

Benzene exposure and hematological effects among offshore workers exposed to crude oil



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Scientific environment

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LIST OF ABBREVIATIONS

ACGIH	= American Conference of Governmental Industrial Hygienists
ANOVA	= Analysis of variance
BAL	= Biological action limit
BEI	= Biological exposure indices
C3	= complement factor 3
C4	= complement factor 4
CD3	= T lymphocytes. Transduces signals from T-cell receptor.
CD4	= T lymphocytes. Marker for helper T cells.
CD8	= T lymphocytes. Marker for cytotoxic T cells.
CD19	= B lymphocytes.
CD56	= natural Killer cells.
CYP 2E1	= cytochrom P450 2E1
DFG	= Deutsche Forschungsgemeinschaft [German Research Foundation]
EKA	= exposure equivalents for carcinogenic substances
GC	= gas chromatography
GSH	= glutathione-S-transferase
IARC	= International Agency for Research on Cancer
ICD-7	= International Classification of Diseases, 7 th edition
ISIC	= International Standard Industrial Classification
IgA	= immunoglobulin A
IgE	= immunoglobulin E
IgG	= immunoglobulin G
IgM	= immunoglobulin M
MS	= mass spectrometry
NDT	= non destructive testing
NACE	= Classification of Economic Activities in the European Union
NIOSH	= National Institute of Occupational Safety and Health
NQO1	= NAD(P)H:quinone oxidoreductase
OEL	= occupational exposure limit
SMR	= standardized mortality ratio
SPME	= solid phase micro-extraction

SUMMARY

Objective: The main objective of the study was to gain more knowledge about the exposure to benzene in the Norway's offshore petroleum industry, its' relation to effects on the hematological system and the risk of hematopoietic malignancies. More specifically we wanted to 1) characterize the benzene exposure in Norway's offshore petroleum industry, 2) investigate the association between exposure to benzene and effects on the immune system, and 3) assess whether workers employed in Norway's offshore petroleum industry have an increased risk of developing hematopoietic malignancies than the general working population in Norway, focusing on the differences in risk according to the subtypes of leukemia in particular.

Methods: In paper I we assessed the workers exposure to benzene in the breathing zone (full work shift) on a crude oil production vessel, including the operation modes ordinary activity, a brief shut down and tank work. In paper II and III we estimated the associations between the benzene exposure and concentrations of benzene in blood and urine among process operators (n=12) and workers maintaining cargo tanks containing crude oil residues (n=13). Referents working in the catering section having the same shift schedule, matched on age and gender, were included. Benzene exposure was measured during three consecutive 12-hour work days. Blood and urine samples were collected prior to the first work shift (baseline), immediately after the third work shift, and prior to the following work shift. In paper IV we investigated the relationship between benzene exposure and alterations of proteins and cells of the immune system, measured by peripheral blood lymphocytes (total lymphocytes, lymphocytes in subpopulations CD3, CD4, CD8, CD19, CD56 and CD4/CD8 ratio), complement factors C3 and C4 and serum concentration of immunoglobulins (IgG, IgA, IgM and IgE).

In paper V, we studied the risk of hematopoietic malignancies among offshore workers identified by the Norwegian Registry of Employers and Employees. All subjects registered with offshore-related industrial classification codes or with work location in

the North Sea from 1981 to 2003 were included. We drew up to six referents per petroleum worker from the general working population matched by gender, age and community of residence. The cohort comprised 27,919 offshore workers distributed on four job categories offshore and 366,114 referents and was linked to the Cancer Registry of Norway, the Norwegian Education Registry and the Norwegian Cause of Death Registry.

Results: Full-shift benzene exposure levels measured in the workers breathing zone during ordinary activity were low for workers on the crude oil production vessel (geometric mean 0.004 ppm, range < 0.001 – 0.22 ppm) (paper I) and also for process operators at a fixed oil- and gas installation (geometric mean 0.005 ppm, range <0.001 - 0.688 ppm) (paper II). The exposure varied considerably, with some measurements being higher than the Norwegian occupational exposure limit of 0.6 ppm for a 12-hour shift. The process operators at the fixed oil- and gas installation and tank workers on the crude oil production vessel had a mean benzene concentration of benzene in blood post-shift of 1.5 nmol/l and 12.3 nmol/l, respectively (paper II and III). Although only the tank workers' benzene concentration in blood differed significantly from referents, the biological uptake was significantly related to the exposure levels of benzene in air in both groups.

In paper IV we found that the tank workers declined (versus referents) in IgM from baseline to post-shift (*t*-test, *P*=0.04), in IgA from baseline to pre–next shift (*t*-test, *P*=0.01) and in CD4 T cells from baseline to post-shift (*t*-test, *P*=0.04). The suppression correlated with benzene exposure, benzene concentrations in blood and urine and time spent in the tank. The groups did not differ significantly in the change in other immune parameters.

In paper V we found that workers in the job category “upstream operator offshore”, who have the potentially highest exposure, had an excess risk of hematopoietic malignancies (rate ratio (RR) 1.90, 95% confidence interval (CI) 1.19–3.02). This was ascribed to increased risk of acute myelogenous leukemia (RR 2.89, 95% CI 1.25–6.67) and multiple myeloma (RR 2.49, 95% CI 1.21–5.13). Rate ratios were highest

for the workers with their first registered engagement in the offshore petroleum industry before 1986. The other job categories had no increased risk, and overall cancer (all sites) did not differ.

Conclusion: In spite of relatively high short term peak exposure to benzene during ordinary activity for several job categories on a crude oil production vessel and for process operators on a fixed oil- and gas installation, the full-shift mean exposure is low. Although both process operators on the fixed oil- and gas installation and tank workers on the crude oil production vessel had a low exposure to benzene, the biological uptake was significantly related to the benzene exposure. The internal concentration of benzene among tank workers was higher than expected at the measured exposure levels. This finding is probably due to an extended work schedule and high work load.

The same tank workers showed acute alterations in the immune parameters IgM, IgA and CD4 T helper cells that correlated with levels of benzene. The clinical significance of the finding for the tank workers' health is not known. Given the complexity of the tank atmosphere and in the work environment in general on oil- and gas installations offshore we cannot exclude a possible contribution of other types of specific or combined exposure, but occupational exposure to benzene is the most likely candidate for the reported decline in immune parameters among tank workers and the risk of acute myelogenous leukemia and multiple myeloma found among offshore workers.

LIST OF PUBLICATIONS

The thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

- I. Kirkeleit J, Riise T, Bråtveit M, Moen BE. Benzene exposure on a crude oil production vessel. *Ann Occup Hyg.* 2006;50(2):123–129. doi:10.1093/annhyg/mei065.
- II. Bråtveit M, Kirkeleit J, Moen BE. Biological monitoring of benzene exposure for process operators during ordinary activity in the upstream petroleum industry. *Submitted.*
- III. Kirkeleit J, Riise T, Bråtveit M, Pekari K, Mikkola J, Moen BE. Biological monitoring of benzene exposure during maintenance work in crude oil cargo tanks. *Chem.-Biol Interact.* 164(1-2):60-67. doi:10.1016/j.cbi.2006.08.017
- IV. Kirkeleit J, Ulvestad E, Riise T, Bråtveit M, Moen BE. Acute suppression of serum IgM and IgA in tank workers exposed to benzene. *Scand J Immunol.* 2006;64:690-698. doi:10.1111/j.1365-3083.2006.01858.x
- V. Kirkeleit J, Riise T, Bråtveit M, Moen BE. Increased risk of hematopoietic malignancies in a historical cohort of upstream petroleum workers in Norway. *Submitted.*

1. INTRODUCTION

1.1 Benzene

1.1.1 Physical and chemical properties

Benzene (C₆H₆, cas nr. 71-43-2) is the parent compound of aromatic hydrocarbons, and is a highly volatile, flammable, clear and colorless liquid. Benzene has a molecular weight of 78.12 g/mol, boiling temperature of 80.1 C° and a vapour density of 2.77.¹

1.1.2 Occurrence, use and occupational exposure

Occurrence. Benzene is a natural component of crude oil and other petroleum products, might be in by-products of operations in coke oven industry and in tobacco smoke.² Benzene was first isolated by Michael Faraday in 1825, and originally produced from coal tar in 1948.³ Today benzene is mainly produced by catalytic reforming of alkanes and cycloalkanes or by cracking certain gasoline fractions.⁴

Use. According to the Product Registry of Norway, The Authorities' Central Register of Chemical Products, total use of benzene in Norway in 2004 was 326,456 tonnes.⁵ The number of products containing benzene was 47, used as raw materials for synthesis and intermediate products, motor fuels, solvents and paint and varnish. In the chemical industry, benzene is industrially the most important of the so-called BTX aromatics (benzene, toluene, xylene), and is used in the production of other chemicals, such as styrene, phenol, cyclohexane, ethylbenzene and cumene.

Occupational exposure. Workers employed in industries such as extraction of crude oil and natural gas, petroleum refineries, transport and distribution of petroleum products, gasoline stations, car repair shops, chemical industry, coke oven industry and shoe manufacturing using benzene-based glues are potentially exposed to benzene.⁶

1.1.3 Toksikokinetics

1.1.3.1 Absorption and distribution

During occupational exposure to benzene, inhalation is the most important route of absorption. Reports indicate that humans absorb 30–52% of the inhaled benzene, depending on the benzene concentration, length of exposure and pulmonary ventilation.⁷⁻⁹

Benzene penetrates skin.^{10,11} However, benzene absorption is not extensive as it evaporates quickly due to a high vapour pressure. Hence, under normal working conditions dermal absorption of benzene by direct contact with crude oil residues or vapour are probably of minor importance.¹²⁻¹⁴ Vermeulen and co-workers¹⁴ assessed the dermal exposure to benzene and toluene on multiple days in 70 subjects in a shoe factory. The mean air concentrations of benzene and toluene were 1.5 and 7.5 ppm, respectively. While a strong correlation between benzene in air and benzene in urine was reported, no relation was found between the measured dermal exposure and benzene in urine.

Benzene is lipophilic and distributes mainly into tissues with high lipid content. A study on dogs reports that distribution of benzene throughout the body occurs rapidly, and that equilibrium values depend on the blood supply.¹⁵ In the same study, bone marrow, fat tissue and urine was shown to contain approximately 20-times higher concentration of benzene than blood, while the corresponding values for muscle tissue and other vital organs were about 1 to 4.7 times the level in blood.

1.1.3.2 Metabolism and elimination

Benzene itself is not regarded as a toxic substance. Several metabolites, as well as interactions between these metabolites, may be necessary to explain the toxic effects of benzene.^{16,17}

Half-time of benzene in blood has been reported to be about 8 hours.^{8,18} Benzene elimination occurs rapidly at first, but slows down owing to the large amount of benzene stored in the fat.¹⁵

1.1.3.3 Modifying factors on toxicokinetics of benzene

The level of benzene and its' metabolites in biological media after a given exposure, as well as the sensitivity to benzene's toxic effects, differs between individuals and also in different situations for the same individual. The variability is caused by biologic factors such as genetic polymorphisms, amount of adipose tissue, gender and environmental influences such as routes of exposure, physical activity, competitive metabolic interaction, smoking, alcohol consumption and dietary habits.¹⁹ Some of these modifying factors are described below.

Polymorphisms of enzymes involved in metabolism of benzene. Individual differences in sensitivity to benzene's toxic effects are explained partly by polymorphisms in enzymes involved in the metabolism of benzene.²⁰ Genetic variations resulting in increased activity of the activation enzymes (phase I) cytochrome P450 2E1 (CYP2E1), microsomal epoxide hydrolase, myeloperoxidase in the bone marrow and/or decreased activity of detoxification enzymes (phase II) have all individually been associated with increased susceptibility to benzene's toxic effects.²¹⁻²³

Physical activity. Physical strain increases the uptake of organic solvents in humans through all routes and modifies the distribution and biotransformation these.^{29,19,24} Zimmer and co-workers²⁵ reported that physical activity of 50 and 75 W lead to significant increases in blood concentrations for a range of hydrocarbon solvent mixtures by mean factors of 1.2 and 1.9, respectively. Nadeau and co-workers²⁶ reported that even light work load intensity might lead to a 2.5- to 4-fold higher absorbed dose of toluene.

Competitive metabolic interaction. The knowledge about possible interference of the metabolic disposition of benzene by concomitant exposure to other organic

solvents is rather limited, but some studies have reported that the uptake and metabolism of benzene is influenced by co-exposure to toluene.^{27,28} Further, elimination of both *t,t*-muconic acid and *S*-phenylmercapturic acid is influenced by co-exposure to other aromatic hydrocarbons.²⁹ Further, Kim and co-workers³⁰ studied the dose-related patterns of benzene metabolism and reported that the production of the toxic metabolites hydroquinone and muconic acid were favoured at low benzene exposure.

1.1.4 Toksikodynamics – with special emphasis on the hematological system

Benzene toxicity is believed to involve biological interactions of multiple reactive benzene intermediates with multiple cellular targets within the bone marrow.^{31,32} In addition to hepatic metabolism, the secondary metabolism of benzene in the bone marrow plays an important role in benzene's myelotoxicity.^{16,17} Especially hydroquinone, *p*-benzoquinone, catechol and muconaldehyde, alone or in combination, are reported to be the most potent metabolites in producing toxicity on the hematopoietic system.¹⁶ A description of benzene's toxic effects on the hematological and hematopoietic system is given below. The review is limited to human data.

1.1.4.1 Effects on the hematological system

Hematotoxic effects. The hematopoietic system and the cells of the bone marrow are the most sensitive target organs for benzene exposure. Repeated occupational benzene exposure over long periods of time may affect several parameters related to the hematological system, including the immune system, causing bone marrow depression expressed as anemia, leucopenia and/or thrombocytopenia.³³⁻³⁷ Significantly lower white blood cell and platelet counts have been found for workers exposed to benzene in the work atmosphere even below the occupational exposure limit of 1 ppm.³³ At present there is no clear evidence of a threshold level below which benzene does not cause hematotoxicity in humans.³⁸

Alterations in the immune system. The immune system, including both innate and adaptive components, is also affected by benzene. These effects include a decrease in

serum immunoglobulins,^{39,40} an anti-benzene antibody response,⁴¹ a decrease in complement levels⁴² and white blood cell levels,^{33,36,37,43} as well as alterations in subpopulations of lymphocytes.^{33,43-45}

1.1.4.2 Hematopoietic malignancies related to benzene

Leukemia. Epidemiological studies provide evidence for a causal association between exposure to benzene and leukemia^{46,47} – acute myelogenous leukemia in particular. Leukemias are monoclonal malignancies of the circulating blood cells, the majority of which originate from individual stem or progenitor cells in the bone marrow. Acute myelogenous leukemia is characterized by an increase in the number of myelogenous cells in the bone marrow and arrest in their maturation, frequently resulting in hematopoietic insufficiency (granulocytopenia, thrombocytopenia, or anemia), with or without leukocytosis.⁴⁸

The association between benzene exposure and the development of specific subtypes of leukemia is still unclear. The most recent meta-analysis of benzene-exposure and leukemia subtypes includes nine cohorts and 13 case-control studies from several industries, and shows a high and significant risk of acute myelogenous leukemia with a positive dose response relationship across study designs.⁴⁷ The risk for developing chronic lymphocytic leukemia was increased in the case-control studies, but not in the cohort studies. The data for chronic myelogenous leukemia and acute lymphocytic leukemia were sparse and inconclusive.

Multiple myeloma. Multiple myeloma (myelomatosis) is a clonal B-cell neoplasm of plasma cells and is characterized by the presence of an elevated number of plasma cells in bone marrow synthesizing and releasing IgA, IgD, IgE, IgG or light chains.⁴⁹⁻⁵⁰ Several biologically plausible risk factors for multiple myeloma have been proposed, such as exposure to benzene, ionizing radiation and diesel exhaust, smoking and alcohol.⁴⁹⁻⁵⁰ However, the etiology of multiple myeloma remains generally unclear in the published literature.

The association between exposure to benzene and multiple myeloma is a contentious issue.⁴⁹⁻⁵² In a meta-analysis of 22 cohort mortality studies consisting of 250 000 petroleum workers, mainly from the refinery and distribution segment, it was concluded that petroleum workers were not at any increased risk of developing multiple myeloma as a result of their exposure to benzene, benzene-containing liquids, or other petroleum products in their work environment.⁵³ On the other hand, in a more recent meta-analysis including seven cohort studies focusing on benzene-exposed workers, including refinery workers, a significant excess in the relative risk (RR) of multiple myeloma was reported in relation to benzene exposure (RR 2.13, 95% CI = 1.31-3.46).⁵⁴

1.1.5 Assessing workers benzene exposure by biological monitoring

Biological monitoring can be defined as the assessment of chemicals or their metabolites in biological media (samples of breath, urine or blood) of exposed workers. Biological monitoring has a potential advantage compared to air sampling as it assesses exposure by all routes, and thereby considers the inter-individual variations in absorption as well as individual variation in metabolism, excretion and bioavailability of the chemical agents.

1.1.5.1 Biomarkers of benzene exposure

The most important biomarkers for benzene exposure are benzene in blood and urine, and the metabolites *trans,trans*-muconic acid and *S*-phenylmercapturic acid in urine. These parameters are sensitive and specific biomarkers of occupational and environmental benzene exposure at levels below 1 ppm.^{55,56}

Benzene in blood. Benzene in blood is in equilibrium with exhaled air. Because of the short half-time of benzene in blood, the timing of sampling is crucial. The collection of blood samples must therefore be performed immediately after the work shift, preferably during the first half-hour after exposure.⁸ A potential confounding factor is the strong influence of smoking.^{8,18,57} Correlation coefficients between benzene

concentration in air and benzene in blood post-shift range between 0.12 to 0.64,^{58,59} depending on the exposure level in air.

Benzene in urine. Traces of unmetabolized benzene, reported to be about 0.1% of totally absorbed benzene in humans, are eliminated unchanged in the urine.⁶⁰ Benzene in urine is recommended as a biomarker of choice at air concentrations below 1 ppm benzene because it is non invasive.^{59,61} In addition the timing of sampling is not as crucial as for benzene in blood. Correlation coefficients between benzene concentration in air and benzene in urine post-shift have been reported to be 0.38–0.98.^{57,62-65}

Smoking - a potential confounder. Cigarette smoke is a known source of benzene exposure,⁶⁶ and is a potential confounder in biological monitoring of benzene. Pekari and co-workers⁸ reported that current smokers not exposed to benzene had a benzene concentration ranging from 12 to 15 nmol/l. The corresponding mean level of non smokers was 0.8 nmol/l. Similar benzene concentrations have been reported in other studies.^{18,57}

1.1.5.2 Standards for chemical exposure in the work environment

Occupational exposure limit. As the knowledge of benzene's hematotoxic effects has increased over the years, the occupational exposure limit for benzene has been extensively revised and reduced, from 100 ppm in 1946 to values ranging from 0.1 to 1 ppm in 2006.⁶⁷ At present the recommended Norwegian occupational exposure limit for benzene is 1 ppm averaged over an 8-hour workday.⁶⁸ However, in general Norwegian offshore workers have 12 hour shifts seven days a week for two weeks with 28 days of leave between the tours. In the guidelines to the Activities Regulations, the Norwegian Petroleum Directorate therefore recommends a safety factor of 0.6 to correct the standard for a 12-hour shift.⁶⁹ Thus, the occupational exposure limit for benzene is 0.6 ppm over a 12-hour workday.

Biological exposure limits. Several countries and organisations have established biological limit values for benzene (table 1).

Table 1 Biological limit values and its corresponding occupational exposure limit (OEL) for selected countries and organisations.

Country or organisation	OEL (ppm)	Biomarker	Biological limit value	Comment	Reference
Finland ^{BAL}	1.0	Benzene	50 nmol/l	Blood End of shift	70
		<i>t,t</i> -muconic acid	14 µmol/l	Urine End of shift	
Germany ^{EKA}	1.0	Benzene	5.0 µg/l	Blood	71
	0.6		2.4 µg/l	End of shift	
	0.3		0.9 µg/l		
	1.0	<i>S</i> -phenylmercapturic acid	0.045 mg/g creatinine	Urine	
	0.6		0.025 mg/g creatinine	End of shift	
	0.3		0.010 mg/g creatinine		
ACGIH ^{BEI}	0.5	<i>S</i> -phenylmercapturic acid	25 µg/g creatinine	Urine End of shift	72
		<i>t,t</i> -muconic acid	500 µg /g creatinin	Urine End of shift	

ACGIH = American Conference of Governmental Industrial Hygienists, BAL = biological action limits, EKA = exposure equivalents for carcinogenic substances, BEI = biological exposure indices, DFG = Deutsche Forschungsgemeinschaft

1.2 Norway's petroleum industry

The petroleum industry can be divided in upstream and downstream segments. The upstream segment refers to exploration, extraction and production of crude oil and natural gas. The downstream segment consists of refinery operations, distribution and retail of the petroleum fractions. In Norway the upstream petroleum industry is confined to the Norwegian continental shelf, and is henceforth denoted Norway's offshore petroleum industry.

Norway's petroleum industry started in 1969 when the Ekofisk oil field was discovered, while the production from the field started in 1971. Today it is Norway's largest industry, accounting for 21 percent of the value creation in 2005.⁷³ The number of employees who works in the upstream petroleum segment differs between the official sources, ranging for 2003 from 14 720 to 28 500.⁷⁴ According to Statistics Norway,⁷⁵ a total of 29 000 people were employed offshore in the upstream petroleum industry in 2005, including 16 800 employees in the sector "Extraction of oil and natural gas" and 11 800 employees in the sector "Service activities incidental to oil and gas extraction".

1.2.1 Norway's offshore petroleum industry

Oil and gas installations used on the Norwegian continental shelf include fixed platforms, semi-submersible platforms, jack-up platforms and floating production systems. These offshore production installations generally consist of a drilling unit, a processing unit and living accommodation (crew area).

Drilling unit. The drilling rig is used to drill and maintain wells, and consists of mud handling devices, derrick, rotary table, drillstring, power generators and auxillary equipment. Most drilling operations, including drilling of wells and installation, disassembling and maintenance of drilling towers, are now often performed by drilling contractors and not the company operating the oil field. The drilling crew typically consists of roustabouts, roughnecks, mud loggers- and engineers, shale shaker operators and well service crew, motormen, derrickmen, assistant drillers, and the

drillers. Drilling rigs operate around the clock. The drilling mud process has been described by Steinsvåg and co-workers.⁷⁶

Processing unit. After arriving the offshore production facility, the effluent (crude oil, natural gas and natural gas liquids) is piped through a closed system of separators and treaters where it is separated into gas, oil, water and solid waste (sand and sediment). The oil and gas are transported to the market (i.e. to an onshore terminal for refining, distribution segments or consumers) via either shuffle tankers or in pipelines. The water produced in the separation process is either reinjected into the well or purified and disposed overboard. The oil-contaminated produced water varies between the oil fields in amount and composition. It is generally a mixture of formation water from the reservoir, injected water used for secondary oil recovery and treatment chemicals added during production. Job categories in the processing area include process operators, mechanics, electricians, instrument technicians and maintenance personnel such as insulators, scaffold crew, industrial cleaners, surface treaters and welders.

1.2.2 Offshore workers' exposure to crude oil and benzene

Benzene is a natural component of crude oil, natural gas, natural liquid gas and produced water. Hence, occupational exposure to benzene is a potential hazard in the offshore petroleum industry. During ordinary operation most of the processes are performed in a closed system, and the exposure is thought to be low. However, whenever the system is opened there is potential for exposure to the oil components. Information about past exposure of benzene in the upstream petroleum industry is scarce, and no good exposure estimates for the different job categories exist. However, due to regulations and other initiatives in the 90ies, it is assumed that there has been a general improvement of the work environment offshore, including reduced benzene exposure.

1.2.2.1 Benzene content in petroleum streams offshore

The composition of petroleum streams and the fraction of benzene differ between the oil- and gas fields depending on several factors such as geological conditions in the

reservoirs and production period of the oil field. Crude oil assays from different regions on the Norwegian continental shelf ($n = 14$) reported a mean and median value of 0.28% benzene by weight, within a range of <0.01–0.66 %.⁷⁷

1.2.2.2 Exposure measurements in the upstream petroleum industry

Some authors have summarized common occupational exposure data from oil companies mainly performed to document compliance with the regulations under the Working Environment Act, and concluded that average exposure during a full shift is low for most job categories.⁷⁸⁻⁸³ An overview of the studies performed in the upstream petroleum industry is given in table 2. The wide ranges of reported exposure values indicate that some workers might experience relatively high benzene exposure over a 12 hour shift. It is expected that specific tasks causing high short-term exposures, such as opening of blind flanges and valves, changing of filters, inspections and maintenance of processing units, pipeline clean-out (“pigging”), spill clean-up and sampling of crude oil and produced water, contribute significantly to the total benzene exposure.

Steinsvåg and co-workers⁸³ pooled full shift benzene measurements from processing- and drilling areas of 12 installations on the Norwegian continental shelf in the period 1994-2003 ($n=367$). They reported arithmetic and geometric mean benzene exposure of 0.037 and 0.0067 ppm, ranging from below level of detection to 2.6 ppm. These measurements did not include cleaning or maintenance of processing equipment (vessels, separators or tanks), thought to give a potential for high exposure to aromatic hydrocarbons such as benzene, toluene and other hydrocarbons.^{78,84}

Table 2 Studies on benzene exposure performed in the upstream petroleum industry.

Industry	Sector/group/task	Sampling strategy	Benzene (ppm)	Range, ppm (min–max)	Reference
Pooled data from Norway’s upstream petroleum industry (1994 – 2003)	Deck (n = 29)	Personal long term (full shift samples of 12 hours)	AM=0.17 GM = 0.0099	< LOD – 2.6	83
	Process (n = 204)		AM=0.036 GM = 0.0084	< LOD – 0.97	
	Laboratory (n = 40)		AM=0.012 GM = 0.0056	< LOD – 0.11	
	Mechanics (n = 78)		AM=0.0062 GM = 0.0020	< LOD – 0.08	
	Electrician (n = 6)		AM=0.015 GM = 0.0058	< LOD – 0.05	
	All (n = 367)		AM=0.037 GM = 0.0067	< LOD – 2.6	
Pooled data from Canada’s upstream petroleum industry	Conventional oil and gas sector (1985-1996)	Personal long term (n=198)	AM = 0.064 GM=0.011	<0.001 – 2.431	80
		Personal short-term (n=21)	AM = 0.399 GM=0.114	0.005 – 3.844	
		Area long- term (n=23)	AM = 0.207 GM=0.007	<0.001 – 2.431	
Pooled data from Australia’s petroleum industry	Upstream operator offshore	Estimated exposure	0.02	—	81, 82
	Cleaning of crude tanks (crude and slop storage)		2.01 Crude (n = 13) and slops storage data (n = 46)	—	
	Cleaning of tanks, separators and vessels containing crude oil		< LOD – 5.8	—	84
Pooled data from US petroleum industry (US)	Storage tank gauging	Personal short term N =124		< 0.01 – 50	78

1.2.3 Cancer risks among workers in the upstream petroleum industry

Only one mortality study has been performed exclusively on workers from the upstream petroleum industry whose primary exposure was to crude oil.^{85,86} The original study comprised production and pipeline workers who worked in the petroleum industry within the years 1946 to 1980,⁸⁵ while the update extended the follow up time to 1994.⁸⁶ In the total cohort comprising 19,588 white men, increased

mortality rates were reported for prostate cancer (SMR 119; 95% CI 100-141) and acute myelogenous leukemia (SMR 192; 95% CI 110-313). When examining mortality rates for acute myelogenous leukemia by job group the SMRs were significantly increased for crude oil workers ever worked as roustabout (SMR 276; 95% CI 142-482) or pumper (SMR 280; 95% CI 127-531). Importantly, mortality was not significantly increased for all causes combined nor for major mortality groups, such as all cancers, lung cancer, stroke, heart disease and respiratory disease. This is in line with other studies performed in the petroleum industry, mainly including refineries and distribution. These show that the overall mortality and overall cancer incidence among these workers are significantly lower than in the general population.⁸⁷⁻⁹⁶ Lewis and co-workers⁹¹ found an increased SMR for aortic aneurysms among marketing and distribution workers (SMR 1.27 (1.04 – 1.53), but the risk disappeared when only subjects with relatively complete work histories were included.⁹²

Several other studies on workers in the petroleum industry, mainly comprising refinery workers and petroleum distribution workers, have reported an increased risk of leukemia^{88,93,95,97,98} and multiple myeloma.⁸⁹ In some studies the increased risk of leukemia disappeared with extended follow up time.^{89,96}

The same studies as described above reported significantly increased risks of prostate cancer,^{95,96,99} kidney cancer,⁹⁶ malignant melanoma,^{91,94-97,99} mesothelioma,^{91,96} pleura,⁹⁴ gall bladder,^{92,94} bladder cancer⁹⁵ and bone cancer.⁸⁸

1.3 Gaps in knowledge

Although Norway has been a producer of oil and gas since 1971 and benzene's leukemogenic effects has been known at least since 1974,¹⁰⁰ benzene exposure in Norway's upstream petroleum industry is poorly described. The lack of measured data also applies to the petroleum industry internationally. Hence, at present we do not have knowledge about the risk posed by benzene on workers in Norway's offshore petroleum industry.

A question of controversy is at which threshold benzene may cause an adverse effect on the hematopoietic system^{33,38,51}. Further, the association between benzene exposure and multiple myeloma^{49,51,52} and leukemia subtypes other than acute myelogenous leukemia⁴⁷ is a contentious issue.

2. AIMS OF STUDY

Our hypothesis was that employees in the Norway's offshore petroleum industry have been and still are exposed to benzene to such a degree that there is an increased risk of hematotoxic effects and/or hematopoietic malignancies.

The main objective of the study was to gain more knowledge of the exposure to benzene in the Norwegian offshore petroleum industry, its' relation to effects on the hematological system and the risk of hematopoietic malignancies. More specifically we wanted to:

- 1) characterize the benzene exposure in Norway's offshore petroleum industry (paper I-III)
- 2) investigate the association between exposure to benzene and effects on the immune system (paper IV).
- 3) assess whether workers employed in Norway's offshore petroleum industry have an increased risk of developing hematopoietic malignancies than the general working population in Norway. We particularly wanted to focus on the differences in risk according to the subtypes of leukemia (paper V).

3. MATERIALS AND METHODS

3.1 Benzene exposure and acute effects of the immune system (papers I-IV)

3.1.1 Offshore installations

Five of the largest oil companies operating on Norway's continental shelf were invited to participate in the study of benzene exposure in the Norway's offshore petroleum industry and possible effects on the hematological system (appendix 2). However, only one of the invited companies accepted the invitation, and the second company in the project was included based on their own initiative. Hence, the present study was restricted to workers employed at one crude oil production vessel and one fixed oil- and gas platform.

The crude oil production vessel included in our study (paper I, III, IV; picture 1 in appendix 1) started production in 1998 and is 214.7 m in length, 38.2 m wide, and contains nine cargo tanks with a storing capacity of 470,000 barrels of crude oil. The production vessel is tied to an unstaffed wellhead platform, which is a transfer point for crude oil from the oil wells on the seabed. From the wellhead the oil is transported to the production vessel through pipelines and risers. The production vessels are equipped with processing facilities. In contrast to fixed oil platforms, which often deliver the crude oil directly to onshore terminals by pipeline, the production vessels store the crude oil in cargo tanks before it is offloaded and transported onshore. While fixed platforms are designed for long term use, production vessels can eliminate the need for expensive long-distance pipelines from the oil well to an onshore terminal and can be used economically on smaller oil fields. Once the field is depleted, the production vessel can move to a new location. As several existing oil fields are in the tail-end production phase and the oil fields being discovered are getting smaller, the demand for crude oil production vessels is increasing.

The fixed platform complex under study (paper II; picture 1 in appendix 1) started production in 1988, and includes three platforms connected to one another with

bridges. The first one is a concrete base platform with process equipment and living quarters, the second is placed on steel jacket and has drilling, production and injection equipment, while the third is a steel platform with gas processing and export equipment. In 2005 the platform complex had an average production of 90,900 barrels of oil and 7.8 million standard cubic meter of gas each day.

3.1.2 Study population

The activity on an offshore installation is normally divided into two main modes of operation; ordinary activity and partly or complete shut down when cleaning and maintaining the processing equipment are done. On crude oil production vessels the tank work is performed both during shutdowns and periodically after tanks are offloaded during ordinary activity, and in the present study tank work was considered as a third mode of operation. A flow diagram showing the included modes of operations and the corresponding papers is given in figure 1.

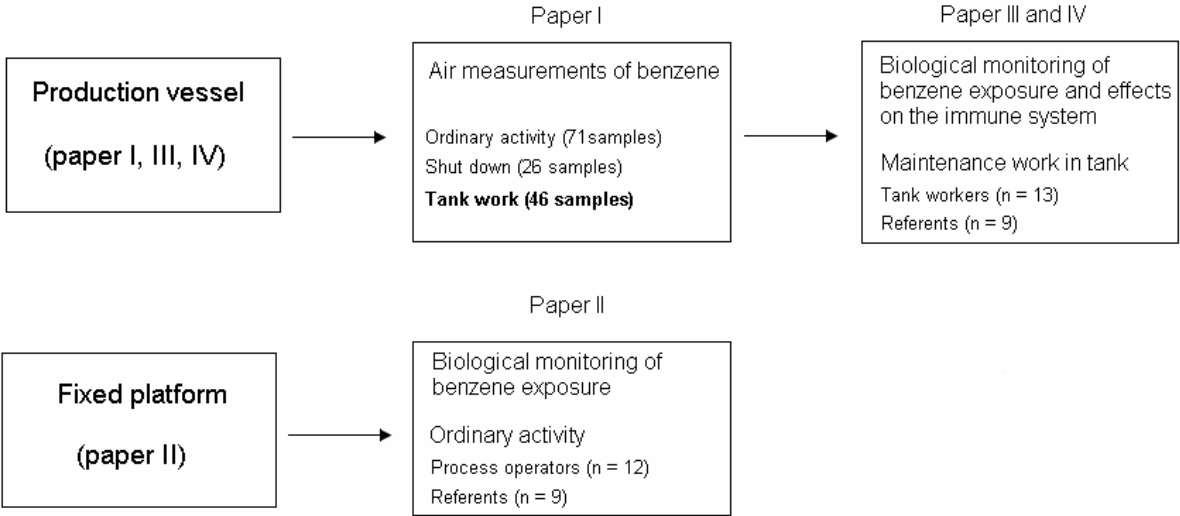


Figure 1 Flow diagram showing the included modes of operations and the corresponding papers. Tank work (bold) in paper I includes both cleaning of a cargo tank and a drain water seal tank and maintenance work in cargo tanks. Biological monitoring of tank workers in paper III and IV includes only tank workers maintaining cargo tanks.

3.1.2.1 Workers from the crude oil production vessel (paper I, III and IV)

Measurements of benzene in air during ordinary activity, shut down and tank work. The individual exposure to benzene during ordinary activity, during a brief shutdown and cleaning of a drain water seal tank was assessed for workers from three of a total of six work shifts over a three week period in March 2004. The air measurements performed on 13 tank workers in July 2004 and April 2005 were also included in the analysis.

The workers included in the study on the production vessel, were divided into four job categories. *Process operators* survey the production process via computers in a central control room, but also have practical tasks such as sampling and analysing oil and the water produced, fault-finding and repairing. The *deck workers* are in the marine department and are responsible for maintaining the vessel, such as the deck, tanks and hull. The *mechanics* repair, replace, adjust and align components of various types of machinery and equipment such as compressors, turbines and pumps. The *contract workers* are employed by contractors and perform jobs for a limited period of time, such as surface treatment, isolation and tank maintenance. Administrative personnel, catering personnel and workers from the department of electricity and instruments were not included in the study. For each sampling period for ordinary activity and during shut down, all eligible process operators (n = 8), deck workers (n = 12) and mechanics (n = 10) entering the processing area on the first day of sampling were invited to participate. All the workers agreed to participate. Contract workers (n = 4) were only included during the shutdown.

Biological monitoring of workers maintaining cargo tanks. The study performed on tank maintenance personnel (paper III and IV) included 13 men performing maintenance work in cargo tanks containing residues of crude oil and nine referents (three women) with shift schedules matching those of the tank workers. Referents were recruited from the catering section on the same vessel. Maintenance work in the tanks (5000–7800 m³) included tank inspection, scaffold building and welding (picture 2 and 3 in appendix 1). The workers used half-mask air-purifying respirators with a

combination filter containing both a particle and an organic gas filter. However, the use of the respirators varied between the workers and the workers replaced the filter with varying frequency.

3.1.2.2 Workers from the fixed platform (paper II)

Biological monitoring of process operators during ordinary activity. The study performed on the fixed platform included 12 process operators during ordinary activity (8 men and 4 women) and nine referents (6 men and 3 women) with shift schedules matching those of the process operators (figure 1). The referents were mainly recruited from the catering section on the same installation. Preliminary exposure assessment during normal operation had identified some work tasks for process operators that were expected to be associated with relatively high, short-term exposure to hydrocarbons. These were inspection and work in the flotation area, sampling and analysis of crude oil and produced water, and sending and receiving pipeline cleaning pigs. The workers used half-mask air-purifying respirators with a combination filter only during work in the flotation area. Typical tasks performed during ordinary activity is given in picture 4 in appendix 1.

3.1.3 Individual exposure to airborne benzene (paper I-IV)

3.1.3.1 Sampling strategy for air measurements

In all studies (paper I-IV) the individual benzene exposure of the workers was monitored using organic vapour passive dosimetry badges (3M 3500[®], St.Paul, MN, USA). The badges were worn in the breathing zone over a full work shift on three consecutive work days (paper II-IV). In paper I the selected workers carried the dosimeter badges on three consecutive days for ordinary activity and two consecutive days during a brief shutdown. The personal exposure to benzene was not measured for referents, as they were assumed not to be exposed to benzene above the background level in the indoor environment.

The tasks performed during the sampling period were recorded using a personal log filled in daily by each worker (paper I and II). An example of the log is given in

appendix 4. For tank workers (paper III and IV) the time spent in tank was systematically logged and used as a surrogate measure of hydrocarbon exposure.

3.1.3.2 Method of analysis

After sampling, the badges were stored in a freezer (-20°C) until they were transported to X-lab in Bergen, Norway, for analysis. The benzene was desorbed in CS_2 and analysed quantitatively and qualitatively by gas chromatography with mass spectrometry.¹⁰¹ In paper II the samples were also analyzed for toluene, ethylbenzene and xylene by the same method as for benzene. The level of detection was 0.001 ppm.

3.1.4 Biological monitoring of benzene and its' relation to effects on the immune system (paper II-IV)

3.1.4.1 Sampling strategy

The study period for all workers comprised three consecutive work shifts. The study protocol for both tank workers and process operators is given in figure 2. Each subject provided three samples of blood and urine. Blood and urine samples were obtained from the referents on the same days following the same time protocol.

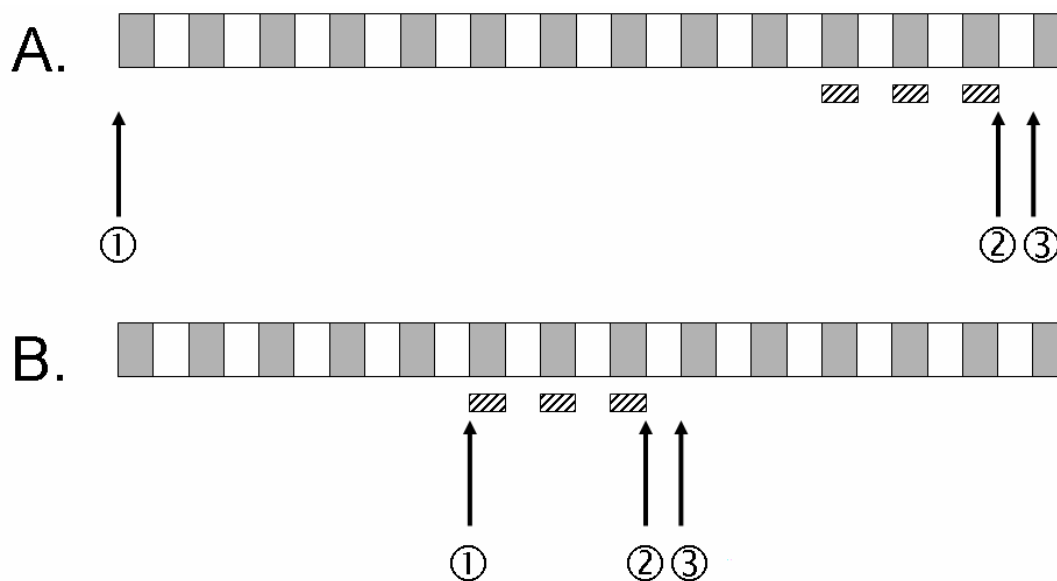


Figure 2 Study protocol for the biological monitoring of process operators during ordinary activity on a fixed platform (A) and tank workers during maintenance work on a crude oil production vessel (B). The white and grey boxes indicate 12 hour intervals, where grey boxes indicate work shifts (12 hours) and white boxes indicate periods of rest (12 hour). The hatched boxes indicate monitoring of benzene in the workers breathing zone (full shift). The arrows indicate the time of collection of the blood and urine samples, where ① is pre-shift sample, ② is post-shift sample, and ③ is pre-next shift sample.

For the process operators on the fixed platform (Figure 1 A) the first sample was collected in the morning at the heliport before departure to the oil production facility (pre-shift), and was considered baseline measurement. Due to extended work shifts (0700-1900 or 1900-0700) and work periods of 14 consecutive days, it has been speculated that the benzene might accumulate during the work period. We therefore collected the second sample immediately after the work shift on the 13th work shift of the offshore work period (post-shift) and a third sample was collected prior to the following work shift (pre-next shift).

The first sample for the tank workers (Figure 1 B) was collected in the morning before the workers entered the tank (pre-shift) and was considered a baseline measurement.

The second sample was collected at the end of the work shift on the third day of tank work (post-shift), and a third sample was collected in the morning on the following day (pre–next shift).

Since benzene has a short half-life in blood,^{8,18} the workers were asked to come directly to the hospital on the installation after changing from work overalls. Further, the workers were asked to refrain from smoking before the blood sample was collected.

All participants completed a self-administered questionnaire including questions on age, sex and whether they were current smokers during the study period (Appendix 5). Smoking was prohibited on the production vessel, but the living quarters had a limited number of designated smoking rooms. Since alcohol consumption is completely banned on offshore oil and gas installations, no participant consumed alcohol during the study period. During the study period, all subjects lived on the installation and were exposed to the same environment in the living areas and had similar work schedules and diet. The referents spent the whole work period inside the living quarters.

3.1.4.2 Biomarkers of benzene exposure (paper II-IV)

Blood samples for determining unmetabolized benzene were collected by venipuncture into Venoject II[®] (Terumo, Leuven, Belgium) tubes (hard plastic) with heparin, and the urine samples for determination of unmetabolized benzene were collected in glass bottles (Pyrex[®], Barloworld Scientific, Staffordshire, UK) with polypropylene stoppers. The samples were stored at 4°C until they were transported to the Biomonitoring Laboratory at the Finnish Institute of Occupational Health in Helsinki, Finland. Upon arrival to the laboratory within 4–7 days after sample collection, the samples were immediately put into vapour-tight vials and kept at 4°C until analysis.

3.1.4.3 Biomonitoring of effects on immune parameters (paper IV)

Blood samples for determining peripheral blood lymphocytes (total lymphocytes, lymphocytes in subpopulations CD3, CD4, CD8, CD19, CD56 and CD4/CD8 ratio) were collected by venipuncture into Vacutainers containing EDTA. The blood samples for determining the serum concentration of immunoglobulins (IgG, IgA, IgM and IgE) and complement factors C3 and C4 were collected into Vacutainer serum separation tubes. The samples were kept at room temperature and transported to Haukeland University Hospital in Bergen, Norway, for analysis within three days after sampling.

3.1.4.4 Method of analysis

Benzene in blood (paper II-IV). The concentration of benzene in blood was analysed by a head-space sampler (Perkin Elmer Headspace sampler HS40, Weellesley, MA, USA) and a gas chromatograph (Perkin Elmer Autosystem Gas Chromatograph) using photoionization detection according to the method described by Pekari and co-workers.^{8,102} The samples with benzene levels at or above 5 nmol/l were analysed by multi-head space extraction as described by Ettore and Jones.¹⁰³ The quantifications were based on an external standard method. The level of quantification was 1 nmol/l.

Benzene in urine (paper II-IV). The urinary level of benzene was analysed using a solid phase micro-extraction–gas chromatograph–iontrap method (SPME-GC-Iontrap-method). The urine sample (500 µl) was transferred to a vial of 2.0 ml containing 100 µl of internal standard chlorobenzene. The sample was injected by a solid-phase microextraction fibre (polydimethylsiloxane, 100 µm) in an autosampler (Varian 8200 CX autosampler, Palo Alto, CA, USA), separated and analysed using a gas chromatograph (Varian Saturn 3400 CX) and a mass spectrometer (Varian Saturn 2000). In SPME mode the absorption time was 20 minutes and desorption time 1 min.

The GC conditions used were as follows: HP-5MS-column (30 m x 0.25 mm, 0.25 µm film thickness, Agilent Technologies, Palo Alto, CA, USA); helium carrier gas at a flow rate of 5 ml/min. A Varian injector liner (0.8 mm i.d.) was used with the injector temperature of 250 °C and splitless injection mode. The MS transferline and source temperatures were 180 °C and 140 °C, respectively. GC oven temperature was

programmed from 40 °C (3 min initial hold) to 100 °C at 10 °C/min, and then to 200 °C at 30 °C/min (final temperature, 1 min hold). Ions 50⁺, 77⁺ and 78⁺ were selected for quantifying benzene. The quantifications were based on an internal standard method. The level of quantification was 1 nmol/l.

Immune parameters (paper IV). Serum concentrations of the immunoglobulins IgM, IgA and IgG and the complement factors were quantified in a Behring nephelometer using monospecific antisera (Behringwerke AG, Germany) using specific antibodies. Serum IgE was determined with Pharmacia UniCAP 1000 System (Pharmacia Diagnostics AB, Uppsala, Sweden).

Total lymphocyte count was performed using the ADVIA[®] 120 Hematology System (Bayer AG, Bayer Healthcare, Tarrytown, NY, USA). For assessing the subpopulations of lymphocytes, blood was processed for flow-cytometric immunophenotyping, erythrocytes were lysed by hypotonic treatment before leukocytes were immunostained with either fluorescein isothiocyanate–conjugated or phycoerythrin-conjugated mouse monoclonal antibodies against defined CD antigens. Antibodies were obtained from Becton Dickinson (Palo Alto, CA, USA). Cell analysis was performed on a Coulter Epics XL flow cytometer (Coulter Electronics Ltd, Luton, UK).

3.1.5 Statistical analysis

The estimates of individual exposure levels to benzene (paper I-IV), toluene, ethylbenzene and xylene (paper II) and concentration of benzene in blood and urine were given both as arithmetic mean, geometric mean and range (minimum and maximum). The distribution of all these variables was tested for normality using the Shapiro-Wilk test. All variables had a skewed distribution and were therefore log-transformed (ln) before comparing subgroups (t-test and ANOVA). Concentrations of individual measurements of benzene below the level of detection were replaced with values equal to the level of detection divided by 2 (paper I and II). Blood and urinary benzene concentrations below the level of quantification and individual benzene

exposure for referents were replaced by values equal to the level of quantification divided by 2 (papers II-IV).¹⁰⁴

The associations between benzene exposure in the work environment and benzene concentration in biological media were estimated using Pearson's correlation coefficient. The associations between change in benzene exposure in the work environment and change in benzene concentration in biological media were also adjusted for the corresponding baseline concentrations by including the baseline concentration as a covariate in regression analyses. Further, these associations were also adjusted for gender, age and smoking by including each of these in separate multiple regression analyses.

Pearson's correlation coefficient was also used for estimating the association between the change in immune parameters for the various time points and the exposure measurements. A few of the immune parameters deviated significantly from normality, and Spearman's rank correlation coefficient was used for these. We also performed multiple regression analysis including the baseline value of the variable in question as a covariate. The associations between the exposure measurements and the various immune parameters were adjusted for sex, age and current smoking by including these in separate multiple regression analyses.

Tests were considered significant at the level of 0.05. We performed all analysis using SPSS 14.0.1 (SPSS Inc., Chicago, IL, USA).

3.2 Risk of hematopoietic malignancies in a historical cohort of offshore workers

3.2.1 Study population and study design

A historical cohort study of the cancer incidence in Norway's offshore petroleum industry was performed. Statistics Norway established the cohort using the information from the Norwegian Registry of Employers and Employees, which is owned by the Norwegian Labour and Welfare Organisation. All employers in Norway

are required to register their employees with a personal identification number, industrial classification codes International Standard Industrial Classification (ISIC) or Classification of Economic Activities in the European Union (NACE), county of work and the first and last date of all their engagements. The Registry requires that all engagements with mean of four hours of work per week, provided that the engagement lasts for at least six weeks, must be registered. By July 31, 2004, the Registry included a total of 1,961,711 workers contributing with 2,126,699 work engagements.⁷⁴

The Norwegian Registry of Employers and Employees was established in 1978, became operational in 1983 and contains employment from 1981 and onwards. Since the Cancer registry included, at time of study, only cases until 2003, we used the employments from 1981 until 2003. Norway's petroleum industry has been operating offshore since the early 1970s and therefore the cohort does not include all workers who were engaged during the period 1970-1980. Still, many of these workers might be included in the cohort with possible new engagements registered after 1981. This means that some of these early subjects might have had a longer engagement offshore than registered in our cohort.

The criteria we used for the cohort of petroleum workers were workers registered with one of the following offshore-related industrial classification codes: ISIC 22 (extraction of crude oil and natural gas), ISIC 5032 (oil drilling), NACE 11100 (extraction of crude oil and natural gas) and NACE 11200 (service activities incidental to oil and gas extraction excluding surveying), or having Norway's continental shelf (North Sea) as the work location.

Based on the workers' location of work (onshore or offshore) and the industrial classification codes for their first registered engagement in the offshore-related petroleum industry, we categorized the petroleum workers into the five job categories 1) upstream operator offshore, 2) drilling and well maintenance offshore, 3) catering offshore, 4) others offshore and 5) petroleum workers onshore.

The category "upstream operator offshore" contained workers registered with the NACE and ISIC code "extraction of crude oil and natural gas". These workers mainly

work in the production and processing unit. This includes job categories such as process technicians, laboratory engineers, control operators and other job groups involved in the production process including stabilization, separation and fractionation of the crude oil, natural gas and natural gas liquids. The category “drilling and well maintenance offshore” includes the ISIC code 50230 (oil drilling) and NACE code 11200 (service activities incidental to oil and gas extraction excluding surveying). NACE code 11200 comprises activities such as drilling of wells and installation, disassembling and maintenance of drilling towers at site on contract and includes job groups such as drill floor crew, derrick employees, mud loggers and engineers, shale shaker operators and well service crew. The category “catering offshore” includes job groups such as catering crew, chefs and housekeeping personnel. The category “others offshore” includes miscellaneous industrial codes and comprises activities contracted out to oil field service companies, such as construction and maintenance personnel and logistics. Finally, “petroleum workers onshore” contains workers registered with an offshore-related engagement without being registered with the North Sea as the location of work. This job category contains workers involved in administering, planning and coordinating the activities offshore.

We drew up to six referents per petroleum worker at random from the general working population, using the same Norwegian Registry of Employers and Employees and the same year of the first engagement of the corresponding petroleum worker. We matched the referents to the petroleum worker by gender, age and community of residence. The crude historical cohort included 71,018 workers from the petroleum industry (“at risk”) and 424,584 referents. We excluded subjects from the cohort if they had had a cancer diagnosis before entering into the cohort ($n = 3784$) and referents if they had had an earlier engagement in the petroleum industry before they were drawn as referents ($n = 29,004$). We allowed subjects to serve as referents for more than one “subject at risk”. The final cohort included 27,919 offshore workers (89% men) distributed on the four offshore job categories comprising 332,063 person-years.

Statistics Norway established and linked the cohort to the Cancer Registry of Norway in April 2006, including all cases of cancer reported up to December 31, 2003 with information on the date of diagnosis and the diagnosis (location, morphology and histology). The cancer cases were coded according to a modified version of the International Classification of Diseases (ICD-7, three-digit codes). The Cancer Registry of Norway is a population-based registry that has systematically collected notifications on cancer since 1952. The registry is for practical purposes complete from 1953. The Cancer Registry of Norway is based on reporting from multiple sources, such as physicians, pathology laboratories and death certificates from Statistics Norway mentioning cancer or cancer-related illnesses, ensuring a high degree of accuracy and completeness. A description of the data sources in respect to completeness, data quality and stability, is given in the report Cancer in Norway 2004.¹⁰⁵ Statistics Norway also linked the cohort to the Norwegian Cause of Death Registry and the Norwegian Education Registry, including the variable highest completed education, ranging from 1 (elementary school) to 6 (PhD degree).

3.2.2 Statistical analysis

We estimated the rate ratios comparing the various working categories with the general working population using the Cox proportional hazard regression model. The subjects were censored at the end of follow-up (December 31, 2003), the date of death or date of diagnosis of another type of cancer than the one being studied, whichever occurred first. We checked the proportional hazards assumption for overall cancer and all hematopoietic malignancies by comparing the estimated $-\ln(-\ln)$ survivor curves for the different groups being investigated. There was no marked deviation from the proportional hazards assumption. We performed multivariate analysis including the independent covariates age, gender, year of first engagement and educational level. We also performed subanalysis including the engagements during the first 5 years only (1981–1985) and including the remaining 18 years (1986–2003).

We performed all analysis using SPSS 14.0.1 (SPSS Inc., Chicago, IL, USA).

3.3 Ethical considerations

We conducted the study with the approval of the Western Norway Regional Committee for Medical Research Ethics, the Norwegian Data Inspectorate/the Norwegian Social Science Data Services and the Directorate for Health and Social Affairs. The Ministry of Health and Care Services gave permission to establish a biobank and to transfer the biological material abroad for analysis.

Informed written consent was obtained from all participants included in the study “Biological monitoring of benzene exposure and effects on the immune system” (appendix 3). All subjects were informed about their own results, both in personal letters, in written reports and/or in oral presentations at their work site.

In the historical cohort study, Rikstrygdeverket (now merged into the Norwegian Labour and Welfare Organisation) gave us permission to use the Norwegian Registry of Employers and Employees, the Cancer Registry of Norway provided data, and Statistics Norway (Ministry of Finance) approved the use of information from the Norwegian Cause of Death Registry and the Norwegian Education Registry.

4. SUMMARY OF RESULTS

4.1 Benzene exposure on a crude oil production vessel (paper I)

The personal exposure to benzene was assessed for 42 workers on a production vessel in the Norwegian sector of the North Sea. The arithmetic and geometric mean of benzene exposure for all measurements (n=139) was 0.427 ppm and 0.018 ppm, respectively. Twenty-five measurements (18%) were below the limit of detection (0.001 ppm), while 10 samples (7.2%) exceeded the occupational exposure limit of 0.6 ppm. The geometric mean exposure was 0.004 ppm (95% CI 0.003–0.006) during ordinary operation, 0.010 ppm (95% CI 0.005–0.020) during shutdown and 0.282 ppm (95% CI 0.163–0.488) during tank work. Workers performing annual cleaning and maintenance of tanks containing crude oil or residues of crude oil had higher levels of exposure than workers performing other tasks, including work near open hydrocarbon-transport systems (all $P < 0.001$). The job categories explained only 5.3% of the variance in exposure, whereas grouping by mode of operation explained 53.8% of the variance and grouping by task 68.0%.

4.2 Biological monitoring of benzene exposure for process operators during ordinary activity in the upstream petroleum industry (paper II)

The exposure to benzene and related aromatics and the uptake of benzene were assessed among 12 crude oil process operators during ordinary activity and among 9 referents. Process operators' arithmetic mean exposure over the three-day study period was 0.042 ppm (range <0.001-0.688 ppm) for benzene, 0.05 ppm toluene, 0.02 ppm for ethylbenzene and 0.03 ppm for xylene. Full-shift personal exposure was significantly higher when flotation work was done during the shift compared to when other tasks were carried out. Work in the flotation area was associated with a short-term (6-15 min) arithmetic mean exposure to benzene of 1.056 ppm (range 0.092-2.326 ppm). The concentrations of benzene in blood and urine were not different between operators and referents at any of the time points. However, when adjusting for

being a current smoker in regression analyses there were significant associations between benzene exposure and post-shift concentration of benzene in blood ($P=0.01$) and urine ($P=0.03$), respectively.

4.3 Biological monitoring of benzene exposure during maintenance work in crude oil cargo tanks (paper III)

The association between the individual concentration of benzene in the breathing zone and the concentration of benzene in blood and urine was analysed among 13 workers maintaining crude oil cargo tanks and nine referents. The individual geometric mean benzene exposure in the breathing zone of the ten workers performing tank work over three consecutive days was 0.15 ppm (range 0.01–0.62 ppm). The tank workers' post-shift geometric mean benzene concentrations were 12.3 nmol/l in blood and 27.0 nmol/l in urine versus 0.7 nmol/l benzene in both blood and urine among the referents. Benzene in the work atmosphere was highly correlated with the internal concentration of benzene both in post-shift blood ($r = 0.87$, $P < 0.001$) and post-shift urine ($r = 0.90$, $P < 0.001$), indicating that the varying use of respirators observed did not explain much of the variability in absorbed benzene.

4.4 Acute suppression of serum IgM and IgA in tank workers exposed to benzene (paper IV)

The associations between benzene exposure and alterations of proteins and cells of the immune system was investigated among 13 tank workers maintaining cargo tanks containing crude oil residues and nine unexposed referents (catering section). The geometric mean benzene concentration in blood post-shift was 12.3 nmol/l among tank workers versus 0.7 nmol/l among the referents. The tank workers declined (versus referents) in IgM from baseline to post-shift (t-test, $P=0.04$) and in IgA from baseline to pre-next shift (t-test, $P=0.01$). The tank workers also declined in CD4 T cells from baseline to post-shift (t-test, $P=0.04$). The benzene concentration in blood post-shift correlated markedly with the variation in the pre-next shift suppression of IgM

($r=-0.52$, $P=0.040$) and IgA ($r=-0.54$, $P=0.031$). The groups did not differ significantly in change in IgG, IgE or lymphocytes in the subpopulations of CD3, CD4, CD8, CD19, CD56 and CD4/CD8 ratio or in the complement factors C3 and C4.

4.5 Increased risk of hematopoietic malignancies in Norwegian offshore workers (paper V)

The Norwegian Registry for employers and employees was used to establish a cohort of 27,919 offshore workers in four job categories and 366,114 referents matched on age, gender and community. After linking to the Cancer Registry of Norway we found that workers in the job category “upstream operator offshore”, who potentially have the highest exposure to crude oil and other products containing benzene among the four groups, had an excess risk of hematopoietic malignancies (RR 1.90, 95% CI 1.19-3.02). The risk was also significantly increased for the subgroups of acute myelogenous leukemia (RR 2.89, 95% CI 1.25-6.67) and multiple myeloma (RR 2.49, 95% CI 1.21-5.13). The risk ratios were highest for the workers with their first registered engagement in the offshore petroleum industry before 1986. No increased risk was found for the other job categories, and no differences were found for overall cancer (all sites). Further, no increased risk was found for lung cancer or upper respiratory organs among the “upstream operator offshore” workers, arguing against smoking being the cause of the increased risk of hematopoietic malignancies.

Although we can not exclude a possible contribution of other specific or combined exposures, occupational exposure to benzene is still the most likely causative agent for this increased risk.

5. DISCUSSION

5.1 Main findings

5.1.1 Air measurements of benzene

5.1.1.1 Ordinary activity (paper I and II)

During ordinary activity full-shift benzene exposure levels measured in the workers breathing zone were low for workers on the crude oil production vessel (paper I) and for process operators at the fixed oil- and gas installation (paper II). The exposure varied considerably, with some measurements being higher than the Norwegian occupational exposure limit of 0.6 ppm for a 12-hour shift.

The low mean exposure to benzene measured during ordinary activity is in accordance with previous studies in the offshore petroleum industry.^{80,81,83} Steinsvåg and co-workers⁸³ pooled full shift measurements (12 hours) of benzene exposure sampled in processing- and drilling area of 12 installations on the Norwegian continental shelf in the period 1994-2003 (n=367). They reported arithmetic and geometric mean exposure of 0.037 and 0.0067 ppm benzene, ranging from below level of detection to 2.6 ppm. A retrospective exposure assessment of benzene in the Australian petroleum industry suggested a mean exposure of 0.02 ppm for the job group “upstream operators offshore”.⁸¹ In the conventional oil and gas sector of the upstream petroleum industry in Canada, 198 personal long-term samples from the years 1985 to 1996 were within the range of <0.001–2.431 ppm, with an arithmetic mean of 0.064 ppm and a geometric mean of 0.011 ppm.⁸⁰ The present study confirms that although relatively high short-term exposure to benzene occurs, the fullshift benzene exposure levels during ordinary activity are low.

5.1.1.2 Short shut down (paper I)

In contrast to ordinary activity, when the processes take place in closed systems which are opened only for shorter periods, it is expected that the benzene exposure is higher during shutdowns where the processing equipment is opened for cleaning and

maintenance. In the present study the exposure differed by a factor of 2.5 between the two modes of operation. The maintenance work during the short shutdown in the present study included opening of hydrocarbon-transport system for visual inspection, but did not include entering separators, tanks or vessels containing crude oil residues, which is done during ordinary shutdowns. The exposure level might therefore be fairly representative for high activity rather than for a real shutdown, which probably would have shown even higher levels of exposure.

5.1.1.3 Tank work (paper I)

Cleaning of tank was associated with markedly higher benzene exposure than both ordinary activity and shut down, with a geometric mean of 4.42 ppm (range 1.14 to 16.75 ppm). Exposure was highest while cleaning the drain water seal tank, implying vacuum pumping of a mixture of water, crude oil and other mixtures of hydrocarbons from the deck. Because of the mandatory use of half-mask respirators during cleaning, the actual personal exposure was probably lower, although little is known about the effectiveness of such protective equipment during tank work. Further, we also know little about the actual use of this protective equipment. In another study benzene exposure during cleaning of crude oil vessels was comparatively high, ranging from non detectable to 5.8 ppm when averaged over the duration of the whole task.⁸⁴ In a retrospective exposure assessment for benzene in the petroleum industry in Australia, Glass and co-workers⁸¹ estimated an exposure level of 2.01 ppm benzene during cleaning of crude tanks. Finally, Runion⁷⁸ have summarized common operational exposure data from the petroleum industry in the United States ($n = 124$) and reported that personal short-term benzene exposure levels during gauging of crude storage tanks ranged from <0.032 to 160 mg/m^3 ($<0.01 - 50$ ppm benzene). The present study confirms that the benzene exposure during cleaning of tanks containing residues of crude oil is markedly above the Norwegian occupational exposure limit of benzene. The use of proper respiratory protection is imperative for this type of work.

5.1.1.3 Determinants of exposure on the production vessel (paper I)

To identify which of the determinants job categories, operation modes and tasks that contributed most to the exposure to benzene, the benzene exposure was assessed by grouping the measurements according to these determinants.

The task performed was a major determinant of exposure; grouping the measurements according to the task performed explained 68% of the variation. Cleaning of tanks containing residues of crude oil showed the highest level, with a geometric mean of 4.42 ppm, more than seven times the Norwegian occupational exposure limit offshore of 0.6 ppm. The measurements taken during maintenance work in cleaned tanks had a geometric mean of 0.15 ppm, about 13 times higher than the exposure during work near open hydrocarbon-transport systems and 74 times higher than the exposure measured during other tasks.

The mode of operation, which partly overlaps with the categories of the task performed, explained 54% of the variation in exposure. The explained variation was mainly caused by the high exposure found among tank workers compared to the other operation modes.

The job categories explained only 5% of the variance in the exposure level on the crude oil production vessel. This indicates that job category is a poor determinant of exposure, probably due to the fact that workers from the different departments often work in teams on a range of activities that are associated with large variation in the day-to-day exposure to benzene.

5.1.2 Biological monitoring of benzene exposure

5.1.2.1 Ordinary activity on a fixed oil- and gas installation (paper II)

With respect to ordinary activity, the concentration of benzene in blood or urine was not significantly different between the process operators and referents at any of the time points. Further, no association between benzene in the breathing zone and concentration of benzene in blood and urine immediately after work hours (post-shift)

or prior to the following work shift (pre–next shift) was found. However, when adjusting for being a current smoker in a multiple linear regression there were significant associations between benzene exposure on the third day of sampling and post-shift concentration of benzene in blood and urine. Benzene exposure and being a current smoker explained 87.1% and 79.1% of the variances in benzene concentration in blood and urine, respectively. Hence, although there was no difference in internal concentration of benzene between process operators and referents, there was an indication of benzene uptake within the range of exposures representative for ordinary activity on the installation.

5.1.2.2 Maintenance work in crude oil cargo tanks (paper III)

Despite a relatively low mean benzene exposure in the work environment of 0.23 ppm (38% of the Norwegian occupational exposure limit for a 12-hour shift) averaged over the three-day study period and use of respirators to a varying degree, the tank workers maintaining crude oil cargo tanks had a significantly higher benzene concentration in both blood and urine than the referents at all time points. Both the benzene exposure in the workers breathing zone and time spent in the cargo tank were highly correlated with the internal concentration of benzene in blood and urine.

The internal concentration of benzene was higher than expected at the measured exposure levels. German Research Foundation⁷¹ has investigated the relationship between the concentration of benzene in the workplace air and in blood when not using personal protective equipment. These relationships, called exposure equivalents for carcinogenic substances (EKA values), allow the determination of the body burden resulting from uptake of the substance exclusively by inhalation. According to these EKA values, exposure to 0.3 ppm benzene in the breathing zone corresponds to a benzene concentration post-shift of 0.9 µg per liter of blood, which is about 11.5 nmol benzene per litre of blood. The group of tank workers in the present study absorbed a similar amount of benzene after being exposed to only 50% of the corresponding exposure level – that is, a geometric mean exposure of 0.15 ppm caused a geometric mean benzene concentration in blood of 12.3 nmol/l. The corresponding arithmetic

value for the mean exposure of 0.23 ppm was a benzene concentration in blood of 17.3 nmol/l. Thus, despite using respiratory protective equipment, the tank workers absorbed more benzene than expected. Several factors might explain the increased absorption of benzene:

i) Extended work hours

Most standards for chemical exposure in the work environment, including occupational exposure limits and biological action limits, apply to workers with a conventional schedule of eight hours per day five days per week rather than 12 hour work days. Although the mean time period the tank workers spent in the tank on the third day of study corresponded only to 44% of the total work shift of 12 hours, the extended work schedule may have contributed to the increased absorption.

ii) Physical strain

Physical strain, as experienced by the tank workers, increases uptake of organic solvents mainly due to increased pulmonary ventilation and blood flow.^{9,19,25,26} Hence, uptake of benzene might be severely underestimated when based exclusively on time-weighted average values of benzene exposure.

iii) Smoking

Finally, although smoking was prohibited in the oil and gas production areas, the living quarters had a limited number of designated smoking rooms. The increased level in tank workers might have been caused by more smokers in the exposed group (three current smokers) as compared to referents (one current smoker). Nevertheless, adjusting for current smoking and the baseline level of benzene did not materially change the reported correlations between the exposure measures for benzene. It should be noted, however, that the number of subjects in this study was not sufficient for evaluating differences in benzene exposure among current smokers and referents.

The most likely explanation of the increased uptake is probably the extended work hours and physical strain.

5.1.3 Acute alterations of immunesystem among tank workers (IV)

The tank workers' relatively low benzene exposure (paper III) correlated significantly with suppression of serum IgM, IgA and CD4 T cell concentrations. Tank workers had a significantly lower IgM at baseline than referents, and the tank workers' IgM further declined to post-shift compared to referents. Whereas the referents' IgA increased non-significantly and was restored in the pre-next shift sample, the tank workers' IgA declined from baseline to pre-next shift. Also the tank workers' total CD4 T cells declined from baseline to post-shift. The suppression of all these immune parameters was highly correlated with benzene exposure in the working environment, benzene in blood and urine and/or time spent in the tank. The groups did not differ significantly in IgG and IgE, complement factors 3 and 4, other subgroups of lymphocytes or CD4/CD8 ratio.

The published literature provides no major support for a toxic effect of benzene on immunoglobulin production. Suppression of IgA and IgG, accompanied by an increased level of IgM, has been reported in painters occupationally exposed to benzene, toluene and xylene,³⁹ whereas another cohort of painters exposed to organic solvents, including benzene, had significantly lower IgM than referents.⁴⁰ Further, Bogadi-Sare and co-workers⁴⁴ found no differences in IgA, IgM or IgG between benzene-exposed shoe workers and controls, but reported a significant association between IgG and benzene exposure in the working environment.

In the present study, changes in concentrations of IgM and IgA took place during a shorter time interval than the half-lives of the immunoglobulins, which are reported to be approximately 5 and 6 days for IgM and IgA, respectively.¹⁰⁶ One explanation for the changes might therefore be enhanced extravasation, maybe owing to receptor-mediated transport, as concentrations of IgG were unchanged. Another explanation might be that benzene impairs or inhibits B-cells from being activated, causing an immediate lowering of the immunoglobuline production.

The reduction in CD4 T cells we reported is even more difficult to interpret. Subpopulations of lymphocytes are suggested to be the most sensitive target cell for

the immunotoxic effect of benzene in human studies.^{33,44,45} In the present study the change in total CD4 T cells was significantly correlated with the exposure to benzene. However, although the tank workers total circulating CD4 T cells declined significantly from baseline to post-shift as compared to referents, the mean CD4 T cells did not significantly differ between the two groups at any of the measured time points. Our results are inconclusive regarding whether benzene exposure or maintenance work in crude oil tanks have an immunosuppressive effect on CD4 T cells.

In addition to being a known source of benzene exposure,⁶⁶ smoking has been reported to influence lymphocyte subpopulations.^{107,108} A synergistic effect of smoking on solvents' immunosuppressive effect has been suggested.^{39,43} Biro and co-workers⁴⁵ reported a significant correlation between smoking and the level of several lymphocyte subsets. However, adjusting for current smoking did not materially change any of the reported associations that we found.

The exposure surrogate "time spent in the tank" correlated slightly higher with the change in both IgM and IgA than did the various direct measures of benzene exposure. The time spent in the tank explained 20% and 43%, respectively, of the variation in the suppression of the immune parameters. Given the complexity of the tank atmosphere, we cannot exclude that combined exposure or specific exposure to other compounds in the tank atmosphere might have caused the reported alterations of the immune system, such as polycyclic aromatic hydrocarbons^{109,110} and ionizing radiation.¹¹¹ Further, the high work load might have influenced the concentrations of the immunoglobulins in tank workers. A significant decrease in serum IgM, IgA and IgG have been reported in men participating in a 5-7 days military training course involving strenuous exercise.¹¹²

The clinical significance of the acute alterations on the immune parameters IgM, IgA and CD4 T helper cells for the tank workers' health is not known. Peripheral blood is not the primary target organ for benzene's toxicity, and measuring the level of immune parameters in serum after a given exposure is not an optimal measure for decreased

immunocompetence. All subjects had individual values within the clinically normal range, and the values of tank workers and referents overlapped considerably. Further, the immune system is a compensatory system likely to have reserve capacity, and few quantitative data have been published on how much the studied immune parameters might change before the risk of disease increases.¹¹³ However, whereas a single depression of these immune parameters at these levels hardly represents any deficiency, we can not preclude that such repeated depressions over longer periods of time, together with co-exposure to other carcinogenic agents and irritants, might represent a health risk.

5.1.4 Increased risk of acute myelogenous leukemia and multiple myeloma in offshore workers exposed to crude oil

Although offshore workers probably have been exposed to relatively low levels of benzene during ordinary activity, offshore workers in Norway's offshore petroleum industry had a significantly increased risk of developing acute myelogenous leukemia and multiple myeloma compared to the general working population. The risk was elevated among upstream operators and workers involved in drilling operations. These workers are assumed to have a potential for high exposure to benzene through contact with either different phases of crude oil, drilling mud containing aromatic hydrocarbons and other products containing benzene. Given the established association between benzene exposure and hematopoietic malignancies,^{46,47} benzene exposure probably caused the increased risk of acute myelogenous leukemia and multiple myeloma observed.

A controversial issue is what levels of exposure benzene poses an increased risk of developing hematopoietic malignancies.^{34,98,114,115} Information about past exposure to benzene in Norway's offshore petroleum industry is scarce,⁸³ and no good exposure estimates exist for the various job categories. The published data on benzene exposure in the petroleum industry indicate that the exposure has been relatively low during ordinary activity,^{80,81,83, paper I and II} but that workers have experienced relatively high

levels of benzene whenever the processing system was opened for cleaning and maintenance of vessels, separators and tanks.^{78,84, paper I}

The association between benzene exposure and the development of specific subtypes of leukemia is still unclear. In our study the risk was highest for acute myelogenous leukemia. The elevated risk of acute lymphatic leukemia was based on only two cases in the exposed groups and therefore not statistically significant. The most recent meta-analysis of benzene exposure and leukemia subtypes includes nine cohorts and 13 case-control studies from several industries. This study found a high and significant risk of acute myelogenous leukemia, with a positive dose-response relationship across study designs.⁴⁷ The risk for developing chronic lymphocytic leukemia was increased in the case-control studies but not in the cohort studies. The data for chronic myelogenous leukemia and acute lymphocytic leukemia were sparse and inconclusive.

Our results on acute myelogenous leukemia were in accordance with previous studies, but the association between benzene exposure and multiple myeloma is a contentious issue.^{49,51,52} A meta-analysis of 22 cohort mortality studies consisting of 250,000 petroleum workers, mainly from refinery and distribution, concluded that petroleum workers do not have an increased risk of multiple myeloma as a result of their exposure to benzene, benzene-containing liquids or other petroleum products in their work environment.⁵³ In contrast, a more recent meta-analysis comprising seven cohort studies focusing on benzene-exposed workers, including refinery workers, reported a significant excess in the relative risk of multiple myeloma in relation to benzene exposure (relative risk 2.13, 95% CI = 1.31–3.46).⁵⁴ Our findings provide further evidence of such a relationship.

The risk of acute myelogenous leukemia and multiple myeloma was highest among the workers who had their first registered engagement in the offshore petroleum industry at the beginning of the study period. One explanation might be that the follow-up time for workers starting later was too short to detect any increased risk. Several authors have discussed the temporal variation of the risk of developing leukemia after exposure to benzene. Finkelstein¹¹⁶ and Silver and co-workers¹¹⁷ reported that the

increased risk in the Pliofilm-cohort declined after 10 years since first exposure, and Glass and co-workers¹¹⁵ reported a similar pattern in the Health Watch cohort from the Australian petroleum industry. This indicates that the follow-up period might have been sufficient also for the workers who, in our study, started from 1986 until the early 1990s. A plausible explanation for the increased risk associated with working in the first period only might be a general improvement of the working environment offshore, including reduced benzene exposure, due to regulations and other initiatives in the 1990s. Nevertheless, such a reduction in exposure levels of benzene has not been documented.

Of the “upstream operators”, 49% had started in the petroleum industry before 1986. In the category “drilling and well maintenance”, 68% of the workers started from 1991 to 2003, possibly because oil companies started to contract out operations such as drilling and well maintenance to drilling contractors from the early 1990s and onwards. We therefore assume that the category “upstream operator” in the beginning of the study period also includes workers involved in the drilling process itself. Further, upstream operators and the drilling personnel have potentially been exposed to benzene through contact with the various phases of crude oil and through contact with drilling mud and other products containing benzene, respectively.

Cigarette smoke is a known source of benzene exposure⁶⁶ and active and passive smoking are associated with risk of acute myelogenous leukemia^{118,119}. We do not have data on smoking in our study. However, the risk estimates were adjusted for level of education, which is sometimes used as a surrogate measure of social class and smoking.^{120,121} Further, the workers in “upstream operator offshore” and “drilling and well maintenance” did not have a higher risk of cancer of the lung and bronchus than the referents. This might indicate that smoking did not contribute substantially to the increased risk of hematopoietic malignancies among these workers.

Given the complexity of the exposure to crude oil and to other agents at offshore work sites, other factors might have contributed to the increased risk of hematopoietic malignancies. Ionizing radiation have been shown to cause both acute myelogenous

leukemia^{122,123} and multiple myeloma.^{49,50} Some petroleum workers are potentially exposed to ionizing radiation during non-destructive testing (NDT) of welding seams, well-logging and contact with produced water, crude oil and sediments emitting low-level ionizing radiation. However, measurements of published individual radiation doses are scarce in the petroleum industry. In a retrospective exposure assessment in the Norwegian petroleum industry it was reported that the annual arithmetic mean dose in 2005 were 0.14 mSv for the NDT-operators and below detection for the loggers, well below present recommended annual limit values of 1 mSv.⁸³ From naturally occurring radioactive materials in the oil and gas industry, Hamlat and co-workers¹²⁴ have estimated maximal effective doses ranging from 0.04 to 0.60 mSv for normal activities and from 0.08 to 1.20 mSv during revision stops. An association between hematopoietic malignancies and other chemical substances, such as formaldehyde¹²⁵ and diesel exhaust⁵⁰ have also been suggested. However, although we cannot exclude a possible contribution of other types of specific or combined exposure, occupational exposure to benzene is the most likely candidate for the increased risk.

5.2 Methodological considerations

5.2.1 Benzene exposure and its' effects on the immune system (I-IV)

5.2.1.1 Study design

Previous studies of the effect of benzene on the hematological system among workers occupationally exposed to benzene have used a cross-sectional design, reporting group differences in immune parameters at one time point only. A prospective design makes it possible to assess the temporal relationship between potential causal factors and the outcome of interest. In this thesis the investigation of possible associations between benzene exposure and acute effects on the immune system was performed during a three day period by assessing the immune parameters before and after cessation of benzene exposure.

In comparative studies it is important to make exposed and reference groups similar with respect to the known sources of variation. We used unexposed referents from the catering section, matched on gender, age and work schedule. Due to a limited number of eligible subjects we had to enroll three unexposed process operators located in the central control room as referents (3 of 17 referents). However, all referents had similar living conditions, shift schedules and diet as the exposed group.

The study group was small, and it could be questioned whether the size was adequate to detect differences in immune function parameters between the groups. Nevertheless, despite the small sample size we found strong and statistically significant associations between benzene exposure and the suppression of IgM, IgA and CD4 T cells. Still, although the number of cases is inherent in the statistical tests performed, the low number of individuals should call for precaution in the interpretation of the results.

5.2.1.2 Exposure assessment

Most studies on the effect of benzene on the hematological system have not characterized the exposure in any detail. In the present study the exposure is measured both by benzene in the breathing zone over a full shift and by internal concentrations

of benzene in both blood and urine. In addition, the time spent in tank was logged and used as a surrogate measure for hydrocarbon exposure and tank work.

Passive dosimeter badges was chosen because they are easy to administrate and do not need pumps that could obstruct the workers. The producer of the badges recommends sampling times less than 12 hours, as was the full work shift in the present study.

Teoretically some analyte could have been lost due to desorption. However, considering the low exposure levels and that the mean sampling time for paper I and II were 9.9 hours (range 43-931 minutes) and 11 hours (range 450-730 minutes), respectively, the sampling time should not affect the measurements significantly.

5.2.1.3 Sources of variation

The levels of biomarkers of exposure and immune parameters as a response to external exposure have intrinsically variabilities both within and between individuals. The variability is caused by biological factors such as genetic polymorphisms, adipose tissue, sex and age, and environmental influences such as routes of exposure, physical activity, smoking, alcohol consumption and diet. Our study was designed to minimize the effect of this intrinsic variability by collecting the biological samples before and after exposure, and from both tank workers and referents simultaneously. During the study period, all subjects lived on board the production vessel and were isolated from their social network on shore. Thus, possible benzene exposure due to hobbies and second jobs did not influence the results. Further, no alcohol was consumed, again reducing the variability caused by factors other than chemical exposure.

5.2.1.4 Generalization of the results

One of the aims of this study was to characterize benzene exposure in Norways offshore petroleum industry. Originally five of the largest oil companies operating on Norway's continental shelf were invited to participate in the study. While only one of the invited oil companies accepted the invitation, the second participating production company took the initiative themselves to be included in the project. Hence, the present study was restricted to workers employed at one crude oil production vessel

and one fixed oil-and gas platform. The results might therefore not be representative for other installations in the offshore petroleum industry. Nevertheless, we have no reason to believe that the present working environment differs much between the installations offshore, although the exposure level will be influenced by factors such as benzene content of the crude oil and natural gas produced, technical design of the work area and measures taken to reduce exposure such as the degree of open vs. closed processing system.

5.2.1.5 Logistical challenges during the study

It is important to highlight the logistic constraints for systematic collection of data at such offshore installations not easy to access. The need for helicopter transport, the unpredictability in planning of tasks and the priorities for personnel due to the limited number of beds offshore might partly explain the reason for not getting access to the other oil companies and the general lack of published exposure data from the offshore petroleum industry.

When the companies themselves monitors benzene exposure in the working environment on offshore installations it is to comply with the regulations under the Working Environment Act or to ensure that control measures are effective. More effort should be made to strengthen the co-operation between the petroleum industry and researchers to optimize the assessment of representative exposure to hazardous chemicals in a more scientific manner. This would enable publication of measurements and possible associated health effects for the benefit of the workers and the society.

Since the number of helicopter flights to the vessel per week is limited, the time between venipuncture and analysis was longer than desired. However, the time till analysis was not longer than the limit set by the laboratory, and the specimens from exposed subjects were included in the same shipment as those from referents.

5.2.2 The historical cohort study

5.2.2.1 Study design

In 1998 the Cancer Registry of Norway established a cohort of 28 000 past and present offshore workers to be used in prospective study on occupational cancer among workers in the upstream petroleum industry from 1998 and onwards.¹²⁶ Due to a shorter latency of hematopoietic malignancies as compared to solid tumors and our assumption of a higher exposure to crude oil and benzene in the early period of Norway's petroleum industry, it is plausible that some workers who were at risk in the 70ies and 80ies had developed this cancer before 1998 and therefore not included in this study. We therefore decided to perform a historical prospective study including also the period before 1998.

Prospective studies are generally very inefficient for studying rare diseases. However, although acute myelogenous leukemia and multiple myeloma are relatively rare, we were able to show a significantly increased risk for these malignancies among "upstream operators offshore". The elevated risk of acute lymphatic leukemia was based on only two cases in the exposed groups, and was therefore not statistically significant. Hence, the data do not allow us to draw any conclusions with respect to this subtype of leukemia.

5.2.2.2 Bias and possible confounding factors

The healthy worker effect is a bias that might occur in occupational mortality studies comparing the working population of interest with general populations that include unemployed subjects. This has been shown for mortality risks for both chronic diseases and cancer.¹²⁷ In addition to using a prospective design, we drew our referents from the general working population and from the same registry as the subjects "at risk", hence reducing this possible healthy worker effect.

Nevertheless, all offshore workers are required to meet rigorous standards of health and fitness for work, leaving a potential for a limited healthy-hiring effect. Most studies performed in the petroleum industry have reported that the overall mortality of

causes and overall cancer incidence among these workers is significantly lower than in the general population.^{89,94,96,99} We matched the subjects and referents for level of education and place of residence, thereby reducing a potential bias due to culture, ethnicity, lifestyle and/or regional environmental pollution, as discussed by Leonard and co-workers.¹²⁷ The Cancer Registry of Norway is the source for cases of cancer among both petroleum workers and referents, thereby avoiding classification bias of the outcome.

5.2.2.3 Heterogenous job categories and potential for misclassification

A major limitation of our study is the lack of good exposure estimates for the job categories included. We have assumed that the surrogate measure of benzene, “contact with crude oil or drilling mud”, was highest in the groups of “upstream operators offshore” and “drilling and well maintenance”. Further, the workers were grouped into job categories based on the industrial classification codes for their first registered engagement in the offshore-related petroleum industry. However, the registered industrial code is dependent on whether, when and how the employer register the employees. Further, the workers have presumably migrated between the different job categories in the given study period. Hence, the job categories used in the analysis of risk of hematopoietic malignancies are heterogenous with respect to exposure. Given the lack of detailed information on occupation, job tasks and description of the occupational exposure in the groups studied, exposure was probably highly, but non-differentially misclassified in this prospective study. Such nonspecific exposure indicators might have caused a marked underestimation of the risk for the individuals with substantial exposure.

5.3 Recommendations for preventive measures

5.3.1 Control of exposure to benzene in the work atmosphere

Benzene is a carcinogenic agent, and there is no evidence for a threshold above which benzene exerts its' effects. Exposure to benzene must therefore be eliminated or reduced as much as possible. However, substitution is not possible with respect to

benzene as a natural component of crude oil and natural gas. One should focus on the task performed rather than job categories when enforcing control measures.

For ordinary process activities offshore, appropriate local exhaust ventilation at the point of origin of benzene and other aromatics should be provided, and cabinets for processes such as sampling of crude oil and condensate should be constructed. It is recommended that the effectiveness of the equipment used in operations such as flotation work, handling of pipeline cleaning pigs and during vacuuming oil contaminated water during cleaning of tanks and separators, should be assessed to limit the duration of exposure. The operators should be involved in discussions on best practice with respect to reducing exposure using the existing equipment or to find effective measures to limiting the duration of exposure.

Today most processing systems offshore are located in open air, indicating a good general ventilation of the workplace by dilution. However, this does not apply to the mud handling systems including shale shaker and slurrification unit in the drilling module, but in recent years there have been considerably improvements in ventilation of these areas on most rigs.⁷⁶

5.3.2 The use of respiratory protection during tank work

Before entering tanks, separators or vessels containing residues of crude oil and condensate from natural gas, the exposure to benzene is often measured using detector tubes or direct reading instruments selective for benzene to decide on the level of protective respiratory equipment. However, in addition to stressing the limitations of using detector tubes for accurate measurement of benzene exposure, Durand and co-workers⁸⁴ found that the measurements made prior to entry of process vessels were not predictive of actual exposure during work. Hence, the consistency between the selected respiratory protection and the actual benzene exposure measured during process vessel cleaning was weak. The workers maintaining the cargo tanks in the present study used air-purifying half mask respirators. We do not have data on the proportion of time the individual workers wore respirators, but some workers seemed to be more conscientious than others. However, the correlation between the personal

benzene exposure and the amount of benzene absorbed was very high, indicating that the use of respirators to varying degrees did not explain much of the variability in absorbed benzene. Further, the tank workers' relatively low benzene exposure correlated significantly with suppression of serum IgM, IgA and CD4 T cell concentrations.

The oil companies and contractors should introduce compulsory use of respirators during cleaning and maintenance of tanks, separators and process vessels, also at levels below the Norwegian occupational exposure limit offshore of 0.6 ppm benzene. In addition, procedures should be implemented with respect to selection of respirators and changes of cartridges in the air-purifying respirators. To help minimise worker exposure to benzene and other chemical agents in the tank atmosphere, the workers performing tank work should be trained in the use, maintenance and not at least have knowledge about the limitations of respiratory protection. The routines ought to be verified by evaluation of the uptake of benzene.

5.3.3 Medical surveillance of tank workers

Cleaning and maintaining tanks, separators etc. are episodic activities. Many tank workers are employed by small companies specializing in cleaning or maintaining oil tanks or separators onshore and offshore. Tank work is physically demanding, and workload is one factor shown to increase the uptake and to modify the distribution and biotransformation of organic solvents. Since the use of time-weighted average exposure data probably underestimates the actual exposure during heavy work load and that health effects of high episodic benzene exposure are not known, these tasks should be considered independently during assessment of exposure rather than just being included in the workers' cumulative benzene exposure.

To assure that the exposure to benzene is controlled, biological monitoring of benzene exposure should be implemented during long lasting work in tanks and separators containing crude oil and other petroleum products known to contain benzene. The frequency of sampling for biological monitoring will depend on the results obtained, as recommended in the general requirements for the performance of procedures for

measurements of chemical agents in general.¹²⁸ The authorities should consider establishing a Norwegian biological exposure limit for benzene.

5.4 Further research

5.4.1 Acute suppression of immune system

At this stage we can not give any explanation for the reported alterations of proteins and cells of the immune system among tank workers exposed to benzene. Studies on a larger number of subjects are warranted to explore the mechanisms of these effects. Further research should explore alterations in the different immune parameters over a longer time-span, including relevant cytokines as effect parameters. In addition to the change in total number of the immune parameters under study, the function of these circulating proteins and cells should be investigated.

Since the use of unmetabolized benzene as a biomarker might underestimate the potential for a toxic effect of low benzene exposure due to an increased production of toxic metabolites,³⁰ metabolites such as *t,t*-muconic acid and *S*-phenylmercapturic acid should be included in exposure assessment for the subjects under study.

5.4.2 Increased risk of acute myelogenous leukemia and multiple myeloma

We found a significantly higher risk of hematopoietic malignancies compared to the general working population in Norway. From the present study one can not conclude on the relation between the specific occupational exposures offshore and the increased risk of subtypes of leukemia and multiple myeloma. There is a general lack of evidence of such associations in the scientific literature. Few studies have ascertained information about specific exposures when increased risks are reported for different types of industries. This makes it difficult to enforce actions for reducing the actual risks. Further, given the lack of detailed information on occupation, job tasks and exposure in the groups studied, exposure was probably highly non-differentially misclassified in this prospective study. This means that the risk for the individuals with substantial exposure might have been markedly underestimated. To investigate the causative agents for the increased risk that we found in this cohort, to improve the

estimates of the association between the various types of exposure and the risk of the subtypes of hematopoietic malignancies, and to contribute with new knowledge on the association between the specific agents and the risk of different subtypes of leukaemia, a case-control study nested within this cohort should be performed.

6. CONCLUSIONS

Although relatively high short term peak exposure to benzene occurs during ordinary activity for several job categories on a crude oil production vessel and for process operators on a fixed oil- and gas installation, the full-shift mean exposure is low.

Although process operators on the fixed oil- and gas installation had a low concentration of benzene in biological media, the biological uptake was significantly related to the benzene exposure.

Despite low benzene exposure in this work atmosphere and the use of personal protective equipment, tank workers maintaining crude oil cargo tanks had a significant uptake of benzene that was highly correlated with the personal benzene exposure and the time spent in the tank. The internal concentration of benzene was higher than expected at the measured exposure levels. This finding is probably due to an extended work schedule and high work load.

The same tank workers showed a significant decline in serum IgM and IgA that was highly correlated with time spent in the tank, benzene exposure in the working environment and benzene concentration in blood and urine. Although less consistent, the results also indicate an alteration in CD4 T cells. However, given the complexity of the tank atmosphere we can not exclude that the combined exposure or specific exposure to other compounds in the tank atmosphere might have caused the reported alterations of proteins and cells of the immune system.

Workers in Norway's offshore petroleum industry exposed to crude oil and other hydrocarbons had a significantly increased risk of developing acute myelogenous leukemia and multiple myeloma. The workers employed before 1986 had the highest risk. Although we cannot exclude a possible contribution of other types of specific or combined exposure, occupational exposure to benzene is the most likely candidate for the increased risk.

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Paper I

Benzene Exposure on a Crude Oil Production Vessel

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Annals of Occupational Hygiene 50(2), Kirkeleit, J.; Riise, T.; Bråtveit, M.; Moen, B. E., Benzene exposure on a crude oil production vessel, pp.123–129. Copyright 2006 Oxford University Press. Abstract only. Full-text not available due to publisher restrictions.

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Abstract

Objectives: The aim was to describe the personal exposure to benzene on a typical crude oil production vessel and to identify factors influencing the exposure level.

Methods: The study population included process operators, deck workers, mechanics and contractors on a production vessel in the Norwegian sector of the North Sea. The personal exposure to benzene during ordinary activity, during a short shutdown and during tank work was monitored using organic vapour passive dosimeter badges (3M□3500). Information on the tasks performed on the day of sampling was recorded. Exposure was assessed by grouping the measurements according to job category, mode of operation and the tasks performed on the sampling day. Univariate analysis of variance was used to test the differences between the groups.

Results: Forty-two workers participated in the exposure assessment, comprising a total of 139 measurements. The arithmetic and geometric mean of benzene exposure for all measurements was 0.43 and 0.02 p.p.m., respectively. Twenty-five measurements (18%) were below the limit of detection (0.001 p.p.m.), while ten samples (7%) exceeded the occupational exposure limit of 0.6 p.p.m. The geometric mean exposure was 0.004 p.p.m. (95% CI 0.003–0.006) during ordinary activity, 0.01 p.p.m. (95% CI 0.005–0.02) during shutdown and 0.28 p.p.m. (95% CI 0.16– 0.49) during tank work. Workers performing annual cleaning and maintenance

of tanks containing crude oil or residues of crude oil had higher levels of exposure than workers performing other tasks, including work near open hydrocarbon-transport systems (all $P < 0.001$). However, because of the mandatory use of respirators, the actual personal benzene exposure was lower. The job categories explained only 5% of the variance in exposure, whereas grouping by mode of operation explained 54% of the variance and grouping by task 68%.

Conclusion: The results show that, although benzene exposure during ordinary and high activity seems to be low in the processing area on the production vessel, cleaning of tanks and performing maintenance work in a cleaned tank have a potential for high exposure.

Keywords: benzene exposure; upstream petroleum industry; production vessel; tank work

Paper II

Biological monitoring of benzene exposure for process operators during ordinary activity in the upstream petroleum industry

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Keywords: benzene exposure; biological monitoring; process operators; ordinary activity

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ABSTRACT

The objective of this study was to characterize the exposure to benzene and related aromatics during ordinary activity for crude oil process operators, and to investigate whether there is an uptake of benzene at these exposure levels. The study was performed on a fixed, integrated oil- and gas production facility located on Norway's continental shelf. The study population included 12 process operators and nine referents. Personal exposure to benzene, toluene, ethylbenzene and xylene was measured during three consecutive 12 hours work shifts by organic vapour passive dosimeter badges. Blood and urine were sampled before departure to the production facility (pre-shift), immediately after the work shift on the 13th day of the work period (post-shift) and immediately before the following work shift (pre-next shift).

Supplementary measurements of hydrocarbons during short-term tasks were done by active sampling using Tenax tubes. Process operators' arithmetic mean exposure over the three-day study period was 0.042 ppm (range <0.001-0.688 ppm) for benzene, 0.05 ppm toluene, 0.02 ppm for ethylbenzene and 0.03 ppm for xylene. Full-shift personal exposure was significantly higher when flotation work was done during the shift compared to when other tasks were carried out. Work in the flotation area was associated with a short-term (6-15 min) arithmetic mean exposure to benzene of 1.056 ppm (range 0.092-2.326 ppm). The concentrations of benzene in blood and urine were not different between operators and referents at any of the time points. When adjusting for being a current smoker in regression analyses there were significant associations between benzene exposure and post-shift concentration of benzene in blood (P=0.01) and urine (P=0.03), respectively. Although relatively high short-term exposure to benzene occurs during ordinary activity for offshore process operators, the full-shift mean exposure is low. There is some evidence for benzene uptake within this range of exposure.

INTRODUCTION

Process operators in the petroleum industry on offshore installations are potentially exposed to a mixture of hydrocarbons from crude oil, condensate from natural gas production and produced water. During ordinary operation the processes take place in closed systems which are opened only for shorter periods for purposes such as sampling of crude oil and produced water, maintenance work, inspection and cleaning of pipelines and process equipment.

The upstream hydrocarbons include aromatics like benzene, toluene, ethylbenzene and xylene. Although benzene is a known carcinogenic (IARC, 1987, Schnatter *et al.*, 2005) and hematotoxic agent (Lan *et al.*, 2004), data on past and present exposure of benzene in the upstream petroleum industry is not extensive. Some authors have summarized common occupational exposure data from oil companies performed to document compliance with recommended limit values, and have concluded that long-term mean benzene exposure is low for process operators (Runion, 1988; Verma *et al.*, 2000; Steinsvåg *et al.*, 2006). During routine offshore oil and gas production, full-shift mean exposures to toluene, ethylbenzene and xylene as well as to benzene, are also reported to be low compared to occupational exposure limits (HSE, 1999). However, the wide ranges of exposure values show that for some workers the exposure might be high also during ordinary activity (Verma *et al.*, 2000; Steinsvåg *et al.*, 2006). Previous exposure studies during ordinary activity have not provided data for specific tasks expected to be associated with short-term exposures to hydrocarbons (Gardner, 2003), and they have not examined whether such exposures explain some of the variability in full-shift exposure levels.

Full-shift benzene exposure for operators on a floating crude oil production vessel was lower during ordinary activity than during maintenance work in a cleaned crude oil tank (Kirkeleit *et al.*, 2006a). However, despite relatively low benzene exposure also during maintenance work in the oil tanks (arithmetic mean 0.23 ppm) the workers had a significantly higher benzene concentration in blood and urine and acute reduction in circulating IgM, IgA and CD4 T cells compared to referents (Kirkeleit *et al.*, 2006b,c). The internal concentration of benzene was higher than expected at the measured exposure levels, which might be related to the physically demanding 12 hours work shifts for tank workers and insufficient use of respiratory protective equipment (Kirkeleit *et al.*, 2006b). Thus, benzene was absorbed and had biological effects

even at exposures below the recommended limit value of 0.6 ppm, and possibly within the range of exposure levels representative for ordinary activity.

The objective of this study was to characterize the exposure to benzene and related aromatics during ordinary activity for crude oil process operators and to investigate the relationship between the individual concentrations of benzene in the breathing zone and the concentrations of unmetabolized benzene in blood and urine in these workers.

METHODS

Study site

The study was performed in October 2005 during ordinary activity on a fixed, integrated oil- and gas production facility located on Norway's continental shelf. Process operators work 12 hours shifts, and survey the upstream processes comprising a closed system of separators and treaters where the effluent is separated into gas, oil, water and solid waste. This surveillance is done via computers in the control room and by inspection in the process areas. They also have practical tasks such as sampling and analysis of oil and produced water, fault-finding and repairing.

Sampling strategy

Study population. The study population originally included 10 process operators (7 men and 3 women) potentially exposed to benzene in the processing area and 9 referents (6 men and 3 women) not expected to be exposed to benzene above the background concentration in the indoor environment. During the study period there was an unexpected relocation of two process workers from the cellar deck where exposure was expected to be relatively high. Two new process operators were enrolled during study period to account for this relocation. Thus, the total number of process operators is twelve. Seven of the referents were recruited from the catering section on the same facility, while two referents were process operators located in the central control room. All process workers who were eligible at the selected day or night shifts and catering personnel with a shift schedule matching that of the process operators were invited to participate. All invited workers participated.

The participants completed a self-administered questionnaire including questions on age, sex and whether they were current smokers during the study period. In addition, the process operators maintained a logbook where they recorded their job tasks and use of personal protective equipment during the respective shifts.

Informed written consent was obtained from all participants. All subjects were informed about their own results. The study protocol was approved by the Western Norway Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services. The Ministry of Health and Care Services gave permission to establish a biobank and to transfer the biological material abroad for analysis.

Personal full-shift exposure to airborne hydrocarbons. The process operators (n=12) were monitored for personal exposure to benzene, toluene, ethylbenzene and xylene during three consecutive day or night shifts (the 11th, 12th and 13th day of the two weeks offshore period), each of 12 hours (0700-1900 or 1900-0700) by organic vapour passive dosimeter badges (3M™ 3500) attached to the worker's collar. Prior to laboratory analysis visual inspection of the sampling badges resulted in rejection of one dosimeter due to splashes with oil contaminated water. The arithmetic mean sampling time for the remaining 35 measurements was 657 minutes (range 450 - 730 minutes)

Biological monitoring. The original 10 process operators monitored for full-shift personal exposure to airborne hydrocarbons also provided three samples of blood and urine for analysis of benzene. The first sample was collected in the morning at the heliport before departure to the oil production facility (pre-shift), and was considered baseline measurement. The second sample was collected immediately after the work shift on the 13th day of the offshore work period (post-shift) and a third sample was collected immediately before shift on the following day (pre-next shift). The two process operators enrolled during the study period only provided two urine samples (post-shift and pre-next shift). Blood and urine samples were obtained from the nine referents on the same days following the same protocol. Due to practical problems, we failed to collect the pre-next shift blood sample from one of the referents. Except for the two process operators enrolled into the study later than the others, all the participants provided urine samples pre-shift, post-shift and pre-next shift.

Exposure measurements during specific work tasks

In a separate set of exposure measurements personal sampling of hydrocarbons during specific tasks was done by tenax tubes connected to pumps (Casella-EEx) at a flow rate of 0.05-0.1 l min⁻¹. The tenax tubes were attached to the worker's collar, and the sampling time (Arithmetic mean 16.4 min, range 3-76 min) was dependent on the duration of the task.

Preliminary exposure assessment had identified four work tasks expected to be associated with relatively high, short-term exposure to hydrocarbons; 1) inspection and work on the flotation package, 2) sampling and analysis of crude oil, condensate and produced water, 3) sending and receiving pipeline cleaning pigs and 4) jetting of separators. In order to make short-term exposure measurements the operators informed the researcher before these work tasks were done during the study period. Jetting of separators was not performed during this period.

Inspection and work on the flotation package. One stage of the separation process of oil and water takes place in the flotation package where oil is skimmed off the upper layer of the two-phase water-oil mixture. Under normal conditions the process operators do not have to inspect the flotation package. During the study period flotation was inspected twice per shift since the content of oil in the produced water was exceeding the limit set by the authorities. The operator opens the trapdoors and when necessary they adjust the separation level. At times they also use a swab to push the oil phase over the separation edge.

Sampling and analysis of petroleum streams (crude oil, condensate and produced water).

During the night shift crude oil is sampled through a short-cut loop, and brought to the laboratory for analysis of water content and specific weight. During day shifts condensate and produced water are manually sampled on small bottles from taps in the production process, and then produced water is analysed for oil content in the laboratory.

Sending and receiving pipeline cleaning pigs. Sending or receiving pig is normally done at least once per third night shift by the process operators. When sending the cleaning pig the trapdoor to the pipeline lock is opened and the pressure equalised before the operators push the pig into the lock. To clean for oil and wax the cleaning pig is left within the lock for about 24 hours before the trapdoor opening, pressure relief and manual pulling of the cleaning pig out of the lock. Thick oil and wax are removed by manual shovelling.

Other tasks with possible short-term exposure. Prior to maintenance work on the processing equipment, which is done by the mechanics, the process operators might have to open, change and close blind flanges and valves which implies a risk of hydrocarbon exposure

Laboratory analysis

The dosimeter badges and the tenax tubes were stored at -4°C before transport to X-lab AS in Bergen, for analysis. The collected hydrocarbons on the dosimeter badges were desorbed by CS₂, while the tenax tubes were thermally desorbed. Benzene, toluene, ethylbenzene and xylene, including *o*-, *m*- and *p*-xylene, were analysed quantitatively and qualitatively by gas chromatography with mass spectrometry (NIOSH, 2003). The levels of detection were 0.001 ppm for benzene and 0.01 for toluene, ethylbenzene and xylene.

Methods for sampling, storage, transport and analysis of blood and urine samples are described in detail by Kirkeleit *et al.* (2006b). In short, the concentration of benzene in blood was analyzed by a head-space sampler (Perkin Elmer Headspace sampler HS40) and a gas chromatograph (Perkin Elmer Autosystem Gas Chromatograph) using photoionization detection according to the method described by Pekari *et al.* (1989;1992). The urinary concentration of benzene was analyzed using a solid-phase microextraction–gas chromatograph–mass spectrometer/ion-trap detection method (SPME-GC-MS/ITD method). The limit of quantification for benzene in both blood and urine were 1 nmol/l.

Occupational exposure limits

The recommended Norwegian occupational exposure limits are averaged over an eight hour work day. In the guidelines to the Activity Regulations, the Norwegian Petroleum Directorate recommends a safety factor of 0.6 to correct for a 12 hour shift, which is relevant for the offshore installations. Thus the recommended occupational exposure limits corrected for 12 hours shifts are 0.6 ppm for benzene, 15 ppm for toluene and xylene and 3 ppm for ethylbenzene. Short-term occupational exposure limits (for periods up to 15 min) are 3 ppm for benzene, 37.5 ppm for toluene and xylene and 10 ppm for ethylbenzene.

Statistical analysis

Personal exposure to benzene, toluene, ethylbenzene and xylene is given as arithmetic mean (standard deviation), geometric mean and range (minimum and maximum). Results from full shift exposure measurements were grouped according to the logbook recordings of work task expected to be associated with short-term exposure to aromatic hydrocarbons. Differences in the various exposure measures between work tasks and between the process operators and referents were analyzed using *t*-tests. Pearson's correlation coefficient was calculated for studying relationships between the different exposure measures at the various time points. The associations between personal benzene exposure in the workplace air and benzene concentration in biological media were also adjusted for the corresponding baseline concentrations by including the baseline concentrations as covariates in regression analyses. Further, these associations were also adjusted for gender, age and for being a current smoker by including each of these in separate multiple regression analyses.

All the exposure measurements and the biomarkers of benzene exposure had a skewed distribution and were therefore log-transformed before statistical analysis (ln). Blood and urinary benzene concentrations and benzene exposure below the limit of quantification and benzene exposure for referents were replaced by values equal to the limit of quantification divided by 2 (Hornung and Reed, 1990). The data were analysed using SPSS version 14.0.1 for Windows.

RESULTS

General characteristics of the study population

The mean age (standard deviation) of the process operators ($n = 12$) and referents ($n = 9$) was 42.3 (SD 12.8) and 44.9 (SD 10.7) years, respectively. Three process operators and four referents reported being current smokers. Personal half-mask with filter for organic vapour (brown) was always used by the operators during work and inspection of the flotation process, but not during other work tasks.

Personal full-shift exposure to benzene and related aromatics

Process operators' arithmetic mean benzene exposure over the three-day study period was 0.042 ppm (range <0.001-0.688 ppm) (Table 1), which is about 7 % of the Norwegian

occupational exposure limit of 0.6 ppm over a 12-hour work shift. The arithmetic mean exposure for toluene (0.05 ppm), ethylbenzene (0.02 ppm) and xylene (0.03 ppm) were even lower compared to the corresponding recommended limit values (Table 1). Significant correlations were found between the exposure to benzene and toluene ($r=0.72$, $P<0.001$), ethylbenzene ($r=0.41$, $P=0.015$) and xylene ($r=0.70$, $P<0.001$), respectively.

There was no significant difference in exposure level between the three consecutive sampling days. For benzene exposure the arithmetic mean for the first day of sampling was 0.07 ppm (range <0.001 -0.69 ppm), for the second day 0.04 (<0.001 -0.40 ppm) and for the third day 0.02 ppm (<0.001 -0.09 ppm).

Personal exposure to benzene, toluene, ethylbenzene and xylene was significantly higher when flotation work was done during the shift compared to when sampling of crude oil and produced water ($P<0.001$) or when other tasks ($P<0.001$) were carried out (Table 1). There was no difference in exposure levels when the work shift included sampling of crude oil or produced water compared to when other tasks apart from flotation work were done (Table 1). Analogous results were found for exposure to toluene, ethylbenzene and xylene (Table 1)

Benzene concentration in blood and urine

The concentration of benzene in blood or urine was not significantly different between the process operators and referents at any of the time points (Table 2). This result was found also among the non-smokers. The arithmetic mean concentration of benzene in blood post-shift was 1.8 nmol/l for both groups. The arithmetic mean concentration of benzene in urine post-shift was 3.9 nmol/l for process operators versus 1.6 nmol/l for referents.

When studying the associations between airborne benzene exposure and the concentration of benzene in blood and urine, referents were assigned exposure values equal to the level of detection for benzene in air divided by two. The benzene exposure on the third day of sampling was not correlated with the internal concentration of benzene immediately after work hours (post-shift) or prior to the following work shift (pre-next shift), neither in blood (post-shift $r = 0.05$, $P = 0.83$; pre-next shift $r = -0.75$, $P = 0.77$) nor in urine (post-shift $r = 0.04$, $P = 0.87$; pre-next shift $r = -0.19$, $P = 0.43$). When including only none-smokers in the correlation analyses, there was a significant association between benzene exposure on the third day of

sampling and post-shift concentration of benzene in blood ($r=0.65$, $P=0.021$). When adjusting for being a current smoker in a multiple linear regression there were significant associations between benzene exposure on the third day of sampling and post-shift concentration of benzene in blood ($P=0.01$) and urine ($P=0.03$), respectively. These models explained 87.1% and 79.1% of the variances in benzene concentration in blood and urine, respectively. Adjusting for other potential confounders such as age, gender and baseline concentrations of benzene in blood or urine did not materially change the associations between benzene exposure and internal post-shift or pre-next shift benzene concentrations.

Short-term exposure during specific work tasks

Work on the flotation package was associated with a short-term arithmetic mean exposure to benzene of 1.056 ppm (range 0.092-2.326 ppm), which is about 35% of the recommended Norwegian short-term occupational exposure limit of 3.0 ppm for periods up to 15 minutes (Table 3). Insignificantly lower levels of benzene were measured during work with pipeline cleaning pigs (Arithmetic mean 0.322 ppm) and when opening process equipment (0.237 ppm). The apparent variability in short-term benzene exposure was higher during flotation work compared to when other short-term tasks were done (Figure 1). The arithmetic mean sampling time for work in the flotation package was 9 min (range 6-15 min), for sampling of petroleum streams 19 min (3-40 min), for pipeline cleaning operations 28 min (4-76 min) and for opening of process equipment 12 min (8-16 min).

Benzene exposure during sampling of crude oil, condensate and produced water (0.021 ppm) was significantly lower and had a low variability compared to other short-term tasks (Table 3, Figure 1). Differences in exposure levels between the different work tasks followed a similar pattern for toluene, ethylbenzene and xylene, respectively (Table 3).

DISCUSSION

During ordinary activity for offshore process operators full-shift exposure to benzene and related aromatic hydrocarbons was generally low compared to recommended Norwegian occupational limits. Work in the flotation area was associated with relatively high short-term exposure to benzene which contributed considerably to the full-shift exposure. Although there was no difference in internal concentration of benzene between process operators and referents, there was an indication of benzene uptake within the range of exposures representative for ordinary activity on the installation.

In the present study the low mean exposure to benzene experienced by the process operators at the fixed oil and gas producing installation is in accordance with previous studies during ordinary activity in the offshore petroleum industry (Kirkeleit *et al.*, 2006a,b; Steinsvåg *et al.*, 2006; Glass *et al.*, 2000). At a floating production vessel, the arithmetic and geometric mean benzene exposure during ordinary activity of process operators was 0.02 ppm and 0.004 ppm, respectively (Kirkeleit *et al.*, 2006a). Steinsvåg *et al.* (2006) pooled personal full shift measurements of benzene exposure in processing- and drilling area from 12 installations on the Norwegian continental shelf in the period 1994-2003 (n=367). In their study the benzene exposure ranged from below the level of detection to 2.6 ppm, with arithmetic and geometric means of 0.037 and 0.0067 ppm, respectively. A retrospective exposure assessment of benzene in the Australian petroleum industry suggested an exposure of 0.02 ppm for the job group “upstream operator offshore” (Glass *et al.*, 2000). In the conventional oil and gas sector of the upstream petroleum industry in Canada, 198 personal long-term samples from the years 1985 to 1996 were within the range of <0.001–2.431 ppm, with an arithmetic mean of 0.064 ppm and a geometric mean of 0.011 ppm (Verma *et al.*, 2000).

In the present study the six full-shift samples with highest benzene exposure included short-lasting work in the flotation area which was carried out by two of the totally twelve process operators. The supplementary short-term measurements indicated high exposure variability for benzene during this task, probably due to many factors such as actual work done, position of the operator, duration of open trapdoors and temperature and composition of the oil/water mixture. Similar flotation package systems have been used on several production platforms constructed during the first period of production on Norway’s continental shelf, but are now

found only on a smaller number of installations. Sampling and analysis of crude oil and produced water did not appear to contribute significantly to full-shift exposure, and short-term measurements indicated low exposure levels within a narrow range for this task. On this installation the partly automated system for sampling of crude oil probably contributed to the low exposure during this task. On most offshore installations sampling of crude oil is mainly a manual task which may result in higher exposures than presently shown. Sending and receiving cleaning pig was associated with higher short-term exposure. However, this task was not performed during the three consecutive days of full-shift sampling. When compared to the respective recommended occupational limit values the exposure to toluene, ethylbenzene and xylene was relatively lower than for benzene, indicating a low health risk for these hydrocarbons.

Smoking is a major respiratory source of benzene uptake (Darrall *et al.*, 1998). In the present study there was no difference in internal benzene concentration between process operators and referents, but when adjusting for being a current smoker there was an association between benzene in the breathing zone and benzene in blood or urine, respectively. Although smoking was prohibited in the oil and gas production areas, the living quarters had a limited number of designated smoking rooms. These present results indicate that even at the relatively low exposure levels during ordinary activity there seems to be an uptake of benzene from the work environment. However, due to the time-dependent elimination of internal benzene, the time-lag between short-term exposures and biological sampling at the end of the work shift might have contributed to a reduced impact of such exposures on the benzene uptake.

Relatively few workers were included in the study, and recruitment of more workers would have strengthened the indicated association between benzene exposure and internal concentration of benzene. The present results with strongly overlapping ranges of exposure between exposed and referents seems to be dependent on both being a current smoker and exposure to benzene in the work environment. Kirkeleit *et al.* (2006b) showed a significant relationship, independent of smoking, between benzene exposure and internal benzene for crude oil tank workers at a geometric mean of 0.15 ppm (range 0.01-0.62 ppm), which is three times higher than presently reported. The arithmetic mean of the post-shift concentration of benzene in blood (17.3 nmol/l) and urine (59.3 nmol/l) of tank workers (Kirkeleit *et al.*, 2006b) was also considerably higher than for process operators in the present study. However,

tank work should be considered as a specific task, quite different from ordinary process work offshore.

In conclusion, although relatively high short-term exposure to benzene occurs during ordinary activity for offshore process operators, the full-shift mean exposure is low. There is some evidence for benzene uptake within this range of exposure.

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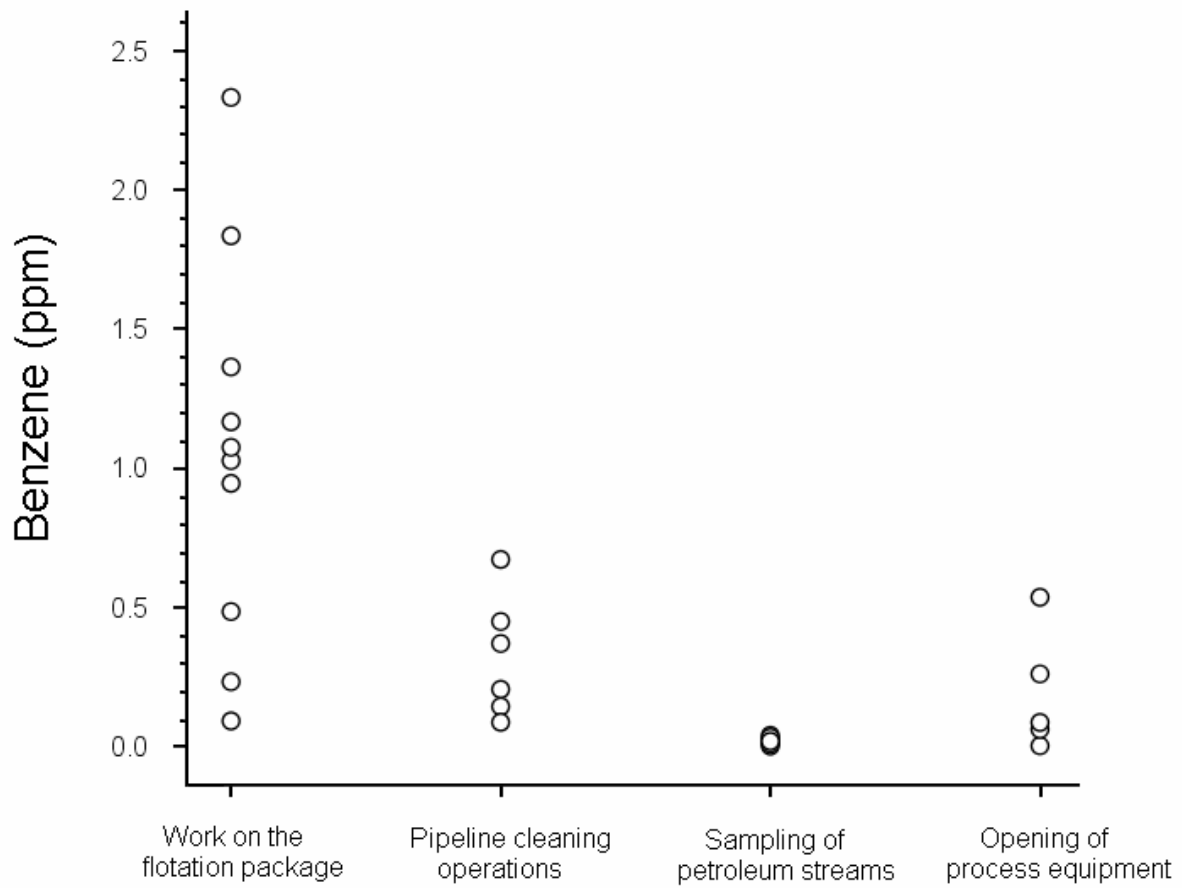


Figure 1 Short-term personal benzene exposure grouped by work tasks on an oil- and gas production facility.

Table 1 Full-shift personal exposure to benzene, toluene, ethylbenzene and xylene for offshore process operators grouped by work task carried out during the shift.

Work task	Benzene (ppm)			Toluene (ppm)			Ethylbenzene (ppm)			Xylene (ppm)			
	Sample n (N) ¹	AM(SD)	GM	Range	AM(SD)	GM	Range	AM (SD)	GM	Range	AM(SD)	GM	Range
Flotation work	6 (2)	0.221 (0.267)	0.114	0.030-0.688	0.21 (0.22)	0.12	0.03-0.41	0.04 (0.03)	0.03	0.01-0.09	0.13 (0.13)	0.09	0.02-0.37
Sampling	11 (4)	0.005 (0.005)	0.003	< 0.001 - 0.014	0.01 (0.01)	0.01	< 0.01-0.56	0.02 (0.01)	0.02	0.01-0.03	0.01 (0.01)	0.01	< 0.01-0.03
Other work tasks	18 (6)	0.005 (0.01)	0.003	< 0.001 - 0.023	0.01 (0.01)	0.01	< 0.01-0.04	0.02 (0.01)	0.02	0.01-0.03	0.01 (0.002)	0.01	< 0.01-0.01
All	35 (12)	0.042(0.132)	0.005	< 0.001 - 0.688	0.05 (0.11)	0.01	< 0.01-0.56	0.02 (0.01)	0.02	0.01-0.09	0.03 (0.07)	0.01	< 0.01-0.37
OEL (12 hours) ²		0.6			15			3			15		

¹Number of samples (Number of workers sampled)

²Recommended Norwegian occupational exposure limit for 12 hour shift

Table 2 Comparison between offshore process operators and referents in mean concentration of benzene in blood (nmol/l) and benzene in urine (nmol/l) pre-shift, post-shift and pre-next shift.

Marker of benzene exposure	Group	n	AM	GM	Range (min-max)	<LOQ
Blood, pre-shift	Process operators	10	2.1	1.4	0.5-6.0	3
	Referents	9	2.5	2.0	0.5-5.0	1
Blood, post-shift	Process operators	10	1.8	1.5	1.0-4.0	0
	Referents	9	1.8	1.5	1.0-4.0	0
Blood, pre-next shift	Process operators	10	2.0	1.6	1.0-5.0	0
	Referents	8	1.6	1.5	1.0-3.0	0
Urine, pre-shift	Process operators	10	5.8	3.0	0.5-29.0	1
	Referents	9	7.7	3.9	0.5-22.0	1
Urine, post-shift	Process operators	12	3.9	1.1	0.5-34.0	7
	Referents	9	1.6	1.1	0.5-4.0	5
Urine, pre-next shift	Process operators	12	1.7	1.1	0.5-9.0	4
	Referents	9	7.9	2.2	0.5-35.0	5

AM: arithmetic mean

GM: geometric mean

<LOQ: number of samples below the limit of quantification

Table 3. Short-term personal exposure to benzene, toluene, ethylbenzene and xylene for offshore process operators during specific work tasks.

¹Recommended Norwegian occupational exposure limit for periods up to 15 minutes

Work task	n	Benzene (ppm)			Toluene (ppm)			Ethylbenzene (ppm)			Xylene (ppm)		
		AM(SD)	GM	Range	AM(SD)	GM	Range	AM(SD)	GM	Range	AM(SD)	GM	Range
Work on the flotation package	10	1.056 (0.690)	0.771	0.092-2.326	1.06 (0.69)	0.82	0.19-2.14	0.49 (0.31)	0.36	0.02-1.11	1.52 (0.97)	1.18	0.15-3.67
Sampling of petroleum streams	7	0.021 (0.014)	0.015	0.002-0.041	0.02 (0.02)	0.01	<0.01-0.04	<0.01 (0.01)	0.003	<0.01-0.02	0.01 (0.01)	0.01	<0.01-0.03
Pipeline cleaning operations	6	0.322 (0.220)	0.258	0.088-0.673	0.29 (0.16)	0.26	0.11-0.52)	0.04 (0.02)	0.04	0.02-0.06	0.16 (0.05)	0.15	0.09-0.24
Opening of process equipment	4	0.237 (0.219)	0.166	0.062-0.537	0.19 (0.29)	0.08	0.02-0.63	0.03 (0.05)	0.005	<0.01-0.11	0.12 (0.21)	0.02	<0.01-0.43
OEL (15 min) ¹	3				37.5			10			37.5		

Paper III

Biological monitoring of benzene exposure during maintenance work in crude oil cargo tanks

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Abstract

We investigated the association between the individual concentrations of benzene in the breathing zone and the concentrations of benzene in the blood and urine among workers maintaining crude oil cargo tanks. Benzene exposure was measured during three consecutive 12 h work days among 13 tank workers and 9 unexposed referents (catering section). Blood and urine samples were collected pre-shift on the first day, post-shift on the third day, and pre-next shift on the following morning. The workers used half-mask air-purifying respirators, but not all workers used these systematically. The individual geometric mean benzene exposure in the breathing zone of tank workers over 3 days was 0.15 ppm (range 0.01–0.62 ppm). The tank workers' post-shift geometric mean benzene concentrations were 12.3 nmol/l in blood and 27.0 nmol/l in urine versus 0.7 nmol/l for both blood and urine among the referents. Benzene in the work atmosphere was highly correlated with the internal concentration of benzene both in post-shift blood ($r=0.87$, $P<0.001$) and post-shift urine ($r=0.90$, $P<0.001$), indicating that the varying use of respirators did not explain much of the variability in absorbed benzene. The results showed that, despite low benzene exposure in this work atmosphere and the use of personal protective equipment to a varying degree, the tank workers had a significant uptake of benzene that correlated highly with benzene exposure. The internal concentration of benzene was higher than expected considering the measured individual benzene exposure, probably due to an extended work schedule of 12 h and physical strain during tank work. Control measures should be improved for processes, which impose a potential for increased absorption of benzene upon the workers.

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Keywords: Benzene; Crude oil; Biological monitoring; Tank work; Extended work shift

1. Introduction

Benzene, a known carcinogenic [1,2] and hematotoxic agent [3], is a natural component of crude oil. Thus, benzene exposure is a potential hazard in the

petroleum industry. During ordinary operation, most of the processes on an oil production facility are confined in closed systems, and the overall exposure to benzene is low [4,5]. However, whenever the processing system is opened there might be potential for high benzene exposure. In a previous study [5], we reported that cleaning and maintaining tanks containing residues of crude oil is associated with individual benzene exposure ranging from 0.004 to 16.8 ppm, with a geometric mean of 0.28 ppm. Similar concentrations of individual benzene

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exposure have been reported during cleaning [6] and gauging the content [7] of crude oil vessels.

During occupational exposure to benzene, the most important route of uptake is inhalation. Reports [8–10] indicate that humans absorb 30–52% of the inhaled benzene, depending on the benzene concentration, length of exposure and pulmonary ventilation. Traces of unmetabolized benzene, reported to be about 0.1% of absorbed benzene in humans [11], is eliminated unchanged in the urine. Benzene in urine has been recommended as a biomarker of choice at air concentrations below 1 ppm benzene because it is a non-invasive, specific and sensitive method [12–14].

Crude oil production vessels store crude oil in cargo tanks before offloading and transport onshore. Cargo tanks are prone to degradation by corrosion and are periodically emptied for internal inspection of the walls to detect pitting, general corrosion and cracks. If such damage is found, the tank must be repaired to avoid leaks. Tank work offshore has several characteristics that may modify the uptake of benzene both through inhalation and dermal exposure. While most standards for chemical exposure in the work environment assume 8 h work days 5 days a week, Norwegian offshore workers have in general 12 h shifts 7 days a week for 2 weeks with 28 days of leave between the tours. In addition, the physical strain of tank work presumably increases the uptake through all routes and might modify the distribution and biotransformation of hydrocarbons [15–18]. Further, although the use of half-mask air-purifying respirators with a cartridge for organic solvents is mandatory during tank work, their efficiency of protection under high workload is questioned. However, given this potential chemical hazard, benzene has previously not been biologically monitored among offshore tank workers. This might partly be due to logistic constraints, such as the need for helicopter transport, the unpredictability in planning of tasks and the priorities for personnel due to the limited number of beds offshore.

The objective of this study was to investigate the relationship between the individual concentrations of benzene in the breathing zone and the concentrations of unmetabolized benzene in blood and urine both before, at the end of the 12 h work shift and on the following morning among workers maintaining crude oil cargo tanks.

2. Methods

2.1. Study population

The study was performed in July 2004 during inspection of one cargo tank and in April 2005 during repa-

ration of two cargo tanks on a crude oil production vessel located on Norway's continental shelf. The maintenance work in the cargo tanks (volume 5000–7800 m³) included tank inspection, scaffold-building and welding. The study population aimed at including 13 men performing tank work, and 9 referents not expected to be exposed to benzene. Referents were mainly recruited from the catering section on the same vessel. All workers who planned to perform tank work in the given study periods and all catering personnel with a shift schedule matching those of tank workers were invited to participate. No subject declined. Before the study period, the length of stay of the participants on the production vessel varied from 1 to 15 days. In that period they only performed ordinary jobs with minor benzene exposure. In a previous study on the same production vessel we reported an arithmetic and geometric mean benzene exposure of 0.02 and 0.004 ppm, respectively, during ordinary activity [5].

Before the maintenance work started, the tanks were cleaned with hot oil and water and purged with inert gases and fresh air. The tanks were ventilated with fresh air as long as work was in progress. The workers used half-mask air-purifying respirators with a combination filter containing both a particle and an organic gas filter. However, the use of the respirators varied between the workers and the workers replaced the filter with varying frequency. The use of respirators was not systematically recorded. The participants completed a self-administered questionnaire including questions on age, gender and whether they were current smokers during the study period. Smoking was prohibited on the production vessel, but the living quarters had a limited number of designated smoking rooms. Since alcohol consumption is completely banned on offshore oil and gas installations, no participant consumed alcohol during the study period.

Informed written consent was obtained from all participants. All subjects were informed about their own results. The study protocol was approved by the Western Norway Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services. The Ministry of Health and Care Services gave permission to establish a biobank and to transfer the biological material abroad for analysis.

2.2. Monitoring of individual exposure to benzene

The study period for all workers comprised three consecutive work shifts. All tank workers were monitored for individual benzene exposure by using organic vapor passive dosimetry badges (3M 3500[®]). The badges were

worn in the breathing zone over a full work shift of 12 h on the three consecutive day shifts. The individual exposure to benzene was not measured for referents as they were assumed not to be exposed to benzene above the background concentration in the indoor environment. The time spent in the tank was systematically logged and used as a surrogate measure of hydrocarbon exposure.

After sampling, the badges were stored in a freezer (-20°C) until they were transported to X-Lab in Bergen, Norway, for analysis. X-Lab is accredited through the intercalibration test of the Norwegian Institute of Occupational Health in Oslo, Norway. Benzene was desorbed in carbon disulfide (CS_2) and analysed quantitatively and qualitatively by gas chromatography with mass spectrometry [19]. The limit of detection was 0.001 ppm.

2.3. Biological monitoring

2.3.1. Sampling of biological specimens

Each subject provided three samples of blood and urine. The first sample was collected in the morning (07:00–09:00) before the workers entered the tank (pre-shift) and was considered baseline measurement. The second sample was collected immediately after the work shift (18:00–21:00) on the third day of tank work (post-shift), and a third sample was collected in the morning (07:00–09:00) of the following day (pre-next shift). Blood and urine samples were obtained from the referents on the same days following the same time protocol. Since benzene has a short half-life in blood [9,20], the workers were asked to come directly to the hospital for collection of biological samples after changing from work overalls. Further, the workers were asked not to smoke before the blood sample was collected.

Blood samples for determination of unmetabolized benzene were collected by venipuncture into Venoject II[®] tubes (hard plastic) with heparin, and the urine samples for determination of unmetabolized benzene were collected in glass bottles (PYREX[®]) with polypropylene stoppers. The samples were stored at 4°C until they were transported overnight to the Biomonitoring Laboratory of the Finnish Institute of Occupational Health in Helsinki, Finland. Upon arrival at the laboratory within 4–7 days after sampling, the samples were immediately put into vapor-tight vials and kept at 4°C until analysis.

2.3.2. Methods of analysis of biological specimens

Benzene in blood: The concentrations of benzene in blood was analysed by a head-space sampler (Perkin-Elmer Headspace sampler HS40) and a gas chromatograph (Perkin-Elmer Autosystem Gas Chromatograph)

using photoionization detection according to the method described by Pekari et al. [9,21]. The samples with benzene concentrations at or above 5 nmol/l were analysed by multi-head space extraction as described by Etre and Jones [22]. The quantifications were based on an external standard method. The limit of quantification was 1 nmol/l.

Benzene in urine: The urinary concentration of benzene was analysed using a solid-phase microextraction–gas chromatograph–mass spectrometer/ion-trap detection method (SPME–GC–MS/ITD method). A total of 500 μl of urine was transferred to a vial of 2.0 ml containing 100 μl of an internal standard solution of chlorobenzene. The sample was injected by a solid-phase microextraction fiber (polydimethylsiloxane, 100 μm) in an autosampler (Varian 8200 CX autosampler), separated and analysed by a gas chromatograph (GC; Varian Saturn 3400 CX) and a mass spectrometer (MS; Varian Saturn 2000). In SPME mode the absorption time was 20 min and desorption time 1 min.

The GC conditions used were as follows: HP-5MS-column (30 m by 0.25 mm, 0.25 μm film thickness, J&W Scientific); helium carrier gas at flow rate of 1 ml/min. A Varian injector liner (0.8 mm internal diameter) was used with the injector temperature of 250°C and splitless injection mode. The MS transfer line and source temperatures were 180 and 140°C , respectively. GC oven temperature was programmed from 40°C (3 min initial hold) to 100°C at $10^{\circ}\text{C}/\text{min}$ and then to 200°C at $30^{\circ}\text{C}/\text{min}$ (final temperature, 1 min hold). Ions 77^{+} and 78^{+} were selected for quantifying benzene. The calculations were based on an internal standard method. The limit of quantification was 1 nmol/l.

2.4. Occupational exposure limits

The recommended Norwegian occupational exposure limit for benzene is 1 ppm averaged over an 8 h workday. In the guidelines to the Activities Regulations, the Norwegian Petroleum Directorate recommends a safety factor of 0.6 to correct the standard for a 12 h shift. Thus, the occupational exposure limit for benzene is 0.6 ppm over a 12 h workday. Finland's biological action limit is 50 nmol benzene per liter of blood post-shift.

2.5. Statistical analysis

The results from both study periods were analysed together. The individual benzene exposure is given as arithmetic mean and geometric mean, 95% confidence interval (95% CI) of the geometric mean and range (minimum and maximum). Differences in the various

exposure measures between the tank workers and referents were analysed using *t*-tests.

When analysing the associations between benzene exposure in the work environment and benzene concentration in biological media, the exposure measured in air on the day of sampling the post-shift sample (third day) was chosen. Pearson's correlation coefficient was calculated for studying relationships between the different exposure measures at the various time points. All the analyses were performed with each worker contributing with one observation only. The distribution of all continuous variables was tested for normality using the Shapiro–Wilk test. All the exposure measurements and the biomarkers of benzene exposure had a skewed distribution and were therefore log-transformed before statistical analysis (ln). The associations between benzene exposure in the work environment and benzene concentration in biological media were also adjusted for the corresponding baseline concentrations by including the baseline concentrations as covariates in regression analyses. Further, these associations were also adjusted for gender, age and smoking by including each of these in separate multiple regression analyses.

Blood and urinary benzene concentrations below the level of quantification and benzene exposure for referents were replaced by values equal to the level of quantification divided by 2 [23]. The data were analysed using SPSS Version 14.0.1 for Windows.

3. Results

3.1. General characteristics of the study population

Only 10 of the 13 tank workers worked in the tank during the 3-day study period. The three other workers performed other tasks with only minor benzene exposure and were excluded from the descriptive statistics and in the comparison of the tank workers and referents. However, all 13 workers and the 9 referents were included in the study of associations.

The mean ages (standard deviation) of the tank workers ($n = 10$) and referents ($n = 9$) were 37.5 (7.7) and 47.2 (6.3) years, respectively. All tank workers were men; three referents were women. The referents included one process operator from the central control room due to few catering personnel. Three tank workers and one referent reported being current smokers.

3.2. Individual exposure to benzene

Each of the 10 workers participating in the maintenance work in the cargo tank was measured daily during

the study period of three work shifts, leading to a total of 30 individual air measurements. After visual inspection of the dosimetry badges, four badges were rejected due to contamination and cutting. The rejection was done before analysis of the dosimeters. The mean sampling time for the remaining 26 measurements was 597 min (range 224–931 min). Due to practical problems, we failed to collect one of the blood samples post-shift and a total of five blood samples pre-next shift. All the participants provided urine samples both pre-shift, post-shift and pre-next shift.

Tank workers' mean benzene exposure over the 3-day study period (26 measurements) was 0.23 ppm for arithmetic mean (range 0.014–0.615 ppm) and 0.15 ppm for geometric mean (95% CI 0.10, 0.23), respectively, corresponding to 38 and 25% of the Norwegian occupational exposure limit of 0.6 ppm over a 12 h work shift. The exposure decreased over the study period, with a geometric mean (95% CI) of 0.22 ppm (0.10, 0.46) the first day, 0.16 ppm (0.07, 0.37) the second day and 0.11 ppm (0.05, 0.25) the third day. The tank workers' mean time periods spent in the tank the first, second and third day were 217, 292 and 316 min, respectively. This corresponds to 30–44% of the total work shift of 12 h.

3.3. Benzene concentration in blood and urine

The concentrations of benzene in blood and urine were all significantly higher among tank workers than among referents at all time points, including the pre-shift sample (Table 1). The geometric mean concentration of benzene in blood post-shift was 12.3 nmol/l in tank workers versus 0.7 nmol/l in the referents. The geometric mean concentration of benzene in urine post-shift was 27.0 nmol/l in tank workers versus 0.7 nmol/l in the referents.

The individual benzene exposure on the third day of sampling was highly correlated with the internal concentration of benzene in blood (post-shift $r = 0.87$, $P < 0.001$; pre-next shift $r = 0.70$, $P = 0.002$) and urine (post-shift $r = 0.90$, $P < 0.001$; pre-next shift $r = 0.94$, $P < 0.001$). The variation in benzene exposure explained 79 and 87%, respectively, of the variation in blood benzene post-shift and urinary benzene pre-next shift (Figs. 1 and 2). Referents were assigned exposure values equal to the limit of detection for benzene in air divided by 2. Imputing the values for these workers might introduce error in the estimates. When the referents were excluded in the analysis, leaving only the 13 exposed workers, the corresponding correlation coefficients were weaker both for blood (post-shift $r = 0.65$, $P = 0.02$; pre-next shift $r = 0.15$, not significant) and urine (post-shift $r = 0.60$,

Table 1

Comparison between tank workers and referents in mean concentration of benzene in blood (nmol/l) and benzene in urine (nmol/l) pre-shift, post-shift and pre-next shift on a crude oil production vessel

Marker of benzene exposure	Group	n	AM	GM	95% CI of GM	Range (min–max)	<LOQ	P
Blood, pre-shift	Tank workers	10	1.7	1.4	0.9, 2.2	0.5–3.0	2	0.03
	Referents	9	0.9	0.9	0.7, 1.0	0.5–1.0	2	
Blood, post-shift	Tank workers	9	17.3	12.3	5.7, 26.4	2.0–38.0	0	<0.001
	Referents	9	0.8	0.7	0.5, 1.0	0.5–1.0	4	
Blood, pre-next shift	Tank workers	10	4.3	3.0	1.6, 5.4	1.0–18.0	0	0.002
	Referents	6	0.8	0.7	0.5, 1.1	0.5–1.0	3	
Urine, pre-shift	Tank workers	10	12.3	6.9	2.8, 16.9	1.0–28.0	0	0.03
	Referents	9	3.4	1.8	0.7, 4.6	0.5–10.0	3	
Urine, post-shift	Tank workers	10	59.3	27.0	11.2, 65.2	3.0–333	0	<0.001
	Referents	9	0.8	0.7	0.4, 1.1	0.5–2.0	7	
Urine, pre-next shift	Tank workers	10	70.5	36.0	11.3, 114	1.0–197	0	<0.001
	Referents	9	0.5	0.5	–	0.5	8	

AM: arithmetic mean, GM: geometric mean, CI: confidence interval, <LOQ: number of samples below the limit of quantification

$P=0.03$; pre-next shift $r=0.75$, $P=0.003$). The time spent in the tank on the third day of study was highly and positively correlated with the benzene concentration in both post-shift blood ($r=0.87$, $P<0.001$) and urine ($r=0.80$, $P<0.001$), explaining 75 and 64% of the variation in blood and urine, respectively.

Adjusting for the baseline concentration of benzene in blood strengthened the reported associations between benzene in air and blood, but did not materially change the associations with benzene in urine (data not shown). Further, adjusting for potential confounders such as gender, age and current smoking did not materially change

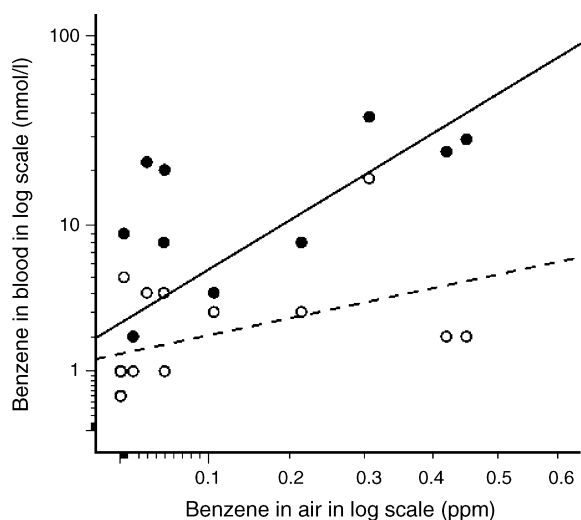


Fig. 1. Association between benzene in the breathing zone on the third day of study and benzene in blood post-shift ($r^2 = 0.79$, $P < 0.001$; solid line (—) with filled circles (●)) and pre-next shift ($r^2 = 0.46$, $P = 0.002$; dotted line (---) with empty circles (○)) among exposed workers and referents on a crude oil production vessel. The concentrations are given in log scale.

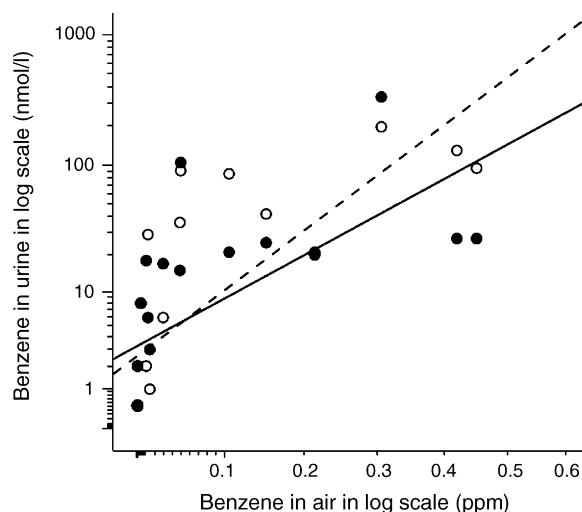


Fig. 2. Association between benzene in the breathing zone on the third day and urine post-shift ($r^2 = 0.81$, $P < 0.001$; solid line (—) with filled circles (●)) and pre-next shift ($r^2 = 0.87$, $P < 0.001$; dotted line (---) with empty circles (○)) among exposed workers and referents on a crude oil production vessel. The concentrations are given in log scale.

the reported correlation coefficients between the exposure measures for benzene.

4. Discussion

Despite a relatively low geometric mean benzene exposure in the work environment of 0.15 ppm among tank workers over the 3-day study period and use of respirators to a varying degree, the tank workers had a significantly higher benzene concentration in both blood and urine than the referents at all time points. Both the benzene exposure in the workers breathing zone and time spent in the cargo tank were highly correlated

with the internal concentration of benzene in blood and urine.

German Research Foundation [24] has investigated the relationship between the concentration of benzene in the workplace air and in blood when not using personal protective equipment. These relationships, called exposure equivalents for carcinogenic substances (EKA values), allow the determination of the body burden resulting from uptake of the substance exclusively by inhalation. According to these EKA values, exposure to 0.3 ppm benzene in the breathing zone corresponds to a benzene concentration post-shift of 0.9 µg per liter of blood, which is about 11.5 nmol benzene per litre of blood. The tank workers in the present study absorbed a similar amount of benzene after being exposed to only 50% of the corresponding exposure level – that is, a geometric mean exposure of 0.15 ppm caused a benzene concentration in blood of 12.3 nmol/l. Thus, despite using respiratory protective equipment, the tank workers absorbed more benzene than expected.

Several factors can explain the increased absorption of benzene. Most standards for chemical exposure in the work environment, including occupational exposure limits and biological action limits, apply to workers with a conventional schedule of 8 h per day 5 days per week rather than 12 h work days. Although the tank workers mean time period spent in the tank on the third day of study corresponded only to 44% of the total work shift of 12 h, the extended work schedule most likely contributed to the increased absorption. The heavy workload of the tank workers might also have caused the increased absorption of benzene due to increased pulmonary ventilation and blood flow [15–18]. While Zimmer et al. [17] reported that physical activity of 50 and 75 W, respectively, lead to a significant increase of the blood concentrations by mean factors of 1.2 and 1.9 for a range of hydrocarbon solvent mixtures, Nadeau et al. [18] reported that even light work load intensity might lead to a 2.5–4-fold higher absorbed dose of toluene. Absorption of benzene through the skin by direct contact with crude oil residues [25] or vapor [26,27], or an altered uptake or modification of the benzene metabolism due to the combined exposure or specific exposure to other compounds [28,29], are probably of only minor importance.

We do not have data on the proportion of time the individual workers wore respirators, but some workers seemed to be more conscientious than others in using a respirator. However, the correlation between the individual benzene exposure and the amount of benzene absorbed was very high, indicating that the varying degree of respirator use did not explain much of the

variability in absorbed benzene. The efficiency of the half-mask respirator for organic solvents is affected by several factors, such as the fitting of the respirator face piece [30,31] and the frequency of cartridge exchange [32].

The correlation coefficients between benzene in the work atmosphere and benzene in urine post-shift and pre-next shift were 0.90 and 0.94, respectively. This finding complements previous studies on exposure to benzene concentrations below 1 ppm, in which correlation coefficients between benzene concentrations in air and benzene in urine post-shift have been reported to be 0.38–0.98 [13,33–36]. Interestingly, Kivisto et al. [36] reported a correlation coefficient as high as 0.97 among coke workers, but this correlation no longer existed when using only samples at or below 1 ppm benzene. The best correlations in the above-mentioned studies were found among non-smokers. In our study, adjusting for current smoking did not materially change the reported correlations between the exposure measures for benzene. However, the number of subjects was not high enough to evaluate differences in benzene exposure among current smokers and referents.

Most guidelines on biological monitoring recommend that the urinary concentration of unmetabolized benzene or its metabolites be monitored in samples collected at the end of the work shift. However, in our study the correlation coefficient between benzene in the breathing zone and urine increased from post-shift to pre-next shift, whereas the opposite was true for benzene in blood. This indicates that the urine sampled could be collected pre-shift on the following morning. However, disturbances such as exposure after the work hours can change the exposure estimation significantly, and post-shift sampling is probably more reliable for estimating exposure at low exposure concentrations.

The results showed that, despite low benzene exposure in this work atmosphere and the use of personal protective equipment, the workers had significant uptake of benzene that was highly correlated with the individual benzene exposure and the time spent in the tank. The internal concentration of benzene was higher than expected at the measured exposure levels, and is probably due to an extended work schedule of 12 h and high work load during tank work. Control measures should be improved for processes which impose a potential for increased absorption of benzene for tank workers.

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Paper IV

Acute Suppression of Serum IgM and IgA in Tank Workers Exposed to Benzene

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Abstract

We investigated associations between benzene exposure and alterations of proteins and cells of the immune system among workers maintaining cargo tanks containing crude oil residues. Individual exposure to benzene, benzene in blood and urine, peripheral blood lymphocytes (total lymphocytes, lymphocytes in subpopulations CD3, CD4, CD8, CD19, CD56 and D4/CD8 ratio), complement factors C3 and C4 and serum concentration of immunoglobulins (IgG, IgA, IgM and IgE) were analysed among 13 tank workers and nine unexposed referents (catering section). Benzene exposure was measured during three consecutive 12-h work days. Blood and urine samples were collected preshift on the first day (baseline), post-shift on the third day, and pre-next shift on the following morning. The time spent in the cargo tank was logged. The individual geometric mean benzene exposure in the breathing zone of tank workers over 3 days was 0.15 p.p.m. (range 0.01–0.62 p.p.m.) (n = 26). The geometric mean benzene concentration in blood post-shift was 12.3 nmol/l among tank workers versus 0.7 nmol/l among the referents. Tank workers showed a decline (versus referents) in IgM from baseline to post-shift (t-test, P = 0.04) and IgA from baseline to pre-next shift (t-test, P = 0.01). They also showed a decline in CD4 T cells from baseline to post-shift (t-test, P = 0.04). Suppression correlated with benzene exposure, benzene concentrations in blood and urine and time spent in the tank. The groups did not differ significantly in the change in other immune parameters. The clinical significance is unknown and warrants further studies.

Paper V

ORIGINAL ARTICLE

Increased risk of hematopoietic malignancies in a historical cohort of upstream petroleum workers in Norway

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ABSTRACT

Background We performed a historical cohort study to investigate whether workers employed in the Norwegian upstream petroleum industry offshore, exposed to crude oil and other products containing benzene, have a higher risk of developing hematopoietic malignancies compared to the general working population.

Method We used the Norwegian Registry for employers and employees, and included all subjects registered with offshore-related industrial classification codes or with the location of work being the North Sea in the period 1981 to 2003. Up to six referents per petroleum worker were drawn from the general working population, matched by gender, age and community of residence. The cohort comprised 27 919 offshore workers distributed on four job categories offshore and 366 114 referents, and was linked to the Cancer Registry of Norway, the Registry for education and the Registry of causes of mortality.

Results Workers in the job category “upstream operator offshore”, who have the potentially highest exposure, had an excess risk of hematopoietic malignancies (RR 1.90, 95% CI 1.19-3.02). This was ascribed to increased risks of acute myelogenous leukemia (RR 2.89, 95% CI 1.25-6.67) and multiple myeloma (RR 2.49, 95% CI 1.21-5.13). Risk ratios were highest for the workers with their first registered engagement in the offshore petroleum industry before 1986. No increased risk was found for the other job categories, and no differences were found for overall cancer (all sites).

Conclusion Workers exposed to crude oil and other hydrocarbons on the Norwegian shelf had a significantly increased risk of developing acute myelogenous leukemia and also multiple myeloma, most likely caused by their occupational exposure to benzene.

INTRODUCTION

Benzene is a known leukemogenic agent.¹⁻⁴ Despite extensive research on benzene exposure and its association with leukemia, there are still questions on the health risk of benzene at low exposure levels and on the relation between exposure and the various subtypes of leukemia.⁴

Benzene is a natural component of crude oil and natural gas. Thus, benzene exposure is a potential hazard in the petroleum industry. Studies of workers in the petroleum industry have reported an increased risk of leukemia,⁵⁻⁸ while the risk of multiple myeloma has been debated.^{9,10} These studies included workers employed in oil refinery operations, distribution and consumption of oil products, and only to a limited degree upstream operations such as drilling and maintenance of oil wells and production of crude oil, natural gas, and natural gas liquids (NGL). Workers in the upstream petroleum segment offshore, who in addition to being potentially exposed to crude oil and natural gas, have also been reported to be exposed to benzene as a component of diesel-based drilling mud and laboratory chemicals.^{11,12}

We wanted to study whether workers employed in the Norwegian upstream petroleum industry offshore exposed to crude oil and other products containing benzene have a higher risk of developing hematopoietic malignancies compared to the general working population in Norway. We wanted particularly to focus on the differences in risk according to the subtypes of leukemia.

METHODS

Study population and study design

We performed a historical cohort study of the cancer incidence in the Norwegian upstream petroleum industry. The cohort was established using the information from the Norwegian Registry for employers and employees (NREE). NREE is owned by the National Insurance Administration (Rikstrygdeverket), and is a registry where all employers are obliged to register their employees with a personal identification number, industrial classification code (International Standard Industrial Classification; ISIC and NACE), county of work and start and stop date of all their engagements. There is no minimum requirement of employment duration for inclusion in the registry.

The Norwegian petroleum industry has been in operation offshore since the early 70ies. The NREE registry was established in 1978, and became operational in 1983 containing employments from 1981 and onwards until 2003. Hence, subjects included in the cohort might have had engagements also before 1981, but these engagements are not included in our data. The inclusion criteria for the cohort of the petroleum workers was that the workers were registered with one of the following offshore-related industrial classification codes: ISIC 22 (Extraction of crude oil and natural gas), ISIC 5032 (oil drilling), NACE 11 100 (Extraction of crude oil and natural gas) and NACE 11 200 (Service activities incidental to oil and gas extraction), or having the Norwegian continental shelf (North Sea) as the location of work.

Based on the workers location of work (onshore/offshore) and the industrial classification codes of their first registered engagement in the offshore-related petroleum industry, the petroleum workers were categorized into the five job categories 1) upstream operator offshore, 2) drilling and well maintenance offshore, 3) catering offshore, 4) others offshore, and 5) petroleum workers onshore. The category “upstream operator offshore” contained solely workers registered with the NACE and ISIC-code *Extraction of crude oil and natural gas*. These workers mainly work in the production and process section. This includes job categories such as process technicians, laboratory engineers, control operators and other job groups involved in the production process including stabilization, separation and fractionation of the crude oil, natural gas, and natural gas liquids (NGL). The category “drilling and well maintenance offshore” includes the ISIC-code 50 230 (*Oil drilling*) and NACE-code 11 200 (*Service activities incidental to oil and gas extraction excluding surveying*). The latter code consists merely of activities such as drilling of wells and installation, disassembling and

maintenance of drilling towers at site on contract, and includes job groups such as drill floor crew, derrick employees, mud loggers- and engineers, shale shaker operators and well service crew. The category “catering offshore” includes job groups such as catering crew, chefs and house keeping personnel. The category “others offshore” includes miscellaneous industrial codes and consists of activities contracted out to oil field service companies, such as construction- and maintenance personnel and logistics. Finally, “petroleum workers onshore” contains workers registered with an offshore-related engagement without being registered with the North Sea as the location of work. This job category contains workers involved in the administration, planning and coordination of the activities offshore.

Up to six referents per petroleum worker were drawn at random from the general working population, using the same registry and the same year of the first engagement of the corresponding petroleum worker. The referents were matched to the petroleum worker by gender, age and community of residence. The crude historical cohort included 71 018 workers from the petroleum industry (“at risk”) and 424 584 referents. Subjects were excluded from the cohort if they had had a cancer diagnosis before entering into the cohort ($n = 3784$) and referents were excluded if they had an earlier engagement in the petroleum industry prior the time they were drawn as referents even if they at this time of inclusion had a “non-exposed” engagement ($n = 29004$). Subjects were allowed to serve as referents for more than one “subject at risk”.

The final cohort comprised 27 919 offshore workers distributed on the four job categories offshore, contributing with 332 063 person-years (table 1). About 89% of the offshore workers were men. The oil drilling section comprised only 4.6% women, while the corresponding percentage in the catering section was 49.1%. Forty-nine percent of the subjects in the category “upstream operator” started in the petroleum industry before 1986. In the category “drilling and well maintenance” as much as 67.8% of the workers started in the period 1991-2003, possibly due to oil companies starting to contract out operations such as drilling and well maintenance to drilling contractors from the early 90ies and onwards. We therefore assume that the category “upstream operator” in the beginning of the study period also includes workers involved in the drilling process itself. Further, while upstream operators have had a potential for exposure to benzene through their contact with the different phases of crude oil, the drilling personnel have had a potential exposure to benzene through contact with drilling mud and other products containing benzene. Therefore, with respect to hematopoietic malignancies, the workers in “upstream operator offshore” and “drilling and well maintenance” were also analyzed as one group.

The total cohort was linked to the Cancer Registry of Norway in April 2006, including all cases of cancer reported up to December 31, 2003 with the information on date of diagnosis and diagnosis (localisation, morphology and histology). The cancers were coded according to a modified version of ICD-7 (3 digit code, International Classification of Diseases, ICD-7). The Cancer Registry is based on reporting from multiple sources, such as physicians, pathology laboratories and death certificates from Statistics Norway where cancer or cancer related illnesses are mentioned, ensuring a high degree of accuracy and completeness (ref). The cohort was also linked to the Registry of causes of mortality and the Registry for education including the variable highest completed education, ranging from 1 (elementary school) to 6 (PhD-degree). The establishment of the cohort and the linking to the different registries were performed at the Statistics Norway.

Statistical analyses

Rate ratios comparing the various working categories with the general working population were estimated using the Cox proportional hazard regression model. Subjects were censored at end of follow up (December 31, 2003), at date of death or date of diagnosis of another type of cancer than the one under study, whichever occurring first.

The proportional hazards assumption was checked for overall cancer and all hematopoietic malignancies by comparing the estimated $-\ln(-\ln S)$ curves for the different groups being investigated. No marked deviation from the PH-assumption was indicated. Multivariate analyses were performed, including the independent covariates age, gender, year of first engagement and educational level. We also performed sub-analyses including the engagements during the first 5 years only (1981 – 1985) and one including the remaining 18 years (1986 – 2003).

All analyses were performed using SPSS 14.0.1 (SPSS Inc., Illinois, US).

Ethical considerations

The study was conducted with the approval of the Western Norway Regional Committee for Medical Research Ethics, the Data Inspectorate and the Directorate for Health and Social Affairs. The National Insurance Administration gave us the permission to use the NREE, the Cancer Registry of Norway provided the data from the Cancer Register, and Statistics Norway, administratively placed

under the Ministry of Finance, approved the use of information from the Registry of causes of mortality and the Registry for highest completed education.

RESULTS

Workers in the job category “upstream operator offshore” had an excess risk of hematopoietic malignancies (RR 1.90), while a non-significant increase was found among workers in the category “drilling and well maintenance” (Table 2). No increased risk of hematopoietic malignancies was found in the other job categories. Differentiating between the subtypes of hematopoietic malignancies, the category “upstream operators” had an increased risk of acute myelogenous leukemia (RR 2.89) and multiple myeloma (RR 2.49) (Table 3). The risk was also increased for these subtypes in the job category “drilling and well maintenance”, but the number of cases was low. When combining these two job categories, the risks were at the same levels. No increased risk of either acute myelogenous leukemia or multiple myeloma was found in the other job categories offshore.

For both acute myelogenous leukemia and multiple myeloma, the risk ratios were highest for the workers with their first registered engagement in the offshore petroleum industry before 1986 (Table 4). “Upstream operators” who started in the petroleum industry before 1986 had a risk of 3.26 of developing acute myelogenous leukemia, while the corresponding risk was 2.85 for multiple myeloma. The same trend was not seen for the job category “drilling and well maintenance”.

The incidence of overall cancer (all sites) among the offshore workers did not differ significantly from the general working population in any of the job categories. However, there were excess risks of cancer in upper respiratory organs among the workers in the catering section (95% CI 1.65 – 6.81), cancer in the oesophagus in the job categories “upstream operator offshore” (95% CI 1.03 – 8.00) and “other workers offshore” (95% CI 1.06 – 6.63), cancer in the lung and bronchus among “other workers offshore” (95% CI 1.07 – 2.00), cancer in pleura among “petroleum workers onshore” (95% CI 1.35 – 5.36), and prostate cancer in the job category “other workers offshore” (95% CI 1.05 – 1.84). The petroleum workers onshore showed a reduced risk of malignant melanoma as compared to referents (95% CI 0.65-0.98).

DISCUSSION

Offshore workers exposed to crude oil and other benzene-containing products on the Norwegian shelf during the period 1981 - 2003 had a significantly higher risk of developing hematopoietic malignancies – particularly multiple myeloma and acute myelogenous leukemia, than the general working population. The increased risk was found among upstream operators and workers involved in drilling operations, the workers assumed to have potential for high exposure to benzene through their contact with either different phases of crude oil, drilling mud containing aromatic hydrocarbons and other products containing benzene. Given the established association between benzene exposure and hematopoietic malignancies,^{1,4} benzene is likely to be the cause of the observed increased risk of acute myelogenous leukemia and multiple myeloma in this study.

A question of controversy is at which level of exposure benzene presents an increased risk of developing hematopoietic malignancies and to what extent peak and high short-term exposures increases the risk.^{2,3,5,13} Information about past exposure of benzene in the Norwegian offshore petroleum industry is scarce,¹¹ and no good exposure estimates for the different job categories exist. The published data on benzene exposure in the petroleum industry indicate that the exposure has been relatively low during ordinary activity,^{11,14-16} but that workers at times have experienced relatively high levels of benzene whenever the processing system was opened during cleaning and maintenance of vessels, separators and tanks.¹⁶⁻¹⁹

The association between benzene exposure and development of specific subtypes of leukemia is still unclear. In the present study the risk was highest for acute myelogenous leukaemia. The risk of acute lymphatic leukemia was also elevated, but based only on two cases in the exposed groups and therefore not statistically significant. The most recent meta-analysis of benzene-exposure and leukemia subtypes including nine cohorts and 13 case-control studies from several industries, found a high and significant risk of acute myeloid leukemia with a positive dose response relationship across study designs.⁴ The risk for developing chronic lymphocytic leukemia was increased in the case-control studies, but not in the cohort studies. The data for chronic myeloid leukemia and acute lymphocytic leukemia were sparse and inconclusive.

While our results on acute myelogenous leukemia were in line with previous studies, the association between benzene exposure and multiple myeloma is a contentious issue.^{9,10,20} In a meta-analysis of 22 cohort mortality studies consisting of 250 000 petroleum workers, mainly from the refinery and

distribution segment it was concluded that petroleum workers are not at an increased risk of multiple myeloma as a result of their exposure to benzene, benzene-containing liquids, or other petroleum products in their work environment.²¹ On the other hand, in a more recent meta-analysis including seven cohort studies focusing on benzene-exposed workers, including refinery workers, a significant excess in the relative risk (RR) of multiple myeloma in relation to benzene exposure (RR 2.13, 95% CI = 1.31-3.46) was reported.²² The findings in the present study give further strong evidence of such a relationship.

We found that the risk of acute myelogenous leukemia and multiple myeloma was highest for those having had their first registered engagement in the offshore petroleum industry in the beginning of the study period. One explanation might be that the follow-up time was too short to detect any increased risk for workers starting in the industry later on. Several authors have discussed the temporal variation of the risk of developing leukemia after an exposure to benzene. Finkelstein²³ and Silver *et al.*²⁴ reported that the increase risk in the Pliofilm-cohort² declined after 10 years since first exposure, and Glass *et al.*¹³ reported a similar pattern in the Health Watch cohort from the Australian petroleum industry. This indicates that the follow-up period might have been sufficient for the workers who, in the present study, started during the period 1986 up to the early 1990's. Further, sensitivity to benzene's toxic effects differs among individuals, explained partly by polymorphisms in enzymes involved in the metabolism of benzene, particularly the cytochrome P450 2E1.²⁵ Half of the "upstream operators" started in the industry before 1986, and one could speculate that the workers who entered this early and who developed acute myelogenous leukemia and multiple myeloma were the subjects most susceptible, leaving a group of less susceptible workers for the rest of the follow-up period. Nevertheless, the most plausible explanation of the increased risk for work in the first period is likely related to a general improvement of the work environment offshore, including reduced benzene exposure, due to regulations and other initiatives in the 90ies.

Cigarette smoke is a known source of benzene exposure,^{26,27} and both active and passive smoking has been associated with risk of acute myelogenic leukemia.^{28,29} We do not have data on smoking in the present study. However, the risk estimates were adjusting for the level of education, that is sometimes used as a surrogate measure of social class and smoking.^{30,31} Further, the workers in the job categories "upstream operators offshore" and "drilling and well maintenance" did not have an increased risk of cancer in lung and bronchus as compared to the referents. This might indicate that smoking have not contributed substantially to the increased risk of hematopoietic malignancies among these workers.

Given the complexity of the exposure both to crude oil and other agents at the offshore work site offshore we can not exclude that other possible leukemogenic factors might have contributed to the increased risk of hematopoietic malignancies. Petroleum workers are potentially exposed to ionizing radiation due to operations such as non-destructive testing (NDT) of welding seams, well-logging and contact with sediments emitting low-level ionizing radiation. Ionizing radiation have been shown to cause both acute myelogenous leukemia³² and multiple myeloma.^{20,33} However, the reported levels are well below present recommended annual limit values.^{11,34}

It has been shown that the healthy worker effect is a bias in occupational mortality studies when comparing the working population of interest with general populations which includes people not at work. This has been shown for mortality risks for both chronic diseases and cancer,³⁵ and is explained both by selection bias, classification bias and confounding effects.³⁶ In addition to using a prospective cohort design, the referents in our study were drawn from the general working population and from the same registry as the subjects “at risk”, hence reducing this healthy worker effect to a certain degree. Nevertheless, all offshore workers are required to meet rigorous standards of health and fitness for work still leaving a potential for a limited healthy-hiring effect. The subjects and referents were matched on level of education and place of residence, thereby reducing a potential bias due to culture, ethnicity, lifestyle and/or regional environmental pollution, as discussed in Leonard *et al.*³⁵ Finally, the Cancer Registry is the source for cases of cancer for both petroleum workers and referents thereby avoiding classification bias of the outcome.

Studies of workers in the downstream petroleum industry, such as transporters, refiners, retailers, and consumers, have reported an increased risk of both prostate cancer, kidney cancer, melanoma, mesothelioma, gall bladder and hematopoietic malignancies.³⁷⁻³⁹ Although we found an excess risk of cancer in upper respiratory organs, oesophagus, lung and bronchus and prostate cancer among some of the job categories offshore, the overall cancer incidence did not differ between the cohorts of petroleum workers offshore, petroleum workers onshore and the general working population. Nevertheless, the relatively short follow up time does not allow us to conclude on the risk of these solid cancer types.

In conclusion, workers exposed to crude oil and other hydrocarbons on the Norwegian shelf during the period 1981 - 2003 had a significantly increased risk of developing acute myelogenous leukemia and multiple myeloma. Although we can not exclude a possible contribution of other specific or

combined exposures, occupational exposure to benzene is still the most likely causative agent for the increased risk. In the lack of exposure measurements and detailed information on job tasks in the groups studied a likely high non-differential misclassification of exposure has taken place in this prospective study. This means that the risk for the individuals with substantial exposure might have been markedly underestimated. To achieve better estimates of the association between the various exposures and the risk of the subtypes of hematopoietic malignancies in this large cohort, a case-control study nested within the cohort will be performed.

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Table 1 Characteristics of the study population.

Characteristic	Referents	Petroleum workers (all)	Onshore workers (all)	Offshore workers			
				Upstream operator offshore	Drilling and well maintenance	Catering offshore	Others offshore
Number of subjects	366 114	70 600	42 681	6734	7049	2417	11 719
Male (%)	283 002 (77.3)	55 376 (78.4)	30 611 (71.7)	5853 (86.9)	6722 (95.4)	1231 (50.9)	10 959 (93.5)
Female (%)	83 112 (22.7)	15 224 (21.6)	12 070 (28.3)	881 (13.1)	327 (4.6)	1186 (49.1)	760 (6.5)
Age, mean (standard deviation)							
<i>At inclusion in the cohort</i>	33.8 (9.5)	33.8 (9.5)	33.9 (9.7)	33.8 (8.1)	32.6 (8.6)	32.6 (10.0)	34.3 (9.6)
<i>At end of follow up</i>	46.3 (11.5)	46.4 (11.4)	46.3 (11.5)	49.6 (11.3)	43.4 (11.2)	47.9 (11.4)	46.7 (10.7)
Education level (mean)	4.2 (1.5)	4.7 (1.6)	5.1 (1.6)	4.2 (1.2)	4.0 (1.2)	3.5 (1.1)	4.0 (1.3)
<i>Tertiary education (%)</i>	28.4	34.4	46.8	18.4	13.9	8.7	15.7
<i>Intermediate education (%)</i>	59.0	53.8	41.7	72.5	74.4	73.6	70.8
<i>Compulsory education (%)</i>	11.4	6.4	4.3	7.2	9.6	16.4	9.8
Start-date in industry (in %)							
<i>Before 1986</i>	28.3	28.3	29.0	49.1	15	47.7	18.0
<i>1986 – 1990</i>	19.4	19.3	16.1	22.8	17.2	19.9	30.3
<i>1991 – 2003</i>	52.3	52.3	54.9	28.1	67.8	32.4	51.7
Person-years at follow up	4 213 716	815 049	482 987	98 341	68 238	33 677	131 808

Table 2 Rate ratios for overall cancer incidence and for all cancer types for the different job categories as compared to referents. The rate ratios are adjusted for gender, age, year of first exposure and education using the Cox proportional hazard regression model. Rate ratios significantly different from unity are given in bold and underlined.

	Referents		Petroleum workers onshore		Upstream operator offshore		Drilling and well maintenance		Catering offshore		Others offshore	
	n	RR	n	RR	n	RR	n	RR	n	RR	n	RR
All sites	11271		1146	0.95	251	0.93	150	0.96	102	1.04	312	1.10
Hematopoietic malignancies	394		42	0.93	20	<u>1.90</u>	9	1.55	2	0.68	6	0.58
Lip	43		1	0.31	1	0.92	2	2.69	0	0	1	0.83
Upper respiratory organs	312		22	0.75	7	0.88	5	1.02	8	<u>3.35</u>	14	1.44
Oesophagus	66		5	0.82	4	<u>2.87</u>	2	2.10	1	1.86	5	<u>2.65</u>
Stomach	298		18	0.64	10	1.12	6	1.52	3	1.32	7	0.84
Large intestine	823		78	0.92	14	0.70	7	0.56	3	0.30	20	0.98
Rectum	506		44	0.87	10	0.81	3	0.42	5	1.20	16	1.12
Liver	51		5	1.32	0	0	0	0	1	2.55	0	0
Pancreas	212		21	1.04	5	1.04	2	0.74	4	1.78	2	0.34
Lung and bronchus	1005		82	0.98	31	1.29	12	0.83	12	1.42	42	<u>1.47</u>
Pleura	45		11	<u>2.70</u>	1	0.97	0	0	0	0	3	2.21
Prostate	1377		158	1.01	31	0.96	22	1.12	3	0.33	54	<u>1.39</u>
Testis	529		46	0.84	18	1.50	8	0.65	5	1.88	18	0.91
Kidney	329		35	1.06	9	0.91	7	1.22	4	1.60	14	1.60
Bladder	482		47	0.97	11	0.88	9	1.36	7	1.84	18	1.34
Malignant melanoma	1110		103	<u>0.79</u>	25	0.88	19	1.24	8	0.92	22	0.76
Skin, other	379		31	0.77	4	0.40	3	0.66	3	1.08	9	1.10
Brain and nervous system	601		69	1.08	10	0.70	8	0.86	4	0.88	16	0.91
Thyroid	138		12	0.68	3	1.12	2	1.43	1	0.65	2	0.81
Breast	861		133	1.05	4	0.54	2	0.91	15	1.13	10	1.63
Lymphoma	655		58	0.86	14	0.82	7	0.66	1	0.20	11	0.60

Table 3 Rate ratios (95% CI) for overall incidence of hematopoietic malignancies, subtypes of leukemia and multiple myeloma among workers in the job categories drilling and well maintenance offshore and upstream operators as compared to the referents. The rate ratios are adjusted for gender, age, year of first exposure and education using the Cox proportional hazard regression model. Rate ratios significantly different from unity are given in bold.

	Referents		Upstream operators			Drilling and well maintenance			Upstream operators and drilling combined		
	n		n	RR	95% CI	n	RR	95% CI	n	RR	95% CI
All hematopoietic malignancies	393		20	1.90	1.19 – 3.02	9	1.55	0.80 – 3.02	29	1.77	1.20 – 2.61
Multiple myeloma	132		9	2.49	1.21 – 5.13	3	1.72	0.54 – 5.44	12	2.24	1.20 – 4.17
Acute lymphocytic leukemia	17		1	2.17	0.29 – 16.6	1	3.35	0.44 – 25.8	2	2.62	0.60 – 11.5
Chronic lymphocytic leukemia	73		3	1.62	0.51 – 5.20	1	0.98	0.14 – 7.14	4	1.39	0.50 – 3.81
Acute myelogenous leukemia	86		6	2.89	1.25 - 6.67	2	1.55	0.38 – 6.35	8	2.35	1.13 – 4.88
Chronic myelogenous leukemia	31		1	1.44	0.19 – 10.7	0	—	—	1	0.75	0.10 – 5.54
Other hematopoietic malignancies	54		0	—	—	1	1.23	0.17 – 8.93	1	0.44	0.061 – 3.22

Table 4 Rate ratios (95% CI) for all hematopoietic malignancies combined, multiple myeloma and acute myelogenous leukemia for the job categories “upstream operators offshore” and “drilling and well maintenance offshore” as compared to the referents when stratifying on the year of the first engagement in the offshore-related petroleum industry (“first exposure”). The rate ratios are adjusted for gender, age, year of first exposure and education using the Cox proportional hazard regression model. Rate ratios significantly different from unity are given in bold.

	Referents		Upstream operators		Drilling and well maintenance		Upstream operators and drilling combined			
	n	n	RR	95% CI	n	RR	95% CI	n	RR	95% CI
<i>First exposure 1981 - 1985</i>										
All hematopoietic malignancies	221	19	2.22	1.37 – 3.60	5	2.28	0.93 – 5.60	24	2.24	1.45 – 3.45
Acute myelogenous leukemia	45	5	3.26	1.28 – 8.30	1	2.51	0.34 – 18.8	6	3.11	1.31 – 7.39
Multiple myeloma	83	9	2.85	1.37 – 5.93	1	1.19	0.16 – 8.67	10	2.47	1.23 – 4.95
<i>First exposure 1986 - 2003</i>										
All hematopoietic malignancies	173	1	0.49	0.07 – 3.49	4	1.24	0.46 – 3.34	5	0.94	0.39 – 2.30
Acute myelogenous leukemia	41	1	1.76	0.24 – 12.9	1	1.26	0.17 – 9.23	2	1.45	0.35 – 6.04
Multiple myeloma	49	0	0	—	2	2.49	0.60 – 10.3	2	1.54	0.37 – 6.37

Appendix I

Appendix 1



(photo: PGS Production)



(photo: Norsk Hydro ASA)

Picture 1. Crude oil production vessel (top) and a fixed oil- and gas installation (bottom) comprising a drilling unit (left), processing unit and living accommodation (middle) and a gas processing and export unit (right).

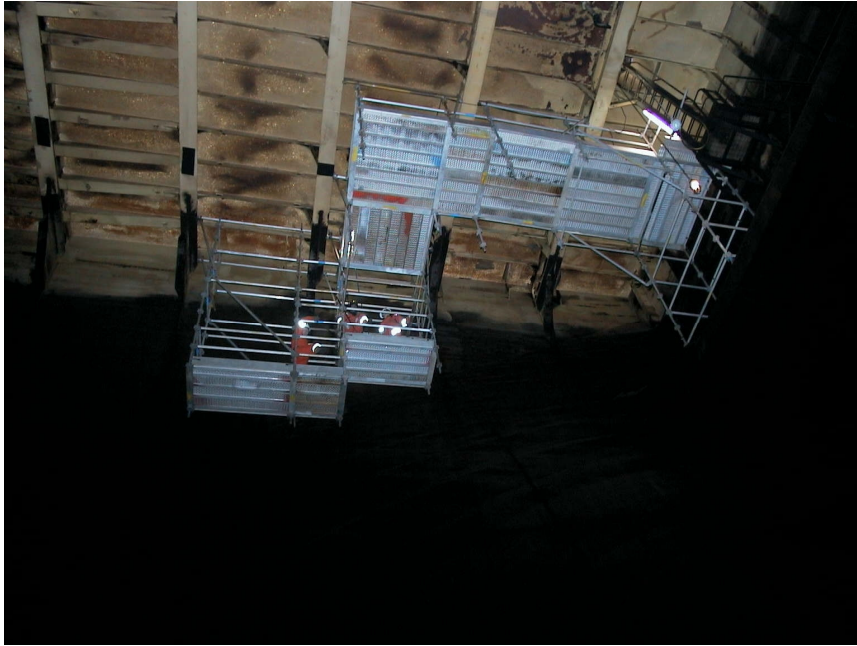


(photo: PGS Production)



(photo: PGS Production)

Picture 2. The photos show inspection of cargo tanks containing crude oil residues on a crude oil production vessel.



(photo: PGS Production)



(photo: Jorunn Kirkeleit)

Picture 3. The photos show workers performing scaffold building (top) and welding (bottom) in cargo tanks containing crude oil residues on a crude oil production vessel.



(photo: Jorunn Kirkeleit)

Picture 4. The photos show a process operator inspecting the flotation package (top left), a process operator receiving a pipeline cleaning pig (top right), a process operator sampling crude oil for analysis (bottom left) and a deck worker turning blind flanges (bottom right).

Appendix II



Bergen, 17.06.2004

FORESPØRSEL OM Å DELTA I PROSJEKTET "GIR EKSPONERING FOR BENZEN PÅ NORSK SOKKEL ØKT RISIKO FOR Å UTVIKLE LEUKEMI?"

Kjemikalieforskriften § 6 stiller krav til at arbeidsgiver skal kartlegge og dokumentere forekomsten av kjemikalier og vurdere enhver risiko for arbeidstakernes helse og sikkerhet forbundet med disse. Seksjon for arbeidsmedisin har satt igang et prosjekt for å studere eksponering for benzen på norsk sokkel og dets helseeffekter. Vi håper at ønsker å delta i prosjektet.

Prosjektet finansieres av Norges forskningsråd, men vi mangler midler til dekning av analysekostnader. Vi søker med dette om at dekker analysekostnadene for 20 arbeidstakere. I tillegg kommer helikoptertransport og forpleining under selve prøvetakingen.

På grunn av prosjektets progresjon ønskes tilbakemelding innen 8. juli 2004.

Kjemikalieforskriften § 6 stiller krav til at arbeidsgiver skal kartlegge og dokumentere forekomsten av kjemikalier og vurdere enhver risiko for arbeidstakernes helse og sikkerhet forbundet med disse. Risikovurderingen skal blant annet særlig ta hensyn til kjemikalienes farlige egenskaper, eksponeringens type, nivå, varighet, hyppighet og eksponeringsveier, samt grenseverdier og administrative normer. Benzene er et kreftfremkallende stoff som er en naturlig bestanddel av råolje. I forskriftens kapittel III, § 16 står det at grenseverdien for benzen ikke skal overskrides. Hudopptaket for benzen kan imidlertid være betydelig for enkelte arbeidsoperasjoner, noe som ikke vil avdekkes ved måling av benzen i arbeidstakerens pustesone.

Seksjon for arbeidsmedisin har igangsatt et prosjekt for å studere eksponering for benzen på norsk sokkel og dets helseeffekter. Som vi sa i brev av 15.12.2003 er det viktig for prosjektets relevans at det utgår fra petroleumsindustrien selv, og at vi håper at Deres selskap vil delta. For å få et representativt utvalg håper vi å inkludere 100 arbeidstakere i prosjektet, fordelt på de største aktørene som opererer på norsk sokkel.

Hensikten med prosjektet er å karakterisere eksponeringen for benzen på norsk sokkel, og å undersøke om vi finner benzen og dets stoffskifteprodukter i blod og urin hos arbeidstakere som jobber på norsk sokkel. Vi vil også undersøke om det er en sammenheng mellom eksponering for benzen og skadelige blodforandringer som kan være forstadier til utvikling av kreft. Prosjektet vil også gi økt kunnskap om biomonitorering av benzen, slik at metoden kan benyttes som et supplement til tradisjonell prøvetaking av benzen i arbeidsluft på norsk sokkel. Videre vil resultater fra prosjektet si noe om behovet for ytterligere tiltak for å redusere eksponeringen offshore.

De biologiske prøvene vil aidentifiseres før de sendes til analyselaboratoriet ved Finnish Institute of Occupational Health i Finland (FIOH), som vil utføre analysene mhp. markører for eksponering. Finnish

Institute of Occupational Health har arbeidet med biologisk monitorering av benzen i nærmere 30 år og har følgelig svært god kompetanse på området. Dr. Kaija Pekari (se vedlagte referanseliste) er involvert i planleggingen av prøvetakingsprotokollen. Blodprøver vil også sendes til Haukeland Universitetssykehus, Bergen, for analyse av blodparametre. Analysene av luftmålingene vil utføres av X-lab, Bergen.

Innsamlede opplysninger og prøvesvar vil bli oppbevart og behandlet konfidensielt. Ved prosjektslutt vil datamaterialet anonymiseres. Ved prosjektslutt vil det bli utarbeidet en egen rapport for hvert av de involverte oljeselskapene. I rapporten vil vi gi en vurdering av dine ansattes eksponering for benzen på installasjonen(e) og eventuelle tidlige effekter. Rapporten vil **kun** inneholde anonymiserte data slik at enkeltpersoner ikke kan identifiseres. Rapporten vil danne grunnlag for at du som arbeidsgiver kan følge opp og forbedre det kjemiske arbeidsmiljøet ved Deres installasjoner. I tillegg vil det bli utarbeidet en rapport som gir en samlet vurdering av eksponeringen for alle de involverte oljeselskapene. Rapporten vil selvsagt **kun** inneholde anonymiserte data både mhp. installasjon og oljeselskap. Prosjektet er klarert av Etisk komité og det er meldt til Personvernombudet for forskning, NSD.

Prosjektet finansieres av Norges Forskningsråd. Vi mangler imidlertid midler til å dekke analysekostnader. Vi foreslår derfor at de involverte oljeselskapene dekker analysekostnadene for 20 arbeidstakere hver. I tillegg kommer helikoptertransport og forpleining under selve prøvetakingen. Analysekostnadene per arbeidstaker som inkluderes i prosjektet er som følger:

EKSPONERINGSMARKØR	ANTALL	KOSTNAD PR. PRØVE	TOTAL KOSTNAD
Benzen i arbeidsatmosfære	3 prøver	1000,-	3000,-
Benzen i blod	3 prøver	750,-*	2250,-
Benzen i urin	- før arbeidsskift (kontroll)	750,-*	2250,-
Stoffskifteproduktet S-fenylmerkaptursyre i urin	- etter arbeidsskift	0,-**	0,-
Stoffskifteproduktet t,t-mukonsyre i urin	- før neste arbeidsskift	750,-*	2250,-
TOTALE KOSTNADER PR. ARBEIDSTAKER			9750,-

* = 89 Euro (subsidiert på grunn av at det er et forskningsprosjekt og samarbeidsprosjekt) ** = samarbeid med Finnish Institute of Occupational Health

Det vil opprettes en egen referansegruppe for prosjektet, med en representant fra hvert selskap. Vi ber om tilbakemelding på hvem som vil representere Deres selskap i denne gruppen. På grunn av prosjektets progresjon ønskes tilbakemelding på både dekning av analysekostnader og representant i referansegruppen **innen 30. juli 2004**.

Om dere skulle ha behov for mer informasjon, kan du kontakte Bente E. Moen på telefon 55 58 61 12 eller e-post Bente.Moen@isf.uib.no, eller Jorunn Kirkeleit på telefon 55 58 61 65/952 00 221 eller på e-post Jorunn.Kirkeleit@isf.uib.no.

Vennlig hilsen

Bente E. Moen
Prosjektleder og lege

Jorunn Kirkeleit
Stipendiat og utførende

Vedlegg:

1. Prosjektbeskrivelse
2. Prøvetakingsprotokoll
3. Informasjon til arbeidstaker og samtykkeskjema

Appendix III



TIL ANSATTE VED

FORESPØRSEL OM Å DELTA I PROSJEKTET "GIR EKSPONERING FOR BENZEN PÅ NORSK SOKKEL ØKT RISIKO FOR Å UTVIKLE LEUKEMI?"

Benzene er et kreftfremkallende stoff som er en naturlig bestanddel av råolje. Seksjon for arbeidsmedisin har igangsatt et prosjekt for å studere eksponering for benzen på norsk sokkel og dets helseeffekter, og spør deg med dette om du vil delta i prosjektet. Prosjektet finansieres av Norges Forskningsråd. I tillegg vil det bli søkt om midler til prøvetaking og analyser fra de involverte oljeselskapene. Dette er frie midler som er gitt, eller vil gis, uten bindinger. Prosjektet avsluttes høsten 2006.

Hensikten med prosjektet er å karakterisere eksponeringen for benzen på norsk sokkel, og å undersøke om vi finner benzen og dets stoffskifteprodukter i blod og urin hos arbeidstakere som jobber på norsk sokkel. Vi vil også undersøke om det er en sammenheng mellom eksponering for benzen og skadelige blodforandringer som kan være forstadier til utvikling av kreft. Arbeidstakeren avleverer en urin- og blodprøve ("nullprøve") før avgang til, eller like etter ankomst til, installasjonen. Den andre og tredje prøven, både urin og blod, avleveres ved arbeidsperiodens slutt eller etter en gitt arbeidsoperasjon (en etter et arbeidsskift og en den påfølgende morgen). Prøvene vil aidentifiseres før de fryses ned og sendes/bringes til analyselaboratoriet ved Finnish Institute of Occupational Health, Finland. Det vil også sendes blodprøver til Haukeland Universitetssykehus, Bergen, for analyse av blodparametre.

Deltakelse i programmet er frivillig. Du kan også trekke deg og/eller tilbakekalle samtykket uten å oppgi årsak. Dersom du trekker deg vil personidentifiserbare opplysninger om deg slettes. Hvis du ønsker det, vil du motta kopi av dine resultater. Dersom vi finner at nivået av markører for eksponering er for høyt, eller om blodverdiene skulle indikere en tidlig effekt på det bloddannende system, vil vi sørge for at du vil få tilbud om oppfølging. Det understrekes at ingen andre enn prosjektmedarbeidere med taushetsplikt får tilgang til dine data, med mindre du ønsker det annerledes. Innsamlede opplysninger og prøvesvar vil bli oppbevart og behandlet konfidensielt. Ved prosjektslutt vil datamaterialet anonymiseres.

Prosjektet utføres i samarbeid med din arbeidsgiver. Det vil bli utarbeidet en rapport fra undersøkelsen som blir oversendt din arbeidsgiver. Rapporten vil **kun** inneholde aidentifiserte data slik at enkeltpersoner ikke kan identifiseres. Rapporten vil danne grunnlag for din arbeidsgivers oppfølging og forbedring av ditt kjemiske arbeidsmiljø. Prosjektet er klarert av Regional komité for medisinsk forskningsetikk Vest-Norge og det er meldt til Personvernombudet for forskning, NSD.

Om du skulle ha behov for mer informasjon, eller om du skulle ha betenkeligheter rundt prosjektet eller dine resultater, kan du kontakte Jorunn Kirkeleit på telefon 55 58 61 65/952 00 221 eller på e-post: Jorunn.Kirkeleit@isf.uib.no.

Vennlig hilsen

Bente E. Moen
Prosjektleder, lege

Jorunn Kirkeleit
Stipendiat (utførende)

SAMTYKKESKJEMA DEL A: ARBEIDSTAKER

Jeg har lest informasjonsbrevet om prosjektet "Gir eksponering for benzen på norsk sokkel økt risiko for utvikling av leukemi?", og har også fått det forklart muntlig. Jeg samtykker i å delta i prosjektet under følgende forutsetninger:

1. Urinprøven vil **kun** analyseres for:
 - Benzen, toluen og xylene
 - stoffskifteproduktet fenylmektursyre
 - stoffskifteproduktet *trans,trans*-mukonsyre
2. Blodprøven vil **kun** analyseres for:
 - Benzen, toluen og xylene
 - blodbilde (hematologiske parametre som antall hvite og røde blodlegemer, blodplater, hemoglobinverdi, hematokrittverdi m.v.)
 - generelle antistoffer
 - perifert proteinbilde
 - genetisk variasjon for enzymer involvert i nedbrytning av benzen
 - analyse av genuttrykk relatert til benzeneksponering og/eller leukemi
3. Prøveresultatene vil bli sendt til prosjektleder ved Seksjon for arbeidsmedisin, Universitetet i Bergen. Videre tilgang til prøveresultatene vil begrenses til det følgende:

Mottaker av resultatene	Individuelle resultater		Gruppe resultater
	Ikke anonymisert	Aidentifisert, men anonymisert for mottaker	Anonymisert
Arbeidstaker	X		
Prosjektmedarbeidere ved Seksjon for arbeidsmedisin som har undertegnet taushetserklæring	X		
Analyselaboratoriet ved Haukeland Universitetssykehus	X		
Analyselaboratoriet Departement of Industrial Hygiene and Occupational Toxicology, Finnish Institute of Occupational Health		X	
Arbeidsgiver			X

4. Jeg ønsker / ønsker ikke å få mine egne resultater og få disse forklart for meg.
5. Jeg kan til enhver tid trekke meg fra prosjektet og tilbakekalle samtykke. Prøven(e) min(e) vil da bli destruert i henhold til Biobanklovens § 14. Likedan kan jeg kreve at helse- og personopplysninger, som er innsamlet sammen med prøven(e) eller som er fremkommet ved analyse eller undersøkelse av materialet, slettes eller utleveres. Anledningen til å tilbakekalle et slikt samtykke eller å kreve destruksjon, sletting eller utlevering er imidlertid begrenset av Biobanklovens § 14.

Arbeidstakerens signatur _____ Dato _____

SAMTYKKESKJEMA DEL B: PROSJEKTLEDER

Jeg samtykker i å overholde de ovenfor nevnte forutsetninger beskrevet i samtykkeskjemaets del A.

Bente E. Moen (prosjektleder) _____ Dato _____

Jorunn Kirkeleit (utførende) _____ Dato _____

Appendix IV



REGISTRERINGSSKJEMA

DRIFTSPERSONELL PÅ



NAVN: _____
 PERSON ID: _____
 DOSIMETER ID: _____
 DATO: _____

Hvilke prøver (av for eks råolje, produsert vann, gass, annet) er tatt, hvor lang tid tok hver prøve og hvor mange prøver er tatt i løpet av skiftet?

Har du sjekket flotasjonsanlegget i dag? Hvor mange og hvor mange ganger?

Hvilke hovedarbeidsoppgaver har du hatt i ditt område i løpet av dagen (avstengningsplaner, avblødninger, ventiljobber og lignende).

Hvor stor del av dagen har du vært inne?

1. i LQ/SKR
2. på lab

Hvor stor del av dagen har du vært på kjellerdekket?

Har du brukt noe personlig verneutstyr, og eventuelt når (åndedrettsvern, hansker)?

Har det hendt uforutsatte hendelser i løpet av dagen, som har gjort at du har vært i kontakt med gass, råolje, spillolje, diesel etc.)?

Har du vært eksponert for andre kjemikalier i løpet av skiftet (avfetting, spraybokser), skriv produktnavn.

Appendix V

SPØRRESKJEMA

PERSONALIA	
Etternavn, fornavn	
Kontaktadresse	
Telefon	
Kjønn	
Fødselsdato	
ARBEIDSHISTORIE	
2.1 Nåværende arbeidsgiver	
2.2 Nåværende arbeidssted	
2.3 Hvilket yrke/tittel har du på dette arbeidsstedet?	
2.4 Hvor lenge har du praktisert i dette yrket i ditt liv?	
Hvilke andre yrker har du hatt? Og hvor?	
RØYKEVANER	
3.1 Hvor lenge er du vanligvis daglig i røykfylt rom?	Antall hele timer: <input type="text"/> <input type="text"/>
3.2 Røyker du selv?	
Sigaretter daglig?	Ja <input type="checkbox"/> Nei <input type="checkbox"/>
Sigarer/sigarillos daglig?	Ja <input type="checkbox"/> Nei <input type="checkbox"/>
Pipe daglig?	Ja <input type="checkbox"/> Nei <input type="checkbox"/>
Aldri røykt daglig	(Sett kryss) <input type="checkbox"/>
3.3 Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet?	Antall år: <input type="text"/> <input type="text"/>
3.4 Hvis du røyker daglig nå eller har røykt tidligere:	
Hvor mange sigaretter røyker eller røykte du vanligvis daglig?	Antall sigaretter: <input type="text"/> <input type="text"/>
Hvor gammel var du da du begynte å røyke daglig?	Alder i år: <input type="text"/> <input type="text"/>
Hvor mange år til sammen har du røykt daglig?	Antall år: <input type="text"/> <input type="text"/>
4. KAFFE/TE/ALKOHOL	
4.1 Hvor mange kopper kaffe/te drikker du daglig?	Antall kopper daglig: Kaffi: <input type="text"/> <input type="text"/> Te: <input type="text"/> <input type="text"/>
4.2 Nyter du alkohol i friperiodene dine?	Ja <input type="checkbox"/> Nei <input type="checkbox"/>
5. BRUK AV MEDISINER	
Med medisiner mener vi alle slags medisiner, både med og uten resept, naturmedisin, vitaminer og mineraler medisin som svelges, inhaleres eller injiseres, stikkpiller, salver, kremer eller dråper.	
5.1 Bruker du medisiner fast? Hvis ja, hvilke?	
5.2 Har du tatt medisiner de tre siste døgn før prøvetakingen av blod og urin? Hvis ja, hvilke og hvor mye?	
Har du tidligere gjennomgått behandling for kreft (stråling, cellegift, m.v.). Hvis ja, hvilken behandling og når?	

Erratum

In paper II “*Biological monitoring of benzene exposure for process operators during ordinary activity in the upstream petroleum industry*”, in the Results , page 10, paragraph 1 (line 1), the pearson’s correlation coefficient for the association between the benzene exposure on the third day of sampling and the internal concentration of benzene in blood pre-next shift should be $r = - 0.08$, not $- 0.75$.

In paper IV “*Acute suppression of serum IgM and IgA in tank workers exposed to benzene*”, in the Discussion, page 696, second column, third paragraph, the references numbered [5,11] should have been numbered [6,12].

