Health hazards and cancer in relation to occupational exposures among Swedish seafarers

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"Ett gott skratt förlänger livet."

Inga Forsell (1912-2012)

HEALTH HAZARDS AND CANCER IN RELATION TO OCCUPATIONAL EXPOSURES AMONG SWEDISH SEAFARERS

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ABSTRACT

This thesis explores health hazards for seafarers in the Swedish merchant fleet, and occupational risks for lung cancer, mesothelioma and hematologic malignancy (HM). A special focus has been exposure to benzene and biomarker levels for work on product or chemical tankers during the mid-1990'ies.

In a case report, we describe two cases of mesothelioma and two cases of lung cancer having worked in the engine room. Cumulative exposures to asbestos were 2 to 5 fibre-years. Other exposures were carcinogenic PAHs and nitroarenes. A web-based survey to active seafarers in the Swedish merchant fleet revealed noise, the risk of accidents, whole-body vibrations and ergonomic strain as main work environment problems. General health, work ability and safety climate were all rated high. Associations were found between lower airway symptoms and soot exposure (PR 2.4, 95% CI 1.1-5.1) and between hearing impairment and noise (PR 1.5; 95% CI 1.3–1.7). Iso-strain was especially common in the service department. Twenty-two percent of men and 45% of women had been subjected to harassments. The tanker study showed a geometric mean for benzene exposure of 0.45 mg/m3 (4hTWA) during a work shift, with a wide range (0.02-143 mg/m3). Correlations were found between exposure and benzene in alveolar air (p<0.0001), unmetabolised benzene in urine (p<0.0001) and ttMA in urine (p=0.0011). All biomarkers increased significantly between pre and post shift samples (p<0.002). In a case-referent study with the observation period 1985 to 2014, the OR for HM was 1.32 (95% CI 0.86-2.02) if work on tankers had started before 1985 and with a cumulated tanker service of at least five years. If work on tankers had started after 1985, the OR was 0.85 (95% CI 0.51-1.43).

In conclusion, health hazards in today's seafaring relate to physical, chemical and psychosocial factors. Work on tankers with mixed open and closed cargo systems might have led to important benzene up-take. Possibly, the risk for HM for seafarers on tankers has decreased during the last decades.

SAMMANFATTNING PÅ SVENSKA

Det finns idag drygt 11 000 aktiva svenska sjömän, men vi vet lite om risker för ohälsa i deras arbetsmiljö. Flera studier har påvisat en högre dödlighet och insjuknande i cancer bland sjömän, bland annat för blodmalignitet (ex. leukemi) vid arbete på tankfartyg. Liknande fynd finns för svenska sjömän, men någon uppföljning har inte utförts under de senaste tjugo åren.

En fallrapport beskriver insjuknande i lungsäckscancer (mesoteliom) på grund av tidigare exponering för asbest samt i lungcancer på grund av asbest och cancerframkallande polyaromatiska kolväten vid arbete i maskinrum.

I en webbaserad enkät med svar från 1972 aktiva sjömän inom svensk handelssjöfart framkom buller, risk för olycksfall, olämpliga arbetsställningar och helkroppsvibrationer som vanliga arbetsmiljöproblem. Bullerexponerade hade oftare en samtidig hörselskada, och buller var mest vanligt vid arbete i maskin. Arbete med vibrerande verktyg var associerat med kärl- och nervpåverkan i händerna. En stor andel av både män och kvinnor hade upplevt kränkningar/trakasserier, i synnerhet från arbetsledningen.

Exponering för bensen, en känd riskfaktor för insjuknande i blodmalignitet, studerades för olika arbetsmoment vid arbete på svenska tankfartyg under mitten av 1990-talet. Resultaten visade på en starkt varierad bensenexponering beroende på arbetsuppgifter. Bensenet togs upp till kroppen bland de exponerade och avlägsnades med utandad luft och med urinen.

Vid genomgång av samtliga fall av blodmaligniteter under 1985 till 2014 bland svenska sjömän fann vi 315 fall. Resultaten visade på en ökad risk för blodmalignitet för de som börjat arbeta på tankfartyg före 1985 och som tjänstgjort på sådan under en total tid av minst fem år. Riskökningen var dock inte statistiskt säkerställd. Vid första anställning på tankfartyg efter 1985 sågs ingen ökad risk.

Sammanfattningsvis anser vi att studierna ger ett viktigt underlag för arbetsmiljöarbetet ombord på fartyg. Vår tolkning av resultaten för blodmalignitet är att det kan finnas en ökad risk för sådan främst efter arbete på tankfartyg med manuell hantering av petroleumlast. Exponeringen för bensen kan bli betydande vid sådant arbete.

LIST OF PAPERS

I. Forsell K, Hagberg S, Nilsson R. Lung cancer and mesothelioma among engine room crew – case reports with risk assessment of previous and ongoing exposure to carcinogens. Internat Marit Health 2007;58:1-4

II. Forsell K, Eriksson H, Järvholm B, Lundh M, Andersson E, Nilsson R. Work environment and safety climate in the Swedish merchant fleet. Int Arch Occup Environ Health 2017;90:161-168. DOI 10.1007/s00420-016-1180-0

III. Forsell K, Liljelind I, Ljungkvist G, Nordlinder R, Andersson E, Nilsson R. Benzene exposure and biomarkers in alveolar air and urine among deck crews on tankers transporting gasoline. In manuscript

IV. Forsell K, Björ O, Järvholm B, Nilsson R, Andersson E. Hematologic malignancy on tankers: A case-referent study among male Swedish seafarers. In manuscript

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CONTENT

ABBREVIATIONS

AlvBe   benzene in alveolar air

AM   Arithmetic mean

AML   Acute myeloid leukaemia

ANLL   Acute non-lymphocytic leukaemia

CI   Confidence interval

CLL   Chronic lymphocytic leukaemia

CYP   Cytochromes P450

dB(A)   decibel, A-weighting

ECHA   European Chemicals Agency

GM   Geometric mean

HM   Hematologic malignancy

HWE   Healthy worker effect

IARC   International Agency for Research on Cancer

ICD-7   International classification of diseases, 7th revision

ICT   Information and communications technology

IMO   International Maritime Organization

Iso-strain   Isolated strain

ITF   International Transport Federation

LOD   Limit of detection

MM   Multiple myeloma

MTIP   Monitoring Totalhydrocarbons Ionizing Photography

N   number (of)

NHL   Non-Hodgkin's lymphoma

NOSACQ   Nordic Safety Climate Questionnaire

OEL   Occupational exposure limit

OR   Odds ratio

PAH   Polycyclic aromatic hydrocarbons

PIN   Personal identification number

ppm   Parts per million

PR   Prevalence ratio

RoRo   Roll-on/Roll-off

RR   Relative risk

SOD   Sign on days

ttMA   trans,trans-muconic acid

TWA   Time-weighted average

UBe   Benzene in urine

WAI   Work ability index

1 BACKGROUND

1.1 The population of Seafarers

On a global scale, merchant seafaring has tripled during the last 30 years, and today, over 90% of all goods are estimated to be transported by ship. There are roughly 1.6 million seafarers operating 50,000 merchant ships worldwide, half of them coming from South-East Asia, and mostly from the Philippines (http://www.ics-shipping.org/shipping-facts/shipping-and-world-trade/global-supply-and-demand-for-seafarers). The number of merchant ships (>100 GT) flying the Swedish flag has diminished from 800 ships in the 70'ies to today's 200 ships, and Sweden as a stakeholder represents less than 0.3% in today's international seafaring (http://sekotidningen.se/artikel/100-ar-av-dramatik/). Although the Swedish maritime work force has decreased, the Swedish Seafarers' Registry (Swedish Seafarers' Registry) informs us that there are still around 13,000 active[1] seafarers, of whom 11,000 are Swedish citizens. During the last 20 years, the percentage of women among Swedish seafarers has increased from 18% to 30%.

Seafaring has undergone major structural changes during the globalisation of the trade. Ships have become larger to carry more cargo, but in the same time, the operating staff has reduced. A modern supertanker might need more than ten kilometres to stop and use a radius of four kilometres to turn around. A container ship can have 20,000 containers, be manned by twenty men, and be over 400 meters long. Modern cruisers might have 6,000 passengers, operated by 2,000 crewmembers - all under a captain's responsibility. Such work parameters put high demands on nautical knowledge, leadership, and preparedness for any hazard on an everyday changing outer environment. In addition, the trade constitutes by no means an exception to digitalization, an increased administrative workload and the introduction of more and more automatic processes, introducing new work demands in seafaring.

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[1] The definition of an active seafarer varies within the trade. For the Swedish Seafarers' Registry, the definition is a seafarer with at least three months of cumulated sea service during the last 1.5 years.

1.2 The seafarers' work environment

Generally, work on a ship is scheduled between a couple of weeks to three months in a row, interpositioned by equal time at home. However, even more extended work periods exist, especially for seafarers from other parts of the world. Scheduling of active service while on board the ship may vary. The "6 h on/6 h off duty system" is still used (even a 4 h on/4 h off duty system has been used in Sweden). It is questionable if time for recovery exists during such circumstances (Eriksen et al. 2006; Harma et al. 2008). Shift work may lead to irregular and improper hours for meals and a disturbed circadian rhythm. Moreover, working on a ship means also living there, on a highly restrained area limiting the possibilities for physical exercise, perhaps longer periods away from family and friends ashore, and with a limited social context on board the ship. The globalisation of the work force has led to crews with sometimes several different native languages and cultures among its members, which might be encouraging but it may contribute to a sensation of solitude.

The psychosocial environment for seafarers has attracted more scientific interest in recent years, not the least since shipwrecking due to fatigue and an elevated occurrence of psychiatric diseases (depression, suicides) and other stress-related diseases, like ischaemic heart disease, and accidental injuries, have been demonstrated among seafarers (Borch et al. 2012; Elo 1985; Otterland 1960; Pukkala et al. 2009; Rafnsson and Gunnarsdottir 1994; Transportstyrelsen 2009).

1.3 Legislation of seafarers' work environment

The work environment of a Swedish seafarer is regulated both on an international level and by Swedish legislation. Internationally, the International Maritime Organisation (IMO) under the United Nations (UN) stipulate legislations, such as security criteria for ships (SOLAS), standards for security training and professional skills (STCW) and environmental aspects in seafaring (MARPOL). The UN affiliate International Labour Organisation (ILO) stipulates rights for the employed seafarer (MLC), and puts forward amendments to the IMO. Such amendments can also be made from the International Transport Federation (ITF), a union-based organisation. Sweden has influence by its unions through the ITF, but also by the state's representative, the Swedish Transport Agency.

In Sweden, the employee's work conditions are regulated under the Work Environment Act (Swe. Arbetsmiljölagen). The act was ratified in 1978, but it was only enacted for seafarers as late as in 2003 (Swedish Work Environment Authority 2018a). This may have put seafarers of risk for delayed improvements in the work environment compared to land based occupations.

IMO states that all merchant seafarers must have a biannual medical examination. The examination has different criteria depending on position held on board, and may also vary with the nation and medical practitioner where it is carried out.

On board the ship, the second mate is generally responsible for medical urgencies and has medical training for that purpose. On ferries a nurse, physician or a whole medical department may be present, especially on cruisers. Swedish seafarers can also, at any time and at any place around the world, contact the Telemedical Advice Services (TMAS), placed in Gothenburg (formally called Radio Medical), for medical consulting.

1.4   Carcinogens and possible causes of cancer in seafarers

1.4.1   Asbestos

There are different kind of asbestos fibres, but all are considered carcinogenic (IARC 1987). Asbestos was previously often present on ships, especially between the 1950'ies and the 1970'ies, for instance as an insulating material in the engine rooms. It could also be transported as a product, where handling of cargo was done manually and often without any or incomplete protection equipment (Figure 1). The use of asbestos was banned in Sweden in the mid-1970'ies, and completely banned from import and use in 1982. Today, any work involving asbestos is strongly regulated with law-enforced special formation and protective measures.

On entering the lungs, asbestos fibres are deposited in the alveoli, where principally macrophages of the immune system, not able to digest the fibres or break them into smaller pieces for excretion, create a fibrous tissue around the asbestos fibres. Some of these encapsulated fibres will be located on or near the pleural or peritoneal mesothelium where the inflammatory response will continue. On an x-ray or at autopsy, typical findings from previous prominent occupational asbestos exposure will present as "plaques". The plaques are innoxious. However,

a chronic inflammatory response around the asbestos fibres are thought to be responsible for the risk of cancer initiation (Wolff et al. 2015).

Figure 1. Stevedores in Gothenburg harbour unloading packages of asbestos in the 1970'ies. The workers only use a protective mask for dust. With permission from the Port of Gothenburg (Göteborgs Hamn AB).

Asbestos exposure is measured by the number of fibres present in air. The cumulative exposure to asbestos is generally summed up in fibre-years, which means the exposure in years to one fibre per millilitre air (one fibre-year could also mean exposure for two years at 0.5 fibre/mL, or any other similar combination). The Occupational Exposure Limit (OEL) in Sweden has since 2004 been 0.1 fibre per millilitre air irrespective of type of asbestos fibre (Swedish Work Environment Authority 2018b).

Occupational exposures to asbestos may eventually lead to plaque formation on the lung mesothelium or to asbestosis, a diffuse interstitial fibrosis of the lung tissue (Wolff et al. 2015). Mesothelioma is caused by asbestos in more than 85% of cases (IARC 1987; IARC 2012; Wolff et al. 2015). In Sweden, an effect of the asbestos ban with decreased incidence in mesothelioma is now observable among younger men (born after 1955) (Jarvholm and Burdorf 2015). In most cases, previous occupational asbestos exposure can be confirmed, mainly work in the shipyards (insulation work) or in car and truck garages (asbestos in disc brakes). While any asbestos exposure is considered a sufficient cause for mesothelioma,

the risk of lung cancer from asbestos exposure has been estimated to a doubled risk at 20-25 fibre-years (Wolff et al. 2015). Smoking is not considered a risk factor for mesothelioma, but for lung cancer, smoking and asbestos display a synergistic effect (IARC 1987; Wolff et al. 2015). Generally, the latency between exposure and cancer is 30 to 50 years for mesothelioma and 10 to 30 years for lung cancer (Burdorf et al. 2005; IARC 1987; Manning et al. 2002).

1.4.2   Polycyclic aromatic hydrocarbons

Polycyclic aromatic hydrocarbons PAHs are nonpolar chemical compounds with at least two benzene rings present, and are formed during incomplete combustion of fossil fuels. Some of them, most notably the PAH benzo(a)pyrene, have carcinogenic effects (IARC 2006; IARC 2012).

The engine room crewmembers may be exposed to PAHs from exhausts or during maintenance work, e.g. cleaning engine parts contaminated with used oils or soot in the crankcase. Since the engine room is a hot environment when the engines are on, a mist from the evaporation of heated oils may form, leading to inhalation of PAHs (Moen et al. 1996). It is, however, dermal exposure and transdermal up-take of PAHs that is most important for work in the engine room (Nilsson et al. 2004; Nordlinder 1999a).

Exposure to PAHs and nitroarenes have been linked to lung cancer with risk estimates (relative risk, odds ratio) generally between one and two (Armstrong et al. 2004; IARC 2006). Most risk estimates come from occupation category (e.g. coke oven worker). PAH-exposure has also been linked to skin cancer and cancer of the urinary bladder (IARC 2012). These cancer forms have all been shown to occur in excess in seafarers (Brandt et al. 1994; Hemmingsson et al. 1997; Nilsson 1998; Rafnsson and Gunnarsdottir 1995). Although exposure by air has been the most studied exposure route in relation to lung cancer, even up-take through the skin has been discussed to increase the risk for lung cancer. The explanation could be the metabolism of PAHs in the liver that forms DNA-binding metabolites (Moorthy et al. 2015), exerting a carcinogenic effect even in lung tissues. In addition, the up-take of PAHs, e.g. in coke-oven or creosote-impregnating workers, can be many times greater by the dermal route than by air (IARC 2010).

There is currently in Sweden an OEL (8hTWA) only for one PAH, namely benzo(a)pyrene, which is 0.002 mg/m3 (no OEL for dermal exposure exists) (Swedish Work Environment Authority 2018b).

1.4.3 Diesel exhausts

During work in the engine room and work on deck, especially during loading and unloading of diesel-driven vehicles (e.g. on RoRo-ships), the crewmembers may be exposed to diesel exhausts (Ulfvarson et al. 1987). Truck drivers may want to heat up their engines prior to disembarkment, ten minutes before is not unusual although generally forbidden onboard, leading to diesel exhaust contamination on deck (Norén M and Åberg J 2012). Diesel exhausts were recently classified a Group 1 carcinogenic exposure by IARC (IARC 2013). The Swedish OEL (8hTWA) for diesel exhausts (NO2) is 2 mg/m3, established in 1990 (Swedish Work Environment Authority 2018b).

1.4.4 Benzene

Benzene (C6H6) is a chemical molecule of six carbons linked into a hexagonal configuration. Benzene in its liquid form is clear and colourless with a sweet odour. It, however, easily evaporates at room temperature, making it susceptible for inhalation. Benzene is the starting material for many products, such as styrene (plastics; rubber), pharmaceuticals and dyes, and it is used as a compound in gasoline to keep the fuel more resistible to high temperatures and pressures (higher octane).

The allowance limit for benzene content in gasoline in Europe is 1% (volume fraction, v/v) since 1998 (European Union 2004), but the previous allowance was 5%, with a common level found in market gasoline between 3-4%. Before that, when lead was allowed in gasoline, from mid-70'ies in Sweden up to mid-80'ies, the benzene content was lower.

Benzene belongs to the organic solvents (like alcohol) and share the same properties, with headache and fatigue (160-480 mg/m3 air for 300 minutes), unconsciousness (4,000 mg/m3; 60 minutes) and death by inhibition of the respiratory reflex (over 60,000 mg/m3; 5-10 minutes) (HPA UK 2007).

The toxic effect from high benzene exposures relates primarily to depression of the haematopoiesis in the bone marrow (low haemoglobin level in the blood and pathologically low cell counts in the bone marrow) (HPA UK 2007). Chronic exposures, like in an occupational setting, may further lead to leukopenia, agranulocytosis, pancytopenia, myelodysplastic syndrome and hematologic malignancy (HPA UK 2007; IARC 1982; IARC 2012).

Benzene is an established risk factor for acute myeloid leukaemia (AML) and acute non-lymphocytic leukaemia (ANLL), the latter being a combination of AML, acute monocytic leukaemia and acute erythroid leukaemia (IARC 2012). Benzene is also suspected to cause both acute (ALL) and chronic lymphocytic leukaemia (CLL), non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) (IARC 2012; WHO 2010).

Risk estimates for leukaemia from benzene exposure varies within countries depending on whether a non-linear approach or a threshold approach forms the basis of risk assessment. In 2017, the European Chemicals Agency (ECHA) argued for the non-linear approach with a risk estimate of four extra cases of leukaemia for 1,000 exposed workers at 1.9 mg/m3 during 40 years (ECHA 2017). ECHA recommended a new OEL (8hTWA) of 0.3 mg/m3 (0.1 ppm). The actual OEL in Europe is 3.25 mg/m3 (1 ppm) (European Union 2004). The Swedish Occupational Exposure Limit (OEL) for benzene exposure dates from 1990 and equals 1.5 mg/m3 (0.5 ppm), with a Short Term Exposure Level (STEL equivalent to 15 minutes' average exposure) of 9 mg/m3 (expressed in the directive as 3 ppm) (Swedish Work Environment Authority 2018b). The International Maritime Organization (IMO) recommends an OEL of 1 ppm and a STEL of 5 ppm (IMO 2003).

In seafaring, tanker deck crewmembers are at risk for occupational exposure to benzene. Work on a tanker includes loading and unloading of benzene-containing cargo and maintenance work, such as tank cleaning operations. Benzene exposure may vary with type of cargo, venting mechanisms and protective equipment used, and ambient meteorological factors (Kirkeleit et al. 2006; Moen et al. 1988; Mowe G 1977). Several studies have shown significant benzene exposures for the deck crew on tankers, especially if the tanker carries benzene-rich products (Bates K 1994; Berlin 1985; Christian F 1986; Moen et al. 1993; Nordlinder and Ramnas 1987). However, previous measurements for benzene exposure on tankers carrying gasoline have mainly been performed on older tanker types and no such study is reported after 1994 (Williams et al. 2005). Certainly, there is a difference

in exposure levels between modern shipping and older types of tankers. Several work tasks switched during 1990'ies in Western countries from manual to semi-automatic or completely automatic manoeuvres.

1.4.5   Toxikokinetics and metabolism of benzene

The absorption of benzene through inhalation is generally estimated to between 45% and over 90%, depending on the dose and the level of physical exertion (Arnold et al. 2013; Boogaard and van Sittert 1996; Pekari et al. 1992). Time is also important, with the greatest absorption taking place during the first minutes of exposure (HPA UK 2007). The dermal uptake in occupational settings represents generally less than six percent of the absorbed dose, but it is often much smaller (ECHA 2017).

Benzene enters the blood from the lungs by diffusion, facilitated by the relatively high water solubility of benzene. From blood to tissues, benzene will again diffuse following a partition coefficient. The metabolism occurs mainly in the liver through the CYP-enzyme systems, forming the primary metabolite benzene oxide, but some metabolism also takes place in the lungs and bone marrow (ECHA 2017).

No clear toxicological effect has been observed for the benzene molecule itself. A leukomogenic effect would rather be caused by the benzene metabolites, although which one or "ones" are not clearly identified. Benzene oxide is conjugated with glutathione (forming S-phenylmercapturic acid, SPMA) or other metabolites, of which hydroquinone is one. This metabolite may be further metabolised in white blood cells (neutrophil granulocytes) to reactive benzoquinones, in which reactive oxygen species are formed. The latter are implicated in carcinogenesis, possibly by oxidative damage to the DNA. During a ring opening metabolic pathway of benzene, trans,trans-muconic acid (ttMA) is formed. A precursor in this chain of events (trans,trans-myconaldehyde) has been shown to induce mutations, DNA-protein crosslinks and DNA-strand breaks in *in vitro* tests (Ducos et al. 1992; ECHA 2017; Fenga et al. 2017; Sajous et al. 2008).

The half-life for benzene in blood has been estimated to eight hours (ECHA 2017). The elimination occurs through the lungs as unmetabolised benzene and the urine as unmetabolised benzene and metabolites of benzene, with only a fraction of the amount in faeces (ECHA 2017; HPA UK 2007). Considering biomarkers of benzene exposure, 17% of the total dose absorbed is excreted as unmetabolised benzene in expiration and only 0.1% as unmetabolised benzene in

urine. For more specific urinary benzene metabolites, ttMA represent 2% to 25% of the absorbed dose and SPMA less than 1%. Less benzene-specific metabolites, responsible for the remaining elimination of benzene, are hydroquinone glucuronide and phenyl sulphate (Arnold et al. 2013; Boogaard and van Sittert 1995; Ghittori et al. 1995; Ong et al. 1996).

Since metabolic pathways for benzene can be saturated, it is also debated how this effects the risk for leukaemia. Kim and Rappaport have argued for a saturated kinetics with two pathways depending on the exposure level: one primarily for exposures above 1 ppm and one primarily for exposures below 1 ppm (Kim et al. 2006; Rappaport et al. 2009). A higher metabolic ratio in the lower exposure ranges could mean a higher toxic effect from benzene exposures than previously considered. In addition, genetic factors are also important when it comes to the rate of metabolism of benzene and type of metabolites formed (Scherer et al. 1998). In summary, the benzene metabolism, biomarker production and perhaps even risk for leukaemia may have inter- and intraindividual variations.

1.4.6 Life style factors

Life style factors, such as smoking, lack of physical exercise, a calorie-rich diet and obesity are often associated with modern seafaring, although the scientific evidence is scarce. In a study on Norwegian seafarers in the 1960'ies, around 80% were active smokers (Baksaas I 1983). For Swedish seafarers in the 1970'ies, the prevalence was 50-70% for officers and 35% for ratings (Nilsson 1998).

1.5 On how to assess occupational exposures

1.5.1 Cumulative exposure and risk of occupational cancer

Epidemiological studies on occupational cancer from different exposures exploring relative risks and dose-linearity often use the notion of cumulative exposure, i.e. the product of intensity and duration of the exposure to the carcinogen (-s). In risk assessment for cancer, this means that the exposure level and time are two equally important factors for the resulting risk (a low exposure for many years equals a high exposure for less years, given that the cumulative

exposure is equal) (Smith 1992). For instance, the risk for leukaemia would increase with increased cumulative exposure.

However, several studies have questioned these assumptions. For instance, in smoking, the duration rather than the dose (number of cigarettes smoked) may be more important (Doll and Peto 1978). Concerning the nature of occupational benzene exposure and risk of leukaemia, a higher risk has been observed for low but long-term exposures to benzene in the Australian Health Watch Study (less than 5 ppm) than for repeatedly short-term higher exposures in the Pliofilm Study (up to 60 ppm) (Vlaanderen et al. 2011).

1.5.2   Biomonitoring

A chemical, like benzene, can be measured in air, reflecting the inhalation of that compound for the workers. However, the exposure assessments above only describe what comes in contact with the individual, and mostly by air.

In biomonitoring, we assess the uptake into the body from an exposure taking into account any route of exposure (air, skin, oral) and exposure sources (occupational, environmental, life style factors) (Angerer et al. 2007). Usually, the biomarker is analysed from urine or a blood sample. This also has the advantage of simplicity, by collecting samples at an occasion where work is not impeded upon (i.e. post shift samples). Analysing a biomarker may also be much cheaper than performing exposure measurements in a complex setting.

Biomarkers are sometimes used in legislation. Benzene and ttMA in urine are used in several countries as Biological Limit Values (BLV) (ECHA 2017).

1.6   The Swedish Seafarers' Registry

An official register of Swedish seafarers has existed in different forms and with different purposes since the 17th century. Initially, registration of Swedish seafarers and their individual sea services were made by Swedish Houses of Seafarers ("Sjömanshus"), which were present in many cities in Sweden (similar information was also gathered abroad at churches for Swedish seafarers). Such

information made it possible for relatives to know about the seafarer's whereabouts, send mail (sic! the former type of mail…) or telegraphed messages.

Between 1969 and 1985, a Seafarers' Registry was held primarily to help the seafarer establish his or her *Curriculum Vitae*, and lay under the Swedish National Labour Market Board (Arbetsmarknadsstyrelsen). The registered sea services were also used for pension assessment during this time (The Seafarers' Pension seized to exist in the mid 1980'ies).

The registry was up until now a paper-based system, but a Government's decision on automatic registry services paved the way for a digitalized Swedish Seafarers' Registry in 1985, under the supervision of the Swedish Maritime Administration (Sjöfartsverket). In 2009, the registry was transferred to the newly established Swedish Transport Agency (Transportstyrelsen), its current owner.

Since 1985, the Swedish Seafarers' Registry has three main purposes: a service to the seafarers, to give basic information for issuing certificates and to inspect the competency and number of the safety manning on board.

During the digitalization, seafarers that were active in 1985 had their prior sea services (in Swedish, "mönstring") entered into the Swedish Seafarers' Registry. Since 2007, ship companies can enter the relevant information into the Swedish Seafarers' Registry themselves.

*Jag passade också på att fråga om koderna **L** och **B** som vi undrade över. De handlar om hur aktiva sjömännen var. **L** står för Landkrabba och **B** för Beckbyxa. (mail correspondence)*

Since 1983, it is compulsory to report sea service data for seafarers on merchant ships (irrespective of seafarer´s nationality) flying the Swedish flag, and for foreign merchant ships with seafarers from a Swedish ship company (Mönstringslag 1983:929). However, for ships flying a non-Swedish flag, there is generally an agreement within the trade's parties to report to the Swedish Seafarers' Registry if the ship owner has connections with Sweden. It has not been compulsory to report sea services of crewmembers from the service department on ships in near trade areas. However, it has usually been done (pers. comm., the Transport Agency). On ships with no connection to Sweden at all it has been up to the individual seafarer to report his or her time on board. In most cases it has been made by handwritten certificates, not registered in the database.

Today, the Swedish Seafarers' Registry has information on individual seafarers' sea services back to 1939, although the vast majority of such historic recordings date mostly back to the 1970'ies. Including non-active/former seafarers, the Swedish Seafarers' Registry has information on seafarers' length of sea service, name of the ship the service took place on, the trade area (geographical area of service), the flag of the ship, the seafarer's position category (officer/rating; deck/engine/service or other) and gender.

For sea services from the time of digitalization (1985) and onwards, the registry also denotes the type of ship of service (e.g. product tanker, or RoRo-ship). The ship's signal, a ship-specific identification number (useful to identify renamed ships) may also be present. For sea service before 1985, only the dates of sea service, ship name and trade area is registered. Of great importance, the Swedish Seafarers' Registry notes the personal identification number (svenska: personnummer), which then enables us to do register-based research.

The Swedish Seafarers' Registry has its weaknesses, mainly depending on the difficulties and massive work with reporting on manual premises to earlier registers. There is no information on the seafarers that ended their seafaring career prior to the digitalization in 1985. Such entries might be found elsewhere (Regional State Archive, or "Landsarkivet", in Gothenburg). The tendency to report seafarers to the Swedish Seafarers' Registry might also have changed with the register's different purposes during the last century.

These are some of the reasons why it is difficult to estimate any loss of data on seafarers and sea services to the Swedish Seafarers' Registry. No such estimation has been done in a more systematic way. The sea service data is not regularly checked for its validity (only upon suspicion) but as it is in the seafarers interest that the sea service information is correct, the quality of the registered data is deemed by the Authority to be on an acceptable level.

The cumulated sea service time per individual is not easily calculated, especially in near home trades with short sea service periods. The number of actual sea service days (termed Sign On Days, or SODs) has been compulsory to report to the Swedish Seafarers' Registry only since 2007 (sic! catering exempted), but was also done before 2007 to some extent. In wider trades, the number of days correspond in most cases to time between sign-on and sign-off, why reporting of days is not necessary. However, for sea services in near trades before the 1980'ies, the entry and exit date of a sea service may correspond to an employment within a ship

company. During such time, in general, there are as much of days free from work as actual workdays (e.g. two weeks work on the ship followed by two weeks on land).

Another weakness with the Swedish Seafarers' Registry is that type of cargo for a given sea service is not noted.

1.6.1   The cohort

At time of our study, the Swedish Seafarers' Registry withheld information on 146,678 individuals. Of these, 105,098 had registered sea services (in total 1,642,629) (Table 1). Other individuals were entered for an eventual sea service but had not any actual sea service registered.

The Bureau of Central Statistics of Sweden (SCB) controlled for death and emigration by linkage with the personal identification number (PIN). SCB also controlled for temporary identification number issued for foreign workforce or re-usage of PINs. Such individuals were excluded for further analysis. Excluded were also seafarers that were deceased before 1985, the start of the observation period. Emigrated seafarers were excluded after an eventual emigration. Seafarers with less than 30 days of cumulated sea service were excluded. Seafarers born before 1920, those with sea services only before 1980 or only after 2013-12-31 were also excluded.

Table 1. Establishing the cohort of Swedish seafarers on merchant ships

	N seafarers	exclusions
Swedish Seafarers' Registry with sea services	105,098	
Deceased <1985	104,997	101
Temporary PIN^	95,461	9,536
Re-used PIN^	95,411	50
First sea service after 2013-12-31	93,541	1,870
Cumulated sea service<30 days	86,318	7,223
Birth date <1920	86,120	198
Last sea service <1980	85,863	257
Total	85,863	19,235

^PIN= personal identification number

The data on sea services per seafarer was in long format and changed to wide format. For overlapping sea service periods, we created a new variable in order to only use the relevant sea service for a certain analysis. This variable, attached to every sea service, indicated the hierarchic position, ship type and/or trade. This means, that if we wanted to analyse a risk for officers on passenger ships in international trade, the corresponding variable syntax could be used. Sea services with the same position, ship type and trade for an exactly the same time frame were assembled into one.

1.6.2   Ship names without known ship type

For sea services prior to 1985, we had to identify the corresponding ship type. In total, we identified 15,258 ship names present in these sea services. The names were compared with ship names present in an inspectors' protocol within the

Swedish Transport Agency and the Agency's Ship Register (N=7,835) for Ship type. For still unclassified ships, we then manually investigated if the same ship name was used in any other Swedish Seafarers' Registry-registrations. Many ship names were evidently misspelt, but could occur at quite some distance from each other in the registry. It was thus "in the eye of the beholder" to identify these. Since tankers were of special concern, we also looked at Swedish ship companies' lists on tankers.

Ship names were sometimes re-used within a ship company but for different physical ships, and even different ship types. Alternatively, a name could be used simultaneously on different ships. In such cases, the "Signal" (ship identification number) would be different. However, it turned out that even this signal could exist for more than one ship and ship type in registrations after 1985. In that case, the nearest in time registered ship type was used for the ship name before 1985.

We also consulted websites held by non-professionals dedicated to the Swedish maritime fleet during the last century (web addresses like kommandobryggan.se, faktaomfartyg.se, 7SEASVESSELS.COM, marinetraffic.com, shipsearchengine, equasis) for individual ship names or for lists on names with the ship prefix M/T (motor tanker).

At the Swedish Shipping Historical Society of Gothenburg (Klubb Maritim-Göteborg), really reluctant ship names could be looked up by way of actual time of sea service and ship company ownership using registries like "Båtologen", "Svensk Sjöfartstidning" or "Lloyds' Register", all done with guidance from the club members.

In the end, the ship type for almost every sea service could be identified (6% of ships with unknown ship type).

1.7   The Swedish Cancer Registry

The Swedish Cancer Registry was funded in 1958 and every physician is obliged by law to report any new malignancy to the registry. The Swedish Cancer Registry in itself does not include work title or any work history.

2 AIMS, METHODS & RESULTS

The overall aim with this thesis was to study Swedish seafarers' work environment in order to identify health-risk associated occupational exposures. This involved addressing exposures, health perceptions and safety in modern seafaring, and the risk for cancer disease and hematologic malignancy in relation to chemical exposures. A special focus was exposures for benzene on tankers, exploring the feasibility and utility of measurements in air and biomarkers in alveolar air and urine in a field study.

One paper (Paper II) investigates occupational exposures, the safety climate and perceptions of health and work ability among seafarers in Swedish merchant seafaring. The other three papers (Paper I, III and IV) investigate cancer-related occupational exposures: asbestos and polycyclic aromatic hydrocarbons and the risk for lung cancer and mesothelioma among engine room crews, and benzene exposure for work on tankers and the risk for hematologic malignancy.

2.1   Paper I

2.1.1   Preamble

This study was initiated by a clinical inquiry from an occupational health centre to a larger shipping company in Sweden, after nine cases of cancer had happened amongst the crew on one of its passenger ferries in just a few years' time (between 2001 and 2006). Four cancer cases were investigated at the department of Occupational and Environmental Health, Sahlgrenska University Hospital in Gothenburg.

2.1.2   Aim

The article wanted to illustrate how cases of lung cancer and mesothelioma in today's seafaring may be caused by previous and on-going occupational exposures, more specifically previous asbestos and on-going PAH-exposures for work in the engine room. Other than assessing causality, the aim was to make a somewhat person-focused description of occupationally induced cancers with a summary of the literature.

2.1.3   Method

All cases referred to the clinic (N=4) were investigated for medical diagnosis and time of diagnosis. Life-style associated factors, such as tobacco smoking, and heredity were estimated. Since only one case was alive at the time of the clinical investigation, such information had to be retrieved from nearest of kin for the remaining three cases.

After confirmation of lung cancer and mesothelioma, the exposure assessment was focused on occupational exposures to asbestos and polycyclic aromatic hydrocarbons (PAH) and nitroarenes during the whole work history as a seafarer. Information on service time, position on board and ship was retrieved from the Swedish Seafarers' Registry.

Exposure to asbestos was quantified in fibre-years, where one fibre-year equals the exposure of one respirable asbestos fibre per mL air during one year (the Swedish OEL is 0.1 fibre/mL during an 8 hours' workday).

2.1.4   Results

2.1.5   Cases
All four cases had mainly worked in the engine room, starting between 1959 and 1967. Two engine room ratings were diagnosed with lung cancer at 54 and 61 years of age, respectively. Both had been smokers for many years - the first during 33 years, the second during 45 years. An engine room rating and one electrical engineer were diagnosed with mesothelioma at 61 and 63 years of age, respectively.

2.1.6   Exposures
The asbestos exposure varied between two to five fibre-years. The exposure had been most prominent between 1960 and 1980 during repair works with handling of insulation with asbestos fibres, mainly in the form of amosite fibres. The air in the engine room had probably had a low level of asbestos fibres during this period. Exposure to PAHs and nitroarenes had been present for each one of the seafarers, especially during repair or maintenance work inside the engine or on engine parts, and especially while in contact with lubricant oils, marine diesel oils and soot. Exposure had mainly been by dermal contact, but also in the form of aerosols.

2.1.7   Causal inference
Smoking and occupational exposure to asbestos were considered risk factors for the lung cancer cases, and occupational to PAHs and nitroarenes were considered contributing risk factors.

For the mesothelioma cases, occupational exposure to asbestos was considered a causal factor.

2.2   Paper II

2.2.1   Preamble

At this time, we had started a website for occupational medicine in seafaring (www.maritimehealth.gu.se). One question that arose in this context was a concern from one of the unions in seafaring, that workers may be exposed to hardeners and isocyanates when painting on board a ship. There had also been a report in the media on some seafarers that after such work had developed allergic contact eczema and asthma.

This also made us start considering which other health-risk associated exposures that are present in today's seafaring. Little information was to be found in the literature. We identified one published paper, based on a mini-survey handed out prior to the biannual obligatory medical examination for seafarers with the following three general questions: 1) Were you exposed to chemical substances during your work (e.g. paint, oil, cleaning materials)? 2) If yes, did you use safety equipment to protect yourself? 3) How would you describe the occupational safety on board the ship? (Jensen et al. 2005).

Remembering our website, we discussed the possibility to use ICT-devices and came up with the idea of a web-based study, to which seafarers would have access from all around the world. This became another important aim with the study: to explore if a web-based survey could better reach out to the ever-moving seafarer population than a classical paperbound survey, which often had given low response rates in others' research (pers. comm. within the scientific network). This is understandable, given the amount of paper mail that a seafarer will encounter when coming home from perhaps a longer sea service.

In order to perform a web survey, certain practical questions had to be sorted out. How does the internet connection work at sea? How can we find and address individuals?

2.2.2 Aim

The aims with this study were to gain knowledge on what seafarers on Swedish merchant ships consider important occupational exposures in terms of chemical, ergonomic or psychosocial factors, and which ones they consider the most problematic ones. The study wanted to explore any associations between certain health indicators and these exposures. A third dimension was the perception of the safety climate and if that differed from land based occupations. The project was to be regarded as a hypothesis-generating study, that is identifying possible associations between occupational exposures and ill health to be further studied.

2.2.3 Method

At an auscultation at the ICT-team at Stena Line, Gothenburg, we learned the prerequisites of internet function at sea, and tested a rudimentary form of the web survey in their satellite communication simulator. Then, a full scale test with the whole survey was done at mid-sea across the Baltic with Tallink. We further tested the web survey on ten seafarers out at work. For the second question, how to find the respondents, we had initiated a cooperation with Tallink, Stena Line and Wallenius to reach out to their employees.

However, in parallel (sometimes it is good not to run to fast into things), we learnt that many seafarers had given their personal e-mail address when in contact with the Transport Agency. This personal e-mail address was then entered into the Swedish Seafarers' Registry. In contrast, when communicating with employees on a boat, the e-mail is seldom personal but linked to a department or position on board. In order to be able to make an individual invitation for participation in the study and to reach out to more seafarers than employed on three ship companies, we opted for the email addresses in the Swedish Seafarers' Registry.

From the Swedish Seafarers' Registry, 10,323 active merchant seafarers were identified, of whom 5,608 seafarers had a valid and personal e-mail address. An invitation was sent for participation in the study, in which we explained that the survey was directed to those having worked on a Swedish flag state ship at least once since January 2010.

The web survey included different sets of questions: exposures, health problems, health and work ability and safety climate. In total, the survey consisted of a

maximum of 170 questions, which for the test panel (10 seafarers) took 30 minutes to complete. Questions on exposure differed between work categories. Since chemical exposures may vary between departments, we made our own questions on this subject, and consulted with our reference group for accuracy. For questions on ergonomic exposures, hand-/arm vibrations and noise, we used established survey questions from the different research groups at our university department. For questions on fatigue, we used the Modified Fatigue Impact Scale. Isolated strain, or "iso-strain," was evaluated according to the job-demand-control model (Karasek et al. 1981; Karasek et al. 1998). For work ability, a single item question for a Work Ability Index (WAI) was used (Ahlstrom et al. 2010; Ilmarinen 2009). For qualitative measure of the safety climate, we used a shorter version of the Nordic Safety Climate Questionnaire (NOSACQ50), called NOSACQ12 (Kines 2011).

Statistics consisted of descriptive analyses for each work category. Differences in prevalence when comparing groups were calculated with Chi-square and t test, expressed in p values, with a 0.05 level of significance. For associations, prevalence ratios with 95% confidence intervals were calculated using the PROC PHREG procedure in SAS 9.4. All analyses were made using SAS© 9.4 and Windows Excel© 2010.

2.2.4   Results

The survey had a 35% response rate (N=1972). Men dominated amongst the respondents (90%). For work category, 61% of respondents belonged to the deck, 31% to the engine room and 7% to the service. Main type of ship was the RoPax/passenger ships (40%), followed by supply, service or research vessels (23%) and tankers (12%), working on all types of trades. Eleven percent were smokers, and 33% ex-smokers.

Among physical exposures that occurred daily or weekly, the predominant types were noise and ergonomic strain in terms of heavy lifting, uncomfortable work positions and strain on the upper extremity. Noise was reported especially from the engine department and ergonomic strain equally from the engine room and the service department. Hand-/arm vibrations from vibrating tools were more common in the engine room, especially for ratings.

Exposure to exhausts was the main chemical exposure reported followed by "dust", especially from the service department, and oils on the skin. Oils on the skin occurred daily/weekly in 88% of engine room crewmembers. Less frequent, but in a health perspective none the less important, exposures were that of asbestos, which 14% of the engine crewmembers and 7% of deck crewmembers reported to occur on rare occasions. Work with thermosetting plastics was common on a rare basis (53% among deck). Ten percent of all seafarers reported they did not have the protection equipment needed in their work.

What was considered work problems generally followed the exposures that had been reported (e.g. noise, oils on skin, exhausts, ergonomics), but factors like "risk of an accident", "vibrations from the hull" or "risk of a contagious disease" were also reported as important work problems.
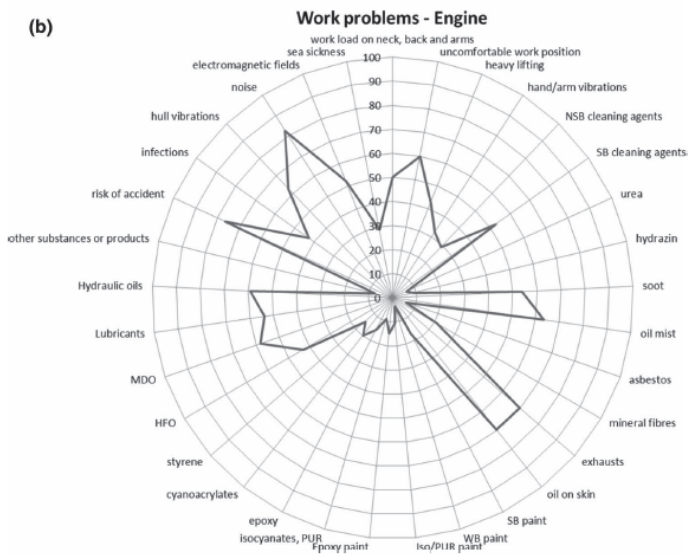

Figure 2. Example of a spider diagram illustrating reported work problems from engine room crewmembers. Percentage (%) for each exposure reported as a work problem

A good or excellent health was reported by 77% and a good or excellent work ability by over 85%. Asthma was reported by 8% and chronic obstructive pulmonary disease by 1%. A hearing impairment was most frequently reported

among the engine room crewmembers (46%). Noise exposed reported more often on a hearing impairment, exposed to hand-arm vibrations reported more of white fingers and neurological symptoms in the hands and exposed to soot, exhausts or dust reported more often on lower airway symptoms.

Regarding psychosocial work factors, 22% of men and 45% of women reported on having been subjected to harassments or offensive actions at the work place at least once during the last year. The offender had most often been the "boss" or the work leader (for men) or a co-worker (for women). Iso-strain was most common in the service department (30%), and among women (27%). Iso-strain was associated with symptoms of headache and sleep disturbances, but also with a personal experience of harassments/offensive actions.

The safety climate was higher among seafarers compared to land based occupations, both on how the respondents ranked their management's/boss' views on safety and that of his or her co-workers. Factors like a non-managerial position, a younger age or having reported on unusual tiredness were associated with a lower safety climate estimates (Table 2).

Table 2. Point estimates of safety climate in seafarers sailing under a Swedish flag, illustrating the seafarers view on their leaders' views on safety (Management Safety Priority), and their own views (General Security Climate)

		N	Management Safety Priority		General Security Climate	
			Mean	p	Mean	p
Work category	deck*	938	3.36		3.32	
	engine	480	3.36	ns	3.32	ns
	service	116	3.51	0.0187	3.44	0.0165
Sex	men*	1374	3.38		3.33	
	women	147	3.30	ns	3.26	0.0803
Management	Manager*	1157	3.40		3.35	
	Non manager	374	3.29	0.0049	3.24	0.0002
Unusual tiredness	no*	1114	3.42		3.38	
	yes	426	3.22	<0.0001	3.19	<0.0001
Age	≤30	327	3.29	<0.0001	3.21	<0.0001
	31-40	402	3.30	<0.0001	3.26	<0.0001
	41-50	348	3.37	0.0097	3.36	0.0115
	>50*	459	3.49		3.45	
Trade	Sheltered*	220	3.24		3.29	
	Near coastal	552	3.31	ns	3.26	ns
	European	437	3.37	0.0169	3.34	ns
	Worldwide	346	3.56	<0.0001	3.45	<0.0001
Type of ship	Ro/Ro. or similar*	230	3.46		3.40	
	Ro/pax. Pass.	604	3.30	0.0014	3.28	0.0007
	Container. Cargo. Bulk	24	3.48	ns	3.36	ns
	Tank	239	3.38	ns	3.35	ns
	Supply. Service or Research vessels	353	3.43	ns	3.38	ns
	other	83	3.34	ns	3.27	0.0287

*)Referent; ns=non significant

2.3   Paper III

2.3.1   Preamble

During the mid-1990'ies, a project was launched for measuring exposure to benzene among deck crewmembers on Swedish product and chemical tankers. The tankers served ports from Oslo in Norway, down the Swedish coast up to Stockholm, to Copenhagen and to some other Danish ports. One also went around the southern coast of England to reach the oil terminals of Finnart, Scotland. An occupational hygienist and a nurse were on board to measure benzene levels and take biological samples from the crew.

2.3.2   Aim

The aim was to increase the scientific knowledge on benzene exposures for deck workers on tankers during the 1990'ies. This would improve the risk assessment for leukaemia in more recent tanker shipping. Objectives were to study benzene exposures for different work tasks, and benzene-associated biomarker levels. All during field conditions for work on tankers carrying gasoline with both closed and manual operations.

2.3.3   Subjects and Method

2.3.4   Subjects and investigated tankers

Four product tankers and one chemical tanker, all flying the Swedish flag, were investigated during the summer months of 1995 and 1998. The tankers in the study had closed systems for loading and unloading but gauging, stripping and tank cleaning were done manually. When the measuring took place, the cargo consisted of 95 or 98 octane, mostly unleaded gasoline. The benzene content of the gasoline was not measured, but at this time, it would typically be 3-4%. Deck crewmembers would work for 4 hours around or inside the tanks, depending on work tasks. After this followed an 8 hours' rest, then a new work shift 12 hours interpreted as non-exposure (navigation or maintenance work).

Exposure to benzene in air was assessed by personal measurements. Uptake and excretion of benzene were monitored by benzene in alveolar air (AlvBe), and in

urine unmetabolised benzene (UBe) and the benzene metabolite trans,trans-muconic acid (ttMA). While the dosimeters were worn during the whole work shift (four hours' Time-Weighted Average, 4hTWA), the biomarker samples were collected just prior to and immediately after the work shift had ended. These samples were taken in a presumably non-exposed area of the ship.

All subjects (N=43) were men with a mean age of 43 years (range 19-60). Twenty-two of them performed benzene-exposure associated work tasks. Also, twenty-two workers were smokers (these were not the same men).

2.3.5   Analytical methods

Benzene in air was collected by a diffusion sampler with a sorbent of active charcoal. The dosimeter was attached to the worker's clothing in proximity of the breathing zone. Benzene in samples was analysed by gas chromatography with a flame ionisation detector (FID). The limit of detection (LOD) for a four hours' measurement was 0.03 mg/m3. Some work tasks were monitored continuously for total count of hydrocarbons, using a photoionization detector ("MTIP"). MTIP would illustrate the nature of the exposure in terms of low/high and continuous/peaks.

For benzene in alveolar air, the subject was asked to exhale and a 100 mL sample was taken during the last part of the exhalation using a manual sampling pump (Ljungkvist and Nordlinder 1995). The LOD was 0.5 ng/L for a 100 mL breath sample.

Urine samples were collected in 250 mL polyethylene bottles, with aliquots transferred to different containers before storage at about -20°C. UBe was analysed with dynamic headspace, the purging gas passing an adsorbent tube filled with Tenax TA and analysed using two-dimensional chromatography and FID detection. The LOD for the method was 7 ng/L (Ljungkvist et al. 2001). ttMA was analysed with an in-house development of a method, presented by Ducos (Ducos et al. 1992), by two-dimensional reversed phase liquid chromatography and UV-detection. The LOD was 0.001 mg/L.

Data was assessed for normality by use of Shapiro-Wilks (significance level 0.05), skewness and kurtosis and visual inspections of q-q-plots. A lognormal distribution was found to best describe the random effects. Results are given with the antilog of data. The difference between pre and post shift samples was analysed by paired T-test. For comparisons between groups (exposed/non-

exposed; smokers/non-smokers), the T-test procedure was used. The 95% confidence intervals for the geometric means were derived using the proc univariate data/cibasic in SAS. If the number of samples were below three, no significance testing was made. Linear regression analysis for correlation was done with Pearson on the logarithmic values. Multiple regressions included age and smoking habits (the GLM procedure). For measurements below LOD, half the LOD was used in the calculations (3 measurements). No data was defined as an outlier. All statistical calculations were done using SAS 9.4.

2.3.6   Results

The geometric mean (0.45 mg/m3) was much lower than the arithmetic mean (4.98 mg/m3). Five out of 38 work shifts exceeded the Swedish OEL (1.5 mg/m3) (Table 3). The highest exposure level was noted for a tank cleaning operation (143 mg/m3; 4hTWA) (Table 4). Benzene exposure was significantly higher for benzene-related work tasks than for other work tasks on board (GM 0.45, 95% CI 0.25-0.83 *vs.* GM 0.02, 95% CI 0.01-0.04, resp.). The MTIP-measurements revealed a considerable variation of the exposure pattern with type of work.

Table 3. Number and percentage of benzene exposed work shifts (4 hours) that were completely above or above half the OEL[1] for occupational benzene exposure. Comparisons with the OEL in Sweden (Swe-OEL), the European Union (EU-OEL) and the OEL-proposal from ECHA in 2017 (ECHA-OEL).

Exposed (N=38)	Swe-OEL		EU-OEL		ECHA-OEL	
	1.5 mg/m3		3.25 mg/m3		0.3 mg/m3	
	N	Percentage (%)	N	Percentage (%)	N	Percentage (%)
Above OEL	5	13	3	8	14	37
Above half the OEL	10	26	5	13	21	55

[1]The remaining four hours were considered having null exposure to benzene for an 8hTWA

All biomarkers (AlvBe, UBe and ttMA) rose significantly among benzene exposed workers from pre shift to post shift samples. Biomarkers correlated significantly with benzene exposure and with each other. An effect of smoking was evident on UBe in pre shift samples but was not observable in post shift samples. Smoking did not correlate with AlvBe, nor with ttMA. Age had no influence on the results.

Table 4. Number of samples, arithmetic mean (AM) with minimum and maximum values and geometric mean (GM) with 95% confidence intervals (95% CI) for benzene exposure measurements (mg/m3) during a 4hours' work shift on five different Swedish tankers. For exposed and non-exposed

		N	AM	Range (min-max)	GM	95% CI
non-exposed		12	0.04	0.01-0.15	0.02	0.01-0.04
exposed		38	4.98	0.02-143	0.45	0.25-0.83
	loading	18	0.58	0.02-7.10	0.17	0.10-0.34
	unloading	12	0.62	0.06-1.90	0.35	0.17-0.74
	stripping	2	3.70	1.00; 6.40	2.53	
	tank cleaning	6	27.34	1.90-143	6.62	1.23-35.49

For non-exposed, there was a small but non-significant rise in UBe and ttMA during a work shift (AlvBe was not followed among non-exposed). There was no correlation between benzene exposure and ttMA in post shift samples (correlation between benzene in air and UBe was not analysed among non-exposed because of too few samples).

2.4   Paper IV

2.4.1   Preamble

The purpose with Paper IV was to identify seafarers with hematologic malignancy (HM) and to examine whether work on tankers with possible benzene exposures was more common for these seafarers compared to seafarers without HM.

2.4.2   Aim

To study the risk of HM among Swedish tanker crews, an exposure-response relation, and the risk for HM in relation to an early (<1985) or later (>1985) work start on tankers.

2.4.3   Method

2.4.4   Establishing the cohort and identifying the cases

As mentioned earlier, the Swedish Seafarers' Registry was digitalized in 1985. However, for sea services prior to that year, we had no other knowledge but the actual dates of service and the corresponding ship's name.

2.4.5   Selection of cases and referents

A nested case-referent study was created from our Swedish Seafarers' Registry-cohort with a sea service between 1st of January 1985 and 31st of December 2014. Cancer cases were identified from linkage with the Swedish Cancer Registry. To be included in the study, a seafarer had to have a service record in the Swedish Seafarers' Registry with a cumulated sea service record of at least 30 days and having reached 20 years of age. Since few women had served on tankers according to the Swedish Seafarers' Registry, the study was restricted to men. A potential case was described as any seafarer that after his first registered sea service had received a diagnosis of HM. To each case, five referents at risk at time of diagnosis of the case were selected at random from within the cohort.

We matched cases and referents by two factors: by birth year (+/- 1 year) and by first year of sea service with respect to three different periods: before 1985, between 1985 and 1992 and later than 1992. Matching by birth year was to control for risk factors for HM associated with each respective generation. Most important would be benzene exposure from smoking, passive smoking and traffic and industrial exhausts. By matching by birth year, we also controlled for effects related to age, i.e. most HMs in adults are more frequent with age. Matching by three different starting periods as a seafarer was done to control for variation in benzene exposure related to changes with time in the work environment (e.g. supposedly lower benzene exposure at work in more recent times). In total, we identified 315 cases, whom we matched with 1575 referents.

2.4.6   Exposure

Exposure was defined as work on either a chemical tanker, a product tanker or a crude oil tanker. Quantification consisted in adding up the number of days on such a tanker and for all tanker services together (cumulated time on tankers). This cumulative time was further classified into one of two categories depending on the starting date for the first tanker employment: before or after 1985. The year 1985 was chosen to differ work on older types of tankers, with open handling and maintenance, while after 1985, more closed systems had become more common on tankers. Work on tankers transporting vegetable oils or gas or any other ship type was classified as "non-exposure".

2.4.7   Statistical methods

Odds ratios (ORs) for HM and subtypes were calculated with 95% CI with a conditional logistic regression. Matching was maintained in all analyses. We investigated ORs at different times from first tanker service (latency) and from last exposure to date of diagnosis.

2.4.8   Results

It was very common both among cases and referents to have worked on a tanker at least once during their career as seafarers (56% and 54%, respectively), especially for those that started out on the seas before 1985 (75% and 71%, respectively). The median of cumulated time of tanker service in years was for the first group 1.94 years for cases and 2.00 years for referents (Table 1 in Paper IV). For the second group (started at sea after 1985), cases had in general worked for 0.23 years on a tanker, and referents for 0.42 years. There were substantially less cases and referents with a tanker service after 1985.

Regarding age at diagnosis of HM, cases who commenced working as a seafarer before 1985 had a mean age at diagnosis of 63 (36-86) years, compared to 49 (21-79) years for cases that started out after 1985.

The OR for HM was 1.16 (95% CI 0.84-1.61; 155 cases) when the first tanker service started before 1985, and 0.85 (95% CI 0.51-1.43; 20 cases) for a tanker start after 1985. The ORs for lymphoma and leukaemia followed the same pattern with a higher OR before and a lower OR after 1985. Only four cases of AML with a tanker service were found, all with a tanker start before 1985.

Including cumulated tanker time into the analyses, we found an OR for HM of 1.32 (95% CI 0.86-2.02; 47 cases) with first start on a tanker before 1985 and with 5 years or more of tanker service (Table 3 in Paper IV). For less cumulated tanker time, the OR was 1.11 (95% CI 0.79-1.55; 108 cases). For MM, the corresponding ORs were 5.24 (95% CI 1.09-25.2; 7 cases) and 2.57 (95% CI 0.70-9.42; 16 cases). There was only one case of MM with tanker service start after 1985.

At 15 to 19 years' latency, the OR for leukaemia was 3.10 (95% CI 1.17-8.22; 8 cases) (Table A2 in Article). Analysing time from end-date of last tanker service, the OR for leukaemia peaked at six to ten years (Table A3 in Paper IV). Cases with CLL occurred mostly after more than 10 years had passed since the last tanker service, with an OR of 5.70 (95% CI 1.26-25.7; 5 cases) at 16 to 20 years past the last end-date of a tanker service.

3   DISCUSSION

3.1   Paper I. The lung cancer and mesothelioma cases

In Paper I, we described two cases of mesothelioma in relation to previous exposure to asbestos, and two cases of lung cancer in smokers in relation to exposure to asbestos, and PAH and nitroarenes. All had worked in the engine room. The cumulative exposure for asbestos was two to five fibre-years.

Swedish seafarers can still be exposed to asbestos in their work, especially the engine room crewmembers. Although reported as a rare exposure in Paper II, such an exposure may still increase the risk of future mesothelioma. In risk assessment for lung cancer due to asbestos exposure, different risk levels are presented. In an up-date of a previous consensus meeting, an asbestos exposure equivalent of 25 fibre-years was considered to represent a doubled relative risk (Wolff et al. 2015). In our study, cancer cases had in summary 2-5 fibre-years, which is comparatively low with the Helsinki criteria. However, other authors present a significantly increased risk for lung cancer at substantially lower levels. Gustavsson et al showed a near doubled relative risk for lung cancer (RR 1.9; 95% CI 1.32-2.74) at four fibre-years (Gustavsson et al. 2002). The Helsinki consensus has also been criticized for insinuating a threshold level for asbestos exposure regarding risk of lung cancer instead of promoting a linear dose-response relationship (Ramazzini Collegium 2016).

Both cases of lung cancer had been smokers at time of diagnosis. Since a synergistic effect, perhaps closer to a multiplicative than an additive effect, has been shown between asbestos and tobacco smoking (Wolff et al. 2015), low cumulative asbestos exposures in smokers may represent comparatively higher risk for asbestos-induced lung cancer than that for non-smokers.

3.1.1   Limitations

In our case report, we did not include exposure to diesel exhausts. Since then, diesel exhausts have been classified as carcinogenic (IARC 2013). In the web survey, 71% of engine crewmembers reported on exhausts at least every week, and 44% for a daily exposure. Presumably, these exhausts were mainly from exhaust leakage from the main engine, where the fuel used is heavy fuel oil and not diesel. Although even such exhausts can contain high levels of PAHs, air

monitoring in engine rooms has shown low if any level of PAHs (Moen et al. 1996). Diesel exhausts may be a more important exposure for deck crewmembers, especially on RoRo ships (Groves and Cain 2000; Ulfvarson et al. 1987).

There is scarce information on risk of lung cancer from dermal exposure to PAHs. Such a link has been proven in some animal studies (IARC 1984a; IARC 1984b; IARC 2006). In occupations with known PAH-exposures and with epidemiological findings of increased risks for lung cancer, such as coke-oven workers, the dermal exposure has also been shown to contribute much more to the internal dose of PAH than inhalation of PAHs (Moorthy et al. 2015). Dermal contacts with oils (that may contain carcinogenic PAHs) was common for engine room crewmembers in the web survey (62% daily exposure) and other studies have shown that PAH-exposure in the engine room comes mainly from dermal contacts with oils (Nilsson et al. 2004; Nordlinder 1999a; Nordlinder 1999b).

If, similarly to asbestos and smoking, there are synergistic effects between asbestos, PAH/nitroarenes and diesel exhausts are yet not fully known. In a case-control study on lung cancer cases from east European countries and the UK, a joint effect close to multiplicative was found for tobacco smoking and PAH (OR 14.1; 95% CI 5.58-35.9) and for asbestos and PAH (OR 4.4; 95% CI 2.17-8.94) in a UK work force (Olsson et al. 2010).

3.2   Paper II. The web survey

The study identified noise, risk of accidents, whole-body vibrations and ergonomic strain as important work environment problems for the seafarers in today's merchant shipping. Noise was reported by 89% of the engine room crewmembers, which was high compared with around 50% for the other work categories, which also corresponded to the reference group of land based industry workers. High levels of noise in the engine room is a well-known problem (Ivergård T 1978; Svendsen and Borresen 1999; Wagner 2008).

We also found a significant association between noise exposure and tinnitus or impaired hearing. Noise in the engine room has previously been linked to hearing impairment among engine room crewmembers (Kaerlev et al. 2008). There are no available studies on the sources of noise for the deck and service departments, even though noise was commonly reported as a work environment problem in these departments.

Noise on a ship can be assumed to exist more or less continually for the crewmembers, even during sleep. Ivergård et al measured 55-65 dB(A) in cabins (Ivergård T 1978). Noise in common quarters and cabins on board the ship could decrease recovery during leisure time and impair sleep. Chronic health effects from noise exposure include increased blood pressure, obesity and diabetes (WHO 2018), which are relatively common diseases among seafarers (Bloor 2000; Borch et al. 2012; Brandt et al. 1994; Elo 1985; Jensen 1996).

The work environment for women was different in some respects compared to men: Lack of a proper safety equipment, ergonomic strain and psychosocial factors in terms of iso-strain and harassments were more frequent among women. There is little information regarding female seafarers' work environment for comparisons. A Swedish report identified women in the service department as more frequently represented in work injuries, with associations to ergonomic strain and falling (Persson and Ljung 2014). A Danish study found a higher mortality for women seafarers than women in land based occupations, related to accidents, lung cancer and heart disease (Hansen and Jensen 1998).

3.2.1 Study strengths

Albeit a low response-rate, answers were represented by many seafarers including both men and women, all categories and positions and types of ships, and trades, as well as a broad range in age and seafaring experience. The web based system worked well (no break down or loss of data), we could reach seafarers wherever they were and the anonymity could be guaranteed, which all supposedly reduced the possibility of biased answers.

3.2.2 Limitations

Questions on department specific exposures (deck, engine, service) were created for the study purpose, assembled in communication with an expert group in seafaring, and were there deemed relevant and accurate. The effects of tiredness on work capacity (fatigue) was assessed by using the Modified Fatigue Impact Scale, which also had no validity ascertained.

Regarding the low-response rate, a sensitivity analysis was made for the association of lower airway symptoms and soot exposure (OR 2.5). In one scenario, we assumed a recall bias among seafarers with symptoms, overestimating their exposure by a factor two compared to seafarers without airway symptoms. This had a major effect (OR=0.45). Assuming that non-

responders had at least half the reported prevalence for responders had little effect (OR=2.4). In summary, the low response rate could give an overestimated association between exposure and symptoms due to a recall bias. However, since the study was not specifically aimed at certain area in occupational health, we assume that this effect was small. At the time for the survey (January to February 2014), no specific work environment topic in seafaring was on the agenda, to our knowledge. Later the same year, harassments among maritime students during their practice on ships were reported in media (an "Act of Intent" was published by the major stakeholders in February 2015, addressing this issue). Studies on participation rates have also shown weak associations with bias (Galea and Tracy 2007).

Our response rate (35%) is low, but not unique and about the same as in national surveys in Sweden. In retrospect, we should however made more effort in the planning process for post-survey evaluation of non-responders, such as gender, whether or not he or she met the inclusion criteria (service on a Swedish merchant ship at any time since 2010), if an e-mail address was invalid or if the recipient's server classified our own e-mail as spam.

3.2.3   Healthy worker effect

In seafaring, the medical examinations (MEs) will cause a selection of individuals. For Swedish seafarers, we think the selection is most evident upon entering the trade (and thus, exclusion cannot be associated with occupational exposures, but rather by occupational demands). It is also rare that the biannual ME excludes a seafarer from further work (reassignment is generally possible). In the Netherlands, a study revealed that only 22 out of 7,229 MEs (0.3%) during one year resulted in "Permanently unfit" (Zevallos et al. 2014).

Still, the seafarer may leave seafaring because of individual health concerns. The high prevalence of good/excellent health and work ability may be biased by a healthy worker effect.

3.3　Paper III. The benzene exposures and biomarkers

We found that work on tankers with manual or mixed manual and automatic handling of the cargo might result in occasional work exposures above the Swedish OEL and with substantial peaks of benzene exposure.

According to a summary on exposure measurements for benzene for marine transports of benzene-containing products, benzene exposures on board tankers transporting gasoline in Europe had arithmetic means around 10 mg/m3 for 8hTWA-measurements (range 0.7-32 mg/m3) (Williams et al. 2005). According to that paper, a publication by Christian&Eyres presented exposure levels between 7.2 and 31.9 mg/m3 (8hTWA) for open handling, and between 0.7 and 7.8 mg/m3 for closed handling of the gasoline. Our arithmetic mean of 4.98 mg/m3 (4hTWA) thus corresponds to the findings from the closed tankers. The Christian&Eyres study was performed during 1977 to 1985, and certain work tasks during the measured 8 hours would certainly have involved manual handling of the cargo or tanks, like in our own study.

3.3.1　Study strengths

The supervision of two well-trained staff within the research team reduced the risk of any sampling error, and a protocol was used to control for any bias in benzene exposure related to smoking, diet or meteorological factors (wind across the bridge, temperature).The laboratory methods had been thoroughly tested in validity, and had low LODs, enabling a sensitive analysis.

3.3.2　Limitations

Specific exposure on skin was not noted during the field study. Re-examining the data in Paper II, we found that 39% of tanker deck crewmembers reported on skin exposure to oils at least once a week, and 13% reported that this occurred on a daily basis. However, dermal uptake of benzene is generally low in occupational settings (ECHA 2017). Also, since we found strong correlations for benzene in air exposure and biomarkers, dermal uptake of benzene, if present, would indeed make a small contribution to the total dose of benzene. Control for dermal exposure would though give a better estimate of the association between up-take and exposure sources.

3.4 Paper IV. Hematologic malignancy and tankers

The study had few cases of acute myeloid leukaemia (AML; N=10), which is the one subgroup of leukaemia most associated with benzene, and even less cases had worked on tankers (n=4). We found no significantly increased overall OR for hematologic malignancy (HM) in the case-referent study. However, OR for work on tankers before 1985 were above one and below one for a later start on tankers. For multiple myeloma (MM), there was a significant OR with more than five years of cumulated time on tankers. The summary is that, if there is an increased risk for HM for tanker work, this risk has presumably decreased with the introduction of modern tanker shipping.

Such a summary seems to have some support, since studies on HM among tanker crewmembers have found increased risks for work in earlier years but lower risks in years that are more recent. The Swedish case-referent study with an observation period of 1971 to 1987 of Swedish tanker crews found an OR for leukaemia of 2.6 (95% CI, 1.1-5.9) (Nilsson et al. 1998). A higher OR for lymphoma and leukaemia was also found among Finnish seafarers with approximately the same study design and observation period (OR 2.26; 95% CI 1.01-5.06) (Saarni et al. 2002). However, for the observation period 1986 to 2002, Kaerlev and co-authors found no increased standardized incidence ratios (SIR) for HM among Danish employees on tankers (Kaerlev et al. 2005). In a recent follow-up study from the same cohort, the SIR was increased for Hodgkin's lymphoma in males having served on tankers (SIR, 3.15; 95% CI 1.41-7.01) (Ugelvig Petersen K 2018). Since benzene is not known to cause Hodgkin's lymphoma, the authors interpreted it as a possible finding of chance.

In contrast to this stands a German study on hospitalization for leukaemia between 1997 and 2007, where Oldenburg and co-authors found an increased Standardized Hospitality Ratio (SHR) for leukaemia among tanker crews (SHR 2.85; 95% CI 2.12-3.75), especially for deck crewmembers (SHR 4.09; 95% CI 2.95-5.53) (Oldenburg et al. 2015).

Since benzene exposure levels have decreased for deck work on tankers, at least in Western Europe, this might have contributed to a decreasing risk for HM after tanker deck service.

3.4.1 Study strengths

The Swedish Seafarers' Registry enabled us with robust data on sea services and ship type for an individual exposure assessment. Quite often, other studies in the field have had to rely on potentially more biased information, such as that from insurance records, or rather crude information on occupational settings (i.e. "seafarer" as only information given). We also had reliable data on cancer from the Swedish Cancer Registry.

3.4.2 Limitations

There is increased support for a link between tobacco smoke, which contains benzene, and the risk of AML (Fiebelkorn and Meredith 2018; IARC 2012). We could not control for smoking in the study. However, we do not believe that the ratio of smokers would be different for seafarers having worked on tankers and those who have not worked on tankers. Of course, this could be suspected since smoking is not allowed while on deck on tankers. However, half of the tanker deck crewmembers in Paper III were active smokers. In addition, the data on sea services indicated that rotation between different ship types is common for seafarers, so there does not seem to be a unique seafarers' subgroup for work on tankers.

It is difficult to estimate the dropout of seafarers and their sea services from the Swedish Seafarers' Registry. No such estimation has been done in a more systematic way. For Swedish seafarers, it is supposedly low, since historic advantages and an incorporated habit in the trade to report.

There may be non-reported cancer cases among Swedish citizens reported to the Swedish Cancer Registry, but the phenomenon appears to be rare. A comparison in 2009 between the Swedish Cancer Registry and the National Patient Registry, which records diagnosis of patients in contact with health care units and hospitals, showed a loss of data of 3.7% (Barlow et al. 2009). It is, however, unclear if such loss of data could be higher for cancer cases among seafarers. Even though these seafarers might seek medical assistance not in Sweden for symptoms that turn out to be a HM, we believe that, because of the reputedly high standard of the Swedish health system, seafarers will opt for a homecoming when treatment is needed. Any loss of cancer cases should not differ between seafarers that have and those that have not worked on tankers.

Work on tankers was common before 1985 for both cases and referents (~70%), which decreased our possibility for contrast for tanker work within the sets of one case and five referents. For tanker work after 1985, we instead had few cases, which lessened the study precision. In the exposure assessment, we might have included too many tanker services with possible occupational benzene exposure. A more specific assessment for benzene should ideally have included knowledge on type of petroleum or chemical cargo (high vs. low benzene contents), but also individual benzene exposures from other source or occupation. This seems all the more important since most tanker services were short, and the average total years as a seafarer represented grossly 20-25% of a normal working life.

4   SUMMARY

Previous exposure to asbestos may still cause cancer in today's seafarers, and seafarers may still be exposed to asbestos. Exposure to PAHs and diesel exhausts may contribute to an increased risk of lung cancer, and synergistic effects may be present between asbestos, PAH, diesel exhausts and tobacco smoking. Noise, risk of an accident, whole-body vibrations and ergonomic strain are important factors regarding seafarers' health as perceived by themselves. However, the deck, engine and service crewmembers also report on different health hazards in their work.

Exposure to benzene may be important for work on tankers and may be assessed on a group level by use of benzene in alveolar air, benzene in urine or ttMA in urine.

The risk for hematologic malignancy for tanker crewmembers seems to have decreased during the last two decades.

5   CONCLUSIONS

Mesothelioma caused by asbestos exposure may still occur. For lung cancer, occupational exposures to asbestos, PAHs and diesel exhausts are important to consider in assessment of causality.

Noise and ergonomic strain are common physical exposures in merchant Swedish seafaring. Exposures to exhausts and oil on the skin are frequent chemical exposures. Whereas the safety climate is high in comparison with land-based occupations, tiredness is associated with lower safety estimates. Engine room and deck crewmembers report that asbestos exposure still occurs in their work.

Exposure to benzene at work on product or chemical tankers carrying gasoline during the 1990'ies was high for certain work tasks involving manual work tasks. Overall, the exposure levels appeared to have decreased with the introduction of closed systems compared with older tankers with only open handling of the cargo.

Work on older types of tankers may increase the risk for hematologic malignancy, but the risk seems to have decreased with the introduction of more modern tankers.

6 FUTURE DIRECTIONS

Since harassments or offensive actions were common among the seafarers, especially among women, it seems important to investigate psychosocial factors when working on ships. Such a study should try to assess the importance of the relatively strict hierarchy for seafarers, communicative challenges between the ship owners and the workers at sea, between the different departments (deck, engine room, service) and the globalisation of the work force. It would also be interesting to study how the psychosocial environment is cared for by the ship companies and identify good examples of framework.

Benzene exposure patterns for work on modern tankers with full automation need to be studied, especially since the risk for leukaemia in relation to exposure dose or pattern is still debated.

The indication of a decreased risk for HM for later work on tankers needs to be further clarified. One possibility is to explore Standardized Incidence Ratios for HM for tanker crewmembers in the cohort of Swedish seafarers, comparing the incidence with the general population. The assessment of benzene exposure can be further explored, e.g. by creating a job exposure matrix.

FUNDING, ETHICAL PERMITS & CONFLICT OF INTEREST

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