Finnish Institute of Occupational Health

Memorandum from the Occupational Cancer Working Group 2013

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ASSIGNMENT AND WORKING GROUP

In a meeting on 13 April 2011, the Committee for Occupational Health of the Finnish Ministry of Social Affairs and Health proposed that the Finnish Institute of Occupational Health take action in order to review the suggestions made in the *Memorandum from the Occupational Cancer Working Group* from 1988. The Finnish Federation of Accident Insurance Institutions (TLV) delivered the memorandum as circular 6/89. The Committee justified the review, for example, by deviations that had occurred in compensation practices in cases of lung cancer caused by asbestos, even though it was generally acknowledged that the compensation practices from 1988 were reasonably up-to-date and were still useful regarding asbestos. However, new information concerning other carcinogens proves that a current review of occupational cancers is in order.

In a meeting on 15 June 2011, the Executive Committee of the Finnish Institute of Occupational Health set up a working group to review suggestions made by the Occupational Cancer Working Group of 1988 in cooperation with the Finnish Ministry of Social Affairs and Health (STM), the Finnish Federation of Accident Insurance Institutions (TVL), and medical experts from trade and industry unions.

The members of the working group, which first met on 23 September 2011, include Kari Kurppa, Panu Oksa, Tiina Santonen, Jukka Uitti, and Henrik Wolff from the Finnish Institute of Occupational Health; Jaakko Hannula, Kristiina Mukala, and Heikki Savolainen from the Finnish Ministry of Social Affairs and Health; Mikael Hedenborg, Teemu Kastula, and Ilkka Torstila from the Finnish Federation of Accident Insurance Institutions (TVL); Kari Haring from the Central Organisation of Finnish Trade Unions (SAK) and Jan Schugk from the Confederation of Finnish Industries (EK). In its first meeting, the working group selected Ilkka Torstila as chairman. Teemu Kastula, Panu Oksa, and Tiina Santonen have, each in turn, acted as the secretary of the group.

The working group convened 15 times and received expert opinions from Anssi Auvinen (occupational exposure to radiation), Timo Kauppinen (occupational exposure to carcinogenic substances), Eero Pukkala (epidemiology of cancer), Timo Tuomi (exposure to quartz and asbestos), Tapio Vehmas (imaging technologies), and Henrik Wolff (pathology of cancer). It also sent out a questionnaire on the assessment and compensation practices used in relation to occupational cancers to 14 states of the European Union (EU). The results of this questionnaire are presented in a separate section of this memorandum.

The updated version of the memorandum adheres to the structure of the 1988 memorandum. However, for example, the contemporary classifications of carcinogenic substances in the EU and references to managing the occupational risk factors related to cancer in EU legislation have been updated.

The new practice for registering occupational accidents and diseases adopted in 2005 and the related cost calculations are described in a separate section.

Most of this memorandum consists of a review of carcinogenic substances according to exposure, complete with a literary overview (Section 5). Finally, the working group has made recommendations based on the review. In addition to the recommendations regarding the compensation of occupational cancers, the working group also takes a stand on the screening of lung cancer caused by exposure to asbestos, the forming of a special group of experts for occupational cancer diagnostics, the combining of gathered exposure information on asbestos, and the use of X-ray radiograph to determine the occurrence date for asbestosis.

After having completed its assignment, the working group cordially presents this report to the Committee for Occupational Health of the Finnish Ministry of Social Affairs and Health.

Helsinki, 30 May 2013

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ABBREVIATIO USED IN THE MEMORANDUM

AB, asbestos body, coated asbestos fibre

AF, attributable fraction

ALL, acute lymphatic leukaemia

AML, acute myeloid leukaemia

ANLL, acute nonlymphocytic leukaemia

ASA, a register of professionals exposed to carcinogenic substances and methods at work

Bq, becquerel, unit of radiation activity

CAS, Chemical Abstract Service, an American chemical substance identification system

CCA, chromated copper arsenate, a wood preservative

CI, confidence interval

CLP, European Parliament and Council (2008) regulation on classification, labelling and packaging of substances and mixtures. Includes, for example, a classification system for carcinogens

CT, computed tomography

DNA, deoxyribonucleic acid

EC, European Commission

EMF, electromagnetic field

EU, European Union

FIOH, Finnish Institute of Occupational Health

FROD, Finnish Register of Occupational Diseases

HIV, human immunodeficiency virus

HR, hazard ratio

IARC, International Agency for Research on Cancer

ICD-10, International Statistical Classification of Diseases and Related Health Problems, a medical classification list maintained by the World Health Organization (WHO)

IRIS, Integrated Risk Information System

MDS, myelodysplastic syndrome

MELA, Finnish Farmers' Social Insurance Institution

MOCA, methylenebis(2)-chloroaniline

mSv, millisievert (see Sv)

PAH, polycyclic aromatic hydrocarbons

ppm, parts per million

ppm-year, cumulative amount of exposure

OEL, occupational exposure limit

OR, odds ratio

PVC, polyvinyl chloride

REACH, Regulation for the Registration, Evaluation, Authorisation and
Restriction of Chemicals, a regulation passed by the European Union

RR, risk ratio, rate ratio

SCOEL, Scientific Committee on Occupational Exposure Limits, a committee
of the European Union that issues expert statements on occupational exposure
limits for chemicals in the workplace, founded in 1995

SIR, standardised incidence ratio

SMR, standardised mortality ratio

Sv, sievert, unit of radiation exposure

TAKO, Employment Accident Compensation Board

TVL, Finnish Federation of Accident Insurance Institutions

UV, ultraviolet

1 OCCUPATIONAL AND ENVIRONMENTAL CANCER

1.1 Background

Cancer is a multifactorial disease. It is also a common disease; about one in three Finns develops cancer during his or her lifetime. In the year 2009, for example, about 29 000 new occurrences of cancer were diagnosed (Pukkala et al., 2011). During the last few decades, morbidity has increased because of the ageing of the population.

Both human behaviour and environmental factors play a part in the origination of most cancers. There are few actual hereditary cancers, but genetic factors may modify the individual risk of developing cancer caused by environmental factors (Joensuu et al., 2007).

Cancer morbidity is somewhat higher for men than for women. According to statistics gathered by cancer associations, the morbidity of cancer among Finnish men has been about 300 for every 100 000 of the population. For women, the number is under 250 for every 100 000 (Pukkala et al., 2011). In Finland, there are also notable differences in the morbidity of cancer between different social groups (Pukkala and Weiderpass, 1999 & 2002). Certain types of cancer have been shown to be related to a low socioeconomic status. These differences are, for the most part, caused by living habits and, for example, smoking (Pukkala, 2011).

The risk factors for cancer can be divided into the following four classes (Pukkala et al., 2011):

> • Biological or inherent risk factors, such as age, gender, the metabolism of foreign substances, hereditary genetic defects and skin type;

> • Environmental risk factors, such as radon, ultraviolet radiation and small particles;

> • Occupational risk factors, such as many chemicals, radioactive materials and asbestos;

> • Risk factors caused by living habits.

Smoking is the biggest individual risk factor for one third of all cancers. The consumption of alcoholic beverages is also a significant risk factor, as it increases the risk of cancer of the mouth, pharynx, larynx, oesophagus, and liver (Baan et al., 2007). Nutrition affects,

for example, cancers of the intestines. In Western countries, obesity has also become a significant risk factor for cancer. In a recent estimate published in Great Britain, obesity was the second most significant risk factor for cancer among women after smoking, whereas, among men, unhealthy eating habits (limited use of fruit and vegetables), occupational risk factors, and the consumption of alcohol were emphasised (Parkin et al., 2011). Sexually transmitted infections (especially HPV, *human papilloma virus*) are also well-known risk factors for cancer. Some nutritional factors and physical activity seem to have a protective effect against certain types of cancer (www.dietandcancerreport.org). Of the environmental risk factors, radon in room air causes about 10% of the lung cancers diagnosed in Finland.

Certain professions have been found to be associated with an elevated risk of cancer. The differences in morbidity between various professions have been studied in the broad Nordic NOCCA research project (Nordic Occupational Cancer, http://astra.cancer.fi/NOCCA). The research found significant occupational differences in the morbidity of several types of cancer. Some of these differences are easily identifiable and are connected with risk factors that have been already noted for certain professions. These include, for example, lung cancer and mesothelioma among plumbers (caused by exposure to asbestos), the risk of lung cancer among miners (caused by exposure to quartz and radon), cancer of the nose among sawmill workers (caused by exposure to wood dust), and lip cancer among fishermen (caused by exposure to ultraviolet radiation). Some differences are not necessarily related to occupational exposures as such, but primarily to differences in living habits (especially smoking, alcohol consumption) between professions. For some deviations, however, there is currently no viable explanation.

1.2   Occupational cancer

The number of occupational cancers or their percentage of all cases of cancer is not exactly known, but estimates can be made on the basis of epidemiological studies. At one time, Doll and Peto (1981) estimated the proportion of occupational cancers in the United States to be about 4% of all cancers (variation 2%–8%). From the studies carried out in Finland, Aitio & Kauppinen (1992) estimated that, in the early 1990s, work was the cause of about 500 cases of cancer annually (2%–3% of all cancers). In addition, according to a Nordic estimate, about 2% of all cancers occurring in Finland in 2000 would have been caused by occupational risk factors (Dreyer et al., 1997). For men, the estimate was 3% of all cancers, whereas, for women, the proportion was less than 0.1% (Dreyer et al., 1997). In turn, Nurminen and

Karjalainen (2001) estimated that the attributable fraction of occupational risk factors was 8% for deaths caused by malignant tumours. Similar estimates have been made also in other countries, for example, Great Britain (Ruston et al., 2010). The variation between different estimates can be explained by methodology, including, for example, the quality of data and exposure. In addition, these kinds of estimates include a great deal of uncertainty, related, for example, to the accuracy of the assessment of exposure levels and the type of epidemiological data on which the estimate is based.

As the exposure levels decrease, the number of occupational cancers will also decrease. Whereas Nurminen and Karjalainen (2001) used epidemiological risk relationships to estimate that, at the end of the 1990's, 85–273 deaths from lung cancer and 56 deaths from mesothelioma were caused by asbestos, Priha et al. (2010) estimated that the current levels of occupational exposure to asbestos will cause about one asbestos cancer (lung cancer or mesothelioma) per year in the future.

It must be noted that the aforementioned assessments describe the percentage of occupational risk factors from total cancer morbidity and that they also include cases in which profession is only one factor contributing to cancer. Only diseases for which occupational exposure is the primary cause can be classified as occupational diseases. Therefore, the assessed numbers of occupational cancers will not be reflected in the compensation system. It is also very difficult associate lung cancer and many other cancers with occupational risk factors. Cancer may manifest itself only after the person has retired, and therefore its relationship to the person's profession is not discovered. In case the person is, or has previously been, a smoker, it may be difficult to prove the occupational nature of the cancer, and also occupational cancer can be attributed to smoking. These factors may lead to occupational cases of cancer being underdiagnosed.

Today, lung cancer and mesothelioma caused by exposure to asbestos are definitely the most important types of diagnosed occupational cancers. Between 1996 and 2009, physicians reported about 1400 cases of cancer to the Finnish Occupational Disease Register (FROD) maintained by the Finnish Institute of Occupational Health (FIOH). Of these cases, 1349 were caused by exposure to asbestos, and 6 by exposure to quartz. The other cases were caused by other isolated exposures. These figures cannot, however, be taken as an indication that such cases do not exist. There is also some underdiagnosis involved.

1.3 Research on cancer risk

The risk of cancer associated with different types of exposure can be studied with either experimental or epidemiological methods. Because the objectives are to identify the types of exposure that increase the risk of cancer and to prevent exposure to them, certain experimental methods (animal testing and cell culture tests) have been developed to identify carcinogenic effects in advance.

Data acquired using animal testing and cell-culture tests do not always predict an increased risk of cancer among humans. If the exposure has been in general use, the increased risk to humans can be studied using epidemiological methods (population research).

1.3.1 Experimental studies

The available information on the carcinogenic effects of chemicals or chemical mixtures available today is primarily based on animal testing. The standard method used for testing carcinogenic properties was developed in a 2-year cancer study carried out on rodents. Certain factors may decrease the importance of results acquired by animal testing when the risk of cancer among humans is being assessed. These factors can include, for example, noted differences in the metabolism of humans and test animals or mechanisms of actions, which are known to be less important for humans.

Although a carcinogenic effect detected in an animal test would be considered to be probably significant for humans, it cannot be definitely stated that the exposure would cause similar cancers in humans as it did in the test on animals. The same substance may cause cancer in very different ways in different species, and, for example, the exposure route affects the probability of each type of cancer. In addition, there is possibly a variation between species with respect to their sensitivity to certain types of cancer. Therefore, it is impossible to evaluate the probability of occupational cancer based on animal testing. However, from the point of view of risk management, the carcinogens found in animal testing must be taken as seriously as those revealed by data on humans.

The use of genotoxicity tests in the assessment of carcinogenic properties is based on the fact that the transformation of a normal cell into a cancer cell is known to occur through genetic mutation. Therefore, a substance that causes mutation is also potentially carcinogenic. Risk of cancer may, however, also be caused by a non-genotoxic method. Therefore, the fact that a substance is not genotoxic does not

mean that it cannot be carcinogenic. In addition to genotoxicity tests, the potential carcinogenic properties of chemicals can be preliminarily assessed using structure-activity relationships. The attitude towards substances whose genotoxic effects are strongly evident must be similar to those whose carcinogenic effects have been noted in animal testing. The probability of an occupational cancer occurring in an exposed group of people cannot, however, be estimated on the basis of genotoxicity tests or structure-activity relationships.

1.3.2 Epidemiological research

Epidemiological research can be used to demonstrate an increased risk of different cancers among an exposed group of people. These studies provide information about the dose–response relationships with respect to humans, as well as the types of cancer that are typical for each exposure. It must be noted, however, that epidemiological research cannot accurately indicate small increases in risk. Therefore, negative epidemiological studies cannot usually be used to completely rule out a risk, even though they may inspire confidence in the insignificance of the risk.

Like other epidemiological studies, also those related to cancer can be carried out either as case-control studies or cohort studies. The long latency of cancer is one of the most important factors that makes the epidemiological study of cancer difficult. The latency period may vary from 5 to 50 years according to the level of exposure and the type of cancer. During this period employees have time to, for example, change jobs, making tracing the exposure difficult, and also expose themselves to other factors, which obscures the results of the study. An extended latency period also creates problems with the estimation of the exposure level since these estimates must be made retrospectively over several years or even decades.

1.3.2.1 Epidemiological concepts

Risk ratio

Epidemiological research creates such statistical indicators as the risk ratio (RR), which illustrates the affiliation between exposure and morbidity. If the RR equals 1.0, the exposure does not increase or decrease morbidity. If the RR is greater than 1.0, the exposure increases morbidity, and, if it is less than 1.0, the exposure decreases morbidity. If the results of the research indicate that RR equals 2, the exposure increases the morbidity twofold. Other epidemiological indicators include the standardised incidence ratio (SIR) and the standardised mortality ratio (SMR), which compare the risk of morbidity and mortality, respectively, to those of the entire population. Another indicator is the odds ratio (OR), which is used for measuring, for example, the effect of exposure ("risk") in case-control studies.

Attributable fraction

The attributable fraction (AF) of exposure refers to the portion of morbidity that would not exist without exposure.

Relationship between the attributable fraction and the risk ratio

The formula $AF=(RR-1)/RR$ is a reduced description of the calculated relationship between the attributable fraction and the risk ratio.

If the RR of a group of employees with a certain exposure level is 2.0 when the group is compared with a group of unexposed employees, the calculated AF of the morbidity caused by the exposure is 50%. In other words, of those among the exposed group that have cancer, 50% have cancer due to the exposure in question, and 50% have developed it for some other reason.

If the RR is 3.0, there is a calculated 67% probability that the exposure in question is the cause of the disease in question. If the RR is 5.0, there is a calculated 80% probability that the exposure in question is the cause of the disease in question. If the RR is 10, there is a calculated 90% probability that the exposure in question is the cause of the disease in question.

Calculated relationship between the risk ratio and the attributable fraction

Attributable fraction = (RR-1) / RR
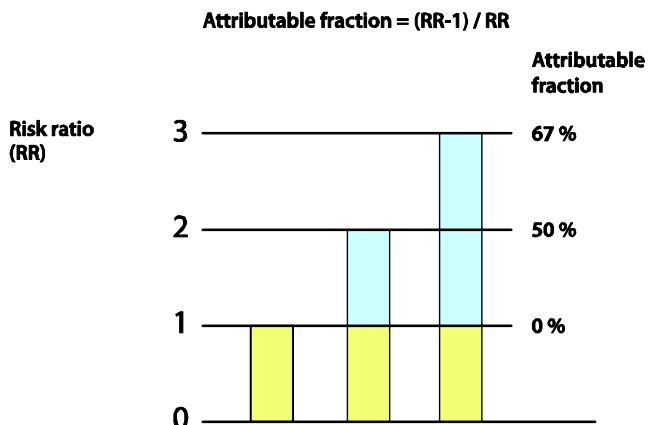
Kari Kurppa

1.3.2.2 Occupational cancer is a diagnosis based on probability

When it comes to the course of a disease or its pathological properties, occupational cancer does not differ from other similar cancers. There is no medical test that would indicate that occupational cancer is caused by work. According to occupational disease legislation, the relationship between a type of exposure and a certain disease must be strong enough to identify exposure as the probable cause of the disease.

An occupational disease diagnosis of an individual employee who has developed cancer must be based on probabilities. The probabilities are derived from the results of epidemiological studies (i.e. scientific appraisal of population experience). If the employee's exposure level is high enough to increase the group-level cancer morbidity more than twofold in comparison with that of the groups of unexposed employees, the cause of cancer is considred probably occupational in individual compensation judgments.

Risk of cancer in relation to exposure

The results of epidemiological research usually provide a basis for the recognition of occupational cancer.

As a diagnostic criterion for occupational cancer, it does not suffice that the employee with cancer has been exposed to a substance known to cause cancer (for instance, to ionising radiation, asbestos, or quartz). The exposure must have been high enough to increase the group-level morbidity of the exposed employees by over twofold in comparison with that of an unexposed group (RR > 2). An epidemiological risk ratio of 2.0 is the theoretical milestone for a 50% probability of causation. In such cases, it can be calculated that every other case of cancer in the exposed group has been caused by exposure.

If the criteria for the exposure classification in an epidemiological study are loose (for example, profession only), and the analysis does not separate a risk for the exposed people according to categories of exposure intensity, the aggregate result may indicate only a slightly elevated risk ratio (RR < 2). Such a result can lead to an erroneous interpretation, according to which the aggregate RR < 2 would apply to all employees of all exposure levels.

Therefore, in informative epidemiological research, exposed employees need to be classified into groups according to their exposure level. Each group classified by the intensity of exposure has its individual level of risk for cancer morbidity. An aggregated epidemiological result does not apply to all of the groups of exposed employees. For the group with the highest exposure, the RR may well be > 2 even though the average RR defined according to all of the research data is < 2.0.

A major part of occupational cancer morbidity cannot be individualised

Occupational cancer morbidity is an entity consisting of both cancer cases that can be recognized as an occupational disease and those that are partly caused by work but are not recognized as an occupational disease.

Only cases for which exposure increases the morbidity to over twofold (RR > 2.0) can be recognized as occupational cancers. Occupational cancers that are not recognized are cases in which the individual intensity of exposure is not high enough for a probability diagnosis, and therefore they cannot be found in occupational disease statistics. Many types of carcinogenic agents related to work are known as weak carcinogens (group level RR < 2.0). Using epidemiological methods it is possible to evaluate the percentage of cancers cause by occupational exposure from total cancer morbidity.

When the causal relations between occupational exposure and cancer morbidity is evaluated, three context levels can be identified.

Context levels of the evaluation of causal relations:

1. Individual epidemiological study
2. Scientific generalisation (available evidence, systematic review)
3. Cause of disease of an individual employee

Individual epidemiological study

When the results of an epidemiological study are being evaluated, the following factors should be taken into account:

- ξ systematic error (bias)
- ξ confounding
- ξ random error
- ξ strength of association
- ξ internal consistency (exposure-response relationship, subgroup results)
- ξ chronological association
- ξ biological credibility

Scientific generalisation

- consistency
  - o reproducibility

- o strength of association (including statistical meta-analysis)
- biological consistency (coherence)
- effect of intervention

In individual cases, the basic prerequisite for evaluating causal relations is that the exposure (quality, level, temporal connection) has been assessed as being high enough to have been able to cause the disease.

<u>Cause of disease of an individual employee</u>

Scientific data approved by the scientific community are used when the probability of occupational cancers of individual employees are being evaluated.

1.3.2.3 Systematic and random error in epidemiology

In epidemiology, errors in results can be caused by systematic error (bias) or random error. Random error can be decreased by increasing the size of the research group, and its magnitude can be characterized using statistical significance or confid-ence intervals. Hidden systematic error is more serious and problematic be-cause it cannot be removed by increasing the size of the research group, and it can-not be corrected or evaluated using statistical methods.

When the risk ratio is low or moderate (RR < 2), the interpretation of epidemiological results is often problematic and distorted by bias mechanisms. Confidence intervals and statistical significance characterize statistical uncertainty (stochastic effect), but they do not measure the distortion caused by systematic error and epistemic uncertainty, whose dimensions are usually much more significant than statistical uncertainty. The lower the risk ratios, the more difficult errors and distortions in epidemiology are to detect.

1.4 Scientific and administrative classification of cancer risk

1.4.1 Classification of chemicals in the European Union

In 2009, Regulation (EC) No. 1272/2008 of the European Parliament and of the Council on the classification, labelling and, packaging of substances and mixtures (CLP regulation) came into force in the European Union (EU). This regulation was based on the United Nations Globally Harmonised System (GHS) of classification and the labelling of chemicals.

According to the regulation, chemical substances that induce cancer or increase its incidence are assigned to one of two hazard categories (1 and 2). The substances must be labelled with appropriate hazard statements and symbols. Category 1 has two subcategories (A and B). Carcinogenic substances are allocated to one of two categories based on the strength of evidence and additional considerations (weight of evidence). In certain instances, exposure route-specific classification may be warranted if it can be conclusively proved that no other route of exposure can cause the hazard. The latter may apply, for example, if the carcinogenicity of a substance is known to be related only to inhalation exposure.

Hazard categories for carcinogens in Regulation (EC) 1272/2008:

Category 1: Known or presumed human carcinogens

- A substance is classified into Category 1 for carcinogenicity on the basis of epidemiological and/or animal data.

Category 1 is further divided into

- Category 1A for substances known to have carcinogenic potential in humans, the classification is primarily based on human evidence.
- Category 1B for substances presumed to have a carcinogenic potential in humans; the classification is primarily based on animal evidence.

Category 2: Suspected human carcinogens

- A substance is placed in Category 2 on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing for placement in Category 1A or 1B, on the basis of the strength of the evidence together with additional considerations.

The classification of a substance into Category 1 affects its use, for example, in consumer products. These are also the primary substances when the need for specific prohibitions and regulations on the use of substances in the EU are considered.

1.4.2 IARC classification

The aforementioned EU classification of substances and mixtures is somewhat different from the classification used by the International Agency for Research on Cancer (IARC), which divides estimated exposure into the following four groups:

Group 1	substances that are carcinogenic in humans
Group 2A	substances that are probably carcinogenic in humans
Group 2B	substances that are possibly carcinogenic in humans
Group 3	substances that are not classifiable as to their carcinogenicity in humans
Group 4	substances that are probably not carcinogenic in humans.

In addition to chemicals, IARC has also classified many medicinal substances (for example, antineoplastic agents and hormonal preparations), as well as physical and biological factors that increase or are suspected to increase the risk of cancer. IARC has also classified some events of exposure, such as work conditions, that increase the morbidity of cancer. The IARC lists of substances that are carcinogenic in humans, probably carcinogenic in humans, and possibly carcinogenic in humans can be found on the website of the organization at http://monographs.iarc.fr/.

1.4.3 List of carcinogenic substances and ASA

In Finland, carcinogenic substances are also classified by the Finnish Ministry of Employment and the Economy resolution (TMp 1060/83 and its updates, see appendices). This is a list of exposures that must be reported to the register of workers exposed to carcinogenic substances and processes (ASA register). The substances in this list differ somewhat from those classified as carcinogens, for example, by the EU.

1.5 EU legislation related to the management of cancer risk in the workplace

In relation to carcinogens or mutagens found at work, the EU has issued Directive 2004/37/EC, which emphasises minimising exposure to carcinogens or mutagens at work, informing employees, and monitoring exposure and employee health. Occupational cases of cancer must be reported to the authorities.

The chemical regulation of the EU [REACH Regulation (EC) No 1907/2006] requires a safety assessment of all widely used chemicals, including carcinogens. The problem with chemicals has been that only some of the widely used ones have been tested and properly evaluated in relation to their carcinogenicity. REACH responds to this deficiency by establishing procedures for collecting and assessing information on the properties and hazards of substances, for defining exposure limits and managing risks related to

substances in different uses. REACH includes mechanisms for restricting, and even prohibiting, the use of the most hazardous, for example, carcinogenic, substances. The REACH regulation does not, however, cover all of the chemical exposures related to occupational cancers, for example, quartz.

2 CURRENT COMPENSATION PRACTICES AND PROBLEMS RELATED TO COMPENSATION

2.1 Legislation and guidelines

The Finnish requirements governing the obligation to report occupational diseases or other work-related diseases within health care are regulated by the Act on Occupational Safety and Health Enforcement and Cooperation on Occupational Safety and Health at Workplaces (44/2006). Section 46 of the Act (1564/2009) states that, if a physician has good reason to suspect an occupational disease or other work-related disease, he or she must immediately report it to the Regional State Administrative Agency, notwithstanding the confidentiality regulations. The report must include the following information:

- Name, personal identification number and other contact information of the person taken ill

- Name and contact information of the employer

- Other relevant contact information

- Type and duration of exposure

- Information about the type and detection of the disease, as well as its harmful effects.

The Regional State Administrative Agency must, according to Section 46, deliver information received from reports to the Finnish Institute of Occupational Health (FIOH) for entry into its Finnish Register of Occupational Diseases (FROD).

Some of the work-related diseases fulfil the criteria for occupational diseases that are to receive compensation from accident insurance institutions. These criteria are defined in the Act on Occupational Diseases (29.12.1988/1343) and its Decree on Occupational Diseases (29.12.1988/1347).

According to the Act on Occupational Diseases, an occupational disease that is to be recognised by an accident insurance institution is a disease that has probably primarily been caused by physical, chemical, or biological factors in the workplace. The Decree on Occupational Diseases contains a list of the commonest occupational diseases and exposures that can cause them.

This list of occupational diseases is not complete or restrictive. A disease not on the list can be recognised as an occupational disease if causation between the disease

and physical, chemical, or biological exposure factors can be identified with reasonable probability.

Both the Finnish Federation of Accident Insurance Institutions (TVL) and the connected Employment Accident Compensation Board (TAKO) have issued specifications for occupational diseases to insurance institutions. An essential specification was the Employment Accident Compensation Board circular 2/2010 about the handling of occupational diseases. The purpose of this circular is to ensure that all cases of occupational disease are processed uniformly and quickly, to secure the legal protection of the insured during the entire process, and to instruct insurance institutions to avoid the transferral of cases from one institution to another. The circular contains, for example, directions related to the manifestation dates for the commonest occupational diseases and the definition of the insurance institution responsible for compensation. To promote the processing of occupational disease cases, sample questions for insurance institutions have also been included in the circular to be used as templates when necessary information is being acquired.

Forensic investigation of causes of death has a significant influence on the determination of severe cases of an occupational disease. According to the Section 7 of the Act on Determining Cause of Death (1.6.1973/459), the police must conduct an investigation, for example, when the cause of death has been an occupational disease or when there is reason to suspect such a cause. According to Section 9 of the Act, a forensic autopsy must be performed if the cause of death cannot be determined on the basis of the medical certificate issued by the physician who performed an external inspection or other information revealed by the investigation. In other words, forensic autopsy is not required to determine the cause of death in occupational disease cases if the attending physician is able to define the cause of death as being an occupational disease that has enabled the patient to receive compensation during his or her lifetime.

It must be noted, however, that compensation paid for occupational diseases is dependent on the practices and agreements of the insurance system, and the decisions of the insurance system are not directly related to the results determining the cause of death. Since the provincial governments were abolished, the National Institute for Health and Welfare has been the authority with jurisdiction over forensic investigations of the causes of death in Finland. It has been in charge of forensic autopsies ordered by the police since 1 January 2010. As a result of the activities of a working group nominated by the Finnish Ministry of Social Affairs and Health, coroners have received guidelines about determining occupational diseases caused by asbestos (handout 23 February 2011, Occupational Disease in Forensic

Investigations for Cause of Death and Practices for Dispensing Compensation for Occupational Diseases, Working Group's Final Report 20 March 2012).

There are no special rules for the compensation of cancer as an occupational disease. The specific criteria used when a case of cancer is recognised as an occupational disease as defined in the Act on Occupational Diseases are mainly based on the report of the Occupational Cancer Working Group from 1988. In accordance with the assignment given to the Working Group, which was nominated by the Finnish Federation of Accident Insurance Institutions (TVL), the report concentrated primarily on cancers caused by exposure to asbestos. The report also defined a generic approach when identifying exposure in cases of cancer. The report of the Working Group was delivered to insurance institutions on 25 January 1989 as circular 6/89 of the Finnish Federation of Accident Insurance Institutions (TVL).

2.2   Compensation practices

When compensation for cancer cases is being assessed, the same principles apply as with other occupational diseases. Proving an occupational disease postulates that:

- A disease that may have been caused by exposure has been detected,

- Exposure can be proven to be work-related, and the quality and level of exposure has been determined,

- Medical differential diagnostics rule out the probability of the disease being caused by some other factor.

The biggest challenge related to compensation for occupational cancer involves proving the individual cause-effect relationship. Although there is much epidemiological evidence on the relationships between, for example, exposure to asbestos and lung cancer and malignant mesothelioma, it is not possible to determine a single reason for these or any other cancers in individual cases with the use of current medical information. Many cancers related to occupational exposure, such as lung cancer and bladder cancer, are also known to be increased significantly by smoking. Therefore, identifying cause and effect in individual cases is even more difficult.

The relationship between exposure to asbestos and lung cancer was suspected already in the 1960's, but, at that time, the causation was not considered to be proven scientifically beyond dispute. In 1961, the first case of lung cancer suspected to have been caused by exposure to asbestos was processed in Finland. In this case, the causation between asbestos exposure and lung cancer could not, however, be shown, and the insured employee was denied occupational disease compensation in

different courts. When the relation between exposure to asbestos and lung cancer was later scientifically proven, the Supreme Court overturned its earlier ruling based on additional evidence, and the matter was returned to Insurance Court. In 1972, the Insurance Court ruled that occupational disease compensation was to be paid in this case. Even before this ruling, insurance institutions had adopted the practice of treating lung cancer among patients suffering from asbestosis as an occupational disease and offered compensation accordingly. It had also become the general practice to offer compensation to lung cancer patients with asbestosis regardless of whether the insured had previously been a smoker or not.

The compensation practices regarding mesothelioma were settled by Insurance Court rulings. In these rulings, a relatively short period of exposure to asbestos was considered to be enough to validate compensation for mesothelioma. For example, in one case of mesothelioma that received compensation, the task of dismantling and building an oven in a period that lasted only one week in one year was considered sufficient exposure to asbestos.

The compensation practice regarding cancers caused by exposure to asbestos has been settled according to the guidelines given by case law and the 1988 report of the Occupational Cancer Working Group. A well-established practice regarding lung cancers caused by exposure to asbestos has been to offer compensation for lung cancer as an occupational disease if the patient has been diagnosed as having asbestosis. In addition, lung cancer has received compensation as an occupational disease caused by asbestos if the patient's work history contains levels of exposure that may increase the risk of cancer twofold. A patient's history of smoking is not taken into account when the decisions are made. Instead, compensation is based on the assessment of the level of exposure to asbestos. Cancer patients may therefore also receive compensation in situations in which asbestosis has not been diagnosed. In these cases, sufficient evidence of the level of exposure (work history, bronchoalveolar lavage or tissue samples, other diagnosed diseases related to asbestos, etc.) is required. The latency period applied for lung cancer is 10 years.

Malignant mesothelioma of the pleura or peritoneum receive compensation as an occupational disease caused by asbestos if the patient's work history contains some exposure and if the latency period is at least 10 years. Smoking is not taken into account when decisions concerning compensation for mesothelioma are made.

If the level of exposure to asbestos seems uncertain in relation to lung cancer, the compensation for the cancer as an occupational disease must be decided according to special measures in individual cases. In borderline or otherwise difficult cases, insurance institutions have developed the practice of requesting a statement from

pneumoconiosis specialist groups at university hospitals or, especially, from the Pneumoconiosis Specialist Group at the Finnish Institute of Occupational Health (FIOH).

Decisions concerning other cancers caused by asbestos have been made according to individual deliberation, and general compensation recommendations cannot be made because of the small number of cases.

Individual deliberation is also required in cases in which some exposure other than asbestos is suspected to have caused cancer. The annual number of such cases in the insurance system has been too low for compensation practices to have been formed. A compensation practice has been agreed upon mainly for lung cancer patients with silicosis.

A recognised occupational disease entitles a patient to compensation, for example, for loss of income, treatment, medical and occupational rehabilitation, aid, and permanent handicap. In fatalities, funeral expenses and a possible family pension are furnished.

The compensation practice for cancers related to asbestos exposure differs from the practice related to other occupational diseases essentially only by the definition of permanent handicap. As the prognosis of lung cancer and mesothelioma is still poor and because they usually advance rapidly and quickly lead to death, compensation for permanent handicap has been agreed upon. A handicap allowance for handicap class 10 is therefore always paid on the anniversary of the diagnosis of lung cancer or mesothelioma. This is also the case in situations in which the status description would not yet entitle compensation for a permanent handicap at such a level. For compensation, the manifestation date of lung cancer in relation to asbestosis is considered to be the same as the manifestation date of asbestosis. In such cases, handicap class 10 usually receives compensation as soon as the cancer has been diagnosed.

When cancer advances in a way that indicates a poor prognosis (e.g., disease advancing despite treatment, occurrence of metastasis, rapid deterioration of the general state of the patient), compensation corresponding to handicap level 20 is paid continuously as an annuity. A handicap allowance of level 20 is also paid if the disease has advanced in the aforementioned manner already on the anniversary of its manifestation. This procedure is implemented to account for a handicap in a rapidly changing and deteriorating situation. A similar handicap compensation practice has been applied to occupational cancers whose prognosis is considered poor, as with lung cancer or mesothelioma.

Despite the fact that the exposure may have ended decades earlier and the person with occupational cancer has been, for example, retired for several years, he or she is entitled to occupational disease benefits as defined in the Employment Accident Insurance Act. If the accident pension is the primary compensation of the patient, it must be determined whether the employee with occupational cancer would be fit for his or her previous occupation. In other words, in most cases, an occupational cancer leads to the granting of an accident pension.

2.3 Statistics

2.3.1 Register of occupational accidents and diseases

Annually, about 25 000–30 000 Finns develop cancer. The number of occupational cancer cases or the total of costs caused by cancer is not exactly known, but the extent of the effect on the insurance system and its expenditures as a result can be studied, for example, from the registers maintained by the Finnish Federation of Accident Insurance Institutions (TLV).

One of the tasks of the TLV is to maintain a register of occupational accidents and diseases as defined by Section 64 (723/2002) in the Employment Accident Insurance Act. The TLV register contains, for example, case-specific information about all registered cases of occupational disease and their compensation. Information about whether an illness has been recognised as an occupational disease has been systematically entered into its register since 2005.

According to the TLV register, about 6000–7000 new or suspected cases of occupational disease have been processed every year according to the statutory accident insurance system in the beginning of the 21st century. The number of new or suspected cases of occupational disease has declined significantly during the last few years. Whereas in 2005, more than 7000 new or suspected cases of occupational disease were registered, the number had declined to about 6000 per year by 2010.

Table 1. Total number of new or suspected cases of occupational disease by the year of registration, 2005–2010.

Year of registration	New and suspected cases of occupational disease
2005	7040
2006	7188
2007	6325
2008	6263
2009	6188
2010	6006

The information in this table is based on the combined register of occupational diseases maintained by the Finnish Federation of Accident Insurance Institutions (TLV), which contains all employees and entrepreneurs, as well as all insurance institutions.

The number of cancer cases receiving compensation as an occupational disease varied between 140 and 170 in 2005–2010. Whereas the total number of new cases of occupational disease has been declining in the last few years, similar development has not occurred for cancers. In 2010, a total of 166 cases of cancer recognised as an occupational disease were registered by the insurance system.

Table 2. Cases of cancer recognised as an occupational disease by the year of registration, 2005–2010.

Year of registration	Registered cases of cancer
2005	155
2006	144
2007	153
2008	171
2009	157
2010	166

The information in this table is based on the combined register of occupational diseases maintained by the Finnish Federation of Accident Insurance Institutions (TLV), which contains all employees and entrepreneurs, as well as all insurance institutions. The cases of cancer correspond to codes C00-D48 of the ICD-10 classification and codes 140-239 of the IDC-09 classification.

An insured person receives compensation for medical expenses and loss of income as a result of an occupational disease from the statutory accident insurance system. In addition to medical and certain other expenses, for example, a daily allowance and an accident pension for the loss of income, as well as handicap compensation paid in compensation for a permanent handicap caused by an accidental injury or occupational disease. Moreover, in cases of fatality, a family pension is paid to children and the widow or widower, as well as funeral compensation to the estate.

In cancer cases, the commonest forms of compensation paid by the statutory insurance system are pensions and other permanent compensations, such as handicap compensation in cases of permanent handicaps. The number of long-term compensation agreements has increased significantly during the last few years. Table

3 presents the amount of insurance compensation (without indexation) paid because of cancers by the type of compensation, as well as the number of cases receiving compensation in 2007–2011.

Table 3. Amounts (without indexation) paid by accident insurance because of cancer by type of compensation and number of compensated cases in 2007–2011.

Year of payment	Compensation for expenses in euros (cases)	Daily allowance in euros (cases)	Pensions and other permanent forms of compensation in euros (cases)	Total in euros (cases)
2007	1 197 514 (240)	1 784 231 (103)	10 240 254 (780)	13 221 999 (1123)
2008	1 191 548 (268)	1 617 195 (91)	11 041 451 (815)	13 850 194 (1174)
2009	1 529 989 (244)	1 703 292 (98)	12 024 517 (858)	15 257 798 (1200)
2010	1 355 234 (247)	2 000 231 (105)	12 743 696 (879)	16 099 161 (1231)
2011	1 768 159 (238)	1 738 819 (84)	13 106 395 (908)	16 613 373 (1230)
Total	7 042 444 (1237)	8 843 768 (481)	59 156 313 (4240)	75 042 525 (5958)

The information in this table is based on the combined register of occupational disease maintained by the Finnish Federation of Accident Insurance Institutions (TLV), which contains all employees and entrepreneurs, as well as all insurance institutions. The cases of cancer correspond to codes C00-D48 of the ICD-10 classification and codes 140-239 of the IDC-09 classification.

Compensation covers the costs of, for example, physicians' fees, medications (excluding free medication), hospital fees, and research expenses. Daily allowances include both a 4-week allowance and what is called an annual income allowance. Permanent compensation covers accident pensions, funeral compensation, family pensions, rehabilitation expenses, and handicap compensation, as well as handicap, garment and guide dog supplements.

If several types of compensation (e.g., the compensation of expenses and daily allowances) have been paid for the same incident in a given year, the incident is shown in both columns.

The euro amounts have been rounded to even values.

2.3.2 Finnish Register of Occupational Diseases

In addition to being registered by the Finnish Federation of Accident Insurance Institutions (TLV), occupational diseases are registered, and the register is published, by the Finnish Institute of Occupational Health (FIOH). The Finnish Register of Occupational Diseases (i.e., FROD) is a research register that is used in occupational health research and the prevention of occupational diseases. Since FIOH is not a statistical authority, the occupational disease publication FROD is not an official statistical record. Official statistics on occupational accidents and diseases are maintained by TLV.

Since 1964, FROD has been used to gather information on patients who undergo a medical examination for a recognised occupational disease, a suspected occupational disease, or some injuries that are reimbursed as occupational accidents. TLV and the Finnish Farmers' Social Insurance Institution Mela provide information related to recognised or suspected cases of occupational disease to FIOH. Information provided to the occupational health authorities by physicians are used to complete this information, especially with regard to respiratory allergies and skin diseases. FROD combines and corrects information that it has received from TLV and MELA about recognised and suspected occupational diseases to conform to the register's statistical basis. In certain instances, this processing leads to a situation in which several individual cases in the TLV material are summarised to one statistical case in the FIOH material. Because the information is managed by FIOH, its cases are not comparable to the TLV cases.

In addition to the total number of cases of recognised and suspected occupational diseases, FROD also publishes a separate list of cases recognised as an occupational disease by the insurance institutions. A recognised case of occupational disease is one for which the insurance institution has received sufficient evidence and has decided to consider the processed case to be an occupational disease. The number of cases recognised as an occupational disease represents the data that have been notified to FIOH. The number increases later as some of the cases of suspected occupational disease are confirmed as the investigation progresses. Therefore, in future publications, the number of recognised cases of occupational disease for previous years is always somewhat higher (see *Occupational Diseases in Finland*, an annual publication of FIOH).

> In 2010, a total of 149 cases of cancer suspected to have been caused by asbestos was reported (in 2009, 152 and in 2008, 158). The number of notified cases of respiratory cancer and mesothelioma was

93 and 55, respectively. There was 1 other cancer case suspected to have been caused by asbestos. The number of reported cases of mesothelioma in 2007–2010 was higher than earlier. In 2005 and 2006, the average number of cases was 39 per year, whereas, in 2007–2010, it was 60 cases per year. The number of reported cases of respiratory cancer, on the other hand, has remained the same (for 2005–2006 an average of 88 cases and for 2007–2010 an average of 87 cases). According to the Finnish Cancer Registry, the manifestations of mesothelioma, which have also been considered to be indicators of exposure to asbestos on the population level, have been as follows (5-year periods): 69 cases (1994–1998), 76 cases (1999–2003), and 92 cases (2004–2008). In 2010, 91 new cases of mesothelioma were reported to the Cancer Registry. There were also 9 cases of cancer caused by something other than asbestos reported. These cancers included 1 lung cancer, 3 urinary tract cancers, 2 nasal cavity cancers, 2 cases of leukaemia, and 1 lymphoma. Of these cancers, 1 nasal cavity cancer caused by exposure to hardwood dust was recognised as an occupational cancer. Of all the diseases related to asbestos, insurance institutions recognised 65% as occupational diseases. However, the proportion of recognised mesotheliomas was 85%. The percentage being higher than the average proves that both the diagnostics and the assessment of exposure were clear. Since there are good practices for diagnosing cases of asbestos-related occupational disease, changes in legislation have less influence on them than on many other types of occupational disease (Oksa et al., 2012).

Full coverage in the registering of occupational diseases has not yet been achieved. Some physicians neglect their responsibility to report occupational diseases. Furthermore, not all physicians and patients associate the disease to the work environment, probably because a long delay of possibly decades and missing work environment information. In general, especially for cancers receiving compensation as occupational diseases, there is underreporting. Underreporting is caused, for example, by the difficulty of physicians to identify the relation between work and an individual case of cancer, as well as by the extended latency periods typical of cancers, both of which make it difficult to identify risk factors and occupational exposure. An example of severe suspected underreporting is the situation in Portugal, where, in a population of 10.5 million, cancers have been reimbursed as occupational diseases in only 21 cases during the last 10 years. In Finland, most of the cancers that have been identified as occupational in origin are caused by

exposure to asbestos, whereas all other causes easily remain unrecognised. This situation suggests underreporting caused by underdiagnosis.

2.4 Problems with compensation

Compensation for cancer as an occupational disease is based on the same accident insurance legislation as the compensation for other occupational diseases. The precondition for receiving compensation is that the primary cause of cancer has probably been work-related exposure. The clinical description and microscopic structure of occupational cancers are, in most cases, no different from cancers not related to work. Since purely medical evidence cannot solve the occupational nature of cancers, compensation decisions are made according to a diagnosis based primarily on exposure information. Because of the long latency period, it is generally difficult to gather data on exposure. On the basis of current legislation, the critical question is whether individual cases of cancer are due to exposure at work or not. As cancer cases are processed according to the same legislation as other occupational diseases, the same principles must be followed as with occupational diseases in general when causation is assessed.

When occupational diseases are considered for compensation, the decisions are based on the assumption that the disease in question has been identified as being caused by exposure at work for the person in question. For a known occupational disease, this causation has usually been proven in the scientific literature beyond dispute.

The problem with occupational diseases is that the diseases themselves must be diagnosed in the first place. In the question of cancer, the problem differs in the sense that the actual cancer diagnosis can usually be made with reasonable certainty. For example, regarding lung cancer, the disease is often determined by its microscopic classification. An accurate diagnosis does not, however, offer any information about the cause of the cancer.

The commonest cause of lung cancer is still smoking. Many work-related exposures, however, individually increase the risk of lung cancer. Therefore, cancer incidents have been considered to be cases of occupational disease when a significantly elevated risk of lung cancer is known to be associated with the exposure in question. Because the proportional effect of possible simultaneous smoking in the origin of cancer cannot be reliably evaluated, it has become common practice to compensate the incident as an occupational disease regardless of the patient's smoking background. Thus far, in current compensation practices, cases have been decided primarily according to the following three criteria:

1. Factors proven to cause cancer among humans
2. Factors with a strong enough effect on cancer causation among humans
3. The employee has been significantly exposed to a cancer-causing agent at work.

On the other hand, cases in which there is epidemiological evidence that exposure to a substance would increase the risk of cancer also among humans but that this increase is relatively small have not been considered for compensation. Examples of such cases are the lung cancers of foundry workers, which have not received compensation as an occupational disease because of the only slightly increased risk ratio.

Despite the aforementioned criteria, establishing an accurate cancer diagnosis and its effect on compensation is sometimes problematic when it comes to mesothelioma. Diagnostics in general may be very difficult, and diagnosing mesothelioma is especially challenging with regard to histology and requires special expertise. In ambiguous cases, it is common practice to ask for a statement from the Pneumoconiosis Specialist Group or the Mesothelioma Panel of FIOH if the opinion of FIOH experts has not already been noted.

Sometimes there are also problems with the compensation for widely spread cancer cases, in which thorough diagnostic investigations may have to be abandoned on the basis of the poor general condition of the patient or a hopeless prognosis. In such cases, for example, mesothelioma may remain undetected or be detected only after the patient has died. Some cases of lung cancer may also lead to similar situations. Occupational diseases cannot, however, be confirmed on the basis of suspicion, and therefore, in these cases, an occupational disease cannot be diagnosed or the diagnosis can be made reliably only after the death of the patient.

When cancer cases are assessed for possible compensation, most of the problems are caused by the evaluation of exposure. Exposure data are gathered both during occupational disease investigations in the hospital and in occupational health clinics. Insurance institutions, for their part, gather information using questionnaires directed towards the patient and his or her previous employers. The quality of the information deteriorates as more time has passed since the exposure ended. Often the patients themselves do not know exactly where and when exposure has occurred, and the employers are no longer available for questioning. Therefore, information about exposure varies, data collection takes a long time, and insurance decisions, as well as compensations, are thus delayed.

3 SITUATION IN SOME EUROPEAN COUNTRIES

In 1990, the European Commission (EC) published its recommendation for occupational diseases (90/326/EEC), and the member states were encouraged to index their occupational diseases according to the pertinent appendix to the recommendation. In 1998, the statistical department of the EC (Eurostat) gathered sample statistics on incidents occurring in 1995. The analysis of this sample of statistics revealed significant problems in coverage, compensation practices, and compensation criteria, all of which made comparisons difficult. In 2003, the EC finished work on revising the recommendation and its appendices (2003/670/EC, notified in document C(2003)3297). The European list of occupational diseases in this recommendation contains items classified according to both pathogen and diagnosis.

Data on recognised occupational diseases with diagnostic definitions are provided to the EC (Eurostat) annually. The list contains 68 primarily reported and 41 voluntarily reported diagnoses. Only the occupational disease items that occur in the occupational disease lists of all, or at least most, of the member states are included in this EODS information. Of the recognised occupational diseases in 2010, 2246 (96%) could be classified according to the appendix. As the information from different countries is still inconsistent, Eurostat has not yet begun publishing its gathered data.

The Occupational Cancer Working Group has primarily investigated cancers that have been recognised as occupational diseases from an international point of view using a questionnaire sent to insurance institutions dealing with occupational diseases in 14 European countries. This questionnaire was primarily intended to determine the criteria used for the compensation of cancers as occupational diseases in these countries, as well as to collect data on the numbers of cancer cases considered to be occupational diseases. Replies were received from the following six countries: Spain, Portugal, Sweden, Germany, Switzerland, and Denmark. The Working Group also focused on studies made by the French research institute Eurogip concerning the compensation of occupational cancers and asbestos-related diseases in Europe. These studies can be obtained in electronic format from the Eurogip home page www.eurogip.fr.

The occupational nature of cancers, as well as other diseases, can be verified from national occupational disease insurance institutions that reimburse them as occupational diseases. However, national social security systems, which also include accident and occupational disease insurance, have not been standardised at the EU

level, which basically means that the preconditions for the compensation of occupational diseases in each member state are still based on the national norms of each individual country. If these national preconditions are met and an occupational cancer is accepted for compensation as an occupational disease, the insured person receives compensation according to the national occupational disease insurance system, which in turn is dependent on the national norm.

The social security regulations of the EU (especially regulations 883/2004 and 987/2009 ratified on 1 May 2010) only govern which country's social security legislation applies to a person travelling in the EU; in other words, their purpose is to aid the coordination of the national social security systems. The preconditions of receiving social security can still be defined on a national level as long as the general principles of the regulations concerning, for example, the demand for equal treatment are not infringed upon. Furthermore, employees must not lose their right to social security when they move from country to country.

The social security regulations of the EU (883/2004 and 987/2009) contain rules on occupational diseases, and they are related to situations in which a person has been exposed to the same risk in several EU countries or the occupational disease grows worse in the EU. The aforementioned regulations amended the previous social security regulations (1408/71 and 574/72), but the basic principles concerning occupational diseases remained unchanged.

When a person has developed an occupational disease and has been exposed to the same risk that causes an occupational disease in several member states, the compensation is paid according to the legislation of the last of these countries. The institution granting the benefits is the competent institution of that country (883/2004, art. 38 and 1408/71, art. 57).

If a person who develops an occupational disease becomes employed in another member state and has not been exposed to the pathogen in question in that state, the decision-making institution that originally furnished compensation for the occupational disease is also responsible for the aggravation of the disease. This institution must bear the cost of the benefits under the provisions of the legislation to which it applies and take into account the aggravation. If, on the other hand, a person has been employed in another member state and is

still exposed to the pathogen in that state, the responsibility for the aggravation of the disease is transferred to this state (883/2004 art. 39, 1408/71 art. 60).

More-detailed instructions about the application of EU regulations to occupational disease issues have been given in Employment Accident Compensation Board circulars 2/2010 and 2/2011, which are specifically related to social security regulations.

In almost all of the European countries included in the Working Group's investigation, the fundamental basis of the compensation regulations for occupational diseases was a nationally confirmed list of occupational diseases. Depending on the system, these lists create more or less strong suppositions that a disease included in the lists is to be recognised as an occupational disease (the *list system*). The level of detail in these national occupational disease lists varies significantly. For example, the French list of occupational diseases is very detailed and contains an exact table of possible diseases, exposures, and approval criteria, whereas, in Switzerland, the occupational disease regulation contains a relatively generic list of different exposures and possibly related diseases.

The more or less varying occupational disease lists are complemented in most European countries by the *off-list or complementary system of recognition*, according to which a disease not mentioned in the occupational disease list can also be recognised as an occupational disease provided that, in individual cases, sufficient probability of cause and effect can be identified between the suspected occupational disease and exposure in a particular occupation. An example of such a complementary system of recognition is the Danish one, in which a disease not mentioned in the occupational disease list can be recognised as an occupational disease if the national body processing occupational diseases (Occupational Diseases Committee) considers the individual disease to be very probably (*beyond reasonable doubt*) caused by special occupational factors.

The most important exceptions to the European combinations of occupational disease lists and recognition procedures are the Swedish and Spanish systems. In Sweden, the recognition of occupational diseases is based on a *proof system*, based on the premise that all diseases can be recognised as occupational diseases provided that an individually diagnosed occupational disease can be proven to have been caused by occupational exposure. In Spain, the premise of the occupational disease system is that a disease can be recognised as an occupational disease only if it has been mentioned in the national list of occupational diseases, and no diseases outside the list can be recognised as an occupational disease.

The German system can also be considered as one kind of an exception to combinations of occupational disease lists and recognition procedures. In its system, the preconditions for the compensation of occupational diseases have been defined in reasonable detail in the list of occupational diseases. Its list is, however, open by nature and can be expanded thanks to the supplement clause of the Decree on Occupational Diseases. According to the supplement clause, new diseases can be added to the occupational disease list, which currently contains 73 items, provided that

- There is medical evidence that certain exposure causes certain a disease (general causation)

- A certain group of people is more exposed than the rest of the population (group-specific characteristics).

On an individual level, the recognition of a disease as an occupational disease requires, also in Germany, that the disease has been included in the list of occupational diseases and that there is causation between the disease and the patient's occupation.

In Finland, more-detailed criteria supplementing the general regulations of the Occupational Disease Act and its amendment, according to which a case of cancer can be recognised as an occupational disease, are primarily based on the report of the Occupational Cancer Working Group of 1988. Similar supplementing instructions or recommendations have been issued also in some other European countries. For example, the Swiss National Accident Insurance Fund SUVA, which manages accident and occupational disease insurance in Switzerland, has issued instructions on how several diseases can be recognised as occupational diseases.

For example, SUVA has issued such complimentary instructions for the compensation of asbestos-related malignant tumours. In some European countries, exact compensation criteria for cancers, as well as other diseases, have already been defined in legislation, and no supplementary instructions or recommendations have been issued. An example of such a country is Spain, whose list of occupational diseases is included in national legislation and contains very specific criteria for the preconditions of a disease that is to be recognised as an occupational disease.

Because of the aforementioned significant differences in the methods used for defining the compensation practices of occupational diseases in different countries, it is extremely difficult to create an all-inclusive list of cancers or exposures that could possibly be recognised in European countries. The occupational disease lists of the investigated countries are very heterogeneous with respect to the listed types of

cancer, as well as exposures. In most countries the occupational disease lists are also open by nature in the sense that, in addition to the cancers and exposures specifically included in the lists, also other types of cancer or cancers caused by other types of exposure can be recognised as occupational diseases in individual cases through different national recognition practices.

The World Health Organization (WHO) and its subordinate IARC have often declared that the reliable assessment of the numbers of occupational cancers is extremely difficult on a global scale. The same applies to the assessment of the numbers on the EU or individual member state level. Some conclusions can naturally be drawn on the basis of the numbers of occupational cancers that receive compensation as occupational diseases. A general estimate is, however, that the numbers in occupational disease statistics do not begin to tell the whole truth about the extent of this phenomenon.

4 REVIEW BY EXPOSURE

4.1 Asbestos and cancer

In this report, asbestos refers to the following fibrous silicates:

a) Actinolite asbestos, CAS No 77536–66–4

b) Amosite asbestos, CAS No 12172–73–5

c) Anthophyllite asbestos, CAS No 77536–67–5

d) Chrysotile asbestos, CAS No 12001–29–5

e) Chrocidolite asbestos, CAS No 12001–28–4

f) Tremolite asbestos, CAS No 77536–68–6.

IARC classifies asbestos as belonging to Group 1, carcinogenic in humans. The EU classification for asbestos is also 1 (CLP Group 1 A).

In Finland, over 300 000 tons of asbestos have been used since the 1910's, most abundantly in the 1960's and 1970's. Most of the asbestos was used in building materials. In addition, employees were exposed to asbestos in shipbuilding, the manufacturing of asbestos-containing products, and car and machinery maintenance. Asbestos materials were also used as protection against heat, as friction material in brakes and clutches, and in several other applications because of its technical properties. The use of chrocidolite asbestos was banned in 1976. The use of other types of asbestos was still allowed until 1994, when their use was completely banned. In practice, all buildings completed before the ban on asbestos may contain asbestos in one form or another.

The Asbestos Committee estimated that, in 1989, as many as 200 000 people had been exposed to asbestos: 150 000 in the building industry, 20 000 in shipyards, 20 000 in auto repair shops, and 10 000 in the manufacturing of asbestos products. In the 2010's fewer than 50 000 of these people were estimated to be still alive. Although the use of new asbestos has been banned, exposure is still possible in asbestos demolition work. Each year, 500–1000 workers with asbestos exposure are notified to the ASA register. Although the use of asbestos is banned and even demolition work can only be done by professionals, many workers are still exposed to asbestos. Because of the long delay between new exposure cases and the

manifestation of health problems, asbestos-related diseases will still occur for a long time. When it comes to asbestos, it must also be noted that the regulations and rules governing the use of asbestos and demolition work, or the failure to adhere to them, do not directly affect the decisions made by the insurance court regarding the compensation of occupational diseases caused by asbestos. According to the Occupational Disease Act, an employee always receives compensation for an occupational disease if exposure at work is probable and the disease can be caused by that exposure.

4.1.1 Cancers caused by asbestos

A long incubation period is typical for asbestos-related diseases. The number of cancers caused by asbestos is estimated to peak in 2010–2015. Because of the extended latency period, new cancer cases caused by asbestos will, however, be diagnosed until the 2020's or even the 2030's among those exposed before the ban of asbestos. According to IARC (2012a), there is sufficient evidence showing a link between exposure to asbestos and an elevated risk of lung cancer, mesothelioma, laryngeal cancer, and ovarian cancer. Limited evidence has been found for a relationship between asbestos exposure and cancer of the colon, stomach, and pharynx. The disease mechanism is considered to be the activation of macrophage cells caused by asbestos fibres, an inflammatory reaction, the formation of reactive oxygen and nitrogen compounds, tissue damage, genotoxicity, aneuploidy and polyploidy, epigenetic changes, the activation of signalling pathways, and apoptosis resistance.

4.1.1.1 Lung cancer

Asbestos fibres have been proven to increase the risk of all traditional types of lung cancer (adenocarcinoma, squamous carcinoma, large-cell carcinoma, and small-cell carcinoma). The current classification of lung cancers includes two other types that can be considered to belong to the same group (adenosquamous carcinoma, with characteristics of glandular and squamous carcinoma, and sarcomatoid carcinoma). There is no proven association between the salivary gland-like carcinomas of the lung and exposure to asbestos. Blue asbestos, (i.e., chrocidolite) is considered to be the most dangerous type of asbestos, while the effect of chrysotile on the risk of cancer is considered to be weaker than that of other asbestos fibres. In practice, the different types of asbestos are not separated; instead all exposure to asbestos is combined. The risk ratio is linear. In an international recommendation, an exposure level of 25 fibre-years doubles the risk of cancer (see page 44 for the definition of fibre-year) (Asbestos, Asbestosis and Cancer, Scandinavian Journal of Work, Environment & Health, 1997).

The level of exposure is also indicated by the number of asbestos bodies (AB) in bronchoalveolar lavage fluid or lung tissue (optical microscope analysis), and the number of asbestos fibres in lung tissue (electron microscope analysis, see page 44). The latency period for lung cancer from the beginning of exposure to the diagnosis of cancer is usually over 20 years (Nordman and Keskinen, 2005). Smoking and asbestos increase each other's effect on lung cancer. The development of asbestos-related lung cancer does not require asbestosis.

Smoking does not affect the occupational cancer decision. Smokers are compared in the same way as non-smokers are. Therefore, the magnitude of the risk caused by asbestos is independent of smoking. The latency period is at least 10 years. The methods recommended for determining the exposure level are screening questionnaires or structured interviews in hospitals and other places of treatment, and, if necessary, use of the centralised national (telephone) interview service of the Finnish Institute of Occupational Health (FIOH), as well as consultation with occupational medicine clinics and pneumoconiosis specialist groups. The questionnaire should be the same for all users.

4.1.1.2 Malignant mesothelioma

Asbestos and erionite, CAS No 12150–42–8, are the known pathogens for malignant mesothelioma. The disease mechanisms are related to the size and shape of these fibres, as well as to their biopersistence. Chrocidolite is the strongest pathogen, whereas the risk caused by chrysotile is significantly lower. Mesothelioma usually oc-curs in the pleura or peritoneum. All cases of malignant mesothelioma of the pleura or peritoneum can be caused by asbestos.

The latency period for malignant mesothelioma is usually long, up to 50 years. Exposure at work does not have to be severe or long-lasting. Exposure of even a couple of weeks has been shown to cause the disease. Malignant mesothelioma has also been found among the families of asbestos workers. Smoking has no effect on morbidity.

4.1.1.3 Laryngeal cancer

IARC has added laryngeal cancer to the list of cancers caused by asbestos (Group 1) (IARC, 2012a). The risk ratio is linear and follows the risk level of lung cancer.

In a meta-analysis of cohort studies, the relative risk was reported to be 1.4 [with a 95% confidence interval (CI) of 1.2–1.6] for all of the patients exposed to asbestos. When the risk was compared between those with high exposure and those with no exposure, the risk ratio was 2.0 (95% CI 1.6–2.5) (Institute of Medicine, 2006).

The relation between the risk of lung cancer and laryngeal cancer has been studied in the following recent publications: Musk et al., 2008; Pira, 2005; Finkelstein and Verma, 2004; Karjalainen et al., 1999. According to these publications the risk relations are similar. The same compensation practices apply to both laryngeal cancer and lung cancer.

4.1.1.4 Ovarian cancer

IARC has added ovarian cancer to the list of cancers caused by asbestos (IARC, 2012a). The risk ratio is linear. In cohort studies, it has been discovered that, for women who have been highly exposed to asbestos at work, there is an elevated morbidity of ovarian cancer. This is the case, for example, among women who manufactured gas masks in a British factory during the Second World War (Acheson et al., 1982). According to another study, asbestos collects in the ovaries of exposed women (Heller et al., 1996).

4.1.1.5 Other types of cancer

A group of IARC specialists considered the evidence of a relationship between exposure to asbestos and colorectal cancer to be limited. The evidence of asbestos causing cancer of the pharynx and stomach was also considered limited (IARC, 2012a).

When it comes to colorectal cancer or cancer of the pharynx and stomach, the evidence concerning asbestos aetiology is limited. According to current knowledge, these types of cancer cannot be considered occupational.

4.1.2 Procedures in suspected cases of occupational cancer

When a case of cancer is suspected to be an occupational disease caused by asbestos, exposure data and a differential diagnosis of the disease are required before the issue is decided. The occupational health specialists and occupational medicine clinics are experts in evaluating the exposure. If necessary, consultation with the pneumoconiosis specialist groups of FIOH and university hospitals, as well as with experts with the Mesothelioma Panel, can also be carried out. The incident is also reported to the occupational safety authorities.

4.1.2.1 Exposure

The level of exposure is determined primarily by studying the employee's work history. Information is gathered from the employee, employers, and the literature. The entire work history is taken into account in an interview. The employee can ask for his or her employment information from the Finnish Centre for Pensions. Different

periods of exposure are combined. The level of exposure should be estimated and calculated as fibre-years of exposure.

Exposure level (fibres/cm3) x exposure period (years) = fibre-years

A low level of exposure is considered to be fewer than 10 fibre-years. Moderate exposure is 10–24 fibre-years, and high exposure requires 25 fibre-years or more.

The employers and tasks exposing the employee to asbestos are recorded, as are the first and last year of exposure and the name of the employer at the time.

Occupational hygiene measurements may be available from the employers. Information about the materials containing asbestos, exposure levels at different times, and occupations can be found in the following books: Riitta Riala: *Asbesti purkutöissä* [Asbestos in Demolition Work] (FIOH, Helsinki 1989); Riitta Riala: *Asbesti* [Asbestos], No. 5 in the series *Altisteet työssä* [Exposure at Work] (FIOH, Helsinki 1992); and Kari Vikström: *Asbestipitoiset tarvikkeet* [Materials Containing Asbestos] (95033) (The Centre for Occupational Safety, Helsinki 1995).

Table 4 presents the exposure levels found in different occupations. The table is based primarily on industrial hygiene measurements carried out in Finland during the 1970's and 1980's, the literature, research, and empirical experiences of both industrial hygiene experts (Linnainmaa M, Tuomi T) and occupational medical experts (Oksa P, Uitti J). The table helps to determine the situations in which high exposure (= 25 fibre-years or more) has been possible. The information in the table represents the "average truth" of an industry, occupation, or task and is therefore useful if there is no exact data available on the employment of the patient. On an individual level, however, the "average truth" may lead to exaggerations or understatements. Therefore, an attempt should be made, if possible, to hold interviews or otherwise gather more-detailed information about the work tasks and exposures during the patient's entire career. When an understanding about all of his or her occupations, including exposure and its duration, is reached through interviews, the patient's asbestos exposure in fibre-years can be calculated more accurately.

Exposure has been possible even after 1994. According to the experience of FIOH experts, measurements taken from the inside of asbestos demolition workers' respirators have usually been 0 fibres/cm^3. In other words, any exposure has probably been "accidental" (i.e., materials have been demolished without them being

known to contain asbestos) or the exposure has been related to work methods or lack of protection. Asbestos diseases have also been reported among persons who have been working in demolition only after 1994 (Ylioinas et al., 2012).

Table 4. Normative exposure levels for different occupations (Linnainmaa, Oksa, Tuomi, Uitti).

	Exposure level/year, fibres/cm^3
Construction–1980	*0.5*
Asbestos spraying <1977	100
Pipe insulation	25
Machining of asbestos concrete plates <1986	20
Construction 1981–1994	*0.3*
Renovation 1950–1994	*1*
Demolition of asbestos insulation <1987	25
Water and sewage pipework (municipal engineering)	*0.3*
Shipbuilding <1977	*5*
Asbestos spraying <1977	100
Shipbuilding 1978–1988	*3*
Vehicle brake and clutch repair work <1988	*0.2*
Maintenance and installation work	*0.3*
(Handling of gaskets, filters, insulating paste, etc. Containing asbestos)	
Asbestos product manufacturing <1989	
Asbestos concrete manufacturing <1970	33
Asbestos concrete manufacturing 1971–	2
Asbestos concrete product manufacturing	1
PVC tile manufacturing <1980	4
PVC tile manufacturing 1981–	1
Asbestos cardboard manufacturing	10
Textile manufacturing	5
Bitumen product and paint manufacturing	1
Mining industry and rock handling,	
with knowledge of asbestos	*0.2*
Asbestos mines <1976	*10*
Drilling and hauling	55
Enrichment <1969	200
Enrichment 1970–	10

Rows in italics in Table 4 are estimates of the generic exposure level of an industry. These estimates include exposure to dust caused by others, as well as sporadic exposure in one's own work. A detailed work history may therefore change the exposure level.

Exposure is also indicated by asbestos bodies (AB) in the bronchoalveolar lavage fluid. These bodies are formed when a person's body covers asbestos fibres with protein in order to eliminate their harmful effects. Determination is made from the bronchoalveolar lavage fluid collected from the (centre section) of the bronchial pathway during bronchial endoscopy using an optical microscope. The results are measured in AB/ml. A result of over 1 AB/ml indicates occupational exposure to asbestos (Asbestos, Asbestosis and Cancer: the Helsinki Criteria for Diagnosis and Attribution: Consensus Report. Scandinavian Journal of Work, Environment & Health 1997; 23: 311–316).

Asbestos bodies can also be assessed from histological tissue samples. The limit used in an international recommendation (Helsinki Criteria) is 2 or more asbestos bodies per square centimetre. Finland is practically the only country in which anthophyllite, which has a strong tendency to form asbestos bodies, has been primarily used. Therefore, in Finland, the appearance of asbestos bodies is common. The formation of asbestos bodies not only depends on the type of asbestos, but also on the person's tendency to form asbestos bodies and possibly also, for example, on the iron content of the air breathed. Therefore, the percentage of coated asbestos fibres from the total asbestos fibre content in the lung tissue varies, and a small number of asbestos bodies does not rule out a high exposure level. For these reasons, it is possible to overestimate or underestimate exposure that is based on asbestos bodies, and the results must be compared with the work history and an asbestos fibre analysis.

A transmission electron microscope (TEM) is used determine asbestos exposure from a sample of cremated lung tissue. The sample should represent normal lung tissue and not, for example, cancer tissue or fibrosis. According to the Helsinki Criteria document, occupational exposure is indicated by one million fibres per gram of dry lung tissue. A high level of exposure to asbestos is indicated by two million amphibole fibres (>5 μm) or five million amphibole fibres (>1 μm) per gram of dry lung tissue. The determination of chrysotile asbestos exposure according to fibre analysis is uncertain because chrysotile is removed from the body faster than other types of asbestos. The determination limits vary between laboratories. According to the current practices of the Finnish Institute of Occupational Health (FIOH), high exposure (sufficient to cause lung cancer or asbestosis) is considered to be a value in excess of 2–3 million (>1μm) fibres per gram of dry lung tissue.

It is not justifiable to take lung tissue samples only for determining exposure to asbestos. Lung tissue can, however, be used if histological samples have been extracted for other reasons (removal of the lung or a part of it, diagnostic biopsies for determining the cause of lung fibrosis, etc.). In autopsies, the main indication may be a suspicion of occupational disease, and, in such cases, samples should be taken for fibre analysis.

Coroners have set up guidelines to help them determine occupational diseases related to asbestos (handout 23 February 2011, *Occupational Diseases in Establishing Cause of Death in Forensic Medicine and Compensation Practices for Occupational Disease, Final Report,* 20 March 2012). In addition, the occupational health committee of the Finnish Ministry of Social Affairs and Health has decided that there is no need to perform a forensic autopsy if the patient's death is caused by lung carcinoma or mesothelioma that has been accepted as an occupational disease. In such cases, it is enough that the cause of death is established by the police on the basis of documents and the medical certificate. Regulatory guidance is being prepared by the Finnish Ministry of Social Affairs and Health.

4.1.2.2   Lung cancer among asbestosis patients

Exposure to asbestos can cause lung cancer without asbestosis. The emergence of asbestosis requires moderate or high exposure and sufficient latency. According to some studies, the risk of lung cancer among asbestosis patients is 2–5 (IARC, 1987). For Finnish asbestosis patients, the risk has been determined to be 8 (SMR) and 10 (SIR) (Oksa et al., 1997).

If a lung cancer patient has asbestosis visible in an imaging analysis or it can be microscopically verified (pathological-anatomical diagnosis), the cancer patient can receive compensation as an occupational disease.

4.1.2.3   Diagnostics and tracking of asbestos exposure, lung cancer screening

There is a legal obligation to keep track of workers who have been exposed to asbestos even after their exposure and work careers have ended. The used follow-up methods have been described in the guidebooks *Terveystarkastukset työterveyshuollossa* [Medical Checks-ups in Occupational Healthcare] (Työterveyslaitos, 2006) and *Asbestisairauksien diagnostiikka ja seuranta* [Diagnostics and Follow-up of Asbestos-related Diseases] (Nordman et al, 2006). Practical instructions can also be obtained from the website of the Finnish Respiratory Association [Hengitysliitto] www.heli.fi, for example, the guides *Vaarallinen asbesti* [Dangerous Asbestos] and *Asbestialtistuneen muistilista* [Checklist for People Exposed to Asbestos].

Lung cancer screening may decrease mortality. The National Lung Screening Trial (NLST, 2011) compared low-dose computed tomography (CT) scans to chest radiographs when screening people with a high risk of lung cancer. This study covered 33 research locations in the United States, and it screened 53 000 current or ex-smokers who were symptomless. The participants were randomly selected three times for yearly CT scans or chest radiographs. The follow-up lasted for about 6.5 years. In October of 2010, the independent Data and Safety Monitoring Board interrupted the study. There had been 354 deaths caused by lung cancer among the people followed by CT screening (of about 26 500 people) and 442 among the control group. Lung cancer mortality decreased a statistically significant 20%. In other words, deaths caused by lung cancer decreased by 88 cases per 26 500 persons screened – 1 for every 300 people. In addition, the total mortality of the screening group decreased. According to a review published in June 2012, lung cancer screening using low-dose CT may be beneficial for certain exposed groups, but the possible harmful effects of the screening, as well as how the results can be applied to other exposed groups, was still unclear (Bach et al., 2012).

4.1.2.4 Forensic pathology

It would be desirable for occupational disease issues to be clarified while the patient is alive. This problem was addressed in an earlier report by a committee of the Finnish Ministry of Social Affairs and Health (*Ammattitaudit oikeuslääketieteellisessä kuolemansyynselvityksessä ja ammattitautikovausjärjestelmän käytännöt, Loppuraportti 20.3.2012* [Occupational Diseases in Forensic Pathology and the Compensation Practices for Occupational Diseases, Final Report 20 March 2012]). Statutory forensic pathology is, however, very important in the diagnosis of occupational diseases, especially if the investigation process is not finished or has not been started. When it comes to a police investigation and a possible forensic autopsy, it is extremely important that as detailed an occupational history as possible is available for the patient, as well as information about possible ongoing processes in the insurance system. The aforementioned committee of the Finnish Ministry of Social Affairs and Health has decided that there is no need to perform a forensic autopsy on a patient who has died from lung carcinoma or mesothelioma if the case has been accepted as an occupational disease. In such cases, it is enough that the cause of death is established by the police on the basis of documents and the medical certificate.

4.2 Quartz

An international cancer research institute (IARC/WHO) has determined that quartz and cristobalite are carcinogenic in humans (Group 1, IARC 1997). This assessment was updated in 2009 (Group 1, IARC 2012a). In a meta-analysis concerning all patients with silicosis, an elevated risk of lung cancer was detected for patients with silicosis [risk ratio (RR) 1.7–2.8)] (IARC 2012a, Table 2.3). In a meta-analysis in which silicosis patients were not separated from those without silicosis, the relative risk point estimates for lung cancer were 1.3–1.4 (IARC 2012a, Table 2.3).

The most recent meta-analysis was carried out by Erren et al. (2009) (38 studies until January 2007). According to this analysis, the relative risk of lung cancer for patients with silicosis was 2.1 (95% CI 2.0–2.3). There was no risk of lung cancer for those without silicosis, the risk ratio being 1.0 (95% CI 0.8–1.3). The analysis was based on three studies in which the proportion of smokers was notable. For eight studies in which smoking was not controlled, the risk of lung cancer for those without silicosis was about 1.2 (95% CI 1.1–1.4).

In addition to the analysis by Erren et al. (2009), IARC has published tables on two other meta-analyses in which the risk of lung cancer was assessed in a group of people exposed to quartz, but without silicosis (IARC 2012, Table 2.3). When the cohort and case-control studies of Kurihara and Wada (2004) were combined, the risk ratio was 1.0 (95 % CI 0.8–1.2). In the cohort study of Pelucchi et al. (2006), it was 1.2 (95% CI 0.9–1.6), and in their case-control study it was 1.0 (95% CI 0.7–1.4).

The assessment of the association between cumulative exposure to quartz and lung cancer morbidity has yielded mixed results. In the meta-analysis (10 studies) by Lacasse et al (2009), the cumulative exposure to quartz was found to be related to an increased risk of lung cancer. The results were nevertheless heterogeneous. The interpretation of the results is made difficult by the fact that the material contained people with and without silicosis, and these groups could not be analysed separately. Therefore, Lacasse et al. did not answer the question of whether the risk of lung cancer is elevated among people exposed to quartz but do not have silicosis.

The exposure to quartz and the mortality of granite workers in Vermont has been monitored for 100 years in studies that have been significant in developing the standards for quartz in the United States. The latest analysis concerning the mortality of 7052 employees was published in 2011 (Vacek et al., 2011). The lung cancer mortality of the employees was higher than expected (SMR 1.4, 96% CI 1.2–

1.5), but no association was found between the cumulative exposure to quartz and lung cancer morbidity (OR 1.0, 95% CI 0.9–1.0). The slight increase in lung cancer mortality was attributed to smoking or other types of exposure.

A large cohort study in the German porcelain industry has analysed silicosis morbidity and lung cancer mortality in relation to work history and the results of 8000 industrial hygiene measurements. The cumulative exposure to quartz was found to be strongly associated with silicosis morbidity, but not with lung cancer mortality (Mundt et al., 2011).

There is uncertainty in the interpretation of the results of epidemiological cancer studies because quartz is a weak carcinogen. The meta risk ratio for lung cancer among silicosis patients is about 2, and the risk estimate is significantly lower when people without silicosis are also included in the same analysis (meta RR 1.3–1.4). Epidemiological studies on the carcinogenicity of quartz can be distorted by the following factors:

- structure of the material and quality of the follow-up;

- separate analysis of people with silicosis and those without it;

- confounding effect of other types exposure;

- effect of smoking;

- differences between socioeconomic groups;

- comparability of control material;

- selective bias in association with occupational disease registers;

- quality of data on cumulative exposure;

- difficulties in defining dose–response;

- selections and methods of a meta-analysis (problems with heterogeneity, *sensitivity analysis*);

- problems and interpretations of statistical modelling, testing, and evaluation.

In Finland, about 70 000 employees are exposed to quartz, especially in mining, quarrying and construction, foundry work, sand blasting using materials containing quartz, and in the manufacturing of glass, porcelain, cement, mortar, brick, concrete and other clay or stone products (Vainio et al., 2005). In the industrial hygiene measurements carried out in 2004–2007 by the Finnish Institute of Occupational Health (FIOH), a high quartz content [i.e., an occupational exposure limit (OEL) of over 0.05 mg/m^3] was detected in mines, quarries, foundries, and a glass factory, as

well as in the manufacturing of roofing felt and concrete products (Saalo et al., 2010).

In conclusion, it can be noted that

- IARC has classified quartz and cristobalite as being carcinogenic in humans

- Patients with silicosis have a double risk of lung cancer

- Not enough evidence exists about increases in risk among patients with lung cancer without silicosis.

4.3   Other chemical factors

This section primarily contains information about chemical substances whose carcinogenicity has been clearly proven. According to their carcinogenicity, these agents have, in most cases, been classified into Group 1 by IARC or into Category 1A by the EU. There are also some substances belonging to IARC Group 2A or EU Group 1B, as well as, for example, nanoparticles, whose carcinogenic properties are not yet well known. These agents have been included in this report either because they are significant sources of exposure in Finnish worklife or because their possible carcinogenicity has lately caused concern. They include, for example, carbon nanotubes.

4.3.1 Polycyclic aromatic hydrocarbons

IARC has evaluated and classified several compounds and mixtures comprised of individual polycyclic aromatic hydrocarbons (PAH) according to their carcinogenicity. Of the individual PAH compounds, only benzo(a)pyrene has been classified into Group 1, whereas cyclopenta[c,d]pyrene, dibenzo[a,h]anthracene, and dibenzo[a,l]pyrene belong to Group 2A. A group of other, less studied individual PAH compounds have been classified into groups 2B and 3. Of the common PAH mixtures, IARC has classified coal tar, soot, coal tar pitch, and diesel exhaust into Group 1 and creosote and bitumen into Group 2B. IARC has also classified occupations that expose employees to PAH compounds as follows: occupational exposures during coal gasification, coal tar distillation, coke production, aluminium production, paving and roofing with coal tar pitch, and chimney sweeping are carcinogenic in humans (Group 1). Occupational exposures during carbon electrode manufacture are classified as probably carcinogenic in humans (Group 2A). Employees in foundries are also exposed to PAH compounds in addition to other

exposure (quartz and metal fumes). IARC has classified iron and steel founding into Group 1 (see Section 5.6). Certain fuel oils, such as kerosene and diesel fuel, may also contain over 5% PAH compounds. Heavy fuel oils and maritime diesel fuel have been classified into Group 2B by IARC, whereas light fuel oils and light diesel fuels have not yet been classified.

The capacity of PAH compounds to cause cancer was first demonstrated already in 1775 among chimney sweeps, who were diagnosed with testicular cancers caused by exposure to soot. In the 1900's the capacity of PAH compounds to cause skin cancer was detected in animal test models when PAH compounds or mixtures were applied to the skin of animals. The association between PAH exposure and the risk of cancer has been researched in several epidemiological studies in different industries in the 20th and 21st centuries. The strongest evidence for a relationship between occupational PAH exposure in relation to lung cancer has been found in coal gasification, coke production, and aluminium production.

A comprehensive study concentrating on lung cancer mortality among 5321 coke oven workers in the United States and Canada in 1952–1982 showed that there was an increased risk of lung cancer among coke oven workers (Costantino et al., 1995). The risk was greatest among employees who had been exposed for 15–19 years and over 20 years (SMR 2.91 and 2.71, respectively) (Costantino et al., 1995). A meta-analysis of 10 cohort studies carried out by Bosetti et al. (2007) showed, on the other hand, an increased risk of lung cancer (RR 1.58, 95% CI 1.47–1.69) among coke oven workers.

Similar risk ratios for lung cancer have been detected in aluminium and gas production and also in coke oven work. The risk ratios in individual studies have mainly varied between a little over 1 and a little over 2 (IARC 2010a).

In studies concentrating on employees exposed to creosote, elevated risks of skin cancer have been detected. In a Swedish cohort study among wood impregnators, an elevated risk of skin cancer (not melanoma) and lip cancer was detected (SIRs of 237 and 250, respectively) (Karlehagen et al., 1992). Exposure to ultraviolet radiation may also have affected the risk. In a Finnish register-based study, an increased risk of lip cancer and skin cancer other than melanoma was detected for round timber workers who had (probably) been exposed to creosote (SIR 306 and 464, respectively) (Pukkala et al., 1995).

For roofing and paving work, there is primarily evidence of an elevated risk of lung cancer. In the United States, Hammond et al. (1976) noted a 2.47-fold risk of lung cancer for roofing employees who had been exposed for over 40 years. In their comprehensive American cohort study, Stern et al. (2000) found the relative risk of

lung cancer mortality among roofing employees to be 1.39. A wide European study (Boffeta et al., 2003a) did not indicate an elevated risk among paving employees. In a meta-analysis by Partanen and Boffetta (1994) on 20 studies, a risk ratio of 1.78 was detected for roofing employees, whereas the risk ratio for paving employees was only 0.87 on the basis of three cohort studies.

In a Swedish cohort study among 5313 chimney sweeps (Evanoff et al., 1993), it was noted that increased lung cancer morbidity correlated with career length. For the entire cohort, the risk of lung cancer was 2.09 (SIR), and, for those who had been exposed for 10–19 years, it was 2.19. For those who had been exposed for 20–29 years, the risk was 2.68, and, for those exposed for over 30 years, it was 2.34. The risk of bladder cancer was also increased (SIR 2.53). The risk of cancer of the oesophagus was also elevated (SIR 3.87), but this value was based on significantly fewer incidents. Skin cancer risk was not elevated. In a register-based study carried out by Pukkala (1995), a lung cancer SIR of 1.35 was noted for chimney sweeps.

WHO (2000) has estimated, based on epidemiological studies carried out among coke oven workers, that the individual risk of lung cancer caused by PAH compounds during lifelong exposure is 6.2×10^{-4} per 1 µg/m^3 as a benzene-soluble fraction of total particulate matter.

In Finland, employees have been exposed to PAHs especially in coke oven work, the creosote impregnation of wood, foundry work, work with coal tar, and coal tar and petroleum-based product manufacturing, as well as through exposure to exhaust fumes (Vainio et al., 2005). The exposure routes vary in different tasks; pulmonary exposure to PAHs is the most significant in coke oven work, whereas exposure in, for example, wood impregnation and the handling of impregnated wood occurs mainly through the skin.

Summary: There is much evidence from different occupations on the association between PAH exposure and lung and skin cancer. The risk and type of cancer depend on the intensity and duration of exposure, as well as on its the primary route. The strongest evidence on the risk of cancer has been detected in coal gasification, coke production, and aluminium production. Exposure to creosote has been linked mainly to skin cancer. The dose–response ratios are unclear.

4.3.2 Diesel exhaust

In 2012, IARC classified the carcinogenicity of diesel exhaust as Group 1.

The IRIS (Integrated Risk Information System) database lists over 30 epidemiological studies about the carcinogenicity of diesel exhaust, ranging over 40 years until the year 2003 (IRIS 2003). Most of these epidemiological studies have

concentrated on certain exposed groups of employees, such as railroad workers, truck drivers, machine operators, tractor drivers, and other operators of diesel engines. Some of the studies are reviews and meta-analyses of earlier research projects.

An increased risk of lung cancer has been detected in 8 of 10 cohort studies. In 5 of these studies, the difference was statistically significant. An increased risk of lung cancer has also been detected in 10 of 12 case-control studies. In 8 of these, the difference was statistically significant. The average relative risk has varied between 1.2 and 1.5. Independent meta-analyses have also detected statistically significant increases in risk (RR 1.33–1.47).

In an ongoing, comprehensive case-control study (Olsson et al., 2009), the results of earlier studies from Germany, Italy, Sweden, France, and Canada have been combined. This study contains 13 412 cases and 16 320 controls. In this study, the OR of the group with the highest exposure was 1.36. A similar amount of increased risk (OR=1.2–1.6) was detected in a Canadian study (Parent et al., 2007), but it was not statistically significant.

A doctoral dissertation published in Finland showed no clear increase in the relative risk of lung cancer caused by exposure to diesel exhaust (Guo, 2005). In a recently published case-control study among mining workers, which was based on comprehensive cohort material, the risk of lung cancer among the most-exposed group was about threefold (Silvermann et al., 2012). English scientists have estimated diesel exhaust to be among the most significant causes of occupational lung cancer (626 cases/year) (Rushton et al., 2008). In a similar study carried out in Finland, the current level of exposure to diesel exhaust has been estimated to be the cause of 9 new cases of lung cancer per year (Priha et al., 2010).

There are no industrial hygiene limits set for diesel exhaust in Finland. According to industrial hygiene measurements, the exposure is highest when diesel vehicles are used in closed spaces such as tunnelling sites and mines.

Summary: Although an association between exposure to diesel exhaust and lung cancer has been detected in epidemiological studies, the risk ratios have usually been relatively low, 1.2–1.5.

4.3.3 Environmental tobacco smoke

In 2002, IARC classified environmental tobacco smoke as carcinogenic in humans (Group 1). This assessment was based on a small, but consistent increase in the risk of lung cancer among the non-smoking spouses of smokers, which was detected in epidemiological studies, and also on the knowledge that environmental tobacco

smoke contains several of the known or suspected carcinogens found in smoke inhaled during active smoking (IARC, 2002).

Among non-smoking people who have been exposed to environmental tobacco smoke in their homes, the risk of lung cancer has been estimated to be 1.2–1.3 times the risk of people that have not been exposed in such a manner. In a meta-analysis published in 2007, exposure to environmental tobacco smoke in the workplace results in a 24% additional risk of lung cancer (Stayner et al., 2007). The risk was affected by both the level and duration of exposure. Among the most exposed people, the risk was twofold. Some studies have also indicated a relationship between environmental tobacco smoke and cancer of the larynx or pharynx. The causality is, however, not as clear as it is with lung cancer (IARC, 2002).

Before legislation banning smoking in Finnish restaurants (effective since 1 June 2007), over 40 000 restaurant employees were exposed to environmental tobacco smoke. Over 30 000 of them were exposed to tobacco smoke from customers or colleagues for over one-fourth of their annual worktime (Kauppinen & Virtanen, 2002). The exposure levels in restaurants varied greatly; when measured as the nicotine content in air, the range was 1 $\mu g/m^3$–100 $\mu g/m^3$ (Kauppinen & Virtanen, 2002). Exposure to environmental tobacco smoke also occurs, for example, in the metal industry, construction, penitentiaries, and many small workplaces. In these other workplaces, the exposure levels have been significantly lower. In addition to active smoking, also passive smoking at home is an important confounding factor when the effect of occupational exposure in the formation of lung cancer is being assessed.

Summary: Although an association between exposure to environmental tobacco smoke and lung cancer has been detected in several epidemiological studies, the risk ratios have been relatively low (1.2–1.3). Therefore, proving that environmental tobacco smoke is a cause of individual lung cancer is difficult.

4.3.4 Benzene

Benzene is an IARC Group 1 carcinogen. In the EU, it has also been classified into the CLP Category 1A. The association between benzene and acute myeloid leukaemia is well known. Benzene has also been suspected to cause other types of haematological cancer, such as multiple myeloma and non-Hodgkin's lymphoma. The evidence concerning these is, however, scarce.

The latency period for leukaemia caused by benzene has usually been considered to be about 10 years or less. The information available about dose–response ratios

varies; according to some studies even exposure as low as 40 ppm-years (e.g., 40 years to 1 ppm, *parts per million*) significantly increases the risk, whereas, in other studies, a significant increase was only detected at 40–200 ppm.

In what is called the Plioform study, the risk of leukaemia (SMR) was 1.45 at the exposure level of 1–40 ppm-years, 3.21 at 40–200 ppm-years, 5.44 at 200–400 ppm-years, and 23.96 at over 400 ppm-years (Rinsky et al., 2002). Based on these data, the relative risk caused by exposure to 1 ppm for 45 years is 2.05. In another significant cohort (Hayes et al., 1997), the risk ratio (RR) of acute non-lymphocytic leukaemia (ANLL) due to an exposure level of 40 ppm-years was 1.9, 4.3 at an exposure level of 40–99 ppm-years, and 3.6 at exposure of over 100 ppm-years. The respective numbers for ANLL and MDS (myelodysplastic syndrome) were 2.7, 6.0, and 4.4. It was noted that the risk correlated the best with the last 10 years of exposure (Hayes et al., 1997). According to some studies, exposure peaks can be significant causes of leukaemia. If an employee has been diagnosed with acute myeloid leukaemia, the following criteria have been suggested to support benzene as an aetiological factor (Natelson, 2007):

- Myelodysplastic syndrome

- Defect in chromosome 5 or 7

- Exposure history in which the cumulative dose can be estimated to be at least 40 ppm-years during the last 10 years

- Poor response to chemotherapy.

It should be noted that the occurrence of acute myeloid leukaemia (AML) increases significantly among older age groups and that these cancers can include chromosome defects that are similar to those found with leukaemia related to benzene exposure among younger people.

In Finland, the highest exposures to benzene in the 2000's were detected primarily in automotive maintenance and installation work, as well as in oil refinery work. In general, excluding individual measurements, these exposures have been clearly lower than the set exposure limit for air (1 ppm = 3.25 mg/m^3) for benzene and the related limit set for biomonitoring measurements (14 µmol/l, concentration in urine). In the 83 measurements carried out in 2004–2007 by the Finnish Institute of Occupational Health (FIOH), the mean value was 0.09 mg/m^3, and 95% of the measurements were below 0.96 mg/m^3. On this basis, it is safe to say that the current risk of leukaemia due to exposure to benzene in Finland is very low. In an occupation-specific follow-up of cancer morbidity, the risk of leukaemia among car

mechanics in the Nordic countries was similar to the risk of other groups of professionals (NOCCA, 2012).

Summary: When the level of exposure to benzene in Finland during the last 10–20 years is taken into account, occupational cancers caused by benzene are improbable. In individual cases, however, if sufficient exposure can be shown (40 ppm-years during the last 10 years), occupational cancer is a possibility for a patient with acute myeloid leukaemia (AML).

4.3.5 Nickel

IARC has classified nickel compounds as being carcinogenic in humans (Group 1). Nickel metal and its alloys, on the other hand, have been classified into cancer Group 2B (possibly carcinogenic in humans). In the EU, metallic nickel and nickel carbonyl have been classified as belonging to Category 2 (H351), and nickel compounds are found in the cancer category of 1A (H350i). The evidence on the carcinogenic effects is the strongest for soluble nickel compounds, but also for nickel oxide and nickel sulphide. These nickel compounds have been found to be associated with both lung and nasal cancer.

4.3.5.1 Lung cancer

Andersen et al. (1996) noted a relationship between cumulative exposure to nickel and the risk of lung cancer. A cumulative exposure of more than 15 mg/m^3 x year to a concentration of soluble nickel increased the risk to RR 3.1 (Table 5). A similar, yet weaker trend was also noted for exposure to nickel oxide (low soluble). At the highest levels of exposure, the risk ratio increased to 1.5–1.6 (IARC, 2012a).

Table 5. Relationship between lung cancer incidence and cumulative exposure to soluble nickel[a] (Andersen et al., 1996; SCOEL, 2011b; IARC, 2012a).

Exposure level (mg/m^3) x year	Mean exposure (mg/m^3) x year	Number of lung cancers (n)	RR[b]	95 % CI
< 1	0.1	86	1.0	–
1–4	2.3	36	1.2	0.8–1.9
5–14	8.8	23	1.6	1.0–2.8
≥ 15	28.9	55	3.1	2.1–4.8

[a] Nickel compounds could not be specified.

[b] Controlled for smoking, age, and nickel oxide exposure.

In Finland, exposure to nickel compounds occurs especially in the electrolytic enrichment of nickel, as well as during the welding and machining of stainless, acid-proof, or special steel (Vainio et al., 2005). In measurements carried out by the Finnish Institute of Occupational Health (FIOH), the median nickel content in air was 0.005 mg/m^3 for the years 1994–1998 (n=335, mean = 0.21 mg/m^3, maximum = 55 mg/m^3), 0.008 mg/m^3 for the years 1999–2003 (n=213, mean = 0.06 mg/m^3, maximum = 2.7 mg/m^3), and 0.005 mg/m^3 for the years 2004–2007 (n=347, mean = 0.04, maximum = 2.7 mg/m^3) (Heikkilä and Saalo, 2005; Saalo et al., 2010). The current occupational exposure limit for nickel compounds (0.1 mg/m^3) was exceeded during these years in 7%–9% of the measured samples (Saalo et al., 2010). Process measurements of nickel compound manufacturing are not included in the FIOH measurements. A high nickel concentration has been detected in, for example, steel machining, metal spraying, metal casting, and grinding and coating. In a study carried out in 1997 on the electrolytic cleaning of nickel, the concentrations of nickel compounds were lower than 0.04 mg/m^3 in samples collected from the inside of a respirator (Kiilunen et al., 1997).

In a cohort study by Grimsrud et al. (2003), similar risks of lung cancer were detected both among nickel electrolysis workers who had been exposed to nickel sulphate before 1953 and among those who were exposed to nickel chloride after 1953 (SIR=5.5 for employees exposed before 1953 and SIR=4.4 for employees exposed after 1953). Significant increases in risk ratios were also detected for other nickel enrichment occupations (SIR 3.3–7.0, depending on occupation). It has also been noted that exposure to poorly soluble nickel compounds (nickel sub-sulphide and nickel oxide) increased the risk of lung cancer (Doll, 1990). In a Finnish study (Anttila et al., 1998), it was found that, for nickel enrichment (exposure to soluble nickel sulphate), the risk of lung cancer was 2.61 for the entire cohort. When the risk of cancer was studied with a latency period of more than 20 years, risk was even higher (SIR=3.38). The average concentration of soluble nickel in the air was 0.25 mg/m^3. Similarly, a clearly elevated risk of lung cancer (SIR=2.00) was noted for smelters after a latency period of more than 20 years.

WHO has estimated that the unit risk factor for nickel-related lung cancer is 3.8 x 10^{-4} µg/m^3. According to this value, it can be calculated that, when an employee is exposed to nickel compounds (different mixtures of nickel compounds) for his or her entire career, at the current occupational exposure limit for nickel of 0.1 mg/m^3, 3 excessive lung cancers are caused for every 1000 exposed employees (3×10^{-3}). When the concentration is 0.01 mg/m^3, 3 excessive cancers occur for every 10 000

exposed employees (3×10^{-4}), and, when the concentration is 0.001 mg/m^3, 3 excessive cancers are caused for every 100 000 exposed employees (3×10^{-5}). This estimate is based on the assumption that the dose–response ratio is linear. There are, however, different views about the form of the dose–response ratio at low levels of exposure. For example, the opinion of the Scientific Committee on Occupational Exposure Limits (SCOEL) is that, on the basis of mechanistic information, there is no risk of cancer when a person is exposed to concentrations of less than 0.01 mg/m^3.

Summary: There is convincing evidence that exposure to nickel compounds is related to lung cancer, but information about the dose–response ratios is inadequate. When the cumulative exposure level increases to more than 2 mg/m^3, the risk ratios may become significant. The evidence on dose–response ratios is the most conclusive concerning soluble nickel, but also low soluble nickel compounds clearly cause cancer. There is no epidemiological evidence about the carcinogenicity of metallic nickel.

4.3.5.2 Sinonasal carcinoma

IARC has evaluated the association between exposure to nickel and sinonasal carcinoma. It states that an increased risk of sinonasal carcinoma is connected with nickel refining, but not with smeltering (unlike the case for lung cancer). The risks are the highest for soluble nickel. There is also independent evidence concerning the risks caused by nickel sulphates and nickel oxides.

In the literature on pathology, exposure to nickel has been found to be associated with squamous cell carcinoma cases. There were no references to histology in the reviewed epidemiological studies.

Most of the information regarding exposure levels can be found in a 1996 publication by Andersen et al., which concentrates on nickel refinery workers. In their research, nickel oxide and soluble nickel compounds were studied separately. A dose–response ratio was identified for both, and nickel oxide was noted to cause a higher risk of sinonasal carcinoma than soluble nickel did. Twelve cases of sinonasal carcinoma were diagnosed among employees who had been primarily exposed to nickel oxide (>15 mg/m^3, SIR 44.7). Other exposures were various mixed exposures. For the employees exposed only to soluble nickel, the SIR was 2.7 (95% CI 0.3–9.8) on the basis of two cases. When the nickel oxide concentration was 1–4 mg/m^3 x year, the SIR for the entire soluble group (the highest category being more than 15 mg/m^3 x year) was 14.3 (95% CI 5.2–31.2). All of the cases of sinonasal carcinoma were diagnosed for people who had been employed before 1956. Thereafter, the risk of sinonasal carcinoma decreased.

In 1998, Järup et al. studied battery workers who were exposed to nickel hydroxide and cadmium oxide. Two of the sinonasal carcinoma cases occurred at a nickel exposure level of more than 2 mg/m^3, and one occurred at an even lower level.

In a Finnish study carried out in a nickel refinery, 2 cases were detected when only a level of 0.04 cases was expected (Anttila et al., 1998).

Summary: There is clearly an elevated risk of sinonasal carcinoma related to nickel refinery work. The exposure level of about 1 mg/m^3 x year can be regarded as an indicating limit. On the other hand, also the diagnosis should be noted; sinonasal carcinoma is a relatively rare tumour whose occurrence is significantly affected by exposure to nickel. On this basis, the link between nickel refinery work and sinonasal carcinoma can be considered sufficient. The EU (EC, 2009) proposes 6 months as the minimum duration of exposure and 15 years as the induction period. Even though the evidence is the most compelling for nickel refinery work, it can be assumed that similar exposure in other occupations can also cause an elevated risk of sinonasal carcinoma.

4.3.6 Chromium (VI)

IARC has classified hexavalent (VI) chromium as carcinogenic in humans (Group 1). In the EU, it has been classified into cancer Category 1A (H350) according to the CLP. There is sufficient evidence showing an association between exposure to chromium (VI) and lung cancer (IARC, 2012a). In addition, some cohort and case-control studies propose that exposure to chromium (VI) could also be linked to sinonasal carcinoma. According to the evaluation by IARC, these results are difficult to assess because, for example, of possible bias mechanisms (IARC, 2012a).

The most compelling evidence for an increased risk of lung cancer exists for the manufacturing of chromates and chromate pigments. The dose–response has been researched in two cohort studies published in the early 2000's concerning chromate manufacturing. In the study by Gibb et al. (2000), the relative risk for all employees exposed to chromium (VI) was 1.8, but when the cumulative exposure level was 0.077–5.25 mg/m^3 x year, the relative risk increased to 2.24. In the study carried out by Luippold et al. (2003), the relative risk (SMR) for all employees exposed to chromium (VI) for an average of 1.58 mg/m^3 x year chromium (VI) was 2.41. For the most exposed group of employees (2.70–23 mg/m^3 x year) the risk was 4.63, whereas, for the second most exposed group (1.05–2.69 mg/m^3 x year), the SMR was 3.65 (95 % CI 2.08–5.92) (IARC, 2012a).

On basis of epidemiological research, SCOEL (2004a) has estimated that the calculated risk of cancer related to exposure to chromium (VI) is 0.5–3 excessive

cases of lung cancer for every 10 000 exposed people at an exposure level of 0.005 mg/m^3. According to the SCOEL calculations, exposure to a chromium (IV) concentration of 0.02 mg/m^3, corresponding to the current occupational exposure limit (0.05 mg/m^3), causes 2–11 excessive deaths because of cancer for every 1000 exposed employees.

In Finland, the workers with the highest exposure to hexavalent chromium are welders and platers, machinists, gas cutters, and construction workers. In addition, metal coating work, wood impregnation, and chromate pigment handling may expose employees to hexavalent chromium. The exposure of welders to chromium (VI) is described in Section 5.3.7, which concerns welding fumes. According to measurements carried out in 1994–2003 by the Finnish Institute of Occupational Health (FIOH), the concentration of chromium (VI) in the workplace air was usually below 0.005 mg/m^3 at chrome-plating facilities in which baths containing chromium (VI) compounds are used (Työterveyslaitos, 2007a). The levels detected in all of the chromium (VI) measurements carried out by FIOH in 1994–2007 remained relatively constant. The median, mean, and maximum values of these measurements were as follows: 0.001, 0.007, and 0.32 mg/m^3, respectively, in 1994–1998; 0.002, 0.003, and 0.063 mg/m^3, respectively, in 1999–2003; and 0.001, 0.007, and 0.21 mg/m^3, respectively in 2004–2007 (Saalo et al., 2010).

Summary: Exposure to chromate compounds has been identified as a cause of lung cancer. There is, however, little information about the dose–response ratios. The widespread nature of lung cancer and other factors increasing the risk of lung cancer make the assessment of the occupational background of cancer difficult on an individual level. Therefore, every suspected case of occupational cancer caused by chromium (VI) compounds must be considered individually, and the level of exposure must be taken into account. An exposure level of 1 mg/m^3 x year can be considered the lower limit for high exposure in relation to lung cancer. Some data suggest a relationship between exposure to chromium (VI) and sinonasal carcinoma, but it is difficult to assess the results of existing research because of, for example, possible publication bias. There is no evidence for the carcinogenicity of metallic chromium or trivalent chromium.

4.3.7 Welding fumes

The welding of stainless steel can expose employees to carcinogenic hexavalent chromium and nickel. In 1990, IARC classified welding fumes as possibly carcinogenic in humans (Group 2B). This assessment was based on epidemiological research that indicated an increase of about 30%–50% in the risk of lung cancer among welders.

In 2001, Nurminen and Karjalainen estimated that 1.6% of the lung cancers occurring among men and 0.1% of those occurring among women could be caused by exposure to chromium (VI) compounds during welding. These values would correspond to 25–30 cases of cancer in Finland annually. The evaluation was based on the risk ratio of 1.4 derived from a study by Droste (1999). Ambroise et al. (2006) carried out a comprehensive meta-analysis containing 60 epidemiological studies published in 1954-2004, in which it was noted that the risk of lung cancer among welders was elevated by 26% (RR 1.26, 95% CI 1.21–1.32). Sørensen et al. (2007) found that the risk of lung cancer among a cohort of 4539 welders was elevated by 35%. Among welders of stainless steel (but not of non-alloyed steel), the risk correlated with the duration of exposure. The mean total fume exposure was 1.6 mg/m^3 for the welders of stainless steel and 3.0 mg/m^3 for those welding non-alloyed steel. For the employees primarily using manual metal arc welding, the risk was higher than for those using other methods (SIR 1.46 vs. SIR 0.72). Manual metal arc welding exposes employees to chromium (VI) more than other ordinary welding techniques do. In the Nordic NOCCA research project, the risk of lung cancer among male welders was found to be SIR = 1.33 (NOCCA, 2012).

Information about exposure to welding fumes based on measurements carried out by the Finnish Institute of Occupation Health (FIOH) has been combined in the FIOH memorandum on the target levels concerning welding fumes (Anttila et al., 2011). In 1994–1998 and 1999–2003, the average total exposure to welding fumes was higher than 5 mg/m^3, whereas, in 2004–2007, the mean was 2.4 mg/m^3 (n=54). The nickel concentrations measured during the welding of stainless steel have typically varied between 0.004 and 0.063 mg/m^3 (soluble nickel <0.001–0.031 mg/m^3) (Työterveyslaitos, 2007b). In the measurements carried out by FIOH, the total chromium concentration in air during stainless steel welding has varied between 0.005 and 0.19 mg/m^3 (Työterveyslaitos, 2007b). Of this concentration, soluble hexavalent chromium has accounted for less than 0.001–0.14 mg/m^3 depending on the welding technique. In manual metal arc welding, the percentage of hexavalent chromium is the highest; almost all of the chromium can be in the hexavalent form.

The primary health-related component of non-alloyed steel is manganese, which is not carcinogenic.

Summary: Although the association between exposure to welding fumes and lung cancer has been shown in several epidemiological studies, the risk ratios have been relatively low (RR < 1.5). The risk is affected by both the welded material and the welding process. The manual metal arc welding of stainless steel exposes employees to the largest amounts of hexavalent chromium, and therefore the risk associated

with it is probably the highest. The welding of aluminium or non-alloyed steel does not expose employees to carcinogenic chromium (VI) or nickel compounds.

4.3.8 Cadmium

In 1993, IARC classified cadmium as carcinogenic in humans (Group 1) on the basis of published research data on cadmium recovery, nickel-cadmium battery manufacturing, and cadmium refinement. These research data indicate a statistically significant increased risk of lung cancer. The classification was later criticised because the early studies contained defects in their control of confounding factors. In the EU, cadmium compounds have primarily been classified into cancer Category 1B (H350) according to the CLP.

Three new cohort studies have been published since then. Two of them found an association between cadmium and lung cancer, but no clear dose–response relations were detected (Järup et al., 1998; Sorahan and Esmen, 2004). One study found a relationship between lung cancer and the cumulative exposure to cadmium and arsenic, but not between lung cancer and cadmium exposure alone (Sorahan & Lancashire, 1997). In the study by Sorahan and Esmen (2004), on the manufacturing of nickel-cadmium batteries in Great Britain, no clear relation was found between cadmium exposure and lung cancer. In the study by Järup et al. (1998) on the manufacturing of nickel-cadmium batteries in Sweden, a risk ratio of 1.76 was determined on the basis of 16 cases of lung cancer. In 2009, IARC verified its classification of cadmium and its compounds and placed it in Group 1. The Finnish Institute of Occupational Health has gathered biomonitoring data about cadmium exposure in Finland since 1974. In these statistics, from the 1970's to the 2000's, the average concentration of cadmium in urine had decreased to less than one-fourth its previous levels. Tin-cadmium solderers have traditionally been the most exposed group of employees.

Summary: There are many uncertainties connected with the risk of lung cancer in relation to exposure to cadmium compounds. Exposure to cadmium in Finland has decreased significantly during the last 40 years.

4.3.9 Cobalt and hard metal

IARC has classified cobalt and its inorganic compounds as being possibly carcinogenic in humans (Group 2B) (IARC, 1991). In the EU, cobalt chloride and cobalt sulphate have been classified into cancer Category 1B (H351) according to the CLP. IARC has stated that there is limited evidence on the carcinogenicity of metallic cobalt in hard metals in humans and inadequate evidence about the carcinogenicity of metallic cobalt in humans.

The data on the carcinogenicity of soluble cobalt salts have been obtained in animal testing. Cobalt sulphate caused lung tumours in mice and rats in a 2-year cancer study (Bucher et al., 1999). The epidemiological data on the carcinogenicity of cobalt compounds are inadequate, but increased lung cancer mortality has been detected in the hard metal industry. Moulin et al. (1998) carried out a comprehensive cohort study including 10 hard metal factories; the study investigated lung cancer mortality among employees exposed to hard metal. The study determined a SMR of 1.30. Wild et al. (2000) repeated the study on the largest hard metal factories included in Moulin's research and determined a SMR of 1.70 for male employees exposed to hard metal. In the highest exposure category, the SMR was 2.02 (95% CI 1.32–2.96).

In the workplace air measurements carried out by the Finnish Institute of Occupational Health (FIOH) in 1994–1998, the average cobalt concentration was 0.095 mg/m^3, and, in 1999–2003, it was 0.084 mg/m^3. High concentrations (exceeding the current occupational exposure limit of 0.05 mg/m^3) were measured, for example, in metal product manufacturing, tool grinding, metal spraying, special glass melting, and spray painting (Heikkilä & Saalo, 2005). The manufacturers of hard metal powder and stellite drill bits are among the employee groups most exposed to cobalt (Vainio et al., 2005). In the grinding of hard metal or stellite drill bits, average concentrations of 0.002–0.24 mg/m^3 were measured in the 1990's. The concentrations had decreased since the 1980's (Vainio et al., 2005).

Summary: Information about the carcinogenicity of cobalt compounds has primarily been gathered from animal testing. Because the epidemiological evidence is inadequate, it is difficult to prove that a cancer has been caused by exposure to cobalt compounds. An elevated risk of lung cancer has been found to be associated with exposure to hard metal, but the evidence is still limited. The risk ratios between lung cancer and exposure to hard metal were 1.3–2 in two recent studies.

4.3.10   Arsenic

IARC has classified arsenic and its inorganic compounds as carcinogenic in humans (Group 1). In the EU, arsenic acid, arsenic trioxide, and arsenic oxide have been classified into cancer Category 1A (H350) according to the CLP.

In epidemiological studies among copper smelters, occupational inhalation exposure has been found to increase the risk of lung cancer. Most epidemiological cohort studies indicate about a 2 to 3 times increased risk in comparison with the risk of an unexposed population (IARC, 2012a). The risk has been noted to increase when the cumulative exposure level is 0.75 mg/m^3 x year or higher. Exposure through drinking

water has been found to have caused skin and bladder cancer, and possibly kidney cancer, in addition to lung cancer, but there is no evidence of an association with occupational exposure (IPCS 2001, IARC 2012a).

In Finland, employees can be exposed to arsenic, for example, in metal manufacturing (copper manufacturing) and the electronics industry. In addition, wood impregnation with preservatives comprised of chromium copper arsenate (CCA) and the handling of impregnated wood that have previously exposed employees to arsenic (CCA) preservatives have been banned since 2003). Significant exposure can also occur during the disposal of hazardous waste, the moving of land masses contaminated with arsenic, and the handling and manufacturing of arsenic alloyed components in the electronics industry (Vainio et al., 2005). By 2002, about 900 workers had been reported to the ASA register as having been exposed to arsenic. The number of reported cases has since increased annually and is now about 1300 cases per year.

Summary: Arsenic has been confirmed to be carcinogenic in humans. If long-term exposure to arsenic can be shown when the cumulative exposure levels are 0.75 mg/m^3 x year or more, there is a possibility of occupational cancer.

4.3.11   Wood dust

IARC has evaluated the association between wood dust and different types of cancer. According to IARC, there is sufficient evidence on the carcinogenicity of wood dust in humans (IARC Group 1), and it has been noted to cause sinonasal carcinoma and nasal cavity cancer.

4.3.11.1 Sinonasal carcinoma

In a combined review of 12 case-control studies (Demers et al., 1995b), evidence has been found for a dose–response for adenocarcinomas among men [OR 0.6, 95% CI 0.6–4.7 at low exposure levels (<1 mg/m^3); OR 3.1 (95% CI 1.6–6.1) at moderate exposure levels (1–5 mg/m^3); and OR 45.5 (95% CI 28.3–72.9) at high exposure levels (>5 mg/m^3)]. There were few cases among women, but two adenocarcinomas were detected at low exposure levels (OR 7.7). There was no clear evidence with respect to the situation with squamous cell carcinoma. The risks were elevated for furniture makers, carpenters, other wood workers, and sawmill workers. Less than a 5-year exposure period was sufficient to cause adenocarcinoma (OR 7.3 *any wood exposed jobs*). There was no additional risk detected for a latency period of less than 20 years from the beginning of employment (OR 1.0).

The findings of the Nordic NOCCA research project were similar to the aforementioned results. Even at low exposure levels, an OR of 3 was detected for adenocarcinoma. For the purposes of this working group, an attempt was made to identify the level of cumulative exposure increasing the *hazard ratio* (HR) of sinonasal-adenocarcinoma to 2. This analysis proved difficult, because there were few incidents at low exposure levels and the HR was not linear. The best estimate was that level would be 3.5–4 mg/m^3 x year. According to the job-exposure matrix used in the NOCCA research and the exposure levels estimated for 1960–1984 , this exposure level is reached in less than 3 years among sawmill workers and in less than 1 year among wood machinery operators. A relatively low level of exposure seems therefore sufficient to increase the HR to 2. It must also be noted that the incidents in this material were from the Nordic countries (Norway, Sweden, Finland, and Iceland) and the exposure was to mixed saw dust. Because of its strong association with exposure, this result may emphasise the relevance of tumour type when the occupational aetiology of a disease being considered.

Adenocarcinoma has been widely associated especially with exposure to hardwood saw dust (Leclerc et al., 1994). In four studies (Nordic countries, United States, Canada, and France), an association between softwood exposure and primarily squamous cell carcinoma has been detected (OR 3.3–1.7). In the aforementioned NOCCA research project, exposure to saw dust did not increase the risk of squamous cell carcinoma. On the other hand, in a recent study among Finnish patients (Siew et al., 2012), the RR for squamous cell carcinoma was 1.98.

Summary: The risk ratios for adenocarcinomas are high and become significant even at low exposure levels. The minimum level of significant exposure is difficult to define. It is worth noting that IARC currently refers simply to hardwood and softwood exposure, whereas earlier references were especially to oak and beech trees. According to IARC, it is impossible to separate the effects of individual wood types. The situation for squamous cell carcinomas is unclear. Increased risks have been detected in some studies but not in others. In any case, the risk ratios are low. According to a statement by the EU (EC, 2009), the lowest intensity of exposure required is unknown. In this statement, the minimum exposure period was considered to be 10 years, whereas 20 years was considered the maximum latency period. The statement mentions exposure to softwood, especially oak and beech, which also affects the compensation criteria in some countries.

4.3.11.2 Nasal cavity cancer

IARC evaluated 9 case-control studies in 1995. An increased risk was detected in most of these studies in occupations related to saw dust exposure (4/5) or the

handling of wood (3/4). The studies had been carried out in several countries, and the OR was 1.5–2.5.

In three of these case-control studies, which took into account smoking and alcohol use, the OR values were 4.1–4.5. Vaughan (1989) and Vaughan and Davis (1991) noted an increased risk for carpenters (OR 4.5) and for all employees who had worked with wood for over 10 years (OR 4.2). Sriamporn et al. (1992) found an increased risk for lumberjacks (OR 4.1).

Since then, two new cohort studies or an update of a previous cohort study has been carried out. Demers et al. (1995a) published a review of five previous cohort studies; it determined a SMR of 2.4 (95% CI 1.1–4.5) for people with confirmed exposure.

In the last three case-control studies, the OR varied from 1.2 to 2.4 (Armstrong et al., 2000; Vaughan et al., 2000; Hildesheim et al., 2001). These studies do not contain any information about the type of wood. The results remained the same when the effect of formaldehyde was controlled. It is worth mentioning that, among people of Chinese origin, there is a genetic propensity towards nasal cavity cancer that is probably also affected by environmental factors.

Summary: The risk ratios related to nasal cavity cancer are not as high as for sinonasal carcinoma, but an association has nevertheless been found in epidemiological studies. However, if clear, long-lasting exposure can be demonstrated, occupational cancer should be considered possible.

4.3.12   Formaldehyde

IARC has estimated that formaldehyde causes nasal cavity cancer and that there is causality between leukaemia and exposure to formaldehyde. IARC also estimates that there is limited evidence that formaldehyde causes sinonasal carcinoma. In the EU, formaldehyde has been classified into cancer Category 1B (H350) according to the CLP.

4.3.12.1 Nasal cavity cancer

In the most recent published review of the largest cohort study in the United States among employees exposed to formaldehyde (Hauptmann et al., 2004), the SMR was 2.10 (95% CI 1.05–4.21). The latency period was 15 years. The average exposure level was 0.45 ppm (as a time-weighted 8-hour average), and the exposure was greater than 2 for 2.6% of the exposed persons. The relative risk (RR) caused by cumulative exposure of 1.5–5.5 ppm-years was 1.19, and with a cumulative exposure of more than 5.5 ppm-years the risk was 4.14. All of the cancer cases were found to be associated with peak exposure levels of over 4 ppm. This study has been

criticised because most of the cancer cases occurred in a single factory. A statistically insignificant increase in risk levels has been detected for embalmers (Hayes et al., 1990), with a proportional mortality ratio (PMR) of 216. Hansen and Olsen (1995) researched industries producing or using formaldehyde in Denmark and found a relative risk (RR) of 3.0 (95% CI 1.4–5.7) for nasal cavity cancer.

Altogether 5 of 7 case-control studies have indicated an increased risk of nasal cavity cancer. In one of them (Vaughan et al., 2000) the OR was 2.1 for the most-exposed group. The effect was emphasised for differentiated squamous cell carcinomas (OR 2.5), as well as for the epithelial NOS group (OR 4.2). For non-differentiated and non-keratinised cancers, the OR was 1.5. In the highest categories, an association between cumulative exposure (in excess of 1.10 ppm-years) and the duration of exposure (more than 18 years) was detected.

In meta-analyses, the OR values have been on the level of 1.3 (Collins et al., 1997). In a combination of three cohorts (including Hauptmann et al., 2004), the SMR was 1.33. A recently published meta-analysis (Bachand et al., 2010), which included both cohort and case-control studies, determined an OR of 1.22 for the case-control studies. For the cohort studies the risk was 0.72.

In Finland, significant exposure, even exceeding the occupational exposure limit (0.3 ppm), has been measured in resin and glue manufacturing, coating, plywood and chipboard manufacturing, histology and pathology laboratory work, and during autopsies.

Summary: For exposure to formaldehyde, a relatively low increase in the risk of nasal cavity cancer has been found. The best quantitative exposure information is related to studies that have been criticised for concentrating on one single factory. The EU (2009) states that the risks are related to exposures causing severe irritation (i.e., inflammation). The mentioned limit value is 0.3 ppm. Special attention should be paid to extremely high concentrations, which can cause irritation.

4.3.12.2 Leukaemia

Excess mortality has been detected in cohort studies in occupations in which formaldehyde is used for tissue fixation, for example, in embalming, pathology laboratories or faculties of anatomy. There is almost no quantitative information about exposure, and therefore funeral home employees have been studied especially in association with embalming (Hauptmann et al., 2009). When a control group was formed of employees who carried out 500 or fewer embalming procedures, the OR was 3.4.

When divided according to the average formaldehyde concentration, cancers were placed rather equally into different concentration groups. With respect to cumulative exposure, the OR was 1.3 or less for employees exposed for 4058 ppm-hours (1950 ppm-hours = 1 ppm-year), 1.9 for employees exposed for 4058–9253 ppm-hours, and 3.2 for employees exposed to higher concentrations. For employees whose career had lasted for fewer than 20 years, the OR was 0.4. The findings have been less clear for factory workers, but some evidence has been obtained (Beane Freeman et al., 2009; Hauptmann, 2003). It seems that the risks were at their highest before the year 1980.

Three case–control studies have been carried out, but the number of exposed employees has been small, and no significant increases in the risk levels have been noted.

In a meta-analysis (Collins & Lineker, 2004), the greatest risk ratios were determined for embalmers (1.6). In the report by Bosetti et al. (2008), the RR for factory workers was 0.9 and that for other professionals was 1.39. Bachand's study (2010) showed the risk of leukaemia to be 1.05 among employees who had been exposed during their careers. In their research, Zhang et al. (2009) included only studies in which exposure was undeniable, and they also used the group with the most exposure to calculate the risk ratio. Their results were an RR of 1.54 for leukaemia and an RR of 1.9 for myeloid leukaemia.

Summary: A risk of leukaemia has been detected especially in association with the use of formalin in tissue fixation. The evidence is less clear for industrial practices. According to results obtained for embalmers, the OR increases beyond 2 after an estimated exposure of about 2 ppm-years. The EU does not consider the association between formaldehyde and leukaemia to be firmly established. In Finland, concentrations exceeding the occupational exposure limit (0.3 ppm) have been measured in departments of pathology during autopsies and in laboratories.

4.3.12.3 Sinonasal carcinoma

In an analysis of 12 case-control studies (Luce et al., 2002), an association between exposure to formaldehyde and squamous cell cancers was found for the group of employees with the highest exposure (>1 ppm), an OR of 2.5 for the men and an OR of 3.5 for the women. For adenocarcinoma, the risk for the men was 3.0 and that for the women was 6.2. In this case, exposure to saw dust was a confounding factor; only 18 cases of 627 had been exposed to formaldehyde only.

In different cohort studies among employees who have not been exposed to saw dust in addition to formaldehyde (embalmers, pathologists, and chemical factory

employees), no indications of increased mortality due to sinonasal carcinoma have been detected.

Summary: No clear association between sinonasal carcinoma and exposure to formaldehyde has been found in epidemiological studies.

4.3.13 Strong (sulphuric) acid fumes

IARC has classified sulphuric acid fumes and other strong acid fumes as carcinogenic in humans (IARC Group 1). The classification is based on positive cohort studies in, for example, the metal industry, where exposure to strong acid fumes has been high during metal pickling tasks, as well as on case-control studies that have supported the association between exposure to sulphuric acid fumes and laryngeal cancer.

In Steenland's cohort (Steenland et al., 1988; Steenland, 1997) of metal industry employees (metal pickling), an RR of 2.3 was detected for laryngeal cancer in the study of 1988. In the follow-up of 1997, the RR was 2.2. The exposure period in this cohort was about 10 years, and the exposure level was approximately 0.19 mg/m^3 (in inhaled air, IARC, 2012c, vol 100F). It was suggested that exposure peaks had an effect on the formation of cancer.

In Finland, the occupational exposure limit for sulphuric acid is 0.2 mg/m^3. According to measurements carried out by the Finnish Institute of Occupational Health (FIOH) in 2004–2007 (n=87), the average level was 0.05 mg/m^3, but, in 40% of the measurements, the air concentrations were 10%–100% of the occupational exposure limit, and in 7% it was over 100% of the limit.

Summary: An association between laryngeal cancer and exposure to (sulphuric) acid fumes has been found for occupations in which the exposure levels have been high. Especially exposure peaks have been suggested to influence the risk of cancer.

4.3.14   Cytostatic drugs

Several chemotherapy drugs are known to be genotoxic. When protection has been insufficient, chromosome damage in peripheral blood lymphocytes or urine mutagenicity related to the exposure to cytostatics has been detected among employees (Sessink & Bos, 1999). The capability of several chemotherapy drugs to cause cancer has been shown either in animal testing or as diagnosed secondary cancers such as leukaemia among treated patients. However, epidemiological research has not been able to show a clearly increased risk of cancer among nurses or pharmacists who have been exposed to cytostatics in their work. In Finland, the levels of exposure to chemotherapy drugs among employees in pharmacy and

nursing work are low according to a study carried out in the early 2000's (Hämeilä et al., 2003).

Summary: No increased risk of cancer from exposure to cytostatic drugs has been shown by epidemiological research.

4.3.15   Aromatic amines

Benzidine, 2-napthylamine, and 4-aminobiphenyl are classic IARC Group 1 carcinogens causing bladder cancer. Their industrial use has been banned for a long time, and it is improbable that cancers caused by these compounds would still be diagnosed even though the latency period for bladder cancer can, in some cases, be up to 50 years.

Of the other aromatic amines, methylenebis(2)-chloroaniline (MOCA) is used in the plastics and rubber industries, as well as in the manufacturing of certain polyurethanes as a hardener. Toluidines (*o*-, *p*-, *m*-toluidines), on the other hand, are used primarily as intermediaries in the chemical industry. They are also IARC Group 1 carcinogens. The IARC classification of MOCA is based on strong animal test evidence, as well as on evidence involving the carcinogenicity mechanisms and genotoxicity of MOCA, including DNA adducts and chromosome defects in the blood and bladder cells of employees.

Epidemiological evidence about the risk of cancer is, however, insufficient. In Finland, exposure to MOCA is low. There is sufficient evidence showing an association between *o*-toluidine and the induction of bladder cancer. In one American study carried out in the chemical industry, a relative risk of 11.1 was detected for employees with more than 10 years of exposure to *o*-toluidine (Ward et al., 1991). There is no epidemiological evidence available for *p*- and *m*-toluidines. There is no exposure data available from Finland.

Summary: The probability of occupational cancers caused by aromatic amines in Finland is very low because of their scarce use in this country. However, if a clear, long-lasting exposure to the aforementioned aromatic amines can be shown, occupational cancer is a possibility for a patient with bladder cancer.

4.3.16   Solvents: styrene and chlorinated hydrocarbon solvents

In addition to benzene, also some other ordinary solvents have been suspected to have carcinogenic effects. These solvents include styrene, classified into Group 2B by IARC (possibly carcinogenic in humans); trichloroethylene and tetrachloroethylene (IARC Group 2A, probably carcinogenic in humans); chloroform, carbon tetrachloride,

and methylene chloride (IARC Group 2B). In the EU, styrene has not been classified as carcinogenic; trichloroethylene has been classified into cancer Category 1B (H350, may cause cancer); and tetrachloroethylene, chloroform, carbon tetrachloride, and methylene chloride belong to Category 2 (H351, suspected of causing cancer).

Evidence on the carcinogenic effects of these solvents is primarily based on animal testing. In animal testing, styrene has caused lung tumours in mice, and it is suspected to be genotoxic also in humans (EU, 2007). Epidemiological evidence about the carcinogenicity of styrene is, however, insufficient, and the relevance of the carcinogenicity data gathered from testing with mice is still debated because of the differences in the lung metabolism of styrene between mice and men (EU, 2007).

Animal test evidence on the carcinogenicity of trichloroethylene is convincing. First of all, it has caused liver and lung cancers in rodents. Lately, also epidemiological evidence has been gathered on the carcinogenicity of trichloroethylene in humans. There is especially evidence on the association between trichloroethylene and kidney cancer (Scott & Chiu, 2006). In a comprehensive Danish research project, an increased risk of kidney cancer correlating with the length of exposure was noted for employees in different industries with exposure to trichloroethylene. For women and men who had been exposed for more than 5 years, the risk ratio (RR) for cancer was 1.5 and 1.6, respectively (Raaschou-Nielsen et al., 2003). In a study by Zhao et al. (2005), an increased risk ratio correlating with exposure was noted for employees in the aerospace industry. For the group with the most exposed employees, the risk ratio for kidney cancer was 4.9 (95% CI 1.2–20). An estimate for the related cumulative exposure levels was not, however, given. Purdue et al. detected a risk of 3.3 when exposure exceeded 234 000 ppm-hours (about 137 ppm-years). In their review article from 2003, Lohi and Kujala stated that, if a kidney cancer patient has been exposed to high concentrations of trichloroethylene through inhalation at work for several decades and no other cause of cancer can be identified, the disease can be considered an occupational disease. When it comes to liver and bile duct cancers, the risk ratios in the study carried out by Raaschou-Nielsen et al. (2003) were 1.1 for the men and 2.8 for the women. An increase in risk as the exposure increased was not as significant as it was with kidney cancer. There is some epidemiological evidence also showing an association between trichloroethylene and non-Hodgkin's lymphoma and leukaemia, but the evidence is not as strong nor as consistent as with kidney cancer. In the meta-analysis by Scott and Jinot (2011), the risk for kidney cancer in the highest exposure group was 1.58.

There has also been strong evidence for the carcinogenicity of tetrachloroethylene in animal testing. In the tests, tetrachloroethylene caused leukaemia, as well as liver and kidney tumours. The epidemiological evidence on the association between

tetrachloroethylene and cancer is limited (IARC, 1999; SCOEL, 2008; WHO, 2006). In some studies, an increased risk of, for example, kidney cancer, oesophageal cancer, and cervical cancer, as well as non-Hodgkin's lymphoma, has been detected for dry cleaning employees (WHO, 2006). Because the widespread use of tetrachloroethylene by dry cleaners only began in the 1960's, the influence of earlier exposure levels on the formation of diagnosed cancers cannot be entirely ruled out (WHO, 2006).

In animal testing, methylene chloride has caused cancer in mice. According to current knowledge, these cancers are associated with a certain metabolite of methylene chloride, produced in larger amounts by mice. There is no epidemiological evidence on the carcinogenicity of methylene chloride. In animal testing, large doses of chloroform have caused liver and kidney cancers, and carbon tetrachloride has caused liver cancers. Neither of these compounds has been shown to be genotoxic, and it has been thought that the carcinogenic effects detected in animal testing are associated with the general liver and kidney toxicity manifested at large doses. There is no epidemiological evidence indicating that these compounds are carcinogenic in humans.

People are exposed to styrene especially in the reinforced plastics industry, where high concentrations exceeding the occupational exposure limits are found. In Finland, exposure to trichloroethylene occurs especially during grease removal from metals. According to measurements carried out by the Finnish Institute of Occupational Health in 1994–2003, the concentrations near steam cleaning basins were over 160 mg/m^3 (the old occupational exposure limit for trichloroethylene; the current limit being 50 mg/m^3) in 12% of the cases and over 80 mg/m^3 in 24% (Vainio et al., 2005). Exposure to tetrachloroethylene is the highest in dry cleaning operations. The average exposure levels in the 1990's and 2000's have usually been 10%–20% of the occupational exposure limit (70 mg/m^3).

Summary: In addition to benzene, there is evidence indicating the carcinogenicity of only a few common solvents. For styrene, tetrachloroethylene, chloroform, carbon tetrachloride, and methylene chloride, the evidence is based on animal testing, and there either is no epidemiological data or the data are insufficient. Because the epidemiological evidence is insufficient, it is difficult to prove that a cancer is caused by these solvents. With trichloroethylene, there is relatively convincing epidemiological evidence, especially for the association of tetrachloroethylene exposure with kidney cancers, but the dose–response ratios are uncertain. In one study, an exposure of about 137 ppm-years led to a 3.3-fold increase in risk. This level would correspond to over 10 years of exposure to concentrations exceeding the occupational exposure limit (10 ppm).

4.3.17   Vinyl chloride

IARC has classified vinyl chloride into Group 1 (carcinogenic in humans). Also in the EU, vinyl chloride has been classified into Category 1A according to the CLP.

The capability of vinyl chloride to cause liver cancer, more specifically angiosarcoma of the liver, is well known. Preceding liver cancer, hepatocellular hyperplasia and fibrosis have been described (Boffeta et al., 2003b). There are also descriptions of specific mutations in the Ki-ras proto-oncogene (G-A transition in codone 13) and tumour suppressor protein p53 (A-T transversion), which are associated with liver cancer caused by vinyl chloride (Dogliotti, 2006). The risk of cancer caused by vinyl chloride is estimated to be $3x10^4$ when the exposure during the entire career of a worker exceeds 1 ppm (SCOEL, 2004b). In epidemiological research, the risk ratios for liver cancer have been on the level of a SMR of 1.36–57.1 (Boffeta et al., 2003b). In some studies the risk has remained elevated even though angiosarcoma of the liver has been removed from the analysis with a reference to the fact that the risk of other liver cell types has also been slightly elevated [e.g., Ward et al., 2001 (SMR 1.27); Mundt et al., 2000 (SMR 1.8); Wong et al., 2002 (SMR 1.78) – described in Boffeta et al., 2003b].

In Finland, exposure to vinyl chloride has primarily occurred in polyvinyl chloride (PVC) production. In measurements carried out in the early 1990's, the average daily exposure was 0.1 ppm. Nowadays, PVC is no longer produced from monomers in Finland. The vinyl chloride residues in PVC have, in the last few decades, been so low that exposure in PVC handling and machining is below the detection limits of the measurement method (Vainio et al., 2005).

Summary: If a patient is diagnosed with angiosarcoma of the liver and long-lasting occupational exposure to vinyl chloride can be shown, the cancer can be considered to be an occupational disease.

4.3.18   1,3-butadiene

IARC has classified 1,3-butadiene into Group 1 (carcinogenic in humans). Also in the EU, 1,3-butadiene has been classified as belonging to Category 1A according to the CLP.

The evidence on the carcinogenicity of butadiene has been primarily derived from the rubber industry. In a study among nearly 17 000 rubber industry employees, Graff et al. (2005) noted that the cumulative exposure to butadiene correlated with an increased risk of leukaemia. The relative risk for mortality from leukaemia was 1.4 when an employee was exposed to butadiene for 0–33.7 ppm-years; 1.2 when the exposure level was 33.7–184.7 ppm-years; 2.9 when the exposure level was 184.7–

425 ppm-years; and 3.7 when the exposure level was 425 ppm-years or more. In addition, it seems that peak exposures (momentary exposure to more than 100 ppm) could be significant from the point of view of cancer risk (Cheng et al., 2007; Delzell et al., 2001).

For the most part, chemical industry process managers, laboratory technicians, and chemical process technology specialists have been reported to the ASA register as employees exposed to butadiene. The production of styrene-butadiene latex has been the main use of butadiene in Finland. Exposure to butadiene was widely studied in the late 1990's in a research project of the Finnish Institute of Occupational Health, which concentrated on the production of butadiene and styrene-butadiene latex. The exposure levels were low. In 1002 industrial hygiene measurements of 1,3-butadiene, the occupational exposure limit of 1 ppm was exceeded only 25 times. Butadiene concentrations in styrene-butadiene latex production were under the detection limit (0.013 ppm) in 70% of the measurements. In 27%, the concentrations were in the 0.013–1 ppm range, and in 3% they exceeded the occupational exposure limit. The maximum values exceeding the exposure limit were 11–21 ppm, and some of the values in excess of the limit were caused by the hose used during the chemical unloading or loading phase becoming unattached. In the production of 1,3-butadiene, the concentrations were 0.013–1 ppm in most of the samples (69%). Altogether 28% of the samples were below the detection limit, and 3% exceeded the occupational exposure limit. When the occupational exposure limit was exceeded, the concentrations remained under 5 ppm (Vainio et al., 2005). Employee or consumer exposure to monomers released from butadiene polymers is minimal or non-existent.

Summary: Exposure to butadiene has been noted to increase the risk of leukaemia. In Finland, exposure to butadiene has been low according to studies carried out already in the 1990's. Therefore the probability of butadiene causing leukaemia in Finland is supposedly low, but, in principle, if significant cumulative exposure (in excess of 180 ppm-years) and high exposure peaks can be shown, occupational cancer is a possibility. It should be noted that the latency period of leukaemia is usually shorter than that of many other cancers.

4.3.19 Ethylene oxide

IARC has classified ethylene oxide into Group 1 (carcinogenic in humans). In the EU, it has been classified as belonging to Category 1B according to the CLP.

In some early epidemiological research, an increased risk of, for example, leukaemia has been detected among employees exposed to ethylene oxide, but this finding has

not been verified by later research. So far, in the most comprehensive American research project, the average risk of leukaemia was similar to the average risk of the entire population. There was, however, a slight dose–response relationship when cancer mortality was studied in relation to cumulative exposure. IARC (2008) considered the epidemiological evidence on the carcinogenicity of ethylene oxide to be limited for humans, and, therefore, the IARC classification is in fact based on both animal testing and evidence on the carcinogenic mechanisms and genotoxicity of ethylene oxide, including chromosome damage in, for example, peripheral blood lymphocytes detected among employees.

Summary: Employees are exposed to ethylene oxide, for example, in the maintenance of hospital equipment. Measurement data from Finland are limited. Because the epidemiological evidence is limited, it is difficult to prove that a cancer has been caused by ethylene oxide.

4.3.20   Leather dust

IARC evaluated the association between leather dust and sinonasal carcinoma in 1987, when the relationship between nasal adenocarcinoma and the boot and shoe industry was noted and the greatest risks were found in occupations with the most exposure to leather dust. In a new monograph (IARC 2012a) IARC has stated that there is sufficient evidence on the carcinogenicity of leather dust and that leather dust causes sinonasal carcinoma.

A combined analysis of 8 case-control studies ('t Mannetje et al., 1999) found evidence of a relationship between sinonasal carcinoma and exposure to leather dust (women's OR 2.7, men's OR 1.9). In this analysis, the OR for adenocarcinoma was 3.0, and that for squamous cell cancer was 1.5. In a recent Italian study (d'Errico et al., 2009), the OR for adenocarcinoma was as high as 26, and, for squamous cell cancer, it was 5 (the result is not significant because it was based on 1 case only). With adenocarcinoma, even a low level of exposure for less than 5 years increased the risk of cancer.

In Finland, exposure to leather dust has been measured in shoemaking businesses. The dust concentrations have been 0.07–1.0 mg/m^3 (Uuksulainen et al., 2002), and they contained leather dust, polymers, and finishing agents. In a Polish shoe factory, the highest measured dust concentration was 0.9 mg/m^3, the highest peak being 14.6 mg/m^3 (Stroszejn-Mrowca & Szadkowska-Stanczyk, 2003).

Summary: The trouble with the association between leather dust and sinonasal carcinoma is that there are few studies investigating leather dust concentrations and their relationship with morbidity. According to d'Errico's et al.'s (2009) research, as

well as to other previous research in the shoe industry, the level and possible type of exposure may have significant effects. As for the diagnosis, leather dust has a clear correlation with the occurrence of adenocarcinoma, similar to that of saw dust. The association of leather dust with sinonasal carcinoma is significantly more probable if the cancer is adenocarcinoma.

4.3.21   Ceramic fibres

IARC has classified ceramic fibres into Group 2B (possibly carcinogenic in humans) on the basis of sufficient evidence from animal testing (IARC, 2002).

Ceramic fibres consist primarily of aluminium silicate. In animal testing, ceramic fibres have caused mesothelioma and lung tumours in rats and hamsters. The mechanism is thought to be transmitted via chronic irritation. SCOEL (2011a) has, in its recent draft of recommendations, stated that a threshold dose can probably be identified for these effects and, when exposure levels remain below 0.3 fibres/cm^3, the risk of cancer is probably non-existent. Epidemiological research has not found any association between exposure to ceramic fibres and cancer or lung fibrosis. In previous research, high exposure levels have been noted to cause pleural plaques among employees. In addition, epidemiological studies have found an association between exposure to ceramic fibres and non-malignant pulmonary effects (bronchitis, decrease in lung function, irritation). The most important application of ceramic fibres is for heat insulation in industrial smelting ovens and kilns (about 30 tons per year (Vainio et al., 2005). There have been a little more than 100 cases of ceramic fibre exposure reported to the ASA register annually, especially from the metal industry, metal manufacturing, and the insulation industry.

Summary: The epidemiological evidence on the causation between cancer and exposure to ceramic fibres is inadequate.

4.3.22   Nanoparticles: carbon nanotubes

Nanoparticles cannot be addressed as a single entity. The properties (and thus carcinogenicity) of nanoparticles are affected both by the properties of the particles (biopersistence, size, shape, and agglomeration or aggregation tendency) and the material (e.g., different metal nanoparticles).

Currently, animal testing data on carbon nanotubes indicate that they may cause inflammatory lung reactions, including lung granuloma and lung fibrosis via inhalation exposure. In addition, there is evidence concerning the genotoxicity of carbon nanotubes (NEG, 2013). The carcinogenicity of carbon nanotubes has not been studied with inhalation tests, but, in animal testing models in which carbon

nanotubes have been introduced intraperitoneally or intrascrotally, they have caused mesothelioma. This information, combined with the existing data on genotoxicity, suggests that the capability of carbon nanotubes to cause mesothelioma may be similar to that of asbestos. No epidemiological evidence is available yet about the carcinogenicity of carbon nanotubes.

The information about exposure to carbon nanotubes in different occupations is also inadequate. Even if significant exposure would have occurred in some occupations, when the latency period required for the formation of mesothelioma or lung cancer is taken into account, it will probably still take several years before this correlation can be epidemiologically proven. Therefore, the current risk of cancer caused by carbon nanotubes in different occupations cannot yet be estimated.

Summary: Because epidemiological evidence and exposure data are currently inadequate, it is impossible to evaluate the risk of cancer caused by carbon nanotubes in different occupations. According to animal testing, carbon nanotubes may have effects that are similar to those of asbestos.

4.4   Physical factors

4.4.1   Ionising radiation

Ionising radiation belongs to IARC Group 1 carcinogens. The risk of occupational cancer caused by ionising radiation has been studied among health care personnel (radiologists and radiographers), nuclear power plant employees, and air crews (cosmic radiation). In a study carried out by Cardisin et al. (2005) among nuclear power plant employees, it was noted that increased exposure of 1 sievert (1 Sv) caused a 1.93 risk ratio for leukaemia. In addition, an association was noted for solid tumours, for which the risk ratio was 0.97 per sievert.

Smoking may explain some of the risk, but scientists have estimated that 1%–2% of cancer mortality among these employees may be caused by radiation. In American studies carried out among radiologists and radiographers, an increased risk of breast cancer was detected among employees who had begun their careers in the 1930's and 1940's (Mohan et al., 2002), and an increased risk of leukaemia was found for those who had been working for over 5 years before 1950 (RR 6.6) (Linet et al., 2005). In a study carried out among Finnish physicians (Jartti et al., 2006), no increase was noted for the risk of cancer. A regression analysis of the cumulative dose indicated a statistically non-significant increase in the risk of cancer. The mean cumulative exposure was 12.7 mSv, the median being 1 mSv.

Altogether 6% of the studied radiologists had been exposed to a cumulative dose in excess of 50 mSv. This research proves that the risk of cancer among Finnish radiologists is low. Air crews are exposed to average doses of 2 mSv annually. Pilots and cabin crews have been shown to have an increased risk of melanoma, which is probably related to spending more holidays in the sun. Among female cabin crews the detected risk of breast cancer was 1.5-fold, but this rate did not correlate with the radiation dose. Therefore, the increase may have been caused by other factors (Pukkala et al., 2012). The same studies also noted an increased risk of leukaemia among female cabin crews; it did not, however, correlate with the cumulative radiation dose (Pukkala et al., 2012).

Summary: Exposure to radiation is known to cause cancer. Among nuclear power plant employees and health care personnel, exposure has been found to be associated especially with leukaemia. Among health care professionals, also the risk of breast cancer has been elevated among employees whose career began before 1950. When it comes to the dose–response relationship of radiation, it is known that an average occupational exposure of 1000 mSv will double the risk of cancer. The dose threshold of occupational radiation is 20 mSv per year. The calculated risk of cancer at such an exposure level is 2 cancers in 10 years for every 1000 exposed employees. In Finland, the exposure levels of air crews and radiology personnel have remained significantly lower during the last few decades (since the 1970's), at 1 or 2 mSv per year. It can therefore be assumed that occupational cancer among employees who have been exposed to radiation after the 1970's is improbable. Among operating radiologists, the average dose during 5 years may sometimes locally exceed 20 mSv per year, which may cause a risk of skin cancer.

4.4.2 Radon

Radon belongs to IARC Group 1 carcinogens. Radon in the soil and its daughter nuclides emit alpha radiation. Radon is known to cause lung cancer, and it has been estimated that the locally high soil radon concentrations in Finland cause about 40 lung cancers among non-smokers and more than 200 lung cancers in conjunction with smoking (Mäkeläinen, 2010).

It is possible to be significantly exposed to radon in mining work, and an increased risk of lung cancer correlating with radon exposure has been detected among mining workers. Improved ventilation technology on mine sites has nowadays lowered the exposure levels. Because radon is formed during uranium decay, especially the mining of uranium ores may expose employees to radon.

In some regions, room air may contain radon in excess of the allowed 200 Bq/m^3, whereas the average concentration is 100 Bq/m^3 (Mäkeläinen, 2010; Kurttio, 2010). Living for 30 years in a radon concentration of approximately 700 Bq doubles the risk of lung cancer by the age of 75 years (Darby et al., 2005). It is usually difficult to separate occupational exposure to radon from environmental exposure.

4.4.3 Ultraviolet radiation

IARC has classified ultraviolet (UV) radiation from the sun as a Group 1 carcinogen. It is known to cause skin cancer: melanoma, squamous cell carcinoma, and basal cell carcinoma. It has also been known to cause lip cancer and certain types of eye cancer (IARC, 2012d). In a joint Nordic research project by Andersen et al. (1999), the risk of skin cancer was not significantly elevated in outdoor occupations in Finland. Similarly, in the NOCCA research project, the risk of skin cancer was not elevated among outdoor workers (Pukkala et al., 2009). On the other hand, the risk of lip cancer was elevated among male fishermen, farmers, gardeners, forestry workers, and sailors, but not among women. For these occupations, the SIR was primarily below 2 (varying between 1.21 and 2.27). Therefore, although UV radiation from the sun is a strong source of exposure also in Finland, the associated risk of occupational cancer is probably low.

4.4.4 Electromagnetic fields

IARC has classified low-frequency electromagnetic fields as possibly carcinogenic in humans (Group 2B) on the basis of epidemiological leukaemia observations among children. The discovered association between electromagnetic fields and cancer is, however, so weak that, based on these studies, it is difficult to prove that electromagnetic fields increase morbidity. Because the evidence is insufficient, it is currently not possible to demonstrate that a cancer is caused by exposure to electromagnetic fields. Employees who can be exposed to electromagnetic fields include, for example, electrical transformer station employees, crack inspectors in the metal industry, employees working close to induction devices, and test users of electric motors.

4.5 Biological factors

Hepatitis B and C may cause an occupational disease if an employee is infected via accidental blood exposure. Chronic hepatitis is more commonly caused by hepatitis C, for which about 50% of the exposed people remain carriers and 20%–30% of them develop chronic active hepatitis, liver cirrhosis, or hepatocellular cancer. This scenario is less probable but not impossible with hepatitis B. If an employee has

already been diagnosed as a hepatitis B or C carrier and has chronic active hepatitis, a possible hepatocellular cancer of that patient is probably also caused by occupational exposure.

Human immunodeficiency virus (HIV) is associated with a propensity for different types of cancer. Especially Kaposi's sarcoma is typical to HIV patients, but also other cancers, such as lymphoma, occur. HIV may cause an occupational disease if an employee is infected via accidental blood exposure.

In addition to the viruses discussed in this section, other carcinogenic viruses include, for example, the Epstein Barr virus and the human papilloma virus (HPV).

4.6   Occupations and professions classified by IARC

IARC has assessed many occupations in which increased cancer morbidity has been detected. Some of them have already been described, for example, in the section on PAH compounds. Occupations that have been lately presented in this context and their related risk of cancer are discussed in the following sections.

4.6.1 Shift work

IARC has estimated that shift work, which disturbs the normal circadian rhythm, is probably carcinogenic in humans (IARC Group 2A). This classification is based on limited evidence from epidemiological studies concentrating on health care professionals and air crews, as well as on evidence from animal testing (IARC 2010b). According to the overall results of epidemiological research, the risk of breast cancer can be increased 1.5-fold after 20–30 years of shift work. This evaluation is not epidemiologically very reliable because, so far, there are only a few results from only a couple of professions (nurses, air crews) and the risk estimates are only moderately elevated. The results are thus susceptible to bias and distortion (see Kolstad, 2008). In a comprehensive Swedish study, the risk of cancer had not increased among men and women working in shifts (Schwartzbaum et al., 2007). In a Finnish study, no association was noted between the risk of breast cancer among flight attendants and flying (Kojo et al., 2005).

4.6.2 Other occupations or professions classified as carcinogenic by IARC

Other exposure situations or occupations classified by IARC include, for example

- Iron and steel foundry work, painting, rubber industry (Group 1)

- Hairdressing (Group 2A)

- Occupational exposure in printing processes, firefighting, occupational exposure in dry cleaners (Group 2B).

When it comes to occupations, it must be noted that the industrial processes and exposures in these occupations may have changed over the years, and these changes may have modified the associated risk of cancer. For example, the risk of bladder cancer detected in the rubber industry (IARC Group 1) was associated with the use of certain aromatic amines in the middle of the 20th century. After the ban on these substances, bladder cancer cases are no longer predicted.

Epidemiological cohort studies have detected a consistently increased risk of lung cancer in iron and steel foundry work. In most of these studies, exposure has occurred before the 1980's. In the NOCCA study, smelters and metal foundry workers had a slightly elevated risk of lung cancer (SIR 1.3, 95% CI 1.3–1.4). In the NOCCA study concerning Finland, a SIR 1.27 was detected for lung cancer in steel and iron foundry workers (Pukkala et al., 2005), and the increased risk was believed to be primarily associated with exposure to quartz. The primary carcinogens in foundries are quartz and PAH compounds, as well as metal fumes [nickel and chromium (VI)].

Painters' work has been found to be associated with an increased risk of lung cancer, mesothelioma, and bladder cancer (IARC 2010b). According to IARC, the risk of lung cancer cannot be completely explained by exposure to asbestos, although it is probably partly responsible for the increased risk of lung cancer (IARC 2010b). No individual factor behind the increased risk of lung or bladder cancer can be identified. Painters are exposed to several solvents and pigments, and some special paints may previously have contained also asbestos. The exposure has, however, changed much over the years; solvents and pigments have improved and solvent-free paints have become commoner. These changes have probably also affected the risk. In the Nordic NOCCA research project, a slightly elevated risk of lung cancer and mesothelioma was detected for painters (SIR 1.27 and 1.77), and a risk of bladder cancer was found for close to the background level (SIR 1.08).

It is possible to be exposed to several carcinogens while working as a firefighter. In 2007, IARC estimated the evidence on the carcinogenicity of firefighting to be limited for humans (IARC 2010b). The IARC review included 19 cohort studies, 11 case-control studies, and 14 other studies with different set-ups. A recent meta-analysis (LeMasters et al., 2006) on 32 studies was included in the review. LeMasters noted that the risk of cancer had increased statistically significantly for 10 of 21 analysed types of cancer. Statistically significant risk ratios (RR) were slightly elevated, between 1.2 and 1.5 – with the exception of testicular cancer (RR 2.02). The results

were uniform in different research set-ups on prostate cancer, testicular cancers, and non-Hodgkin's lymphoma, as well as multiple myeloma.

Since the publication of Lemasters' meta-analysis, two comprehensive studies have been reported (Ma et al., 2006; Bates 2007) that have been added to LeMasters' meta-analysis material by the IARC working group. In this new analysis, the risk of three types of cancer was statistically significantly elevated: the occurrence of testicular cancer was increased by 50% (RR variation 1.2–2.5 in cohort studies); the risk of prostate cancer was elevated by 30% (RR 1.1–3.3), and the occurrence of non-Hodgkin's lymphoma was increased by 20% (RR 0.9–2.0).

In a new review carried out on Nordic material, a slight, general increase in cancer morbidity was detected for firefighters with respect to several types of cancer. Morbidity from prostate cancer was the highest in the age group of under 50 years, SIR 2.61 (95% CI, 1.35–4.56). For the group of over 70-year-olds, the morbidity was 2.61 (95% CI 1.29–4.80) for mesothelioma and 1.9 (95% CI 1.35–2.65) for adenocarcinoma of the lung (Demers et al., 2011).

5   WORKING GROUP RECOMMENDATIONS

The Working Group's recommendations for the compensation of certain cancers as occupational diseases in relation to different exposures are presented in Section 6.1, and the recommendations for cancer screening, the evaluation of exposure, and the standardisation of diagnostics can be found in Section 6.2.

5.1   Recommendations for the compensation of occupational cancers

The list of elements and compounds listed in this section is not exhaustive. They have been selected on the basis of existing research data on their carcinogenicity and because employees are exposed to them in Finland. These exposures have been classified by IARC as primarily belonging to Group 1 according to their carcinogenicity or to the EU category of 1A. There are, however, some exposures that belong to IARC Group 2A or EU Category 1B, as well as some with few data on their current carcinogenicity, for example, nanoparticles. These exposures have been included either because they are important in Finnish worklife or because they have lately caused widespread concern for their possible carcinogenicity, as is the case, for example, with carbon nanotubes. These recommendations reflect current knowledge about the carcinogenicity of different exposures and related evidence. As knowledge is gained, the situation may change, and therefore the recommendations must always be reviewed in the light of current knowledge.

Smoking does not prevent the evaluation of a possible occupational cancer. If nothing else is mentioned in relation to an exposure or cancer, the latency period of a compensated occupational cancer must be at least 10 years. The latency period is the time between the beginning of exposure and the diagnosis of cancer.

In general, exposures and cancers can be divided into the following three groups:

- Exposures with strong epidemiological evidence. With such exposures the main challenge is to define the minimum exposure criteria for a diagnosis of an occupational disease. Examples are mesothelioma among employees exposed to asbestos and lung cancer among silicosis patients.

- Exposures associated with cancer in epidemiological studies and situations in which the risk ratio (RR) increases beyond 2. Such exposures may lead to a patient receiving compensation for an occupational disease after the consideration of individual circumstances.

- Exposures with evidence of carcinogenicity derived only from animal testing and/or with a weak or modest association with cancer in epidemiological studies (RR < 2). These exposures do not generally lead to compensation for an occupational cancer.

5.1.1 Asbestos

5.1.1.1 Mesothelioma

The connection between asbestos exposure and malignant mesothelioma is indisputable. There is no clear dose-response relationship. Instead, malignant mesothelioma even appears with low exposure levels. All employees who are exposed to asbestos and develop malignant mesothelioma receive compensation for an occupational disease. The latency period should be at least 10 years. Smoking is not a factor in the formation of mesothelioma.

5.1.1.2 Lung cancer

The association between asbestos exposure and lung cancer is also indisputable. The dose-response relationship is linear. High exposure is considered to be related to a doubled risk of cancer. The limit for high exposure according to international recommendations is 25 fibre-years, as indicated in the work history of the patient (Table 4, in Section 5.1.2.1) or a sufficient number of asbestos fibres in lung tissue. When the number of asbestos fibres in lung tissue is estimated, the faster degradation of chrysotile fibres and their removal from the system must be taken into account. The exposure level is also indicated by the number of asbestos bodies (AB) in bronchial lavage fluid or lung tissues (optical microscope analysis). The latency period of lung cancer from the beginning of exposure to the time of the cancer diagnosis should be at least 10 years. Smoking and asbestos increase each other's effect on the appearance of lung cancer. However, smoking does not affect the decision concerning occupational cancer.

5.1.1.3 Lung cancer in asbestosis patients

According to research data, the risk of lung cancer among asbestosis patients is two- to fivefold. If a lung cancer patient has been diagnosed with asbestosis, she or she can receive compensation for an occupational disease. The manifestation date is the manifestation date of the asbestosis.

5.1.1.4 Laryngeal cancer

The relationship between asbestos exposure and laryngeal cancer is indisputable. The risk ratio is linear and correlates with the risk level of lung cancer. High exposure

(25 fibre-years) is considered to be associated with a doubled risk of cancer, see Table 4 in Section 5.1.2.1. The latency period from the beginning of exposure to the time of the cancer diagnosis should be at least 10 years. Smoking does not affect the occupational cancer decision for compensation. Unlike lung cancer, the manifestation date of laryngeal cancer is not considered to be related to the manifestation date of asbestosis.

5.1.1.5 Ovarian cancer

IARC has decided that ovarian cancer can be related to asbestos exposure (IARC 2012a). Increased morbidity to ovarian cancer has been reported for women exposed to high asbestos levels in their work, but the relation between asbestos exposure and ovarian cancer is considered uncertain in research data. Ovarian cancer can be recognised as an occupational disease after the consideration of individual circumstances.

5.1.1.6 Other cancers

Evidence on the asbestos aetiology of colon, throat, and stomach cancers is limited. On the basis on current knowledge, these cancers cannot be considered occupational among employees exposed to asbestos.

5.1.2 Crystalline silica

Crystalline silica (quartz, cristobalite, tridymite) are carcinogenic in humans. The group level risk of lung cancer is twofold among patients with silicosis (i.e., stone dust pneumoconiosis), but there is no epidemiological evidence concerning the risk of lung cancer among employees without silicosis (RR being 1).

Silicosis indicates sufficient exposure to crystalline silica. Lung cancer diagnosed in an employee who has been radiologically or histologically diagnosed as having silicosis is recognised as an occupational disease. The manifestation date of the cancer is not considered to be the same as the manifestation date of the silicosis. On the basis of current knowledge, lung cancer in an employee without silicosis cannot be recognised as an occupational disease caused by exposure to quartz.

5.1.3 Other occupational exposures and situations causing exposure

5.1.3.1 Carcinogenic metals and metal compounds

Exposure to nickel compounds has been found to be associated with lung cancer. The existing knowledge on the dose-response relationships is, however, inadequate. According to current knowledge, when the cumulative exposure remains below 2 mg/m^3 x year (for example, 20 years at an exposure level of 0.1 mg/m^3), the risk ratios are so low that the probability of occupational cancer is low. The evidence concerning the carcinogenic effects is the strongest for soluble nickel compounds, but also low-soluble nickel compounds are clearly carcinogenic. According to SCOEL, when a person is exposed to average concentrations of 0.01 mg/m^3 or less, there is no risk of cancer.

Lung cancer can be recognised as an occupational disease after the consideration of individual circumstances if the exposure levels have been high (cumulative exposure in excess of 2 mg/m^3 x year). These levels apply to both soluble and low-soluble nickel compounds. No evidence exists on the carcinogenicity of metallic nickel. The minimum duration of exposure is 1 year, and the latency period should be at least 10 years.

Nickel refinement has been found to be associated with sinonasal carcinoma. A cumulative exposure level of 1 mg/m^3 x year can be considered as a guideline for the exposure limit. The minimum duration of exposure is 6 months, and the latency period should be at least 10 years.

Exposure to hexavalent chromium (chromium (VI)) has been identified as a cause of lung cancer. There is, however, little information about the dose–response relationships. An exposure level of 1 mg/m^3 x year (e.g., 10 years to a concentration of 0.1 mg/m^3) can be considered as a guideline for the limit of sufficient exposure in relation to lung cancer, since exposure to higher concentrations doubles the risk ratios. Lung cancer can be recognised as an occupational disease after the consideration of individual circumstances if the exposure levels have been high. The minimum duration of exposure is 1 year, and the latency period should be at least 10 years.

There is information suggesting a relation between exposure to chromates and sinonasal carcinoma, but the association is uncertain. There is no evidence on the carcinogenicity of metallic chromium or trivalent chromium.

Although a connection between exposure to welding fumes and lung cancer has been found in several epidemiological studies, the risk ratios have been low or weak.

The risk is affected by both the material to be welded and the welding process used. Manual metal arc welding of stainless steel exposes employees to the highest levels of hexavalent chromium, and, therefore, the risk associated with it is probably the highest. Welding of aluminium or non-alloyed steel does not expose employees to carcinogenic chromium (VI) or nickel compounds. An occupational disease diagnosis may be appropriate after the consideration of individual circumstances if the lung cancer patient has been doing manual metal arc welding of stainless steel for most of his or her career without adequate protection. In such cases, exposure can be considered to be significant.

There is evidence for a connection between cadmium compounds and lung cancer, but the risk ratios have been low. Therefore, employees exposed to cadmium can receive compensation for lung cancer as an occupational disease after the consideration of individual circumstances if the exposure levels have been high over a long period of time.

Information about the carcinogenicity of cobalt compounds has primarily been gathered from animal testing. Because the epidemiological evidence is inadequate, cancer cannot be recognised as an occupational disease among employees exposed to cobalt compounds.

An elevated risk of lung cancer has been found to be associated with exposure to hard metal, but the evidence is still limited. In research projects that have detected an increased risk of cancer, the risk ratios have been low or weak. Lung cancer among employees exposed to hard metal can be recognised as an occupational disease in individual cases only after the consideration of individual circumstances if the exposure levels have been high over a long period of time.

There is evidence for an association between arsenic exposure and lung cancer. Lung cancer can be recognised as an occupational disease among exposed employees in individual cases and after the consideration of individual circumstances if the exposure levels have been high. An exposure level of 0.75 mg/m^3 x year or more can be considered the guideline for the limit of sufficient exposure in relation to lung cancer. The minimum duration of exposure is 1 year, and the latency period should be at least 10 years.

5.1.3.2 Mixtures containing polycyclic aromatic hydrocarbons, i.e., PAH compounds

There is evidence of an association between PAH exposure and lung cancer, as well as with skin or lip cancer in different occupations. The strongest evidence of the risk of lung cancer has been detected in coal gasification, coke production, and aluminium

production. In recent studies, employees who had been exposed to creosote, with the exception of chimney sweeps, were found to have an increased risk of skin cancer. Exposure to UV radiation may have also affected the risk. If lung cancer is diagnosed and long-term exposure to PAH compounds in, for example, coal gasification, coke production, and aluminium production can be shown, lung cancer can be recognised as an occupational disease in individual cases and after the consideration of individual circumstances. Skin and lip cancers (excluding melanoma) can be recognised as occupational diseases after the consideration of individual circumstances if long-term exposure to creosote in wood impregnation can be demonstrated.

Exposure to diesel exhaust fumes has been found to be associated with lung cancer. In epidemiological studies, the risk ratios have usually been low or weak, but they may become significant among the most-exposed employees, such as employees working in underground mines. An occupational disease diagnosis can be made in individual cases and after the consideration of individual circumstances if high, long-term exposure can be shown.

5.1.3.3   Environmental tobacco smoke

Exposure to environmental tobacco smoke has been found to be associated with lung cancer. In epidemiological studies, the risk ratios have been relatively low or weak. There are no special groups whose risk ratios would be higher. When the risk levels remain low, it is difficult to estimate the occupational nature of the disease. Therefore, environmental tobacco smoke is not considered a reason for compensating lung cancer as an occupational disease.

5.1.3.4   Solvents

The connection between exposure to benzene and acute myeloid leukaemia (AML) is well known. The exposure levels to benzene in Finland during the last 10–20 years have however been very low. Therefore, occupational cancers caused by benzene are no longer probable. However, if sufficient exposure (i.e., 40 ppm-years) during the last 10 years can be proven, cancer is compensated as an occupational disease. An occupational disease diagnosis is supported by the occurrence of the myelodysplastic syndrome preceding cancer, a defect in chromosome 5 or 7, and poor response to chemotherapy.

In addition to benzene, only a few other solvents commonly used in Finland have been found to be carcinogenic. When it comes to styrene, tetrachloroethylene, chloroform, carbon tetrachloride, and methylene chloride, the evidence is based on animal testing, and there is either no epidemiological data or the data are insufficient. Because the epidemiological evidence is insufficient, cancer among

employees exposed to these substances is not eligible for compensation as an occupational disease.

There is epidemiological evidence for an association between trichloroethylene and kidney cancer. The data on the dose-response relationship is, however, insufficient. Kidney cancer can be recognised as an occupational disease in individual cases after the consideration of individual circumstances if the employee has been exposed to high trichloroethylene concentrations in his or her inhaled air over several decades.

5.1.3.5   Dusts and fibres

For saw dust exposure, the risk ratios for sinonasal adenocarcinomas can be very high. The increased risk is especially associated with exposure to softwood saw dust. In the Nordic countries, exposure to saw dust is caused by mixed saw dust, and the exposure levels significant for the risk of adenocarcinoma are reached already in a few years. The minimum latency period from the beginning of exposure is considered to be at least 10 years. According to the EU, the maximum latency period since the exposure has ended is 20 years. Sinonasal adenocarcinoma among employees who have been greatly exposed to saw dust is recognised as an occupational disease.

When it comes to saw dust exposure and squamous cell cancer, the data on their relationship is contradictory, and the risk ratios remain low. Sinonasal squamous cell cancer can be compensated as an occupational disease in individual cases after the consideration of individual circumstances if high, long-term exposure to saw dust can be shown.

There is evidence of an association between nasal cavity cancer and exposure to saw dust, but the risk ratios are low. Nasal cavity cancer can be recognised as an occupational disease in individual cases after the consideration of individual circumstances if high, long-term exposure to saw dust can be proven.

The problem with the association between leather dust and sinonasal carcinoma is that only a few studies have investigated leather dust concentrations and their relationship with morbidity. Exposure to leather dust has, however, a clear correlation with adenocarcinoma. Sinonasal adenocarcinoma caused by exposure to leather dust can be recognised as an occupational disease in individual cases after the consideration of individual circumstances if high, long-term exposure can be shown.

Epidemiological evidence about the carcinogenicity of ceramic fibres is inadequate. Current information about the carcinogenicity and exposure to carbon nanotubes is also inadequate. Because the evidence is inadequate, cancer caused by these factors is not recognised as an occupational disease.

5.1.3.6   Other carcinogenic chemicals

Exposure to formaldehyde causes a relatively low increase in the risk of nasal cavity cancer when the rarity of this tumour is taken into account. According to the EU, the risks are related to exposures that cause severe irritation. Nasal cavity cancer caused by exposure to formaldehyde can be recognised as an occupational disease in individual cases after the consideration of individual circumstances. So far, no clear connection between nasal and sinus cancer and exposure to formaldehyde has been found.

In certain occupations, an association between leukaemia and formaldehyde exposure has been identified. Leukaemia can be recognised as an occupational disease in individual cases after the consideration of individual circumstances if high, long-term exposure can be demonstrated.

Exposure to butadiene has been noted to increase the risk of leukaemia. Cumulative exposure to doses exceeding 185 ppm-years can be considered as the limit of high exposure. High exposure peaks also affect the formation of cancer. Leukaemia can be recognised as an occupational disease in individual cases after the consideration of individual circumstances if high, long-term exposure to butadiene can be proven.

A connection between laryngeal cancer and exposure to (sulphuric) acid fumes has been noted in conditions in which exposure levels have been high. Laryngeal cancer can be recognised as an occupational disease in individual cases after the consideration of individual circumstances if high, long-term exposure can be shown.

Because the epidemiological evidence for a connection between exposure to cytostatics or ethylene oxide is inadequate, cancer caused by these compounds is not recognised as an occupational disease.

The probability of occupational cancers caused by aromatic amines is very low in Finland because their use was limited already 50 years ago. If, however, a clear, long-lasting exposure to the aforementioned aromatic amines can be shown, bladder cancer can be recognised as an occupational disease.

If a patient is diagnosed with angiosarcoma of the liver and long-lasting occupational exposure to vinyl chloride can be demonstrated, the cancer can be recognised as an occupational disease. It should be noted, however, that the exposure levels in Finland have been so low for so long that the probability of this occupational disease occurring is low.

5.1.3.7   Physical factors

Exposure to ionising radiation is known to cause cancer, and a connection with several types of cancer has been noted. In occupational exposure, the association has been found primarily with leukaemia, and, for health care, the association is with breast cancer. When it comes to the dose-response relationship for radiation, it is known that an average occupational exposure of 1000 mSv will double the risk of cancer. The dose threshold of occupational radiation is 20 mSv/year. The calculated risk of cancer at such an exposure level is 2 cancers in 10 years for every 1000 exposed employees. In Finland, the exposure levels of air crews and radiology personnel have remained significantly lower during the last few decades (since the 1970's), at 1–2 mSv/year. It can therefore be said that occupational cancer among employees who have been exposed to radiation after the 1070's is improbable. However, among operating radiologists, the average dose during 5 years may sometimes locally exceed 20 mSv/year, a level which may cause a risk of skin cancer. These individual cases can be compensated as an occupational disease after the consideration of individual circumstances.

Radon is known to cause lung cancer. Living for 30 years in a radon concentration of approximately 700 Bq doubles the risk of lung cancer by the age of 75 years. Previously, employees at mine sites could undergo significant radon exposure, but improved ventilation technology has nowadays lowered the exposure levels. It is usually difficult to separate occupational exposure to radon from environmental exposure. Lung cancer can be recognised as an occupational disease in individual cases after the consideration of individual circumstances if primarily occupational exposure can be proven.

Ultraviolet radiation is known to cause skin cancer: melanoma, squamous cell carcinoma, and basal cell carcinoma. In addition, an association with lip cancer and certain eye cancers has also been detected. In Nordic epidemiological studies, the risk of skin cancer was not elevated, and the risk of lip cancer was only slightly increased. Skin or lip cancer can be recognised as an occupational disease in individual cases after the consideration of individual circumstances if high exposure can be shown.

The connection between electromagnetic fields and cancer is uncertain. Because the evidence is inadequate, cancer suspected to have been caused by electromagnetic fields is not recognised as an occupational disease.

5.1.3.8 Biological factors

If an employee has been diagnosed as a hepatitis B or C carrier and has chronic active hepatitis caused by occupational exposure, a possible hepatocellular cancer of that patient is considered to be connected with the same exposure and is therefore recognised as an occupational disease. HIV infection is also associated with a propensity for different types of cancer. Especially Kaposi's sarcoma is typical among HIV patients, but also other cancers such as lymphoma occur. If the HIV infection has been caused by occupational exposure, any cancer related to the HIV infection is recognised as an occupational disease.

5.1.3.9 Shift work and other occupations classified as carcinogenic by IARC

Shift work, which disturbs the normal circadian rhythm, is probably carcinogenic in humans. It increases the risk of breast cancer slightly after 20–30 years of such work. The additional risk caused by shift work disturbing the normal circadian rhythm is, however, so low that there is no probable cause for making an occupational disease diagnosis.

When it comes to other occupations classified as causing a risk of cancer, the situation must be evaluated case by case, and the epidemiological evidence about the occupation in question and the exposures related to it (individual exposure and its severity in that occupation, type of cancer and latency period from the beginning of exposure to the diagnosis of disease) must be taken into account.

5.2 Other recommendations of the working group

5.2.1 Lung cancer screening among people exposed to asbestos

According to a review published in June 2012, lung cancer screening using low-dose CT may be beneficial for certain exposed groups, but it is still unclear whether the screening may cause harm and whether the results can be expanded to other exposed groups (Bach et al., 2012).

Especially smokers exposed to asbestos have a significant risk of lung cancer. The current obligatory 3-year follow-up using chest radiographs has no effect on lung cancer mortality. The follow-up of patients exposed to asbestos should be modified in such a way that those with a high risk of lung cancer would be checked annually or bi-annually with the use low-dose CT scanning.

5.2.2 Forming a specialist group for occupational cancer diagnostics

The Working Group recommends that the Finnish Institute of Occupational Health form a multi-disciplinary group of specialists for evaluating suspected cases of occupational cancer. This group would follow the available scientific research, concentrating on occupational cancers and their aetiology. The purpose of this group would be to standardise and keep up-to-date with respect to the evaluation of cancer causes. Upon request, this group would provide an expert statement on whether an individual employee's cancer fulfils the criteria set for an occupational disease.

5.2.3 Standardisation of data collection regarding asbestos exposure

The Working Group recommends uniform practices for investigating asbestos exposure. In order to determine exposure, screening methods using questionnaires in hospitals and other care facilities are recommended. If exposure is probable, but the level is unclear, exposure data should be specified through the use of structured interviews carried out by experts. These experts should be personnel from occupational health facilities, occupational medicine clinics, or pneumoconiosis expert groups. If necessary, the centralised national (telephone) interview service of the Finnish Institute of Occupational Health can be used.

5.2.4 Using chest radiographs to define the manifestation date of asbestosis

If the asbestosis diagnosis of a cancer patient has already been verified on the basis of regular chest radiographs and the manifestation date has been defined accordingly, no further action is required. If asbestosis is diagnosed at the same time as cancer, the manifestation date of the asbestosis should be based on the results of thin slice CT–HRCT (computer tomography–high-resolution computer tomography) scans or tissue sampling. This practice is necessary because the most-reliable asbestosis diagnosis is based on the results of HRCT scans. Only if HRCT scans or a tissue sample is unavailable, should the diagnosis be based on, and the manifestation date defined by, other types of CT scans or native chest radiographs.

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The memorandum from the Occupational Cancer Working Group 2013 is meant to update the suggestions made in the Memorandum from the Occupational Cancer Working Group from 1988. Its aim is to give recommendations regarding the diagnosis and compensation of occupational cancers.

In addition to the recommendations regarding the compensation of occupational cancers, the working group also takes a stand on the screening of lung cancer caused by exposure to asbestos, the forming of a special group of experts for occupational cancer diagnostics, the combining of gathered exposure information on asbestos, and the use of X-ray imaging determining the occurrence date for asbestosis.

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