MERLOD/2009/5

INTERNATIONAL LABOUR ORGANIZATION

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Meeting of Experts on the Revision of the List of Occupational Diseases (Recommendation No. 194)
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Contents

1. 1.2.5. Diseases caused by radio frequency radiation

General information on the agent

1. Radio frequency (RF) radiation is defined here as electromagnetic fields with frequencies ranging from 100 kilohertz (kHz) to 300 Gigahertz (GHz). Man-made sources of RF radiation are used in a variety of applications in industry (dielectric heaters and welders, induction heaters), telecommunications (radio and television broadcasting, cellular telephony), navigation (GPS, radar), medicine (surgical and therapeutic diathermy, MRI) and research. Sources generating high levels of RF fields are typically found in certain workplaces, while sources used by the general public generate comparably much lower fields near the user.

Interaction mechanisms

2. Human exposure to RF fields can produce effects that may be classified as direct or indirect.

- *Direct* effects result from direct interaction of RF fields with the human body. For high power RF radiation, the main effect is mainly due to energy absorption and increase of temperature in the whole or parts of the body. This thermal effect carries all the known implications of heating in biological systems. For the broad range of radio frequencies, cutaneous perception of heat and thermal pain is unreliable for detection, because the thermal receptors are located in the skin and do not readily sense the deep heating of the body caused by these fields. Another biological effect is the microwave auditory effect (through thermoelastic expansion) when exposed to pulsed RF radiation, although this does not represent an adverse effect.

- *Indirect* effects may result from physical contact with an object at a different electric potential from the body. These include RF contact currents (shocks, burns, vicinity to metallic objects such as metallic implants or jewellery) and interference with medical electronic equipment and devices (such as pacemakers or implantable cardioverter defibrillators).

3. Numerous national and international reviews [1] on the health effects of RF radiation have been published to date. These have reviewed biological and epidemiological studies on humans and animals regarding both thermal and non-thermal effects.

[1] The Health Council of the Netherlands (HCN 2004-2009), The UK Independent Expert Group on Mobile Phones (IEGMP 2000), The Royal Society of Canada Expert Panel on RF (Krewski et al. 2001a, b; 2007); UK independent Advisory Group on Non-Ionizing Radiation Protection (AGNIR 2001, 2003); US National Council for Radiation Protection (NCRP 2003); French Agency for Environmental Health Safety (AFSSE 2003, 2005); Swedish Radiation Protection Authority (SSI 2004-2008); Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR, January 2009; ICNIRP Review of Exposure to high frequency electromagnetic fields, biological effects and health consequences (100 kHz–300 GHz), to be published Summer 2009 (www.icnirp.org); ILO/ICNIRP/WHO: *Safety in the use of radio frequency dielectric heaters and sealers: A practical guide*, Geneva, 1998 (Occupational Safety and Health Series, No. 71).

4. International guidelines [2] address direct effects and provide occupational and general public exposure limits in the form of basic restrictions and reference levels. Because RF energy deposition in the body depends on the frequency of the RF field, the exposure limits vary with frequency.

Dosimetry

5. The dosimetric quantity used for RF radiation is the specific absorption rate (SAR, measured in watts per kilogram), either as a whole-body average SAR or as a partial-body localized SAR. The SAR of a biological body depends upon such exposure parameters as frequency of the radiation, intensity, polarization, configuration of the radiation source and the body, reflection surfaces and body size, shape and electrical properties. The SAR spatial distribution inside the body is highly non-uniform and may produce internal temperature gradients. At frequencies above 10 GHz, the energy is deposited close to the body surface. The time-temperature profile must be considered in assessing biological effects.

Specifically including diseases caused by radio frequencies in the ILO List of occupational diseases?

A brief review of the scientific background

6. All the scientific reviews agree on the existence of acute adverse *thermal* effects. The medical consequences of thermal injury depend on what tissues are involved, how well they are suffused with blood and whether they can regenerate. Besides the medical consequences of thermal injury, the most consistent effects of acute RF exposure on human subjects are the thermoregulatory responses of the cardiovascular system to RF-induced heating.

7. The evidence from volunteer studies suggests that cognitive function can be adversely affected by whole-body heat stress, resulting in increased levels of unsafe behaviour and reduced task performance, but this has proved difficult to quantify in volunteer studies.

8. Thermally significant RF exposure can impair male fertility and cause increased embryo and foetal losses and increase the incidence of fetal malformations and anomalies. Such effects have not been consistently shown at exposure levels that do not induce temperature elevation of 1°C or more. The effects of overexposure may be diverse depending on the intensity, duration and physical characteristics of the radiation and the anatomical part exposed. From epidemiological studies, the evidence is strongest for spontaneous abortion and perhaps sex ratio. However, potential confounding by other aspects of work activity needs to be considered.

9. Cataracts in the eyes of rabbits is a well established thermal effect of RF exposure. However, primates appear less susceptible to cataract induction than rabbits, and opacities have not been observed in primates following either acute or prolonged exposures. A few epidemiological studies of cataracts in workers were performed, but the study designs were limited with respect to exposure assessment and selection of unexposed workers.

[2] ICNIRP: Guidelines for Limiting Exposure to Time-Varying Electric, Magnetic, and Electromagnetic Fields (up to 300 GHz). Health Physics 74 (4), 494–522; 1998; IEEE C95.1-2005 "IEEE Standards for Safety Levels with Respect to Human Exposure to Radio Frequency Electromagnetic Fields, 3 kHz to 300 GHz", IEEE C95.1-2005, 2006.

10. Thermal effects are well established and form the basis of international limits for occupational exposure. Occupational exposures below those limits should therefore avoid any adverse health effects resulting from heating caused by RF fields.

11. Recent concern has focused more on exposure to lower-level RF radiation from mobile telephony. Concerning cancer-related effects, the recent in vitro and animal genotoxicity and carcinogenicity studies are fairly consistent overall and indicate that such effects are unlikely at SAR levels up to 4 W kg^{-1}. The rise in risk of non-Hodgkins lymphoma (OR of 3.15; 95 per cent CI=0.63-15.87) for RF radiation high exposure found by Karipidis et al., for instance, was based on very small numbers. [3] Similarly, a review of cytogenetic studies conducted by Verschaeve in 2008 [4] has revealed that in the majority of these studies RF-exposed individuals have increased frequencies of genetic damage (such as chromosomal aberrations) in their lymphocytes or exfoliated buccal cells. However, these predominantly positive findings are limited by the lack of radiation dosimetry.

12. Overall, conclusions from epidemiological studies show that there is no cancer site for which there is consistent evidence, or even an individual study providing strong evidence, that occupational exposure to RF affects risk.

13. Exposure and methodology limitations leave unresolved the possibility of an association between occupational RF and cancer.

14. The evidence to date suggests that there are no consistent effects of non-thermal RF exposures on cardiovascular physiology, on circulating hormone levels or on auditory or vestibular function, except for the auditory perception of pulsed RF such as the characteristic of radar.

15. Undoubtedly, given the seriousness of potential non-thermal health effects of RF, in an attempt to compile relevant data, it is advisable to monitor suspected RF-induced diseases with a parallel effort in providing dose measurements and analysing them for early warning and prevention purposes.

Countries and areas including radio frequency-related diseases in their lists of occupational diseases

- Canada
- Chile
- China
- Colombia
- Costa Rica (shortwave)
- Czech Republic
- Ecuador
- Hong Kong (China) (electromagnetic)

[3] K.K. Karipidis et al.: "Occupational exposure to ionizing and non-ionizing radiation and risk of non-Hodgkin lymphoma", *Int. Arch. Occup. Environ.* Health, Aug. 2007; 80(8), 663–670. Epub 2 Mar. 2007.

[4] L. Verschaeve: "Genetic damage in subjects exposed to radio frequency radiation", *Mutat. Res.* Mar.–June 2009; 681(2-3), 259–270.

- Hungary
- Italy
- Japan
- Kenya (exposure to electromagnetic radiations)
- Republic of Korea
- Lithuania
- Mexico
- Norway
- Portugal
- Poland
- Serbia
- Switzerland
- United Kingdom

2. 1.3.7. Malaria

General information on the agent

16. Malaria is the most important of the parasitic diseases of humans, with transmission in 107 countries containing 3 billion people and causing 1–3 million deaths each year. Four protozoan species of the genus *Plasmodium (P. falciparum, P. vivax, P. ovale,* and *P. malariae)* cause nearly all malarial infections in humans. As for the geographical distribution of the plasmodia, *P. falciparum* predominates in Africa, New Guinea, and Haiti, while *P. vivax* is more common in Central America. The prevalence of these two species is approximately equal in South America, the Indian subcontinent, eastern Asia, and Oceania. *P. malariae* is found in most endemic areas, especially throughout sub-Saharan Africa, but is much less common. *P. ovale* is relatively unusual outside Africa. Human infection begins when a female anopheline mosquito inoculates plasmodial sporozoites from its salivary gland during a blood meal. Almost all deaths are caused by falciparum-type malaria.

17. Every year, *Plasmodium falciparum* infects 300 to 500 million persons. Sub-Saharan Africa, parts of South America and South-East Asia are particularly affected. Approximately 1 per cent of all non-immune travellers who acquire *P. falciparum* infection die. Malaria also takes an economic toll, cutting economic growth rates by as much as 1.3 per cent in countries with high disease rates. [5]

Exposure at work

18. In countries or areas without endemic malaria:

- *"Airport/port malaria"* results from infective bites of mosquitoes that have travelled on board an airplane. Mosquitoes can survive a flight even in non-pressurized wheel

[5] www.who.int/mediacentre/factsheets/fs094/en/index.html.

bays. [6] In 29 patients from 1969 to 1988, most cases occurred within a distance of 2 kilometres from the next airport, but longer distances are also possible when vectors are transported further, for example in a car.

- *"Baggage"* malaria: the possibility of carrying infective mosquitoes within items of baggage to non-endemic areas or to areas far from international airports has been suspected in a number of previous cases. An occupational risk for malaria can therefore be assumed for: (1) flight and ground crew; (2) airline pilots and co-pilots; (3) dockers; (4) left luggage office operators; (5) baggage inspection operators; (6) duty free shop personnel; (7) cleaners; and (8) business travellers.

- *Nosocomial transmission*, from direct blood contact (in which blood or parasite-containing fluids from a parasitaemic patient enter the bloodstream of a secondary patient). The incubation time following direct blood contact or needle stick injuries ranges from 4 to 17 days. An occupational risk for malaria can therefore be assumed for: (1) physicians; (2) nurses; (3) hospital personnel assigned to invasive therapeutic procedures; (4) laboratory staff; (5) personnel charged with the transportation of biological samples from the ward to the laboratory.

19. In countries or areas with endemic malaria:

- transmission by local *competent vectors*: [7] according to the WHO, some occupational categories are at high risk of malaria, even in endemic areas, such as soldiers, forestry workers and gem miners. A specific professional category is represented by non-immune migrant workers (moving between countries or within a country) occupied with gem mining in forests, logging, agriculture and construction. [8]

- expatriates' malaria: *P. falciparum* malaria is also a major occupational illness that accounts for several deaths per year and numerous lost working days among the expatriate population working or living in high-risk malarial areas and among business travellers.

Specifically including malaria in the ILO List of occupational diseases?

A brief review of the scientific background

20. It is evident that malaria can be an occupational disease, and it is possible to identify specific activities particularly at risk, or conditions which enable the establishment of a diagnosis with a causal relationship between the occupational exposure and the disease. A study in an area of intensive vegetable farming in Côte d'Ivoire showed that malaria led to

[6] R.C. Russell: "Survival of insects in the wheel bays of a Boeing 747B aircraft on flights between tropical and temperate airports", in *World Health Organization Bulletin*, 1987, 65, 659–662.

[7] L.L. Robert et al.: "Plasmodium-infected Anopheles mosquitoes collected in Virginia and Maryland following local transmission of *Plasmodium vivax* malaria in Loudoun County, Virginia", *J. Am. Mosq. Control Assoc.* June 2005, 21(2), 187–193.

[8] WHO: *World Malaria Report 2008*, at http://malaria.who.int/wmr2008/malaria2008.pdf.

absences from work of up to 26 days in a ten-month period. [9] In July 2006, the Medical Service of the French armed forces was alerted to an outbreak of malaria in a French battalion: 17 cases occurred in two weeks among 410 soldiers returning from Côte d'Ivoire. [10]

21. It is extremely important for business travellers to be well informed and advised on their considerable risk for contracting malaria, on prevention measures such as avoidance of mosquitoes bites and taking anti-malaria tablets (appropriate prophylactic regimens) when visiting malarial regions, and on the significant complications that can result from infection versus the possibility of developing serious adverse reactions to the medication. [11]

22. Malaria is mainly a non-occupational disease. In the absence of clear exposure criteria, there is a very high risk of a wrong attribution of the disease to occupation, and individual cases need a specific evaluation. For instance, in a case report referred to by Zoller et al., [12] despite the complete homology found between the primary case (a pregnant women) and secondary case (a physician), and the consequent confirmation of the former as the source of the infection in the latter, it was not possible to identify an occupational contact or exposure.

Diagnostic criteria and process including key aspects of the evaluation

23. Any fever occurring within two years of leaving a malaria-endemic area should be investigated immediately, as symptoms for some temperate strains of *P. vivax* may not be evident until 18 months after a bite from a carrier mosquito.

24. Malaria can be recognized easily as an occupational disease in the following cases:

- Infection from direct blood contact (in which blood from a parasitaemic patient or other parasite-containing fluids enter the bloodstream of a secondary patient) occurs in a working situation; in this case, the "primary" case has to be identified. This is valid both for workers living and working in non-endemic and endemic areas *(nosocomial malaria).*

- Infection in workers who have travelled from non-endemic areas to endemic areas, including migrant and seasonal workers and any occupational situation which forces the worker to live in endemic areas *(local competent vector malaria).*

- Workers employed in international airports, in this case even without evidence of travel in endemic areas *(airport malaria).*

[9] C. Haweks and M. Ruel: "The links between agriculture and health: an intersectoral opportunity to improve the health and livelihoods of the poor", in *World Health Organization Bulletin*, Dec. 2006, 84(12), 984–990, Review.

[10] L. Ollivier et al.: "Chemoprophylaxis compliance in a French battalion after returning from malaria-endemic area", *J. Travel Med.*, Sep.–Oct. 2008, 15(5), 355–357.

[11] P. Hymel and W. Yang: "Review of Malaria Risk and Prevention for Use in Corporate Travel", *J. Occup. Environ. Med.*, 2008; 50, 951–959.

[12] T. Zoller et al.: "Malaria transmission in non-endemic areas: Case report, review of the literature and implications for public health management", *Malaria J.*, Apr. 2009, 20, 8, 71.

25. There are situations in which it is very difficult to distinguish between occupational and non–occupational disease; notably cases of malaria occurring in endemic areas, where people can be infected either at the workplace or in the living environment. In these cases, it is necessary to do a case-by-case evaluation. The variables involved need to be considered, including:

- Night work in endemic areas: since it is known that most anopheline mosquitoes bite between dusk and dawn, when the bite is not identified, malaria is likely to be due to residential exposure.
- Rural work in endemic areas: agricultural workers very often work from sunrise to sunset and are exposed to mosquito bites in the most critical periods of the day.
- Frequency of the at-risk activities.

26. In these conditions, and taking into account the difficulties of establishing firm diagnostic criteria, if not specifically listed, malaria is still covered by the "open item" (item 1.3.10) in the List as such is already the case with item 29 in the list of occupational diseases in Schedule I of Convention No. 121.

Countries specifically including malaria in the national lists of occupational diseases

- Angola
- Argentina
- Australia
- Belgium
- Brazil
- Czech Republic
- Denmark
- Finland
- Hungary
- Italy
- Japan
- Luxembourg
- Mexico
- Norway
- Portugal
- Philippines
- Serbia
- Spain
- Switzerland
- United Kingdom (offshore workplaces)

3. 2.1.8. Extrinsic allergic alveolitis caused by the inhalation of organic dusts arising from work activities (to include mists from contaminated oils)

General information on the agent

27. Metalworking fluids (MWFs) are complex mixtures composed of a water–oil emulsion containing biocides and various additives to improve performance and stability. Lubrication and cooling of machines are involved in operations such as cutting and drilling of metal parts, as well as aiding the removal of the waste metal. MWFs are typically recycled via sumps, and even though biocides are often added, contamination by microorganisms can occur; they are excellent culture media for bacterial and fungal growth and may therefore act as an infectious source for employees coming into contact with them. High numbers of bacteria can be found in preserved as well as non-preserved MWFs. Bacteria, especially those with human pathogenic potential, can develop resistance to biocides and are detectable for weeks and months in preserved MWFs. [13]

28. Hypersensitivity pneumonitis, or extrinsic allergic alveolitis (EAA), is an inflammatory disorder of the lung, involving alveolar walls and terminal airways, that is induced, in a susceptible host, by repeated inhalation of a variety of organic agents. "Farmer's lung" is the term most commonly used for hypersensitivity pneumonitis due to inhalation of antigens present in mouldy hay, such as thermophilic actinomyces, micropolyspora faeni, and the aspergillus species. The frequency of hypersensitivity pneumonitis varies with the environmental exposure and the specific antigen involved. The very early (acute) reaction is characterized by an increase in polymorphonuclear leukocytes in the alveoli and small airways. This early lesion is followed by an influx of mononuclear cells into the lung and the formation of granulomas that appear to be the result of a classic delayed (T cell-mediated) hypersensitivity reaction to repeated inhalation of antigen and adjuvant-active materials. [14] Type III reaction and Type IV hypersensitivity reactions are dominant in the subacute and chronic phase of the disease, respectively.

Exposure at work

29. Lubrication and cooling of machines involved in operations such as cutting and drilling of metal parts, as well as aiding the removal of the waste metal (for example, in automobile production, engine manufacturing, metalworking, and car parts manufacturing).

30. Exposure assessment:

- Cultivation and characterization of bacteria in oils with and without preservative-inactivating substances.

[13] S. Dilger, A. Fluri and H.G. Sonntag: "Bacterial contamination of preserved and non-preserved metal working fluids", *Int. J. Hyg. Environ. Health*, 2005, 208(6), 467–476. Epub 30 Sep. 2005.

[14] G.W. Hunninghake and J.N. Kline: "Hypersensitivity pneumonitis", in *Harrison's Principles of Internal Medicin*", 16th edition.

- The precipitin reaction is also a marker of asymptomatic exposure. [15]

Specifically including extrinsic allergic alveolitis due to contaminated oils in the ILO List of occupational diseases?

A brief review of the scientific background

31. Pulmonary effects of MWFs are quite often reported in exposed workers and can be considered occupational diseases.

32. Bernstein et al. reported extrinsic allergic alveolitis in six workers at a car parts factory in Michigan, all of whom had precipitins due to *Pseudomonas fluorescens*, which was also cultured from the MWFs. [16]

33. Other reports include eight clusters of extrinsic allergic alveolitis thought to be related to MWFs in the mid-1990s, where non-tuberculous *Mycobacterium* and *Aspergillus* species were identified as possible causative organisms.

34. An investigation into the outbreak of extrinsic allergic alveolitis reported in Europe in 2003–04 detected a large number of affected workers, not only with extrinsic allergic alveolitis but also with occupational asthma. Mist from used MWFs were suspected of being the likely cause. [17]

35. Mycobacterium contamination of MWF sumps has been linked in one study with two outbreaks of hypersensitivity pneumonia. [18]

36. In the work carried out by Fishwick et al, [19] precipitating IgG to *Pseudomonas* species was found in workers with respiratory or nasal symptoms. Furthermore, two of them had reported work-related symptoms. Despite a heavy growth of both fungi and bacteria in the metalworking fluids, only *Pseudomonas* was cultured from air samples. The undetectable levels of endotoxin in the air suggest a possible specific immune-mediated mechanism. This is supported by the finding of precipitating antibodies to both *Pseudomonas* extract and to used metalworking fluids extract (and raised IgG to Pseudomonas in those with the strongest precipitating bands).

37. The preliminary results of an investigation carried out by the US NIOSH at an automobile brake manufacturing facility in Ohio found that exposure to aerosolized non-tuberculous

[15] P. Dawkins et al.: "An outbreak of extrinsic alveolitis at a car engine plant", *Occup. Med.* (Lond.), Dec. 2006, 56(8), 559–565, Epub 9 Nov. 2006.

[16] D.I. Bernstein et al.: "Machine operator's lung: A hypersensitivity pneumonitis disorder associated with exposure to metalworking fluid aerosols", *Chest* 1995, 108, 636–641.

[17] W. Robertson et al.: "Clinical investigation of an outbreak of alveolitis and asthma in a car engine manufacturing plant", *Thorax*, Nov 2007, 62(11),: 981–990, Epub. 15 May 2007.

[18] A. Gupta and K.D. Rosenmann: "Hypersensitivity pneumonitis due to metal working fluids: Sporadic or under-reported?", in *American Journal of Industrial Medicine*, 4,: 423–433, 2006.

[19] D. Fishwick et al.: "Respiratory symptoms, immunology and organism identification in contaminated metalworking fluid workers: What you see is not what you get", *Occup. Med*. (Lond.), May 2005, 55(3), 238–241.

mycobacteria (NTM) might be contributing to the observed respiratory illnesses such as hypersensitivity pneumonia. [20]

38. Moreover, a case of acute hypersensitivity pneumonitis caused by *Paecilomyces variotii* and *Paecilomyces nivea* growing in an oil fan heater has been described by Hara et al. [21]

39. In an engine-manufacturing plant in Wisconsin, an outbreak of extrinsic allergic alveolitis fluids was reported. It was suggested that there was a biocontaminant, but no specific organism was implicated.

40. In the Connecticut outbreak, [22] three sources of water-based aerosols were identified, but again no specific organism was identified.

Diagnostic process and criteria

41. A *prediction* rule for the clinical diagnosis of hypersensitivity pneumonitis has been developed by the International Hypersensitivity Pneumonitis Study Group. Six significant predictors of hypersensitivity pneumonitis (exposure to a known antigen, positive predictive antibodies to the antigen, recurrent episodes of symptoms, inspiratory crackles, symptoms developing 4–8 hours after exposure, and weight loss) were retrospectively developed then validated in a separate cohort. This diagnostic paradigm has a high predictive value in the diagnosis of hypersensitivity pneumonitis, without the need for invasive testing. In cases where only a subset of the criteria is fulfilled, the diagnosis is less clearly established. It is clear, however, that the diagnosis of hypersensitivity pneumonitis is established by (1) consistent symptoms, physical findings, pulmonary function tests, and radiographic tests; (2) a history of exposure to a recognized antigen; and (3) ideally, identification of an antibody to that antigen. In a few circumstances, bronchoalveolar lavage (BAL) and/or lung biopsy may be needed. Provocation tests may be useful but are not essential for the diagnosis. [23]

42. Pulmonary effects of MWFs have been widely investigated, even from the toxicological point of view, but most evidence strongly suggests that the microbial changes that occur in fluid composition, during use and storage in the workplace, are responsible for those effects.

43. In conclusion, based on the available data, extrinsic allergic alveolitis from MWFs may be included in the broad group of "Extrinsic allergic alveolitis caused by the inhalation of organic dusts" (it is evident that the causal agent is "organic"). Alternatively, a more comprehensive denomination of the item may be proposed, for example: "Extrinsic allergic alveolitis caused by the inhalation of organic dusts and other microbial or organic derivatives".

[20] Centers for Diseases Control and Prevention: "Respiratory illness in workers exposed to metalworking fluid contaminated with nontuberculous mycobacteria", Ohio, 2001, JAMA, 19 June 2002, 287(23), 3073–3074.

[21] J. Hara et al.: "A case of acute hypersensitivity pneumonitis associated with an oil fan heater", *Am. J. Med. Sci.*, Jan. 2006, 331(1), 35–36.

[22] M.J. Hodgson et al.: "Hypersensitivity pneumonitis in a metal-working environment", *Am. J. Ind. Med*. 2001, 39, 616–628.

[23] G.W. Hunninghake, J.N. Kline: "Hypersensitivity pneumonitis", in *Harrison's Principles of Internal Medicine*, op. cit.

Countries and areas specifically including extrinsic allergic alveolitis in their lists of occupational diseases

- EU
- Algeria
- Angola
- Argentina
- Austria
- Bangladesh
- Belgium
- Brazil
- Canada
- China
- Colombia
- Denmark
- Finland
- France
- Germany
- Hong Kong, China (farmer's lung)
- Hungary
- India
- Indonesia
- Italy
- Kenya (farmer's lung)
- Latvia
- Malaysia
- Nicaragua
- Romania
- Saudi Arabia (allergic respiratory diseases due to animal and other allergenic agents including chemical, dust or allergenic microorganisms)
- Serbia
- South Africa
- Spain
- United Kingdom

4. 2.3.7. Carpal tunnel syndrome due to extended periods of repetitive forceful work, work involving vibration, extreme postures of the wrist, or a combination of the three

General information on the disorder

44. Carpal tunnel syndrome (CTS) is a compression neuropathy due to entrapment of the median nerve within the carpal tunnel at the wrist. It affects about 5 per cent of the general adult population and has an annual incidence of 1 per 1,000 person years. One systematic review found that according to some studies, women are three times more likely to develop the condition than men. Other conditions associated with CTS include pregnancy, rheumatoid arthritis, diabetes mellitus, hypothyroidism and acromegaly.

45. According to the consensus criteria [24] for its classification in epidemiological studies, CTS is defined on the basis of the occurrence of the following symptoms:

- Numbness, tingling, burning, or pain in at least two of digits 1, 2 or 3;
- Palm pain, wrist pain, or radiation proximal to the wrist.

Exposure at work

46. Construction and agriculture are considered the most hazardous occupations with regard to possible CTS.

Specifically including CTS due to extended periods of repetitive forceful work, work involving vibration, extreme postures of the wrist or a combination of the three, in the ILO List of occupational diseases?

A brief review of the scientific background

47. In terms of work exposure, repetitive and forceful exertions of the hand, sustained awkward postures of the wrist, and the use of vibrating hand tools, all seem to be associated with a high risk of CTS. A recent prospective study carried out in France has demonstrated an association between CTS and some working sectors, such as agriculture, construction and many manufacturing sectors. [25]

48. Epidemiological studies have identified several combinations of work factors, individual factors, and psychosocial factors related to CTS. These factors include female sex, obesity, pregnancy, and medical conditions including diabetes mellitus, thyroid disease, and osteoarthrosis in the wrist.

[24] D. Rempel et al.: "Consensus criteria for the classification of carpal tunnel syndrome in epidemiologic studies", *Am. J. Public Health*, Oct. 1998, 88(10), 1447–1451.

[25] Y. Roquelaure et al.: "Attributable risk of carpal tunnel syndrome according to industry and occupation in a general population ", Arthritis Rheum, 15 Sep. 2008, 59(9), 1341–1348.

49. A systematic review of the relevant literature conducted by van Rijn et al. provides consistent indications that CTS is associated with an average hand force requirement of more than 4 kg, repetitiveness at work, and a daily eight-hour energy-equivalent frequency-weighted acceleration of 3.9 ms^{-2}. [26]

50. Palmer et al. found reasonable evidence that regular and prolonged use of hand-held vibratory tools increases the risk of CTS more than twofold and found substantial evidence for similar or even higher risks from prolonged and highly repetitive flexion and extension of the wrist, especially when allied with a forceful grip. [27]

51. According to Sauni et al., there is a strong correlation between cumulative exposure to hand-arm vibration and the occurrence of CTS symptoms. [28] A study conducted among supermarket cashiers in Italy demonstrated that intensive manual work together with inadequate recovery time might have generated an impairment of the median nerve at the wrist level proportionally increasing with duration of hand use. [29]

52. A quantitative score based on the Bradford Hill Criteria (qBHs) was used by Lozano-Calderón et al. to evaluate 117 articles presenting original data regarding the aetiology of CTS. The average qBHs was 12.2 points (moderate association) among biological risk factors, compared with 5.2 points (poor association) for occupational risk factors. [30]

Diagnostic process and criteria

53. In the case of CTS observed in a worker exposed to the typical risk factors, such as repetitive and forceful exertions of the hand, sustained awkward postures of the wrist, and use of vibrating hand tools for a prolonged period (years) and for a significant proportion of the working day (50 per cent of working time, as an indicative guide value), the diagnosis of occupational disease can be reached without significant doubts (work as the causal agent, and no less than a co-causal factor).

54. In the case of CTS observed in a worker not exposed for a prolonged period and for a non-significant proportion of working time, the diagnosis of occupational disease can be reached only on the basis of the application of rigorous scientific criteria taking into account all other possible aetiologies and risk factors, in particular female sex, obesity, pregnancy, diabetes mellitus, thyroid disease, and wrist osteoarthrosis.

55. Owing to the multifactorial aetiology, it seems inappropriate to attribute CTS to a single and specific risk factor, because hand/arm vibration are usually associated with repetitive

[26] R.M. van Rijn et al.: "Associations between work-related factors and the carpal tunnel syndrome – A systematic review", *Scand. J. Work Environ. Health.* Jan. 2009, 35(1), 19–36.

[27] K.T. Palmer, E.C. Harris, D. Coggon: "Carpal tunnel syndrome and its relation to occupation: a systematic literature review", *Occup. Med.* (Lond.). Jan. 2007, 57(1): 57–66.

[28] R. Sauni et al.: "Dose-response relationship between exposure to hand-arm vibration and health effects among metalworkers", *Ann. Occup. Hyg.*, Jan. 2009, 53(1), 55–62.

[29] R. Bonfiglioli et al.: Relationship between repetitive work and the prevalence of carpal tunnel syndrome in part-time and full-time female supermarket cashiers: A quasi-experimental study", *Int. Arch. Occup. Environ. Health*., 2007 Jan., 80(3), 248–253.

[30] S. Lozano-Calderón, S. Anthony and D. Ring: "The quality and strength of evidence for etiology: Example of carpal tunnel syndrome", *J. Hand. Surg.* [Am], Apr. 2008, 33(4), 525–538.

and forceful exertions of the hand and sustained awkward postures of the wrist, and the specific aetiological role of single risk factors can hardly be assessed.

Countries and areas specifically including carpal tunnel syndrome in their lists of occupational diseases

- EU (paralysis of the nerves due to pressure)
- Angola
- Argentina
- Australia
- Belgium (nerve paralysis due to pressure)
- Brazil
- Canada (Ontario)
- Colombia (occupational cramp of hand or forearm caused by repeated movements of fingers, hands or forearms)
- Denmark
- Ecuador
- France
- Germany (pressure-induced nerve damage)
- Hong Kong, China
- Hungary (peripheral nerve damage due to pressure)
- Italy
- Kenya
- Republic of Korea
- Latvia (diseases of peripheral nerves and musculoskeletal system)
- Lithuania (diseases caused by frequent monotonous, strenuous movements)
- Luxembourg (nerve paralysis due to prolonged local pressure)
- Malaysia (cramp of the hand or forearm due to repetitive movements)
- Poland (chronic diseases of peripheral nerve system caused by pressure on nerve trunks
- Portugal (pressure on nerves or nerve plexuses due to work postures) (paralyses)
- Romania
- Saudi Arabia (test diseases – hands and fingers)
- Serbia
- South Africa
- Spain
- Switzerland (peripheral nerve paralysis due to pressure)
- United Kingdom

5. 2.4. Mental and behavioural disorders (to be replaced with "psychological disorders")

General information on the disorders

56. Mental and behavioural disorders as defined in the WHO International Statistical Classification of Diseases and Related Health Problems (10th Revision, 2007) (ICD-10) and psychological disorders caused by psychosocial factors at work are increasing in modern society. Both issues are addressed in the following sections.

57. According to WHO (2001), mental and behavioural disorders represent about 12 per cent of total health disorders. In the United States, about one in four adults suffers from a diagnosable mental disorder in a given year, and about one in 17 suffers from a serious mental illness. In addition, mental disorders are the leading cause of disability in the United States and Canada for ages 15–44. [31] In Europe, 14 per cent of the population report a lifetime history of some mood disorder, 13.6 per cent some form of anxiety disorder and 5.2 per cent some type of alcohol disorder. Major depression and specific phobias were the most common single mental disorders. [32]

58. According to the third European Survey on Working Conditions, carried out in 2000 in the then 15 Member States of the European Union (EU), 28 per cent of workers complained of stress at work, mainly due to working very fast (56 per cent of those affected), tight deadlines (60 per cent), having no influence on the task order (33 per cent), or having monotonous work (40 per cent).

59. A recent international survey among key stakeholders in the new EU Member States and the candidate countries revealed that almost 90 per cent of the respondents stated that in their countries stress is considered to be a cause of disease, and that stress and mobbing result from poor work organization. [33]

60. A similar percentage of complaints about work stress (30.8 per cent) has been recorded in Canada (36.7 per cent in men and 29.0 per cent in women). [34]

61. High costs for the individual, the company and society as a whole, are significant not only in terms of workers' health and well-being, but also as regards work ability and

[31] R.C. Kessler et al.: "Prevalence, severity, and comorbidity of twelve-month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R)", in *Archives of General Psychiatry*, June 2005, 62(6) :617–627; WHO: *World Health Report 2004: Changing history*, Annex, table 3: Burden of disease in DALYs by cause, sex, and mortality stratum in WHO regions, estimates for 2002, Geneva, 2004.

[32] J. Alonso et al.: "Prevalence of mental disorders in Europe: Results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project", *Acta Psychiatr Scand, Suppl*., 2004, (420), 21–27).

[33] S. Iavicoli et al.: "Fact-finding survey on the perception of work-related stress in EU candidate countries", in S. Iavicoli (ed.): *Stress at work in enlarging Europe*, Rome, National Institute for Occupational Safety and Prevention, 2004, pp. 81–97.

[34] Statistics Canada: *Canadian Community Health Survey: Mental Health and Well-Being*, 2003, at www.statcan.ca/Daily/English/030903/d030903a.htm.

performance efficiency, absenteeism and turnover, commitment and safety, as well as in terms of social consequences and compensative interventions. [35]

62. In October 2004, the European Representatives of Employers and Employees (UNICE/UEAPME, CEEP and ETUC) signed a Framework agreement on work-related stress, aimed at "identifying, preventing, eliminating or reducing problems of work-related stress, that may reduce effectiveness at work and may cause ill health". The document states that work-related stress has been identified at international, European and national levels as a concern for both employers and workers, and consequently tackling stress at work can lead to a greater efficiency and improved occupational health and safety, with consequent economic and social benefits for companies, workers and society as a whole.

Exposure at work

63. Stress at work, and the consequent mental and behavioural disorders, are related to working conditions and type of job; it is also affected by many "mediators" such as age, gender, personality (factors such as neuroticism, over-commitment, locus of control), psychophysical and social conditions. Occupational stress is the negative consequence of a distorted relationship between worker and work environment (mental/physical load, work organization, social relationships), where both components (work demands and human resources) are interacting to cause varying degrees of maladjustment and health impairment.

64. The demand/control/support model [36] highlight the fact that the combination of high psychological demands and low decision latitude (that is, poor chance of influencing decisions and developing skills) is dangerous to health.

65. The effort/reward imbalance model [37] points out that high effort, intrinsic or extrinsic, is associated with health risk when it is not appropriately recognized with material, social or psychological rewards. Furthermore, there are several intervening factors, related not only to high cognitive and emotional stress but also to scarce coping strategies, that are strongly influenced by personal characteristics (i.e. commitment), lack of control on working conditions, social support by colleagues, and recognition by supervisors. The most important single stress factor at work is the fear of losing one's job. Information, participation and recognition are essential for stress management at work.

66. At work, people can suffer from such disorders independently or before entering the job, whereas others may develop such disorders during their working life, with or without the involvement of job constraints, which in turn could represent causal or aggravating factors.

[35] ILO: *Mental health and work: Impact, issues and good practices*, World Health Organization and International Labour Organization (www.wfmh.org) 2000, ILO: *Preventing stress at work*. ILO, Conditions of Work Digest, Vol. 11/2, European Commission (Occupation & Social Affairs): *Guidance on work-related stress: Spice of life or kiss of death*. Office of EU community Publications, 2000; T. Cox, A. Griffiths, E. Rial-Gonzales: "Research on Work-related Stress", European Agency of Safety and Health at Work, Office for Official Publications of the European Communities, Luxembourg, 2000.

[36] R.A. Karasek: "Job demands, job decision latitude and mental strain: Implication for job redesign", in *Administrative Science Quarterly*, 1979, 24, 285–307; J.V. Johnson, E.M. Hall: "Job strain, work place social support, and cardiovascular disease: A cross-sectional study of a random sample of the Swedish working population", *Am. J. Public Health*, 1988, 78, 1336–1342.

[37] J. Siegrist, D. Klein, K.H. Voight: "Linking sociological with physiological data: The model of effort-reward imbalance at work", Acta Physiol. Scand. 1997, 161, 112–116.

On the other hand, it is plausible that people suffering from major disorders are less frequently employed, or more frequently excluded from work activities [38] and manifestations could be different in working and general populations. [39]

67. Chronic anxious and depressive disorders have negative impacts on mood (irritability and emotional exhaustion), cognitive function (memory, concentration, vigilance), human relations (personal conflicts), behaviour (lower work accomplishment and performance efficiency, absenteeism, alcohol and drug consumption) and physical condition (tiredness, fatigue, gastrointestinal, cardiovascular and neurotic troubles and disorders).

68. The "burnout syndrome" is one of the most important clinical syndromes related to working conditions. According to Maslach and Jackson [40] it is the result of chronic stress at the workplace which has not been successfully dealt with. It is characterized by emotional exhaustion, depersonalization (negativism/cynicism) and loss of personal accomplishments at work, and is found prevalently in caring and social professions (social workers, teachers, nurses, doctors, security officers). Emotional exhaustion is the main factor which entails behavioural and operational changes at work with a consequent decrease of engagement and productivity, increased absenteeism and reduced work ability, as well as disturbed family and social relations. [41] The main psychiatric symptoms are, in addition to chronic fatigue and continuous exhaustion, concentration and memory disturbances, anxiety and depressive disturbances, which may even lead to suicide, and drug addictions. Common somatic symptoms are headaches, gastrointestinal disorders (irritable stomach, diarrhoea), or cardiovascular disturbances (tachycardia, arrhythmias).

Diagnostic process and criteria

69. In general, "mental disorders" refers to any clinically significant behavioural or psychological syndrome characterized by the presence of distressing symptoms, impairment of functioning, or significantly increased risk of suffering (pain, death or disability).

70. On the other hand, the term "psychological disorder", although often used as a synonym for mental disorder (see, for example, the Diagnostic and Statistical Manual of Mental Disorders, DSM-IV), generally implies less severe clinical conditions in terms of emotional and behavioural symptoms, albeit with similar manifestations and syndromes.

[38] S.L. Ettner: "The relationship between labor market outcomes and mental and physical health: Exogenous human capital or endogenous health production?", in *The economics of disability*, (Greenwich, CT, JAI Press, 2000, pp. 1–32); D.E. Marcotte, V. Wilcox-Gök and D. Salkever: "The labor marker effects of mental illness: The case of affective disorders", in *The economics of disability* (Greenwich, CT, JAI Press, 2000, pp. 181–210).

[39] E. Archambault, G. Côté and Y. Gingras: "Bibliometiric analysis of research on mental health in the workplace in Canada, 1991–2002", report prepared for the Institute of Neurosciences, Mental Health and Addiction, and the Institute of Population and Public Health Canadian Institutes of Health Research, 2003; E.R. Berndt et al.: "Health care use and at-work productivity among employees with mental disorders", in *Health Affairs (Project Hope)*, 2000, 19(4), 244–256.

[40] C. Maslach and S.E. Jackson: "The measurement of experience burnout", in *Journal of Occupational Behaviour*, 2, 1981, 99–113.

[41] A. Weber and A. Jaekel-Reinhard: "Burnout syndrome: A disease of modern societies?", in *Occupational Medicine*, Vol. 50, 2000, pp. 512–517.

71. The pathological effects due to work stress mainly concern the neuropsychic, cardiovascular and gastrointestinal systems. The most common symptoms are irritability, emotional troubles, negative attitudes towards other persons, headache, dyspepsia, and sleep troubles. These generic symptoms may be chronic and develop into more specific disorders, such as chronic anxiety, depression, permanent sleep disorders, as well as chronic gastroduodenitis, colitis and ulcer, hypertension, arrhythmia and ischaemic heart diseases. [42]

72. Nevertheless, mental health problems and stress at work, with their consequent negative effects on work ability and productivity, are still the object of many discussions and disputes, owing to a poor knowledge and definition of these items, on the one hand, and to the difficulty of distinguishing the "work" component from the more general context.

73. A crucial aspect is that work stress-related effects, such as mental and behavioural disorders, have a multifactorial origin, including personal, social and work factors, which can be combined in different ways according to the specific living and working conditions of the workers. Furthermore, the link between behavioural disorders and actual exposure to psychosocial risk factors, in terms of severity and duration able to significantly affect mental health, is often difficult to establish. Moreover, it is not always possible to identify a dose–response relationship and in many cases, that relationship may be affected by personal conditions or situations.

74. The multidimensional and multifaceted aspects of the problem make the role and activity of the occupational health physician very complex and delicate, as both appraisal and implications refer to several different domains covering psychological, physiological, sociological, pathological, economic, organizational and legal issues. [43]

75. Assessment of work demands, in terms of job content, work load, working hours, time pressure, responsibility, participation, human relations, and work/non-work conflicts, requires integrated competences and a systematic approach with other professionals, including occupational psychologists, sociologists, ergonomists and managers.

76. In this context, the contribution of the occupational health physician is absolutely relevant, since it is not only important to quantify the "external" work load, but also much more decisive to assess the individual "response", which in most cases is the crucial factor in the imbalance.

77. The occupational health physician can be supported by standardized inventories and checklists, such as Effort/Reward Imbalance (ERI), Occupational Stress Indicator (OSI), Occupational Stress Inventory Revised Edition (OSI-R), or Job Content Questionnaire (JCQ), but still has to set up appropriate diagnostic tools according to the specific work activity, so as to analyse the problem in as systematic an approach as possible.

78. Good interdisciplinary cooperation between occupational health physicians, family doctors and specialists (psychologists, psychiatrists, neurologists, cardiologists) is necessary for a correct and appropriate diagnosis, given the need for a precise assessment of health impairment, its relationship with working conditions, the involvement of intervening factors related to personal and social conditions, and differential diagnosis with other primary or secondary psychological and psychosomatic disorders regardless of working conditions.

[42] C.L. Cooper (ed.): *Handbook of stress, medicine, and health*, CRC Press, Boca Baton, 1996.

[43] A. Fingret: "Occupational mental health: A brief history", in *Occup. Med*., Vol. 50, No. 5, pp. 289–293, 2000.

Changing the title "mental and behavioural disorders" to "psychological disorders"?

A brief review of the scientific background

79. Many epidemiological data support a significant association between psychosocial risk factors at work and chronic psychological disorders, both with specific features (e.g. post-traumatic stress disorder or burnout) and non-specific features, such as chronic fatigue, chronic anxiety, depression, or "adjustment disorders".

80. Stress, in the form of live events or demands upon the organism that perturb psycho-physical homeostasis, has been associated with a variety of psychological and mental disorders including anxiety, depression, panic disorder, burnout, chronic fatigue syndrome, as well as with a number of important somatic diseases including hypertension, coronary heart diseases, ulcers, strokes, immunological and metabolic disorders, and even cancer. [44]

81. As regards mental disorders, work stress has been found to be significantly associated with psychophysical exhaustion, chronic anxiety, depression, burnout, and consumption of psychotropic drugs. [45] Stansfeld et al. [46] recorded an increased risk (1.7 in women and 2.6 in men) of psychological disorders under chronic stress at work, and Grzywacz and Dooley [47] found a four times higher risk of depression associated with poorer working conditions. The mortality risk for cardiovascular diseases more than doubles higher when associated with long-term work stress. [48]

82. The multifactorial origin (including personal, living and working conditions) and the multifaceted outcomes make it hard clearly or surely to attribute the mental and behavioural disorders with work-related psychosocial hazards, as it is often difficult to separate endogenous from exogenous components and to establish or exclude the influence of possible "confounders", such as personality and other previous or concurrent mental disorders. This is further complicated by the similarity in terms of clinical symptoms between common illnesses and specific stress-related disorders (for example in case of chronic anxiety and depression).

[44] C.L. Cooper (ed.): *Handbook of stress, medicine, and health*, CRC Press, Boca Baton, 1996.

[45] D.E. Marcotte, V. Wilcox-Gök and D.P. Redmon: "The labor market effects of mental illness: The case of affective disorders", Research in Human Capital and Development (Stamford, JAI Press); I. Niedhammer and J. Siegrist: "Facteurs psychosociaux au travail et maladies cardiovasculaires: Apport du modèle du déséquilibre efforts/récompenses", in *Revue d'Epidémiologie et de Santé Publique* 46, 398–410, 1998; P.A. Landsbergis et al.: "The patterning of psychological attributes and distress by 'job strain' and social support in a sample of working men", in *Journal of Behavioural Medicine* 15(4), 379–405, 1992.

[46] S. Stansfeld et al.: "Work characteristics predict psychiatric disorders: Prospective results from the Whitehall II Study", in *Occupational and Environmental Medicine*, 56, 302–327, 1999.

[47] J.G. Grzywacz, D. Dooley: "Good jobs to bad jobs: Replicated evidence of an employment continuum from two large surveys", in *Soc. Sci. Med*., 2003, 56, 1749–1760.

[48] M. Kivimâki et al.: "Work stress and risk of cardiovascular mortality: Prospective cohort study of industrial employees", in *British Medical Journal*, 325, 857–860, 2002; R. Beaglehole and R. Magnus: "The search for new risk factors for coronary heart disease: Occupational therapy for epidemiologists?", in *International Journal of Epidemiology* 31: 1117–1122, 2002; R.A. Karasek et al.: "Job characteristics in relation to the prevalence of myocardial infarction in the US Health Examination Survey (HES) and the Health and Nutrition Examination Survey (HANES)", in *American Journal of Public Health*, 78(8), 910–918, 1988.

83. From the individual point of view, it has to be taken into account that, in many cases, subjective and qualitative aspects prevail over "objective" and quantitative ones. Therefore the classical "cause–effect" models of traditional risk assessment (used for physical and chemical agents) are not mechanically applicable in such contexts, since the negative consequences on health and well-being are mainly conditioned by "intervening" factors related to the person (personality, behaviour, coping strategies, family and social support), giving rise to a very high inter-individual variability. It is common to observe that some well-known "stressful" situations or jobs do not affect all people in the same way, and some jobs or tasks regarded as not especially stressful may cause high levels of stress for some people under certain conditions.

"Mental and behavioural disorders" vs "psychological disorders"

84. "Mental" refers to the process of thinking. It also refers to the state or the health of a person's mind. "Behavioural" means relating to the behaviour of a person or animal, or to the study of their behaviour. Psychological means concerned with a person's mind and thoughts.

85. The expression "mental and behavioural disorders" is widely used in official bodies dealing with the classification of diseases, for example:

(1) The term "mental disorders", as defined in the fourth edition of the standard Psychiatric Diagnostic and Statistical Manual (DSM-IV) published by the American Psychiatric Association, encompasses a broad range of conditions characterized by patterns of abnormal behavioural and psychological signs and symptoms that result in dysfunction. The DSM-IV-PC (Primary Care) manual provides a useful synopsis of mental disorders most likely to be seen in primary care practice. The current system of classification is multiaxial and includes the presence or absence of a major mental disorder (axis I), any underlying personality disorder (axis II), general medical condition (axis III), psychosocial and environmental problems (axis IV), and overall rating of general psychosocial functioning (axis V). The category "Adjustment disorders" (code 309) includes several disorders with anxiety, depressed mood, disturbance of conduct, and mixed disturbance of emotions and conduct, which may be related also to work stress.

(2) According to the "Medical Subject Headings (MeSH)" – a comprehensive controlled vocabulary for the purpose of indexing journal articles and books in the life sciences created and updated by the United States National Library of Medicine (NLM) – the expression "mental disorders" indicates "a psychiatric illness or diseases manifested by breakdowns in the adaptational process expressed primarily as abnormalities of thought, feeling, and behaviour producing either distress or impairment of function".

(3) According to Harrison's Principles of Internal Medicine (15th edition), "the implication that mental disorders lack a physical cause is unfortunate and incorrect, and the term survives only for want of a better substitute. Mental disorders are highly prevalent in medical practice and may present either as a primary disorder or as a co-morbid condition …".

(4) In the 10th (2007) edition of the International Classification of Diseases (ICD-10), published by the WHO, Chapter V *Mental and Behavioural Disorders* includes the following blocks:

Mental and behavioural disorders (F00-F99)

- F00-F09 Organic, including symptomatic, mental disorders
- F10-F19 Mental and behavioural disorders due to psychoactive substance use
- F20-F29 Schizophrenia, schizotypal and delusional disorders
- F30-F39 Mood [affective] disorders
- F40-F48 Neurotic, stress-related and somatoform disorders
- F50-F59 Behavioural syndromes associated with physiological disturbances and physical factors
- F60-F69 Disorders of adult personality and behaviour
- F70-F79 Mental retardation
- F80-F89 Disorders of psychological development
- F90-F98 Behavioural and emotional disorders with onset usually occurring in childhood and adolescence
- F99 Unspecified mental disorder

86. In view of the above, the term "mental and behavioural disorders" as used by the WHO seems to indicate a broad spectrum of disorders relating to mind and behaviour. The term "psychological disorders" seems less used and to have a wider meaning.

87. However the expression "mental and behavioural disorders" causes concern among some professionals in some countries owing to its stigma potential (psychiatric illness or diseases). The term "psychological disorders" seems more related to symptomatology than to diagnosis; however it may be more suitable for indicating the broad range of alterations in psychological balance and wellness arising from work-related stress and nuisances, taking into account the psychological background in a multifactor perspective of the causes of the disorders.

Countries including mental and behavioural disorders in the national lists of occupational diseases

- Australia (mental disorders)
- Brazil
- Chile
- Colombia
- Ecuador
- Hungary (diseases due to psychosocial factors)
- Italy
- Republic of Korea
- Latvia (diseases caused by overload, psychoneurosis)
- Lithuania (occupational diseases due to stress)

- Nicaragua
- Romania (psychic and behavioural disorders)

6. 3.1.20. Formaldehyde (HCHO)

General information on the agent

88. Formaldehyde (H_2CO, methanal CAS N° 50-00-0) is a lighter-than-air flammable gas with a characteristic pungent odour and very high water solubility (up to 55 g/100 ml). Formaldehyde is industrially produced by catalytic oxidation of methanol.

89. The saturated water solution (formalin) and solid forms such as the trimer (trioxane) and the polymer (para-formaldehyde) are the main forms of formaldehyde in industrial use.

90. Currently, formaldehyde is considered to be:

- A "substance which causes concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment" (category 3) (European Economic Community, 2004).
- A "potential occupational carcinogen (nasal cancer)" (US National Institute for Occupational Safety and Health (NIOSH) 2005).
- A "substance with carcinogenic potential for which a non-genotoxic mode of action is of prime importance" (category 4) (Deutsche Forschungsgemeinschaft (DFG) 2006).
- A substance "reasonably anticipated to be a human carcinogen" (NTP 2005).
- A "suspected human carcinogen" (category A2) (American Conference of Government Industrial Hygienists (ACGIH) 2006).

HCHO IARC classification (2006)

91. There is sufficient evidence of the carcinogenicity of formaldehyde in humans. There is also sufficient evidence in experimental animals for the carcinogenicity of formaldehyde. *Overall evaluation*: Formaldehyde is carcinogenic to humans *(Group 1)*.

92. The results of the last update (Hauptmann et al. 2004) were key findings in the last IARC classification evaluation. Further studies indicate that the evidence of an association in this cohort is debatable. This aspect will be discussed in the following paragraphs of this document.

Exposure at work

93. The main use of formaldehyde is as a building block for the production of hard thermoset (non-mouldable) resins and foams and of building adhesives by condensation with phenol, melamine and urea. These resins are used to make plywood and chipboard, and formaldehyde can be released into the air throughout the life of those materials, starting from mechanical sawing to build furniture, roofing and walls to the gradual ageing of the manufactured items under ambient conditions. Formaldehyde-based resins are also used as

finishers to make crease-resistant fabrics, water-resistant disposable paper such as toilet paper, and roll towels.

94. Other uses of formaldehyde as a chemical intermediate are in the preparation of methylene diphenyl diisocyanate (a component of urethane polymers) and of pentaerythrol (a component of paint resins and the starting material for the preparation of PETN – pentaerythritol tetranitrate explosive).

95. At present, the long-standing use of formaldehyde as a disinfectant and preservative (with uses ranging from household and sanitary disinfection and cleaning to corpse embalming) is gradually giving way to other chemicals.

96. There is a potential for occupational exposure to formaldehyde in the chemical plants where it is produced or converted into other products, in the production and use of plywood and chipboard, fabrics and paper, in biological laboratories, and in industrial, sanitary and household cleaning.

97. Occupational settings and uses include: [49]

- factories producing formaldehyde-based resins;
- assembly of plywood and particleboard;
- health services;
- the textile industry, to produce crease-resistant and flame-retardant fabrics;
- foundries, as core binders;
- factories creating moulded plastic products;
- use as a tissue preservative and disinfectant in embalming fluids;
- use for preserving tissue samples in histopathology laboratories;
- the construction industry (workers who varnish wood floors);
- agriculture (preservative for fodder and as a disinfectant for brooding houses);
- forestry (lumberjacks can be exposed to formaldehyde from the exhaust of their chain saws).

Exposure routes

98. Formaldehyde occurs in occupational environments mainly as a gas. Formaldehyde-containing particles can also be inhaled when paraformaldehyde or powdered resins are used in the workplace. [50] These resins can also be attached to carriers, such as wood dust. Exposure may also occur dermally when formalin solutions or liquid resins come into contact with skin.

[49] WHO: *Concise International Chemical Assessment Document 40: Formaldehyde*, Geneva, 2002.

[50] International Agency for Research on Cancer (IARC): *Summaries and evaluations, FORMALDEHYDE (Group 2A)*, Vol. 62, 1995, p. 217, CAS No. 50-00-0, Chem. Abstr. Name: Formaldehyde.

Specifically including cancer caused by HCHO in the ILO List of occupational diseases?

A brief review of the scientific background

99. A statistically significant excess of deaths from nasopharyngeal cancer (NPC) was shown in the largest and most informative cohort study of industrial workers by the US National Cancer Institute (NCI), with a strong exposure–response correlation between the cancer mortality rate and peak and cumulative exposures. [51] An excess of deaths from NPC was also observed in a proportionate mortality analysis of the largest US cohort of embalmers, [52] and an excess of cases of NPC was observed in a Danish study of proportionate cancer incidence among workers at companies that manufactured or used formaldehyde.

100. While the results of the NCI study of Hauptmann et al. (2004) showing an association between NPC and occupational exposure to formaldehyde were fundamental in the IARC decision to consider formaldehyde as carcinogenic in humans, further studies indicate that the evidence of an association in this cohort is debatable. Mortality from NPC in the NCI cohort was statistically significantly elevated when compared with that of the US general population in the total cohort, and trends tests were significant when considering two out of four exposure metrics (peak exposure, cumulative exposure) in the internal analysis. However, as previously reported by Tarone and McLaughlin, [53] these results were not confirmed when one plant (the Wallingford plant) was excluded. Furthermore, internal comparison analysis using alternative categorization reveals that none of the relative NPC risk was statistically significantly increased in any category of exposure (Marsh and Youk), [54] and re-analyses of the data highlighted the inappropriateness of the exposure assessment used by Hauptmann et al. in 2004 (Marsh et al., 2007). [55]

101. In the other cohorts (US by Pinkerton et al. [56] and UK by Coggon et al. [57]), no increased risk of NPC was observed. Owing to the low prevalence of NPC, the case–control studies may be more appropriate for detecting an increased mortality from NPC. However, the evidence of an increased risk of NPC reported in the two case–control studies is not very convincing.

[51] M. Hauptmann et al.: "Mortality from solid cancers among workers in formaldehyde industries", *Am. J. Epidemiol*, 159, 2004, 1117–1130.

[52] R.B. Hayes et al.: "Mortality of US embalmers and funeral directors", in *Am. J. Ind. Med.*, 18, 1990, 641–652.

[53] R.E. Tarone and J.K. McLaughlin: "Mortality from solid cancers among workers in formaldehyde industries", in *Am. J. Epidemiol*, 161, 1089–1090, 2005.

[54] G.M. Marsh and A.O. Youk: "Reevaluation of mortality risks from nasopharyngeal cancer in the formaldehyde cohort study of the National Cancer Institute", in *Regul. Toxicol. Pharmacol*, 42 (3), 275–283, 2005.

[55] G.M. Marsh et al.: "Work in the metal industry and nasopharyngeal cancer mortality among formaldehyde-exposed workers", in *Regulatory Toxicology and Pharmacology*, 48, 308–319, 2007.

[56] L.E. Pinkerton, M.J. Hein and L.T. Stayner: "Mortality among a cohort of garment workers exposed to formaldehyde: An update", in *Occup. Environ. Med.*, 61 (3), 193–200, 2004.

[57] D. Coggon et al.: "Extended follow-up of a cohort of British chemical workers exposed to formaldehyde", in *J. Natl., Cancer Inst.*, 95 (21), 1608–1615, 2003.

102. The study of Hildesheim et al. [58] reported that individuals with a high average intensity of exposure were at a statistically significant increased risk of NPC. No increased risk or trend was suggested for the metrics evaluated (cumulative exposure, duration of exposure, year since first exposure, age at first exposure). Levels of exposure were uncertain and exposure estimates were only based on occupational exposure history but no ambient measurements were available. The meta-analysis performed by Collins et al. [59] reported a slight excess of NPC in industrial workers, medical specialists and embalmers in cohort studies, but no association after correction for unreported expected deaths. Case-control studies showed variable results, with a common lack of information in the exposure assessments. The authors concluded, based on the meta-analysis that "taken together, the cohort and case-control studies do not provide convincing evidence of a causal relationship between formaldehyde and nasopharyngeal cancer."

103. Since NPC is very uncommon, all epidemiological studies suffer from having only a very small number of cases. In these conditions, statistical significance (presence or absence) can be affected by very small numbers, and the results may not be sufficiently robust. Moreover, due to the small numbers of NPC cases detected, despite the widespread use of formaldehyde in the world, it can be assumed that, if present at all, the carcinogen potential of HCHO is not very strong.

104. Human studies fail to demonstrate any dose–response relationship. Experimental studies conducted in rats suggest that the carcinogenic activity of formaldehyde is associated with cytotoxic/proliferative mechanisms (inflammation). Therefore protection from these effects associated with formaldehyde exposure should be sufficient to protect from its potential carcinogenic effects in humans. Another key aspect of the evaluation is the growing evidence that the risk is mainly associated more with peak exposures than with TWA. In this light, monitoring systems aimed at identification and measurement of peaks are recommended to better protect workers, to collect full and sound exposure data and to create a data base adequate to perform a retrospective exposure assessment of observed cases.

105. In a conservative view, it can be stated that, on the basis of current knowledge, NPC can be attributed to formaldehyde when it occurs in workers exposed to doses capable of inducing inflammatory local response. Other cases need a case-by-case evaluation based on rigorous scientific criteria and taking into account all the different variables involved in the evaluation.

106. A number of epidemiological studies document a significant association between occupational exposure to formaldehyde and excess mortality from leukaemia. A new meta-analysis of these published studies provides evidence of an association with leukaemia, particularly of the myeloid type. It seems plausible that formaldehyde could produce damage to the target hematopoietic stem cells via the three possible mechanisms, namely: (a) by damaging stem cells in the bone marrow directly, as most other leukaemogens do; (b) by damaging hematopoietic stem/progenitor cells circulating in the peripheral blood;

[58] A. Hildesheim et al.: "Occupational exposure to wood, formaldehyde and solvents and risk of nasopharyngeal carcinoma", in *Cancer Epidemio. Biomarkers Prev.*, 10 (11), 1145–1153, 2001.

[59] J.J. Collins, J.F. Acquavelly and N.A. Esmen: "An updated meta-analysis of formaldehyde exposure and upper respiratory tract cancers", in *J. Occup. Environ. Med.*, 39 (7), 639–651, 1997.

and (c) by damaging the primitive pluripotent stem cells present within the nasal turbinates and/or olfactory mucosa. [60]

HCHO and leukaemia: Biological plausibility [61]

107. It is unlikely that HCHO reaches the bone marrow and causes toxicity, owing to its highly reactive nature (this is true for several reactive substances). HCHO is mainly a contact irritant. As regards (b), there is no evidence that it can damage the stem and progenitor cells, the target cells for leukaemogenesis. There is no credible experimental animal model for formaldehyde-induced leukaemia.

Histology

(1) Nasopharingeal cancer (squamous cell; indifferentiated or non-keratinizing).

(2) Myeloid Leukemia.

Latency Period: no univocal data available.

108. For these reasons, the most recent epidemiological studies conclude that the statement "formaldehyde is carcinogenic to humans" is probably too strong. [62]

109. Owing to the present uncertainties and the differences in the evaluations performed by different national and international organizations, if a specific listing of the agent is not considered, cancer caused by formaldehyde is still covered by the "open item" under the section on occupational cancer in the ILO list.

Countries specifically including cancer caused by HCHO in the national lists of occupational diseases

- Brazil
- (Colombia – generic occupational cancer)
- Denmark
- El Salvador
- Italy (List II)
- Malaysia
- Switzerland

[60] L. Zhang et al.: "Formaldehyde exposure and leukemia: A new meta-analysis and potential mechanisms", *Mutation Research* 681, 150–168, 2009.

[61] R. Golden, D. Pyatt, and P.G. Shields: "Formaldehyde as a potential human leukemogen: An assessment of biological plausibility", *Crit. Rev. Toxicol*. 36, 135–153, 2006; D. Pyatt, E. Natelson, and R. Golden: "Is inhalation exposure to formaldehyde a biologically plausible cause of lymphohematopoietic malignancies?", *Regul. Toxicol. Pharmacol*. 51, 119–133, 2008.

[62] S. Duhayon et al.: "Carcinogenic potential of formaldehyde in occupational settings: A critical assessment and possible impact on occupational exposure levels", *Int. Arch. Occup. Environ. Health*, 81, 695–710, 2008.

7. 3.1.21. Hepatitis B Virus (HBV) and C Virus (HCV)

General information on the agents

110. Hepatitis B virus is a DNA virus from the Hepadnaviridae family with 4 serotypes and 7 genotypes. Hepatitis C virus is an RNA virus with 6 genotypes and more than 100 subtypes.

111. The most important world-wide occupational risks are from hepatitis B, followed by hepatitis C and hepatitis A, while other viruses very seldom cause occupational hepatitis. Hepatits A virus is not suspected of possible carcinogenicity.

112. Hepatitis B is a self-limiting disease in up to 90 per cent of patients. Some who recover from the acute phase can develop a chronic active hepatitis which can lead to liver cirrhosis and hepatocellular carcinoma in up to 30 per cent of patients.

113. About 50 per cent of hepatitis C patients develop a carrier stage that can sometimes evolve into liver cirrhosis and hepatocellular carcinoma.

114. Chronic hepatitis can occur in 1–10 per cent of HBV and 50–70 per cent of HCV infected patients. Chronic active hepatitis (B or C) can lead to liver cirrhosis and hepatocellular carcinoma. The carcinogenicity of HBV and HCV in the absence of liver fibrosis is less firmly established, even though some data support this hypothesis.

115. Chronic infections with HBV and HCV are classified by IARC as carcinogenic to humans (Group 1).

HBV – IARC Classification

116. There is sufficient evidence in humans for the carcinogenicity of chronic infection with hepatitis B virus.

117. There is inadequate evidence in experimental animals for the carcinogenicity of hepatitis B virus. Some hepadnaviruses closely related to hepatitis B virus produce hepatocellular carcinoma in susceptible species.

118. *Overall evaluation:* Chronic infection with hepatitis B virus is carcinogenic in humans (Group 1).

HCV – IARC Classification

119. There is sufficient evidence in humans for the carcinogenicity of chronic infection with hepatitis C virus.

120. There is inadequate evidence in experimental animals for the carcinogenicity of hepatitis C virus.

121. *Overall evaluation:* Chronic infection with hepatitis C virus is carcinogenic in humans (Group 1).

Exposure at work

122. Any occupation involving or likely to involve exposure at the workplace to biological samples, body fluids, and blood and its derivatives, carries the risk of exposure to HCV. This includes health-care workers, laboratory personnel, staff in prisons, police, mental institutions, ambulance crews and other rescue services.

Specifically including cancer caused by hepatitis B virus and hepatitis C virus in the ILO List of occupational diseases?

A brief review of the scientific background

Histology

123. Hepatocellular carcinoma is a typical inflammation-induced cancer.

Direct oncogenic potential

124. Hepatitis viruses have a direct oncogenic potential: HBV is a DNA virus that can integrate in the host genome, altering the expression of endogenous genes and also leading to genomic instability. In addition, proteins coded for by the viral genome, most prominently the HBx protein, can exert profound effects on critical growth and survival regulatory pathways in the hepatocyte promoting cell immortalization. HCV is a single-stranded RNA molecule; at least four of the HCV gene products (core, NS3, NS4B, and NS5A) have been shown to interact with numerous cellular proteins and to exhibit oncogenic activity in cellular and in vivo models. [63]

125. Activation of oncogenes and the role of tumour suppressor genes, such as retinoblastoma and p53 genes, have also been well documented (HBV and pRB; HBV and p53; HBV-HCV and Wnt/beta-catenin; HBV-HCV and MAPkinase). [64]

Pathogen Associated Molecular Patterns (PAMPs)

126. Infectious agents release macromolecules which can activate the innate immune system through the "toll-like receptors" with the consequent release of cytokines like IL6 and TNFalfa (tumour progression) and EGFR signalling system ligands, the first step in chronic inflammation, fibrosis and hepatocarcinogenesis.

Pathology

127. Autopsy results suggest that hepatocellular carcinoma occurs with greatest frequency (38 per cent) in association with cirrhosis due to chronic HBV infection, haemochromatosis and chronic HCV infection. [65]

[63] C. Berasain et al.: "Inflammation and liver cancer: New molecular links", in *Ann. N.Y. Acad. Sci.*, 1155, 206–221, 2009.

[64] R.N. Aravalli, C.J. Steer, E.N.K. Cressman: "Molecular mechanisms of hepatocellular carcinoma", in *Hepatology*, 2008, 48, 2047–2063.

[65] IARC monograph.

Epidemiological data

128. Few data on liver cancer among occupational risk categories are available in the scientific literature. Even though there is no doubt about the existence of a specific occupational risk from sequelae of blood-borne diseases for health care workers, epidemiological studies do not provide univocal data. Examples are given below.

129. Luckhaupt and Calvert (2008): Case control study based on death certificates: among males, employment in the health-care sector was significantly associated with death from cirrhosis and death from liver carcinoma; among females, employment in the health-care industry was not significantly associated with increased risk of death from either carcinoma of the liver or cirrhosis. Employment as a health-care worker, especially as a nurse, was found to be negatively associated with death from liver carcinoma among females. On the other hand, employment in the health-care industry was significantly associated with death from HCV among both males and females. [66] This apparently contradictory finding can probably be explained by the fact that acute B and C hepatitis are not a frequent event in health-care work (hepatitis is usually the consequence of an accident, and the incidence has been significantly reduced by the introduction of hepatitis B vaccination). A further argument comes from the lack of accurate information about lifestyle and sexual habits, which is not reflected in death certificates. Even though the authors clarify that they have considered just death "without contributing alcohol-related causes" and have used some proxy like marital status for sexual habits, no conclusion about a gender-related risk differentiation can be drawn.

130. Peipins et al. (1997): find no mortality excess for liver cancer among nurses. [67] This is a case-control study based on death certificates as well, so the same limitations described for the abovementioned study are valid.

Diagnostic process and criteria

131. Based on the available data, it seems reasonable to conclude that:

(1) Any hepatocellular carcinoma occurring in a patient suffering occupational chronic hepatitis can be considered as occupational cancer. The risk is highest in cirrhotic patients, as well as in patients with strong evidence of inflammation.

(2) In cases of hepatocellular carcinoma observed in workers with evidence of previous occupational infection, who have recovered without evolution into chronic hepatitis (a condition often observed in hepatitis B infection), the presence of an occupational cancer is highly improbable.

132. To diagnose occupational cancer caused by HBV or HCV, evidence is needed of an episode in which blood, tissue or other potentially infectious fluid (e.g. peritoneal, cerebrospinal, pericardial, pleural, synovial or amniotic fluid) could have entered the bloodstream of the worker through percutaneous injury (e.g. a needle stick or cut with a sharp object), non-intact skin (e.g. abraded, affected by dermatitis, chapped) or mucous membrane/conjunctiva (not frequent). The risk of transmission of HBV and HCV infection from urine, vomit, faeces, saliva, nasal secretions, sweat, or tears is present only if these media are contaminated by blood.

[66] S.E. Luckhaupt, G.M. Calvert: "Deaths due to bloodborne infections and their sequelae among health-care workers", in *Am. J. Ind. Med.*, Nov. 2008, 51(11), 812–824.

[67] L.A. Peipins et al.: "Mortality patterns among female nurses: A 27-state study, 1984 through 1990", in *Am. J. Public Health*, Sep. 1997, 87(9), 1539–1543.

133. Since the link between liver cirrhosis and liver carcinoma is established and well known, the carcinogenic risk related to virus infection itself, without liver fibrosis, is less evident and each case needs a separate and specific evaluation.

Histology

134. Hepatocellular carcinoma: Latency period: 20–40 years after viral infections.

135. In this light, it might be concluded that the strong evidence suggests that cancer caused by hepatitis B and C viruses mainly affects chronic hepatitis, and in particular cirrhosis, patients. When there is cancer without liver fibrosis, the carcinogenic risk is less evident. Consequently, specific evaluations of individual cases are necessary. If HBV and HCV are not specifically listed as carcinogens, cancer caused by HBV and HCV can appropriately be addressed by the "open item" (3.1.22 in the occupational cancer section).

Countries specifically including post-hepatitis hepatocellular carcinoma in the national lists of occupational diseases

- Algeria
- Denmark (cancer of the liver)
- France
- Italy
- Republic of Korea
- (Colombia – generic occupational cancer)

8. 3.1.X. Crystalline silica (to include as a carcinogen)

General information on the agent

136. Crystalline silica is a specific physical form of silicon dioxide present in substantial quantities (between 20 and nearly 100 per cent) in sand, sandstone and granite, and often forming a significant proportion of clay, shale and slate. The main forms of crystalline silica of concern for occupational health are quartz, cristobalite and tridymite.

137. Because of experimental and human studies suggesting an association between exposure to crystalline silica and an excess of pulmonary malignancies, crystalline silica inhaled in the form of quartz or cristobalite from occupational sources is classified by the IARC as carcinogenic to humans (Group 1).

138. An excess of lung cancer related to occupational exposure to crystalline silica is reported in several epidemiological studies that strongly support an association between silicosis and lung cancer, whilst the association between silica exposure and lung cancer, in the absence of pulmonary fibrosis, is less established, and firm conclusions cannot be drawn on the basis of current knowledge.

139. The increased risk of lung cancer silicosis is supported by epidemiological studies, consistently showing cancer risk estimates around 2.0 in silicosis patients, after adjusting

for the effects of cigarette smoking, compared with exposed non-silicotics or the general population.

Silica IARC Classification

140. Crystalline silica inhaled in the form of quartz or cristobalite from occupational sources is carcinogenic to humans (Group 1).

Exposure at work

141. Many rocks and sands containing crystalline silica in health-threatening proportion are used in mixtures with Portland cement and gravel in the preparation of concrete for building purposes. All over the world occupational exposure to crystalline silica occurs in mining and building works such as quarrying and tunnelling. Crystalline silica is also employed for abrasive sand blasting of buildings and of cast metal items.

Specifically including cancer caused by crystalline silica in the ILO List of occupational diseases?

A brief review of the scientific background

142. Overall, and after controlling for smoking, silicosis is associated with a 60 per cent increase in the risk of lung cancer. [68] A later study showed an exposure–response relationship between silica and lung cancer above a threshold level estimated at 1.84 mg/m^3 per year. The increased risk is particularly evident when the cumulative exposure to silica is high, well beyond the limit recommended by the US National Institute of Occupational Safety and Health (0.05 mg/m^3 as a time-weighted average for up to a ten-hour workday during a 40-hour work week over a 30-year period).

143. The risk of lung cancer at cumulative exposure lower than 1.84 mg/m^3 remains uncertain. The definition of a dose-response relationship is complicated by the wide range of exposures to respirable silica reported in the original studies, the heterogeneity among studies, and the confounding effect of silicosis that cannot be fully assessed. [69]

144. Moreover, the complex pattern of interactions leading to lung cancer among silica-exposed workers and the possible presence of other occupational and environmental lung carcinogens has to be considered. [70]

145. In particular, the role of cigarette smoking in strengthening the carcinogenic potential of silica has to be clarified: the meta-analysis by Erren et al. suggested just a marginally elevated risk of lung cancer [RR = 1.2; 95 per cent CI (1.1–1.4)] for those studies without

[68] Y. Lacasse et al.: "Metaanalysis of silicosis and lung cancer", in *Scand. J. Work Environ. Health*, 2005, 31, 450–458.

[69] Y. Lacasse et al.: "Dose-response meta-analysis of silica and lung cancer causes control".

[70] T. Brown: "Silica exposure, smoking, silicosis and lung cancer – Complex interactions", in *Occupational Medicine*, 2009, 59, 89–95.

adjustment for smoking habits, while a pooled RR estimate of 1.0 [95 per cent CI = (0.8–1.3)] was found for those where the adjustment was made. [71]

Diagnostic process and criteria

146. In case of evidence of lung cancer observed in silicosis-affected workers, the diagnosis of occupational neoplasm is clear. Since the causal relationship between prolonged and repeated exposure to silica in the absence of silicosis and the occurrence of cancer has not been firmly established, in non-silicosis patients the diagnosis of occupational cancer must be based on the application of rigorous scientific criteria taking into account all other possible aetiologies.

147. In this light, it might be concluded that the strong evidence is that cancer caused by crystalline silica mainly affects silicosis patients. In cases observed without lung fibrosis, the carcinogenic risk is less evident. Consequently, specific evaluations of individual cases are necessary. If crystalline silica is not specifically listed as a carcinogen, cancer caused by crystalline silica can appropriately be addressed by the "open item" in the occupational cancer section (3.1.22).

Countries specifically including cancer caused by crystalline silica in the national lists of occupational diseases

- Brazil
- Colombia (generic occupational cancer)
- Denmark
- France
- Germany
- Italy
- Monaco
- United Kingdom

[71] T.C. Erren et al.: "Is exposure to silica associated with lung cancer in the absence of silicosis? A meta-analytical approach to an important public health question", in *Int. Arch. Occup. Environ. Health*, 6 Dec. 2008 [E. pub ahead of print].