

Occupational Environmental Medicine

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Lymphohaematopoietic malignancy around all industrial complexes that include major oil refineries in Great Britain

P Wilkinson, B Thakrar, P Walls, M Landon, S Falconer, C Grundy, P Elliott

Abstract

Objectives—To examine the incidence of lymphohaematopoietic malignancy around industrial complexes that include major oil refineries in Great Britain after recent public and scientific concern of possible carcinogenic hazards of emissions from the petrochemical industry.

Methods—Small area study of the incidence of lymphohaematopoietic malignancies, 1974–91, within 7.5 km of all 11 oil refineries (grouped into seven sites) in Great Britain that were operational by the early 1970s and processed more than two million tonnes of crude oil in 1993.

Results—Combined analysis of data from all seven sites showed no significant ($p < 0.05$) increase in risk of these malignancies within 2 km or 7.5 km. Hodgkin's lymphoma, but no other malignancy, showed evidence ($p = 0.02$) of a decline in risk with distance from refineries, but there was an apparent deficit of cases of multiple myeloma near the refineries ($p = 0.04$).

Conclusion—There was no evidence of association between residence near oil refineries and leukaemias, or non-Hodgkin's lymphoma. A weak positive association was found between risk of Hodgkin's disease and proximity to major petrochemical industry, and a negative association with multiple myeloma, which may be chance findings within the context of multiple statistical testing.

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Keywords: small area; lymphohaematopoietic malignancy; oil refineries

Oil refining and other petrochemical processes may lead to low level emissions of compounds with possible carcinogenic potential including benzene¹ and 1,3-butadiene.² A cohort study in the United Kingdom of mortality among oil refinery workers, who would be expected to have higher exposures to these compounds than residential populations, has not shown an excess risk of leukaemia or other haematopoietic malignancy.³ Few studies of cancer risks among residential populations living near to petrochemical industry have been reported. A United States study found high rates of cancer of the lung, nasal cavity and sinuses, and skin among the resident male population in counties where the petroleum industry is most heavily concentrated, but no significant in-

crease for lymphohaematopoietic malignancy.⁴ Another study in the United States suggested high rates of lung cancer near petrochemical plants.⁵ A study of the geographical distribution of childhood leukaemia and other childhood cancers in Great Britain reported a tendency for clustering near emission sources of (among other things) volatile petroleum products,⁶ although the methodology of this study with residential post codes as a proxy for populations had previously been questioned.⁷ A more recent study of the same data set similarly found an association of childhood cancers with emission sources based on comparisons between address at birth and at death.⁸ By contrast, studies of cancer incidence and mortality among residents living close to a petrochemical plant in south Wales were largely reassuring.^{9, 10} We report here a study of lymphohaematopoietic malignancy around all industrial complexes that include major oil refineries in Great Britain.



The seven oil refinery sites. (1) Milkford Haven: three refineries: Elf, Texaco and PCC, and Gulf; (2) Coryton (two refineries: Mobil and Shell); (3) Immingham (two refineries: Lindsey and Conoco); (4) Esso, Fawley; (5) Shell, Stanlow; (6) Phillips Imperial, Teesside; (7) BP, Grange-overlook.

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Table 1 Observed (O) cases, observed/expected (O/E) ratios (95% CI) of lymphohaematopoietic malignancy within 2 km and 7.5 km of industrial complexes that include major oil refineries, and results of Stone's tests

Cell type	0 - 2 km		0 - 7.5 km		Stone's tests	
	O	O/E (95% CI)	O	O/E (95% CI)	Unconditional p	Conditional p
All ages						
All lymphatic and haematopoietic	417	0.95 (0.86 to 1.04)	3827	0.98 (0.95 to 1.01)	0.64	0.51
Multiple myeloma	57	0.74 (0.56 to 0.96)	625	0.89 (0.82 to 0.96)	0.04	0.52
All leukaemias	169	1.06 (0.91 to 1.23)	1446	1.01 (0.96 to 1.07)	0.58	0.78
Lymphoid leukaemias	71	1.00 (0.78 to 1.26)	597	0.94 (0.86 to 1.02)	0.24	0.55
Acute lymphatic leukaemia	27	1.09 (0.72 to 1.59)	197	0.95 (0.82 to 1.09)	0.24	0.17
Chronic lymphatic leukaemia	42	0.99 (0.71 to 1.33)	364	0.91 (0.82 to 1.01)	0.31	0.77
Myeloid leukaemias	81	1.14 (0.91 to 1.42)	666	1.05 (0.98 to 1.14)	0.31	0.38
Acute myeloid leukaemia	44	0.99 (0.72 to 1.33)	420	1.05 (0.95 to 1.16)	0.57	0.50
Chronic myeloid leukaemia	31	1.42 (0.97 to 2.02)	207	1.06 (0.92 to 1.22)	0.25	0.71
Hodgkin's lymphoma	54†	1.01 (0.76 to 1.32)	443	0.97 (0.89 to 1.07)	0.05	0.02
Non-Hodgkin's lymphoma	137	0.92 (0.77 to 1.08)	1313	1.00 (0.94 to 1.05)	0.99	0.77
Ages 0 to 14						
All lymphatic and haematopoietic	25	0.99 (0.64 to 1.46)	180	0.93 (0.80 to 1.08)	0.37	0.12
All leukaemias	19	1.00 (0.60 to 1.56)	138	0.94 (0.79 to 1.11)	0.73	0.38
Lymphoid leukaemias	16	1.08 (0.62 to 1.76)	104	0.91 (0.74 to 1.10)	0.60	0.38
Myeloid leukaemias	2	0.66 (0.08 to 2.38)	22	0.93 (0.59 to 1.41)	0.74	•
Hodgkin's lymphoma	2	0.77 (0.09 to 2.80)	18	0.89 (0.53 to 1.40)	0.07	•
Non-Hodgkin's lymphoma	4	1.15 (0.31 to 2.96)	24	0.91 (0.58 to 1.35)	0.28	•

†Test did not converge because of small numbers

†Includes 1 duplicate registration. Conditional Stone's test for Hodgkin's disease remained significant ($p=0.03$) after its exclusion.

Methods

The study was carried out with the Small Area Health Statistics Unit postcoded health database. It examined cancer risk near all 11 oil refineries in Great Britain, operational by the early 1970s, which processed more than two million tonnes of crude oil in 1993. They were grouped into seven sites of one to three refineries (figure). Each was treated as an extended emissions source. The incidence of lymphohaematopoietic malignancy was examined in eight bands around refinery perimeters with outer limits at 0.5, 1, 2, 3, 4.5, 5.6, 6.6, and 7.5 km. For descriptive purposes cancer incidence was also examined at 0-2 km and 0-7.5 km.

The following diagnostic groups of the international classification of diseases 8th (ICD-8) and 9th (ICD-9) revision were studied for all ages and 0-14, 15-64, and ≥ 65 age groups: lymphatic and haematopoietic malignancy (ICD-8 200-207; ICD-9 200-208, 238.6); multiple myeloma (ICD-8 203; ICD-9 203, 238.6) (not separately examined for the 0-14 age group); non-Hodgkin's lymphoma (ICD-8 and 9 200,202); Hodgkin's lymphoma (ICD-8 and 9 201); all leukaemias (ICD-8 204-207; ICD-9 204-208); lymphoid leukaemia (ICD-8 and 9 204); and myeloid leukaemia (ICD-8 and 9 205). Acute and chronic subdivisions of the last two were examined for all ages.

Cancer incidence was studied for all years for which national cancer registration data were available: 1974-89 for England and Wales and

1975-91 for Scotland. Population counts by band around each site were estimated from census small area statistics with the 1981 census for years up to and including 1986, and the 1991 census thereafter. Expected (E) numbers of cancer registrations were calculated by year and band from annual rates in Great Britain stratified by 5 year age group, sex, and quintile of the Carstairs deprivation index to adjust for possible socioeconomic confounding. Rates were further adjusted with disease specific standardised regional registration ratios. Because of the disparity in years for which cancer registration data were available, national rates for 1974 were computed from 1974 registrations for England and Wales and 1975 registrations for Scotland; and 1990 and 1991 rates were computed from 1989 registrations for England and Wales and those for the relevant year in Scotland.

Formal hypothesis tests were based on the maximum likelihood ratio test of Stone.¹⁴ This gives a test of decline in risk with distance against a null hypothesis of constant risk in all the bands. As Stone's unconditional test can be significant either where there is a decline in risk with distance or where the relative risk in at least one of the bands does not equal 1.0, we also carried out a conditional test. This specifically tests for decline in risk¹⁴ and consequently is the test of primary interest. Significance values were based on Monte Carlo methods using 999 simulations. Results from the seven industrial sites were combined by pooling the likelihood ratios from each one and comparing their sum with values obtained from simulated data.

Results

Results are presented here at all ages and for both sexes combined, and at ages 0-14 years. Age specific results, and results for each of the seven grouped industrial sites, are available on request. Over all refinery sites combined, there were 417 cases (439.9 expected) of lymphohaematopoietic malignancy within 2 km of an oil refinery (observed/expected (O/E) ratio

Table 2 Observed (O) cases and observed/expected ratios (O/E) by distance from refinery sites: all ages

Outer radius of band (km)	Multiple myeloma		All leukaemias		Hodgkin's lymphoma		Non-Hodgkin's lymphoma	
	O	O/E	O	O/E	O	O/E	O	O/E
0.5	4	0.46	14	0.74	14*	2.18	14	0.81
1	8	0.58	25	0.84	7	0.66	23	0.81
2	45	0.82	130	1.17	33	0.91	100	0.96
3	55	0.83	137	0.99	43	0.93	116	0.92
4.5	103	0.79	275	1.02	101	1.11	250	1.02
5.6	128	0.87	316	1.07	88	0.96	276	1.01
6.6	147	1.03	279	0.96	81	0.88	278	1.02
7.5	135	0.99	270	0.99	76	0.94	256	1.02

*Includes 1 duplicate registration, exclusion of which reduces the O/E ratio within 0.5 km to 2.02

0.95, 95% confidence interval (95% CI) 0.86 to 1.04); and 3827 cases (3902.4 expected) within 7.5 km (O/E 0.98, 95% CI 0.95 to 1.01, table 1). None of the age and cell type specific subgroups separately examined showed a significant increase in risk within 0–2 km or 0–7.5 km. The conditional Stone's test for Hodgkin's lymphoma, uncorrected for multiple testing, suggested a decline in risk ($p=0.02$) with distance from the sites, almost entirely due to an excess within 0.5 km (14* observed cases, 6.43 expected, table 2). None of the conditional Stone's tests for other malignancies (including Hodgkin's and non-Hodgkin's lymphoma combined) suggested a decline in risk with distance from the sites (tables 1 and 2). The significant ($p=0.04$) unconditional Stone's test for multiple myeloma at all ages reflected a deficit of these cancers from 0–7.5 km.

Discussion

Except for Hodgkin's disease, our study provides no evidence to suggest that populations living close to industrial complexes that include large oil refineries in Great Britain have an increased risk of lymphohaematopoietic malignancy. This is consistent with the findings of broad scale studies of lymphatic and haematopoietic malignancy in areas containing petroleum works in the United States¹⁵ and with occupational studies of oil refinery workers in the United Kingdom.¹ Although some studies have reported excesses of leukaemia in refinery workers,^{16,17} a recent overview of cohort studies from the United Kingdom and North America suggests no excess for cell type specific leukaemias,¹⁸ and oil refining probably contributes little to environmental levels of benzene and other petroleum products.¹⁹

The decline in risk with distance from oil refineries for Hodgkin's disease must be viewed in the context of multiple testing and the general tendency of Hodgkin's disease to cluster.²⁰ That benzene might be a contributory factor in Hodgkin's disease has been hypothesised by Aksoy *et al*,²¹ and there have been reported associations of Hodgkin's disease with occupation in the chemical industry,²² with other occupations entailing handling of chemicals,^{23–25} and with exposure to diesel exhaust.²⁶ However, none of these studies provides direct evidence relating to the petrochemical industry. In our study, there was a twofold risk of Hodgkin's disease (14 cases) within 0.5 km of refineries, and it is this which accounts for the positive Stone's test. This is compatible with a highly localised environmental hazard, although the risk within 2 km was almost identical to the regional expectation, and it was fractionally below expectation within 7.5 km. There was an unexplained deficit of cases of multiple myeloma within 7.5 km.

*Checks on a sample of cases revealed a duplicate registration of Hodgkin's disease in the 15–64 year age-band within 0.5 km of a refinery. After exclusion of this duplicate the O/E ratio for Hodgkin's disease (all ages) within 2 km was 0.99 (95% CI 0.74–1.30); the conditional Stone's test remained significant ($p=0.03$).

Limitations to the interpretation of the study are imposed by several factors including lack of exposure information. Measurements of volatile organic compounds, including benzene, near petrochemical plants have been made previously.^{27,28} For example, near the Baglan Bay plant,⁹ most of the measurements were <5 ppb,²⁸ and with exposure to low concentrations of ambient benzene there is great uncertainty about the possible cancer risks.²⁹ Other factors limiting interpretation include the small area (ecological) nature of the study, uncertainties about population estimates for years between the census years and migration, and possible unmeasured confounding factors. The results cannot reliably be interpreted for specific cell types and age groups at individual sites, given the reliance on routine data sources and the fact that this would depend on multiple and non-independent analyses of subgroups, each with limited statistical power.

Overall the study is estimated to have had 80% power to detect an excess of around 11% in lymphohaematopoietic malignancy at the 5% level within 2 km of refineries. We conclude that within the limitations of the small area approach based on routine data sources, there was no significant evidence of association between residence near to industrial sites containing major oil refineries and leukaemias or non-Hodgkin's lymphoma, and there was a negative association with multiple myeloma. Weak evidence of a positive association with Hodgkin's disease needs to be considered within the context of there being little, if any, other epidemiological evidence specifically relating Hodgkin's disease with the petrochemical industry.

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Correspondence and editorials

Occupational and Environmental Medicine welcomes correspondence relating to any of the material appearing in the journal. Results from preliminary or small scale studies may also be published in the correspondence column if this seems appropriate. Letters should be not more than 500 words in length and contain a minimum of references. Tables and figures should be kept to an absolute

minimum. Letters are accepted on the understanding that they be subject to editorial revision and shortening.

The journal also publishes editorials which are normally specially commissioned. The Editor welcomes suggestions regarding suitable topics; those wishing to submit an editorial, however, should do so **only** after discussion with the Editor.

Biological monitoring to assess exposure from use of isocyanates in motor vehicle repair

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Abstract

Objectives—To develop a method for the measurement of a metabolite of hexamethylene diisocyanate (HDI), an isocyanate, and use it to assess the exposure of sprayers employed in motor vehicle repair shops.

Methods—Urine samples were taken from sprayers wearing personal protective equipment and spraying in booths or with local exhaust ventilation, from bystanders, and from unexposed subjects. Samples were analysed for a metabolite of HDI, hexamethylene diamine (HDA), by gas chromatography-mass spectrometry (GC-MS).

Results—HDA was detected in four sprayers and one bystander out of 22 workers. No HDA was detected in the urine of unexposed subjects.

Conclusions—Exposure to isocyanates still occurs despite the use of personal protective equipment and the use of a booth or extracted space. Health surveillance is likely to be required to provide feedback on the adequacy of controls even if such precautions are used and to identify cases of early asthma. Biological monitoring can provide a useful additional tool to assess exposure and the adequacy of controls in this group of exposed workers.

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Keywords: isocyanate; health surveillance; biological monitoring

Isocyanates are highly reactive chemicals used in two component spray paints, adhesives, and in the manufacture of polyurethanes. They may also be released during cutting and welding of materials. Isocyanates are the commonest identified cause of occupational asthma in national and regional reporting schemes with the job title "spray painter" being the most commonly specified job.

Various methods have been reported for the measurement of isocyanates in air and there has been considerable effort to improve the reliability of these methods. However, problems still remain. As control of exposure usually relies on air fed full face respirators, overalls, and gloves and the use of ventilated booths or ventilated spaces, air monitoring will give no indication of the actual exposure a worker receives. The efficacy of such measures to prevent exposure, subsequent sensitisation, and the development of occupational asthma is not well established. Biological monitoring has

the potential to measure a worker's body burden received by all routes of exposure (oral, inhalation, and dermal).

Because of the frequency of occupational asthma in this group, workers using isocyanates are required to undergo health surveillance unless the risk assessment carried out under the Control of Substances Hazardous to Health Regulations 1994 (COSHH) draws the conclusion that there is little or no risk to their health from their workplace activities.

Several studies have reported that dermal contact with isocyanates can induce respiratory symptoms in animals^{5,6} indicating that isocyanates may be dermally absorbed and biological monitoring has been used to study dermal absorption in humans. Whether dermal absorption, if it occurs in humans, has any potential to lead to respiratory sensitisation is also unknown. Being able to estimate exposure to isocyanates through the development of a urinary assay for metabolites may be a useful way of assessing exposures by respiratory or dermal contact and the effectiveness of control measures.

1,6-Hexamethylene diisocyanate (OCN(CH₂)₆NCO, (HDI)) is widely used in two component spray paints by the motor vehicle repair industry and is finding increasing use as a replacement for toluene diisocyanate. Most HDI prepolymer based car paints contain a complex mixture of HDI monomers, polymers, HDI biuret, etc, but still contain small amounts of free HDI (0.5%-1%).

1,6-Hexanediamine (HDA) has been detected in the urine (after hydrolysis) of car spray painters who use HDI based spray paints, and there have been several published methods for the analysis of HDA in urine.¹⁰⁻¹⁵ Most of the published methods use acid hydrolysis with concentrated (≥ 6 M) hydrochloric acid.¹²⁻¹⁴ Other studies have used either alkaline or acid hydrolysis, reporting slightly better recoveries for the alkaline hydrolysis. We have studied both hydrolysis techniques but have persevered with the acid hydrolysis in line with most other researchers. Use of alkaline hydrolysis gave inconsistent results and variable, sometimes high, blank values. These problems were not encountered with acid hydrolysis. The free HDA is then derivatised and analysed, usually, by gas chromatography-mass spectrometry (GC-MS).

Materials and methods

SAMPLING STRATEGY

Consent for the study was obtained from the Health and Safety Executive (HSE) research ethics committee.

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Five motor vehicle repair shops that use isocyanate paints were identified by an inspector from the HSE through routine visiting and local knowledge. They consisted of two national dealerships that employ full time paint sprayers and three smaller garages (two of which had a single owner who carried out intermittent spraying, and the third, which had employees who sprayed and did other work). All followed published HSE guidance in wearing full face air fed helmets and spraying either in a ventilated booth¹⁶ or in a controlled spray space."

It was possible to recruit both subjects (sprayers) and controls at the same place of work at three of the sites, at a fourth the unexposed person was a member of HSE staff because the sprayer worked alone. At one of the larger dealerships a group of people working just outside the spraying area were also recruited to act as bystanders. All participants were provided with an information sheet and signed a consent form after discussing the study with one of the researchers (NRW). All sprayed alone in the booth or ventilated space.

Due to the reportedly short half life (about 1.5 hours¹⁷) of HDA in urine, samples were collected before, during, and after the shift to detect any short term exposure as well as an estimate of the 8 hour time weighted average exposure.

PILOT STUDY

A pilot study was undertaken in 1996 at one of the larger dealerships.

Subjects provided urine samples on the day of spraying before starting spray work, at in the middle of the shift, and at the end of the day. They recorded the amount of time spent spraying and the personal protective equipment worn. Bystanders and controls also provided three samples at the same times as the sprayers.

The samples were labelled with the person's name and either the time or the number of the sample but without the details as to whether they were sprayer, unexposed, or bystander. Samples were frozen for despatch and sent by courier to the Health and Safety Laboratory in Sheffield for analysis.

FULL STUDY

The full study involving five companies was carried out in the same way except that because of the nature of the activities only the firm in the pilot study provided samples from bystanders. Samples were collected and despatched in a similar way, frozen and sent blind to the laboratory for analysis.

ANALYTICAL PROCEDURE

1,6-Hexanediamine (98%), 1,7-heptanediamine (HpDA), heptafluorobutyric anhydride (HFBA), and hydrochloric acid were obtained from Aldrich. Diethyl ether and toluene (high performance liquid chromatography (HPLC) grade) were purchased from Rathburns. Sodium hydroxide solution (10 M) and sulphuric acid were purchased from Fisher. Water was purified through a Millipore Milli-Q system. An aliquot of HpDA solution (internal standard) was added to the sample urine (2 ml). Concentrated sulphuric acid (200 µl) was then added. Samples were mixed thoroughly and then hydrolysed at 100°C for 90 minutes. Samples were then cooled and 2 ml sodium hydroxide solution (10 M) was added.

After hydrolysis, 4 ml diethyl ether was added and the samples were extracted for 20 minutes, then centrifuged. About 3 ml of the organic layer was transferred and evaporated to dryness under a stream of nitrogen. Samples were then resuspended in 500 µl toluene and derivatised with 50 µl HFBA at 55°C for 1 hour. Samples were then cooled, evaporated to dryness, and reconstituted in 100 µl toluene.

The samples were analysed by GC-MS with negative ion chemical ionisation (with methane as reagent gas). Samples (1 µl, splitless) were injected (at 350°C) onto a BP-5, 25 mx0.32 mm internal diameter fused silica capillary column (1 µm film thickness). The oven temperature ramped from 150°C (initially held for 1 minute) to 280°C at 10°C/min where it was held for 1.5 minutes. The interface temperature was 280°C and the source was held at 200°C. With selected ion monitoring, ion m/z 449 was monitored for HDA and m/z 462 for HpDA.

Concentrations of HDA in urine were corrected for creatinine concentration according to the method of Jaffe *et al.*¹⁸

Results

ANALYTICAL METHOD

The method was shown to be linear (defined as a least squares regression coefficient >0.99) over the concentration range 0–500 nmol/l with a detection limit of 5 nmol/l. The within and between assay coefficients of variation for the method were 4% and 10% respectively (n=10).

PILOT STUDY

No HDA was detected in any sample taken before the shift nor in any of the samples provided by bystanders or unexposed subjects. Low levels of HDA (1 and 2 nmol/l) were detected in samples from the middle and the end of the shift respectively for two of the sprayers.

Table 1 Demography and control measures of companies involved

Company number	Demography and control measures
1	A large dealership with full time sprayers working on large vehicles in a designated area with local exhaust ventilation. Sprayers wore full face air fed respiratory protective equipment (RPE), disposable overalls (worn with the hood down exposing the head), and latex gloves.
2	This was a small garage with a single owner/sprayer carrying out intermittent spraying of cars in a homemade ventilated booth. While spraying he wore a full face air fed helmet with disposable overalls (hood down) and no gloves.
3	A large dealership with full time sprayers carrying out car spraying in a ventilated booth with full face air fed RPE, disposable overalls, and latex gloves.
4	A small garage with an owner/sprayer carrying out car spraying intermittently. He wore a full face air fed mask and sprayed in a ventilated booth wearing disposable overalls (with the hood down) and latex gloves.
5	This was a small garage with several designated sprayers who sprayed cars in a ventilated booth wearing full face air fed RPE and wearing disposable overalls and latex gloves.

Table 2 Urinary results and spray time details for the full study

Company	Worker	Sex	HDA concentration ($\mu\text{mol/mol}$ creatinine)			Spraying time (h) between samples	
			Sample 1	Sample 2	Sample 3	Samples 1-2	Samples 2-3
1	Sprayer	M	11.00	10.00	4.00	2.00	0.00
	Sprayer	M	ND	ND	ND	3.00	2.50
	Sprayer	M	ND	ND	ND	3.00	2.50
	Bystander	M	ND	ND	ND	NA	
	Bystander	M	ND	ND	ND	NA	
	Bystander	M	ND	6.00	12.00	NA	
	Unexposed	M	ND	ND	ND	NA	
	Unexposed	F	ND	—	ND	NA	
	Unexposed	M	ND	ND	ND	NA	
2	Sprayer	M	N	D	N	D	1.25
	Unexposed	F	ND	—	—	NA	0.00
3	Sprayer	M	ND	ND	1.00	0.25	0.10
	Sprayer	M	N	D	N	D	0.30
	Sprayer	M	ND	ND	ND	0.75	0.30
	Unexposed	M	N	D	N	D	NA
4	Sprayer	M	ND	ND	ND	0.75	0.50
	Unexposed	F	N	D	N	D	NA
5	Sprayer	M	ND	ND	ND	NA	
	Sprayer	M	1.00	ND	ND	3.00	1.00
	Sprayer	M	ND	3.00	1.00	3.00	1.00
	Unexposed subject	M	ND	ND	ND	NA	

*No spraying undertaken on the sampling day.

— No sample provided; ND=none detected; NA=not applicable.

FULL STUDY

A total of 11 sprayers, three bystanders, and eight unexposed subjects were identified from the five participating companies. Samples were collected from all participants except for one unexposed subject who only provided two samples. The companies are described in table 1 and the urinary results are presented in table 2.

None of the unexposed subjects had detectable concentrations of HDA in any of the three samples. One bystander (company 1) had notable concentrations of HDA in samples from the middle and at the end of the shift. Four sprayers had concentrations of HDA. One in particular (company 1) had high concentrations in the samples taken before and in the middle of the shift, which fell by the end of the shift.

Discussion

ANALYTICAL METHOD

The method was shown to be linear over the concentration range studied. The coefficient of variation between assays (10%) and detection limit (5 nmol/l) were comparable with other recently reported methods.¹⁴

PILOT STUDY

The pilot study showed that sprayers could receive low internal exposure to isocyanates despite wearing respiratory protective equipment and spraying in a ventilated area. It also showed that it is possible to spray isocyanates while using control measures without receiving a detectable exposure. In the pilot study none of the bystanders or unexposed subjects had any detectable concentrations of HDA.

FULL STUDY

The full study again showed that workers can absorb isocyanates during spraying operations despite wearing full face air fed masks and using ventilated spray booths or extracted work

areas. Four sprayers had detectable concentrations of HDA (two had detectable concentrations in their sample before the shift) and one bystander had detectable concentrations of HDA.

Workers for small companies are not necessarily more at risk of exposure. Indeed, in this study the companies with only one sprayer (companies 2 and 4) had no detectable concentrations of HDA in urine. Also, the duration of spraying did not affect the likelihood of exposure (table 2, sprayers at company 1).

Biological monitoring does not determine the route of exposure—this could have been oral, dermal, or through inhalation although inhalation is the most likely route given the lack of published evidence for the absorption of isocyanates through the skin. During feedback with participants it became clear that exposure may occur when the sprayers lift their visors to inspect the quality of their work—this was reported at several garages. Field work done by the HSE has shown that isocyanate concentrations in booths and spray spaces may remain considerable ($>20 \mu\text{g}/\text{m}^3$ (in excess of the maximum exposure limit)) for some time after spraying has stopped. Clearance times of up to 5 minutes for bespoke booths and up to 30 minutes for spray spaces have been recorded. If sprayers and other workers are not aware of the importance of clearance times they may inadvertently expose themselves sometime after spraying has finished. Similarly baking during the spray bake cycle can drive off isocyanate monomer creating considerable concentrations in the vapour within the booth or spray space during baking and for sometime after.

In the case of company 1, the work involved spraying large lorries rather than cars and this involved some spraying above head height—an activity which may be relevant for the fit of respiratory protective equipment and subsequent detection of the metabolites in the urine of sprayers at this company.

The short initial half life of HDA means that the urine sample only represents exposure over the past 2-4 hours. It is therefore possible that part time sprayers may have been exposed but that metabolite concentrations were too low and too quickly excreted to show that an exposure had occurred. However, it has also been reported¹⁴ that low amounts can be detected in urine 15-20 hours after an oral dose of HDA. There is therefore the possibility of accumulation of HDA in the body during the working week.

Recent work on other isocyanates has also shown that other adducts of isocyanate in plasma may break down over time causing excretion of the diamine metabolites for an extended period. Concentrations of toluene diamine (up to $5 \mu\text{mol}/\text{mol}$ creatinine) could be detected several days, even weeks, after exposure had ended. It is possible that this may also be true for HDA.

However, the concentration found in the samples reported here is higher than previously reported for adduct breakdown, and the wash out found would be more consistent with the

initial half life (1.5–2 hours) than adduct breakdown. It would therefore seem that the most likely explanation of the positive samples before the shift would be an inadvertent short term high exposure before the sample was provided. The sprayer at company 1 with positive concentrations of HDA had a possible exposure before the sample taken before the shift. Urinary concentrations of HDA were maintained while spraying for 3 hours before the sample taken in the middle of the shift. Between providing that sample and the one taken after the shift no spraying was undertaken; this is reflected in the drop in the urinary HDA concentration (suggesting a half life consistent with that reported of about 2 hours).

In the case of the bystander at company 1 discussion with the person showed that while not spraying himself he did think that he may have gone to speak to a sprayer at work.

The concentrations of HDA detected in this study are similar to those found in other studies.^{13,14} Brorson et al.¹³ reported a mean value of HDA after the shift of 20 $\mu\text{mol/mol}$ creatinine after 7.5 hours exposure to 25 $\mu\text{g/m}^3$ HDI whereas Maitre et al.¹⁴ measured a value of 12 $\mu\text{mol/mol}$ creatinine for HDI exposure at the same concentration from a survey of workers.

The study has shown that it is possible to spray isocyanates without exposure to them if respiratory protective equipment and suitable extraction is provided but the results also suggest that exposure can occur despite the use of such precautions. Much effort has rightly gone into publicising the importance of the selection, fit, and maintenance of respiratory protective equipment; such effort will be wasted if consideration is not also given to the behaviour which workers adopt to do their job—that is, a human factors approach to prevention of ill health due to isocyanates is needed.

Conclusion

This study has shown that exposure to isocyanates can occur despite the use of full respiratory protective equipment and ventilated booths. It has also shown that urinary metabolites (HDA) can be used to identify these exposures and to assess the adequacy of controls. The evidence of exposure despite precautions highlights the continued need to improve control procedures, to provide health surveillance to check the efficacy of controls, and to provide information and instruction and training for workers in motor vehicle repair shops.

Further work is recommended to conduct a cross sectional industrial survey and the possible establishment of a biological monitoring benchmark value to assess control of exposure.

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