

Associations of Symptoms Related to Isocyanate, Ureaformol, and Formophenolic Exposures with Respiratory Symptoms and Lung Function in Coal Miners

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The respiratory effects of diphenylmethane diisocyanate (MDI)-based resins and ureaformol- and formophenolic-based resins, used in coal mining, are unknown. This cross-sectional study of 354 miners evaluated respiratory health in miners with MDI-related symptoms (IS) and ureaformol/formophenolic-related symptoms (UFS). The protocol included clinical examination, chest radiograph, questionnaire on respiratory symptoms, smoking habit, job history, resin handling, and spirometry. Resin handling concerned 27.7% of the miners. IS affected 5.6%, and 1.4% also after work. UFS affected 22.6%, and 2.3% also after work. Wheezing affected 35.6%; chronic cough, expectoration, or bronchitis about 10%; dyspnea 5.4%; and asthma 2.8%. The miners with UFS had significantly more frequent chronic cough, expectoration, chronic bronchitis, dyspnea, and wheezing, whereas those with IS at and after work had markedly lower FVC, FEV₁, MMEF, FEF_{50%}, and FEF_{25%}. These findings raise the possibility of deleterious effects of exposures to MDI and ureaformol/formophenolic resins on respiratory health and lung function in coal miners during their working life. *Key words:* 4,4'-diphenylmethane diisocyanate; ureaformol; formophenolic; respiratory symptoms; lung function.

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Diphenylmethane diisocyanate (MDI)-based resins and ureaformol and formophenolic-based resins have been used to maintain grounds, construct dams, and prevent rock falls since 1978 in the Lorraine coal mines (15,400 miners) in northeastern France. The effects of occupational exposures to MDI and formaldehyde in some industries (manufacture of polyurethane products, car industry, wood-product manufacturing, manufacture or use of

formaldehyde, strand board manufacture) and occupations (plywood workers, painters, embalmers, etc.) include allergic contact dermatitis, skin and respiratory tract irritation, immune sensitization and asthma, hypersensitivity pneumonitis, respiratory symptoms, decreased lung function, nasopharyngeal cancers, and leukemia.¹⁻¹⁰ A worker can develop allergic contact dermatitis after recurrent exposures over months to a few years, and once sensitized, the individual can develop asthmatic attacks in response to very low levels of exposure.¹¹ The symptoms can persist after work.³ As MDI is a less volatile diisocyanate, skin contact may be a major route of exposure, and this can induce isocyanate sensitization.² As a more lipophilic isocyanate, MDI may penetrate biological barriers more easily, thus reaching biologically susceptible sites faster than the less lipophilic isocyanate.⁵ The effects of MDI on health have been observed at concentrations near or lower than threshold values.¹² Inhalation of formaldehyde mainly induces internal cytotoxicity and affects the upper respiratory tract due to its high hydro-solubility.

In the Lorraine coal mines, about a fourth of the miners at face handled resins. Levels of exposures to MDI differed between various work places and between the various tasks of the miners. At levels of exposure to MDI below threshold values¹² and with intermittent (<100 working days a year) exposures to ureaformol and formophenolic, related symptoms such as asthma and allergic contact dermatitis have been observed.¹³ In coal miners who experience respiratory symptoms and alterations in lung function,^{14,15} chronic exposures to MDI and ureaformol and formophenolic resins may worsen these diseases. The risk may be higher among the workers with isocyanate-related symptoms (IS) and those with ureaformol/formophenolic-related symptoms (UFS). An understanding of the impacts of MDI and ureaformol/formophenolic exposures may be useful when designing preventive measures, and for occupational physicians who are treating exposed miners. However, there has been no epidemiologic study in coal miners, and no study of intermittent exposures. Most studies have focused on workers with persistent exposures. Furthermore, coal miners are exposed to coal dust and underground environments. The present study evaluated respiratory symptoms,

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chronic bronchitis, asthma, and lung function in miners with IS or UFS.

MATERIALS AND METHODS

When this study was performed, the Houillères du Bassin de Lorraine, in northeastern France, employed 10,046 underground miners and 5,371 surface workers. Among the underground miners, about 2,500 worked at the face of the mine, and about 1,500 were aged 33 to 47 years old, and had worked for ten years or more at the mine face. Standard high-kilovoltage posteroanterior and lateral chest films at maximum inspiration were made for each worker every two years at the worker's yearly medical examination. These films were routinely read by the collieries' occupational physicians, who were trained to grade small opacities according to the ILO classification.¹⁶

Of the 1,500 previous miners, about 1,430 had normal radiographs according to ILO criteria¹⁶ (70 workers had radiographs classified 0/1+; about 100 workers among all the miners of the firm). The sample studied included 395 workers randomly selected among the latter miners. Subjects were limited to those in the age group 33–47 years for two reasons: a sufficient exposure duration was needed, and the miners are retired after 48 years of age. The study took place in 1996–1997. Miners who had pneumoconiosis were excluded because they were not employed for resin handling or in workplaces with resin exposures. The subjects were contacted by the research team, which included researchers, chest specialists, epidemiologists, and occupational physicians.

Three types of resins were used in the mining operation: formolphenolic resins, obtained by polycondensing phenol and formol; urea-formol resins, obtained by polycondensing formol and urea, and polyurethane resins. The resins were handled by the miners at the face of the mine only. The higher levels of exposure were from direct contacts during transport, preparing and injecting the resins, and maintenance of materials for injection. The MDI-based resins were injected in ventilated work places whereas ureaformol and formophenolic-based resins were injected in spaces with little ventilation (to avoid heating and conflagration due to the presence of air and oxygen). Each injection procedure lasted 30 minutes, and the workers were at the injection sites during this task only.

The protocol consisted of: 1) a clinical examination; 2) a chest radiograph; 3) elicitation of demographic characteristics (date of birth, height, weight, etc.), respiratory symptoms, and smoking habit, using the questionnaire of the European Steel and Coal Community (ESCC)¹⁷; 4) determination of job activities performed, and isocyanate, ureaformol, and formophenolic exposures (defined as the total number of resin-handling days); 5) isocyanate-related symptoms (IS) and urea-

aformol- and formophenolic-related symptoms (UFS) observed at and outside of work: allergic disorders caused by direct contacts (during transport, preparing of the resins and their injection, and maintenance of materials for injection) (for eye, face, hand, arm, thorax, other locations); fume-related irritation (throat irritation, chest oppression, breathing difficulties, wheezing); allergic symptoms (eczema, rhinitis, conjunctivitis, asthma); headache; vertigo; sick feeling; nausea (this questionnaire was administered to all the participants in the study); and 6) spirometry. This protocol was administered during a day when the miner did not work (but the day was treated as a normal working day so that the worker did not lose income) because of the time needed. Air concentrations at some work places during and after injections were regularly measured (but not for every injection). Cumulated dust exposure was calculated with the method proposed by Attfield and Moring¹⁸ for each miner from the miner's job history and from dust measurements at various sites of the coal mine. The estimates were defined by the summations of dust measurements (mg/m^3) for the times spent in various workplaces. Cumulative dust exposure was calculated until June 1996 and expressed as milligrams of dust per cubic meter multiplied by years exposed ($\text{mg}/\text{m}^3 \times \text{yr}$).

Spirometric measurements were made with the computerized spirometer based on a Fleisch No. 3 pneumotachograph (Spiromatic; L. Martin, Paris, France). Each subject, in the sitting position and with the nose obstructed, generated three valid flow-volume curves (with the control curve on the screen showing the shape of the curve, and a difference in vital capacity [VC] of less than 5%). From the envelope curve, i.e., the composite curve obtained by superimposing the curves at their starting point, or full inspiration, we calculated FVC, FEV_1 , maximum midexpiratory flow (MMEF), and maximal expiratory flows at 50% and 25% of VC ($\text{FEF}_{50\%}$ and $\text{FEF}_{25\%}$, respectively).¹⁹

All the protocol procedures and measurements were done at the occupational medicine center over four months, by trained chest specialists-researchers,¹⁴ except for administering the questionnaire on jobs and isocyanate, ureaformol, and formophenolic exposures, which was done by two persons who had participated in several epidemiologic studies and who were familiar with conditions in the coal mines and resin-related disorders.

The study protocol was approved by the National Ethics Committee for Medical Research of France. All the subjects had given prior written consent to participate.

Statistical Analysis

To compare the IS workers or the UFS workers with symptom-free subjects for respiratory symptoms, asthma, and chronic bronchitis, we used the chi-square independence test, crude relative risk, and relative risk

TABLE 1 Prevalences of Isocyanate-, and Ureaformol/Formophenolic-related Symptoms (n = 354)

	Isocyanate-related Symptoms (%)			Ureaformol/Formophenolic-related Symptom (%)		
	At Work Only	Both at and Out of Work	Total	At Work Only	Both at and Out of Work	Total
Any symptom	4.2	1.4	5.6	20.3	2.3	22.6
Allergic direct contact	1.1	0.8	2.0	4.0	0.3	4.2
Eye and face	0.3	0.6	0.8	2.3	0.3	2.6
Hand and arm	0.6	0	0.6	1.7	0	1.7
Other locations	0.3	0.3	0.6	0	0	0
Fume-related irritation	1.7	0.3	2.0	6.5	0.6	7.1
Throat irritation	0.6	0	0.6	3.1	0	3.1
Chest oppression	1.1	0	1.1	2.0	0.3	2.3
Other irritations	0	0.3	0.3	1.4	0.3	1.7
Allergic symptoms*	0.6	0.3	0.8	2.3	1.4	3.7
Eczema	0.3	0.3	0.6	0.8	1.4	2.3
Rhinitis	0	0	0	0.3	0	0.3
Conjunctivitis	0.3	0	0.3	0	0	0
Others	0	0	0	1.1	0	1.1
Headache	0.8	0	0.8	4.8	0	4.8
Vertigo, sick feeling, nausea	0	0	0	4.0	0	4.0

*No asthma was observed.

adjusted for age (± 5 years), tobacco consumption (± 5 pack-year), and cumulated dust exposure (± 10 mg-year/ m^3), with the Mantel-Haenszel test. Relationships between lung function and IS or UFS were assessed using the multiple linear regression model, taking into account age, height, tobacco consumption, and cumulated dust exposure. All the analyses were made via the Stata program (Stata Corporation: Stata Statistical Software: release 5.0. 702 University Drive East, College Station, Texas: Stata Corporation, 1997).

RESULTS

The sample included 354 participants (participation rate 90%). Mean (SD) age of the subjects was 39.2 ± 3.5 years (range 33–48 years), mean height 1.75 ± 0.06 m (range 1.58–1.90 m), mean weight 82.2 ± 11.8 kg (range 49–128 kg), mean duration of work underground 18.7 ± 3.8 years (range 12–31 years), mean cumulated dust exposure 48.3 ± 19.7 mg-year/ m^3 (range 18–138 mg-year/ m^3). The current smokers and ex-smokers represented 40.0% and 34.8%, respectively; average tobacco consumption was 9.3 ± 8.8 pack-years (range 0–40 pack-years).

The MDI concentrations measured at some workplaces during and after injections were rather small: about 0.00005 ppm, lower than $0.8 \mu\text{g}/\text{m}^3$, which is the detection limit in air samples (the eight-hour time-weighted average [TWA]) is 0.01 ppm in France, and the ten-hour TWA is 0.005 ppm in the United States¹²). This would be due to the humidity of the coal mine atmosphere (95%), the temperature (26° Celsius), and the ventilation ($25 \text{ m}^3/\text{s}$). For phenol, air concentrations generally were lower than 10 ppm, the

threshold limit value (TLV) ceiling in France (the eight-hour TWA is 5 ppm in France¹²), although some higher peaks had been observed. For formaldehyde, air concentrations frequently exceeded the TLV ceiling (1 ppm in France), with an average value of 2 ppm at resin-handling workplaces (maximum 2.6 ppm in 1997), but the means of concentrations measured with personal dosimetry badges (Dräger Biocheck F) during working days with resin handling were between 0.4 and 0.7 ppm (the eight-hour TWA is 0.5 ppm in France and the TLV is 0.3 ppm in the United States^{12,20}).

Of the group of miners studied, 19.7% handled MDI-based resins (9.0% for 1–49 days and 10.7% for ≥ 50 days), and 25.1% had been exposed to ureaformol/formophenolic-based resins (12.4% for 1–49 days and 12.7% for ≥ 50 days). The maximum was 100 working days a year, and 900 working days during the whole period of resin use in the firm (1978–1996). The prevalence of wheezing was 35.6%, chronic expectoration 11.0%, chronic cough 10.2%, chronic bronchitis 8.2%, dyspnea stage ≥ 1 5.4%, and asthma 2.8%. Regarding lung function, no decreased values were found for FVC ($104.9 \pm 12.4\%$ predicted), FEV_1 ($101.1 \pm 13.4\%$ predicted), and FEV_1/FVC ($99.1 \pm 7.4\%$ predicted), whereas MMEF ($84.4 \pm 24.4\%$ predicted), $\text{FEF}_{50\%}$ ($88.8 \pm 26.9\%$ predicted) and $\text{FEF}_{25\%}$ ($73.0 \pm 27.1\%$ predicted) had clearly reduced values.

Table 1 shows that the IS affected 5.6% of the miners (21.1% of those who had handled resins ≥ 50 days, 6.2% who had handled them 1–49 days, and 3.5% of the others), and 1.4% of them also experienced these symptoms after work. The symptoms observed were allergic direct contact-related disorders (2.0%), fume-related irritation (2.0%), and allergic symptoms (0.8%). The

UFS affected 22.6% of the miners (53.3% of those who had handled resins ≥ 50 days, 34.1% of handling them 1–49 days, 15.9% of the others), and 2.3% of them had these symptoms both at and after work. The symptoms were allergic direct contact-related disorders (4.2%), fume-related irritation (7.1%), allergic symptoms (3.7%, eczema 2.3%), headache (4.8%), and vertigo, sick feeling, or nausea (4.0%).

The miners who suffered from UFS had a significantly higher prevalence of chronic cough, chronic expectoration, chronic bronchitis, dyspnea, and wheezing (adjusted relative risk between 2.16 and 3.60, vs the subjects with both no IS and no UFS) unlike those with IS (Table 2). It should be noted that there were few subjects who were markedly exposed to both MDI and ureaformol/formophenolic. Among the 80 subjects with UFS and 20 subjects with IS, only three had experienced both IS and UFS.

Table 3 shows that the subjects who suffered from IS both at and after work had markedly lower values for FVC, FEV₁, MMEF, FEF_{50%}, and FEF_{25%}, unlike those with UFS. Expectedly, the relationships of age, tobacco consumption, and dust exposure with lung function were confirmed.

DISCUSSION

The results of the study show that IS and UFS affected a high proportion of coal miners, that UFS was associated with respiratory symptoms and chronic bronchitis, and that the subjects who had IS both at and outside of work had altered lung function. Nearly all of the miners who had handled these resins experienced IS or UFS, and although the symptoms did not generally persist for a long time after working, a great proportion of miners suffered both during and outside of work. Similar IS and UFS were observed in the other studies.^{9,21} It should be noted that the participation rate of the subjects was high. Our findings provide new data for the coal mine setting with particular working conditions and environment.

Among the 72% of the workers studied who reported never working directly with the resins, some reported IS or UFS. This was in fact expected, as Petsonk et al. observed in job activities that required the workers to travel throughout the exposed areas (maintenance for instance) were also at risk.¹⁰ It should be noted that no asthma-like symptom due to resin handling was observed among the miners studied. During the years 1980–1986 some asthma-like symptoms had been diagnosed because of exposures to higher concentrations, but none has been observed since 1987 due to specific protective measures.

The miners with IS both at and outside of work had noticeably decreased FVC, FEV₁, MMEF, FEF_{50%}, and FEF_{25%}, i.e., altered vital capacity and obstructive syndrome, independently of tobacco consumption and

dust exposure, in a mine setting where the MDI concentration was rather small. Although their exposures had been intermittent, these miners had a high exposure level: they had handled the MDI-based resins on more than 700 working days during their employment in the mines. Thus, our study shows that recurrent exposures to small MDI concentrations resulted in marked alterations in vital capacity and expiratory flows. These results were consistent with those of others.²² However, the exposure level in workplace air may be underestimated when using concentration measurements. Herbert et al. found FEV₁/FVC to be decreased in production workers of a plant producing oriented strand board from aspen and balsam wood, who were simultaneously exposed to MDI-based resins (MDI air concentrations between 0.001 and 0.003 ppm), formophenolic-based resins (air concentrations 0.05 ppm or less), and respirable wood dust (air concentrations 0.05 to 0.50 mg/m³), compared with the control group; the exposed workers experienced more frequent respiratory symptoms (especially dyspnea and wheezing), and there were significant associations between these symptoms and decreased FEV₁.⁵ Kaaria et al. observed that, during molding of rigid polyurethane foam, the MDI concentrations were below the limit of detection in most (64%) of the air samples collected in the worker's breathing zone, and they suggested that monitoring of urinary 4,4'-methylenedianiline would be an appropriate method of assessing MDI exposures in work environments with low or undetectable MDI concentrations in air.²³ Petsonk et al. reported that an increased effect of MDI on asthma-like symptoms was observed in individuals working with and having a high exposure levels for MDI among non-smokers, and more markedly among smokers, but not in workers entering MDI areas. They also found a significantly decreased FEV₁ in workers with asthma-like symptoms.¹⁰ Jakobsson et al. reported that presently active pipelayers with recent high levels of MDI-based polyurethane exposure showed a significant reduction in FEV₁ compared with controls.²⁴ Litorin et al. found an association between spraying of glue containing MDI or HDI, but not glue using, and a slight reduction of lung function, while surprisingly FEV₁ was slightly improved among the workers with work-related symptoms.³ It should be noted that in the latter study³ lung function was measured during work days in the factory, while in our study it was measured during days when the miners did not work. Possibly, dust exposure may increase the vulnerability of coal miners. Our study did not find an association between the IS and respiratory symptoms. This result would be explained by the fact that the miners studied had not been exposed daily and the MDI concentrations had been small. Similar results have been reported from other studies of workers with low levels of exposure,^{22,25–27} contrary to other studies that have shown

TABLE 2 Relationships of Isocyanate-related Symptoms and Ureaformol/Formophenolic-related Symptoms with Respiratory Symptoms, Chronic Bronchitis, and Asthma

	Symptom-Free Subjects ^a (n = 257)		Subjects with Isocyanate-related Symptoms (IS, n = 20)		Subjects with Ureaformol/Formophenolic-related Symptoms (UFS, n = 80)	
	(%)	(%)	Crude RR, 95% CI	Adjusted RR ^b , 95% CI	Crude RR, 95% CI	Adjusted RR ^b , 95% CI
Chronic cough	9.8	15.0	1.63	0.45-5.95	2.64†	1.36-5.14
Chronic expectoration	12.1	10.0	0.81	0.18-3.64	1.93*	1.00-3.71
Chronic bronchitis	7.4	5.0	0.66	0.08-5.17	2.38*	1.17-5.17
Dyspnea stage 1 or over	4.7	5.0	1.07	0.13-8.68	2.86*	1.19-6.90
Wheezing	26.2	25.0	0.94	0.33-2.69	1.94†	1.15-3.27
Asthma	1.6	0.0	(1)	(1)	2.42	0.53-11.1
					3.7	2.63

*p < 0.05, †p < 0.01, ‡p < 0.001.

^aWith no isocyanate- or ureaformol/formophenolic-related symptoms.

^bAdjusted for age (5 years), tobacco consumption (5 pack-years), and cumulative dust exposures (10 mg-year/m³), with the Mantel-Haenszel test. RR = relative risk. In bold type: prevalence significantly different from that for symptom-free subjects (chi-square independence test).

‡(1) Not computable. There were three subjects in both IS and UFS groups.

TABLE 3 Associations of Isocyanate-related Symptoms and Ureaformol/Formophenolic-related Symptoms with Lung Function: Regression Coefficient ± SD

	FVC (L)	FEV ₁ (L)	FEV ₁ /FVC (%)	MMEF (L)	FEF _{50%} (L/s)	FEF _{25%} (L/s)
Age (years)	-0.039† ± 0.0090	-0.035† ± 0.0080	NS	-0.034* ± 0.017	NS	-0.028† ± 0.0092
Height (m)	7.02‡ ± 0.53	4.63‡ ± 0.46	-17.4‡ ± 5.12	1.89* ± 0.94	2.95* ± 1.18	NS
Tobacco consumption (pack-years)	-0.0066§ ± 0.0037	-0.011† ± 0.0032	-0.14† ± 0.035	-0.029† ± 0.0065	-0.038† ± 0.0081	-0.014‡ ± 0.0036
Cumulative dust exposure (mg-years/m ³)	NS	NS	-0.054‡ ± 0.015	-0.0076† ± 0.0029	-0.011† ± 0.0036	-0.0033* ± 0.0016
Isocyanate-related symptoms						
At work only (n = 15)	NS	NS	NS	NS	NS	NS
Both at and outside of work (n = 5)	-0.62* ± 0.26	-0.62* ± 0.26	NS	-1.23† ± 0.46	-1.39* ± 0.59	-0.63* ± 0.25
Ureaformol/formophenolic-related symptoms						
At work only (n = 72)	NS	NS	NS	NS	NS	NS
Both at and out of work (n = 8)	-0.12§ ± 0.071	NS	NS	NS	NS	NS
Intercept	-5.81‡ ± 0.031	-2.72‡ ± 0.027	113.8‡ ± 0.30	2.40‡ ± 0.055	0.22† ± 0.070	3.01‡ ± 0.030
Explained variance	40%	34%	10%	14%	12%	12%

*p < 0.05, †p < 0.01, ‡p < 0.001, §NS but with p < 0.09.

Note: All factors presented in this table were included in the multiple linear regression model. Weight had a nonsignificant regression coefficient for all variables.

increased respiratory symptoms.^{7,28} These discrepancies could be explained by the fact that the types and levels of exposures and the categories of workers were different. It may be noted that the well-known effects of age, dust exposure, and tobacco consumption on lung function¹⁵ were confirmed in the present study.

Another important finding is that UFS affected most ureaformol/formophenolic-based resin handlers, and the symptomatic subjects had markedly more frequent chronic cough, expectoration, bronchitis, dyspnea, wheezing, and asthma (adjusted relative risks between 2.16 and 3.60). It appeared that the subjects with UFS had higher frequencies for all respiratory symptoms, chronic bronchitis, and asthma. This would be explained by the strong associations between these disorders. These results were expected, as the air concentrations of the hazardous substances were rather high. Our results were consistent with those by other researchers who have shown that chronic inhalation of formol vapors can generate respiratory symptoms,^{5,6,8} and especially respiratory tract irritations, chronic bronchitis, and wheezing.^{9,29} However, no formol-related asthma was observed in our study. The association of formaldehyde exposure and respiratory symptoms is well known, especially when the air concentrations exceed 2 ppm,^{30,31} which they did in the resin-handling areas, although the exposures of workers had been intermittent (maximum 100 working days a year, and 900 working days during the whole period of resin use in the firm). Sensory irritation of the eyes and respiratory tract in response to inhalational exposures to formaldehyde has been reported at 0.08 ppm and above in a human study.³² The inhalation of formaldehyde mainly induces internal cytotoxicity and affects the upper respiratory tract due to its high hydro-solubility, while penetrations at the level of alveoli of the lung are weaker. That may be why no association was found between UFS and altered lung function in our study. Other investigators have also found a nonsignificant impact of formaldehyde on lung function,^{29,33,34} while still others have found alterations in lung function among workers with rather high air concentrations.^{6,21}

CONCLUSION

The present study provides new data concerning the impacts of intermittent exposures to MDI, ureaformol, and formophenolic in coal miners. IS and UFS were frequent among resin handlers and UFS was associated with respiratory symptoms and chronic bronchitis, and persistent IS with altered lung function. These findings show the importance of following up exposed workers, especially those who have respiratory symptoms or altered lung function. Careful control of MDI respiratory-tract exposures is important¹⁰ and appropriate surveillance of the workers, especially by the occupational

physicians, could facilitate more rapid diagnoses and helpful interventions.

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