



# RETROSPECTIVE EXPOSURE ASSESSMENT IN THE NORWEGIAN OFFSHORE PETROLEUM INDUSTRY

*-A seminar addressing the methods and challenges of retrospective  
exposure assessment*

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## **Abstract:**

On March 21, 2007 a group of invited international and national experts, and participants from a wide variety of institutions in Norway representing regulatory agencies, oil companies, contractors, regional occupational health departments, and research institutions met in Stavanger, Norway to discuss retrospective exposure assessment in the Norwegian Petroleum Industry. The one-day seminar was organized as a plenary session with presentations followed by a panel discussion and comments from the participants. The participants heard invited presentations from the international experts. Topics addressed in the presentations were:

- a) Qualitative and semi-quantitative methods for retrospective exposure assessment
- b) Quantitative methods for retrospective exposure assessment and use of biomarkers in assessing exposure
- c) Methods for assessing dermal exposure
- d) Retrospective assessment of benzene exposure in the Australian petroleum industry.

In addition to the four international experts two national experts presented:

- a) An exposure assessment project on carcinogens in the Norwegian offshore industry
- b) A prospective cohort of Norwegian Petroleum workers established by the Cancer Registry of Norway.

An attempt has been made to present major issues confronting the field of retrospective exposure assessment in the Norwegian Petroleum Industry, and several clear messages come through this report.

1. The industry was challenged to do a complete exposure assessment of all workers, all agents, and all jobs. Exposure information can especially be used to perform risk assessments in combination with information from the literature and form a basis for current and future epidemiologic studies

2. The suggested exposure evaluation of the industry may provide a basis for medical evaluation of individual patients from the oil industry, i.e. for establishing a relationship between work in the industry and work-related illnesses.
3. A literature review of agents and health risks relevant to the oil industry was recommended.
4. Epidemiologic studies should be initiated only when clear research questions have been formulated.
5. Focused (historical) exposure assessment studies should be conducted that are tailored to specific research questions/hypotheses.

**Stikkord:** Retrospektiv eksponeringskarakterisering, yrke, epidemiologi, petroleumsindustri

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# 1. PREFACE

Exposure to chemical substances in the Norwegian offshore petroleum industry has been extensively addressed in White Paper No. 12 (2005-2006) "*Health, environment and safety in the petroleum activities*". The Petroleum Safety Authority has organized a pilot project<sup>1</sup> with the objective to identify and verify needs for research and development in the area of chemical exposures and potential health risks. The pilot project will describe historical exposures and aims to evaluate retrospective exposure assessment methodology. As part of this ongoing pilot project a seminar on methodologies for retrospective exposure assessment was organized. The objective of the seminar was to outline strategies and methods to assess historical chemical exposures for epidemiologic studies and to discuss needs and prospects for the development of activities on exposure assessment in the Norwegian offshore industry.

The seminar was organized by staff from the National Institute of Occupational Health, Oslo, Norway. The organizing committee developed the agenda for the seminar and topics for discussion, and selected the invited speakers. The selection of invited participants was a joint effort by the Petroleum Safety Authority, the organizing committee, and members of the reference group<sup>2</sup> of the pilot project. The seminar agenda is attached in Appendix A.

This report was compiled and edited by the workshop organizing committee and reflects the deliberations and recommendations that emerged during the seminar and not the views of the seminar sponsors or authors of this report. The participants were invited to send comments/questions to the organizing committee after the meeting. No comments were submitted directly to the organizing committee. There has been incidental contact between participants and invited speakers after the meeting to clarify some issues raised during the meeting but this was not considered to be relevant to this summary report.

The organizing committee hopes that this report will be helpful in defining the current efforts and applications related to chemical exposures and health risks in the Norwegian offshore industry, as well as providing direction for further work in this area.

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<sup>1</sup> Petroleum Safety Authority pilot project team: Janne Lea Svensson (project leader); Sigvart Zachariassen; Hilde Nilsen; John Arne Ask

<sup>2</sup> Reference group of pilot project: Halvor Erikstein, SAFE; Vemund Digernes, Norsk Industri; Kyrre Loen, Norges Rederiforbund; Jakob Nærheim, OLF; Aud Nistov, OLF; Bjørn Romsbotn, Fellesforbundet; Tom Lund, Lederne; Harald Sjonfjell, NOPEF

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## **Invited speakers**

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Prof. Dick Heederik, University of Utrecht, Netherlands

Dr. John Cherrie, Institute of Occupational Medicine, United Kingdom

Dr. Deborah C. Glass, Monash University, Australia

Dr. Magne Bråtveit, University of Bergen, Norway

Dr. Tom K. Grimsrud, Cancer Registry, Norway

Speaker biographies are attached in Appendix B.

## **Acknowledgements**

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The organizing committee wishes to thank Dr. Helge Kjuus and Dr. Dag G. Ellingsen, National Institute of Occupational Health, for comments on this report, and

Dr. Pål Molander for chairing the seminar.

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<sup>3</sup> Chair and secretary for the Petroleum Safety Authority pilot project

## **2. WORKSHOP SUMMARY AND CONCLUSIONS**

On March 21, 2007 a group of invited international and national experts, and participants from a wide variety of institutions in Norway representing regulatory agencies, oil companies, contractors, regional occupational health departments, and research institutions met in Stavanger, Norway to discuss retrospective exposure assessment in the Norwegian Petroleum Industry. The one-day seminar was organized as a plenary session with presentations followed by a panel discussion and comments from the participants. The participants heard invited presentations from the international experts. Topics addressed in the presentations were:

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In addition to the four international experts two national experts presented:

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An attempt has been made to present major issues confronting the field of retrospective exposure assessment in the Norwegian Petroleum Industry, and several clear messages come through this report.

1. The industry was challenged to do a complete exposure assessment of all workers, all agents, and all jobs. Exposure information can especially be used to perform risk assessments in combination with information from the literature and form a basis for current and future epidemiologic studies.
2. The suggested exposure evaluation of the industry may provide a basis for medical evaluation of individual patients from the oil industry, i.e. for establishing a relationship between work in the industry and work-related illnesses.
3. A literature review of agents and health risks relevant to the oil industry was recommended.
4. Epidemiologic studies should be initiated only when clear research questions have been formulated.
5. Focused (historical) exposure assessment studies should be conducted that are tailored to specific research questions/hypotheses.



### 3. INTRODUCTION

Due to the rising interest in chemical exposures in the Norwegian offshore industry, a seminar entitled “Retrospective exposure assessment in the Norwegian Petroleum Industry” was held at the Petroleum Safety Authority on March 21, 2007, in Stavanger. Most of the participants were invited because of their sincere interest in exposure assessment. They came from industry, both large and small, regional occupational health departments, academia, and government. All were from Norway except one participant from the US. Four of the speakers were international well known experts in the field of exposure assessment for epidemiologic studies, and two were national experts. The participants heard about recent advances in the field of retrospective exposure assessment and also about ongoing national projects in the Norwegian Petroleum industry.

#### **Measurement data reported from industry**

Prior to the seminar and as part of the pilot project the Petroleum Safety Authority visited 22 companies that were asked to provide all exposure measurements that have been collected. A brief description of the data were presented at the meeting by Dr. Berit Bakke. In short:

- Twelve of the 22 companies (which includes both operators and contactors) submitted overviews
- The data set consists of about 7000 measurements of 40-50 different agents
- About 70% of the samples submitted were collected after the year 2000
- No samples collected prior to 1980 were submitted
- About 70% of all measurements were stationary samples
- Biological measurements included 84 measurements of mercury in urine and 209 measurements of isocyanates in urine
- No dermal samples were reported

The industry data include few measurements for most of the agents measured, except for oil mist and oil vapor, which have been increasingly measured over the last decade.

To complete the picture the organizing committee searched the exposure database EXPO at the National Institute of Occupational Health for additional measurements in the industry.

There was most likely an overlap of some of the measurements found in EXPO and the measurements reported by the industry. A brief description of these data follow:

- In total 3600 measurements on several agents were available. 40% of these were oil mist/oil vapor measurements.
- In addition, about 3500 measurements of mercury in urine were available prior to the year 2000 and another 1000 measurements of mercury in urine after 2000.

A preliminary conclusion from this data collection is that the documentation on levels for most agents is limited. It appears that the number of biological measurements of mercury in urine has been severely underreported by the industry because only 84 of the 4500 results found in EXPO register were reported.

## 4. SUMMARIES FROM PRESENTATIONS

Four international speakers delivered plenary session presentations where they summarized state-of-the-art knowledge in the field of retrospective exposure assessment for occupational epidemiologic studies. Prior to the meeting they were given background information on the Norwegian offshore industry and ongoing studies in the industry (Appendix C).

Two national experts presented experience with studies in the Norwegian offshore industry. The objective of the plenary presentation was to provide the participants with new insight in exposure assessment methods and also serve as a platform for the following discussion. Below we give a short summary of each presentation and recommendations that were given. Where there were comments from the participants we have reported them. The extended abstracts are attached in Appendix D.

### **Dr. Patricia A. Stewart: “The Challenges of Exposure Assessment”**

Dr. Stewart gave a detailed description of the process of retrospective exposure assessment. Several components of exposure assessment were identified and recommendations for the oil industry were identified. A short summary follows:

#### *1) Identification of the hazard*

Recommendations for offshore oil studies included: evaluate agents based on statistical power, rather than on toxicity; evaluate exposure to individual agents (e.g., polycyclic aromatic hydrocarbons) within mixtures, where possible, particularly where the specific agent occurs in multiple mixtures across the rig; and analyze possible synergistic effects of multiple agents using cluster type of analyses.

#### *2) Selection of an exposure metric*

Recommendations for offshore oil studies included: look at other exposure metrics besides full-shift averages (e.g., for benzene and oil mist, peaks; for benzene, dermal exposure; for tetrachloroethylene, peaks; and for lead and chromium, ingestion) and incorporate recovery time and level of physical activity.

3) *Development of exposure groups based on determinants of exposure*

Exposure groups should be based on the same exposure profile with the same approximate mean and distribution under the same exposure scenario for the agent and metric being assessed.

Recommendations for offshore oil studies included: formally identify exposure determinants and assess each job title/department/rig combination for these determinants; review previously developed job groups from the University of Bergen based on determinants; and develop new groups, keeping them as precise as possible based on similarity of determinants for each agent, each metric and exposure scenario.

4) *Estimation of exposure levels*

Recommendations for the offshore oil studies included: use published measurement data of well-documented tasks to estimate differences among determinants or jobs (e.g., brush vs. spray painting) for developing either semi-quantitative or quantitative estimates; use other determinant information with measurement data to predict exposures in unmeasured situations (e.g., vapor pressure to estimate the exposure of an agent in a mixture containing another measured agent; the percentage of benzene in a mixture in one measured situation to estimate the same situation with a different amount of benzene for developing either semi-quantitative or quantitative estimates; and using semi-quantitative estimates for dermal exposure). Identifying the range of the exposure levels of the exposure categories when developing semi-quantitative estimates was also recommended.

Recommendations for developing quantitative estimates for offshore oil studies included: rely on task measurements rather than job titles (e.g., benzene, see Kirkeleit *et al* (2006)<sup>4</sup>); use a hierarchy of methods, rather than a single method; identify a level of confidence on the estimates; and evaluate uncertainty and sensitivity.

5) *Validation of the methods*

Recommendations for offshore oil studies included: for agents with few measurement data, develop an estimation approach, use that same approach for jobs/tasks where measurement data are sufficient (e.g., for benzene and/or oil mist/vapor) and compare the estimates with the measurement data; conduct other

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<sup>4</sup> Kirkeleit *et al.* Ann. Occup. Hyg., Vol. 50, No. 2, pp. 123–129, 2006

reliability studies such as the one by Steinsvåg *et al* (2007)<sup>5</sup>, where sufficient measurement data do not exist; and use the results from these efforts to indicate confidence of estimation method.

### **Prof. Dick Heederik: “Benefits of modern quantitative exposure assessment approaches in occupational epidemiology”.**

Prof. Heederik gave a talk on quantitative exposure assessment in cohort and case-control studies. He discussed issues and challenges in quantitative exposure assessment and use of biomarkers in exposure assessment. Special attention was given to issues such as:

#### *1) Variability of exposure*

Exposure varies over time, between groups of workers, between workers, and within workers. When interested in estimating long-term exposure, variability over time may complicate the exposure assessment and can lead to underestimation of exposure response relationships. However, when the sources of variability are known, and determinants of exposure have been identified, accurate estimation of the exposure is possible and the effect of variability over time does not necessarily complicate exposure estimation.

#### *2) Estimation process (individual or group based)*

Exposure estimation on the individual level is potentially the most accurate approach; however, when variability over time is large, the required measurement effort is large in order to avoid biases in the exposure response-relationship. Exposure grouping strategies are more efficient, in terms of the required measurement effort, but at the expense of a reduced precision in the estimate of the exposure-response relationship and thus also the power of a study to detect an association between exposure and response.

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<sup>5</sup> Steinsvåg *et al*. *Occup Environ Med*. 2007 Jan 16; [Epub ahead of print]

3) *Exposure data*

A prerequisite for quantitative exposure assessment is the availability of exposure data. In retrospective studies the approach has been taken to collect available data, and combine the data in large databases.

4) *Exposure assessment strategy*

Detailed description of the exposure assessment strategy (compliance, worst case or random sampling), the sampling (dust fraction, fume, otherwise), and the chemical analysis is required so that conversions can be applied to make the data comparable and useful. Worst-case exposure measurements can be used as long as information is available about the frequency of occurrence of the worst-case situations.

5) *Determinants of exposure*

When data are available, an analysis can be undertaken to analyze relationships between exposure levels and determinants of exposure for the different agents.

6) *Molecular epidemiological approaches*

Novel analytical techniques facilitate measurement of multiple biomarkers or markers of genetic susceptibility. Biomarkers can, if chosen appropriately, contribute to the weight of evidence on exposure-response relationships and can also give insight in the etiology of disease. A problem of many biomarkers is the relatively poor signal to noise ratio: biomarkers vary strongly over time and as a result have little advantage over exposure measurements. However, some examples exist, like benzene, where application of biomarkers gave new insight in potential effects at very low exposure levels that are expected to be detectable only with great difficulty in cancer incidence or mortality studies.

General recommendations for the offshore industry:

1. Application of quantitative exposure assessment in new industries and for new exposures requires a careful consideration of the research questions and planning on the subsequent research approaches to be taken.
2. In cohort studies, databases should be created, which contain ancillary information collected together with the measurements. This determines the

possibilities in statistical analyses for retrospective exposure assessment. Data from different countries can be used if the process is similar.

3. Biomarker studies: a) tailor made exposure assessment strategies are required for low intermittent exposures, b) high resolution strategies are required given the exposure levels encountered today in the offshore industry.

### **Dr. John W. Cherrie: “Assessment of dermal and inhalation exposure for an epidemiological study in the offshore oil industry”.**

Dr. Cherrie gave an overview of methods and strategies for assessing dermal exposure in epidemiologic studies. Several important issues were addressed:

#### *1) When is dermal exposure important?*

From the preliminary information provided from the Norwegian offshore industry Dr. Cherrie suggested that oil, oil-based drilling muds, glutaraldehyde, benzene and other solvents are hazards that can be taken up via the skin. It is not clear whether risks of local skin disease are relevant to the substances present offshore, although wet work and/or wearing impermeable gloves can cause this type of risk.

#### *2) A conceptual model of dermal exposure*

The key information to be drawn from the conceptual model is the importance of the concentration of the hazardous substance in the *stratum corneum* layer (SCL) in determining uptake, along with the area of skin and the duration of exposure. The mass of contaminant in the SCL is of secondary importance in this respect. Also, the model shows that the process by which people become exposed is complex, but in many situations working at the work site and air concentrations will be the important determinants of dermal exposure. Similarly, work clothing may provide protection against absorption.

#### *3) Assessing skin exposure*

Recommendation: The best method for use in the Norwegian offshore industry will almost certainly depend on the substance to be assessed. A simple practical method of measuring low volatility substances may be skin wiping. For volatile agents the patch

sampler described by Lindsay *et al* (2006)<sup>6</sup> may offer some possibilities, although it is not available commercially. A wet-work sampler recently developed by Institute of Occupational Medicine, UK could offer a suitable way to assess dermatitis risk<sup>7</sup>.

4) *Comparison of inhalation and dermal exposure measurements*

Recommendation: It is difficult to be sure about the necessity of measuring dermal exposure in addition to inhalation exposure for an epidemiological study in the offshore industry. It is probably advantageous to collect some data about current exposure and identify whether inhalation and dermal exposures are correlated and whether dermal exposures are important in relation to inhalation exposure to the disease of interest.

5) *Models and data*

In some studies there are only limited data on exposure, perhaps only from recent times. In these cases investigators have sought to rely on exposure models sometimes in combination with measurements.

6) *Dermal exposure models and measurements*

The dermal exposure model DREAM was presented. This is a method for semi-quantitative dermal exposure assessment based on a detailed questionnaire to characterize tasks and to produce estimates of dermal exposure levels using the Schneider *et al* (1999)<sup>8</sup> conceptual model as a framework. The DREAM model, which is based on a sound conceptual model, provides a structured approach to semi-quantitative dermal exposure assessment. Combined with a limited amount of current measurement data it could provide a suitable tool for reconstruction of past dermal exposures. Combined with some current dermal exposure data the DREAM method could provide a more quantitative assessment.

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<sup>6</sup> Lindsay FE, Semple S, Robertson A, Cherrie JW. (2006) Development of a Biologically Relevant Dermal Sampler. *Ann Occup Hyg.* 26; 50 (1): 85-94.

<sup>7</sup> Cherrie JW, Apsley A, Semple S. A new sampler to assess dermal exposure during wet work. (2007) *Ann Occup Hyg.* 51(1):13-18.

<sup>8</sup> Schneider T, Vermeulen R, Brouwer DH, Cherrie JW, Kromhout H, Fogh CL. (1999) A conceptual model for assessment of dermal exposure. *Occupational and Environmental Medicine*; 56: 765-773.



Overall recommendations:

It is not possible to say *a priori* whether, for an epidemiological study, an assessment of dermal exposure to chemicals used in an industry is necessary or worthwhile. If there is an high correlation between inhalation and dermal exposure in specific jobs, it may not be possible to separate the effects of these two routes of exposure in the study analysis. Also, dermal exposure may not make an important contribution to the total exposure. Some initial investigation of these aspects, e.g. a pilot study to assess dermal exposure relative to inhalation exposure, would enable an informed decision to be made about what strategy might be best.

Assessment of skin exposure in relation to dermatitis requires special consideration and may require a completely different approach than that used for chemicals giving rise to systemic risks. A prospective design would be feasible if one wanted to evaluate the relationship between exposure and dermatitis. It is important to notice that it may not be the oil that is causing dermatitis, but other factors such as wet work, protective clothing, temperature, and the humidity offshore, possibly together.

### **Dr. Deborah C. Glass: “Experiences from exposure assessment in the Australian petroleum industry”.**

Dr. Glass gave a description of the Australian Health Watch cohort, which is a prospective cohort study of employees in the Australian petroleum industry who have worked for more than 5 years. It compares the mortality and cancer incidence of the cohort with that of the Australian population. Subjects are actively followed and regularly matched with the Australian national death and cancer registries. In addition, cohort members are encouraged via periodic health letters to self-report illness. The study was set up in 1981 and closed for further recruitment in 2000.

Dr. Glass also reported from a case-control study that was nested in the Health Watch cohort where they investigated whether the excess of lympho-hematopoietic cancers, identified among male members of the Health Watch cohort, was associated with benzene exposure. She gave an in-depth description of the exposure assessment methodology that was applied

for this study. Briefly, a job history was prepared for each study subject, based on data that had been collected largely prospectively from cohort interviews.

For each case and control, the tasks carried out within each job, the products handled, and the technology used, were identified from structured interviews with contemporary colleagues using job specific questionnaires. Exposure to benzene was retrospectively estimated for each individual using an algorithm. The interviews and assessments were done anonymously and case-blind. Benzene exposure measurements, supplied by Australian petroleum companies, were used to estimate exposure for specific tasks or jobs. Some supplementary data were used from the literature. Forty-nine different base estimates were calculated taking the arithmetic mean of the available measured personal exposure data. The base estimates were validated by comparison with data from the literature.

Where necessary, multipliers were used to estimate exposure levels for tasks where no suitable measured data were available. This was based on methodology used in similar petroleum industry case-control studies by other investigators.<sup>9</sup> A time-weighted exposure level was estimated for each job. This was multiplied by the number of years in that job and the results summed for each individual to give an exposure estimate in ppm-years. The intensity of the highest exposed job was identified. The results showed that the exposure was low; 85 percent of the cumulative exposure estimates were less than 10 ppm-years. Matched analyses showed that leukemia risk was significantly increased for the subjects with >16 ppm-years cumulative exposure and/or greater than 0.8 ppm for the intensity of the highest exposed job with an odds ratio (OR) of 51.9 (5.6-477). The risk of leukemia was associated with exposure that occurred within 15 years of diagnosis; the association with exposure prior to this period was weaker. The inclusion of occasional high exposures e.g., as a result of spillages, reduced the odds ratios.

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<sup>9</sup> Armstrong TW, Pearlman ED, Schnatter RA, Bowes SM, Murray N, Nicolich MJ. Retrospective benzene and total hydrocarbon exposure assessment for a petroleum marketing and distribution worker epidemiology study. *Am Ind Hyg Assoc J.* 1996;57:333-43.

Lewis SJ, Bell GM, Cordingley N, Pearlman ED, Rushton L. Retrospective estimation of exposure to benzene in a leukaemia case-control study of petroleum marketing and distribution workers in the United Kingdom. *Occup Environ Med.* 1997;54:167-75.

#### Recommendations:

- 1) The Health Watch exposure assessment methodology is too detailed to apply to a cohort study; in the absence of the personalization derived from co-worker interviews the methodology is similar to using an *a priori* job exposure matrix.
- 2) In a case-control study, the methodology could be used for exposures such as total hydrocarbons, dust, or mineral oil, because measured exposure data are available.
- 3) The methodology is less useful for estimating exposure to exposures such as asbestos, formaldehyde, and noise, which may vary from facility to facility in less predictable ways.
- 4) Significant skin exposure could be factored in, but is complicated by significant between-worker variability.
- 5) The effect of long shift patterns or uncertainties from bad weather are difficult to account for. Perhaps the collection of biological monitoring data is appropriate.
- 6) The use of a relational exposure database allows alterations to the base estimates or background levels to be made and thus, the risks to be reevaluated easily.
- 7) The choice of an exposure metric used in an assessment should depend on the endpoint being investigated. Cumulative exposure or intensity of exposure may need to be lagged. Exposure rate may be an important risk factor.
- 8) Real world measured exposure data should be used as far as possible as the basis for the exposure estimation although some extrapolation will almost certainly be needed. The limitations of the real world data must be identified and the effect of these limitations on risks estimates be evaluated as far as possible.

#### **Dr. Magne Bråtveit: “Overview of exposure assessment project in the Norwegian offshore industry”.**

Dr. Bråtveit reported from an exposure assessment study in the Norwegian offshore industry. He described the procedures used to collect retrospective information on occupational exposure to carcinogenic agents in the Norwegian offshore industry from 1970-2005 and the method used for assessing exposure to 18 carcinogenic agents in 27 job categories over 4 time periods. The main objective of this study was to provide retrospective exposure information on carcinogenic agents to support an ongoing prospective cohort study in the Norwegian offshore industry (the Cancer Registry prospective cohort study, see next paragraph).

Written documentation on risk assessments, monitoring reports and other relevant documentation were collected from oil companies, contractors, and relevant authorities. 83 key personnel were interviewed on work processes, chemicals in use and exposures. Based on the collected information and job titles (n=294) from the Cancer Registry questionnaire from 1998<sup>10</sup>, 27 job categories were defined for which exposures to carcinogenic agents was assessed.

Monitoring reports on measurements of oil mist and oil vapor were found from 37 drilling facilities in the period from 1979 to 2004. Three different hydrocarbon base oils were identified during this period (i.e., diesel oil (1979-84), low aromatic mineral oil (1985-1997), non-aromatic mineral oil (1998-2004)). Measurements from the period prior to the mid 1980s showed high exposure to oil vapor (arithmetic mean=1217 mg/m<sup>3</sup>). A downward time trend was indicated for both oil mist and oil vapor. Results from measurements on 12 installations in the period from 1994 to 2003 show that exposures to benzene generally were low. The job group highest exposed to benzene was deck workers (arithmetic mean=0.17 mg/m<sup>3</sup>) and the lowest exposed job group was mechanics (arithmetic mean=0.0062 mg/m<sup>3</sup>).

To assess historical exposures a group of 8 experts attended a two-day meeting. Two weeks prior to the meeting the experts were handed instructions and guidelines for filling out the assessment schemes. Summary documents of background information were provided at the meeting. During the first day the experts individually assessed exposure to 1836 agent/job category/time period combinations. On the second day of the meeting the experts had a group discussion to assess exposure in a plenary session and a consensus was reached. The overall results indicate good interrater agreement on exposure, and agreement between an individual and the panel consensus (considered as the gold standard) show that the experts' individual ratings agreed highly with the panel consensus.

Dr. Bråtveit identified some limitations of the study: 1) installation specific assessments not feasible, 2) broad job categories, 3) less exposure information on earlier years, and 4) short time frame on expert assessments.

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<sup>10</sup> A questionnaire from the Cancer Registry prospective offshore cohort which was answered by 28000 present and former offshore workers

- Concern was raised from panel experts about assessing exposure only for the 27 job categories that were developed in the exposure assessment study, and possibly the 294 job titles from the Cancer Registry cohort. A small number of job categories can often hide substantial variability in exposure or exposure levels within the groups. Grouping of such heterogeneously exposed jobs may generate substantial misclassification of exposure. [See also recommendation no. 3, p. 10 from Patricia Stewart.]

### **Dr. Tom K. Grimsrud: “The Norwegian Offshore Cohort”.**

Dr. Grimsrud described the establishment at the Cancer Registry of Norway of a prospective cohort in the Norwegian offshore industry. The initiative for a study of cancer incidence and cause-specific mortality came from the Norwegian Oil Industry Association. The cancer incidence and mortality may be compared with the general population, and selected groups of workers may also be compared within the cohort (internal comparison). The project started in 1996 by an attempt of identifying present and former workers on the platforms. The main contributors to the list of potential workers were the oil companies, contracting companies, labor unions, safety training schools, and the National Archives of Norway. Experience from offshore work could not be verified from other sources than the workers themselves, and in 1998, a self-administered questionnaire was distributed by mail to the 57,000 potential offshore platform workers alive in Norway. The questionnaire included questions on offshore job history, other occupations, leisure time activities, and life style factors such as smoking, alcohol consumption, physical activity, and nutrition. Details on workers' offshore work included: job title and job category (specified by the respondent), year of employment, duration of employment, work shift, administrative tasks, information on platform and employer, full or part time, offshore/onshore proportion of work hire.

The survey gathered 35,000 answers (a response rate of 62%). Of these, 7,000 respondents stated never to have worked on a platform. The remaining 28,000 constitute the cohort to be followed up. After approximately 10 years of follow-up, the cohort will be linked to the Cancer Registry database and the Cause of Death Registry in Statistics Norway, for further analyses (e.g, standardized incidence and mortality ratios; regression analyses).

Dr. Grimsrud identified some limitations of the study: 1) some of the data on offshore work (except first and last job) exist only as scanned pictures (not as text), 2) no repeated

questionnaire is planned (would require new applications to the Committee for Research, Ethics, and Data Inspectorate, as well as funding), and 3) a delay in reporting due to the need of more follow-up time with prospective study design compared to a cohort defined from historical personnel files.

Participants raised some concern related to the cohort:

- The relatively low response rate
- The start of follow-up of the cohort in 1999 was considered late because many workers who were employed in the early years of the offshore industry when exposures were probably much higher than today were not included. [NB: Dr. Grimsrud showed in his presentation that about 26% (n=7000) of the cohort members had their first employment between 1965 and 1979.]
- No clear hypothesis [NB: Dr. Grimsrud later stated that the study will be used for a general evaluation of mortality and cancer incidence as well as more specific investigations depending on available information, earlier reports and findings in the present study.]
- It is not clear how the study will make use of the exposure assessment information and how accurate the exposure estimates will be [NB: see also comment on Dr. Bråtveit's report from the exposure assessment study, p. 17]

Comment from the panel:

It is important to obtain additional information on changes in exposures over time and which jobs were present on different offshore installations. It was suggested to obtain a complete work history and make visits to installations to find out what exposure measurements represent. [NB: Dr. Grimsrud's comment on information available as scanned pictures.]

## **5. PANEL DISCUSSION AND QUESTIONS FROM PARTICIPANTS**

The main objective of the panel discussion was to elaborate on methods for retrospective exposure assessment in the offshore industry and to discuss prospects and needs for studies in the offshore industry. Since no specific study has been initiated for this purpose, the organizing committee organized the discussion around five different agents (i.e. oil mist/oil vapor, benzene, oil (dermal exposure), hydrogen sulphide, and mercury), which are common in the offshore industry, but also have a variable amount of measurement data available. The experts were then asked to comment on the prospects of methods that could be used for future studies involving these agents. The objective of mentioning specific agents was to guide the discussion into areas of quality of data, amount of data available and relevance of studying various agents. The presentations from the University of Bergen exposure assessment project and the prospective cancer cohort study from the Cancer Registry of Norway served as a starting point for the panel discussion. To supplement the information given by Dr. Bråtveit on exposure assessment in the Norwegian offshore industry, Dr. Jorunn Kirkeleit, University of Bergen, briefly presented work on benzene exposure in the Norwegian offshore industry.

After the panel discussion the floor was opened for discussion to provide an opportunity for the participants to ask questions to the international and national speakers at the seminar. A variety of issues were raised. The fact that the participants addressed different topics related to exposure assessment and studies in the Norwegian Petroleum Industry with international experts reinforced the significance of this seminar.

Dr. Wijnand Eduard served as moderator. The thoughts and ideas of speakers and participants expressed in the discussion following the presentations were recorded on videotape to assist in the preparation of this report.

The following central themes emerged during the discussion are summarized:

## **Clearly defined research questions/hypotheses must be defined.**

The expert panel had the following comments:

- The industry needs to set up a prioritized list of agents and outcomes. This has to be done on the basis of exposure info and what is known about the hazards or risks potentially associated with these exposures. If risk assessment cannot be done on the basis of available data, or if there is knowledge gaps in the literature new studies are warranted. From the prioritized list hypotheses can be generated and exposure studies that meet the needs of these hypotheses can be designed.
- Many carcinogenic agents evaluated in the study from the University of Bergen (e.g. asbestos) are probably not needed to study in new epidemiologic studies. There are sufficient scientific data already published in the international literature on several agents present in the offshore industry to evaluate health risks there now. New epidemiologic studies in the offshore industry are not always likely to contribute to new insights in risks which are better than those that can be obtained on the basis of above described risk assessments approaches. These agents should, however, be included in exposure assessments.
- Agents, which are not specific to the offshore industry, e.g. isocyanates, may be studied better in other industries (e.g. paint sprayers) where the exposure is extensive. Drilling fluid may be interesting to study as it is specific to the offshore industry.
- New studies in this industry need to consider the effect of confounding by less well-characterized factors, e.g. the influence of shift schedule.

## **Suggestions for hypothesis generation**

It was suggested by the panel experts to carry out a pilot project (1-2 years) where all existing data sources are evaluated. Specific attention should be given to 1) what is available, and 2) what is the quality of data. This phase is needed to avoid carrying out studies that will not provide useful answers. A serious error that must be avoided is that poorly designed studies may fail to detect existing health risks. Included in this should be developing a comprehensive and detailed understanding of the processes, the tasks, and the exposures of workers.



Examples of data sources<sup>11</sup>:

1) *Work history and job descriptions*

Employment personnel records and job descriptions are useful sources for reconstructing workers' past exposures throughout their periods of employment. These records provide the principal link between workplace environmental data and workers' exposure experience.

2) *Measurement data*

All available measurement data on exposures of interest in the Norwegian offshore industry (e.g. industry, EXPO<sup>12</sup>) must be evaluated for completeness with regard coverage of specific environments and jobs, and time periods. Furthermore, the quality of the available exposure data must be evaluated. A large proportion of the data are stationary measurements. All data must be evaluated although personal measurements are preferred when assessing exposure. Stationary measurements may be useful for evaluating determinants of exposure. One limitation, which should be acknowledged, is that stationary measurements are sometimes derived from monitors designed for safety surveillance e.g. leaks or taken to evaluate engineering control, and thus, such measurements may not be representative of personal exposure. People move around and may be in closer contact with sources of exposure as they work. To evaluate the quality of stationary measurements it may be useful to send out questionnaires to rig owners on the sampling strategy and recorded determinants from stationary measurements. An analysis of any determinant information should be done to estimate effects of various determinants on exposure level. A large number of measurements of mercury in urine were identified in the EXPO register. It may be possible to identify jobs of the individuals from whom the mercury samples were collected. The information on the jobs could be used in an exposure assessment e.g., by grouping the measurements in tertiles to see if any jobs dominate in these groups.

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<sup>11</sup> See also: Checkoway, Pearce and Kriebel: *Research Methods in Occupational Epidemiology*, 2nd ed, Vol. 34, Oxford University Press, 2004

<sup>12</sup> EXPO: database at the National Institute of Occupational Health (NIOH) where all samples which are analyzed at NIOH are stored.

3) *Disease data*

Disease data, including case data, need to be systemized to evaluate if there are real differences in health outcome between offshore workers and the general population. This may also provide information on the appropriate study design for different diseases. Questionnaires are often filled out when acutely ill patients are admitted to hospitals or medical facilities. Such information may be used to identify possible causal factors, and generate hypotheses. Small pilot studies could then be designed. For example, suggestions were made for health effects from exposure to hydrogen sulphide gas. A crude measure of exposure could be evaluated, e.g. are there differences in health effects between workers who have worked in fields with low and high sulphur content in the crude oil? However, using a crude metric such as this could result in not finding an association if it exists, due to grouping of high and low exposed subjects in the same exposure category.

Note: Health outcomes from some agents that have been measured may be difficult to measure in an epidemiological cohort study, e.g. the relatively subtle effects from mercury exposure.

4) *Literature data*

A review of published evidence on health risks of various agents in the offshore industry should be compiled. It should be evaluated if risks are related to exposures from remote past or from exposures that are still present today in the industry.

### **Comments related to study design for future studies in the offshore industry**

- The choice of the study design should be based on type of health effect (rare or frequent disease; long or short latency time etc.).
- Detailed exposure assessment is required in all study designs.
- To address health risk in the offshore industry it may be preferable to initiate studies with participation from several countries. A larger number of study subjects than those available in the Norwegian offshore industry will increase study power. This is necessary to accurately evaluate the risk, especially for less common diseases. The availability of measurement data may also increase.
- If many case-control studies are likely to be initiated in this industry the resources needed for exposure assessment will not be much less than for a full exposure assessment of the complete cohort.

### **Comments related to the quality of measurement data**

- Possible sources of error in the exposure measurements should be evaluated and characteristics of these sources of errors should be specified:
  - o Analytical method
  - o Sampling method
  - o Stationary sampling
  - o Sample duration (e.g. short term vs. 8 hrs samples)
  - o Sampling strategy (e.g. representative, task-specific, worst case)
  - o Reason for sampling (e.g. research, compliance testing)
  - o Information on determinants

These concerns were raised for oil mist and oil vapor measurements that have been collected, but will also be relevant for other agents. Different sampling and analysis methods have been applied from the early 1970s. In the earliest period when diesel oil was used in the drilling fluids, only the vapor phase was collected on charcoal tubes. Sampling time may have been up to 8 hours. For drilling fluids containing mineral oils sampling was performed using cassettes with glass fiber filters to collect the oil mist only. Since about 1992 the sampling method was modified to collect both mineral oil mist and vapor using a cassette with glass fiber filter followed by charcoal tube. To minimize evaporation from the filter and thus

underestimating the aerosol phase, a sampling time of maximum of 2 hours was recommended for both the filter method and the combined filter/tube method.

Other comments:

- The data on oil mist and vapor measurements that were collected by the University of Bergen had scarce information on determinants of exposure.
- It is very important to collect relevant good quality contextual data (i.e. determinants) along with any measurements. This should be stressed in any future measurement programme.
- One comment was made on the passive sampler used for sampling benzene. The 3M 3500 badge has major limitations due to humidity and temperature and this may be of concern in the offshore industry. In addition, no information on peak exposure is obtained. The latter is a problem with many of the sampling methods that are currently in use.

#### **Comments and questions from the participants**

- It is important to state in the Petroleum Safety Authority pilot project 'Historical exposure and potential health risks' what questions can be answered, how these questions can be answered, and what are the costs. It is also important to address the impact of the media on the agenda.
- To increase access to exposure data it was suggested to establish a central exposure registry that can be used by occupational health departments and other certified individuals or organizations.
- It was recommended that the company industrial hygienists design monitoring reports that include information on determinants of exposure.
- It is not clear if companies have collected enough information to understand their exposures in order to manage their health surveillance.
- Effects of shift length on health needs to be evaluated.
- Much information is available from qualitative risk assessments and chemicals used in drilling the wells in the companies.
- Complete lists of persons transported by helicopter to the oil platforms are available from 1983. These lists do also include information on the department in which the employees worked.

- It was pointed out that Norway follows the EU regulations on chemicals. In the future the industry has to provide risk evaluations according to the REACH scheme.
- One former offshore worker presented his personal experiences as an offshore worker including information on health effects that have been identified in a group of former offshore workers. He stated that they shared common symptoms, which may point at a common cause.
- The expert panel was asked to comment on how to proceed with exposure evaluations of patients from the offshore industry exposed to a complex mixture of known and unknown agents. The following comments were given:
  1. Epidemiologic studies can identify occupationally related diseases. However, the available exposure information suggests that the exposure levels are lower than those associated with the substantial risks identified in the literature.
  2. Epidemiology is frustrating because it takes so long time to complete studies. However, if we do not do a good job we may risk reaching erroneous conclusions, i.e., in most cases not finding relationships even when the exposure represents a health risk. Good data are vital for future evaluations of health risk. Epidemiologic studies will not protect previously exposed workers, but may prevent future disease.

Diseases with excess risks compared to the general populations may also help to evaluate if a disease is related to occupation. See also paragraph on Suggestions for hypothesis generation.
  3. The industry was recommended to conduct a complete exposure assessment of all workers, all agents, and all jobs. This will give important information that can be used to reduce the risk for current and future adverse health effects and can serve as a starting point for future epidemiologic studies.

## **6. CONCLUSIONS AND RECOMMENDATIONS**

The following points represent a summary of central themes that emerged throughout the seminar from invited speakers as well as other participants. No substantial disagreements were encountered during the discussions. However, the points are not intended to represent a consensus among experts and participants.

1. The industry was challenged to do a complete exposure assessment of all workers, all agents, and all jobs. Exposure information can especially be used to perform risk assessments in combination with information from the literature and form a basis for current and future epidemiologic studies.
2. The suggested exposure evaluation of the industry may provide a basis for medical evaluation of individual patients from the oil industry, i.e. for establishing a relationship between work in the industry and work related illnesses.
3. A literature review of agents and health risks relevant to the oil industry was recommended.
4. Epidemiologic studies should be initiated only when clear research questions have been formulated.
5. Focused (historical) exposure assessment studies should be conducted that is tailored to the research questions/hypotheses.

## APPENDICES

### Appendix A. Seminar agenda

#### SEMINAR ON HISTORICAL EXPOSURE ASSESSMENT IN THE NORWEGIAN OFFSHORE INDUSTRY

March 21 2007, Norwegian Petroleum Safety Authority, Stavanger, Norway

#### PROGRAM OUTLINE

Chair: Research Director Dr. Pål Molander, National Institute of Occupational Health, Norway

Registration and coffee/tea: 8:15 am-9:00 am

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09:00-09:10	Welcome and introduction to seminar	Bjarne Håkon Hansen, Minister of Labor and Inclusion Dr. Pål Molander, National Institute of Occupational Health
<b>Session 1:</b>		
09:10-09:25	Description of the Norwegian offshore industry	Janne Lea Svensson, Petroleum Safety Authority Norway
09:25-10:05	The Challenges of Exposure Assessment	Dr. Patricia A. Stewart, US
10:05-10:45	Benefits of modern quantitative exposure assessment approaches in occupational epidemiology	Prof. Dick Heederik, University of Utrecht, NL
10:45-11:10	Coffee/tea break	
11:10-11:50	Assessment of dermal and inhalation exposure for an epidemiological study in the offshore oil industry	Dr. John Cherrie, Institute of Occupational Medicine, UK
11:50-12:30	Exposure Assessment for the Health Watch Case-Control Study	Dr. Deborah C. Glass, Monash University, AU
12:30-13:30	Lunch	
<b>Session 2:</b>		
13:30-14:00	Overview of exposure assessment project in the Norwegian offshore industry– carcinogenic agents	Dr. Magne Bråtveit, University of Bergen, Norway
14:00-14:30	Presentation of the Norwegian offshore cohort	Dr. Tom K. Grimsrud, Cancer Registry of Norway
14:30-15:00	Coffee/tea break	
15:00-16:30	Round table discussion on methods, and needs and prospects in the development of activities on exposure assessment in the Norwegian offshore industry	<i>Contributors:</i> Patricia A. Stewart; Dick Heederik, Deborah C. Glass, John Cherrie, Magne Bråtveit, Tom K. Grimsrud. <i>Moderator:</i> Wijnand Eduard
16:30-17:00	Summary, closing	Dr. Pål Molander m.fl.

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## **Appendix B. Speaker biographies**

### **Patricia A. Stewart**

Dr. Stewart has substantial experience in assessing chemical exposures in the workplace. After receiving her masters' degree in industrial hygiene, she worked for the US Occupational Safety and Health Administration as a compliance officer and then moved to the national office as a technical resource person. In 1982 she went to the National Cancer Institute (NCI), where she assessed occupational exposures for epidemiologic studies. She received her doctoral degree in 1994 from Johns Hopkins University. In her 24 years at the NCI, she worked on numerous cohort studies, including seven that had over 10,000 study subjects, and assessed exposures of formaldehyde, acrylonitrile, solvents, and diesel exhaust, and other agents. She also assessed exposures to solvents, metals, exhausts, polychlorinated biphenyls, and a number of other agents for 25 case-control studies. Her particular interest at NCI was improving exposure assessment in epidemiologic studies. One of her contributions in this area was developing over 100 job and industry-based questionnaires addressing tasks, exposures, and the work environment for use in population-based case-control studies. She recently retired from NCI, but is still working part-time on on-going NCI studies. Over her career she visited over 300 work sites and has taken thousands of measurements.

Dr. Stewart has served on the organizing or technical committees of four international conferences on exposure assessment and three working groups developing monographs for the International Agency for Research on Cancer (IARC). She has been a reviewer for most of the major occupational health journals. She has published over 130 peer-reviewed papers.



## Dick Heederik

EDUCATION/TRAINING			
INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University Wageningen	MSc	1984	Environm sciences (obtained <i>cum laude</i> )
University Wageningen	PhD	1990	Environm and Occup Health

### Tenure positions

- From January 1st 1984 Faculty place at the Wageningen Agricultural University at the Departments of Epidemiology and Public Health (former Department of Environmental and Tropical Hygiene) and Air Pollution.
- Since January 1st 1993 an Associate Professorship of Occupational Epidemiology has been obtained at the Department of Environmental Sciences, Environmental and Occupational Health Group, Wageningen Univerity and Research Center.
- Since January 1st 2000 Associate Professor at the University of Utrecht, Institute for Risk Assessment Sciences, Division of Environmental and Occupational Health, head of the Work and Health section.
- Appointment as Professor of Occupational Health Risk Analysis from January 1st 2003 at the University of Utrecht, Institute for Risk Assessment Sciences, Division of Environmental and Occupational Health with a cross appointment at the TNO Institute for Applied Research, Department on Chemical Exposure Assessment.
- Head of the Division of Environmental Epidemiology at IRAS Utrecht University from January 1<sup>st</sup> 2005.

### Awards

- Talent Stipend for young researchers from the Netherlands Organization for Scientific Research (1996) used for a one year exchange at the University of British Columbia, Vancouver, Canada.
- Burger penning from the Dutch Association for Occupational Medicine for outstanding epidemiological research on occupational allergies (1997).
- British Occupational Hygiene Society. Thomas Bedford Memorial Prize of a paper on exposure limits for sensitizers (Ann Occup Hyg 2002; 46: 439-446).

### **International experience**

- In 1987 a four-month research period was spent at the Institute of Occupational Medicine, Statistics Branch, Edinburgh, Scotland. Work on methods to correct for measurement error in the exposure in environmental epidemiological studies using linear regression models (LISREL)
- October 1991 - March 1992 research into exposure assessment for epidemiological purposes at the Epidemiology Branch of the Department of Respiratory Disease Studies at the National Institute for Occupational Health and Safety, Morgantown, USA, as a Visiting Scientist.
- January 1997 - December 1997 research into the relationships between exposure to high molecular weight sensitizers and occupational allergy in laboratory animal workers and bakery workers at the Occupational Hygiene Programme, University British Columbia, Vancouver, Canada, supported by a 'Talent' stipend from the Netherlands Organization for Scientific Research (N.W.O.).

### **Output**

(co) author of more than 180 peer reviewed papers on exposure assessment, and the epidemiology of occupational asthma, reproductive outcomes and cancer.

## **John Cherrie**

John Cherrie is Research Director at the Institute of Occupational Medicine (IOM) in Edinburgh, Scotland and Honorary Reader in the Department of Environmental and Occupational Medicine at the University of Aberdeen. He has a wide range of research interests including exposure assessment for regulatory risk assessment, dermal exposure assessment, occupational epidemiology, inadvertent ingestion of chemicals and several other topics. He is currently co-editing the fourth edition of the book *Monitoring Health Hazards at Work*. John is also President-elect of the British Occupational Hygiene Society.

The IOM is a not for profit research and consulting organization based in Scotland, with three offices in England. It employs over 120 staff, mostly scientists and technicians with a small medical group. Typically IOM is involved with 20 to 30 research projects at any one time, covering risks from chemicals, environment and health, nanotechnology, human sciences and other topics.

Further information about our work can be obtained from our website [www.iom-world.org/](http://www.iom-world.org/)

Copies of all IOMs research reports can be obtained free of charge from our Online Library <http://www.iom-world.org/research/libraryentry.php> (registration required).

Contact John Cherrie at [john.cherrie@iom-world.org](mailto:john.cherrie@iom-world.org)

## **Deborah Glass**

Deborah Glass MA, Cert Ed, MSc, PhD Dip Occ Hyg, MAIOH COH graduated from Cambridge University and did a Masters in Occupational Health and Hygiene at Aston and then worked in industry as an occupational hygienist. She joined the Institute of Occupational Health, University of Birmingham as a consultant occupational hygienist, and became a lecturer in Occupational Hygiene in 1989 doing teaching, research and some survey work. She went to Australia in 1995 and worked on the Health Watch case-control study completing a PhD with Deakin University based on this work. She worked part time at Deakin University between 2002 and 2006, and looked after students doing the Post Graduate Diploma in Occupational Hygiene.

Deborah joined Monash University in 1998 and is currently employed as a Senior Research Fellow in the Monash Centre for Occupational and Environmental Health. Her main role is being a Chief Investigator on the Health Watch prospective cohort study of cancer and mortality, which was established in 1981 and the longest running occupational cohort in Australia. She has also undertaken a nested case control study of benzene exposure and leukaemia, using data from the Health Watch cohort, which found a higher risk of leukaemia at low exposure than had been found in previous studies. As a result of this work and in particular the high quality exposure assessment used in this study, she is collaborating with US and UK researchers in a pooled case control study of leukaemia in the petroleum industry with Exxon-Mobil Biomedical Services Inc., Imperial College and the University of Pittsburgh, funded by CONCAWE.

Deborah has also been involved with several other occupational and environmental health studies including the Australian Gulf War veterans' study. She has carried out exposure assessment in a prostate cancer study and a study of childhood acute lymphatic leukaemia. She also has interests in air pollutants and is collaborating with the CSIRO Climate Research Group in a study modelling exposure to air toxics in Melbourne and was involved in a study of non-occupational benzene, toluene, ethyl benzene and xylene exposure in the general community.

Deborah is a Member of the ACGIH TLV committee. She is a member of the Australian Institute of Occupational Hygienists (AIOH), was on AIOH Council, is a member of the

Continuing Education subcommittee and is chair of the Education committee. She is a member of BOHS, and Australasian Epidemiological Association. She was a member of the Scientific Advisory Committee for the Deseal-Reseal Health Study of aircraft maintenance workers.

She has been on several national and international conference committees, reviews papers and has been an invited speaker at international conferences. She was Highly Commended in the 2005 Victorian Public Health awards for the Health Watch case control study. She was part of the winning team for the Gulf War Veterans study in the same awards. She has over 30 peer reviewed papers and in addition more than 75 other publications including reports and published abstracts.

### *Monash University*

Monash is a dynamic and internationally recognised university with a long established tradition in providing excellence in education. It is highly regarded for its innovative approach to teaching, research and learning and our graduates are sought after by employers from Australia and overseas. Monash is one of the prestigious Group of Eight universities which are Australia's leading research institutions.

The university is home to 95 research centres and is involved with 17 cooperative research centres. In addition, Monash has research links with more than 110 institutions throughout the world. Monash has built a strong international reputation in research especially in fields such as stem cell science, nanotechnology, reproductive biology, drug development and discovery and road safety.

The Monash community includes more than 54,000 students from over 130 countries, over 6,000 full-time staff and an extensive network of 190,000 alumni.

Monash has 8 campuses, six in Australia, one in Malaysia and one in South Africa, as well as centres in London, UK and Prato, Italy.

*The Department of Epidemiology and Preventive Medicine (DEPM)*

DEPM was established in 1969 at the Monash University Medical School - Alfred Hospital. DEPM plays a prominent role in public health medicine in Australia. The core skills of the department relate to epidemiology (the study of the distribution, risk factors and causes of disease) and its application to problems in clinical medicine and public health.

*Monash Centre for Occupational and Environmental Health (MonCOEH)*

Formed over 10 years ago, MonCOEH has grown rapidly, and now employs approximately 30 research, professional, teaching and administrative staff. Formerly a Unit located within the DEPM, MonCOEH was conferred Centre status in August 2005, in recognition of its active research, teaching and advisory programs in occupational and environmental health. Malcolm Sim is Professor and Director of MonCOEH.

MonCOEH's research interests span aetiological studies in industry groups to identify occupational risk factors for disease, veteran and military health research, occupational disease surveillance, exposure assessment and environmental health hazards and risk assessment. Funding comes from industry and government bodies, and our research involves collaboration with national and international partners. The Australian Centre for Human Health Risk Assessment, (ACHHRA), headed by Prof Brian Priestly, is closely affiliated with MonCOEH.

MonCOEH coordinates several postgraduate programs in the area of occupational and environmental health, all of which are suitable for part or full time study. Senior Centre staff supervise several PhD students, researching projects in occupational and environmental health across industry. The Centre also tailors short courses in occupational and environmental epidemiology for government and professional bodies.

## **Magne Bråtveit**

Dr. Bråtveit has worked at the Section for Occupational Medicine since 1996. His main area of research is within occupational exposure assessment. He has been involved in research projects in different workplaces such as car repair shops, zinc production, cement industry and mining. Some of this research takes place in developing countries through a project on respiratory problems among workers in dusty industries. The last 5 years he has worked on projects related to occupational exposure to benzene, other carcinogens and mineral oil in the offshore petroleum industry.

Section for Occupational Medicine is a part of the Medical Faculty at the University of Bergen. We work in multidisciplinary groups and have gathered experience from a broad range of projects focusing on both traditional and modern work life problems. In addition to the previously mentioned research the Section runs projects within various areas such as maritime and naval health and safety, hairdressers work environment and indoor climate and health. We have annual courses for medical students, and since 1998 we have in cooperation with Centre for International Health offered a Master Programme in Occupational Hygiene.

## **Tom K. Grimsrud**

Dr. Grimsrud is a medical doctor, and a specialist in occupational medicine, PhD with an epidemiological thesis on nickel-related lung cancer (University of Oslo, 2004).

He is a researcher at the Cancer Registry of Norway, Department for Etiological Research, worked with occupational cancer, cancer incidence in municipalities, smoking habits and cancer. He is a coordinator for the Janus Serum Bank (a biobank with serum samples from 330 thousand Norwegian men and women collected since 1973).

## **Appendix C. Background information provided for the international experts**

- Papers published by the University of Bergen (1-5).
  - Short presentation of prospective cohort established by the Cancer Registry of Norway.
  - List of agents
  - Preliminary list of diagnoses from patients from the offshore industry
  - List of health effects mentioned in media
- 
- (1) Kirkeleit J, Riise T, Bratveit M, Pekari K, Mikkola J, Moen BE. Biological monitoring of benzene exposure during maintenance work in crude oil cargo tanks. *Chem Biol Interact* 2006 Dec 1;164(1-2):60-7.
  - (2) Kirkeleit J, Ulvestad E, Riise T, Bratveit M, Moen BE. Acute suppression of serum IgM and IgA in tank workers exposed to benzene. *Scand J Immunol* 2006 Dec;64(6):690-8.
  - (3) Kirkeleit J, Riise T, Bratveit M, Moen BE. Benzene exposure on a crude oil production vessel. *Ann Occup Hyg* 2006 Mar;50(2):123-9.
  - (4) Steinsvag K, Bratveit M, Moen BE. Exposure to oil mist and oil vapour during offshore drilling in Norway, 1979-2004. *Ann Occup Hyg* 2006 Mar;50(2):109-22.
  - (5) Steinsvag K, Bratveit M, Moen BE. Exposure to carcinogens for defined job categories in Norway's offshore petroleum industry, 1970-2005. *Occup Environ Med* 2006 Oct 16.



## Appendix D. Abstracts

### “The Challenges of Exposure Assessment”

Dr. Patricia Stewart, Stewart Exposure Assessments, LLC

The importance of exposure assessment in occupational epidemiologic studies cannot be overstated. Exposure assessment is just one of the criteria that establish causality, but it can have a significant effect on the results of the study. It is, therefore, important to develop valid and reliable estimates, because poor estimation of exposure can result in over- or underestimating disease risks, as well as possibly missing an association. Poor exposure assessment can also affect the credibility of the study.

There are several components of exposure assessment. The first is identification of the hazard. Although this step seems to be straightforward, it may not be, because of the lack of information on the agent causing the disease or because of the presence of an agent that is actually a mixture containing several toxic agents (e.g., oil mist). In addition, agents can act synergistically, so that ignoring one agent that is important in a synergistic relationship could result in missing an association. Recommendations for offshore oil studies include evaluating agents based on statistical power, rather than on toxicity; evaluating exposure to individual agents (e.g., polycyclic aromatic hydrocarbons) within mixtures, particularly where the specific agent occurs in multiple mixtures across the rig; and analyzing possible synergistic effects of multiple agents using cluster analyses.

The second component is selection of an exposure metric. Historically, full-shift estimates have been the primary metric developed due to their assumed relationship to chronic disease and to investigators' familiarity of this metric from evaluating compliance situations. This metric, however, may not be the most appropriate one, and estimating only it could result in missing an association. Other metrics that could be of toxicologic importance include the average intensity during exposed periods, peaks, ceilings, and various locations on the distribution, such as the 90<sup>th</sup> percentile. Dermal, and possibly ingestion, hazards may also have toxicologic relevance. Because the offshore oil employees work 12-hour shifts and several tasks employees perform (e.g., tank cleaning) require strenuous work, recovery time and physical activity could be important. A criticism of examining multiple metrics is that such an examination can be used as a “fishing expedition.” However, investigators can identify one or two metrics *a priori*, which then should be the basis of the primary

interpretation of the study results. Presenting results of other metrics can provide useful information that can be explored in future investigations. Recommendations for offshore oil studies include looking at other metrics besides full-shift averages (e.g., for benzene and oil mist; for benzene, dermal exposure; for tetrachloroethylene, peaks; and for lead and chromium, ingestion) and incorporating recovery time and level of physical activity. The importance of forming appropriate exposure groups is often overlooked. The goal of developing exposure groups is to have small within group variability and large between group variability. The best way to do this is to keep the groups as precise as possible at this stage of the process (preferably job title) and combining jobs later in the estimation and/or analytic states later. The precision with which the jobs are grouped is dependent, however, on the level of detail in the work histories and the monitoring data. If they only provide general information, being more precise may be difficult. In any case, by keeping the original exposure groups as precise as possible, grouping can be done during the estimation process whenever a new agent is being evaluated, whether that is at the time of the grouping or many years later.

Exposure groups should be based on the same general exposure profile with the same approximate mean and distribution under the same exposure scenario for the agent and metric being assessed. To do this, a comprehensive and well-documented understanding is needed of the exposure determinants of the jobs, for example, tasks, their frequency and duration, the location, engineering controls and protective equipment, source of the agents, processes, dates of changes, etc. (Stewart et al., 1992). In the past this was done by casual observation; however, now that we understand the concept of exposure determinants, the evaluation can be formalized and made rigorous to ensure appropriate grouping. Task has often been found to be a significant source of variability (e.g., see Kirkeleit et al., 2006). The criteria to group, then, should not be based simply on job title, but also on task, or task and other determinants. For example, in a study of acrylonitrile workers, we found differences in locations of people with the same job title resulted in substantially different exposures for these workers (Stewart et al., 1998). The criteria of having the same profile, mean, distribution, and exposure scenario may result in an exposure group for each agent and each metric being evaluated, because oftentimes different agents/metrics are affected by different determinants or the same determinants differently. Recommendations for offshore oil studies include: formally identifying exposure determinants and assessing each job title/department/rig for these determinants; reviewing previously developed job groups based on determinants; and

developing new groups, keeping them as precise as possible based on similarity of determinants for each agent, each metric and exposure scenario.

The next step in the assessment process is to estimate exposure levels. In cohort studies, due to the lack of individual-specific measurements, we assume that all individuals with the same job title have the same exposure level. We use a job exposure matrix approach, where all individuals with the same job title for the same year are assigned the same exposure level. An estimate needs to be developed then for each job/year period. First, for efficiency, exposure time periods should be developed based on changes in determinants (indicated in the job profiles) and they may be different for different agents. The next step is the actual estimation. The technique selected for the exposure assessment depends on the number of measurements (there may not be enough to develop quantitative estimates), characteristics of the monitoring data and the work histories (lack of detail in either may require further grouping of jobs) and analytic considerations. The estimates can be qualitative, semi-quantitative (e.g., low, medium, high), or quantitative.

Semi-quantitative estimates have several disadvantages. First, they assume that every job within the same exposure category has the same exposure level, which can result in misclassification, because in actuality there can be large differences in exposure levels within the same category. Semi-quantitative estimates require the development of weights for exposure metrics such as cumulative or average exposure, because subjects usually have jobs with more than one exposure level that results in their being in more than one exposure category over their employment. Semi-quantitative estimates decrease comparability across studies because “low” may mean different levels in different studies. Moreover, investigation of the disease mechanism must, by necessity, be relative unsophisticated. There are, however, times when such estimates are necessary: when measurement data are insufficient for quantitative estimates; when published data are being used; and when predicting exposure levels by estimating the effect of determinants to modify exposure levels of a measured job or task.

Recommendations for the offshore oil studies include: using published measurement data of well documented tasks to estimate differences among determinants or jobs (e.g., brush vs. spray painting); using other determinant information with measurement data to predict exposures in unmeasured situations (e.g., vapor pressure to estimate the exposure of an agent in a mixture containing another measured agent; the percentage of benzene in a mixture in one measured situation to estimate the same situation with a different amount of benzene; and

using semi-quantitative estimates for dermal exposure. Identifying the range of the exposure levels for each of the exposure categories is also recommended.

Quantitative estimates are the most appropriate type of exposure estimates for epidemiologic studies for several reasons. First, developing quantitative estimates forces the industrial hygienist to think carefully about the exposure situation in terms of a familiar measurement scale. Also, it has been suggested that the high disease risks, such as was seen with asbestos, are not likely to be found now; thus, the likely higher degree of misclassification that is found with semi-quantitative estimates could result in missing associations. Also, quantitative estimates can be used for evaluation of exposure-response relationships, investigation of disease mechanisms, and risk assessment. These types of estimates also allow comparability across studies.

One concern often cited about measurements is that they are compliance oriented and therefore “worst case”. Although this may be true, oftentimes “worst case” means the highest exposed jobs are measured, rather than the highest exposure level. Also, it has been found that “worst case” situations are difficult to predict or identify on a casual basis. Some studies have compared compliance data to data thought to be representative of average exposure levels and have found the compliance data to be higher than the representative data, whereas others have not. This contradiction may be a function of the timing of the measurement (with reference to newly enacted standards), the agent or population under study, or random variation. Other issues regarding measurement data are that most epidemiologic studies do not have sufficient measurement data for all exposure groups; even when exposure groups have been measured often there is only a small number of measurements available so that the representativeness of the data is questionable; and the measurements may cover unusual situations at a frequency disproportional to the occurrence of the situations or they may be evaluations of process controls, be of short duration or represent area concentrations, rather than personal exposures. All of these situations limit the usefulness of the data, but do not necessarily mean that the data cannot be of some use.

Methods that can be used when measurements are sufficient include: calculation of means, developing statistical or deterministic models; using task measurements from one job weighted by time to estimate the exposure level of all job titles performing the task (a similar approach can be used with location); and using measurements (or estimates) from a parallel agent. Estimation methods used when measurements are sufficient will not be described here, as they are the subject of a later presentation.

When measurements are not sufficient, the precise exposure groups developed during the exposure group step may be collapsed into broader groups by relaxing the criteria of the grouping. For example, if the criterion for an estimate is based on five or more measurements, measurement means could be calculated for all jobs with five or more measurements. Jobs without five measurements could be grouped with other jobs based on similar exposure determinants. Any measurements associated with those jobs could be included in a calculation of a mean, along with measurements of any of the jobs in that same group with more than five measurements. A second estimation approach when the number of measurements is limited is to use measurements that describe, for example, exposure levels under certain conditions. As described for semi-quantitative estimates, information from published data on the effect of a determinant could be used to modify the exposure level experienced during the task under one condition to estimate the exposure under another condition. Finally, professional judgment could be used to estimate determinants without measurement data (published or otherwise) or to group jobs even further.

Where measurement data are not sufficient to use one approach across all jobs and all years, it may be appropriate to use several estimation methods to derive estimates. If this approach is taken, it is useful to identify a confidence level associated with each of the methods, so that the study subject holding jobs with less reliable estimates can be excluded from certain analyses. Such an approach was taken in a study of acrylonitrile workers. Four types of methods were used, because estimates based on measurement means could only be developed for less than 10% of the jobs (Stewart et al., 1998). A level of confidence was associated with each method. Analyses using all the estimates and using only the estimates of higher confidence resulted in the same exposure-response curve, which increased confidence in the results (Blair et al., 1998). Another approach to evaluating uncertainty is to conduct sensitivity analyses on various parameters used (e.g., the weights placed on differences between jobs or determinants). This approach was taken in the acrylonitrile study for estimating the effects of engineering controls. The best, the likeliest minimum and the likeliest maximum effect were used to develop three different sets of estimates. Because there was no difference in the exposure-response relationships using the three sets of estimates, the effect estimates were considered to be reasonable (Blair et al., 1998). Finally, the variability of exposures around the mean could be another approach to analyzing sensitivity.

Recommendations for developing quantitative estimates for offshore oil studies include relying on task measurements rather than job titles (e.g., benzene, see Kirkeleit et al., 2006);

using a hierarchy of methods, rather than a single method and identifying a level of confidence on the estimates; and evaluating uncertainty and sensitivity.

The last component of exposure assessment process is validation of the methods, i.e., evaluating the accuracy and the reliability of the estimates. This is of crucial importance for increasing the credibility of the study. Unfortunately, few studies have been able to conduct validation studies, primarily due to the lack of sufficient measurement data. It is rare that there are sufficient measurements for a particular job in a particular year to feel assured that a mean of those data represents the actual exposure level. For this reason, the term “validation” may imply a stricter referent than is actually the case. Because of the question of how representative the data are, a better term might be method evaluation. Approaches taken by others have included taking biological samples, reconstructing historical conditions, removing a subset of monitoring data and, for evaluating reliability, having multiple raters estimate the exposure levels, such as what was done for the evaluation of carcinogen exposures (Steinsvag et al., 2007). We took a different approach in our acrylonitrile study. Independent of the estimation step in the epidemiologic study, we applied our estimation methods to a variety of jobs that we knew had sufficient measurement data to meet our criterion of five measurements per job per time period. The estimates were developed, however, without using the measurement data. The estimates were then compared to the measurement data to determine how well the estimation process worked (Stewart et al., 2003). Because the effort was independent of the estimation process, the measurement data were then used in exposure assessment and we had information on how well the various estimation methods worked. Recommendations for offshore oil studies are that for agents with few measurement data, develop an estimation approach, use that same approach for jobs/tasks where measurement data are sufficient (e.g., for benzene and/or oil mist/vapor) and compare the estimates with the measurement data; conduct other reliability studies such as the one by Steinsvag et al., (2007), where sufficient measurement data do not exist; and use the results from these efforts to indicate confidence of estimation method.

Several practical considerations should be understood regarding exposure assessments. A careful, documented, and credible exposure assessment takes a substantial commitment in resources. We have generally spent seven person-years over more than a ten-year time period in our studies to complete the exposure assessment. A good assessment requires an industrial hygienist who has statistical expertise or resources. In addition, the industrial hygienist must be creative, organized, and persistent, have the courage to take new approaches, and have the ability to do often tedious and detailed work.

Documentation of the process and all decisions is crucial, particularly if there is any possibility of future studies that could include new investigators to the study. Coding, rather than entering free text, should also be done wherever possible to reduce review time and increase efficiency. Finally, relational databases should be used wherever possible to prevent the need to make multiple entries of the same data into multiple databases, thus reducing discrepancies, and therefore, error among the data bases.

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## **“Benefits of modern quantitative exposure assessment approaches in occupational epidemiology”**

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Quantitative assessment of historical exposure in both cohort and case-control studies is becoming the norm in occupational epidemiology. Accurate quantitative exposure assessment

and assignment are crucial for establishing exposure-response relations in epidemiology. The concepts for quantitative exposure assessment and a range of approaches have been developed over the last two decades. One of the major issues which need to be dealt with in exposure assessment is exposure variability. Exposure varies over time, between workers and between groups of workers. When one is interested in estimating long term exposure, especially variability over time may complicate the exposure assessment and can lead to underestimation of exposure response relationships. However, when the sources of variability are known, and determinants of exposure have been identified, accurate estimation of the exposure is possible and the effect of variability over time does not necessarily complicate exposure estimation. Different exposure estimation approaches are possible: on the individual level or for groups of workers. Exposure estimation on the individual levels is potentially the most accurate approach, however, when variability over time is large, the required measurement effort is large in order to avoid biases in the exposure response relationship. Exposure grouping strategies are more efficient, in terms of the required measurement effort, but at the expense of a reduced precision in the estimate of the exposure response relationship and thus also the power of a study to detect an association between exposure and response. A prerequisite for quantitative exposure assessment is the availability of exposure data. In retrospective studies the approach has been taken to collect data which has been sampled and combine the data in large databases. Detailed description of the exposure assessment strategy (compliance, worst case or random sampling), the sampling (dust fraction, fume, otherwise), the chemical analysis is required so that conversions can be applied to make the data comparable and useful. Worst case exposure measurements can be used as long as information is available about the frequency of occurrence of worst case situations. When data are available, a combined analysis can be undertaken to analyze relationships between exposure levels and determinants of exposure for the different agents for which data has been collected.

Some examples will be presented; exposure assessment components within large scale retrospective cohort studies on occupational exposure to bitumen and benzene and cancer risk. An important aspect of the application of the detailed quantitative exposure data is the application of advanced statistical analytical tools. When the exposure estimates are sufficiently refined, advanced statistical tools can be used to observe the shape of exposure response relationships. Smoothing approaches allow detailed evaluation of the shape of exposure response relationships and even exposure thresholds, levels below which no excess risk may be present.



New possibilities are created by molecular epidemiological approaches. Novel analytical techniques facilitate measurement of multiple biomarkers or markers of genetic susceptibility. Although application of biomarkers in many areas of occupational epidemiology is still limited, they are expected to find wider use. Biomarkers can, if chosen appropriately, contribute to the weight of evidence on exposure response relationships and can also give insight in the etiology of disease. A problem of many biomarkers in the relatively poor signal noise relationship: they vary strongly over time and as a result have little advantage over exposure measurements. However, some examples exist, like for benzene, where application of biomarkers gave new insight in potential effects at very low exposures, which are expected to be detectable only with great difficulty in cancer incidence or mortality studies.

In summary, quantitative exposure assessment becomes a more established approach. The methodology is well described in many examples. Application in new industries and for new exposures requires a careful consideration of the research questions and planning on the subsequent research approaches to be taken.

## **Assessment of dermal and inhalation exposure for an epidemiological study in the offshore oil industry**

Dr. John W Cherrie, Institute of Occupational Medicine, Edinburgh, UK.

### **1. Introduction**

Occupational skin disease is an important problem in most societies and this issue has been extensively discussed in the Norwegian media. For chemical exposure it is generally necessary to have repeated and fairly prolonged skin contact before there is any risk of skin disease. However, dermal exposure may also result in systemic uptake of chemicals through the skin, which adds to the contribution from inhaling the substance.

With the exception of specific activities such as pesticide use there have been very few routine measurements of dermal exposure made in industry. Consequently it is often unclear whether dermal exposure is truly an important contribution to aggregate exposure from all routes. Also, there is no scientific consensus about the most appropriate method for dermal

exposure measurement, which means that measurements made using different methodologies may be incompatible.

This paper addresses the importance of dermal exposure compared to inhalation exposure for organic solvents and other substances encountered in the offshore oil industry along with skin exposure to irritants and skin allergens, and whether skin contact is an important route exposure route that should be incorporated in epidemiological studies. Possible strategies for dermal and inhalation exposure assessment are discussed and some recommendations are made for exposure assessment in the planned epidemiological study in the Norwegian offshore oil industry.

## **2. When is dermal exposure important?**

Chemicals diffuse through the *stratum corneum* due to the concentration gradient between the skin contamination layer (SCL: is a mixture of sweat, sebum and other material on the skin) and the tissue around the peripheral blood supply. Most gases/vapours are not taken-up by the skin in any significant quantity as the concentration gradient is too low. One important exception is glycol ethers, where dermal vapour exposure may contribute almost as much to total body burden as inhalation.

Liquids are much more likely than either vapours or solids to permeate through the *stratum corneum*. For solids to pass through skin they must first dissolve into the SCL, although there is some suggestion that nanometer size particles can penetrate through the SCL intact. High molecular weight liquids (> 500 daltons) with an octanol-water partition coefficient less than about -1 or greater than 4, are unlikely to permeate through the skin. In most cases, without information about permeation characteristics of a substance in a mixture, it is generally prudent to assume that a low molecular weight liquid has the potential for skin uptake. The components in a liquid mixture are important and may increase or decrease the ability of a specific substance to pass through the skin. Finally, occlusion of the exposure site by clothing or personal protective equipment may increase absorption through the skin.

Some substances have the potential to cause dermatitis or allergic skin disease. For example, exposure to oil-based mud or some of its constituent chemicals has been shown to cause skin disease. Also, prolonged repeated contact with water or aqueous solutions/suspensions, or prolonged wearing of protective gloves can cause irritant contact dermatitis.

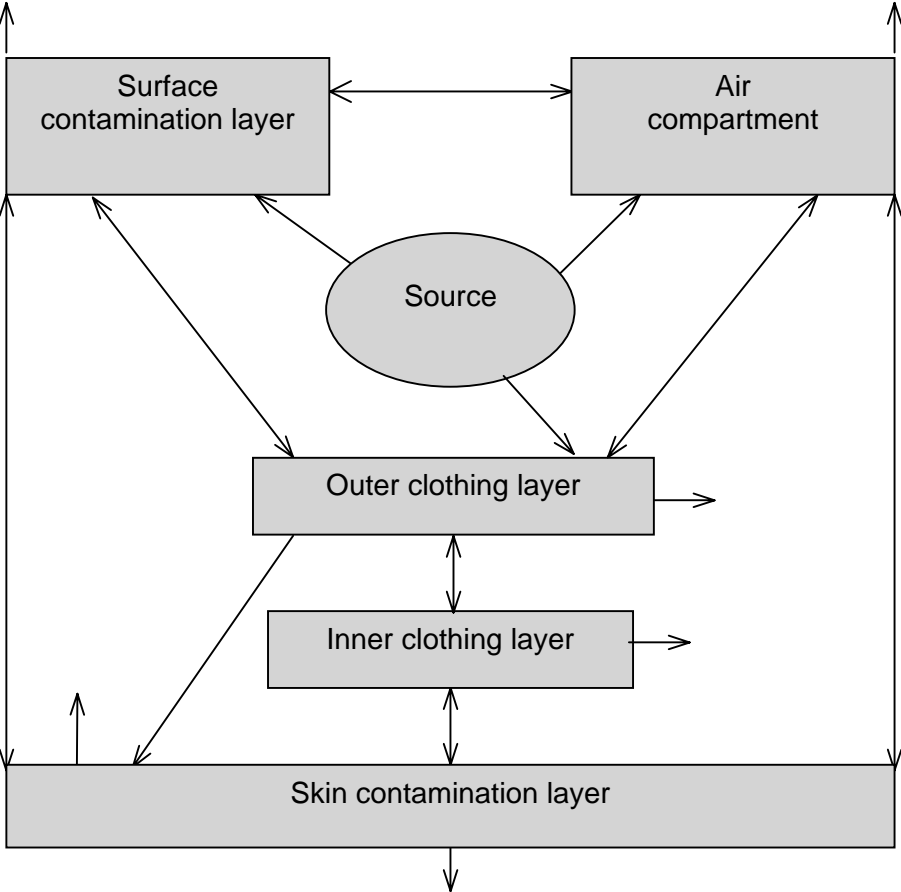
From the preliminary information provided it would appear that oil, oil-based drilling muds, glutaraldehyde, benzene and other solvents are hazards that could be taken up via the skin. It is not clear whether risks of local skin disease are relevant to the range of substances present offshore, although wet work and/or wearing impervious gloves could be implicated in causing this type of risk.

### 3. A conceptual model of dermal exposure

Schneider and colleagues have published a conceptual model of dermal exposure.

In this model dermal exposure is conceptualised according to a number of compartments and transfer routes (see Figure 1). Key transfer routes depend on the particular work situation, e.g. someone handling oil in a container may have direct splashes onto the SCL and the outer clothing contaminant layer from the source, along with direct contact of these layers with surfaces contaminated by oil. Use of the conceptual model can help in the analysis of the main routes and compartments of interest in relation to dermal exposure. There are currently attempts to extend the above conceptualization to inhalation exposure.

Figure 1 – A simplified vision of the Schneider et al dermal exposure model



The key information to be drawn from the conceptual model is the importance of the concentration of the hazardous substance in the SCL in determining uptake, along with the area of skin and the duration of exposure. The mass of contaminant in the SCL is of secondary importance in this respect.

Also, the model shows that the process by which people become exposed are complex, but in many situations surfaces within the work space and the air compartment will be the important determinants of exposure. Similarly, work clothing may provide protection against dermal exposure.

#### **4. Assessing skin exposure**

There are several methods that are used to measure dermal exposure and these can broadly be categorised as being based on:

- intercepting contaminants before they land in the SCL or on clothing;
- removal of contaminants from the SCL after exposure;
- *in situ* methods, which for example may use fluorescent tracer compounds as a surrogate for the substance to be assessed.

As with all measurements it is important that when the data are collected the investigator should obtain good descriptive information about the exposure context, including details of contact with contaminated surfaces, evidence of liquid splash or powder on surfaces, presence of large particles in the air which may impact on worker, clothing worn with a record of visible contamination, glove type, reuse of gloves etc.

The main interception method used is patch sampling, which typically involves an adsorbent patch of cotton cloth with an impermeable backing. These samplers are typically used to sample low volatility liquids e.g. oils or pesticides. Patches attached to the outside of clothing are said to assess *potential* exposure. Samples inside clothing are said to assess *actual* dermal exposure. Typically, several patches are worn simultaneously and an estimate of whole body exposure is obtained by extrapolation. An alternative interception method is the cotton “suit sampler”. Suit analysis gives a direct estimate of whole body contaminant mass landing on the SCL and/or clothing.

Lindsay *et al* (2005) have developed a prototype patch sampler to measure volatile liquids. The sampler is based on an activated charcoal adsorbent patch covered with a diffusion membrane and backed with an impervious layer. In this way it mimics the diffusion processes that dictates dermal uptake. Preliminary data from two field trials suggests that for volatile agents dermal uptake may not be very important compared to inhalation exposure. Plain activated charcoal patches can substantially overestimate the exposure on the skin of workers.

Skin stripping is a removal technique that can assess contaminant - it has been used for acrylates, jet fuel and metals that have started to permeate through the skin. Adhesive tapes are used to remove ('strip') sequential layers of *stratum corneum* and any contaminant residues present in the skin. These are then chemically analysed to obtain an estimate of the mass of substance in the *stratum corneum*.

The main removal techniques are: hand washing; hand rinsing and skin wiping. These techniques provide an estimate of the mass of contaminant substance in the SCL at a point in time.

Fluorescent tracer *in situ* dermal exposure assessments are highly specialised research tools. Small amounts of a fluorescent agent are added to the contaminant source.

After work the skin is imaged with UV light using a video-camera linked to a computer system to estimate tracer mass and so contaminant mass.

Cherrie *et al* (2007) have developed a novel method of assessing dermal exposure in relation to wet-working and irritant dermatitis. This method uses an electronic sensor to determine the wetness on the hand. It can be used to measure the total time the hand is wet and the number of times the hand is wet then dry. It is these exposure parameters that are probably most closely related to the risk of dermatitis rather than the total mass of water on the hand or the area of skin wet.

Biological monitoring can provide an indirect assessment of dermal exposure, but without inhalation exposure data and contextual information this type of measurement is of limited value. However, if dermal exposure is the only important route (e.g. pesticides), it can be helpful on its own.

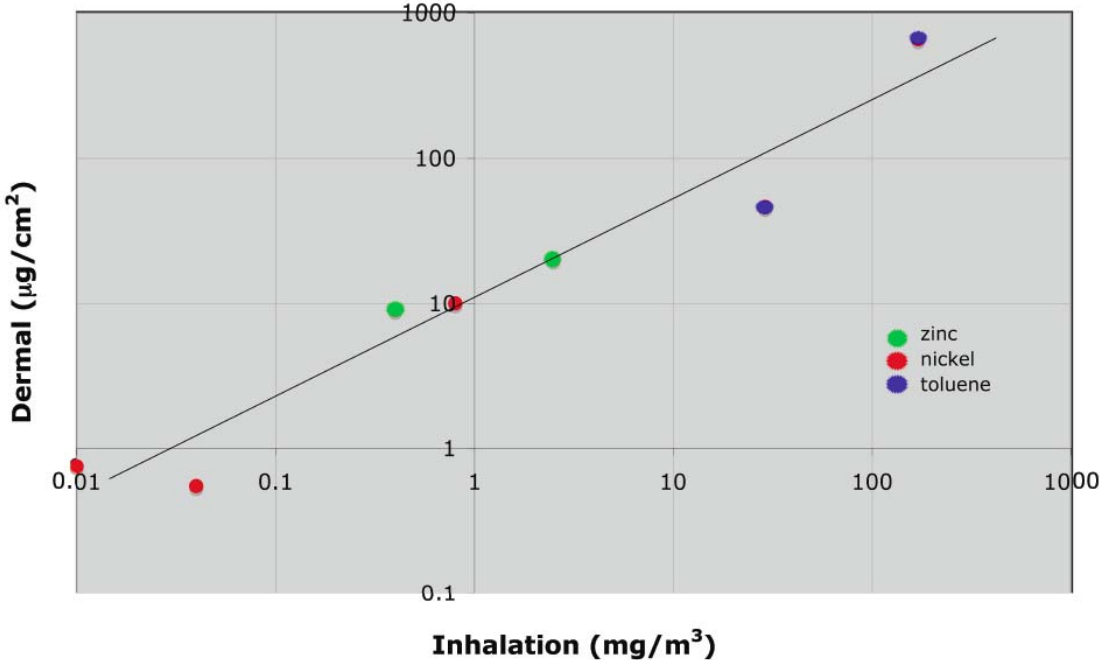
The best method for use in the Norwegian offshore industry will almost certainly depend on the substance to be assessed. A simple practical method of measuring low volatility substances may be skin wiping. For volatile agents the patch sampler described by Lindsay *et al* (2006) may offer some possibilities, although it is not available commercially. The wet-work sampler could be suitable to assess dermatitis risk.

### 5. Comparison of inhalation and dermal exposure measurements

There are very few cases where both inhalation and dermal exposures have been measured simultaneously in situations where there is potential exposure by both routes. We have completed a number of studies in metals manufacturing or processing industries. In these studies we have measured inhalable metal concentration and have used a skin wiping methodology to assess the dermal exposure, e.g. Hughson and Cherrie (2001) and Hughson (2005). We also have data from the IOM prototype dermal sampler for toluene (Lindsay *et al*, 2006). Alongside this sampler we collected inhalation exposure data using diffusion samplers.

Figure 2 shows the data for the average air and skin exposure for seven workplaces: two where toluene was used, two where zinc compounds were manufactured and three nickel workplaces.

Figure 2 – Average inhalation and dermal metal and toluene exposures



It is clear that there is a good correlation between both the inhalation and skin measures, despite the differences in the methodologies used, the workplaces and the agents monitored. It is quite possible that this is a coincidence, but it should be recognised that there are links between the air, surface and skin contamination layer in the conceptual model with contaminant being exchanged between each. Provided there is a reasonable level of exchange between these compartments there will be a correlation between inhalation and dermal exposure.

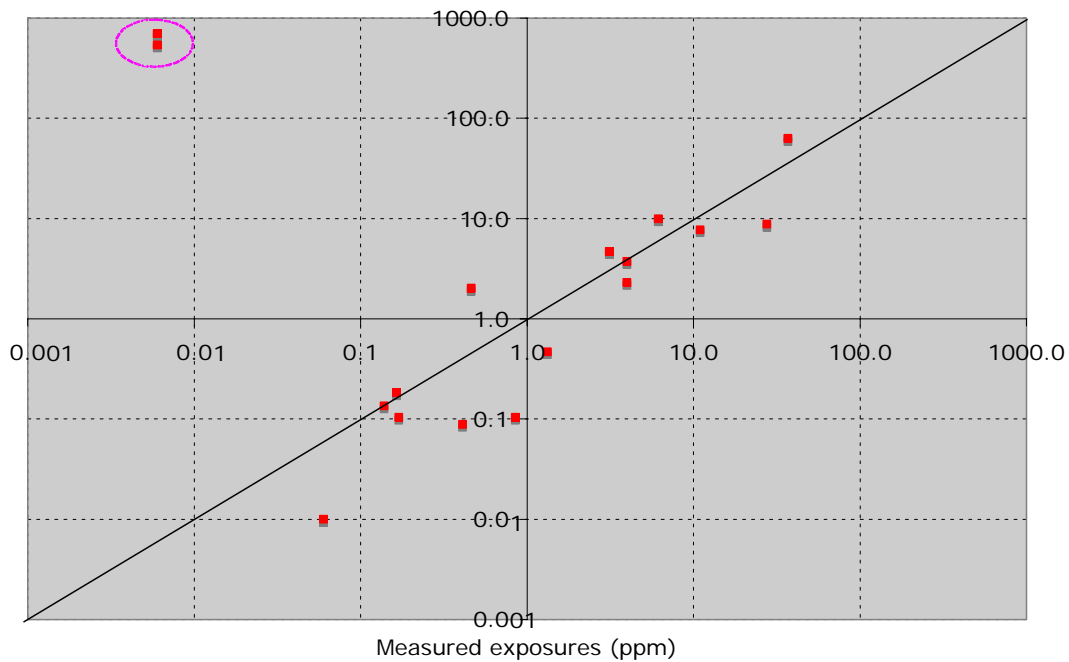
It is difficult to be sure about the necessity of measuring dermal exposure in addition to inhalation exposure for the epidemiological study. It is probably advantageous to try to collect some data about current exposure and identify whether inhalation and dermal exposures are correlated, and whether dermal exposures are important in relation to inhalation exposure.

## **6. Models and data**

There has traditionally been a strong reliance on objective measurements of exposure in epidemiological studies and in situations where there are copious amounts of data this has been a productive strategy. However, in some studies there are only limited data, perhaps only from recent times. In these cases investigators have sought to rely on exposure models sometimes in combination with measurements.

Cherrie and colleagues developed a simple model for estimating exposure for a study of workers in the man-made mineral fibre manufacturing industry, which has been further developed and validated (Cherrie *et al*; 1996, Cherrie and Schneider; 1999, Cherrie; 1999). The method has been applied in several other studies and has been validated in diverse situations such as very low aerosol exposures in pharmaceutical manufacture and high benzene exposure in developing countries. For example, Figure 3 shows data from a validation exercise carried out with benzene exposure in several industries.

Figure 3 – Validation studies of the Cherrie *et al* model for benzene exposure



These data were obtained by a single assessor who was presented with a written description for 17 scenarios without knowledge of the exposure measurements for each scenario. Exposure was assessed using the model and then the result was plotted against the average measured exposure. There is clearly a strong correlation between the measured and estimated values, with the exception of one pair of scenarios (top left of the graph) where the information from the written description was misleading. The correlation coefficient on the log-transformed scale for the data excluding these values was 0.92.

The model can provide reliable assessments of inhalation exposure. Use of measurement data can provide greater reassurance about the reliability by anchoring specific assessments.

### 7. Dermal exposure models and measurements

One would ideally wish to have a corresponding model for dermal exposure that could form the basis of estimates for the epidemiological study. Unfortunately, there are no models that can provide as reliable predictions and so some greater reliance on measurements in combination with a model will be required to give reliable reconstructions of past exposure.

The best candidate dermal exposure model for use in epidemiological studies is DREAM (van Wendel de Joode *et al*, 2002). This is a method for semi-quantitative dermal exposure



assessment based on a detailed questionnaire to characterise tasks and produce estimates of dermal exposure levels using the Schneider *et al* conceptual model as a framework. In an assessment of the accuracy of the DREAM model the correlation between measured and estimated exposures ranged from 0.19 to 0.82 (van Wendel de Joode *et al*, 2005). The authors concluded that DREAM could provide semi-quantitative estimates of exposure where there was a good contrast between groups included in a study.

This method could be used in combination with dermal exposure measurements to provide improved reliability of assessments.

There are no good models for dermal exposure to irritants in relation to dermatitis risks.

## **8. Discussion**

It is not possible to say *a priori* whether for an epidemiological study an assessment of dermal exposure to chemicals used in an industry is necessary or worthwhile. If there is an important correlation between inhalation and dermal exposure in specific jobs then it may not be possible to separate the effects of these two routes of exposure in the study analysis. Also, dermal exposure may not make an important contribution to aggregate exposure. Some initial investigation of these aspects would enable an informed decision to be made about what strategy might be best.

The DREAM model provides a structured approach to semi-quantitative dermal exposure assessment, which is based on a sound conceptual model. Combined with a limited amount of current measurement data it could provide a suitable tool for reconstruction of past dermal exposure. Combined with some current dermal exposure data the DREAM method could provide a more quantitative assessment.

Assessment of skin exposure in relation to dermatitis requires special consideration and may require a completely different approach to that used for chemicals giving rise to systemic risks.

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## **“Exposure assessment in the Petroleum industry”**

Dr. Deborah Glass, Monash University, AU

### *The Health Watch Cohort*

Health Watch is a prospective cohort study of employees in the Australian petroleum industry who have worked for more than 5 years. It compares the mortality and cancer incidence of the cohort with that of the Australian population. The cohort includes employees from

offices, upstream extraction and processing sites, refineries, terminals and airports all over Australia.

The cohort includes about 18,000 employees of which some 1,300 are women. Health Watch commenced in 1981, with an administered interview and this survey was repeated in 1986, 1991, 1996 and 1999. About 95% of eligible employees have participated.(1) At the surveys, subjects provided demographic details, health status information, smoking and alcohol data and details of their work history. Subjects were actively followed and regularly matched with the Australian national death and cancer registries. In addition cohort members are encouraged via periodic health letters to self report illness.

#### *Case-Control study*

A case-control study nested in Health Watch investigated whether the excess of lymphohematopoietic cancers, identified among male members of the Health Watch cohort, was associated with benzene exposure. The cases were identified by self report and by search of the state and national cancer registries. Cases of non-Hodgkin lymphoma (NHL) (n=31), multiple myeloma (MM) (n=15) and leukemia (n=33) were identified between 1981 and 1999. Cases were individually age-matched to 5 controls.(2) The upstream workers in the case control study included fitters (rig mechanic), benzene-exposed upstream operators (platform operator), some laboratory and office workers and other upstream workers not thought to be exposed to benzene e.g. helicopter pilot, radio operator, security guard.(3) About 60 of the 395 individuals in the case control study were upstream workers. The case control study had no workers from production vessels as described in Kirkeleit et al. (4)

#### *Benzene exposure assessment*

A job history was prepared for each subject, based on data which had been collected largely prospectively, from the four cohort interviews that took place between 1980 and 1999.(5) For each case and control, the tasks carried out within each job, the products handled, and the technology used, were identified from structured interviews with contemporary colleagues using job specific questionnaires. Exposure to benzene was retrospectively estimated for each individual using an algorithm in a relational database, see Figure 1. The interviews and assessments were done anonymously and case-blind.

Benzene exposure measurements, supplied by Australian petroleum companies, were used to estimate exposure for specific tasks or jobs. Some supplementary data was sought from the literature. Forty-nine different base estimates (BEs) were calculated taking the arithmetic mean of the available measured personal exposure data. Values below the limit of detection

(LOD), were assigned half the LOD.(6) The BEs were validated by comparison with data from the literature.(7)

Where necessary, multipliers were used to estimate exposure for tasks where no suitable measured data were available. This was based on methodology used in similar petroleum industry case control studies by other investigators.(8, 9) A time weighted exposure was estimated for each job. This was multiplied by the number of years in that job and the results summed for each individual to give an exposure estimate in ppm-years. The intensity of the highest exposed job was identified.(7, 10)

### *Results*

More than half of the subjects started work after 1965 and had an average exposure period of 20 years. Exposure was low, 85 percent of the cumulative exposure estimates were less than 10 ppm years. Matched analyses showed that non-Hodgkin lymphoma and multiple myeloma were not associated with benzene exposure. Leukemia risk however, was significantly increased for the subjects with >16ppm years cumulative exposure OR 51.9 (5.6-477) or greater than 0.8 ppm intensity of highest exposed job.(5, 11) The risk of leukaemia was associated with exposure within 15 years of diagnosis, the association with exposure prior to this period is weaker.(12) The inclusion of occasional high exposures e.g. as a result of spillages, reduced the odds ratios, when the exposure was treated as a continuous and as a categorical variable. (5)

### *Discussion*

The exposure assessment raises some interesting questions.

#### **Question 1 Which Metric(s) is the most appropriate predictor of risk associated with benzene exposure?**

Possible metrics include duration, cumulative exposure (ppm-years), intensity of exposure (ppm) for the highest or longest job. Cumulative exposure and intensity of exposure were strongly correlated in our study. Goodness of fit statistics did not allow us to identify which was the better metric. (2).

It is possible that the rate or pattern of exposure is important. We found some evidence that exposure to high concentrations of benzene is associated with increased risk. (2) If latency is important, perhaps exposure more than 15 years prior to diagnosis should be discounted in future risk assessments.

#### **Question 2 Is there recall bias in this approach to exposure assessment?**

This could come from 2 sources, firstly from job histories supplied by the cases. However most of these were collected prospectively in our study. This might not be the case in a non-

nested case-control study. Secondly it could come from the co-worker information because they identified the person and knew their case-status and thought harder about cases' exposure to benzene. The evidence is that this probably did not happen in our study because unlike leukemia, increased risk of NHL and MM were not associated with benzene exposure.

### **Question 3 What is no exposure?**

Identification of those who are not exposed or exposed to only background levels is important. These are the referent group against whom the risk of those who are occupationally exposed is measured. For benzene no-one is absolutely unexposed.

### **Question 4 Does the exposure metric include all exposures?**

This method of exposure assessment will not capture infrequent but potentially high exposures which were too rare to be included in data making up the BEs e.g. tanker spillages, drum double fills. It would also not include possible historic exposures such as floor mopping, washing overalls or washing hands in petrol. We therefore estimated the exposure contributed by such High Exposure Events (HEEs), added them to the cumulative exposure for appropriate workers and re-estimated the risk.(5)

### **Question 5 How should data that are apparently outliers be handled?**

When preparing the data for the BEs all the available data was used except where there were implausible outliers. The decision about what is or is not an outlier can be difficult to make.(7)

### **Question 6 How should data sets with several limits of detection be handled?**

A substantial proportion of data below the limit of detection and the presence of multiple LODs in a single data set can make data handling problematic. It creates a non-normal distribution and artificially reduces the observed variability.

### **Question 7 What variance is there in the exposure data?**

High between-worker variance in exposure is could result in differential risks between individuals in the workforce. This exposure assessment method cannot take account of individual differences such as breathing rate. distance from source e.g. height, effectiveness (or lack of effectiveness) of control devices in the real world. (13)

### **Other issues:**

There is more data about some jobs/tasks than others so that there is more uncertainty about some BEs. Some BE modification factors were based on expert evaluation, which is notoriously difficult to verify. Pre 1975 data sparse so that exposures that took place before that time are difficult to estimate accurately. Occupational exposure to many substances has probably decreased over time. (14)

### **How transferable is the methodology?**

The methodology is too detailed to apply to a cohort study, in the absence of the personalisation derived from co-worker interviews the methodology is similar to using an *a priori* job exposure matrix (JEM). In a case control study, the methodology could be used for exposures such as total hydrocarbons, dust or mineral oil, because measured exposure data are available. The methodology is less useful for estimating exposure to exposures such as asbestos, formaldehyde and noise which may vary from facility to facility in less predictable ways. Significant skin exposure could be factored, in but is complicated by significant between-worker variability.

The effect of long shift patterns, or uncertainties from bad weather(15) are difficult to factor in. Perhaps the collection of biological monitoring data is appropriate.(16)

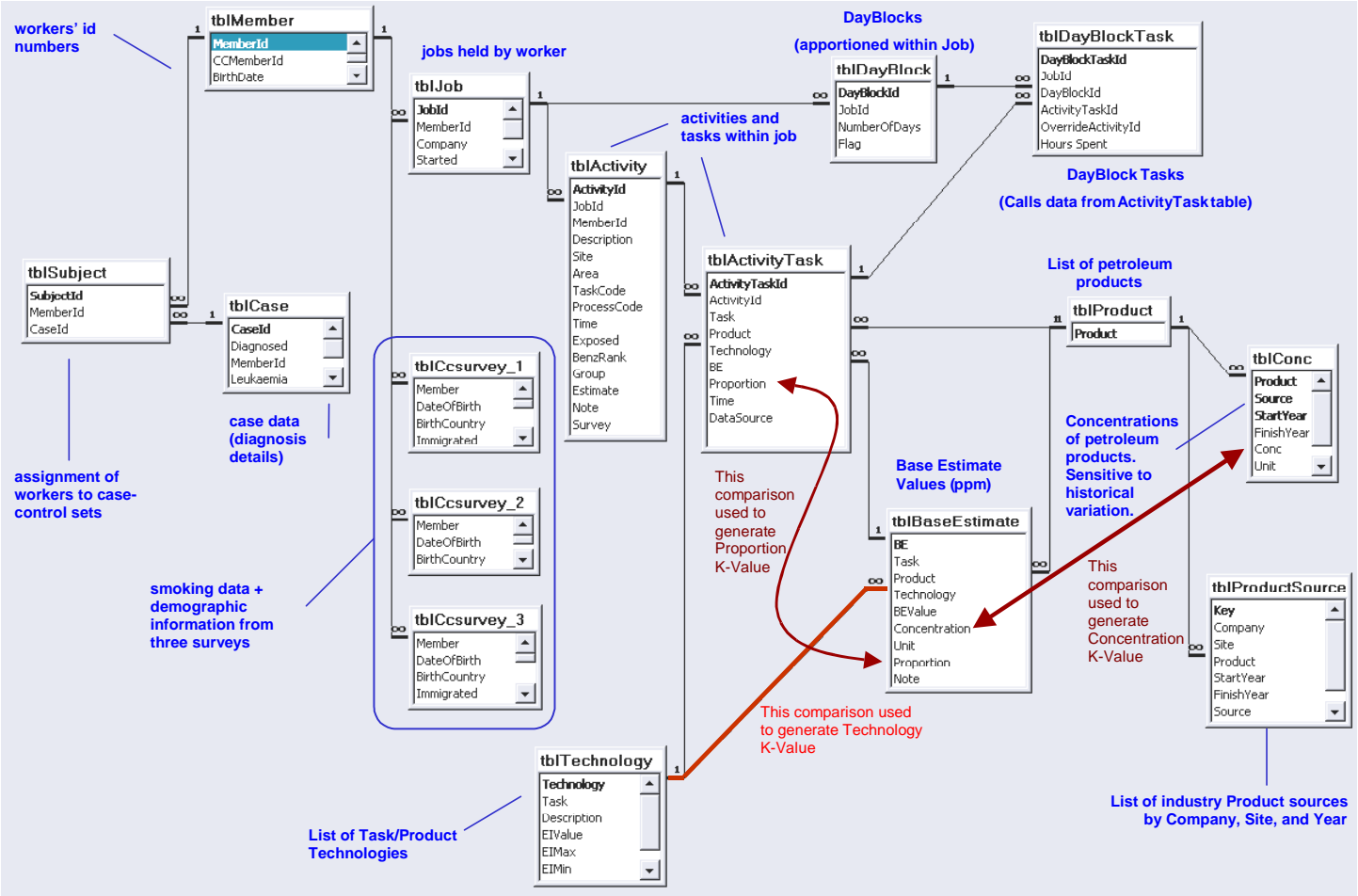
### *Conclusions*

The Health Watch exposure assessment methodology delivered a precise but flexible exposure assessment. The use of a database allows alteration to BEs or background levels to be made relatively easily and the risks to be reevaluated.

The choice of metric used in an assessment should depend on the endpoint being investigated. Cumulative exposure or intensity of exposure may need to be lagged and exposure rate may be an important risk factor.

Real world measured exposure data should be used as far as possible as the basis for the exposure estimation although some extrapolation will almost certainly be needed. The limitations of the real world data must be identified and their effect on risks evaluated as far as possible.

Figure 1 Schematic presentation of the relational database for the case control study



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