we wanted to test if the preventive regime commonly used in the Czech Republic can detect vulnerable subjects at a higher risk of allergic occupational diseases earlier. According to Czech legislation, spirometry and physical examination (including medical history) are mandatory in workers exposed to isocyanates: firstly at the start of work, in 3 months, and then once a year.

In the exposed group, more than half of the workers (15 of 26, 58%) reported cough at work and almost half of the workers (11 of 26, 42%) reported dyspnoea at work. The cough disappeared when they were out of work for a longer period (e.g., on holiday). On the other hand, the decreased FEV1 or FEV1/FVC ratio value was present in only three workers. They were all smokers and reported cough not only at work but also outside the workplace. In these subjects, another cause of their breathing problems can be considered (e.g., chronic obstructive pulmonary disease).

FeNO is considered a useful tool in the monitoring of allergic inflammation in the airways (13–15). FeNO reflects the degree of airway eosinophilia in asthma and can be elevated after a positive allergen challenge with isocyanates (16). In our study, FeNO was highly and repeatedly elevated in 5 of 26 workers in the exposed group. All of them mentioned cough and/or dyspnoea at the workplace, and one subject had eye burning and bleeding from nose at the workplace. It is known that FeNO results can be lowered in smokers (10). In the exposed group, 58% of the subjects were smokers. This could be why FeNO values were normal in smokers from the exposed group who reported allergic and breathing problems at work. This fact could be a limitation to widespread FeNO testing in employees. In the exposed group, all five subjects with elevated FeNO were currently non-smokers. It seems that the use of FeNO as an objective marker for early detection of allergic changes due to exposure to diisocyanates could be more useful than spirometry, but only in non-smokers.

In the current study, the workplace air concentration of diisocyanates was not measured, but analysis for the related diamines in urine from the exposed and control groups indicated the presence of 4,4´-MDI at the workplace, as the concentration of 4,4´-MDA in the exposed group was significantly higher than in the control groups. It shows the significance of regular BET for

Table 4. *Analysis of diamines from urine in exposed and control group (N = 35)*

Parameter	Unit	Exposed group (n = 26) Mean ± CI	Control group (n = 9) Mean ± CI	p-value
1,6-HDA	μg/l	0.59 ± 0.36	1.4 ± 1.9	0.381
2,6-TDA	μg/l	0.063 ± 0.019	0.026 ± 0.014	0.003
2,4-TDA	μg/l	0.041 ± 0.011	0.0193 ± 0.00474	0.001
IPDA	μg/l	0.153 ± 0.027	0.16 ± 0.12	0.862
1,5-NDA	μg/l	0.0134 ± 0.0060	0.0037 ± 0.0023	0.004
4,4´-MDA	μg/l	1.73 ± 0.66	0.071 ± 0.035	< 0.001
1,6-HDA	μg/g creatinine	0.40 ± 0.20	1.2 ± 1.3	0.219
2,6-TDA	μg/g creatinine	0.047 ± 0.012	0.073 ± 0.087	0.535
2,4-TDA	μg/g creatinine	0.032 ± 0.010	0.042 ± 0.041	0.617
IPDA	μg/g creatinine	0.135 ± 0.043	0.30 ± 0.26	0.206
1,5-NDA	μg/g creatinine	0.0069 ± 0.0021	0.0047 ± 0.0028	0.277
4,4´-MDA	μg/g creatinine	0.94 ± 0.24	0.092 ± 0.039	< 0.001

1,6-HDA – 1,6-hexamethylene diamine; 2,6-TDA – 2,6-toluenediamine; 2,4-TDA – 2,4-toluene diamine; IPDA – isophorone diamine; 1,5-NDA – 1,5-naphthalene diamine; 4,4´-MDA – 4,4'-methylenediphenyl diamine

The coverage (confidence) intervals (CI) were calculated on the level of significance $\alpha = 0.05$.

the monitoring of workplace exposure, which is also reported by other authors (17). The detection of diisocyanate metabolites is possible not only in the urine but also in the plasma (18). However, for widespread monitoring, the use of urine is more convenient for employees. A finding of non-zero levels of diamines in the control group of office workers most likely does not indicate an occupational exposure but background levels of environmental origin. We also found similar levels of diamines in another group of controls not related to the factory. Moreover, background levels of diamines (4,4´-MDA: median 0.2 µg/l, 95th percentile 0.4 µg/l) in occupationally unexposed workers were also reported in a Swedish study (19).

The occurrence of isocyanates in the workplace environment means the possibility of sensitisation to these agents in some employees. Not only the airways but also the skin are the main routes for the sensitisation (4). The protection of airways was requested in the most exposed sites in the factory. Despite this, some employees did not wear gloves when manipulating the glue in a "cold" form when they were repairing the machine or changing the barrel.

CONCLUSIONS

We found out in our study that the majority of the subjects working with isocyanates exhibited some type of breathing or allergic symptoms (dyspnoea, cough, and/or rhinitis). Despite these health problems, these people continue to work in a hazardous environment and the possibility of worsening of their problems is still increasing. The regular check-ups performed by occupational physicians, which include only the medical history, physical examination and spirometry are not sensitive enough to reveal the initial allergic symptoms. Very often, the employees dissimulate during the regular examination, because they do not want to lose their job. More sensitive objective methods, such as FeNO, could help to identify subjects with initial allergic symptoms and send them for other specific allergological and pneumological examinations. The regular use of the BET (by urine analysis) can also be a useful tool to reveal subjects at higher risk for possible sensitisation because they have a higher exposure.

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Conflict of Interests

None declared

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