



Information notices on occupational diseases: a guide to diagnosis



European Commission

Information notices on occupational diseases: a guide to diagnosis

European Commission

Directorate-General for Employment, Social Affairs and Equal Opportunities
F4 unit

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PREFACE

Professor Tar-Ching Aw (Chairman, European Union -EU- Expert Group on diagnosis of occupational diseases)

Introduction:

Agreed criteria for diagnosing occupational diseases will help in ensuring consistency in clinical decisions, and contribute to management of individual cases and prevention of disease in occupationally-exposed groups. The European Commission (EC) produced its first schedule of occupational diseases in 1962. Other agencies and organizations in different countries also have their lists of occupational diseases, although guidance on recognizing such diseases is less readily available. In recognition of this need, the EC produced a document in 1963 titled 'Medical particulars on diseases recorded in the European schedule of occupational diseases.' This was updated in 1994 by a working group of EU experts, resulting in the publication of 'Information notices on diagnosis of occupational diseases.' A revision of the 1994 document was commissioned ten years later. The current document 'Criteria for the diagnosis of occupational diseases' is a result of the efforts of a new EU expert working group. The group included several experts who worked on the 1994 document and new members from different EU countries. In addition, observers representing unions and industry were invited. Implications that the conclusions of the group might have on workers' rights to compensation as per the systems applicable in each case and/or system were felt to be outside the group's remit. The full list of members and their areas of expertise is attached (Table I).

Procedure:

The process that was adopted to produce the revised new document was as follows:

- a) Experts in occupational health were invited by the Secretariat of DG Employment, Social Affairs and Equal Opportunities to join the working group. A chairman was elected, a *rapporteur* appointed and a small editorial team formed to work with the EC Experts Group Secretariat on preparing and finalizing the document.
- b) The European schedule of occupational diseases (Annex I of Commission Recommendation 2003/670/EC of 19 September 2003¹) was considered by the group, and sections of the list were allocated to teams of group members for review and updating. The experts were asked to retrieve relevant new published evidence, assess previous information and new papers, and consult colleagues in their own organizations.
- c) Revised versions of the items on the schedule were circulated to all group members for comments, and discussed over the course of 10 main meetings and 4 special working group meetings of the experts in Luxembourg and Brussels. Final versions were accepted through agreement by consensus.
- d) Items listed in Annex 2 of the European schedule (Diseases suspected of being occupational in origin) were not part of the remit of the current working group.
- e) The manuscript was completed in October 2007, fully checked by February 2008 and submitted to the EC Experts Group Secretariat for publication before which several editorial amendments would be necessary.

Other possible strategies considered for updating the document included individual expert opinion to full evidence-based review with assessment and ranking of all papers obtained through libraries by defined search terms. A full evidence-based review was not adopted because of the recognized

¹ http://eur-lex.europa.eu/Result.do?T1=V1&T2=2003&T3=670&RechType=RECH_naturel&Submit=Search

paucity of epidemiologic papers on clinical occupational disease and poisonings related to many of the occupational agents in Annex I. This is especially the case for acute exposures and acute effects, where most of the publications available are case reports of poisonings, case series, or findings from animal experiments. A consensus view of experts, following consideration of documents produced by teams of experts liaising with their own organizations was therefore used, and was in keeping with the strategy used for the 1994 document.

Diagnosis of Occupational Disease

The key criteria for diagnosing an occupational disease in any individual are:

- a) **The clinical features must fit in with what is known about the health effects following exposure to the specified agent.** The symptoms and signs should fit, and this may be supported in some cases by suitable diagnostic tests.
- b) **There must be indication of sufficient occupational exposure.** Evidence on exposure may be obtained through taking the occupational history, results of occupational hygiene measurements taken at the workplace, biological monitoring results, and/or records of incidents of over-exposure.
- c) **The time interval between exposure and effect must be consistent with what is known about the natural history and progress of the disease.** Exposure must precede health effects. However, in some conditions such as occupational asthma, a past history of childhood asthma and/or asthmatic attacks occurring before occupational exposure, does not automatically rule out the possibility of a workplace agent causing subsequent asthmatic attacks.
- d) **The differential diagnosis must be considered.** There are non-occupational conditions that have similar clinical features as occupational diseases, and a physician will have to take this into account before diagnosing or excluding an occupational disease.

As an additional aid to diagnosing occupational diseases, this document has retained the following concepts for exposure:

- i. **Minimum intensity of exposure** – This is the minimum level of exposure that is required to cause disease. Lower exposures are unlikely to lead to occupational disease. This concept is applicable especially for toxic agents. For agents that are carcinogenic or allergenic, it is not usually possible to define a minimum threshold dose. Direct acting carcinogens in molecular amounts are in theory capable of affecting cellular DNA and initiating carcinogenesis. However, for some carcinogens, it may be possible to identify a threshold of initiation of adverse health effects. Allergens may require substantial exposure to cause sensitization. But once an individual is sensitized, minute amounts can be capable of eliciting an allergic response.
- ii. **Minimum duration of exposure**
This is the shortest exposure period for which disease can occur. Periods of exposure less than this are unlikely to cause disease.
- iii. **Maximum latent period**
This refers to the length of time from cessation of exposure, beyond which it is unlikely that any disease can be attributed to the exposure. For example, acute myocardial ischemia occurring a year after an acute exposure to carbon monoxide is not attributable to that exposure.
- iv. **Minimum induction period**
This is the shortest period from beginning of exposure to beginning of disease below which the exposure would have been unlikely to have caused the disease. For example, lung

cancer developing within a year after first exposure to asbestos is unlikely to be attributed to that exposure.

Where possible, guidance values for these descriptors of exposure have been provided for many of the specific agents. Additional pointers to the possibility of occupational disease include worsening of symptoms at work, improvement of health away from the workplace, and clusters of similar cases from the same work area. In some instances, occupational factors may be synergistic with non-occupational factors.

Use of Airborne Occupational Exposure Limits

Exposure to airborne workplace hazards can be assessed by means of ambient air monitoring. These occupational hygiene measurements are interpreted by comparison against occupational exposure limits (also termed occupational exposure standards, threshold limit values, workplace exposure levels). The limits are not intended for use in diagnosing occupational disease. However, where information is available indicating workplace exposures exceeding such limits, this can be an indication of poor control of exposure to hazards. Evidence of considerable excessive exposure to individuals provides additional support for a possible diagnosis of occupational disease. However, a safety factor is incorporated in the setting of most occupational exposure limits, and this should be considered when occupational hygiene monitoring results are used to support a diagnosis of occupational disease.

Some occupational exposure limits differ between agencies that produce them. This reflects the uncertainty in setting standards based on limited data, and on the difference in philosophy and approach between agencies. For the purpose of referring to occupational exposure limits; the expert group used the latest set of values produced by SCOEL and ACGIH available to them at that time (2007 standards). The most recent versions of these standards are available from the website of the EU SCOEL (**Scientific Committee on Occupational Exposure Limits**)², and that of the ACGIH (**American Conference of Governmental Industrial Hygienists, Inc**)³. Readers should refer to the most recent edition of any standards and be aware of the limitations in using them as an aid to diagnosing occupational disease.

Biological Monitoring

The analysis of biological samples such as blood or urine to determine the presence and amount of a substance or its metabolites is another way of quantifying workplace exposure. Its use in the diagnosis of occupational disease is in confirming exposure or over-exposure. Acute effects from occupational exposure to a chemical can be attributed to that specific chemical if substantial amounts are detected in biological samples. Biological monitoring standards (e.g. Biological Exposure Indices or Biological Monitoring Guidance Values) are not intended for specific use in clinical diagnosis. These values, available from various organizations such as BAT (Germany), the HSE (the Health & Safety Executive in the UK) and the ACGIH (US), can indicate work exposures that result from inadequate control of hazards in the workplace, or be indicative of exposures above what can be practically achieved in similar workplaces through 'the best procedures for systems of work'. **Caution must be exercised in using these indices for purposes other than monitoring of exposure to workplace hazards.** Where applicable, readers are advised to consult the most recent ACGIH biological exposure indices³- For some chemicals

² http://ec.europa.eu/employment_social/health_safety/scoel_en.htm

³ <http://www.acgih.org/store/ProductDetail.cfm?id=652>

SCOEL recommends Biological Limit Values (BLV) (see website⁴) *e.g.* the Chemical Agents Directive (CAD) contains a BLV for lead.

Occupational cancers and occupational allergies

Occupational cancers

- a) result from workplace exposure to a known carcinogen
- b) tend to affect individuals at a younger age, especially if their initial exposure to the carcinogen occurs early in their working life
- c) may arise in a group of individuals with similar occupational exposure
- d) are more likely to develop if there are concomitant exposures to carcinogens (occupational or non-occupational) affecting the same target organs, *e.g.* a multiplicative risk of lung cancer if there is simultaneous exposure to asbestos and cigarette smoking.

Malignancies that are caused by occupational agents are often difficult to distinguish from those of non-occupational origin. There are often no unique pathological or histological features. There may be markers of exposure, such as ‘ferruginous bodies (asbestos bodies)’ in sputum samples of asbestos-exposed workers, or keratotic lesions and pigment changes of the skin in arsenic-exposed individuals, or blood or urine samples showing evidence of systemic absorption of chemical carcinogens. These markers only support exposure, but do not confirm a diagnosis of occupational cancer. However, there are some cancers that are strongly associated with occupational exposures *e.g.* adenocarcinoma of the nose (wood dust exposure), angiosarcoma of the liver (vinyl chloride monomer), mesothelioma (asbestos).

In the diagnosis of occupational cancer, the criteria for other occupational diseases above also apply. An important consideration is whether the agent to which the individual is exposed is a human carcinogen.

The EU has produced its list of recognized carcinogens, which is applicable in EU Member States. The key legal instrument is Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances⁴ but the European Commission adopted a new proposal for a Regulation on the Classification, Labelling and Packaging of Substances and Mixtures COM(2007) 355 which will replace (after a transitional period) certain provisions of the current directives related to the classification, packaging and labelling of dangerous substances (Directive 67/548/EEC) and preparations (Directive 1999/45/EC).

The new proposal incorporates the classification criteria and labelling rules agreed at UN level, the so called Globally Harmonised System of Classification and Labelling of Chemicals (GHS)⁵. It will introduce new classification criteria, hazard symbols (pictograms) and labelling phrases, while taking account of elements which are part of the current EU legislation.

Under the EU system, substances and preparations can be classified for carcinogenic effects as follows:

- a) Category 1: Substances known to be carcinogenic to man. There is sufficient evidence to establish a causal association between human exposure to a substance and the development of cancer.

⁴ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31967L0548:EN:NOT>

⁵ http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html

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- b) Category 2: Substances which should be regarded as if they are carcinogenic to man. There is sufficient evidence to provide a strong presumption that human exposure to a substance may result in the development of cancer, generally on the basis of:
 - appropriate long term animal studies,
 - other relevant information.
 - c) Category 3: Substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment. There is some evidence from appropriate animal studies, but this is insufficient to place the substance in category 2.

The International Agency for Research on Cancer (IARC) evaluates and lists substances, mixtures, and processes, grouping them into:

- a) Group 1 agents: Carcinogenic to humans
- b) Group 2A agents: Probably carcinogenic to humans
- c) Group 2B agents: Possibly carcinogenic to humans
- d) Group 3 agents: Not classifiable as to carcinogenicity to humans
- e) Group 4 agents: Probably not carcinogenic to humans

The American Conference of Governmental Industrial Hygienists, Inc. (ACGIH) has a similar allocation of five categories for carcinogenicity:

- a) Category A1: Confirmed human carcinogen
- b) Category A2: Suspected human carcinogen
- c) Category A3: Confirmed animal carcinogen with unknown relevance to humans
- d) Category A4: Not classifiable as a human carcinogen
- e) Category A5: Not suspected as a human carcinogen

Categorisations of carcinogens by all three organizations (EU, IARC and the ACGIH) are available from their respective websites (EU, IARC) or may be ordered directly from the organisations – See references list below.

Reference to these sources can assist in determining whether an individual has an occupational cancer. As is the case for toxic agents, documented exposure to both occupational and non-occupational carcinogens would require the physician to decide either on the basis of ‘a balance of probability’ or on the relative contributions of each exposure to the disease.

Occupational allergies

The target organs most commonly affected by occupational allergens are the skin and the respiratory tract. Agents capable of causing skin and/or lung sensitization are indicated as such in the ACGIH handbook on TLVs and BEIs. Individual susceptibility is especially relevant, as atopic individuals (those with a personal or family history of eczema, asthma, hay fever, or allergic rhinitis) are more likely to develop allergies to some agents compared to non-atopics. Skin patch tests can be used in confirming a diagnosis of occupational skin allergy. Clinical investigations for respiratory allergy include skin prick tests, measurement of immunoglobulins, and bronchial provocation test.

Caution in use of investigations

Caution is advised in the choice and use of invasive procedures such as liver biopsy, or clinical investigations such as bronchial provocation test. These procedures have a recognized risk of possible severe side effects *e.g.* anaphylaxis from bronchial provocation tests. They should therefore be performed only in hospitals or medical facilities with ready access to full emergency clinical support.

Use of this document

A diagnosis of an occupational disease has implications for prevention, health care, and actions for workplaces, industry, worker representatives and for the individual and his/her treating physician;. This updated document is intended as a guide and a source of information for clinicians, occupational health practitioners, hygienists, scientists, social partners, national authorities, and other health professionals with a responsibility and/or interest in the diagnosis of occupational diseases. New information appearing after availability of this document should be taken into account, and kept under periodic review.

This document contains information on entries listed on Annex I of the European Schedule of Occupational Diseases. The entries are presented in the order in which they are listed in the schedule. To minimize unnecessary duplication of material, a few entries with similar end-points *e.g.* skin cancer from soot, tar, bitumen, pitch, etc., or resulting from similar exposures *e.g.* vibration, have been grouped together.

Also and with a view to provide for a transition from the previous version of the 'Information notices' of 1994 to the present one, while keeping to the mandate given to the group to work on the basis of the Annex I of Commission Recommendation 2003/670/EC, some entries of the former version not reflected in the Annex I listing are included where there is a best fit in the mentioned Annex I. This is the case, for instance, of the former entries on Methylene chloride or Trichloroethylene, now in Annex I entry 117 on *Halogenated derivatives of the aliphatic or alicyclic hydrocarbons*, or of the former ones on *Methyl acrylate* and *Dithiocarbamates*, now in Annex I entry 202 on *Occupational skin ailments caused by scientifically recognised allergy-provoking or irritative substances not included under other headings*.

An alphabetical key-word index with Annex I and page numbers follows the main body of text.

Comments and advice on this publication should be sent in writing, to the attention of the Head of Unit, to:

**European Commission,
Directorate General Employment, Social Affairs and Equal Opportunities,
Directorate F (Social Dialogue, Social Rights, Working Conditions, and Adaptation to Change),
Unit F.4 (Health, Safety and Hygiene at Work):
Euroforum building,
10, rue Robert Stumper,
L-2557 Luxembourg**

The European Commission reserves the right to revise the contents of this document when deemed necessary. Comments and advice received will be taken into consideration at that time.

References

1. IARC complete list of agents evaluated and their classification (available in <http://monographs.iarc.fr/ENG/Classification/index.php>)
 2. EU Carcinogens list as per the respective classification and labelling provided for under Directive 67/548/EEC (available in ESIS, European chemical Substances Information System) in <http://ecb.jrc.it/esis/index.php?PGM=cla> ⁶
 3. SCOEL documents, available in http://ec.europa.eu/employment_social/health_safety/scoel_en.htm
 4. American Conference of Governmental Industrial Hygienists, Inc. (2007). Threshold Limit Values for chemical substances and physical agents & Biological Exposure Indices. Cincinnati, Ohio: ACGIH publications (may be ordered from the ACGIH website) in <http://www.acgih.org/store/ProductDetail.cfm?id=652>
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⁶ Searches possible by Index, EC or CAS number as well as substance name, risk phrases, Seveso categories, etc.

Table 1**Members of expert working group:**

Name of Expert	EU Country	Organisation/Contact	Areas of expertise
Prof. Tar-Ching Aw (chairman)	UK	University of Kent, Canterbury (up to 2007); presently based at United Arab Emirates University	Occupational Medicine, Toxicology
Dr. Syed Ahmed (<i>Rapporteur</i>)		East Kent Hospitals NHS Trust, and University of Kent, Canterbury (up to 2007), presently at Royal Dutch Shell, London	Occupational medicine, Otorhinolaryngology
Prof. Dominique Choudat	France	Group Hospitalier Cochin, AP- HP, University Paris Descartes	Occupational medicine, Respiratory diseases
Dr. Claudio Colosio	Italy	Department of Occupational and Environmental Health, University of Milan	Occupational Medicine, Agriculture, Toxicology
Dr. Paul Cullinan	UK	National Heart & Lung Institute (Imperial College), London	Occupational Medicine, Respiratory Medicine
Prof. Maija Eglite	Latvia	Agency of Riga Stradins University - Institute of Occupational Safety & Environmental Health	Occupational and Radiological Medicine, Toxicology
Prof. Vito Foa	Italy	Department of Occupational and Environmental Health, University of Milan	Occupational Medicine, Toxicology, Industrial Hygiene
Dr. Rob FM Herber.	Netherlands	Tollenslaan 16, Bilthoven	Toxicology
Prof. Perrine Hoet	Belgium	<i>Université Catholique de Louvain</i> , Unit of Industrial Toxicology and Occupational Medicine, Brussels	Occupational Medicine, Toxicology
Dr. Sigurd Mikkelsen	Denmark	Copenhagen University Hospital, Glostrup	Occupational medicine
Dr. Teake Pal	Netherlands	<i>Coronel Instituut</i> , University of Amsterdam	Occupational medicine, Toxicology, Respiratory medicine
Prof. Cezary Palczynski	Poland	Nofer Institute of Occupational Medicine, Lodz	Occupational medicine, Clinical medicine, Respiratory medicine
Dr. Markku Sainio	Finland	Finnish Institute of Occupational Health, Helsinki	Occupational medicine, Neurology
Prof. Dieter Szadkowski	Germany	<i>Ordinariat für Arbeitsmedizin der Universität</i> , Hamburg	Occupational medicine, Internal medicine, Toxicology
Dr. Jane F. Thomsen	Denmark	Copenhagen University Hospital, Glostrup	Occupational medicine, Ergonomics
Dr. Gert van der Laan	Netherlands	<i>Coronel Instituut</i> , <u>University of</u> Amsterdam	Occupational Medicine
Dr. Ralf Wegner	Germany	<i>Ordinariat der Universität und Zentralinstitut für</i>	Occupational medicine

Dr John English	UK	<i>Arbeitsmedizin und Maritime Medizin</i> , Hamburg Nottingham University Hospital	Occupational medicine, Occupational dermatology
Dr Jane Hitchins (Ad hoc support for editorial work)	UK	East Kent Hospitals NHS Trust, and University of Kent, Canterbury	Occupational Medicine
Dr. Gerd Heuchert (Ad hoc support on chemicals carcinogenicity)	Germany		Toxicology

Observers

Ms. Thora Brendstrup	Denmark	United Federation of Danish Workers, Copenhagen	Representative of the Trade Union Group of the ACSH
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EU Secretariat, Luxembourg, Directorate General Employment, Social Affairs and Equal Opportunities, Directorate F (Social Dialogue, Social Rights, Working Conditions, and Adaptation to Change), Unit F.4 (Health, Safety and Hygiene at Work):

Dr. Jaume Costa (till 15.05.2005)

Dr. Jesus Alvarez-Hidalgo (till 09.05.2006)

Dr Jorge Costa-David (from 16.12.2005)

We also thank the organisations and individuals mentioned below; they provided advice and opinions on several of the topics discussed:

Dr. Enrico Occhipinti, CEMOC - Policlinico, Mangiagalli, Regina Elena Foundation, Milan, Italy

Prof.s Lorenzo Alessio and Stefano Porru - Department of Experimental and Applied Medicine, Section of Occupational Medicine and Industrial Hygiene - University of Brescia, Italy

Prof. Massimo Bovenzi, Clinical Unit of Occupational Medicine, Department of Public Health Sciences - University of Trieste, Italy

Prof. Paolo Carrer, Depart. of Occupational and Environmental Health - University of Milan, Italy.

Information for readers

General

This publication consists of:

- A table of contents,
- The Corpus (information notices),
- An index with a single alphabetical key-word and cross-reference index printed on blue paper; and finally
- The full text of the Commission recommendation mentioned above (with its Annex I concerning the adoption of a European schedule of occupational diseases).

The Corpus contains the information notices on the diagnosis of occupational diseases which have been given Annex I sequential numbers (the Annex I numbers of Commission Recommendation 2003/670/EC) to facilitate cross-referencing between the individual notices and possibly also to versions in other languages.

The reader will find that some information notices refer to several items of the European schedule of occupational diseases and have been grouped together for the purpose of this publication.

Some additional sections have been added on overarching topics to complement the information provided on individual entries.

The Corpus is followed by an alphabetical key-word index printed on blue paper. This index is listed by Annex I numbers (Commission Recommendation 2003/670/EC) and they are used for the cross-referencing.

Layout of information notices

Information notices rely on a systematic use of a number of standard terms.

The causal agent (definition of causal agent) is described in its common states and forms. The main occupational uses and sources of exposure listed are the most common ones offering the greatest risks of known exposure.

The effects are divided into two parts namely acute and chronic, and are then subdivided in local and systemic manifestations. These effects are described by signs and symptoms. For more detailed descriptions of diseases and specific methods of investigation the reader is recommended to refer to texts on occupational health.

A structured approach with specific concepts has been used to determine the causal relationship between an exposure and a specific effect (disease) – see Preface.

The European Commission reserves the right to revise these information notices as the need arises and any comments received will be taken into consideration at that time.

Acrylonitrile

Definition of causal agent

Acrylonitrile (vinyl cyanide) is at room temperature a volatile, flammable, colourless liquid with a weakly pungent odour. The vapours are explosive, with cyanide gas being produced. It may polymerize spontaneously, particularly in the presence of oxygen or visible light.

Main occupational uses and sources of exposure:

Acrylonitrile is used in the manufacture of synthetic fibres and plastic materials. The large majority is used in the production of acrylic and modacrylic textile fibres and (>50%). Other large uses include acrylonitrile-butadiene-styrene and styrene-acrylonitrile plastics, nitrile-butadiene rubber and other polymeric materials or production of acrylamide and adiponitrile.

Toxic effects

1. Acute poisoning

☐ Irritant effects

Acrylonitrile irritates skin, eyes and respiratory tract. See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

2. Allergic effects

Acrylonitrile may cause allergic dermatoses. See section on *Occupationally caused allergic contact dermatoses* in Annex I entry nr. 202.

3. Systemic effects

Manifestations similar to cyanide poisoning (see the *hydrogen cyanide* document Annex 104.01, 104.02). Symptoms include e.g. headache, dizziness, weakness, nausea, irritability and at high doses convulsions and respiratory depression. Liver effects, manifested initially as an elevation of liver enzymes are also possible.

Exposure criteria:

Minimum intensity of exposure:

Occupational exposure confirmed, and if possible assessed, by:

- history and study of the working conditions providing evidence of massive inhalation of acrylonitrile vapours or significant skin contact with liquid acrylonitrile;
- and, if available:
 - o workplace air monitoring.

For other effects the exposure levels are uncertain.

Minimum duration of exposure: from a few minutes to a few hours depending on the intensity of exposure.

Maximum latent period: 24 hours.

Arsenic or compounds thereof

Definition of causal agent

Arsenic is a silver-grey element that exists in four different oxidation (valence) states. It occurs most commonly in the atmosphere as vapour and particulates in the As(III) – ‘arsenite’ - or As(V) – ‘arsenate’ - states.

The main inorganic compounds of concern include: arsenic trioxide As_2O_3 , copper arsenite $\text{Cu}(\text{AsO}_2)_2$, sodium arsenite NaAsO_2 , lead arsenate $\text{Pb}_3(\text{AsO}_4)_2$ and arsenic pentoxide As_2O_5 .

Main occupational uses and sources of exposure:

Manufacture and use of some pesticides such as in cotton or tobacco farming and processing, manufacture and use of wood containing preservatives, non-ferrous (Cu, Zn, Pb) smelting, coal burning, microelectronics, optical industry, glassmaking and tanning. Most industrial exposure is respiratory or dermal but oral exposures are probably also important. The use of arsenic in many compounds is now banned or restricted in most countries.

Toxic effects

1. Local effects

- At high concentrations inorganic arsenic compounds are irritant to the skin, eyes and mucous membranes.
- Repeated high nasal exposures may lead to septal ulceration or perforation.

Exposure Criteria:

minimum intensity of exposure: 0.1 mg/m^3

minimum duration of exposure: immediate

maximum latent period: a few minutes for acute irritant effects
6 months for septal perforation

2. Systemic effects

□ skin

- palmar and plantar hyperkeratosis
- hyperpigmentation, depigmentation
- arsenical warts

☐ **nervous system**

- sensorimotor polyneuropathy (with decrease in peripheral nerve conduction velocity)
- encephalopathy (following very high acute exposures)

☐ **peripheral circulation**

- vasospasticity and Raynaud's syndrome

Exposure Criteria:

For neurological, peripheral circulation and non-malignant skin effects:

minimum intensity of exposure: 0.05 mg/m³

minimum duration of exposure: 6 months

maximum latent period: 1 year

☐ **malignancy**

- lung cancer

Exposure Criteria

minimum intensity & duration of exposure: 250 µg/m³.years

maximum latent period: not appropriate

induction period: 15 years

- skin cancer

minimum duration of exposure: 1 year

induction period: 5 years

Beryllium (glucinium) or compounds thereof

Definition of causal agent

Beryllium is the lightest metal.; it is a grey hard metal, with chemical properties between those of aluminium and magnesium.

Its commonest ores are beryl (double silicate of aluminium and beryllium) and bertrandite. Very pure gem-quality beryls are known as blue-green aquamarine and green emerald. It is the inhalation of insoluble beryllium compounds which seems to cause the most serious health problems; these include beryllium oxide and various alloys, the most important being copper-beryllium alloy.

Main occupational uses and sources of exposure:

Beryllium extraction and metallurgy; manufacture and processing (melting, grinding, welding, drilling) of beryllium alloys (for springs, switches, relays, connectors in automobiles, computers, radar and telecommunications equipment; high strength non-sparking tools; moulds for metal, glass, and plastic items; sports equipment such as golf clubs and bicycle frames; and dental bridges and related applications); beryllium soluble salts, such as beryllium fluoride, chloride, and sulfate, are used in nuclear reactors, in glass manufacture, and as catalysts for certain chemical reactions. Beryllium oxide is used to make ceramics for electronics and electrical equipment. Pure beryllium metal is used in nuclear weapons and reactors, aircraft and space vehicle structures, and other instruments. Because of its unique properties, beryllium is used in many high-technology consumer and commercial products.

It is no longer used in fluorescent lamps.

Toxic effects

☐ Skin

Irritant contact dermatitis; allergic contact dermatitis; ulcerating granulomas; and allergic dermal granulomas.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by history and study of working conditions providing evidence of exposure to beryllium compounds.

Minimum duration of exposure: May be very short (ulceration and subcutaneous granulomas develop if small beryllium crystals penetrate the skin).

Maximum latent period: granulomas: one month.

Skin irritation and sensitisation: See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

□ Acute beryllium disease

In acute disease, beryllium (mainly soluble salts) acts as a direct chemical irritant, causing a nonspecific inflammatory reaction of the upper or lower respiratory tract or both. Tracheo-bronchitis may occur, but the most serious complication is chemical pneumonitis the severity of which depends on the intensity of exposure. Chemical pneumonitis occurred in almost all workers exposed to 1000 µg beryllium/m³ and above and in none exposed to less than 100 µg/m³ and appears to be reversible at concentrations of less than 1000 µg beryllium/m³ (condition of historical interest).

□ Chronic beryllium disease (CBD)

Workers exposed to beryllium may develop a specific hypersensitivity detectable by a beryllium lymphocyte transformation (proliferation) test on blood or broncho-alveolar lavage samples. The risk of hypersensitivity seems to be related to genotype; in susceptible workers it may develop at very low levels of exposure.

Chronic beryllium disease is a granulomatous lung disease caused by inhalation of insoluble beryllium dusts and characterized by the accumulation of CD4+ T cells and macrophages in the lower respiratory tract and in the presence of beryllium hypersensitivity.

Diagnostic criteria include:

- history of beryllium exposure
- restrictive or mixed obstructive/restrictive changes in lung function; loss of diffusing capacity
- changes on chest X-ray similar to those of sarcoidosis
- histological evidence of non-caseating granulomas in bronchial tissue
- a positive beryllium lymphocyte transformation test.

Exposure criteria :

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by history and study of working conditions providing evidence of repeated or prolonged exposure to beryllium. The probability of developing sensitisation or CBD appears to be very low when the exposure level is kept < 0.02 µg/m³. Skin exposure to fine beryllium particles might provide an alternative route for sensitization.

Minimum duration of exposure: unknown

Maximum latent period: none

□ **Bronchial cancer**

Since the causal relationship between prolonged or repeated exposure to beryllium and the occurrence of a bronchial cancer has not been firmly established, and due to the multicausality of the occurrence of this type of cancer, the recognition of the occupational origin must lie on a thorough assessment based on rigorous scientific criteria taking into account all other possible aetiologies.

Each case must therefore be considered separately.

See also section on *Occupational cancers* in the **Preface**.

Carbon monoxide

Definition of causal agent

Carbon monoxide (CO) is, at ambient pressure and temperature, a colourless, odourless and non-irritant gas generated by incomplete combustion of organic material (coal, paper, wood, oil, gasoline, gas). It has a > 200-fold greater affinity for haemoglobin than oxygen.

Main occupational uses and sources of exposure:

The largest sources are motor vehicle exhaust, heating facilities, incineration and industrial processes. Occupations with potential exposure are numerous: garage personnel, fire-fighters, tunnel workers; petroleum, metallurgical, gas and chemical industries workers. Direct and/or indirect exposure to cigarette smoke also contributes to carbon monoxide exposure. Methylene chloride (used as paint stripper) is also metabolised to carbon monoxide, resulting in increased carboxyhaemoglobin levels (see section on *Methylene chloride* in Annex entry nr. 117).

Toxic effects

The principal cause of carbon monoxide toxicity is tissue hypoxia due to carbon monoxide binding to haemoglobin.

1. Acute and subacute effects

10%-30% Carboxyhaemoglobin (HbCO):

Headache, dizziness, weakness, nausea, confusion, disorientation and visual disturbances

30-50% HbCO:

Exertional dyspnoea, increases in pulse and respiratory rate, severe headache and syncope >50% HbCO:

Convulsion, coma, cardiopulmonary arrest. Complications occur frequently in carbon monoxide poisoning: immediate death, myocardial impairment, hypotension, arrhythmias, pulmonary oedema. Delayed development of neuropsychiatric impairment may occur within 1-3 weeks. Carbon monoxide poisoning during pregnancy may cause foetal death, developmental disorders and cerebral anoxic lesions in the foetus

□ Exacerbation of ischaemic heart disease:

Prolonged exposure to carbon monoxide which gives rise to levels of carboxyhaemoglobinaemia in excess of 5 % can exacerbate a pre-existing heart disease, for example aggravation of angina pectoris and arrhythmia.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed by:

- History and analysis of the working conditions revealing a significant exposure to carbon monoxide,
- and, if available:
 - workplace air monitoring
 - biological monitoring:
 - carboxyhaemoglobin concentration in blood (sample taken at the time of removal from exposure before any treatment) or increase of carbon monoxide in exhaled breath.
 - The appearance of symptoms depends on the concentration of CO in the air, the duration of exposure, the degree of exertion, individual susceptibility, pre-existing cardiovascular or neurological diseases etc. (Note that the carboxyhaemoglobin concentration in heavy smokers can be as high as 10%)

Minimum duration of exposure: A few minutes to a few hours depending on the intensity in case of acute exposure, two weeks in case of sub acute exposure.

Maximum latent period:

For acute effects: 24 hours

For cardiovascular or neurological effects: 1 month

2. Chronic effects

Not well defined, although, prolonged exposure to carbon monoxide which gives rise to carboxyhaemoglobinaemia in excess of 20%, or following severe acute carbon monoxide poisoning can cause chronic detriment in neurobehavioural functioning.

Carbon oxychloride (phosgene)

Definition of causal agent

Carbon oxychloride is a colourless gas at ambient temperature and pressure with an odour of mouldy hay. The gas is heavier than air. It has a boiling point of 8.33° Celsius.

Main occupational uses and sources of exposure:

Carbon oxychloride is a widely used chemical intermediate, primarily in the preparation of a large number of organic chemicals. It is used in the synthesis of isocyanate-based polymers, carbonic acid esters and acid chlorides; and in the manufacture of dyestuffs, some insecticides and pharmaceuticals.

This gas is also generated when a volatile, chlorinated hydrocarbon compound has contact with flames or hot metal; thus it is a potential hazard for fire fighters, welders and dry cleaners.

Toxic or irritant effects

1. Acute respiratory effects

- respiratory tract irritation
- pulmonary oedema
- asphyxiation
- death

Delayed pulmonary oedema may develop after a (latent) period of up to 48 hours after exposure.

2. Acute ocular

- irritation and burning of the eyes

3. Acute dermal

- irritation and burning of the skin

Minimum intensity of exposure: 0.8 mg/m⁻³

Minimum duration of exposure: seconds

Maximum latent period: 48 hours

Hydrocyanic acid (hydrogen cyanide)

Definition of causal agent

Hydrogen cyanide (HCN) is a colourless gas which liquifies at 26° C. It may thus be found in the workplace as either a gas or a liquid. It has the characteristic odour of bitter almonds but a third of the population cannot detect this smell. Hydrogen cyanide is highly flammable and explosive.

The toxicity of the gas lies in the cyanide radical which is a powerful enzyme inhibitor especially for respiratory enzymes and acts as a chemical asphyxiant.(see also Annex I entry nr. 104.02 on cyanides and compounds thereof).

Main occupational uses and sources of exposure:

Used as a fumigant, rodenticide and insecticide; chemical intermediate in the manufacture of plastic and synthetic fibres; the gas may be generated in blast furnaces, coke ovens or in the combustion of polyurethane foam.

Hydrocyanic acid can penetrate the intact skin (see also Annex I entry nr. 104.02 on *Cyanides and compounds thereof*)

Toxic effects

1. Local irritant effects

Hydrogen cyanide gas is a mild irritant of the upper respiratory tract and mucous membranes.

Skin and eye irritation may follow from contact with the liquid. At high exposure, pulmonary oedema and laryngeal spasm may occur.

Guide values:

Irritation occurs at around 35 ppm

100 ppm is barely tolerable for one hour.

See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

2. Acute systemic effects

The clinical picture is due to the affinity of the cyanide ions for cytochrome-oxidase, and the respiratory pigments such as haemoglobin:

- headache, dizziness, nausea, vomiting
- bitter almonds taste (see above)
- tachypnoea, dyspnoea
- angina pectoris

anxiety, stupor, loss of consciousness
tachycardia, metabolic acidosis, convulsions, coma, death.

Concentrations

mg/m ³	ppm	Response:
300	270	Immediately fatal
200	180	Fatal after 10 minutes
150	135	Fatal after 30 minutes
120 to 150	110 to 120	Fatal after 30 to 60 minutes or later, or life threatening
50 to 60	45 to 54	Tolerated for 30 to 60 minutes without effect
20 to 40	18 to 36	Slight symptoms after several hours

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed by:

- history and analysis of the working conditions providing evidence of a significant exposure to this substance (notice should be taken of skin absorption),
- and, if available:
 - biological monitoring:
 - urinary thiocyanates, blood cyanide

Minimum duration of exposure: A few minutes to a few hours depending on the intensity of exposure.

Maximum latent period: 24 hours.

Symptoms may take several weeks to resolve completely. However long term effects (especially neurological) following prolonged tissue hypoxia may occur.

Cyanides and compounds thereof

Definition of causal agent

The common cyanides used in industry are alkaline cyanide salts of sodium, calcium (“black cyanide”) or potassium. They are white powders, flakes, or granules with a faint almond odour.

These cyanides release hydrogen cyanide (HCN) on exposure to acid. These simple salts of hydrocyanic acid have a toxicity similar to hydrocyanic acid, due to the release of cyanide ions. They act as chemical asphyxiants.

Main occupational uses and sources of exposure:

Sodium and potassium cyanides are used in the extraction of gold and silver ores; electroplating; cleaning and heat treatment of metals; hardening of metals; as raw materials in the manufacture of dyes, pigments, nylon and chelating agents. Cyanides are extensively used as laboratory agents. They are also used as insecticides and fumigates; calcium cyanide is used mainly as a fumigant.

See Annex I entry nr. 104.01 on *Hydrocyanic acid*.

Toxic effects

2. Local effects

Cyanides are irritant to the skin, eyes, and respiratory tract.

They can cause epistaxis and ulceration of the nasal septum. Prolonged contact with aqueous cyanide solutions can cause caustic burns.

Chronic irritation of the skin is rare but may include itching, discolouration of the skin and ulceration.

See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

3. Acute systemic effects

Clinical picture is due to the affinity of the cyanide ions for cytochrome-oxidase, and the respiratory pigments such as haemoglobin:

- headache, dizziness, nausea, vomiting
- bitter almonds taste
- tachypnoea, dyspnoea
- angina pectoris
- anxiety, stupor, loss of consciousness
- tachycardia, metabolic acidosis, convulsions, coma, death.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed by:

- history and analysis of the working conditions providing evidence of a significant exposure to this substances (notice should be taken of skin absorption),
- and, if available:
 - biological monitoring:
 - Urinary thiocyanates, blood cyanide

Minimum duration of exposure: A few minutes to a few hours depending on the intensity of exposure.

Maximum latent period: 24 hours.

Isocyanates

Definition of causal agent

Isocyanates constitute a group of highly reactive chemicals used on a large scale for the production of flexible polyurethane foam. They are generally synthesized by the reaction of amines or their hydrochlorides with phosgene. Toluene diisocyanate (TDI), diphenyl-methane isocyanate (MDI) and hexamethylene diisocyanate (HDI) are most often used in the production of polyurethane articles.

Main occupational uses and sources of exposure:

Aliphatic isocyanates such as HDI polymers are used primarily in external coatings and paints. Aromatic isocyanates such as MDI and TDI are used to produce a number of products such as flexible and rigid foams, adhesives, and sealants. MDI is also used to manufacture truck bed liners, synthetic leather, and laminated wood products

Toxic effects

1. Irritant and corrosive effects

The crucial mechanism of toxicity is connected with the direct influence of isocyanates on oxidative stress in cells. These chemicals can create quite persistent connections with glutathione and they are the cause of increased production of reactive free radicals.

Isocyanates irritate the skin and the ocular and respiratory mucous membranes.

Direct contact (or exposure to high concentrations) can lead to palpebral and corneal disorders with eye burns, photophobia, blepharospasm, conjunctival hyperhaemia and superficial corneal ulcerations.

Irritation of the airways may lead to an acute pulmonary oedema with bronchoconstriction and possible development of severe bronchiolitis, death from acute respiratory distress syndrome or fibrosis-type sequelae.

Guide values: (methyl isocyanate)

irritation of ocular mucous membrane: exposure > (470µg/m³); 0.2 ppm

palpebral and corneal disorders: exposure > (117.5 mg/m³); 50 ppm

acute pulmonary oedema: exposure > (117.5 mg/m³); 50 ppm

See section on ***Occupationally caused irritation of the skin and mucous membranes*** in Annex I entry nr. 202.

2. Immuno-allergic effects (Diisocyanates)

□ Allergic contact dermatitis

Allergic contact dermatitis due to isocyanates is observed very rarely.

See section on *Occupationally caused allergic contact dermatoses* in Annex I entry nr. 202.

□ Allergic rhinitis and conjunctivitis

See Annex I entry nr. 304.07 on *Allergic rhinitis caused by the inhalation of substances consistently recognised as causing allergies and inherent to the type of the work.*

□ Asthma

It is well documented that isocyanates are a cause of occupational asthma. Humoral as well as cellular mechanisms are involved in the pathogenesis. Immediate or late allergic reactions or both can occur. The specific humoral immune response can be IgE as well as IgG mediated, but many patients with sensitisation to isocyanates have no demonstrative serum antibodies against isocyanates.

Inhalation challenge remains the gold standard for confirming a diagnosis of diisocyanates asthma in an individual worker. Testing should be performed in specialized centres and conducted by experienced personnel, with all safety measures as recommended by international guidelines. Transient increases in non-specific airway hyperresponsiveness may persist as long as 30 days after a diisocyanate challenge.

See Annex I entry nr. 304.06 on *Allergic asthmas caused by the inhalation of substances consistently recognised as causing allergies and inherent to the type of work.*

□ Allergic alveolitis

See Annex I entry nr. 304.01 on *Extrinsic allergic alveolitis.*

3. Chronic obstructive bronchopathy

Expert evaluation is necessary to determine to causal link between exposure to isocyanates and the onset of chronic obstructive bronchopathy.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure to isocyanates confirmed, if possible assessed, by:

- History and study of exposure conditions providing evidence of prolonged or repeated exposure to isocyanates;
- and, if available:
 - biological monitoring;
 - workplace air monitoring;

Guide value: atmospheric concentration TDI > 0.036 mg/m³ (0.005 ppm)

MDI > 0.047 mg/m³ (0.02 ppm)

Minimum duration of exposure: 10 years

Maximum latent period: Five years

Cadmium or compounds thereof

Definition of causal agent

Cadmium is a silver-white, malleable metal which is highly resistant to corrosion.

Its compounds include: cadmium acetate, cadmium sulphide, cadmium sulpho-selenide, cadmium stearate, cadmium oxide, cadmium carbonate, cadmium sulphate, cadmium chloride

Main occupational uses and sources of exposure:

Used for manufacture of Nickel-Cadmium (Ni-Cd) batteries; electroplating other metals, mainly iron and steel; in alloys; as pigments in paints and as stabilizers in plastics. It is also encountered in the recovery of other metals.

Toxic effects

1. Acute effects

☐ 'Metal fume fever'

Pseudo-influenza type syndrome usually occurring shortly after acute exposure to Cadmium Oxide (CdO) fumes and causing irritation and dryness of the nose and throat, coughing, headache, weakness, shivering, fever, etc. Metal fume fever usually resolves spontaneously.

☐ Acute broncho-pneumonia (chemical pneumonitis)

The first stage is very similar to (and often confounded with) the typical "metal fume fever". After some hours, development of symptoms suggesting the onset of an acute upper respiratory tract infection: irritation and dryness of nose and throat, cough, headache, dizziness, weakness, chills, fever, chest pain and breathlessness which may progress to serious consequences such as pulmonary oedema or respiratory failure. Death occurring several days after acute exposure to cadmium is usually due to pulmonary oedema.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by history and study of working conditions providing evidence of intense inhalation of cadmium oxide fumes (CdO fumes are formed readily when the metal is heated in air).

It has been estimated that an 8-hour exposure to 5 mg/m³ may be lethal and an 8-hour exposure of 1 mg/m³ is considered as immediately dangerous for life.

Minimum duration of exposure: From a few minutes to a few hours depending on the intensity of exposure.

Maximum latent period: The first symptoms usually appear within 48 hours following exposure.

2. Chronic effects

□ Nephropathy

Nephrotoxicity in occupationally exposed subjects is usually a tubular dysfunction associated with an increased urinary excretion of Low Molecular Weight (LMW) proteins such as β -2 microglobulins (β 2M) and retinol binding protein (RBP). An effect on the glomerulus may also be observed in cadmium-exposed workers, as indicated by increased urinary excretion of HMW proteins including albumin, immunoglobulin G (IgG) or transferrin. Overt clinical disease is rare.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- history and study of working conditions providing evidence of repeated or prolonged exposure to cadmium;
- and, if available:
 - biological monitoring (levels below which nephropathy is unlikely to be due to occupational exposure to cadmium)
guide values (depending on the duration of exposure):
CdU > 5-10 μ g/g creatinine
 - workplace air monitoring
guide values: atmospheric concentration > 2 μ g/m³.

The critical concentration of cadmium in the renal cortex associated with increased incidence of renal dysfunction in an occupational setting (mainly low molecular weight proteinuria) is estimated to be about 200 ppm, equivalent to an urinary Cd excretion of about 5-10 μ g Cd/g creatinine. This threshold is considered as clinically relevant because several studies have indicated that when CdU > 10 μ g/g creatinine renal changes are irreversible and may lead to an exacerbation of the age related decline in the glomerular filtration rate. Changes in renal biomarkers of unknown health significance and predictive value can occur at lower levels.

Minimum duration of exposure: Several years depending on the level of exposure

Maximum latent period: Cd is a highly cumulative agent. The first signs of renal damage may develop several years after documented exposure.

□ Pulmonary lesions

Long-term inhalation exposure to cadmium can lead to decreased lung function (obstructive syndrome) and emphysema.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

-
- history and study of working conditions providing evidence of repeated or prolonged exposure to cadmium ;
 - and, if available :
 - biological monitoring (levels below which a pulmonary lesion is unlikely to be due to occupational exposure to cadmium)
 - guide values: CdU > 5-10 µg/g creatinine
CdB > 5-10 µg/L
 - workplace air monitoring
 - guide values: atmospheric concentration > 2 µg/m³.

Minimum duration of exposure: about 10 years.

Maximum latent period: Five years.

□ Lung cancer

An increased risk of lung cancer has been found among workers in foundries and battery manufacturing plants where exposure to cadmium has been confirmed. However, the causal relationship between lung cancer and prolonged exposure to cadmium or cadmium compounds has not been firmly established.

See also section on ***Occupational cancers*** in the **Preface**.

□ Bone

Cadmium has been known to cause bone demineralisation with accompanying severe bone pain (well described in 'Itai Itai' disease in Japan). However this resulted from environmental contamination (particularly in elderly women) and not from occupational overexposure.

Individual case reports of bone effects following heavy occupational Cadmium exposure have occurred in specific groups of individuals especially post-menopausal women with vitamin D deficiency.

Chromium or compounds thereof

Definition of causal agent

Chromium is a hard solid, blue-white to steel-grey, lustrous metal very resistant to wear and corrosion. It is found in nature only in the combined state and it forms a number of compounds with oxidation states ranging from -II to +VI; the compounds of +III (chromic) and +VI (chromates) are the most used for industrial purpose. Cr(VI) is an oxidizing agent that may react with reducing (organic) matter to form the most stable Cr(III).

Soluble Cr(VI) compounds: ammonium chromate, potassium chromate, sodium chromate, potassium dichromate, sodium dichromate, ammonium dichromate, chromic trioxide (chromic anhydride or chromic acid).

Non-soluble or slightly soluble Cr(VI) compounds: barium chromate, lead chromate, calcium chromate, strontium chromate, zinc chromate, mixed zinc and potassium chromate.

Cr(III) compounds: chromium acetate, chromic oxide, chromium orthophosphate, chromium pyrophosphate, chromium sulphate, chromium sulphide.

Main occupational uses and sources of exposure:

The stainless steel production and welding (in which the chromium VI and chromium III could be found); manufacture of alloys (VI and III), metal-plating industry (VI and III); manufacture of pigments (VI and III, chrome yellow); chromate production from iron chromate (VI); wood preservation (VI, chromic anhydride); tanning leather industry (III except for 2 bath processes used in the past and in which chromium VI was employed); smaller amounts are used in chemical manufacturing, textiles (dyeing, silk treating, printing, moth proofing wool), toners for copying machines, magnetic tapes, lithography, photography (fixing baths), and as catalysts; traces of chromium in cement. Chromium picolinate (III) is used as a dietary supplement

Toxic effects

The physiological responses to chromium and its compounds are wide and vary functionally depending of the different oxidation states and the toxicological potential; further, within each valency group, toxicity can vary according to solubility.

In humans and animals, Cr(III) is an essential trace nutrient required for normal energy metabolism (Glucose Tolerance Factor). In contrast, the strong oxidizing potential of Cr(VI) explains much of their irritating and toxic properties.

1. Local effects

□ Irritant and corrosive effects

Chromium (VI) (aerosols, dusts, liquid) irritates or even corrodes the skin and the mucous membranes of the eyes and respiratory tract (the spraying of chromic acid can give rise to serious eye lesions and intense exposure to chromic acid particulates may give rise to pulmonary oedema). Also acute oral Cr(VI) toxicity is probably a result of bleeding due to irritation and corrosion (gastroenteritis, hepatic necrosis, acute tubular necrosis with renal failure).

Chrome ulcers (chrome “holes”)

Deep, round holes, clearly marked, usually at the base of the nails, the finger joints, the skin between the fingers, the back of the hand and the forearm (may also appear at other sites). The lesions are only slightly painful, tend to be clean, if at all, but they take a long time to heal and scars are left.

Perforation of the nasal septum

Intense Cr(VI) airborne exposure for two weeks, or less intense exposure for several months (maximum latent period 10 years) may cause painless ulceration, accompanied by foul nasal discharge, sited approximately 1.5 to 2 cm from the lower anterior part of the nasal septum but may extend to the upper posterior part.

See section on ***Occupationally caused irritation of the skin and mucous membranes*** in Annex I entry nr. 202.

□ Allergic effects

Allergic dermatitis

Cr(VI) penetrates undamaged skin (the ulcer does not seem to bear any relationship to the development of allergic sensitization) and subsequently combines with proteins. Contact hypersensitivity due to chromium compounds is caused by a direct effect as haptene into the skin, where chromium is conjugated with autologous proteins to form a full antigen.

See section on ***Occupationally caused allergic contact dermatoses*** in Annex I entry nr. 202.

Asthma

Respiratory sensitization, by inhalation of Cr(VI) compounds may develop (chemical substances of low molecular mass), resulting in generalized bronchospasm and typical asthmatic attacks, which occur on subsequent low exposure levels to dusts, aerosols or welding fumes.

See Annex I entry nr. 304.06 on ***Allergic asthmas caused by the inhalation of substances consistently recognised as causing allergies and inherent to the type of work.***

2. Systemic effects

□ Chronic obstructive bronchopneumopathy

Prolonged inhalation of Cr(VI) particulates can cause chronic respiratory irritation with hyperaemia, chronic inflammation of the lung, chronic bronchitis, bronchopneumonia, and emphysema.
Respiratory function: reduction in FEV₁ and maximal expiratory flow.
Possibility of complication in the form of an infection.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed by

- history and a study of working conditions providing evidence of prolonged or repeated exposure to Cr(VI),
- and, if available;
 - biological monitoring
 - workplace air monitoring.

Minimum duration of exposure: 10 years

Maximum latent period: Five years.

□ Lung cancer

There is no evidence that exposure to metallic chromium or Cr(III) compounds causes cancer in man, while Cr(VI) soluble and insoluble compounds have been linked with increased risk for human lung cancer (dose-response relationships have been established). Cr(VI) carcinogenesis may result from the formation of mutagenic oxidative DNA lesions consequential to the intracellular reduction to the trivalent form.

Carcinogenicity by the oral route of exposure cannot be determined.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed by

- history and a study of working conditions providing evidence of prolonged or repeated exposure to Cr(VI) compounds,
- and, if available;
 - biological monitoring
 - workplace air monitoring

Minimum duration of exposure: 1 year

Minimum induction period: 15 years

Maximum latent period: not determinable.

See section on ***Occupational cancers*** in the **Preface**.

Mercury or compounds thereof

Definition of causal agent

Elemental mercury is a silver-grey liquid at room temperature which vaporises slowly. Mercury is produced mainly from the cinnabar ore (HgS). Secondary mercury is recovered from heating scrapped mercury-containing products and industrial waste. It readily forms amalgams with other metals. Its inorganic compounds are numerous and include oxides, sulphates, chlorides and nitrates.

Organic compounds (alkyl- such as (di)methyl mercury and aryl-mercury such as phenylmercury) are not considered today as major occupational risks. The most common compound is methyl mercury; the main source of exposure is non-occupational: biotransformation of inorganic mercury compounds into methyl mercury when in contact with water and soil explains high concentrations of organic mercury in fish and other sea foods. Seafood consumption increases the levels of organic mercury in blood.

Main occupational uses and sources of exposure:

Main forms of mercury at the work place are the elemental metallic mercury and its inorganic compounds. Organic compounds were previously widely used as fungicides, algaecides, insecticides and disinfectants.

Occupational elemental mercury exposure can occur in chemical industry in the production and reuptake of mercury compounds, in chloralkali industry, in the manufacture, maintenance, repair and extinction of measuring instruments, in the manufacture of lamps, in chemical processes using mercury as a catalyst, and in laboratories. Mercury amalgams were widely used in dentistry and mining industry uses mercury to amalgamate gold and silver. Main route of exposure is inhalation.

Inorganic mercury compounds are used as catalysts in plastic industry, as reagents in laboratories, in manufacture of galvanic batteries, and in chloralkali industry and exposure occurs in handling mercury-containing industrial waste (fluorescent lamps). Previously also used in felt hat industry and in the treatment of the fur. Main route of absorption is ingestion.

Toxic effects

Acute poisoning

- Respiratory tract (elemental mercury vapours). Massive exposure can cause cough, dyspnoea, chest pain, chemical bronchitis, bronchiolitis, pneumonitis and pulmonary oedema.

-
- Oral cavity and gastrointestinal tract (mercury vapours and inorganic mercury compounds): metallic taste, excessive salivation, gingivitis and stomatitis, nausea, vomiting, abdominal pain and diarrhoea.
 - Skin rashes, non-allergic and allergic reactions (elemental mercury and its divalent inorganic compounds)
See documents on occupationally caused irritant and allergic contact dermatoses
 - Conjunctivitis (elemental mercury vapours).

1. Systemic effects

☐ Nervous system effects

Inhalation of elemental mercury vapours: headache, tremor, myoclonus and fasciculations, hallucinations, irritability, emotional lability, violent behaviour and suicidal tendency.

☐ Renal effects

Transient proteinuria, tubular impairment, and in severe cases, tubular necrosis and renal failure (elemental mercury and inorganic compounds).

Exposure criteria

for elemental mercury and inorganic compounds:

Minimum intensity of exposure:

Occupational exposure confirmed, and if possible assessed, by:

- history and study of the working conditions showing evidence of (sub) acute exposure to mercury,
- and, if available:
 - Biological monitoring (B-Hg preferred to U-Hg in acute exposures):
Inorganic mercury in blood (B-Hg-i) >18 µg/dl
Mercury in urine >500 µg/g creatinine
 - workplace air monitoring: Elemental mercury and inorganic compounds:
1 mg/m³.

Minimum duration of exposure: A few hours to a few days depending on the intensity of exposure.

Maximum latent period: 7 days.

Chronic poisoning

Inhalation of elemental mercury vapour causes predominantly kidney and nervous system toxicity. Inorganic mercury compounds affect mainly the gastrointestinal tract and the kidneys. Alkyl-mercury ((di)methyl mercury) causes nervous system toxicity by ingestion, inhalation or skin contact.

☐ Oral cavity and gastrointestinal tract

See **acute effects**. Dark mercurial line along the gingival margins, loosening or loss of teeth, alveolar destruction on radiographs, digestive disturbances, chronic gastritis, and gastroenterocolitis.

□ Nasal effects

Nasal irritation, epistaxis, disturbances of taste and smell.

□ Nervous system effects

Tremor at rest in eyelids, face, fingers and hands, and it may fluctuate in severity. The tremor is first intentional but in more severe cases postural.

Neuropsychiatric manifestations (erethism): emotional lability, excessive timidity, irritability, mental hyperactivity and outbursts of temper, anxiety, depression.

Cognitive dysfunction: difficulties in concentration, memory deficits, reduced psychomotor speed and precision.

Peripheral nervous system: sensory loss, decreased sensory and motor velocities on electroneuromyography.

General symptoms: insomnia, fatigue and headache.

In alkyl-mercury toxicity the sensory, visual, auditory and cerebellum functions are affected.

□ Renal effects

Renal damage leads to albumin and proteinuria (nephrotic syndrome). Membranous nephropathy, minimal change nephropathy and anti-glomerular basement membrane anti-body mediated renal disease may develop.

□ Dermatological effects

See **acute effects**.

□ Reproductive effects

Maternal exposure to alkyl mercury compounds, in particular methyl mercury during the first trimester of pregnancy may cause severe mental and motor retardation in children.

Exposure criteria: for elemental mercury and inorganic compounds;

Minimum intensity of exposure:

Occupational exposure confirmed, by:

- history and study of the working conditions showing evidence of prolonged/repeated exposure to mercury,
- and, if available:
 - biological monitoring (U-Hg preferred to B-Hg in stable chronic exposures):
Mercury in urine > 50 µg /g creatinine, early effects have been described > 35 µg /g creatinine.
 - workplace air monitoring showing levels well in excess of 0.02 mg/m³ (8 hour TWA)

Minimum duration of exposure: a few months to a few years depending on the intensity of exposure.

Maximum latent period: Late appearance of renal and central nervous system degeneration is possible. A latent period cannot be defined.

Manganese or compounds thereof

Definition of causal agent

Manganese is a very hard steel-grey metal. The most common forms, metallic Mn, Mn^{+2} , Mn^{+3} , Mn^{+4} and Mn^{+7} , are found mainly as $MnCl_2$, $KMnO_4$, $MnSO_4$, $MnPO_4$, MnO_2 and Mn_3O_4 . Mn is used in the hardening of alloys e.g. iron containing alloys. Ferromanganese contains at least 65% and manganese steel 10-14% manganese. The main organometallic manganese compounds are methylcyclopentadienyl manganese tricarbonyl (MMT) and manganese ethylene bisdithiocarbamate (Maneb).

Main occupational uses and sources of exposure:

Occupational exposure is mainly through the inhalation of dusts and fumes containing manganese. This may occur in ores during extraction and processing, or steel preparation using manganese, dry battery manufacturing, machining of manganese containing steel and in welding. Exposure may occur in the handling of gasoline and jet fuel with MMT.

Manganese oxides are used in lithium batteries, and in the dye, glass, ceramic and textile industry, and as an oxidizing agent in the chemical industry and in the manufacture of matches and fungicides (Maneb). Manganese chloride is a raw material for drugs e.g. multivitamin tablets and animal food supplements. Manganese sulphates are used in fertilizers, ceramics, glazes and varnishes, food supplements, and fungicides. Potassium permanganate is used as an oxidant in the production of circuit boards, in surface treatment of metals, in drug and chemical industry, and as a bleach, photographic development chemical, disinfectant, deodorizer, anti-algal agent in water treatment, raw material of dyes, auxiliary substance in tanning, and in the extraction of iron or manganese from solutions.

Toxic effects

☐ Acute poisoning

Skin and mucous membranes

Manganese compounds are irritant to the skin, eyes and mucous membranes, at high exposure levels. Sensitization occurs rarely. Potassium permanganate can cause considerable corrosive damage to the mucous membranes, skin and eyes.

Respiratory system

Inhalation may cause irritation and inflammation of the airways with cough, bronchitis, and pneumonitis, and impaired respiratory functions.

Exposure criteria:

Minimum intensity of exposure:

Occupational exposure confirmed, and if possible assessed by:

- history and study of the working conditions showing evidence of acute exposure to manganese;
- and, if available:
 - workplace air monitoring showing exposures considerably above occupational exposure standards.
 - serum, blood and urine manganese levels reflect recent exposure, but due to large inter-individual variation, the monitoring can only be done on a group basis.

Minimum duration of exposure: from a few minutes to a few hours depending on the intensity of exposure.

Maximum latent period: 48 hours.

Chronic poisoning

Respiratory system

Effects similar to acute poisoning.

Central nervous system

Inhalation of manganese dusts or fumes can cause encephalopathy and manganism -which is a Parkinsonian syndrome with neuropsychiatric manifestations.

The early and most subtle non-clinical effects are mainly motor but may also be cognitive.

Manganism progresses through several stages:

- (i) Symptoms such as malaise, somnolence, apathy, emotional lability, impotence, loss of libido, weakness, lethargy, anorexia, and headaches.
- (ii) Impaired memory and judgement, anxiety and sometimes psychotic manifestations such as hallucinations.
- (iii) Progressive bradykinesia, dysarthria, axial and extremity dystonia, paresis, gait disturbances, rigidity, intention tremor, postural instability, impaired coordination and mask-like faces.
The disease may be reversible, but when advanced may progress many years after removal from exposure.

Manganism should be differentiated from Parkinson's disease (PD) and other forms of parkinsonism. Clinical picture is similar to PD, however, certain features support manganism: symmetric impairment, postural or kinetic tremor (vs. resting tremor in PD), early onset of gait dysfunction with peculiar high-stepped gait, tendency to fall backwards, pronounced dystonia, facial grimacing, psychiatric disturbances early in the course of disease, earlier age of onset (vs. on average >60 years in PD) and poor response to levodopa. Neuronal damage is mainly in the *globus pallidus*, with the *substantia nigra* not affected.

Magnetic resonance imaging (MRI) and positron emission tomography with DOPA capture (PET-DOPA) may assist in differentiating between Parkinson's disease and manganism.

Exposure criteria:

Minimum intensity of exposure:

Occupational exposure confirmed, and if possible assessed, by:

- work history and study of the working conditions showing evidence of prolonged/repeated exposure to manganese;
- and, if available:
Workplace air monitoring consistently showing levels above 5 mg Mn /m³ (inhalable dust) is associated with an increased risk of clinical manganism. Small non-clinical decrements in motor neurobehavioural function have been reported at levels above 0.1 mg/m³ respirable or 0.5 mg/m³ inhalable manganese. Pulmonary effects are not expected at exposure levels $\leq$ 1mg/m³.

Minimum duration of exposure: A few months

Maximum latent period: A few decades

Nitric acid

Definition of causal agent

Colourless, yellow or red fuming liquid with an acrid, suffocating smell. It is often used in an aqueous solution. Fuming nitric acid is concentrated nitric acid that contains dissolved nitrogen dioxide. Nitrous vapours are formed when nitric acid enters in contact with metals organic matter (nitration of cotton or other cellulose containing materials).

Used primarily to produce ammonium nitrate fertilizer. Other uses are in the industry, in the production of metallic nitrates, oxalic, phthalic, and sulphuric acids, nitrites and nitrous acids, trinitrophenol, trinitrotoluene, nitroglycerine, ethylene glycol dinitrates and dyes. It is also used in metal cleaning, jewellery production and pharmaceutical industry.

Toxic effects

☐ Acute irritative effects

Nitric acid is a corrosive irritant to skin, eyes, and mucous membranes. It is not combustible. Liquid causes second or third degree burns after short contact. Solutions >30% are highly corrosive to skin. Solutions <30% are irritants.

Nitrogen dioxide and nitric oxide are usually present as hazards whenever nitric acid is used.

Occupational exposure may lead to acute pneumonia and pulmonary oedema, which usually develops after a latent period of 6 to 24 hours. In some cases, the latency from oedema onset can reach 72 hours after exposure.

Exposure criteria:

Minimum duration of exposure: Minutes to hours depending on the intensity of exposure

Maximum latent period before onset of disease: 72 hours.

Immediately Dangerous to Life or Health: 25 ppm

Oxides of Nitrogen

Definition of causal agent

Nitrogen oxides (NO_x). (Synonym: nitric oxides).
Nitrogen monoxide (NO). (Synonym: nitric acid)
Colourless, barely water soluble gas, oxidizes readily to NO₂.
Nitrogen dioxide (NO₂): reddish-brown, barely soluble gas with sweet- sour odour. Condenses below 21 °C. Heavier than air. Nitric acid (HNO₃) and nitric oxide (NO) form in the presence of water.
Dinitrogen monoxide (N₂O) (synonyms: nitrous oxide, laughing gas). Colourless gas with a sweetish odour, heavier than air.
Nitrogen tetraoxide (N₂O₄): polymer of NO₂; occur together at the usual ambient temperatures.

Main occupational uses and sources of exposure:

Nitrogen dioxide: found industrially in arc and inert gas shielded welding in small unventilated rooms. By-product in the manufacture of dyes and explosives. May be evolved from silage.

Dinitrogen monoxide: used as anaesthetic gas.

Toxic effects

1. Local effects

Nitric oxide and nitric tetraoxide are irritant to the eyes, respiratory tract and skin.

2. Systemic effects:

Initial signs/symptoms include burning of throat and chest, nausea, fatigue, shortness of breath and coughing.

Severe exposures to nitric oxide may result in methemoglobinemia, hypoxemia, pulmonary oedema, lung inflammation and decreased pulmonary vascular resistance, particularly in patients with heart disease or pulmonary hypertension.

Impairment of pulmonary function may occur in the absence of acute symptoms.

Latent symptoms may include nervousness, rapid and shallow breathing, cyanosis, mental confusion, and loss of consciousness.

Exposure criteria:

Minimum duration of exposure: Minutes to hours depending on the intensity of exposure.

Methemoglobinemia has been reported in workers exposed to concentrations above 10 ppm. This value has been used for limit setting.

Ammonia

Definition of causal agent

Ammonia is a colourless, suffocating, penetrating, acrid-smelling gas at ambient temperature and pressure and weighs less than air. It may easily be liquefied under pressure and it dissolves readily in water to form ammonium ions.

Main occupational uses and sources of exposure:

The major use of ammonia and its compounds is as fertilizers. Ammonia is also used for the synthesis of nitric acid and sodium carbonate; in the synthesis of numerous organic compounds used as dyes, drugs, in fibres and plastics, in explosives, in various metallurgical processes and in industrial facilities as a refrigerant for cooling and freezing. Ammonia solutions are used as cleansing agents. It is a product of coal distillation (coke ovens, gasworks) and released in the putrefaction of bio-organic materials.

Toxic effects

1. Acute effects

☐ Irritant and corrosive effects:

Ammonia may cause severe irritation of the skin, eyes and respiratory tract. Accidental exposures to concentrated aerosols of ammonium solutions or high concentrations of ammonia gas can result in nasopharyngeal and tracheal burns, airway obstruction, and bronchiolar and alveolar oedema. Recovery without pulmonary *sequelae* is usual but bronchial hyper responsiveness, chronic bronchitis, bronchiectasis, obliterative bronchiolitis and fibrosis have been reported after short-term exposure to high levels of ammonia.

Direct contact with liquid ammonia produces skin and ocular lesions of varying degrees of severity. It causes alkali burns, resulting in liquefaction of the tissue and deeper penetrations. Transient blindness, corneal abrasions, and sustained corneal damage are possible.

See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by history and study of working conditions providing evidence of acute exposure to ammonia. And if available, workplace air monitoring:

Guide values:

- Odour threshold: ~20 ppm
- Exposures to levels exceeding 50 ppm result in immediate irritation to the nose and throat; however, tolerance appears to develop with repeated exposure. Exposure to an air concentration of 250 ppm is bearable for most persons for 30–60 minutes. Exposure to 300 ppm is considered to be immediately dangerous to life and health.

Minimum duration of exposure: seconds to minutes.

Maximum latent period: the first manifestations should appear during exposure or within a few hours.

Nickel or compounds thereof

Definition of causal agent

Nickel is a lustrous, grayish white metal which is ductile, malleable and hard, with a fibrous structure.

Main occupational uses and sources of exposure:

Electrolytic nickel-plating; manufacture of nickel cadmium batteries; coin and kitchen utensil manufacture; preparation of special steels (heat and corrosion-resistant).

Toxic effects

☐ Allergic contact dermatitis (nickel itch)

See section on *Occupationally caused allergic contact dermatoses* in Annex I entry nr. 202.

☐ Asthma

See Annex I entry nr. 304.06 on *Allergic asthmas caused by the inhalation of substances consistently recognised as causing allergies and inherent to the type of work*.

☐ Cancer of the respiratory tract

Sinonasal cavities, ethmoid sinuses, trachea, bronchi, lung parenchyma.

There is no firm evidence that metallic nickel is carcinogenic to humans. With regards to the carcinogenicity of nickel species there is evidence implicating nickel sulphides and nickel oxides. It is unclear if solubility of nickel compounds is an important determining factor in carcinogenicity.

Exposure criteria (for cancer of the respiratory tract):

Minimum intensity of exposure: Occupational exposure confirmed by:

- History and study of working conditions providing evidence of prolonged or repeated exposure to nickel compounds
- and if available:
 - Biological monitoring (qualitative).
 - Workplace air monitoring.

Minimum duration of exposure: Six months.

Induction period: 15 years.

See section on *Occupational cancers* in the **Preface**.

Nickel carbonyl

Definition of causal agent

Nickel carbonyl, Ni (CO)₄ is a volatile liquid, easily decomposing into nickel and CO..

Main occupational uses and sources of exposure:

Intermediate product of nickel refining.

Toxic effects

☐ Acute inhalation

First phase: immediate

Non-specific gastro-intestinal and neurological symptoms: nausea, vomiting, headache, dizziness, vertigo, profound weakness, etc.

Second phase: delayed

Insidious, signs and symptoms are delayed (12 to 36 hours), cough, hyperpnoea, cyanosis, tachycardia, chemical pneumonitis, acute pulmonary oedema, risk of respiratory failure, circulatory collapse, cerebral oedema resulting in death in five to 15 days. Possibility of the development of chronic respiratory insufficiency (sequelae).

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- History and study of working conditions providing evidence of intense exposure to nickel carbonyl;
- and if available:
 - biological monitoring: nickel in urine (qualitative);
 - workplace air monitoring.

Minimum duration of exposure: From a few minutes to a few hours, depending on intensity of exposure.

Maximum latent period: 48 hours.

Phosphorus or compounds thereof

Definition of causal agent

Phosphorous exists in three forms: white (yellow), red and black. The first is the most toxic.

Occupationally important phosphorous compounds include:

Phosphoric acid, phosphorus pentoxide, phosphorus pentachloride, phosphorus pentasulphide, phosphorus chloride, phosphorus oxychloride and phosphine gas (see below). The last can be produced from contact between phosphoric acid and metals or by heating phosphoric chloride.

Main occupational uses and sources of exposure:

White phosphorus is used in the manufacture of explosives, rodenticides and fertilisers. Red phosphorus is used in the manufacture of matches. Black phosphorous has not been used in industry.

Toxic effects

1. Local irritation

- The fumes of white phosphorus (which ignites spontaneously in air) are irritant to the eyes and respiratory tract. High exposures may induce pulmonary oedema; and prolonged exposures chronic bronchitis.
- Solid phosphorus can cause burns to the skin on direct contact.
- phosphoric acid, phosphorus pentoxide, phosphorus pentachloride, phosphorus chloride and phosphorus oxychloride are also irritant to the eyes, skin and respiratory tract.
- Inhalation of phosphorus pentoxide, phosphorus pentachloride, or phosphine gas can cause a delayed (maximum latent period 72 hours) pulmonary oedema.

minimum intensity of exposure: unknown

minimum duration of exposure: seconds

maximum latent period: immediate for local irritant/caustic effects. 72 hours for pulmonary oedema.

2. Systemic effects

- Prolonged exposure to white phosphorus at high concentrations causes anaemia and necrosis of the maxilla ('phossy jaw') with profuse salivation, loosening of the teeth and lesions on the oral mucosa.

Phosphine

Definition of causal agents

Phosphine is a colourless gas that can be produced by the reaction of water or acids with metallic phosphides. Accidental production can take place when phosphoric acid comes in contact with metals, when heating phosphorus chloride, and during the production of acetylene gas.

Main occupational uses and sources of exposure:

Phosphine is used as a fumigant and as a dopant in microelectronics manufacturing, in the semiconductor industry to introduce phosphorus into silicon crystals, as a fumigant (mainly in the past) and as a polymerization initiator.

1. Local effects

Phosphine exposure may cause toxic effects to brain, kidneys, heart, and liver with, in the most severe cases, cardiovascular collapse or pulmonary oedema (maximum latent period 72 hours from exposure), preceded by fluorescent green sputum and acute dyspnea.

When low concentrations are inhaled, headaches, dizziness, tremors, general fatigue, gastrointestinal distress, and substernal pain may be observed. Death may be preceded by tonic convulsions which may ensue after apparent recovery.

Exposure criteria:

Minimum intensity of exposure: Exposure confirmed and, if possible, assessed, by:

- History and study of working conditions providing evidence of acute exposure to arsine;
- And, if available:
 - Workplace air monitoring

Minimum duration of exposure: fatalities are possible in case of exposure of 30-60 minutes at concentrations not lower than 400-600 ppm, but serious health effects may take place also for exposures to 5 to 10 ppm for several hours.

TWA in different countries are comprised between 0,023 and 0,3 ppm, STEL values between 0,1 and 1, while ceiling values are 0,3 ppm.

Maximum latency period: from a few minutes to 72 hours, depending on the dose.

Lead or compounds thereof

Definition of causal agent

Lead is a soft, malleable, blue-grey metal characterized by high density, ductility and corrosion resistance. Its melting point is 327.4° C and it gives off fumes at temperatures greater than 500° C. Elemental lead is poorly soluble in water and in dilute acids. It dissolves in nitric acid, acetic acid and hot concentrated sulphuric acid.

The inorganic salts of lead (II), lead sulphide and oxides of lead are in general not very soluble in water. Of the common lead compounds, the acetate, the carbonate, the chlorate and the nitrate are easily soluble in water. Moderately soluble compounds include the chloride, the chromate and the stearate.

The most important organic lead compounds are tetraethyl lead (TEL) and tetramethyl lead (TML). They are practically insoluble in water but dissolve readily in organic solvents, fats and lipids.

Main occupational uses and sources of exposure:

Exposure occurs in lead mines and a wide variety of industries, including procedures involved in the production of lead metal and its compounds and alloys with antimony and copper, manufacture of batteries, accumulators, ammunition, ceramics, jewellery, glass and pigments, and in the pottery, shipbuilding, construction, demolition and scrap industries. High exposure is seen in lead scrap foundries, radiator repair, bronze foundries and during the grinding, welding and cutting off materials painted with lead-containing paints. The source of absorbed lead is mainly the inhaled fume and dust or ingested soluble lead salts.

The exposure to organic lead is declining with the lessening use of leaded gasoline. Inhalation and dermal exposure are the main routes of organic lead exposure.

Toxic effects of lead and its inorganic compounds

The adverse effects involve, nervous, gastrointestinal, renal, haematopoietic, cardiovascular and reproductive systems.

1. Acute and subacute poisoning

Lead is a cumulative poison and the acute symptoms are usually the manifestation of (sub)chronic poisoning.

☐ Non-specific signs

Signs and symptoms include pallor, malaise, asthenia, headache, dizziness, loss of memory, anxiety, depression, irritability, sleep disturbances, numbness of extremities, muscle and joint pain, lower back pain and limb weakness.

☐ Gastrointestinal tract

The manifestations include nausea, vomiting, constipation, anorexia, abdominal discomfort and colic.

☐ Nervous system

In severe cases, impaired consciousness and confusion may develop which may progress into stupor and coma, accompanied by seizures. Brain pathology shows oedema, increased permeability of capillary endothelium with perivascular hemorrhagic exudates.

☐ Haematopoietic system

Anaemia.

☐ Renal functions

Renal tubular defect with glycosuria and aminoaciduria, which may progress to oliguria and acute renal failure.

Exposure criteria:

Minimum intensity of exposure:

- Occupational exposure confirmed, and if possible assessed, by:
- history and study of the working conditions showing evidence of exposure to lead,
- and, if available:
 - biological monitoring:
 - Blood: lead levels (B-Pb) > 80 µg/dl
- abdominal colic: rare below blood lead levels of 80 µg/dl,
- proximal tubular damage: unlikely below 100 µg/dl,
- encephalopathy: unlikely below 100-120 µg/dl.

Minimum duration of exposure: from a few hours to a few days depending on intensity of exposure.

Maximum latent period: uncertain

2. Chronic poisoning

☐ Gastrointestinal system

Similar, but milder as in acute poisoning (see above). A blue-gray pigmentation (“lead line”) may be present at dental margins of the gums as a sign of exposure.

☐ Non-specific effects

Similar, but milder than in acute poisoning. Arthralgias and myalgias may occur proximally in the extremities.

☐ Haematopoietic system

Inhibition of the enzymes for haeme synthesis. Decreased activity of the delta aminolevulinic acid dehydratase (ALA-D), is the earliest detectable biochemical effect of lead. This results in abnormally high blood levels of free erythrocyte protoporphyrin (FEP) and urinary excretion of ALA, zinc protoporphyrin (ZPP) and coproporphyrin. Measurements of these metabolites have been used as diagnostic tests in lead poisoning. Hypochromic, normocytic or microcytic anemia occurs.

☐ Nervous system

Central nervous system effects range from subjective symptoms and neuropsychological performance impairment to progressive encephalopathy with psychiatric symptoms, fatigue and lethargy.

Peripheral nervous system effects range from reduced nerve conduction velocities to a predominantly motor type neuropathy. Distal sensory loss and muscle weakness may be present. Bilateral wrist drop is a rare event. Nerve biopsies indicate segmental demyelination and secondary axonopathy.

☐ Renal functions

High exposure can lead to tubular damage and chronic interstitial fibrosis. Tubular dysfunction presents with azotemia aminoaciduria, glycosuria and phosphaturia.

☐ Reproductive system

Female: Maternal exposure associates with miscarriage and low birth weight of infants.

Male: Lead associates to a reduced semen quality (sperm count and motility, volume, morphology).

Exposure criteria:

Minimum intensity of exposure:

Occupational exposure confirmed, and if possible assessed, by:

- history and study of the working conditions showing evidence of prolonged or repeated exposure to lead,
- -and, if available:
 - biological monitoring: These values are given as guide.
Blood: lead levels (B-Pb) > 40 µg/dl

Erythrocyte protoporphyrin and urinary delta-amino laevulinic acid (ALA) are used as markers of biological effect.

Various adverse effects begin to occur after prolonged exposure to different levels of blood lead (B-Pb):

- subjective symptoms and objective cognitive performance impairment > 40 µg/dl
- tubular damage > 70 µg/dl (early tubular dysfunction > 40 µg/dl)
- reproductive effects > 40 µg/dl
- anaemia > 50 µg/dl
- gastrointestinal symptoms > 60 µg/dl,
- nerve conduction reduction > 70 µg/dl

Minimum duration of exposure: from a few months to a few years depending on the intensity of exposure.

Maximum latent period: Cannot be specified (renal and nervous system degeneration).

Toxic effects of organic lead

The clinical picture is dominated by central nervous system toxicity.

1. Acute (subacute) poisoning

□ Nervous system

Initial effects are anorexia, nausea, vomiting, insomnia, fatigue, weakness, headache, tremulousness, aggression, depression, irritability, restlessness, hyperactivity, disorientation, confusion and disturbing dreams. Massive intoxication presents with acute mania, psychosis, hallucinations (e.g. hair on tongue, insects on body), convulsions, delirium, tremulousness with choreiform movements and gait disturbances, coma and death.

□ Mucosal irritation

Inhalation induces sneezing, irritation of upper respiratory tract. Eye and skin contact induces itching, burning and redness.

□ Gastrointestinal system

Symptoms may include abdominal discomfort, anorexia, vomiting and diarrhoea.

2. Chronic poisoning

Signs and symptoms similar as in acute poisoning but may be subtle. The clinical picture typically includes irritability, insomnia, disturbing dreams, hallucinations, psychosis, anorexia, nausea, vomiting, tremulousness and ataxia.

Exposure criteria:

Minimum intensity of exposure:

Occupational exposure confirmed by:

- history and study of the working conditions showing evidence of acute (often accidental), prolonged or repeated exposure to organic lead,
- and, if available:
 - biological monitoring:
Urine: urinary tetraethyl lead (U-Pb) levels > 150 µg/dl.

Note: absence of changes in the blood count or in the metabolites of haem synthesis. The blood lead (B-Pb) levels are normal or only moderately elevated < 50 µg/dl.

Minimum duration of exposure:

acute poisoning: hours;

chronic poisoning: from a few months to a few years depending on the intensity of exposure.

Maximum latent period:

acute poisoning: ten days;

chronic poisoning: years (nervous system degeneration).

Sulphuric acid and sulphur oxides

Definition of causal agent

Sulphuric acid (H_2SO_4) is a colourless or slightly brown, hygroscopic, oily liquid. Vaporization can begin from 30°C . Sulphur trioxide is emitted when heated.

Fuming sulphuric acid (synonym: oleum), a solution of sulphur trioxide in concentrated sulphuric acid, produces thick white fumes in the air.

Sulphur dioxide (SO_2) is a colourless pungent gas, heavier than air. It converts to sulphurous acid (H_2SO_3) in water.

Sulphur trioxide (SO_3) (synonym: sulphuric acid anhydride) is a solid crystalline substance which develops pungent-smelling fumes in the air and converts under thermic reaction with water to sulphuric acid (H_2SO_4).

Main occupational uses and sources of exposure:

Sulphuric acid is used as battery acid in accumulators, electroplating and in the production of fertilizer as well as in laboratories.

Sulphur dioxide occurs when sulphur is burnt (combustion of fossil fuel) and in the smelting process of metal ore. It is used as a coolant (in liquid form), for vulcanization of rubber, as a bleaching agent or for obtaining sulphuric acid.

Sulphur trioxide is an intermediate product in the manufacture of sulphuric acid and oleum and is used for sulphonation of organic acids.

Toxic effects

1. Acute, local effects

☐ Irritant and corrosive effects

SO_2 is converted to sulphurous acid by moisture on sweating skin or on mucous membranes. H_2SO_4 is harmful not only as a liquid but also as acidic vapour and, because it has a great affinity for water, it corrodes the skin and the underlying tissue.

Although the following effects apply for both substances, SO_2 mainly produces irritant effects and H_2SO_4 produces the caustic effects.

These substances are highly irritant for the skin (burns), the eyes (possibility of keratoconjunctivitis, deep corneal ulcerations, eyelid lesions) and the respiratory tract (in severe cases: bronchoconstriction, laryngospasm, pulmonary oedema, with a latent period of variable length). Acute exposures to high concentrations of sulphur dioxide may cause bronchial hyper

responsiveness (Irritant Induced Asthma or Reactive Airways Dysfunction Syndrome) that may persist for several years.

Exposure criteria:

Minimum intensity of exposure

- Occupational exposure confirmed, if possible assessed by history and study of exposure conditions providing evidence of skin contact or inhalation;
- And if available:
Workplace air monitoring:
Guide values:
 - > 2.7 mg/m³ (1 ppm) SO₂ (SCOEL 1998 STEL 15 min): irritation symptoms,
 - > 1040 mg/m³ (400 ppm) SO₂: death in a few minutes

Minimum duration of exposure: seconds to minutes depending on the intensity of the exposure

Maximum latent period: The first manifestations should appear during exposure or within a few hours.

Chronic effects

Chronic irritation leads to drying and ulcerations of the skin (particularly the hands), chronic paronychia and perionychia, reddened glossy tongue and taste disturbances.

Chronic irritation of the respiratory tract can cause ulcerations of the nasal septum, nose-bleeding and possibly atrophic rhinitis and chronic obstructive ventilation disturbance.

See section on ***Occupationally caused irritation of the skin and mucous membranes*** in Annex I entry nr. 202.

☐ Damage to dental enamel

The compounds affect particularly the incisors: loss of lustre, streaks, decalcification, yellow or brown flecks, increased sensitivity to temperature changes.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed by:

- History and analysis of the working conditions showing evidence of prolonged/repeated exposure to these substances.

Minimum duration of exposure: A few months.

Maximum latent period: The first manifestations should appear during exposure

Laryngeal cancer

An increased risk of laryngeal cancer has been found after chronic exposure to strong-inorganic-acid mists containing sulphuric acid. There is little evidence in support of a causal relationship between mist containing sulphuric acid and lung cancer. However, there is sufficient evidence for classifying strong-inorganic-acid mists containing sulphuric acid as carcinogenic (IARC group 1).

Exposure criteria

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed by:

-
- History and study of the working conditions showing evidence of significant prolonged exposure of sulphuric acid containing mist

Minimum duration of exposure: 5 years

Minimum induction period: 10-20 years

Carbon disulphide

Definition of causal agent

Carbon disulphide (CS₂) is a colourless, volatile liquid with vapours denser than air. The liquid yellows on exposure to air and light. It is highly reactive and very flammable: vapours can ignite spontaneously at temperatures above 102°C. In its pure state it has a sweet, pleasing and ether-like odour; usually it has an offensive odour due to minor impurities such as mercaptans.

Main occupational uses and sources of exposure:

Carbon disulphide is mainly used in the production of viscose rayon fibre, cellulose film and other viscose products. It is also used as a solvent and for the manufacture of pesticides, dyes, drugs and in rubber curing.

Toxic effects

1. Local effects

☐ Irritant effects

Carbon disulphide causes irritation to the skin and the eyes.

See Annex I entry nr. 202 on *Occupationally caused irritation of the skin and mucous membranes*.

2. Systemic effects

Acute effects

Central Nervous System Effects

☐ Neurological and neurobehavioral manifestations

Hyperexcitability and mental confusion, narcosis, delirium, hallucinations, suicidal tendencies, psychosis, loss of consciousness, coma.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- history and study of working conditions providing evidence of considerable exposure to CS₂;
- and, if available:
 - Biological monitoring:
2-thiothiazolidine-4-carboxylic acid (TTCA) in the urine and/or CS₂ in the exhaled air
 - Workplace air monitoring:
Guide value: atmospheric concentration > 600 mg/m³ (200 ppm)

Minimum duration of exposure: From a few minutes to a few hours depending on intensity of exposure.

Maximum latent period: 24 hours

□ Chronic effects

The complex nature of the metabolic effects of exposure to carbon disulphide results in a unique set of toxic effects on the target organs. These effects may appear separately or together. They can be grouped, into effects on the central nervous system, the peripheral nervous system, the cardiovascular system and the reproductive system.

□ Effects on the central nervous system

- Chronic toxic encephalopathy: fatigue, headache, drowsiness, memory loss.

See Annex I entry nr. 135 on *Encephalopathies due to organic solvents which do not come under other headings*.

Parkinsonism: damage to the extra-pyramidal system.
Retrobulbar optical neuritis

□ Effects on the peripheral nervous system

Polyneuropathy of the mixed sensory/motor type, predominantly affecting the lower limbs.

□ Cardiovascular effects

An increased risk of cardiovascular diseases in people exposed to CS₂:

Hypertension, Angina pectoris, increased arteriosclerosis, excess mortality from myocardial infarction.

□ Reproductive effects

These have been reported in exposed males (reduced sperm count and changes in sperm morphology) and females (menstrual disorders). Reduced fertility is also a recognised effect.

Exposure criteria:

Minimum intensity of exposure: occupational exposure confirmed, if possible assessed, by:

- history and study of working conditions providing evidence of prolonged or repeated exposure to CS₂;
- and, if available:
 - 2-thiothiazolidine-4-carboxylic acid (TTCA) in the urine, CS₂ in the exhaled air
 - Workplace air monitoring
 - Recommended SCOEL value: airborne concentration > 15 mg/ m³ (35 ppm)

Minimum duration of exposure: one year

Chronic encephalopathy: 10 years

Maximum latent period: Uncertain

Vanadium or compounds thereof

Definition of causal agent

Vanadium is a greyish white metal which resists corrosion. Its most common compounds are vanadium pentoxide (V_2O_5), vanadium dioxide (VO_2), vanadium trioxide (V_2O_3), sodium metavanadate ($NaVO_3$), vanadium tetrachloride (VCl_4).

Main occupational uses and sources of exposure:

Metal manufacture; photography; manufacture of colouring substances; catalyst in the production of sulphuric acid and phthalic anhydride; in the manufacture of alloys for the production of special, highly elastic steels which are resistant to vibrations (ferro-vanadium); alloys with other metals (Cu, Co, Ti, Cr); cleaning of boilers and flues in which vanadium-containing oils have been burnt.

Local toxic effects

☐ Allergic contact dermatitis:

See section on *Occupationally caused allergic contact dermatoses* in Annex I entry nr. 202.

☐ Asthma

See Annex I entry nr. 304.06 on *Allergic asthmas caused by the inhalation of substances consistently recognised as causing allergies and inherent to the type of work*.

☐ Irritant effects

Vanadium, especially vanadium pentoxide produces irritation of the eyes and the upper and lower respiratory tract. In more serious cases it can lead to bronchitis and bronchopneumonia, reversible after exposure has ceased

Repeated or prolonged exposure may lead to chronic irritation of the upper respiratory tract (rhinitis, pharyngitis, chronic bronchitis, etc.).

See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

Exposure criteria:

Minimum intensity of exposure:

Occupational exposure assessed, by:

-
- History and analysis of the working conditions showing evidence of exposure to vanadium; vanadium exposure causes a characteristic green discolouration of the tongue.
 - and, if available:
 - biological monitoring: as vanadium pentoxide
- workplace air monitoring:
Guide values: vanadium pentoxide 0,05 mg/m³

Minimum duration of exposure: A few hours to a few days depending on the intensity of exposure.

Maximum latent period: 48 hours.

Chlorine

Definition of causal agent

At ambient temperature and pressure chlorine is a green-yellow gas, which is heavier than air and has a pungent, suffocating smell.

Main occupational uses and sources of exposure:

Chlorine is widely used in the chemical industry for the synthesis of derivatives such as: hydrochloric acid, hypochlorite, calcium and zinc chloride, organic chlorine compounds. It is also used as a bleaching agent in the textiles and paper industries, and is a powerful disinfectant in water purification.

Toxic effects

1. Acute effects

☐ Irritant and corrosive effects

Chlorine may cause severe irritation of the skin, eyes and respiratory tract (pulmonary oedema). Recovery without pulmonary sequelae is usual but some complications have been reported such as bronchiolitis, pulmonary fibrosis and emphysema. Accidental and repeated exposure to high concentrations of chlorine may cause bronchial hyper responsiveness (Irritant Induced Asthma or Reactive Airways Dysfunction Syndrome) and chronic rhinitis that may persist for several years.

Direct contact with liquid chlorine produces severe ocular lesions and skin damage.

See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

Exposure criteria:

Minimum intensity of exposure

- Occupational exposure confirmed, if possible assessed by history and study of exposure conditions providing evidence of skin contact or inhalation.
- Workplace air monitoring:
Guide values: atmospheric concentration well above 1.5 mg/m³ Cl (0,5 ppm) (STEL, SCOEL)

Minimum duration of exposure: Seconds to minutes depending on the intensity of the exposure.

Maximum latent period: The first manifestations should appear during exposure or within a few hours.

Chronic effects

An increased risk of asthma (Relative Risk > 2) and chronic obstructive pulmonary disease has been established in pulp-mill workers and domestic cleaners. Repeated exposure to chlorine may be one of the causal agents.

Exposure criteria

Minimum intensity of exposure

- Repeated occupational exposure confirmed, if possible assessed by history and study of exposure conditions providing evidence of inhalation.

Workplace air monitoring:

Guide values: atmospheric concentration above 1.5 mg/m³ (0.5 ppm) (STEL, SCOEL)

Minimum duration of exposure: Seconds to minutes depending on the intensity of the exposure

Maximum latent period: The first manifestations should appear during the period of employment causing exposure.

Bromine

Definition of causal agent

Bromine is a highly reactive element with a melting point of -7°C and a boiling point of 59°C. At ambient temperature it is a reddish-brown liquid with a pungent vapour. On dissolution in water it forms hydrobromous/bromic acids which dissociate to release bromide ions that may be absorbed systemically.

Main occupational uses and sources of exposure:

Manufacture of flame-retardants; manufacture of anti-knock compounds (ethylene dibromide) for petrol; manufacture of fumigant (methyl bromide); water treatment; dyes; pesticides; pharmaceuticals; photographic processing. Many of these uses have been restricted or banned in recent years.

Toxic effects

- irritation of the upper and lower respiratory tracts
- pneumonitis, pulmonary oedema
- bronchiolitis obliterans,
- irritation of the eyes
- irritation of the skin, chemical burns, destructive ulcers

Exposure Criteria:

minimum intensity of exposure: well above 1.4 mg/m³ (0.2 ppm)

minimum duration of exposure: immediate

induction period: immediate

maximum latent period: a few minutes for acute irritant effects;
24 hours for pneumonitis;
several months for bronchiolitis obliterans.

Iodine

Definition of causal agent

At ambient temperature iodine is a dark grey, crystalline solid; heating produces a violet vapour

Main occupational uses and sources of exposure:

Manufacture of medicinal iodine-containing compounds for topical use; photographic processing.

Toxicity and irritancy

Irritant effects

- irritation of the upper and lower respiratory tracts
- irritation of the eyes with corneal staining
- irritation of the skin, chemical burns, staining

minimum intensity of exposure: well above 0.1ppm

minimum duration of exposure: immediate

induction period: immediate

maximum latent period: a few minutes for acute irritant effects

Fluorine or compounds thereof

Definition of causal agent

At ambient pressure and temperature, fluorine is a corrosive pale greenish-yellow gas with a bitter smell. It is highly reactive and combines with practically all other organic and inorganic substances with the exception of nitrogen and oxygen. It reacts with water to form hydrofluoric acid.

Hydrofluoric acid (synonyms: fluorohydric acid, anhydrous hydrofluoric acid, hydrogen fluoride) is a highly volatile, colourless gas or liquid, very soluble in water and has a bitter smell.

Main occupational uses and sources of exposure:

Fluorine: Synthesis of organic and inorganic fluorine compounds; oxidizer in rocket fuel.

Hydrofluoric acid: Production of organic and inorganic fluorine compounds; catalyst (particularly in paraffin alkylation in the petroleum industry); insecticide; arrest of fermentation in brewing; fluorination processes; removing sand from metallic castings; glass polishing; frosting and etching glass and enamel; decomposing enamel.

Fluorides: electrolyte in aluminium manufacture; flux in smelting nickel, copper, gold, silver; catalyst for organic reactions; fluoridation agent for drinking water; bleaching agent; insecticides, rodenticides; fermentation inhibitor; cleaning graphite, metals, windows, glassware; preparation of fertilizer from phosphate rock by addition of sulphuric acid.

Toxic effects

I. Fluorine and hydrogen fluoride

Local effects

☐ Irritant and corrosive effects

Fluorine and hydrofluoric acid are particularly irritating to the skin, eyes and respiratory tract (possibility of bronchospasm, laryngospasm and acute pneumonitis, pulmonary oedema in the event of massive exposure).

Epistaxis and sinus trouble may develop on low chronic exposure to these compounds.

Cutaneous contact with hydrofluoric acid may lead to extremely painful burns. The chemical burns cause deep tissue destruction and may become symptomatic until several hours after contact, depending on the dilution.

Possibility of developing systemic symptoms by hypocalcaemia caused by binding of fluoride ions to calcium ions following skin absorption from burn sites.

See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed by:

- Anamnesis and study of exposure conditions providing evidence of skin contact or inhalation.
- And if available:
 - Workplace air monitoring:
Guide values:
Fluorine: atmospheric concentrations well above 3.16 mg/m³ (2 ppm)
Hydrogen Fluoride: atmospheric concentrations well above 2.5 mg/m³ (3 ppm)

Minimum duration of exposure: seconds to minutes

Maximum latent period: The first manifestations should appear during exposure or within a few hours.

II. Inorganic fluoride compounds

Local effects

□ Irritant effects

Some inorganic fluoride compounds are irritating to the skin, eyes and respiratory tract. Epistaxis and sinus trouble may develop on the low chronic exposure to fluorides.

Fluorides are suspected to be one of the causal agents of 'potroom asthma' in workers of the aluminium manufacturing industry

Exposure criteria:

Minimum intensity of exposure

- Occupational exposure confirmed, if possible assessed by history and study of exposure conditions providing evidence of skin contact or inhalation.
- And if available: Workplace air monitoring:
Guide values: atmospheric concentration above 2.5 mg/m³ of fluorine ions

Minimum duration of exposure: Seconds to minutes depending on the intensity of the exposure

Maximum latent period: The first manifestations should appear during exposure or within a few hours

□ Systemic effects

Skeletal fluorosis: Excessive absorption of fluorides may result in osteosclerosis; that is recognizable by X-ray (first signs of changes in density appearing in the lumbar spine and pelvis). Usually some ossification of ligaments occurs.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed if possible assessed by:

- Anamnesis and study of the working conditions showing evidence of excessive and prolonged or repeated exposure to inorganic fluoride dusts or vapours.
- And, if available:
 - Biological monitoring: Significant increase in the urinary level of fluoride during the working day. For exposed workers; urine fluoride should be less than 4 mg/l, when taken in pre-shift samples; and less than 8 mg/l when taken in post shift samples. Other non occupational sources of fluoride intake should be checked. Workers not presently exposed but having had fluorosis do not usually have elevated urine fluoride values.
 - Workplace air monitoring:
Guide value:
Atmospheric concentration above 2.5 mg/m³ of fluorine ions

Minimum duration of exposure: One year.

Maximum latent period: One year

Aliphatic or alicyclic hydrocarbons derived from petroleum spirit or petrol

Definition of causal agent

Aliphatic hydrocarbons are organic compounds in which carbon atoms are joined together in straight or branched chains that can be either saturated or unsaturated. The simplest aliphatic compound is methane (CH₄), followed by ethane (C₂H₆) etc.

The following aliphatic hydrocarbons items are covered under this heading:

- n-hexane
See Annex I entry nr. 136 on *Polyneuropathies due to organic solvents which do not come under other headings.*
- n-heptane

Other specific substituted hydrocarbons are covered in their own sections, i.e.:

118 Butyl, methyl and isopropyl alcohol

119 Ethylene glycol, diethylene glycol, 1,4-butanediol and the nitrated derivatives of the glycols and of glycerol

120 Methyl ether, ethyl ether, isopropyl ether, vinyl ether, dichloroisopropyl ether, guaiacol, methyl ether and ethyl ether of ethylene glycol

121 Acetone, chloroacetone, bromoacetone, hexafluoroacetone, methyl ethyl ketone, methyl n-butyl ketone, methyl isobutyl ketone, diacetone alcohol, mesityl oxide, 2-methylcyclohexanone

Alicyclic hydrocarbons are organic compounds that contain one or more closed rings of carbon atoms. The term alicyclic specifically excludes carbocyclic compounds with an array of π -electrons characteristic of aromatic rings. Compounds with one to five alicyclic rings of great variety and complexity are found in many natural products such as steroids and terpenes. There are no well documented cases of ill health arising from occupational exposure to alicyclic hydrocarbons.

n-hexane

Definition of causal agent

n-hexane is a colourless, highly volatile, liquid aliphatic hydrocarbon with a distinctive smell.

Main occupational uses and sources of exposure:

Essentially used as a solvent (especially in glue).

Toxic effects

1. Local effects

□ Irritant effects

n-hexane causes irritation of the skin, eyes and respiratory tract.

See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

2. Systemic effects

□ Narcotic syndrome

Headache, vertigo, nausea, drowsiness, weakness, confusion, loss of consciousness, sometimes coma.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- anamnesis and study of exposure conditions providing evidence of acute n-hexane intoxication by inhalation or skin contact;
- and, if available:
 - biological monitoring
 - workplace air monitoring:
guide values:
atmospheric concentration $> 3.5\text{g/m}^3$ (1000 ppm).

Minimum duration of exposure: From a few minutes to a few hours, depending on the intensity of exposure.

Maximum latent period: 24 hours.

□ Sensorimotor polyneuropathy

Signs and symptoms

Clinical picture showing distal sensorimotor polyneuropathy, predominant in the lower limbs: distal paraesthesia, various sensory anomalies (touch, vibration, etc.), cramp-like pains; muscle weakness, paresis of the limbs (predominant in the lower limbs), paralysis, muscle atrophy, quadriplegia, paralysis of the respiratory muscles.

Electrophysiological examination shows axonal disorders.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- anamnesis and study of exposure conditions providing evidence of prolonged/repeated exposure to n-hexane. Assessment must also take account of skin absorption;
- and, if available:
 - biological monitoring:
 - guide values:
 - urine: 2-hexanol, 2,5-hexanedione (>5 mg/g creatinine at end of shift)
(2,5-hexanedione is also a metabolite of methyl-n-butylketone)
 - blood: n-hexane (> 150 µg/L during exposure)
 - exhaled air: n-hexane (> 40 ppm during exposure)
 - workplace air monitoring:
 - guide values:
 - atmospheric concentration: > 176 mg/m³ (50 ppm).

These concepts need to be reassessed if there is a possibility of potentiation by other organic solvents of the ketone type (especially methyl-n-butylketone).

Minimum duration of exposure: One month.

Maximum latent period: Six months.

☐ Chronic toxic encephalopathy

See Annex I entry nr. 135 on *Encephalopathies due to organic solvents which do not come under other headings*.

n-heptane

Definition of causal agent

N-heptane ($\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$) (synonyms: methyl hexane, dipropyl methane, hexyl methane, n-heptyl hydride) is a colourless, highly inflammable liquid which is fairly insoluble in water but readily soluble in alcohol, petrol and chloroform.

Main occupational uses and sources of exposure:

It is a constituent in various special benzines and fuels (up to 40 %). It is mainly used in the rubber industry (for tyre manufacture).

Pure n-heptane (> 90 %) is only used for laboratory analysis.

Toxic effects

1. Local effects

☐ Irritant effects

Liquid n-heptane is irritant to the skin and mucous membranes.

See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

2. Systemic effects

☐ Narcotic syndrome

Headaches, dizziness, nausea, drowsiness, weakness, confusion, unconsciousness, possibly coma.

Exposure criteria:

Minimal intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- anamnesis and analysis of the working conditions showing evidence of an acute exposure to n-heptane (take into account possibility of skin absorption),
- and, if available:

- workplace air monitoring: guide values:

Atmospheric concentration well above 2000 mg/m³ (900 ppm); at 5000 ppm, light central nervous system symptoms occur after 4 to 7 minutes.

Minimum duration of exposure: From a few minutes to a few hours depending on the intensity of exposure.

Maximum latent period: 24 hours.

Annex 117

Halogenated derivatives of the aliphatic or alicyclic hydrocarbons

In this class of hydrocarbons one hydrogen has been replaced by halogen fluorine (F), chlorine (Cl), bromine (Br), or iodine (I)]

[Examples: trichloroethylene, tetrachloroethylene, methylene chloride, carbon tetrachloride, chloroform,]

The following items are covered under this entry:

- methylene chloride
- trichloroethylene
- tetrachloroethylene
- vinylchloride monomer
- methylbromide

Methylene chloride

Definition of causal agent

Methylene chloride CH_2Cl_2 (dichloromethane or methylene dichloride) is a colourless, volatile, water-soluble liquid. It has a sweetish odour detectable by most individuals above 200 to 300 ppm, although adaptation to the odour can occur. At 2300 ppm the odour is strong and intensely irritating.

Methylene chloride is metabolized in part to carbon monoxide. In presence of fire, methylene chloride may result in phosgene production.

The toxicity of methylene chloride is related to the toxicity of the other similar solvents and of carbon monoxide.

Main occupational uses and sources of exposure:

Degreasing agent used as paint and varnish remover; propellant for aerosol sprays; solvent for plastic and blowing agent for foams.

Toxic effects

1. Local effects

□ Irritant effects

Methylene chloride is irritant to the skin, eyes and respiratory tract (pulmonary oedema, coma). See document on occupationally caused irritation of the skin and mucous membranes.

2. Systemic effects

Acute

☐ Narcotic syndrome

Headache, nausea, vertigo, drowsiness, weakness, confusion, loss of consciousness, sometimes coma.

Possibility of cardiovascular and neurological sequelae, the intensity of which depends on the severity of the exposure.

Exposure criteria:

Minimal intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

— anamnesis and analysis of the working conditions showing significant exposure to methylene chloride,

— and, if available:

- biological monitoring:
exposure confirmed by measurement of dichloromethane in blood and carboxyhaemoglobinaemia
guide values:
an increase of 4 % or more in carboxyhaemoglobin (in non-smokers) within an hour of exposure, or a similar increase of carbon monoxide in exhaled breath within two hours of exposure.
- workplace air monitoring: guide values:
at exposures to 2 300 ppm over 5 minutes or for longer exposures above 300 ppm, dizziness results.

Minimum duration of exposure: A few minutes to a few hours depending on the intensity of the exposure.

Maximum latent period: The first symptoms should occur during the exposure and at the latest within 24 hours.

No evidence of adverse effects on workers' health has been found following exposures at concentrations of about 350 mg/m³ (100 ppm) for several years.

Chronic

☐ Chronic toxic encephalopathy

Similarly to other organic solvents, methylene chloride can cause, in repeated, prolonged exposures, chronic toxic encephalopathy (See Annex I entry nr. 135 on ***Encephalopathies due to organic solvents which do not come under other headings***).

☐ Exacerbation of ischaemic heart disease

Prolonged exposure which gives rise to levels of carboxyhaemoglobinaemia in excess of 10% can exacerbate a pre-existing ischaemic heart disease.

Due to the multicausality of the occurrence of these pathologies, particularly tobacco smoking, the recognition of the occupational origin must be individually evaluated by experts.

To be attributable to the exposure to methylene chloride, the cardiovascular sequelae should occur not later than one month following the acute exposure.

□ Cancer

Inhalation exposure to methylene chloride is associated with development of cancer in mice, but not in rats and hamsters. It is well known that the mouse model may not be adequate to point out a carcinogenic risk to humans, due to significant differences in methylene chloride metabolism. Therefore, the results of the studies conducted in mice are not relevant to humans.

Trichloroethylene

Definition of causal agent

Trichloroethylene ($\text{CHCl}=\text{CCl}_2$) (synonyms: trichloroethene, chlorylene, TRI) is a non-inflammable fluid with a chloroform-like odour. It is not readily soluble in water but soluble in organic solvents. Vapour/air mixtures are explosive. Decomposition occurs on exposure to heat, with formation of dichloro-acetylene, hydrochloric acid fumes, carbon monoxide and phosgene (see the documents concerning these substances).

The principal metabolites of trichloroethylene are trichloroethanol and trichloroacetic acid.

Main occupational uses and sources of exposure:

Trichloroethylene is used as a solvent and extracting agent and as an insecticide. It is also a component of certain stain removers.

Toxic effects

1. Local effects

□ Irritant effects

Trichloroethylene can cause irritation of the skin and mucous membranes.

See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

2. Systemic effects

Acute

□ Narcotic syndromes

Headache, dizziness, nausea, drowsiness, weakness, confusion, loss of consciousness, possibly leading to coma.

NB: In patients undergoing treatment, trichloroethylene can also cause cardiac arrhythmia as a result of depression of the threshold of sensitivity to catecholamines.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- anamnesis and study of working conditions providing evidence of acute exposure to trichloroethylene,
- and, if available:
 - Biological monitoring

-
- trichloroethanol in blood > 5 mg/L (end of shift sample)
 - trichloroacetic acid in urine > 100 mg/L
 - Workplace air monitoring
 - 108 mg/m³ (20 ppm): perceptible odour,
 - 594 mg/m³ (110 ppm): increase in reaction time may occur,
 - 6,9 g/m³ (1 280 ppm): state of prenarco-sis after six minutes,
 - 13,5 g/m³ (2 500 ppm): rapid full narco-sis.

Minimum duration of exposure: From a few minutes to a few hours, depending on intensity of exposure.

Maximum latent period: 24 hours.

Chronic

□ Chronic toxic encephalopathy

Similarly to other organic solvents, trichloroethylene can cause, in repeated, prolonged exposures, chronic toxic encephalopathy (See Annex I entry nr. 135 on *Encephalopathies due to organic solvents which do not come under other headings*).

□ Damage to cranial nerves

Hypoaesthesia, paraesthesia of the trigeminal nerve.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- anamnesis and study of working conditions providing evidence of prolonged or repeated exposure to trichloroethylene (taking account of the possibility of cutaneous absorption),
- and, if available:
 - biological monitoring:
 - guide values:
 - trichloroethanol in blood: > 5 mg/L
 - trichloroacetic acid in urine: > 100 mg/L
 - workplace air monitoring:
 - guide value:
 - atmospheric concentration well above 270 mg/m³ (50 ppm).

Minimum duration of exposure:

Chronic toxic encephalopathy:	10 years.
Damage to trigeminal nerve:	Several years.

Maximum latent period:

Chronic toxic encephalopathy:	The first signs of nervous system disturbance should occur in the year following cessation of exposure.
Damage to the trigeminal nerve:	Immediate.

□ Cancer

A wide debate is at present running in the scientific community, with a wide range of opinions about classification, but available data support the characterization of trichloroethylene as a human carcinogen (renal cancer). Nevertheless, the onset of this neoplasm is confined to few cases characterized by very high exposures in the past, especially peak exposures.

A practical threshold was found in rats at 250 ppm.

It is not possible, at the current status of knowledge, to define criteria for diagnosis of occupational cancer due to trichloroethylene. Cases of renal cancer occurring in very heavily exposed workers should be considered as possible occupational diseases.

Tetrachloroethylene

Definition of causal agent

Tetrachloroethylene (CCl₂=CCl₂) (synonyms: tetrachlorethene, perchloroethylene) is a colourless, volatile, flammable solvent with a smell similar to the ether's one. When heated, it breaks down with the production of carbon monoxide, phosgene and hydrochloric acid fumes. 80 to 90% of the absorbed dose is excreted unchanged with exhaled air. A small amount (< 3%) is biotransformed in trichloroacetic acid.

Tetrachloroethylene has a prolonged biological half life because of accumulation in body fat.

Main occupational uses and sources of exposure:

This compound is widely used for dry cleaning, textile treatments and metal degreasing.

Toxic effects

1. Local effects

☐ Irritant effects

Tetrachloroethylene can cause irritation of the skin and mucous membranes.

See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

2. Systemic effects

Acute

☐ Narcotic syndromes

Headache, dizziness, nausea, drowsiness, weakness, confusion, loss of consciousness, possibly leading to coma.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- anamnesis and study of working conditions providing evidence of acute exposure to tetrachloroethylene, f
- and, if available:
 - biological monitoring
Tetrachloroethylene in blood > 1 mg/L (prior to the next shift sample)
 - workplace air monitoring

Guide values:

680 mg/m³ (100 ppm): slight smell; dizziness; headache after several hours of exposure.

34 g/m³ (5000 ppm): strong smell; symptoms after few minutes of exposure.

Minimum duration of exposure: From a few minutes to a few hours, depending on intensity of exposure.

Maximum latent period: 24 hours.

Chronic

□ Chronic toxic encephalopathy

Similarly to other organic solvents, trichloroethylene can cause, in repeated, prolonged exposures, chronic toxic encephalopathy (See Annex I entry nr. 135 on *Encephalopathies due to organic solvents which do not come under other headings*).

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

— anamnesis and study of working conditions providing evidence of prolonged or repeated exposure (taking account of the possibility of cutaneous absorption),
— and, if available:

- biological monitoring: blood tetrachloroethylene concentration.
- workplace air monitoring:
guide value:
atmospheric concentration well above 345 mg/m³ (50 ppm).

Minimum duration of exposure: 10 years.

Maximum latent period: Chronic toxic encephalopathy: The first signs of nervous system disorder should appear no later than one year after the end of the exposure.

□ Cancer

Tetrachloroethylene has induced liver cancer in mice and renal tubular tumours in male rats. Some studies suggest that it might cause cancer in humans, but the evidence is inconclusive. Interpretation is hampered by concomitant exposure to other solvents and limited by lack of control for lifetime related factors.

Vinyl chloride monomer

Definition of causal agent

At normal temperature and pressure, vinyl chloride is a gaseous monomer.

Main occupational uses and sources of exposure:

Mainly used in the production of polyvinyl chloride.

Toxic effects

□ Irritant effects

Vinyl chloride monomer may be irritant to the skin (irritant dermatitis), the eyes (keratoconjunctivitis) and the upper respiratory tract.

See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

□ Narcotic syndrome

Headache, dizziness, nausea, somnolence, weakness, confusion, unconsciousness, may lead to coma.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- anamnesis and study of working conditions showing evidence of intense exposure to vinyl chloride monomer at atmospheric concentration $> 2.08 \text{ g/m}^3$ (800 ppm)
- and, if available:
 - workplace air monitoring:
guide value: atmospheric concentration $> 2.08 \text{ g/m}^3$ (800 ppm).

Minimum duration of exposure: From a few minutes to a few hours, depending on intensity of exposure.

Maximum latent period: 24 hours.

□ Raynaud's phenomenon in the hands and feet

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- anamnesis and study of exposure conditions showing evidence of prolonged/repeated exposure to vinyl chloride monomer;
- and, if available:
 - workplace air monitoring:
guide value: atmospheric concentration $> 130 \text{ mg/m}^3$ (50 ppm).

Minimum duration of exposure: One year.

Maximum latency period: Three years.

□ Acro-osteolysis in the terminal phalanges of the hands and feet

May accompany angioneurotic disorders. Confirmed by X-ray (loss of structure from bones)

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

— anamnesis and study of exposure conditions showing evidence of prolonged/repeated exposure to vinyl chloride monomer;

— and, if available:

- workplace air monitoring:
guide value: atmospheric concentration > 130 mg/m³ (50 ppm).

Minimum duration of exposure: One year.

Maximum latent period: Three years.

□ Distal skin disorders

Scleroderma-like syndrome with smooth, shiny skin, possibly accompanied by general symptoms (arthralgia, myalgia).

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

— anamnesis and study of exposure conditions showing evidence of prolonged/repeated exposure to vinyl chloride monomer;

— and, if available:

- workplace air monitoring:
guide value: atmospheric concentration > 130 mg/m³ (50 ppm).

Minimum duration of exposure: One year.

Maximum latent period: Three years.

□ Liver fibrosis with portal hypertension

Portal hypertension syndrome.

Fibrosis confirmed by histology or indirectly by echography.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

— anamnesis and study of exposure conditions showing evidence of prolonged/repeated exposure to vinyl chloride monomer;

— and, if available:

- workplace air monitoring:

guide value: atmospheric concentration $> 130 \text{ mg/m}^3$ (50 ppm).

Minimum duration of exposure: Two years.

Maximum latent period: 30 years.

Minimum induction period: Five years.

□ Liver Tumours

Angiosarcoma and hepatocellular carcinoma of the liver.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- anamnesis and study of exposure conditions showing evidence of prolonged/repeated exposure to vinyl chloride monomer;
- and, if available:
 - workplace air monitoring:

SCOEL assessed the risk of hepatic angiosarcoma upon exposure for working life time and concluded for 3×10^{-4} for 1 ppm and 9×10^{-4} for 3 ppm.

Minimum duration of exposure: 10 years.

Minimum induction period: 10 years.

See also section on ***Occupational cancers*** in the **Preface**.

Methyl bromide

Definition of causal agent

At ambient temperature and pressure, methyl bromide is a colourless and normally odourless gas which is heavier than air. At high concentrations its smell resembles that of chlorine.

Main occupational uses and sources of exposure:

Used as insecticide and nematocide via fumigation (greenhouse, grain silos etc.), rodenticide, refrigerant, methylation agent in the chemical industry.

Toxic effects

1. Local effects

□ Irritant effects

Methyl bromide is highly irritating to the ocular and respiratory mucous membranes (pulmonary oedema may develop after a latency period of 6 to 24 or even 48 hours). It causes erythema, blisters and swellings.

As a liquid, methyl bromide is also highly irritant to the mucous membranes and causes severe skin burns.

See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

2. Systemic effects

□ Acute neurological syndrome

Signs and symptoms:

Headache, vertigo, sleepiness, blurred vision, nausea, vomiting, anorexia.

Dysarthria, ataxia, muscular incoordination, twitching, fasciculations, myoclonia, trembling, convulsions.

Healing may be very slow and there may be sequelae (motor impairment, cortical deafness, optic neuritis).

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- anamnesis and study of exposure conditions showing acute poisoning by methyl bromide via inhalation or skin contact;
- and, if available:
 - biological monitoring:
blood: bromide (qualitative dose);
 - workplace air monitoring

Minimum duration of exposure: From some minutes to some hours, depending on the intensity of exposure.

Maximum latent period: 24 hours.

□ Chronic toxic encephalopathy

Some studies are available suggesting the capacity of this compound to cause chronic toxic encephalopathy in repeated, prolonged exposures (See Annex I entry nr. 135 on ***Encephalopathies due to organic solvents which do not come under other headings***).

Due to its toxic acute properties, long term exposures are very unlikely.

Butyl, methyl and isopropyl alcohol

Definition of causal agent

The butyl, methyl and isopropyl alcohols are aliphatic hydrocarbons in which one hydrogen atom is replaced by a hydroxyl group.

Butyl alcohol (butanol) exists in four isomeric forms: 1-butanol, 2-butanol, isobutanol and tertiary butanol

Main occupational uses and sources of exposure:

The three alcohols are used as solvents and detergents in industry.

The uses of the isomers of butanol differ, as only 2-butanol may be used in perfumes and tertiary butanol as a hydrophilic agent. Methyl alcohol is widely used as a denaturing agent for ethanol, marketed for technical use. Isopropyl alcohol is used as a disinfectant

Toxic effects

1. Local effects

☐ Irritant effects:

These substances cause irritation to the skin, eyes and respiratory tract.

See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

Allergic contact dermatitis:

Isopropyl alcohol is a sensitizer and may cause allergic contact dermatitis.

See section on *Occupationally caused allergic contact dermatoses* in Annex I entry nr. 202.

Exposure criteria

Minimum intensity of exposure: Occupational exposure confirmed if possible assessed by:

- History and study of exposure providing evidence of skin contact or inhalation

Minimum duration of exposure: Irritation skin and mucous membranes: A few minutes to a few hours depending on the intensity of the exposure

- Allergic skin reaction: Normally several instances of exposures are required. In a sensitized person one period may be enough to cause the skin lesions

Maximum latent period

- Irritation skin and mucous membranes: The symptoms must appear during exposure or within 48 hours at the latest
- Allergic reaction: A few days

□ Systemic effects

- **Acute neurotoxic effects:** Acute neurotoxic effects like optic neuropathy and an extrapyramidal syndrome after methanol intoxication and acute encephalopathy after isopropylalcohol intoxication have only been described after ingestion. Under normal working conditions they are not expected to occur after inhalation.
- **Chronic toxic encephalopathy:** As a result of exposure to significant quantities over a long period chronic toxic encephalopathy may develop.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed by:

- History and analysis of the working conditions showing evidence of prolonged/repeated exposure to these substances taking into account the possibility of cutaneous absorption.
- And if available workplace air monitoring: guide values: methanol > 260 mg/m³ (SCOEL), butanol > 100 ppm (ACGIH), propanol > 200 ppm (ACGIH)

Minimum duration of exposure: 10 years, this could be less in case of exposure to particular high concentrations

Maximum latent period: Initial symptoms of mental impairment should be present within one year of cessation of exposure.

See Annex I entry nr. 135 on *Encephalopathies due to organic solvents which do not come under other headings.*

Ethylene glycol, diethylene glycol, 1,4-butanediol and the nitrated derivatives of the glycols and of glycerol

Definition of causal agent

Glycols are aliphatic hydrocarbons which possess two hydroxyl groups.

Ethylene glycol ($\text{HOCH}_2\text{-CH}_2\text{-OH}$) or ethanediol, diethylene glycol ($\text{HOCH}_2\text{-CH}_2$) and 1,4 butanediol ($\text{OH}(\text{CH}_2)_4\text{OH}$) are liquids with a fairly low vapour pressure.

Main occupational uses and sources of exposure:

Ethylene glycol and diethylene glycol are widely used in industry and have various applications. Ethylene glycol is often used in antifreeze or liquid coolants, while diethyleneglycol is often used for de-icing, in brake fluids, lubricants, mould-release agents and inks, as a textile softening agent, plasticizer. Glycols are used as an intermediate in chemical synthesis of some plastics and polyester fibres.

1,4 butanediol is used industrially as a solvent. Some butanediols are used in cosmetics.

Local toxic effects

□ Irritant effects

These substances may cause slight irritation of the skin and mucous membranes.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed by history and study of exposure conditions providing evidence of skin contact or inhalation.

Minimum duration of exposure: irritation of mucous membranes: seconds to minutes

Irritant dermatitis: several days

Maximum latent period: irritation of mucous membranes: The first manifestations should appear during exposure

Irritant dermatitis: The first manifestations should appear during exposure or within 48 hours at the latest

See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

□ Systemic effects

For ethylene glycol and diethylene glycol acute systemic toxicity has only been described after ingestion. Ingestion of 1 mg/kg body weight can lead to severe intoxication starting with central nervous depression, followed by metabolic acidosis and ultimately renal failure.

Under normal working conditions these glycols are unlikely to cause harmful effects. They have a low vapour pressure at room temperature. There is therefore a risk for inhalation only at high temperature or where aerosols are formed. The level of absorption through the skin is low.

**Methylether, ethyl ether,
Isopropyl ether, vinyl
ether,
dichloroisopropylether,
guaiacol, methyl ether
and ethyl ether of
ethylene glycol**

Definition of causal agents

With the exception of methyl ether all ethers are colourless, volatile liquids. They form explosive peroxides in air and/or daylight.

Main occupational uses and sources of exposure:

Ethers are used as organic solvents. Methyl ether, ethyl ether and vinyl ether are mainly used as anaesthetic agents. Methyl ether is also used as a refrigerant, an aerosol dispersant and a rocket propellant. Ethyl ether and dichloroisopropyl ether are industrial solvents for fats, oils, resins and waxes. Isopropyl ether is a commercial paint and varnish stripper, rubber adhesive, component of aircraft fuel, and is used to extract nicotine from tobacco. Guaiacol is used in printing inks and in surface coatings. It is also used as a therapeutic agent (expectorant).

Toxic effects

1. Local effects

Prolonged or repeated skin contact may result in irritant dermatitis. Dermatitis is less likely from guaiaicol and has not been reported for dichloroisopropyl ether.

High concentrations of ether may also cause irritation of the ocular mucous membranes and respiratory tract. Diethyl ether is less irritating to the eyes and throat than to the nose.

See section on ***Occupationally caused irritation of the skin and mucous membranes*** in Annex I entry nr. 202.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed by history and study of exposure conditions providing evidence of skin contact or inhalation.

Minimum duration of exposure: Mucous membranes: seconds to minutes
Irritant dermatitis: several days

Maximum latent period: Mucous membranes: The first manifestations should appear during exposure

Irritant dermatitis: The first manifestations should appear during exposure or within 48 hours at the latest.

2. Systemic effects

☐ Narcotic syndrome

Headache, vertigo, nausea, drowsiness, weakness, confusion, unconsciousness, possibly coma.

Toxic quantities of guaiacol may be absorbed through the skin and then causes muscular weakness, cardiovascular collapse and paralysis of vasomotor centres.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by history and study of working conditions showing intense exposure to the substances, taking into account the possibility of cutaneous absorption of guaiacol and dichloroisopropyl ether (as opposed to diethyl ether).

Minimum duration of exposure: From a few minutes to a few hours, depending on the intensity of exposure.

Maximum latent period: 24 hours.

☐ Chronic toxic encephalopathy

Chronic toxic encephalopathy can develop as a result of exposure to significant quantities over a long period.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed by:

- History and analysis of the working conditions showing evidence of prolonged/repeated exposure to these substances taking into account the possibility of cutaneous absorption.

Minimum duration of exposure: 10 years, this could be less in case of exposure to particular high concentrations

Maximum latent period: Initial symptoms of mental impairment should be present within one year of cessation of exposure.

See Annex I entry nr. 135 on *Encephalopathies due to organic solvents which do not come under other headings*.

NOTE: Some compounds of ether that are known to cause serious health effects in exposed workers have been included below even though they do not have a specific mention in Annex I.

Ethylene glycol monomethyl ether (2-methoxyethanol, EGME), ethylene glycol Monoethyl ether (2-ethoxyethanol, EGEE)

Definition of causal agents

Glycol ethers derive from the combination of a glycol and one or two alcohols. They are volatile liquids.

Main occupational uses and sources of exposure:

These compounds are used chiefly as solvents and co-solvents (lacquers, resins, pigments, etc.), in the micro-electronics industry (manufacture of semiconductors), as constituents of hydraulic fluids and in the manufacture of radiography film, cellophane and copper-laminate circuit boards.

Toxic effects

☐ Irritant effects

Prolonged or repeated skin contact may result in irritant dermatitis. Direct contact or exposure to the fumes at high concentrations can cause irritation of the conjunctivae and irritation of the respiratory tract.

Exposure criteria:

Minimum intensity of exposure

- Occupational exposure confirmed, if possible assessed by history and study of exposure conditions providing evidence of skin contact or inhalation.

Minimum duration of exposure:

Irritation of conjunctivae and the respiratory tract: seconds to minutes
Irritant dermatitis: several days

Maximum latent period:

Irritation of conjunctivae and the respiratory tract: The first manifestations should appear during exposure
Irritant dermatitis: The first manifestations should appear during exposure or within 48 hours at the latest

See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

☐ Systemic effects

Bone marrow depression

Prolonged exposure to ethylene glycol ethers may cause macrocytic anaemia and granulocytopenia.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed by:

- History and analysis of the working conditions showing evidence of prolonged/repeated exposure to these substances taking into account the possibility of cutaneous absorption.

-
- And if available workplace air monitoring

Minimum duration of exposure: A few weeks to a few months depending on the intensity of the exposure

Maximum latent period: Signs of haematological effects should be present within 1-2 months after cessation of exposure.

Chronic toxic encephalopathy

As a result of exposure to significant quantities over a long period chronic toxic encephalopathy may develop.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed by:

- History and analysis of the working conditions showing evidence of prolonged/repeated exposure to these substances taking into account the possibility of cutaneous absorption.
- And if available workplace air monitoring

Minimum duration of exposure: 10 years, but can be less in case of exposure to particular high concentrations

Maximum latent period: Initial symptoms of mental impairment should be present within one year of cessation of exposure.

See Annex I entry nr. 135 on *Encephalopathies due to organic solvents which do not come under other headings*.

Reproductive toxicity

Exposure to both EGME and EGEE may interrupt spermatogenesis and possibly also lead to reduced fertility in exposed women.

EGME and EGEE exposure have been associated with increased risk of miscarriage and particularly EGME has been associated with an increased risk of several types of congenital malformations.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed by:

- History and analysis of the working conditions showing evidence of prolonged/repeated exposure to these substances taking into account the possibility of cutaneous absorption.
- And, if available:
 - Workplace air monitoring

Minimum duration of exposure: Fertility: prolonged and repeated exposure

Congenital malformations: prolonged and repeated exposure during pregnancy

Maximum latent period: Fertility: A few months

Congenital malformations: nine months

Bis-chloromethyl ether (BCME) and chloromethyl-methyl ether (CMME)

Definition of causal agents

Main occupational uses and sources of exposure:

Bischloromethylether was used extensively in the past as a chemical intermediate in organic synthesis, in polymers and in textile production. At present, small amounts of the compound are used in the chemical industry, mainly as an intermediate in the production of ion-exchange resins, usually in sealed systems. A further use is as a laboratory reagent. It can also be spontaneously produced by the reaction of formaldehyde with hydrogen chloride. Chloromethyl-methyl ether is a colourless liquid with an irritating odour. It is used as a methylating agent.

Toxic effects

1. Local effects:

The vapours are strongly irritant to the eyes and the respiratory tract.

Skin contact may cause erythema and necrosis, eye contact may cause corneal necrosis.

Exposure criteria:

Exposure confirmed and, if possible, assessed, by:

- History and study of working conditions providing evidence of exposure;
- And, if available:
 - Workplace air monitoring

Minimum intensity of exposure: Threshold for irritation: 10 ppm.

The high exposures necessary to cause acute local effects are very unlikely because of an extremely suffocating odour, even in minimal concentrations, of these compounds.

Minimum duration of exposure: A few minutes to a few hours, depending on the intensity of exposure.

2. Systemic effect:

☐ Acute effects

Both compounds are acutely toxic by inhalation or ingestion, but, due to their suffocating odour at very low concentrations, human acute poisonings are not described in literature.

☐ Chronic effects

Exposure of workers to BCME and chloromethyl-methyl ether is associated with an increased risk of lung cancer. The most common tumours are small cell carcinomas. The risk increases with an increase of the levels of exposure, and reaches the highest levels in the most heavily exposed workers.

Lung cancer

Exposure criteria:

Occupational exposure confirmed and, if possible assessed, by:

- History and study of working conditions providing evidence of significant prolonged exposure;
- And, if available:
 - Workplace air monitoring

Workplace air monitoring:

Guide value: airborne concentrations > 0.001 ppm

Minimum duration of exposure: 5 years.

Induction Period: 10 years

Maximum latent period: Not known

**Acetone, chloroacetone,
bromoacetone,
hexafluoroacetone,
methyl ethyl ketone,
methyl n-butyl ketone,
methyl isobutyl ketone,
diacetone alcohol,
mesityl oxide, 2-
methylcyclohexanone**

Definition of causal agent

These aliphatic hydrocarbons are usually very volatile, flammable and infinitely soluble with water.

Main occupational uses and sources of exposure:

They are used as chemical feedstock, a formulating solvent for commercial products, and an industrial process solvent. They are used as a formulating solvent for a variety of paints, inks, resins, varnishes, lacquers, surface coatings, paint removers, and automotive care products. Like other organic solvents they are used in cleaning and degreasing.

Toxic effects

1. Acute effects:

☐ Irritant effects

These substances irritate the eyes, the skin and the respiratory tract. High exposures may lead to chemical pneumonitis.

See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

☐ Narcotic effects

Inhalation can cause central nervous system depression, nausea and vertigo. Exposure far above OEL may result in unconsciousness.

2. Chronic effects

☐ Sensorimotor polyneuropathy

MBK (Methyl Butyl Ketone) can cause polyneuropathy. The clinical picture and the histopathology is similar with that produced by n-hexane because they share the same toxic metabolite n-hexadione. Neuropathy generally appears within a year of first exposure, reaches its severity in weeks. Removal from exposure leads to recovery, which in most severe cases may not be complete. MEK (Methyl Ethyl Ketone) containing solvent mixtures are associated with polyneuropathy.

Use of MBK is very restricted.

☐ Chronic toxic encephalopathy

Chronic exposure to MEK containing solvent mixtures may increase the risk of toxic encephalopathy.

See Annex I entry nr. 135 on *Encephalopathies due to organic solvents which do not come under other headings*.

Organophosphorous esters

Definition of causal agent

Organophosphorous insecticides (OP) are derivative of esters, amides or thiols of phosphoric, phosphonic, phosphorothionic or phophonothioic acids. They act through an inhibition of acetylcholinesterase (AChE). This effect is not usually present in organophosphorous herbicides.

Main occupational uses and sources of exposure:

Use in agriculture and public health as insecticides and herbicides. Occupational exposure may occur also during the production and formulation of these compounds.

Toxic effects

1. Acute systemic effects

The time of onset and sequence of symptoms and signs are function of the type of OP compound, the entity of the absorbed dose and the absorption and metabolic pathways.

The clinical picture of acute organophosphorous insecticide poisoning is attributable to the inhibition of AChE activity in the nervous system and to the consequent acetylcholine accumulation in the nerve synapses and neuro muscle junctions (muscarinic and nicotinic systems).

Organophosphorous herbicides are not characterized by a significant acute toxicity.

Miscellaneous effects:

Profuse sweating, lacrimation, disturbed vision, muscular fasciculation, asthenia.

Effects on the digestive apparatus

Increases salivation, nausea, vomiting, diarrhoea, abdominal cramps.

Effect on the respiratory apparatus

Bronchial hypersecretion, tightness of chest, bronchioconstriction, dyspnoea, pulmonary oedema.

Effect on the cardiocirculatory system

Arrhythmia, hypotension, shock

Effect on the nervous system

Headache, dizziness, agitation, anxiety, mental confusion, tremors, convulsions, coma.

Exposure criteria:

Minimum Intensity of Exposure: Occupational Exposure confirmed, if possible assessed by:

-
- Anamnesis and study of working conditions showing a significant exposure. Also the possibility of skin absorption has to be taken into account.
 - Significant reduction of AchE activity (at least 30%, but usually 50% as compared with baseline levels).
 - When possible, it is recommended the determination of the compound or its metabolites in biological fluids.
 - Environmental monitoring

Minimum duration of exposure: from a few minutes to several hours, depending on the intensity of exposure and the compound cause of poisoning.

Maximum latent period: three days.

2. Delayed effects

Intermediate syndrome

Onset: from 1 to 4 days after exposure.

Duration: 5-18 days.

Symptoms and signs: onset of proximal muscle weakness immediately after the acute cholinergic crisis, which might evolve into respiratory failure.

Exposure criteria:

Minimum Intensity of Exposure: Evidence of a previous severe acute OP poisoning (see ***exposure criteria for acute effects***).

Maximum latent period: from 1 to 4 days after exposure.

Peripheral neuropathy

Certain OP compounds may cause a peripheral neuropathy, usually involving motor nerves of the lower limbs. Exceptions are possible.

Symptoms and signs: typical picture of the second motor neuron impairment. In some cases, after the recovery of the flaccid paralysis, a spastic paralysis appears, consequent to an impairment of the first motor nerve at the level of the spinal cord.

Exposure criteria:

Minimum Intensity of Exposure: Evidence of a previous severe acute OP poisoning (see “exposure criteria for acute effects”).

Maximum latent period: from 7 to 20-25 days after exposure and cholinergic crisis.

Neurobehavioral effects

Severe acute OP poisoning may lead to neurobehavioral changes with some features similar to those described in Annex I entry nr. 135 on ***Encephalopathies due to organic solvents which do not come under other headings***.

Exposure criteria:

Minimum Intensity of Exposure: Evidence of a previous severe acute OP poisoning (see “exposure criteria for acute effects”).

Maximum latent period: Unknown

NOTE: Information about Carbamates are included in entry 122 (Organophosphorous Esters) because, although they are not organophosphorous compounds, acute overexposures cause clinical effects very similar to those of organophosphorous poisoning.

Carbamates

Definition of causal agent

Carbamates are nitrogen substituted urethanes. The salts and esters of substituted carbamic acid are more stable than carbamic acid itself. This stability is at the basis for the synthesis of many derivatives that are used as pesticides. Carbamate pesticides can be subdivided into three main classes: the substituted methyl substituted insecticides, the aromatic hydrocarbons substituted herbicides and the benzimidazole substituted fungicides.

Main occupational uses and sources of exposure:

Use in agriculture and public health as insecticides, fungicides and herbicides. Occupational exposure may occur also during production and formulation of pesticides.

Toxic effects

1. Acute systemic effects

The clinical picture of acute carbamate poisoning is attributable to the inhibition of AChE (acetylcholinesterase) activity in the nervous system and to the consequent acetylcholine accumulation in the nerve synapses and neuro muscle junctions (muscarinic and nicotinic systems). Since, compared to Organophosphorous compounds, carbamates are weaker AChE inhibitors, the duration of AChE inhibition is shorter and the severity of the signs and symptoms of poisoning is usually lower.

Miscellaneous effects:

Profuse sweating, lacrimation, disturbed vision, muscular fasciculation, asthenia.

Effects on the digestive apparatus:

Increases salivation, nausea, vomiting, diarrhoea, abdominal cramps.

Effect on the respiratory apparatus:

Bronchial hypersecretion, tightness of chest, bronchioconstriction, dyspnoea, pulmonary oedema.

Effect on the cardiocirculatory system:

Arrhythmia, hypotension, shock

Effect on the nervous system

Headache, dizziness, agitation, anxiety, mental confusion, tremors, convulsions, coma.

Exposure criteria:

Minimum Intensity of Exposure: Occupational Exposure confirmed, if possible assessed by:

- History and study of working conditions showing a significant exposure. Also the possibility of skin absorption has to be taken into account.
- Significant reduction of AChE activity (at least 30%, but usually 50% as compared with baseline levels).
- When possible, the determination of the compound or its metabolites in biological fluids is recommended.

Environmental monitoring

Minimum duration of exposure: From a few minutes to several hours, depending on the intensity of exposure and the compound cause of poisoning.

Maximum latent period: 24 hours.

Organic Acids

Definition of causal agent

The term “Organic Acids” or “Carboxylic Acids” defines chemical compounds characterized by the general formula R-COOH. As a general rule, these molecules are polar and, similarly to alcohols, can create hydrogen bonds with several other similar molecules. Based on their hydrogen content, these compounds can be divided in the subgroups of saturated and unsaturated organic acids. Moreover, based on the characteristics of the molecules, they can be further subdivided in aliphatic and aromatic compounds.

Saturated as well as unsaturated compounds can be used in a variety of applications, mainly in the production of synthetic fibres, resins, plastics, dyestuffs, or as intermediates or solvents in cosmetic or food applications. Some specific uses are described as follows:

Aliphatic organic acids

Formic acid: reducing agent for wool, dyeing and decalcifying, tanning, depilation and treatment of hides, latex coagulation, regeneration of old rubber, electroplating, animal food additive, food preservative and flavour adjuvant, brewing antiseptic, glue in aircraft industry.

Acetic acid: synthetic fibres production, cellulose and acetate, acetate rayon, plastics, printing, food preserving, pharmaceuticals, and photographs.

Unsaturated carboxylic acids: in polymeric materials, as chemical preservatives, as soap and food component.

Oxalic acid: textile finishing, stripping, cleaning, calico printing, dying paint, varnish, rust removal, dye manufacturing, paper, ceramic, photography and rubber industry.

Unsaturated polycarboxylic acids: resin manufacture, edible preservatives, mordant in dyeing.

It is important to underline that most of these compounds are normal constituents of human metabolism.

Aromatic organic acids

This group is very large and includes either nitro or halogen derivatives, and their aromatic esters. These compounds are addressed in the chapter “halogenated derivatives of aromatic hydrocarbons”. Aromatic organic acids are used for the synthesis of dyes, elastomers, medicine, pesticides and several plastic materials.

Local effects

Exposure to organic acids (either aliphatic or aromatic) can cause irritation of the eyes, skin and mucous membranes. Formic, acetic, oxalic, maleic, and malonic acids are irritant also in aqueous solution.

Minimum intensity of exposure: The irritation capacity depends on the strength of the single acid, its water solubility and its capacity of penetrating the intact skin and mucous membranes. It is inversely related to the concentration of the solution.

Exposure criteria:

Occupational exposure confirmed and, if possible, assessed, by history and study of working conditions showing evidence of exposure.

Workplace air monitoring: depending on the compound.

Guide value: atmospheric concentration exceeding STELs, with a particular attention for very high concentrations.

Minimum duration of exposure: a few minutes

Induction period: not applicable. Usually effects are observed after no more than a few hours from exposure/contact.

See section on ***Occupationally caused irritation of the skin and mucous membranes*** in Annex I entry nr. 202.

Allergic effects

Some organic acids may cause, rarely, sensitization. The most known sensitising compound of this group is formic acid: the risk of sensitization is higher in subjects exposed to formaldehyde.

Possible sensitizing agents are also malonic, acrylic, methacrylic and maleic acids.

Eyes and upper respiratory tract are usually involved, but also contact dermatitis has been reported.

Exposure criteria:

At least one previous episode of exposure. This criterion might not apply to subjects previously sensitized to formaldehyde and exposed to formic acid.

See:

- Annex I entry nr. 304.06 on ***Allergic asthmas caused by the inhalation of substances consistently recognised as causing allergies and inherent to the type of work,***
- Annex I entry nr. 304.07 on ***Allergic rhinitis caused by the inhalation of substances consistently recognised as causing allergies and inherent to the type of the work*** and
- section on ***Occupationally caused allergic contact dermatoses*** in Annex I entry nr. 202.

Table***Some common carboxylic acids and their synonyms***

Common name	Synonym/s	Systematic name	Formula
Formic	Formylic Hydrogen carboxylic	Methanoic	HCOOH
Acetic	Ethylic Methanecarboxylic	Ethanoic	CH ₃ COOH
Propionic	Methylacetic Ethanecarboxylic	Propanoic	CH ₃ CH ₂ COOH
Butyric	Ethylacetic 1-propanedicarboxylic	Butanoic	CH ₃ (CH ₂) ₂ COOH
Oxalic	Etanedionic	Ethanedioic	HOOC-COOH
Malonic	Carboxyacetic Dicarboxymethane	Propanedioic	HOOCCH ₂ -COOH
Acrylic	Acroleic Vinylformic	2-propenoic	CH ₂ CH-COOH
Crotonic	3-methylacrylic	(<i>trans</i>)-2-Butenoic	CH ₃ (CH) ₂ -COOH
Methacrylic	2-methylene-propionic	2-methyl-1-propionic	CH ₂ C(CH ₃)S-COOH
Maleic	<i>Cis</i> -1,2-ethylene- dicarboxylic	(<i>cis</i>)-2-Butenedioic	HOOC-(CH) ₂ -COOH
Fumaric	<i>Trans</i> -1,2-ethylene- dicarboxylic	(<i>trans</i>)-2-Butenedioic	HOOC-(CH) ₂ -COOH
□-naphthoic	□-naphthalene- carboxylic	1-Naphthoic	1-C ₁₂ H ₁₁ -COOH
□-naphthoic	p-naphthalene- carboxylic	2-Naphthoic	2-C ₁₂ H ₁₁ -COOH
Benzoic P- <i>tert</i> -benzoic	Benzenecarboxylic	Benzoic 2- <i>tert</i> -butylbenzoic	C ₆ -H ₅ -COOH p-(CH ₃) ₃ C-COOH

Formaldehyde

Definition of causal agent

Formaldehyde (methanal, formic aldehyde) is a colourless gas, flammable at ambient temperature. Workplace exposure is usually associated with the use of a 30 to 50% (by weight) of an aqueous solution called “formalin”. It is also a product of normal body metabolism.

Main occupational uses and sources of exposure:

Exposure to formaldehyde occurs during its production: the synthesis of formol-based plastics; the manufacture of several chemical substances; any kind of activity where there is the need of doing disinfection, including embalming; in the textile industry (dressing of hides and fabrics). It is also released during the combustion of a number of organic materials (incinerators, car exhaust fumes, etc.), and from chipboard made using formaldehyde based resins.

Toxic effects

1. Local effects

☐ Irritant Effects

Formaldehyde is extremely irritant to the eyes, to the mucous membranes of the respiratory tract and to the skin. Intense exposure may cause pulmonary oedema. Because of its irritant effects, it is likely to aggravate any pre-existing asthma

Minimum intensity of exposure:

Guide values are:

Irritation of the eyes: 0.1 ppm = 0.12 mg/m³

Irritation of the respiratory tract: 0.5 ppm = 0.6 mg/m³

See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

☐ Allergic Effects

Formaldehyde is a well known skin sensitizer but the likelihood of respiratory sensitisation is uncertain.

See Annex I entry nr. 304.06 on *Allergic asthmas caused by the inhalation of substances consistently recognised as causing allergies and inherent to the type of work* and section on *Occupationally caused allergic contact dermatoses* in Annex I entry nr. 202.

2. Systemic effects

❑ Nasopharyngeal cancer

The causal relationship between prolonged or repeated exposure to formaldehyde and nasopharyngeal cancer has been suggested by epidemiological studies, although the debate among experts still continues, particularly on dose/effect relationship. It appears that there is not a significant cancer risk for exposures at concentrations lower than those capable of causing inflammation and severe irritation and therefore cell proliferation.

Exposure criteria:

Occupational exposure confirmed and, if possible, assessed, by anamnesis and study of working conditions showing evidence of exposure.

Workplace air monitoring:

Guide value: atmospheric concentration exceeding peak values of 0.3 ppm, with a particular attention for very high concentrations, able to cause irritative effects.

Minimum duration of exposure: six months

Maximum latent period: does not apply

Induction period: More than 10 years

Due to the uncertainty still present, each case needs a separate evaluation.

❑ Other cancers

Leukaemia

The evidence of a causal relationship between leukaemia and occupational exposure to formaldehyde has been suggested by some epidemiological studies but is not firmly established.

Sinonasal cancer

There is only very limited epidemiological evidence that formaldehyde causes sinonasal cancer in humans.

Aliphatic nitrated derivatives

Definition of causal agent

The most important nitroalkanes ($C_nH_{2n+1}NO_2$) are nitromethane (nitrocarbol), nitroethane and 1-nitropropane/2-nitropropane. The boiling points are 101.2 °C /112-116 °C/132 °C/119-122 °C. These substances are colourless, oily liquids with a fruity odour (nitroethane). Vapour/air mixtures can be explosive.

Main occupational uses and sources of exposure:

Nitromethane is used as a solvent and as an intermediate in organic synthesis. It is used in the manufacture of pharmaceuticals, pesticides, explosives, fibres and coatings; It is a component of some fuels, too. Nitromethane is added in small amounts to many halogenated solvents and aerosol propellants as a stabilizer. Nitroethane is used as a solvent, as fuel additive and in the organic synthesis. Occupational exposure to 2-nitropropane occurs primarily in its production and use as a solvent in inks, adhesives, paints and coatings. The exposure route is by inhalation and by skin (nitromethane, 2-nitropropane especially).

Toxic effects

1. Local effects

☐ Irritant effects

These substances are dermal irritants; they irritate the eyes and the respiratory tract. See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

2. Systemic effects

Acute

Drowsiness, headache, nausea, unconsciousness, cough and vomiting are described after inhalation. Nitroethane shows effects on the blood with formation of methaemoglobin resulting in cyanosis. Effects may be delayed.

Exposure criteria:

Minimum intensity of exposure: occupational exposure confirmed, if possible assessed, by:

Anamnesis and study of working conditions providing evidence of particularly intense exposure to these substances, especially by skin contact.

Minimum duration of exposure: Brief.

Maximum latent period: 24 hours

Chronic

See Annex I entry nr. 135 on ***Encephalopathies due to organic solvents which do not come under other headings.***

Chronic exposure may lead to liver injury. There is inadequate evidence in humans for the carcinogenicity of 2-nitropropane.

Exposure criteria:

Occupational exposure confirmed, if possible assessed, by:

History and study of working conditions providing evidence of particularly intense exposure to these substances, especially prolonged or repeated skin contact.

Minimum duration of exposure: unknown

Maximum latent period: unknown

Benzene or counterparts thereof (the counterparts of benzene are defined by the formula: C_nH_{2n-6})

Definition of causal agent

Benzene is a volatile, colourless, liquid, aromatic hydrocarbon whose vapours are heavier than air, with a boiling-point of 80°C.

Main occupational uses and sources of exposure:

In the past, benzene was widely used as a solvent (in glues, paints, varnishes, lacquers, scouring of metal parts, for dry cleaning and in printing inks); present in amounts of 20% or more in solvent-mixtures in the 50s and 60s; and up to 5% in the 70s. Currently, such uses are strictly regulated (mostly present in solvent mixtures in concentrations of < 0.1 %). Nevertheless the worldwide production of benzene is still growing (Western Europe 10 million tonnes in 2004). It is still present in car fuel (1 to 2% in petrol). It is used in the synthesis of a variety of chemical products (styrene, cumene, cyclohexane, nitrobenzene, chlorobenzene, phenol). Exposure is also possible during the production of benzene via coal tar distillation or from petroleum or when cleaning tanks in which benzene has been stored. It is also a natural part of crude oil and cigarette smoke. Benzene is absorbed by the skin at a rate of 1 mg/cm²/h.

Toxic effects

1. Local effects

☐ Irritant effects

Benzene is an irritant to the skin, eyes and respiratory tract.

See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

2. Systemic effects

☐ Narcotic effects

Headaches, dizziness, nausea, drowsiness, confusion, unconsciousness, possibly coma.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- History and study of working conditions showing evidence of acute benzene poisoning;
- and, if available: workplace air monitoring; biological monitoring.

Guide values:

Concentration	time	clinical effects
25 ppm	8 h	no acute clinical symptoms
50-150 ppm	5 h	headache, lassitude, weakness
500 ppm	1 h	vertigo, drowsiness, nausea
7500 ppm	½ h	dangerous to life

Minimum duration of exposure: From a few minutes to a few hours, depending on the intensity of exposure.

Maximum latent period: 24 hours.

□ Non-carcinogenic haematological effects

Hypoplasia: thrombocytopenia and/or leucopenia, and/or anaemia

Hyperplasia: thrombocytosis, and/or leucocytosis, and/or erythrocytosis

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by: History and study of working conditions providing evidence of exposure to benzene; and, if available:

Biological monitoring

- blood: benzene
- urine (end of shift sample): t,t-muconic acid, S-phenylmercapturic acid

Workplace air monitoring

Any benzene values found in blood, urine or in terms of the atmospheric concentration require judgment as it should be noted that it is problematic to give a value for the atmospheric concentration and nearly impossible to establish a limit for benzene in blood or the metabolites.

In any event, exposure levels well above current standards and indicating poor control of exposure in the workplace, are therefore likely to have a role in causing ill-health (See section on ***Use of Airborne Occupational Exposure Limits*** in the ***Preface***).

Minimum duration of exposure: A few days are sufficient to cause depression of the bone marrow when exposure takes place at high atmospheric concentrations (160 mg/m³) (> 50 ppm). One month for other haematological effects.

Maximum latent period:

- One year for medullary hyperplasia.
- One month for medullary depression.

Leukaemia

The most common form is acute myeloblastic leukaemia. The relationship between exposure to benzene and development of various other forms of leukaemia or non Hodgkin lymphomas continues to be investigated (See section on ***Occupational cancers*** in the ***Preface***).

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:
History and study of working conditions providing evidence of excessive exposure to benzene (both by inhalation and skin absorption); and, if available:

Biological monitoring

- blood: benzene > 5 µg/l;
- urine (end of shift sample) t,t-muconic acid > 2 mg/l, S-phenylmercapturic acid >45 µg/g creatinine.

Workplace air monitoring

- Guide values (for previous exposures): atmospheric concentration > 1 ppm:

Minimum duration of exposure: Six months unless there are antecedents of medullary aplasia.

Maximum latent period: Does not apply.

Induction period: Five years.

☐ Effects on reproduction

Benzene is mutagenic to germ cells. See document on reproductive risks from occupational exposures.

Counterparts of benzene

Definition of causal agent

The most important counterparts of benzene are toluene, xylene and ethylbenzene. Toluene (methylbenzene) boils at 110.6 °C, it is volatile and easily flammable at ambient temperature and pressure. The technical product may contain small amounts of benzene, in the past up to 25%. Xylene (dimethylbenzene) exists in three isomeric forms: ortho, meta and para (boiling point 144.4, 139.1, 138.3° C). Technical grade xylene contains a mixture of these isomers and also some ethylbenzene (boiling point 136.2° C). All these counterparts of benzene are colourless liquids with an aromatic, sweet gasoline-like odour.

Main occupational uses and sources of exposure:

Toluene is mainly used in the production of benzoic acid, benzaldehyde, explosives and many other organic compounds; as a solvent for paints, lacquers, adhesives, etc; petrol additive; extraction agent.

Xylene is widely used as a solvent and thinner for paints and varnishes, often in combination with other organic compounds and as a solvent in glues and printing inks.

Ethylbenzene is used for the production of styrene, as solvent in paints and lacquers and in the rubber and chemical manufacturing industries. It is found in crude oils and combustion products.

Toluene; xylene and ethylbenzene are all absorbable through the skin.

Toxic effects

1. Local effects

☐ Irritant effects

All these products may irritate the skin, eyes, and respiratory tract, especially ethylbenzene. See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

2. Systemic effects

Acute

Headache, dizziness, nausea, drowsiness, weakness, confusion, unconsciousness and possibly coma, memory loss, nausea, hearing and colour vision loss. Liver damage at high solvent levels may occur.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- History and study of working conditions providing evidence of acute exposure, and if available:
- Biological monitoring
- Toluene: toluene in blood, o-cresol in urine;
- Xylene: xylene in blood, methylhippuric acid in urine;
- Ethylbenzene: 2-, and 4-ethylphenol or mandelic acid plus phenylglyoxylic acid.
- Workplace air monitoring

Guide values

toluene

2.5 ppm		odour threshold
100 ppm	8 h	no symptoms, very mild headache possible
200 ppm	8 h	mild irritant effects
400 ppm	8 h	irritation, incoordination
800 ppm	3 h	pronounced nausea
4000 ppm	1 h	narcosis

xylene

1 ppm		odour threshold
100 ppm	4 h	no effect on reaction time
200 ppm	4 h	irritant effects, prolonged reaction time, impairment of vestibular and visual function
300 ppm	2 h	performance decrement (decrements in psychometric tests such as memory span and choice reaction time)
700 ppm	1 h	dizziness

Minimum duration of exposure: From a few minutes to a few hours, depending on the intensity of exposure.

Maximum latent period: 24 hours.

3. Chronic effects

- See Annex I entry nr. 135 on *Encephalopathies due to organic solvents which do not come under other headings*.
- High chronic toluene exposure may induce liver enlargement.
- There is inadequate evidence in humans for the carcinogenicity of ethylbenzene.
- Toluene in air concentrations about 100 ppm is mutagenic to germ cells.

Naphthalene or naphthalene counterparts (the counterpart of naphthalene is defined by the formula C_nH_{2n-12})

Definition of causal agent

Naphthalene (synonyms: naphthalin, naphthene, tar camphor, white tar) is a white or colourless polycyclic aromatic hydrocarbon of crystalline structure. It volatilizes and sublimates at room temperature with a characteristic moth ball or strong coal tar odour (melting point 80,5 °C, boiling point 218° C). Explosive vapour may be formed above 80° C. Naphthalene and its derivatives (1-, 2-methylnaphthalene) are by-products of industrial coke and gas production, alkyl-naphthalenes are in the fraction with a distillation point between 204° C and 288° C.

Main occupational uses and sources of exposure:

Naphthalene is used in the chemical industry as the starting product in the synthesis of a number of products such as wood preservatives. Relevant workplaces and work processes are coking plants, creosote impregnation, distillation of coal tar, and the manufacture of refractories, graphite electrodes, aluminium and moth balls. Exposure can occur in the dye industry. Naphthalene has been used as lavatory deodorant discs, as intestinal antiseptic, vermicide and in the treatment of pediculosis and scabies. Exposure routes are inhalation and skin contact.

Toxic effects

1. Local effects

☐ Irritant effects

These products irritate the skin, eyes and respiratory tract. In some cases, contact with the eyes can lead to punctiform keratitis and, in particularly serious cases, corneal ulcerations. The irritant effect of alkyl-naphthalenes varies: some substances in the naphthalene family have marked effects, whereas others such as methylnaphthalene have lesser irritant effects.

See section on ***Occupationally caused irritation of the skin and mucous membranes*** in Annex I entry nr. 202.

2. Systemic effects

☐ Acute

On inhalation naphthalene causes headache, confusion, excitement, dizziness, nausea, vomiting, sweating, trembling and, in severe cases, convulsions. In some cases there may be dysuria, haematuria and haemolytic anaemia, particularly in subjects with a congenital glucose-6-phosphate dehydrogenase deficiency. Renal insufficiency and hepatic necrosis may follow.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:
History and study of working conditions providing evidence of particularly intense exposure to naphthalene,
and, if available, workplace air monitoring

Guide value: Well above 10 ppm

Minimum duration of exposure: A few minutes to a few hours, depending on level of exposure.

Maximum latent period: 15 days

☐ Chronic

Chloracne (Small, pale yellow cysts and comedones) occurs from exposure to chloronaphthalenes. In very severe cases, inflammatory lesions occur with larger cysts, abscesses, follicular hyperkeratosis. The main sites affected are the face (nose generally excluded), neck, shoulders, chest, back, and scrotum. This condition is extremely persistent and may last for decades, even after exposure has ceased.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:
History and study of working conditions providing evidence of prolonged/repeated exposure to chloronaphthalenes (usually penta- and hexachloronaphthalene derivatives). Skin contact is most often the cause of this condition, but inhalation and ingestion may also be responsible.

Minimum duration of exposure: A few weeks to a few months depending on level of exposure.

Maximum latent period: Six months.

Cataracts may follow chronic exposure. There is inadequate evidence in humans for carcinogenicity of naphthalene.

Vinylbenzene and divinylbenzene

Definition of causal agent

Vinylbenzene (styrene) is a colourless to yellow, oily liquid with a boiling point of 145° C with a sweet, floral odour at low concentrations and sharp penetrating, disagreeable odour at high levels. Divinylbenzene (vinylstyrene) exists as a mixture of its ortho-, meta- and para-isomers. It is a clear, slightly amber, strongly aromatic smelling liquid with a boiling point of 195° C.

Main occupational uses and sources of exposure:

Occupational exposure to vinylbenzene occurs during synthesis and manufacture of polymers (polystyrene), copolymers (styrene-butadiene latex preparations, acrylonitrile-butadiene-styrene resins) and unsaturated polyester resins. It is also used as a solvent and as an additive in aircraft fuel.

Divinylbenzene is used in the synthesis and manufacture of resins, plastics, composites and latexes, too. It is used as a monomer in the manufacture of insecticides and as an ion-exchange resin in water purification and in dentistry.

The exposure route for both substances is by inhalation; divinylbenzene is also absorbed following skin contact.

Toxic effects

1. Local effects

☐ Irritant effects

Vinylbenzene and divinylbenzene cause irritation to the skin and mucous membranes (See section on '*Occupationally caused irritation of the skin and mucous membranes*' in Annex I entry nr. 202).

2.6 g/m³ (600 ppm): intense irritation

3.4 g/m³ (800 ppm): immediate acute symptoms

Guide value (vinylbenzene):

0,43 – 1,3 g/m³ (100 - 300 ppm): irritation of eyes, nose, and upper respiratory tract

2. Systemic effects

☐ Acute

Narcotic syndrome

Headache, lassitude, dizziness, nausea, drowsiness, weakness, unsteady gait, confusion, loss of consciousness and possibly coma.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- History and study of working conditions providing evidence of intense exposure (taking account of the possibility of cutaneous absorption);
- and if available:
 - Biological monitoring
Vinylbenzene in the blood
Vinylbenzene: mandelic and phenylglyoxylic acid in the urine,
 - Workplace air monitoring (vinylbenzene):

Guide value:

Atmospheric concentration well above 426 mg/m³ (100 ppm)

300 - 800 ppm: central nervous system depression

5000 ppm: immediately dangerous to life

Minimum duration of exposure: From a few minutes to a few hours, depending on intensity of exposure

Maximum latent period: 24 hours

3. Chronic effects

Chronic toxic encephalopathy (See Annex I entry nr. 135 on *Encephalopathies due to organic solvents which do not come under other headings*).

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

History and study of working conditions providing evidence of prolonged or repeated exposure (taking account of the possibility of cutaneous absorption);

□ Biological monitoring

Vinylbenzene: Mandelic and phenylglyoxylic acid in the urine (> 600 mg/g creatinine);

Workplace air monitoring (vinylbenzene):

Guide value: atmospheric concentration: well above 86 mg/m³ (20 ppm)

Minimum duration of exposure: See Annex I entry nr. 135 on *Encephalopathies due to organic solvents which do not come under other headings*.

Maximum latent period: See Annex I entry nr. 135 on *Encephalopathies due to organic solvents which do not come under other headings*.

Peripheral neuropathy and reversible impairment of colour discrimination (tritan type) have been described. There is some suggestion of an interaction between vinylbenzene, noise exposure and hearing loss. Hepatic function may be altered in some cases. Studies on carcinogenicity are inconclusive (possible occurrence of leukaemias and lymphatic tumours is debatable).

Halogenated derivatives of the aromatic hydrocarbons

Definition of causal agent

The benzene nucleus is the basic chemical entity of this group of substances which can be divided into three subgroups:

- (i) benzene derivatives in which one or more hydrogen atoms have been replaced by one or more halogen atoms.
Main substances: chlorinated benzene: mono-, di-, tri-, hexachlorobenzene; brominated benzene: monobromobenzene; chlorinated toluene: mono-, trichlorotoluene;
- (ii) biphenyls and polyphenyls in which one or more hydrogen atoms have been replaced by one or more halogen atoms;
Main substances: polychlorinated biphenyls (PCB), polybrominated biphenyls (PBB)
- (iii) Polynuclear compounds composed of two or more fused benzene rings in which one or more hydrogen atoms have been replaced by one or more halogen atoms.
Main substances: chlorinated naphthalene: hexachloronaphthalene.

Main occupational uses and sources of exposure:

- (i) Chloro-, bromobenzenes, chlorotoluene: mainly used as solvents, pesticides, herbicides, fungicides and chemical intermediates;
- (ii) Polychlorinated, polybrominated biphenyls: dielectric fluids in condensers and transformers, lubricant, plasticizers, synthetic rubber, fireproofing material
- (iii) Chloronaphthalenes: manufacture of electric condensers, insulation of electric cables and wires, additives for extreme pressure lubricants.

Toxic effects

Halogenated derivatives of benzene

1. Local effects

☐ Irritant effects

These substances can be irritant for the skin, eyes and respiratory tract. See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

2. Systemic effects

☐ Narcotic syndrome

Headache, vertigo, nausea, drowsiness, weakness, confusion, unconsciousness, possibly coma. There is inadequate evidence in humans for the carcinogenicity of 1,4-dichlorobenzene, alpha-chlorotoluene.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- History and study of working conditions providing evidence of an intense exposure to monochlorobenzene or monobromobenzene or alpha-chlorotoluene for example. The possibility of skin absorption should be considered.

Guide values

alpha-chlorotoluene

0,05 ppm		odour threshold
1 ppm	5 min	mildly irritant for eyes
2 ppm		headache, weakness, sleepiness
17 ppm	1 min	unbearable irritation of the respiratory tract

Minimum duration of exposure: A few minutes to a few hours depending on the intensity of exposure.

Maximum latent period: 24 hours.

Halogenated derivatives of biphenyls (for example PCB)

1. Local effects

☐ Irritant effects

These substances can be irritant for the skin. See section on **Occupationally caused irritation of the skin and mucous membranes** in Annex I entry nr. 202.

2. Systemic effects

☐ Chloracne

Small straw-coloured cysts and comedones.

More severe cases: inflammatory lesions with larger cysts, abscesses, follicular hyperkeratosis.

The lesions typically involve the face (nose generally spared), then the neck, shoulders, chest, back and scrotum.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by: history and study of the working conditions showing evidence of acute or repeated/prolonged exposure to these substances; generally occurs after skin contact but also inhalation and ingestion.

Minimum duration of exposure: A few weeks to a few months depending on the intensity of exposure.

Maximum latent period: Six months.

☐ *Other adverse effects*

Generally reversible functional impairment of the liver, rarely more severe disturbances. Other impairments as lipidosis, endocrinological alterations, for instance in thyroid metabolism, immunological abnormalities and in single cases also obstructive airway disease are discussed. There is inadequate evidence in humans for the carcinogenicity of PCB.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by: anamnesis and study of the working conditions showing evidence of repeated/prolonged exposure to PCB, PBB (the possibility of skin absorption should be taken into account), and, if available:

- biological monitoring:
PCB in plasma (especially congeners 28, 52, 101, 138, 153, 180)

Minimum duration of exposure: Six weeks

Maximum latent period: Six months.

Halogenated derivatives of naphthalene

1. Local effects

☐ *Irritant effects*

These substances can be irritant for the skin, eyes and respiratory tract. See section on ***Occupationally caused irritation of the skin and mucous membranes*** in Annex I entry nr. 202.

2. Systemic effects

☐ *Toxic hepatitis*

Liver impairment ranging from functional and reversible disorders to acute liver atrophy.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by: history and study of the working conditions showing evidence of repeated/prolonged exposure to hexachloronaphthalene (the possibility of skin absorption should be taken into account).

Minimum duration of exposure: A few months.

Maximum latent period: Six months.

☐ *Chloracne*

Small straw-coloured cysts and comedones.

More severe cases: inflammatory lesions with larger cysts, abscesses, follicular hyperkeratosis.

The lesions typically involve the face (nose generally spared), then the neck, shoulders, chest, back and scrotum.

The disease is extremely persistent and in some cases may last for decades after cessation of exposure.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by: history and study of the working conditions showing evidence of acute or repeated/ prolonged exposure to hexachloronaphthalene. Generally occurs after skin contact but also inhalation and ingestion.

Minimum duration of exposure: A few weeks to a few months depending on the intensity of exposure.

Maximum latent period: Six months.

Phenols or counterparts or halogenated derivatives thereof

Definition of causal agent

Phenols are aromatic alcohols consisting of a hydroxyl group directly attached to an aryl ring. The most important phenols are phenol (hydroxybenzene), catechol (1,2-dihydroxybenzene) and cresols (ortho, meta, para-methylphenol). Major compounds of the halogenated derivatives are the chlorophenols as 2,5-dichlorophenol, 2,4,6-trichlorophenol and, especially, pentachlorophenol.

Phenol is a white crystalline solid which turn pink or red on exposure to air and light (melting point 43° C). In water it is entirely soluble. Phenol has a characteristic acrid odour. Catechol is a white to tan solid with a melting point about 105° C. Cresols consist either of a white crystalline solid or a yellowish liquid (melting points between 11° C and 35 °C) with a phenol-like odour. Chlorophenols are solids at room temperature, except for 2-monochlorophenol, which is a liquid. Technical grade chlorophenol products are a heterogeneous mixture of chlorophenols. They often include as microcontaminants polychlorinated organics as dibenzodioxins, dibenzofuranes or biphenyls. Pentachlorophenol (PCP) is a solid, odourless substance consisting of needle-like crystals. It acts by decoupling reactions in the oxidative phosphorylation process, which explains its systemic effects.

Main occupational uses and sources of exposure:

Phenol is used for the production of phenolic resins, bisphenol A, caprolactam, chlorophenols and several alkylphenols and xlenols. Phenol has been used as disinfectant and antiseptic. Catechol exposure exists in the production of insecticides, perfumes, drugs, in metal plating and in coal processing. Cresols are used as disinfectants, preservatives, and chemical intermediate, partially as solvent (o-cresol) and in the dye industry (p-cresol), too. Chlorophenols are used in the lumber industry, pesticide manufacture and application; worth mentioning is the use of treated wood for construction, railroad ties or telephone poles. The exposure route of all these organics is by inhalation and through the skin.

Toxic effects

1. Local effects

☐ Irritant effects

All these products are strong dermal irritants, they irritate the eyes. Local skin effects range from painless blanching or erythema to corrosion and deep necrosis. Inhalative exposure results in irritations of the respiratory system. See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

2. Systemic effects

□ Acute

Phenols are rapidly absorbed by the skin, which may lead to systematic poisoning:

Target organs are central nervous system, kidneys, liver. Symptoms: cardiac dysrhythmias, renal failure, neurological effects as convulsions, coma, death. Especially pentachlorophenol can cause hyperthermic syndrome: Excessive sweating, rapid weight loss and dehydration in severe cases: loss of consciousness, convulsions, death by heart failure, respiratory arrest, pulmonary oedema.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

History and study of working conditions providing evidence of particularly intense exposure to these substances, especially by skin contact, and, if available, workplace air monitoring, better biological monitoring.

Guide values:

Pentachlorophenol:

Painful irritation of the nasal mucous membranes at 1 mg/m³; workers accustomed to exposure may be able to tolerate up to 2.4 mg/m³.

Signs of systemic poisoning at 3 to 10 mg PCP/L urine or 40 to 80 mg/L blood. Fatal intoxications: 28 to 520 mg/L urine, 46 to 173 mg/L blood.

Minimum duration of exposure: A few minutes to a few hours, depending on level of exposure.

Maximum latent period: Hours to a few days

□ Chronic

Chronic exposure may provoke chloracne: Small, pale yellow cysts and comedones; in severe cases: inflammatory lesions with larger cysts, abscesses, follicular hyperkeratosis. Main sites: face (nose generally excluded), less frequently neck, shoulders, chest, back, and scrotum. This condition is extremely persistent and may last for decades, even after exposure has ceased. Other non-carcinogenic hazards are not really available, but symptoms of liver toxicity may be present (Chlorophenols). There is inadequate evidence in humans for the carcinogenicity of phenols or counterparts or halogenated derivatives thereof.

Exposure criteria:

Occupational exposure confirmed, if possible assessed, by:

History and study of working conditions providing evidence of particularly intense exposure to these substances, especially prolonged or repeated skin contact, and, if available, biological monitoring.

Guide values:

Phenol: Well above 200 mg total phenol/L urine

Pentachlorophenol: Well above 0.3 mg/L urine; well above 1 mg/L blood

Minimum duration of exposure: A few weeks to a few months depending on the intensity of exposure.

Maximum latent period: Six months.

Naphthols or counterparts or halogenated derivatives thereof

Definition of causal agent

Naphthols (hydroxynaphthalenes) are derivatives of naphthalene. The most important are the isomers α -naphthol (naphthalen-1-ol) and β -naphthol (naphthalen-2-ol).

α -naphthol forms colourless, sublimable crystals with phenolic odour, which darken by light (melting point 96 °C). β -naphthol is crystalline (melting point 122.5° C) with a white to yellowish-white colour and slight phenolic odour. Halogenated derivatives are chloro- and bromonaphthols.

Main occupational uses and sources of exposure:

Naphthols are used as intermediates for organic synthesis; manufacture of dye stuffs, rubber and others. In the past β -naphthol has been used as an antiseptic.

Toxic effects

The naphthols are considered to be more toxic than naphthalene, β -naphthol being slightly less toxic than the α -naphthol. Naphthol may be absorbed through the skin.

1. Local effects

☐ Irritant effects

Naphthols are dermal irritants, they irritate the eyes. See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

2. Systemic effects

☐ Acute

Headache, nausea, vomiting, abdominal pain, injury of liver and kidney and symptoms of central nervous system (unconsciousness, convulsion) are described after oral ingestion. Occupational poisoning has occurred after inhalation of β -naphthol dust. In children treatments with ointments containing 2 % β -naphthol caused fatalities.

Exposure criteria:

Minimum intensity of exposure: occupational exposure confirmed, if possible assessed, by:

History and study of working conditions providing evidence of particularly intense exposure to these substances, especially by skin contact.

Minimum duration of exposure: Unknown

Maximum latent period: Unknown

☐ Chronic

Chronic inhalation exposure or prolonged skin contact may lead to slight or moderate effects on organs such as the liver and kidneys. Injury to the cornea and lens of the eyes has been described.

Exposure criteria:

Occupational exposure confirmed, if possible assessed, by:

History and study of working conditions providing evidence of particularly intense exposure to these substances, especially prolonged or repeated skin contact.

Minimum duration of exposure: Unknown

Maximum latent period: Unknown

Halogenated derivatives of alkylaryl oxides and halogenated derivatives of alkylaryl sulphonates

Definition of causal agent

Alkylaryloxides: halogenated derivatives of alkylaryl(R-O-Ar) oxides or halogenated ethers of alkyl and aryl. The most important group are the halogenated derivatives of methylphenylether: 2-chloromethylphenylether, 2,4-dichloromethylphenylether, tri-, tetra-, pentachloromethylphenylether; brominated, iodized, fluorinated derivatives of methylphenylether

Alkylarylsulphonates: the basic compound is benzenesulphonic acid with an alkyl group attached to the other end of the benzene ring. With metal hydroxides their corresponding metal salts are synthesized. Further halogenation produces the halogenated derivatives. Examples: chlorinated polypropylene benzene sulphonate, chlorinated hexane benzene sulphonate.

Main occupational uses and sources of exposure:

Alkylaryl oxides: use limited to synthesis in organic chemistry. The most used substance is 2-chloroanisole which is a methoxyphenyl agent.

Alkylaryl sulphonates: some sulphonates are important household items and some are used medically as bactericides and antiseptics, as such, or as part of mixtures.

Toxic effects

There are no available data on human toxicity implicating alkylaryloxides. However alkylarylsulphonates are known to cause adverse health effects, as discussed below.

Local effects

☐ Irritant effects

The halogenated derivatives of alkylarylsulphonates can induce mucous membrane irritation, and in some cases defatting of the skin after repeating exposure leading to irritant dermatitis.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed by history and study of exposure conditions providing evidence of skin contact or inhalation.

Minimum duration of exposure: Mucous membrane irritation: seconds to minutes
Irritant Dermatitis: several days

Maximum latent period: Mucous membrane irritation: The first manifestations should appear during exposure.

Irritant Dermatitis: The first manifestations should appear during exposure or within 48 hours at the latest.

See section on ***Occupationally caused irritation of the skin and mucous membranes*** in Annex I entry nr. 202.

□ Allergic contact dermatitis

Some halogenated derivatives of alkylarylsulphonates can induce allergic contact dermatitis. See section on ***Occupationally caused allergic contact dermatoses*** in Annex I entry nr. 202.

Minimum intensity of exposure: Occupational exposure confirmed if possible assessed by history and study of exposure providing evidence of skin contact.

There is no dose/effect relationship for the onset of allergic contact dermatitis.

Minimum duration of exposure: Normally several instances of exposure are required to cause sensitisation. In a sensitized person a single subsequent exposure may be enough elicit skin effects.

Maximum latent period: Allergic reaction: A few days

Benzoquinones

Definition of causal agent

Benzoquinone is an oxidizing agent. It is a volatile, flammable solid that forms yellow crystals. The compound sublimates as soon as heat is applied, forming toxic gases. It has a penetrating odour resembling that of chlorine.

Main occupational uses and sources of exposure:

Benzoquinone is used chiefly as an intermediate in the manufacture of hydroquinone, dyes and fungicides. It is also used in photography, in tanning hides, in making gelatine insoluble and in strengthening animal fibres.

Its wide use is due to its ability to transform certain nitrogen compounds into a variety of coloured substances.

Note: *The following item is covered under this entry:*

- **Leucoderma**

Toxic effects

☐ Irritant effects

Irritates the respiratory and ocular mucous membranes (causing conjunctival irritation and, in some cases, oedema and severe corneal ulceration).

See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

☐ Ocular effects

Chronic exposure may cause gradual brownish discolouration of the conjunctiva and cornea confined to the palpebral fissure. Small opacities and structural corneal changes result in loss of visual acuity. The pigmentary changes are reversible, but the more slowly developing structural changes in the cornea may progress.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed by a history of occupational exposure and study of exposure conditions providing evidence of prolonged or repeated exposure to benzoquinone.

Minimum duration of exposure: Two years.

Maximum latent period: One year.

Leucoderma

Definition of causal agent

The agents involved mainly belong to the phenols and catechols group. Most are used as antioxidants in the chemical and photographic industries, or in cosmetics and pharmaceuticals. They are also used in adhesives and disinfectants.

The main causal agents are listed below.

Main occupational uses and sources of exposure:

Occupationally caused leucoderma (vitiligo, achromia) refers to depigmentation of the skin caused by occupational exposure to chemicals.

Diagnostic criteria

- Clinical: hypopigmented and depigmented patches appear at the site of skin contact. These are usually on the exposed areas of the hands and forearms, although covered areas may be affected in some cases.
Neither facial leucoderma nor depigmentation due to steroids, hydroxyquinoline sulphate or butyl hydroxyanisole are normally associated with occupational exposure. The depigmentations may be mottled and patchy or confluent and symmetrical. There may be some inflammation.
There is a tendency for spontaneous but slow repigmentation after discontinuation of exposure.
- History: occupational exposure to a substance known for its depigmenting properties.

Exposure criteria:

Intensity of exposure: Assessed via history.

Minimum duration of exposure: A few days. Leucoderma normally appears after direct and repeated skin contact, although similar effects have been reported following inhalation.

Maximum latent period: Several months.

Agents responsible for occupationally caused leucoderma (open, non-exhaustive list)

Phenols: p-tert-butyl phenol
 p-tert-amyl phenol
 o-phenyl phenol
 chloro-2 amino-4 phenol

Catechols: catechol (pyrocatechol)
 menthyl catechol (o-hydroxyanisole)
 4-isopropyl catechol

Hydroquinone, benzoquinone, monobenzone

Aromatic amines or aromatic hydrazines or halogenated, phenolic, nitrified, nitrated or sulfonated derivatives thereof

Definition of causal agent

Aromatic amines are chemical compounds derived from aromatic hydrocarbons by the replacement of at least one hydrogen atom by an amino group (-NH₂).

Most common compounds: aniline, aminophenol, 4-aminodiphenyl, 2-naphthylamine, toluidine, 4,4-diaminodiphenyl-methane (MDA), benzidine, phenylendiamine.

Main occupational uses and sources of exposure:

Synthesis of dyes and pigments; used as intermediates in the manufacture of isocyanates; accelerators and anti-oxidants in the rubber industry; pharmaceutical industry; production of herbicides. The production and use of the following aromatic amines have been banned in the EU, according to Council Directive 88/364/EEC: 2-naphthylamine, 4-aminobiphenyl, benzidine, 4-nitrodiphenyl and their salts.

Toxic effects

Most of the aromatic amines are able to penetrate the intact skin.

1. Local effects

☐ Irritant effects

Aromatic amines can irritate the skin, eyes and upper respiratory tract.

See section on ***Occupationally caused irritation of the skin and mucous membranes*** in Annex I entry nr. 202.

☐ Allergic effects

Some aromatic amines induce hypersensitivity in the skin and respiratory tract, *e. g.*: p- (m-) phenylenediamine, nitroanilines, 2-aminophenol.

2. Systemic effects

Acute

☐ Haematological disorders

Methaemoglobinaemia

At methaemoglobin levels > 10%, cyanosis occurs

At methaemoglobin levels > 20 to 25%, hypoxia occurs

At higher methaemoglobin levels: low blood pressure, headache, and nervous system dysfunction.

Haemolytic anaemia

Presence of HEINZ bodies in red blood cells.

Exposure criteria:

Minimum intensity of exposure:

Occupational exposure confirmed by:

- history and study of working conditions providing evidence of repeated acute or intense exposure to aromatic amines (taking into account the possibility of absorption via the skin)

Minimum duration of exposure: From a few minutes to a few hours depending on the intensity of exposure.

Maximum latent period: Several days.

□ Liver effects

Most occupational over-exposures with aromatic amines lead to transient liver function abnormalities. Disorders of the liver ranging from reversible functional abnormalities to severe atrophy. Jaundice occurred in cases of ingestion of MDA.

Chronic

□ Cancer of the bladder

Cancer of the bladder (and, to some extent, cancer of the efferent urinary passages) resulting from prolonged exposure to certain aromatic amines, especially benzidine, 2-naphthylamine, 4-aminodiphenyl, o-toluidine and others. To some extent the risk is dependent upon the individual speed of metabolic acetylation of these compounds; persons with a slower acetylation rate have a higher risk than those with faster acetylation.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed by:

- history and study of working conditions providing evidence of prolonged/repeated exposure to the above mentioned aromatic amines (taking into account the possibility of absorption via the skin)

Minimum duration of exposure: One year

Minimum induction period: 10 years

Maximum latent period: Not known

See section on ***Occupational cancers*** in the **Preface**.

Aliphatic amines and halogenated derivatives thereof

Definition of causal agent

Aliphatic amines are derivatives of ammonia in which one or more atoms are replaced by one, two or three alkyl or alkanol radicals. The more commonly used amines are gases or fairly volatile liquids.

For example: Monoamines I monomethylamine
 II dimethylamine, diethylamine
 III trimethylamine triethylamine
 Polyamines: diamine
 ethylenediamine
 tetramethylenediamine
 hexamethylenediamine
 Triamine
 diethylenetriamine
 Alkanolamine: ethanolamine
 triethanolamine
 dimethylethanolamine
 Halogenated derivatives: chloramine

Main occupational uses and sources of exposure:

Chemical intermediates in the synthesis of pharmaceutical products, pigments, ion exchange resins, emulsifiers and detergents used in the plastics industry (catalysers, hardeners) and textiles, leather, and photography industries. Several amines (ethanolamines) are used in lubricating oils, or as solvents. Some types of flux in welding rods contain aliphatic amines. Other uses are: Corrosion-inhibitor (triethylamine), vulcanization in rubber industries (dimethylamine), synthesis of EDTA, medicaments, pesticides (ethylenediamine), raw material for polyamid and polyurethane production (hexamethylenediamine). Used as a disinfectant (chloramine).

Toxic effects

Some aliphatic amines can easily penetrate the skin

1. Allergic

☐ Allergic contact dermatitis

The main allergenic aliphatic amines are: dimethylamine, ethylenediamine, tetramethylenediamine, hexamethylenediamine, chloramine.

See section on *Occupationally caused allergic contact dermatoses* in Annex I entry nr. 202.

□ Asthma

Main allergenic substances: dimethylethanolamine, ethylenediamine, diethylenediamine.

See Annex I entry nr. 304.06 on *Allergic asthmas caused by the inhalation of substances consistently recognised as causing allergies and inherent to the type of work*.

□ Allergic rhinitis and conjunctivitis

Main allergenic substances: as above.

See Annex I entry nr. 304.07 on *Allergic rhinitis caused by the inhalation of substances consistently recognised as causing allergies and inherent to the type of the work*.

2. Irritant and corrosive effects

Aliphatic amines are bases and form strongly alkaline solutions. They are (in gas, liquid or vapour form) highly irritant for the skin and mucous membranes, some causing local necrosis (monomethylamine, dimethylamine). Because of the high volatility some aliphatic amines cause local frostbite (monomethylamine).

See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

Corneal oedema

Aliphatic amines may cause corneal oedema with vesicles resulting in a visual impression of fog or 'halos' around lights. These ocular effects are transient.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed by history and clinical examination showing evidence of irritation to the eyes and exposure to aliphatic amines.

Minimum duration of exposure: Brief.

Maximum latent period: 48 hours.

3. Systemic effects

Some aliphatic amines may lead to disturbances of the central nervous system (ethylene-diamine) or have been described to cause increased muscle tone (2-(dimethylamino)ethanol).

Nitrated derivatives of aromatic hydrocarbons

Definition of causal agent

The term 'aromatic nitrocompounds' covers a group of compounds in which at least one hydrogen atom of the benzene ring has been replaced by a nitro-group (NO₂). Some of them, such as the nitrated derivatives of phenol, are considered in a separate section (See Annex I entry nr. 128.01 on *Phenols or counterparts or halogenated derivatives thereof*).

Only the other most widely used compounds are considered here.

Nitro-, dinitrobenzene: one/two hydrogen atoms of the benzene ring have been replaced by one/two nitro-groups.

Dinitrobenzene exists in three isomers: ortho-meta-, para-. Dinitro-, trinitrotoluene: two/three hydrogen atoms of the toluene ring have been replaced by two/three nitro-groups. The main constituents of industrial grade dinitrotoluene (DNT) are 2,4-DNT and 2,6-DNT.

Main occupational uses and sources of exposure:

They are used as solvents, in the production of dyes, pigments, explosives, cosmetics, pesticides, plastics and pharmaceuticals. They are also used in the chemical, textile and paper industries and in chemical laboratories.

Nitrobenzene: Used in the production of aniline; as a solvent for some paints; in the manufacture of chemical products; in shoes and floor polishes and in leather dressings.

Dinitrobenzene: Mainly used in the synthesis of dyestuffs, explosives and celluloid production.

Dinitrotoluene: Mainly used in the synthesis of organic compounds and dyes and in explosives production.

Trinitrotoluene: mainly used as an explosive.

4-Nitrodiphenyl: This compound has been banned from production and use in the European Union.

Toxic effects

Nitrobenzene

1. Local effects

☐ Irritant effects

Nitrobenzene can be irritant to the skin and mucous membranes.

See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

☐ Allergic contact dermatitis

Nitrobenzene is a rare cause of allergic dermatitis.

2. Systemic effects

Acute

☐ Haematological disorders

- **Methaemoglobinaemia**
cyanosis at methaemoglobin levels > 10%,
hypoxia at methaemoglobin levels > 20 to 25%,
at a later stage: hypotension, headache, nausea, impairment of mental ability , central nervous system impairment.
- **Haemolytic anaemia** presence of Heinz bodies in red cells.

Exposure criteria:

Minimum intensity of exposure:

occupational exposure confirmed by:

- history and study of working conditions showing evidence of acute or intense repeated exposure to this substance. The possibility of skin absorption should be taken into account.
- and, if available:
 - Biological Monitoring: dose-dependent levels of methaemoglobin
 - workplace air monitoring.

Minimum duration of exposure: A few minutes to a few hours depending on the intensity of exposure.

Maximum latent period: Four days.

Dinitrobenzene

1. Local effects

☐ Irritant effects

Dinitrobenzene can be irritant to the skin and respiratory tract.

See section on ***Occupationally caused irritation of the skin and mucous membranes*** in Annex I entry nr. 202.

2. Systemic effects

Acute

☐ Haematological disorders

- **Methaemoglobinemia**
Cyanosis at methaemoglobin levels > 10%,
Hypoxia at methaemoglobin levels > 20 to 25%,

at a later stage: hypotension, headache, nausea, impairment of mental ability, central nervous system impairment.

- **Haemolytic anaemia** presence of Heinz bodies in red cells.

Exposure criteria:

Minimum intensity of exposure:

occupational exposure confirmed, and if possible assessed, by:

- history and study of working conditions showing evidence of acute or intense repeated exposure to this substance. The possibility of skin absorption should be taken into account.
- and, if available:
 - biological monitoring: dose-dependent levels of methaemoglobin. .
 - workplace air monitoring.

Minimum duration of exposure: A few minutes to a few hours depending on the intensity of exposure.

Maximum latent period: Four days.

Dinitrotoluene

1. Local effects

□ Irritant effects

Local irritative effects are uncommon.

See section on ***Occupationally caused irritation of the skin and mucous membranes*** in Annex I entry nr. 202.

2. Systemic effects

Acute

□ Haematological disorders

- **Methaemoglobinemia**
Cyanosis at methaemoglobin levels > 10%,
Hypoxia at methaemoglobin levels > 20 to 25%,
at a later stage: hypotension, headache, nausea, impairment of mental ability, central nervous system impairment.

Exposure criteria:

Minimum intensity of exposure:

occupational exposure confirmed, and if possible assessed, by:

- history and study of the working conditions showing evidence of acute or intense repeated exposure to this substance. The possibility of skin absorption should be taken into account.
- and, if available:
 - biological monitoring: dose-dependent levels of methaemoglobin. .
 - workplace air monitoring.

Minimum duration of exposure: A few minutes to a few hours depending on the intensity of exposure.

Maximum latent period: Four days.

Trinitrotoluene (TNT)

1. Local effects

□ Irritant effects

Trinitrotoluene may be irritant to the mucous membranes: eyes, nose, throat.

Acute dermatitis is uncommon, however prolonged or repeated exposure may cause a dermatitis characterized by papular eruption, oedema and desquamation. Sometimes orange staining of the hands arms and face occurs.

See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

□ Allergic contact dermatitis

Trinitrotoluene is a rare cause of allergic contact dermatitis.

2. Systemic effects

Acute

□ Haematological disorders

- **Methaemoglobinemia**
Cyanosis at methaemoglobin levels > 10%,
Hypoxia at methaemoglobin levels > 20 to 25%,
at a later stage: hypotension, headache, nausea, impairment of mental ability, central nervous system impairment.

□ Acute hepatitis

Cases of jaundice have been reported in those exposed to large amounts of trinitrotoluene. Deaths from toxic hepatitis have occurred.

Exposure criteria:

Minimum intensity of exposure:

occupational exposure confirmed, and if possible assessed, by:

- History and study of working conditions showing evidence of acute or repeated exposure to TNT
The possibility of skin absorption should be taken into account
- and, if available:
 - workplace air monitoring.

Minimum duration of exposure: A few minutes to a few hours depending on the intensity of exposure.

Maximum latent period: Four days.

Acute hepatitis: seven days

Chronic

□ Aplastic anaemia

Aplastic anaemia with purpura have been reported in workers exposed to TNT in ammunition plants.

Exposure criteria:

Minimum intensity of exposure: occupational exposure confirmed, and if possible assessed, by:

- History and study of working conditions showing evidence of acute exposure to TNT. The possibility of skin absorption should be taken into account
- and, if available:
 - workplace air monitoring.

Minimum duration of exposure: A few months.

Maximum latent period: Six months.

4-Nitrodiphenyl

See Annex I entry nr. 129.01 on *Aromatic amines or aromatic hydrazines or halogenated, phenolic, nitrified, nitrated or sulfonated derivatives thereof.*

Nitrated derivatives of phenols or their counterparts

Definition of causal agent

These substances are dinitro-derivatives of phenol (dinitrophenol, dinitro orthocresol, dinoseb and their salts) and the halogenated derivatives of hydroxybenzonitrile (ioxynil, bromoxynil). All trigger oxidative phosphorylation reactions and this explains their systemic effects.

Main occupational uses and sources of exposure:
Mainly used as herbicides.

Toxic effects

1. Local effects

These substances irritate the skin and ocular and respiratory mucous membranes.

See section on ***Occupationally caused irritation of the skin and mucous membranes*** in Annex I entry nr. 202.

Absorption of these substances by any route results in yellow staining of various tissues e.g. skin, conjunctivae and sclerae.

2. Systemic effects

☐ Acute effect

Hyperthermia with profuse sweating, rapid weight loss.

☐ Subacute effects

Gastrointestinal symptoms:

Abdominal pains, vomiting, diarrhoea and in some cases toxic hepatitis.

Exposure criteria:

Minimum intensity of exposure: Severe occupational exposure confirmed, if possible assessed, by:

- History and study of working conditions showing significant exposure to these substances. The possibility of skin absorption should be taken into account.
- and if available
 - Biological monitoring: Identification of the substance or its metabolites in biological blood and urine.
 - Workplace air monitoring

Minimum duration of exposure: A few minutes to a few hours, depending on intensity of exposure.

Maximum latent period:

Acute effects Two days

Subacute effects: Seven days

Antimony and derivatives thereof

Definition of causal agent

Antimony is a silver-white, brittle metal with no significant use in its unalloyed state. Its inorganic and organic compounds include antimony triphosphite, antimony tri-pentasilfide, antimony trichloride, antimony potassium tartrate and sodium antimony dimercaptosuccinate.

Main occupational uses and sources of exposure:

Antimony extraction and refining; alloys (lead, copper, tin) especially in the production and disposal of lead acid storage batteries, solder, bearings, type metal, ammunition and cable sheathing. High-purity antimony is used as a dopant in semiconductors. Intermetallic compounds of antimony such as aluminum antimonide, gallium antimonide and indium antimonide are used for thermoelectric devices.

Antimony trioxide is used as a fire retardant for plastics, textiles, rubber, adhesives, pigments, and paper. Antimony is used in glass, ceramic and enamel industries, in rubber and plastic manufacture, as a paint pigment and in the making of fireworks and matches.

Toxic or irritant effects

☐ Irritant

- Antimony and its inorganic compounds are irritating to the skin, eyes and respiratory tract. Repeated contact may cause a papular or pustular skin rash in areas where sweating occurs.
- Intense exposure to vapours may induce perforation of the nasal septum or pulmonary oedema.
Repeated exposure to antimony oxides may cause orange staining of the teeth

Pneumoconiosis (stibiosis):

Chronic exposure to antimony trioxide may, rarely, induce a benign ('overload') pneumoconiosis which is usually asymptomatic. Fibrosis does not occur.

minimum intensity of exposure: unknown but well above 0.5mg/m³.

minimum duration of exposure: six months

maximum latent period: none

Stibine (antimony hydride)

Definition of causal agent

Stibine is a colourless gas that can be formed when nascent hydrogen comes into contact with metallic antimony, when some antimony compounds come into contact with acid or in the case of electrolytic processing, including battery charging.

Main occupational uses and sources of exposure:

Stibine is used as a dopant in the microelectronics industry and as a fumigating agent (mainly in the past). [A dopant is an agent added to a semiconductor lattice in low concentrations in order to alter the optical/electrical properties of the semiconductor.]

Toxic effects

1 Acute systemic effects

□ Haemolytic syndrome

Stibine causes a rapid and severe Coombs-negative haemolytic anaemia. Main symptoms of stibine poisoning are: headache, asthenia, dizziness, abdominal cramps, nausea and vomiting, cardiovascular symptoms, and, in the most severe cases, jaundice and acute renal failure due to acute tubular necrosis.

Respiratory irritation:

Stibine may cause severe respiratory effects.

Exposure criteria:

Minimum intensity of exposure: occupational exposure confirmed, if possible assessed, by:

- History and study of working conditions showing evidence of acute exposure to stibine, at levels exceeding the established limit values
- And, if available:
 - Workplace air monitoring

Minimum duration of exposure: a few minutes to a few hours, depending on intensity of exposure.

Maximum latent period: 48 hours

Nitric acid esters

Definition of causal agents

Compounds formed out of nitric acid and alcohols. The major representatives are nitric acid esters of polyalcohols (Nitro derivatives of glycols and glycerol) such as

- Nitroglycerin (glyceryl trinitrate), an oily, slightly yellow liquid, highly explosive substance, with percutaneous absorption.
- Nitroglycol (ethyleneglycol dinitrate), a clear colourless liquid with high percutaneous absorption, less explosive than nitroglycerin
- Propylene glycol dinitrate (PGND or 1,2-Propanediol dinitrate)

Main occupational uses and sources of exposure:

Used as explosive, pharmaceutical, marine engine fuel, occupational exposure can occur both in the production and handling of these products

Toxic effects

1. Acute and subacute effects

These agents are vasodilators and as such can affect the cardiovascular system, the blood and the nervous system.

Subacute exposure causes vasodilatation, tachycardia, and hypotension. This can be followed by bradycardia and collapse. Flushing of the face, headache, dizziness, restlessness, confusion, hallucination, syncope, convulsions and coma may occur. Other features are nausea, vomiting, diarrhoea, cyanosis, methaemoglobinaemia and respiratory failure. Fatal collapse may occur. Effects are enhanced by alcohol consumption.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed by

- history and evaluation of exposure conditions showing significant exposure by inhalation or skin contact
- and, if possible
 - by workplace air monitoring
 - biomonitoring (drug use of glyceryl trinitrate should be taken into consideration).

Minimum duration of exposure: Minutes to hours depending on the intensity of exposure

Maximum latent period before onset of disease: A few hours.

2. Chronic effects

Prolonged exposure results in the development of tolerance (acclimatisation, tachyphylaxis) to the cardiovascular effects. However, disruption of chronic exposure, even for a few days, may interrupt this acclimatisation and can result in malaise, weakness, vomiting, dizziness, headache, or impaired vision. Severe chest pains, palpitations, and even sudden death may also result. 'Monday morning' headaches or angina pectoris occur in workers on the first day back at work after a weekend break.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed (percutaneous, inhalation) by history, and if possible by

- workplace air monitoring : nitroglycerin >> 0.05 ppm (0.47 mg/m³), nitroglycol >> 0.05 ppm (0.32 mg/m³)
- biomonitoring at the end of working-day (>0.5 µg/l 1,2- or 1,3-glyceryl dinitrate in plasma/serum as a metabolite of nitroglycerin; >0.3 µg/l ethyleneglycol dinitrate in blood); drug use of glyceryl trinitrate should be taken into consideration.

Minimum duration of exposure: 5 – 10 years depending on the intensity of exposure

Maximum latent period before onset of disease: one week.

Vague gastrointestinal symptoms and Raynaud's phenomenon have been described but there is no good evidence on the causal relationship with exposure to these compounds.

Hydrogen Sulphide

Definition of causal agent

Hydrogen sulphide (H₂S) is produced in geological active areas or in the process of anaerobic decomposition of organic substances. It is a colourless, flammable gas with a pungent odour of rotten eggs. In high concentrations it can rapidly paralyse the sense of smell. It is heavier than air and displaces oxygen.

Main occupational uses and sources of exposure:

Geothermal and fossil fuel energy extraction, petrol industry, farming (stirring of manure, opening of vessels), sewage (sugar producing), sludge workers, fish processors, roofers (handling with heated tar and asphalt), viscose industry, pulp and paper manufacturing waste water canals, cemetery workers (tombs), knacker's yards.

Toxic effects

1. Acute and subacute effects

At low concentrations irritant effects predominate as airway irritation and stinging of eyes (keratoconjunctivitis, punctate corneal erosion). At high concentrations for prolonged periods, bronchopneumonia and pulmonary oedema may occur with signs of central nervous system disturbances: headache, vertigo, dizziness, nausea and vomiting.

High exposure leads to sudden unconsciousness and death by respiratory paralysis. Short inhalation periods may be sufficient depending on the level of exposure.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed by history and if possible, by workplace air monitoring:

Guide values:

- | | |
|--|-------------------------------------|
| • Odour threshold: | 0.01 mg/m ³ (0.8 ppm) |
| • Bronchial constriction in asthmatic individuals: | 2.8 mg/m ³ (2 ppm) |
| • Increased eye complaints: | 5.0 mg/m ³ (3.6 ppm) |
| • Fatigue, headache, dizziness: | 28 mg/m ³ (20 ppm) |
| • Olfactory paralysis: | > 140 mg/m ³ (> 100 ppm) |
| • Respiratory distress: | > 560 mg/m ³ (> 400 ppm) |
| • Death: | > 700 mg/m ³ (> 500 ppm) |

Minimum duration of exposure: A few seconds to a few hours, depending on the intensity of exposure

Maximum latent period: A few minutes

2. Chronic effects

Gastrointestinal and neurological effects have been described in case reports, but there is no good evidence for a causal relationship with H₂S exposure.

Encephalopathies due to organic solvents which do not come under other headings

Definition of causal agent

Encephalopathy can result from exposure to organic solvents and other agents in the workplace e.g. lead, mercury. Chronic Toxic Encephalopathy (CTE) caused by solvents is characterized by

- 1) impairment of memory and other cognitive functions (abstraction, thinking, planning, etc).
- 2) impaired emotional control and motivation, eg. emotional lability, irritability, initiative and energy

According to the WHO classification, three stages of increasing severity are considered:

Type 1: Organic affective syndrome. Clinical manifestations are depression, irritability, loss of interest in daily activities. .

Type 2: Mild chronic toxic encephalopathy. Fatigue, mood disturbances, memory complaints, attentional complaints. Impairment of psychomotor function (speed, attention, dexterity), short term memory and other neuropsychological impairment.

Type 3: Severe chronic toxic encephalopathy. Loss of intellectual ability of sufficient severity to interfere with social or occupational functioning. Impairment of several modalities including memory, abstract thinking and judgment. There are other disturbances of cortical function and changes in personality. Psychometric types of abnormality similar to mild CTE. More pronounced and pervasive functional deficits. Some neurophysiological and neuroradiological abnormalities.

Type 1 is reversible if exposure is discontinued. Type 2 is reversible in some cases but not in others. Type 3 cases are uncommon and poorly reversible, but non-progressive once exposure has ceased.

In this document a description is given of the diagnostic criteria of the pathological entity corresponding to a mild chronic toxic encephalopathy (WHO type II cases).

Main occupational uses and sources of exposure:

Occupational exposure to organic solvents can be seen in painting and coating, degreasing and industrial cleaning, dry cleaning, extraction, rubber and polymer manufacturing, eg polystyrene production. Organic solvents are also used in adhesives, pharmaceuticals and printing inks. Occupations at risk include: painters, printers, workers in the paint and ink manufacturing, polyester workers (laminators), users of adhesives, carpet layers, parquet fitters, degreasers, printers.

Diagnostic criteria

Signs and symptoms: the history must include abnormal subjective complaints concerning two or more of the following functional areas:

Impairment of memory, concentration, attention, intellectual activities, decreased initiative, loss of leisure-time interests, prolonged chronic fatigue, depressed mood, emotional lability and irritability.

□ Neuropsychological assessment

The neuropsychological test battery should include tests of verbal and visual memory, attention, psychomotor speed, visual analysis and construction and abstraction ability. Furthermore, the test battery should include tests that reflect primary intellectual ability: it should be evaluated from performance in these tests together with information from the history on education and other information on previous intellectual level of functioning.

The level of cooperation and effort should be evaluated clinically or by special tests.

Intellectual and cognitive impairment may be assumed if the performance on sensitive tests is generally lower than that of the lowest 5% for a normal population of similar age and intellect. Test performance should be abnormal in at least one test in each of two functional areas.

Neurological examination: usually normal. Mild signs of poor coordination and polyneuropathy may be present. Cerebral atrophy and Electroencephalographic (EEG) changes may be present in severe cases.

Differential diagnosis of Chronic Toxic Encephalopathy; consider other diseases as:

- Major depression
- Sleep disorders
- Neurodegenerative disorders: Alzheimer's disease, Parkinson's disease
- Neurovascular disorders
- Neoplasms: brain tumors, paraneoplastic symptoms
- Metabolic causes: avitaminosis, thyroid disorders
- Other toxic encephalopathies: alcohol, drugs, lead, mercury
- Traumatic brain disorders

The list is not exhaustive.

The diagnosis should be established as a result of examinations by a specialist in occupational medicine, a neurologist and a neuropsychologist in conjunction.

Exposure criteria:

Minimum intensity of exposure:

- Occupational history of significant exposure to organic solvents
- Notice should be taken of skin absorption and of the fact that often exposure to mixtures of solvents exist.
- If available data from:
 - biological monitoring
 - workplace air monitoring

Present information suggests that levels of exposure above those presented below, taking place over a period of 5-10 years are required to induce chronic encephalopathy. These concentrations refer to an eight-hour working day:

- Toluene 375 mg/m³ (100 ppm)
- Xylene 435 mg/m³ (100 ppm)
- Styrene 210 mg/m³ (50 ppm)
- Pentane 1500 mg/m³ (500 ppm)
- White spirit 600 mg/m³ (100 ppm)

This list is non-exhaustive and other solvents need to be considered.

Corresponding exposure to solvent mixtures can be derived by adding the exposures contributed by the individual solvents.

Minimum duration of exposure: Usually 10 years but can be less in case of exposure to particularly high concentrations.

Maximum latent period before onset of the disease: Initial symptoms of mental impairment usually manifest before cessation of exposure and a latent period is usually not applicable. The exact time of initial symptoms may be difficult to establish since they develop gradually. If a latent period longer than a few months develops, it suggests the presence of other causative factors.

Induction period: does not apply

Polyneuropathies due to organic solvents which do not come under other headings

Definition of causal agent

Two organic solvents recognised as causing polyneuropathy are: n-hexane and Methyl-n-butyl ketone (MnBK). A description of specific chemicals with adverse peripheral nervous effects is in the document on n-Hexane (Annex I entry nr. 116) and MnBK (Annex I entry nr. 121).

Main occupational uses and sources of exposure:

Organic solvents are used in cleaning and degreasing, as diluents of paint, printing ink, glue and varnish and as raw material in the plastic industry, and in the elution processes of food and drug industry and in laboratories. The use of n-Hexane and methyl n-butyl ketone has been restricted.

Definition

Polyneuropathies are functional disturbances or pathological changes in the peripheral nervous system. They may affect the motor, sensory or autonomic nervous systems separately or in conjunction. Anatomically, damage may be seen in small myelinated, small non-myelinated fibres or large myelinated fibres. Electrophysiologically, dysfunction of nerve fibres (axons) reduces action potentials and damage to the myelin sheaths slows nerve conductivity. The effects may be acute or chronic and recovery is variable.

Diagnostic criteria:

Polyneuropathies are common neurological disorders with diverse aetiologies. Thus, the differential diagnosis is crucial. The combination of neuropathic symptoms, signs, and electrodiagnostic findings provides the most accurate diagnosis of distal symmetrical polyneuropathy.

Solvent-induced polyneuropathies usually manifest as symmetrical sensory or sensory-motor lesions involving distal parts of the extremities, typically the lower limbs, and present with sensory symptoms. Symmetric, multifocal, pure motor or autonomic neuropathy is not typical. Polyneuropathies due to high exposure to n-hexane and methyl n-butyl ketone were acute and severe.

Exposure criteria:

See Annex I entry nr. 116 on *Aliphatic or alicyclic hydrocarbons derived from petroleum spirit or petrol*, including the section on **n-hexane**, and Annex I entry nr. 121 on *Acetone, chloroacetone, bromoacetone, hexafluoroacetone, methyl ethyl ketone, methyl n-butyl ketone, methyl isobutyl ketone, diacetone alcohol, mesityl oxide, 2-methylcyclohexanone*.

Skin diseases and skin cancers caused by soot, tar, bitumen, pitch, anthracene or compounds thereof, mineral and other oils, crude paraffin, carbazole or compounds thereof, by-products of the distillation of coal

Definition of causal agent

The incidence of skin cancer is increasing in the general population. This is probably due to increased exposure to the sun. Nevertheless, squamous cell carcinoma is also causally related to occupational exposure to fossil fuel derivatives containing polynuclear aromatics. In practical terms, workers are rarely exposed to only a single group of such compounds and virtually never to a single polynuclear aromatic compound. Thus the epidemiological and experimental evidence for a human carcinogenic effect varies from firm (soot, coal tar, coal tar pitch, certain kinds of mineral oils), excluding for example white mineral oils), through probable/possible (bitumen and bitumen-derived products, some single polynuclear aromatic compounds), to inadequate for the purpose of evaluation (many single polynuclear aromatic compounds). However, both anthracene and carbazole (among certain other polycyclic aromatic hydrocarbons, PAHs) are major components of the total amount of polynuclear aromatic compounds in the environment, with human exposure occurring primarily through smoking tobacco and inhaling polluted air. Paraffins are aliphatic hydrocarbons, and one of the main components of crude oil.

See also Annex I entry nr. 502.01 on *Cataracts caused by heat radiation* and Annex I entry nr. 502.02 on *Conjunctival ailments following exposure to ultraviolet radiation*.

Toxic effects

1. Local effects

☐ **Irritant effects**

Some of these substances can cause irritation of the skin.

See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

☐ **Allergic contact dermatitis**

These compounds are not usually considered as skin sensitizers, but there is a possibility of phototoxicity with certain PAH-mixtures such as coal tar pitch.

See section on *Occupationally caused allergic contact dermatoses* in Annex I entry nr. 202.

□ Acne

Indistinguishable clinically from the acne of teenage years. The lesions affect the exposed areas or where the oils can saturate clothing; generally the dorsal surfaces of the hands, extensor surfaces of the arms and the anterior surfaces of the thighs.

The condition is not as persistent as chloracne and cyst formation is not a feature.

Occupational exposure to oils can aggravate idiopathic acne or cause comedones, follicular plugging and even folliculitis.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- history and study of working conditions showing evidence of acute or repeated/prolonged exposure of skin to metal working fluids.

Minimum duration of exposure: A few weeks to a few months depending on the intensity of exposure.

Maximum latent period: Six months.

□ Cancer

Generally chronic dermatitis, acne, keratosis, papillomata precede malignancy with ulceration, local spread and, eventually, distant metastases.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- history and study of working conditions showing evidence of repeated/prolonged skin exposure to the abovementioned complex PAH-mixtures, which has been shown to cause skin cancers in humans.

Minimum duration of exposure: Six months.

Minimum induction period: Usually 20 years, but five years in some of the cases described (workers exposed to tar and sunshine).

Attention is drawn to the multicausality of this pathology.

See section on ***Occupational cancers*** in the **Preface**.

Occupational skin ailments caused by scientifically recognised allergy-provoking or irritative substances not included under other headings

Definition of causal agent

Occupational skin diseases are represented by allergic and irritant contact dermatitis and also contact urticaria.

Allergic contact dermatitis (ACD) results from a T-cell-mediated immune response against haptens applied onto the skin. ACD is a disease, presenting as a pruritic eczema, characterized by erythema and vesicles, which develop within 24-48 h at the site of hapten penetration in sensitized individuals.

Irritant contact dermatitis (ICD) may be acute and it is commonly the result of a single exposure to an irritant. Chronic irritant dermatitis usually develops as a result of cumulative exposure to multiple irritants, resulting in disruption of the skin barrier function.

Contact urticaria is type -1 allergic response and the reaction is immediate, occurring within about 15 minutes after contact with the relevant substance.

Main occupational uses and sources of exposure:

The main agents are listed in the annex I, but there are a lot of substances or their mixtures which should be included in it i.e.: glyceryl monothioglycolate and derivatives, balsam Peru and others fragrances, chlorhexidine, glutaraldehyde, mercaptobenzothiazole and derivatives, colophony, Cl+Me-isothiazolinone and derivatives, plant products, urea, melamine formaldehyde resins and many others.

Note: The following items are covered under this entry:

- Occupationally caused allergic contact dermatoses
- Occupationally caused irritation of the skin and mucous membranes

And

- Methyl acrylate
- Dithiocarbamates
- Methylmethacrylate

Diagnostic criteria

Symptoms:

Allergic contact dermatitis is usually confined to the area of skin that comes in contact with the allergen, typically hands or face. It may present with pruritus redness, vesicles, scaling fissuring or secondary excoriation. In some cases the area of lesions is much larger than the area of contact.

In irritant contact dermatitis the symptoms can take many forms: redness, itching, crusting, swelling, blistering, oozing, dryness, scaliness, thickening of the skin. Most attacks are slight and confined to the hands and forearms, but can affect any part of the body that comes in contact with an irritating substance.

Main symptoms of contact urticaria: red, itchy skin, inflamed skin, welts (in hives).

Anamnesis: The development of the skin lesions are in direct relationship to the work schedule. There is a recurrence of the disease on re-exposure to the same agent.

Immunological criteria: Allergic contact dermatitis is investigated by patch testing for all the suspected substances present at the workplace. The relevance of a positive reaction must be assessed.

There is no test for irritant contact dermatitis. The diagnosis is made by the history of exposure to known irritants and the exclusion of allergy on appropriate patch testing.

In cases of contact urticaria, prick tests and estimation of specific IgE antibodies in blood should be performed.

Exposure criteria

See below sections on:

Occupationally caused allergic contact dermatoses and on

Occupationally caused irritation of the skin and mucous membranes.

Occupationally caused allergic contact dermatoses

Definition of causal agent

The most common presentation for occupationally caused dermatoses are those of allergic contact dermatitis (synonym: allergic contact eczema), of contact urticaria and protein contact dermatitis.

Main causal agents are complex molecules with a molecular mass of less than 1000 Daltons, which are haptens or incomplete antigens, or proteins, which are complete antigens. Haptens are the most common cause of allergic contact dermatitis

A large number of substances may be responsible for occupationally caused allergic dermatoses. The main categories, with some examples are:

- I** Low molecular mass substances
Metals and/or their compounds (e.g. nickel and its compounds, hexavalent chromium compounds, water-soluble trivalent chromium compounds, cobalt compounds)
Rubber and plastic chemicals (e.g. accelerators: resins, hardeners)
Dyes and dye intermediates (e.g. paraphenylene-diamine)
- II** Macromolecules
Substances of animal or plant origin e.g. natural rubber latex
- III** Photo-allergens
Plants, fragrances

Diagnostic criteria

An allergic skin disease may be dependent on:

- personal factors, including genetic factors,
- exogenous factors: chemical structure of the sensitizing agent, its concentration, the type of diluting agent or dispersant used (these may act as irritants through lipolytic action, modifying the pH of the skin and the skin defence system),
- site and extent of contact
- climatic conditions: e.g. temperature, humidity, sunlight (ultraviolet radiation).

Sites of the lesions: linked with contact with the product in question. In some cases the area of lesions is larger than the area of contact.

History: occupational exposure to a substance known to trigger dermatoses. The development of the skin lesions are in direct relationship to the work schedule. There is recurrence of the disease on re-exposure to the same agent.

Immunological criteria

Patch tests should be carried out for all the suspected allergens present at the workplace. The interpretation of the results requires expertise in patch testing and dermatology. In cases of photo-sensitivity and contact urticaria, special test should be carried out (e.g. photo patch tests, prick test).

If positive, these tests together with appropriate sites of lesions and anamnesis provide adequate proof of the occupational origin of the disease, although such an origin cannot be wholly discounted if the tests are negative.

Exposure criteria

Minimum intensity of exposure: There is a dose/effect relationship in the onset of allergic contact dermatitis, but in individual cases it usually is not possible to determine it retrospectively. Usually the exposure is greater for sensitization than for elicitation.

Minimum duration of exposure: In exceptional cases, a single contact is sufficient to cause sensitization (with dinitrochlorobenzene, dinitrofluorobenzene and methacrylates). Normally, several instances of exposure are required over periods which vary enormously in length. The sensitization period is generally 10 to 15 days from the first occupational contact, but usually much longer. After this period, any further exposure causes the lesions to appear rapidly. If sensitization occurs prior to occupational exposure the minimum exposure period may be shorter.

Maximum latent period: A few days.

Occupationally caused irritation of the skin and mucous membranes

Definition of causal agent

Considered as causing irritation: non-corrosive substances and preparations which, through immediate, prolonged or repeated contact with the skin or mucous membranes, cause inflammation

Considered as corrosive: substances and preparations which, on contact with living tissues, cause severe damage.

A substance can cause irritation at low concentrations and be corrosive at higher concentrations.

Some physical agents are capable, in themselves, of producing an irritation reaction, such as, for example, dusts in contact with the mucous membranes of the eyes or respiratory tract or even by cutaneous friction.

Substances which meet the requirements to be classified according to the criteria in Annex IV of Council Directive 67/548/EEC as corrosives, irritants or sensitizers, may be identified by a risk phrase on the container as follows:

R 21: harmful to skin

R 34: causes burns,

R 35: causes severe burns,

R 36: causes irritation to the eyes,

R 37: causes irritation to the respiratory tract,

R 38: causes irritation to the skin,

R 41: risk of severe damage to the eyes.

R 43: may cause sensitization by skin contact.

Skin irritation

Diagnostic criteria:

Clinical effects: the symptoms range from erythema (simple irritation) to third-degree chemical burns (corrosion) and, in the case of repeated exposure, to contact dermatitis.

Many factors can contribute to the occurrence and severity of the lesion, such as the degree of water and lipid solubility and liposolubility of the substance, its concentration, the duration of exposure, interaction with other substances, individual factors (e.g. resistance, sweating or dryness of the skin), and physical factors (e.g. occlusion, friction, laceration of the skin and ambient temperature and humidity).

There is also the possibility of dermatitis caused by irritation due to particles carried in the ambient air.

Exposure to "strong irritants" and corrosive agents:

- local reversible inflammatory reaction immediately following a single application,

-
- in severe cases: caustic effect, chemical burns with necrosis and the possibility of sequelae (scarring).

For example: strong alkalis and acids.

Exposure to "relatively mild irritants":

These are substances which, under normal conditions of use, only cause irritation of superficial skin layers or substances causing defatting of the skin resulting in dermatitis after prolonged exposure.

The symptoms generally only appear after repeated or prolonged contact. Physical factors and multiple chemical exposure often play a role. For example: soaps and detergents.

Repeated long-term exposure:

Thickening and lichenification of the skin (with painful fissures) can occur after several days or weeks of continuous mild irritation, which can develop into chronic dermatitis.

Account should be taken of the possibility of splashes, and of immersion where occlusion increases the irritation (for instance: under rubber or plastic gloves or soaked clothes).

Exposure criteria:

Minimum intensity of exposure: Assessed by anamnesis revealing skin contact with a potentially irritating substance taking into account the process.

There is the possibility of the irritability of the skin persisting: a worker who has developed an irritation reaction to a product may, in some cases, develop greater susceptibility while, clinically, his skin appears to have recovered. The irritation reaction reappears far more rapidly if there is subsequent contact with the substance responsible.

Minimum duration of exposure: Usually, several months, but range from a few minutes to a few hours to several weeks, or even longer depending on the intensity of exposure.

Maximum latent period: The symptoms must appear during exposure or within 48 hours at the latest.

Irritation of the mucous membranes

□ Irritation of the eyes

Diagnostic criteria:

Clinical effects: the symptoms range from simple conjunctival irritation and tearing to severe corneal damage. Reactions can be diffuse and delayed.

Exposure criteria:

Minimum intensity of exposure: Assessed by anamnesis revealing occupational exposure of the eyes to a potential irritant.

Minimum duration of exposure: Acute irritation: A few minutes to a few hours depending on the intensity of exposure.

Chronic irritation: Seven days.

Maximum latent period: The symptoms must appear during exposure or within 48 hours at the latest.

□ Irritation of the respiratory tract

Irritation may be caused by dusts, fumes, vapours and aerosols.

As in the case of skin irritation, many factors can contribute to the appearance and severity of the lesions.

Some asthmatics or workers suffering from a disease of the respiratory tract, such as chronic bronchitis, may show increased sensitivity to the action of the irritants.

Particular sensitivity in some subjects who have no respiratory disease is possible.

Smoking or simultaneous exposure to different substances should be taken into account.

Diagnostic criteria:

Clinical effects: range from rhinitis and cough to laryngitis, bronchitis or even chemical pneumonia, pulmonary oedema and obliterating bronchiolitis.

Sequelae may occasionally include emphysema and fibrosis.

Bronchial hyper-reactivity syndrome:

Intense acute exposure to an irritant substance may cause an asthmatic response or bronchial hyperactivity in some workers.

The water solubility of the substance is an important factor in determining the site of action:

- | | |
|---------------------|---|
| very soluble: | upper respiratory tract symptoms, within seconds: the irritant effects generally provide adequate warning preventing overexposure, e.g. ammonia, sulphur, dioxide; |
| moderately soluble: | upper and lower respiratory tract symptoms, within minutes, e.g. chlorine, fluorine; |
| slightly soluble: | lower respiratory tract symptoms, insidious onset. The effects can be delayed (6 to 24 or even up to 72 hours), but are often (but not always) preceded by upper respiratory tract symptoms, e.g. ozone, phosgene, nitrogen oxides. |

Exposure criteria:

Minimum intensity of exposure: Variable, according to the potency of the substance.

Minimum duration of exposure: Acute irritation: A few minutes to a few hours depending on the intensity of the exposure.

Chronic irritation: Should be assessed by a competent person.

Maximum latent period: The onset of symptoms should occur during exposure or within 72 hours at the latest. Delayed symptoms are possible with poorly soluble substances.

The first signs of bronchitis should appear during the period of employment causing exposure to the suspected substance.

Methyl acrylate

Definition of causal agent

Methyl acrylate is a colourless, volatile, flammable liquid with an acid odour. It polymerizes easily on standing, and the process is accelerated by heat, light and peroxides. It can react vigorously with oxidizing agents.

Main occupational uses and sources of exposure:

Methyl acrylate is used primarily as a acrylonitrile comonomer in the preparation of acrylic and methacrylic fibres. These are used in clothes and furnishings. Methyl acrylate has also been used in the preparation of thermoplastic coatings, adhesives and sealants and amphoteric surfactants for shampoos and vitamin B1. It may also be used as a microencapsulation mixture component or for the polymerization of radioactive waste into block form. It can serve as a resin in the purification and decolouration of industrial effluents or aid in the timed release and disintegration of pesticides.

Toxic effects

☐ Irritant effects

Methyl acrylate is a lacrymating agent and irritates the mucous membranes. See above section on *Occupationally caused irritation of the skin and mucous membranes*.

☐ Allergic contact dermatitis

Methyl acrylate causes sensitization of the skin. Cross reaction may occur with the following compounds: methyl vinyl ketone, 4-vinyl pyridine, trimethylol propane triacrylate and pentaerythritol triacrylate.

No cross reaction with acrylamide and methyl methacrylate is observed.

See above section on *Occupationally caused allergic contact dermatoses*.

Dithiocarbamates

Definition of causal agent

Dithiocarbamates are disulphide carbamate analogues chemically derived from carbamic acid. They are hydrophiles and form heavy, water-soluble metallic complexes with metals such as, for example, manganese, zinc, iron, sodium. Some metallic dithiocarbamate compounds used as fungicides are insoluble in water but soluble in non polar solvents.

Main occupational uses and sources of exposure:

Dithiocarbamates are mainly used in agriculture as fungicides and herbicides. Some dithiocarbamates are used in the chemical industry, as accelerators in the synthesis of plastics, or in vulcanization processes.

Local toxic effects

☐ Irritant effects

Dithiocarbamates may cause slight skin irritation.

See document on occupationally caused irritation of the skin and mucous membranes.

☐ Allergic effects

Dithiocarbamates (notably manganese and zinc derivatives) can cause allergic contact dermatitis.

See above section on *Occupationally caused allergic contact dermatoses*.

Chronic systemic effects

Dithiocarbamates, and in particular ethylenebisdithiocarbamates can exert, for very high exposures, a goitrogenic effect, due to the inhibition of the synthesis of thyroid hormones exerted by the main metabolite of these compounds, ethylenethiourea (ETU). As a consequence of the decrease of the synthesis of thyroid hormones, there is a compensative hypersecretion of thyroid stimulating hormone (TSH) which causes the goitrogenic effects. A goitrogenic effect has been observed in the past in heavily exposed workers, but it has never been reported in most recent periods.

The suspicion of a possible carcinogenicity for humans of ETU (thyroid cancer) in the conditions of exposure typical of the workplace has been ruled out by IARC.

Methylmethacrylate

Definition of causal agent

Methylmethacrylate (MMA) is a clear, colourless, flammable liquid with an unpleasant, strong, acid odour. It is slightly soluble in water but very soluble in alcohol and ether. The odour threshold lies between 0.2 and 0.6 mg/m³ in air. The chemical properties are defined by its highly reactive double binding. The monomer is readily polymerized by light, heat, oxygen, ionizing radiation and catalysts because of its ability to form a radical.

Main occupational uses and sources of exposure:

Methylmethacrylate is primarily used in the manufacturing of polymethylmethacrylate (PMMA) to fabricate crystal-clear or coloured plastics, the so-called acrylic glasses, clear ceramic-like resins, and for acrylic moulding and extrusion powder.

The monomer and polymers have wide applicability in medical technology. MMA serves as a medical spray adhesive or non-irritant bandage solvent. It is also used to coat corneal contact lenses and to manufacture artificial nails. In orthopaedic surgery it is used as a bone cement for fixation of metal and plastic prostheses.

Toxic effects

□ Irritant effects

Methylmethacrylate can be irritating to the skin, eyes and mucous membranes.

See above section on *Occupationally caused irritation of the skin and mucous membranes*.

□ Allergic effects

— Allergic contact dermatitis

Methylmethacrylate can cause allergic dermatitis. In some cases, tenderness is observed, outlasting the duration of the eruption.

See above section on *Occupationally caused allergic contact dermatoses*.

— Allergic rhinitis and conjunctivitis

See Annex I entry nr. 304.07 on *Allergic rhinitis caused by the inhalation of substances consistently recognised as causing allergies and inherent to the type of the work*.

— Asthma

See Annex I entry nr. 304.06 on *Allergic asthmas caused by the inhalation of substances consistently recognised as causing allergies and inherent to the type of work*.

Silicosis and Silicosis combined with pulmonary tuberculosis

Definition of causal agent

Silica is silicon dioxide. Free silica is the most important component of the earth's crust and exists in crystalline, micro-crystalline and non-crystalline (amorphous) forms:

1. the main types of crystalline silica are quartz, trydimite and cristobalite. The last two are more fibrogenic to the lungs than quartz.
2. micro-crystalline (crypto-crystalline) silicas include flint, chalcedony and chert.

Diatomite is the most important form of amorphous silica. It is composed of the skeletons of microscopic marine animals and is not fibrogenic. When heated it forms cristobalite or trydimite.

Main occupational uses and sources of exposure:

Mining (of almost any material) and other underground working such as tunnelling: quarrying of sand, sandstone, slate and other silica-containing rocks: masonry and sculpture: foundry work and the repair or demolition of blast furnaces: sand crushing and blasting: sandstone milling and grinding: manufacture and use of abrasives including carborundum: glassmaking: ceramic manufacture: vitreous enamelling: the use of silica as a filler in the paint, rubber, plastics and woodworking industries.

Toxic effects

4. *Pneumoconiosis ('silicosis')*

- Ordinary ('nodular', 'chronic', 'classical') silicosis, occurring after long exposures to silica. The disease may be 'simple' or 'complicated', depending on its radiographic appearance and extent. In some cases there is rapid progression ('accelerated' silicosis). Ordinary silicosis predisposes to pulmonary tuberculosis.

Diagnostic features:

Symptoms: few, if any, unless extensive disease when cough and breathlessness are common.

Radiology: bilateral, multiple, discreet rounded opacities and reticulation usually in the upper zones. In advanced disease the size and number of opacities increases and they may conglomerate ('complicated' silicosis). Rheumatoid nodules may be present. High resolution CT scanning is more sensitive than plain chest radiography. *Lung function:* mixed restrictive/obstructive pattern in advanced disease.

Minimum intensity of exposure: usually above $50\mu\text{g.m}^{-3}$ crystalline free silica.

Minimum duration of exposure: five years (two years in accelerated disease)

Maximum latent period: none

- Acute silicosis (alveolar proteinosis) can develop after relatively short exposures to very high concentrations of crystalline silica of small particle size. Acute silicosis predisposes to pulmonary tuberculosis.

Diagnostic features:

Symptoms: rapidly developing cough, breathlessness and loss of weight.

Radiology: bilateral alveolar filling pattern.

Lung function: restriction with loss of gas transfer.

Minimum intensity of exposure: well above $50\mu\text{g.m}^{-3}$ crystalline free silica

Minimum duration of exposure: three months

Maximum latent period: one year

- Diatomite pneumoconiosis is a rare outcome of exposure to diatomite amorphous silica.

Minimum intensity of exposure: above $50\mu\text{g.m}^{-3}$ crystalline free silica

Minimum duration of exposure: five years

Maximum latent period: none

Note: the following are not ‘silicosis’ as prescribed in Annex 1. The evidence that either is attributable to silica is not as strong as it is for silicosis.

5. Chronic obstructive pulmonary disease (COPD)

- Chronic bronchitis and airflow obstruction are common among workers exposed for long periods to silica; in most cases the degree of obstruction that is attributable to silica exposure is small. COPD may occur in the absence or presence of silicosis.

Minimum intensity of exposure: unknown but may be below the intensity required to induce silicosis.

Minimum duration of exposure: five years

Maximum latent period: none

6. Lung cancer

- Crystalline silica is probably a bronchial carcinogen. The evidence is stronger in the presence of silicosis; the risk is higher in smokers and among those working in manufacturing industries (rather than primary mining) where silica is used.

Minimum intensity of exposure: above $50\mu\text{g.m}^{-3}$ crystalline free silica.

Minimum duration of exposure: five years

Maximum latent period: none

7. Autoimmune disease/nephropathy

Any relationship between silica exposure and autoimmune diseases or nephropathy has not been firmly established. Cases of these diseases in silica-exposed workers require specific evaluation before reaching any conclusion on a causal association.

Annex I 301.21,
 301.22,
 302,
 306,
 308

Asbestosis (301.21)

Mesothelioma following the inhalation of asbestos dust (301.22)

Complication of asbestos in the form of bronchial cancer (302)

Fibrotic diseases of the pleura, with respiratory restriction, caused by asbestos (306)

Lung cancer following the inhalation of asbestos dust (308)

Definition of causal agent

Asbestos is a fibrous silicate which exists in various forms:

- Serpentine: chrysotile
- Amphiboles: crocidolite, amosite, actinolite, tremolite, anthophyllite.

All these fibres are capable of causing the diseases mentioned below, although their biological activities are different.

Main occupational uses and sources of exposure:

Exposure sources and levels have evolved substantially in recent decades. In Europe, exposure levels have fallen significantly, and some types of exposure have disappeared from many European countries (extraction and handling of asbestos-bearing rock, carding, spinning and weaving the fibres, manufacture of asbestos cement, sprayed coatings, manufacture of vehicle brakes, etc). Asbestos has been used in many applications, and exposure can still occur in connection with coatings remaining in place, insulation, ovens, construction materials containing asbestos etc.

Certain working operations dealing with asbestos still in place may involve significant exposure (asbestos removal, building maintenance, dismantling/refurbishment of ships, etc.).

Asbestos Exposure Assessment

Diseases linked to asbestos exposure develop very slowly; usually several decades after exposure. Mineralogical analysis of biological samples for asbestos fibres and bodies can provide information additional to a person's work history. The presence of asbestos bodies or fibres does not prove the existence of an asbestos-related disease but, in cases of doubt, may confirm exposure to asbestos. Guidance on identifying subjects with a high probability of asbestos exposure is available from the Helsinki Consensus Report 2005 which recommends values for asbestos bodies/fibres in biological samples.

Each laboratory must establish its own reference values. The median values for occupationally exposed groups should be well above the reference values.

□ Adverse effects

The following are distinct clinical entities associated with asbestos exposure. The presence of one does not imply the existence of other asbestos related diseases.

□ Asbestosis (Annex I nr. 301.21)

Bilateral, diffuse, interstitial pulmonary fibrosis caused by exposure to asbestos.

Asbestosis is similar to many other fibroses and the diagnostic criteria below must be used with a history suggestive of asbestos exposure.

Diagnostic criteria:

There are no specific anatomo-pathological criteria for the diagnosis of asbestosis. The following criteria, together with a history of asbestos exposure, suggest the diagnosis of asbestosis and provide a basis for assessing its severity:

- *Symptoms and signs:* breathlessness; persistent bilateral late inspiratory basal crepitations; clubbing
- *Chest X-ray:* diffuse interstitial opacities (usually reticular or reticulonodular), mainly in the lower lung fields
- *Computerized tomography:* diffuse interstitial opacities mainly in the lower lung fields
- *Lung function tests:* restriction, reduction in gas transfer, decrease of the flow rates at low volume (flow-volume curve).

These features do not necessarily appear simultaneously, and the order in which they occur may differ from one subject to another. At present in industrialised countries, most cases of asbestosis show up only on radiological examinations without progression to respiratory insufficiency. Early disease that is only visible on CT scanning requires expert radiological assessment.

Exposure criteria:

Minimum intensity of exposure: confirmed occupational exposure, assessed by history and study of working conditions, providing evidence of prolonged and repeated heavy exposure to asbestos, and by (where feasible):

- Estimation of a cumulative exposure index from exposure times, type of occupational activity and concentrations in the air which might have been measured at the place of work. There is evidence that the risk of developing asbestosis at cumulative exposures of <25 fibres.ml⁻¹.year is low.
- significant concentrations of asbestos bodies or fibres in the sputum, fluid from bronchoalveolar lavage or lung parenchyma.

Minimum duration of exposure: 5 years. This may be shorter in the event of heavy exposure.

Maximum Latent Period: not applicable

Minimum induction period: 5 years

These are localised, usually focal, bilateral hyaline thickenings (fibrosis) of the parietal pleura; they are sometimes (partially) calcified. Their presence does not imply the existence of other asbestos related diseases. On their own they do not usually cause symptoms or deficits in lung function.

Exposure criteria:

Minimum intensity of exposure: confirmed occupational exposure, assessed by history and study of working conditions providing evidence of exposure to asbestos. This exposure may be confirmed by the presence of asbestos bodies or fibres in biological samples (sputum, fluid from bronchoalveolar lavage or lung biopsy)

Minimum duration of exposure: unknown

Maximum latent period: not applicable.

Minimum induction period: usually more than 10 years. The onset of pleural plaques is related to the time since first exposure.

□ Other benign lung diseases

- ***Asbestos pleural effusions***

Diffuse exudative pleural reaction, with or without symptoms and often recurrent.

- ***Diffuse pleural thickening***

Diffuse thickening mainly of the visceral pleura, accompanied by parenchymal strips or atelectasis caused by twisting or deterioration of the bottom of the ipsilateral pleural sac. It often follows asbestos pleurisy. It may be accompanied by a restrictive syndrome or a decline in total lung capacity.

- ***Rounded atelectasis***

Twisting of a segment of lung parenchyma in contact with an area of visceral pleural fibrosis.

Exposure criteria

Minimum intensity of exposure: confirmed occupational exposure, if possible assessed by history and study of working conditions providing evidence of prolonged or repeated exposure to asbestos

Minimum duration of exposure: unknown

Maximum latent period: not applicable.

Minimum induction period: usually more than 10 years. With high exposures it may be less.

□ Malignant mesotheliomas (Annex I nr. 301.22)

- Primary malignant tumour of the pleura
- Primary malignant tumour of the peritoneum
- Primary malignant tumour of the pericardium.

80-90% of pleural mesotheliomas are attributable to occupational exposure to asbestos. Smoking does not increase the risk. The risk of mesotheliomas increases considerably in relation to time since first exposure. Exposure to amphibole asbestos fibres carries a far higher risk of mesothelioma than does chrysotile asbestos exposure.

Diagnostic Criteria

The diagnosis of mesothelioma is a pathological diagnosis. Its presence may be suggested by:

-
- Characteristic clinical features including chest pain, pleural effusion, breathlessness and weight loss
 - Standard radiology and computed tomography
 - Histological examination of biopsy specimen
 - Immunocytochemistry may be helpful in distinguishing the chief differential diagnosis of secondary adenocarcinoma.

Exposure criteria:

Minimum intensity of exposure: confirmed occupational exposure, if possible assessed by history and study of working conditions providing evidence of exposure to asbestos. Some occupations (for example those involved with the refurbishment of office buildings) may incur unrecognised exposure to asbestos, in which case a history of occupational exposure may be unreliable.

Minimum duration of exposure: usually a few years but shorter exposures (as low as 3 months) have been described.

Minimum induction period: usually more than 20 years but rarely, cases associated with high exposure have been described with shorter induction periods

– See section on ***Occupational cancers*** in the **Preface**

□ **Primary bronchial cancer (Annex I nr. 302)**

Asbestos may cause a primary bronchial cancer. The presence of asbestosis increases the likelihood of causal association between asbestos and primary bronchial cancer. However, asbestosis is not essential for the development of primary bronchial cancer arising from asbestos exposure.

The risk is increased considerably by smoking. Since tobacco smoke is the main risk factor for bronchial cancer, it must be considered carefully alongside workplace exposures in attributing an occupational cause.

Diagnostic Criteria:

All histological types of bronchial cancer have been linked to asbestos exposure. The diagnosis is pathological. Its presence may be suggested by:

- Characteristic clinical features including haemoptysis, cough, weight loss, and pleural effusion.
- Standard radiography and computed tomography. PET scanning may be helpful.
- Cytological examination of sputum, bronchial aspiration or bronchial lavage
- Histological examination of biopsy specimen

Exposure criteria:

Minimum intensity of exposure: confirmed occupational exposure, assessed by history and study of working conditions, providing evidence of prolonged and repeated heavy exposure to asbestos, and by (where feasible):

- Estimation of a cumulative exposure index from exposure times, type of occupational activity and concentrations in the air which might have been measured at the place of work.

There is evidence that the risk of developing bronchial cancer at cumulative exposures of $<25 \text{ fibres.ml}^{-1}.\text{year}$ is low.

- significant concentrations of asbestos bodies or fibres in the sputum, fluid from bronchoalveolar lavage or lung parenchyma.
- the presence of asbestosis (the presence of pleural plaques suggests exposure to asbestos but does not reflect the exposure level).

Minimum duration of exposure: usually a few years.

Minimum induction period: usually more than 15 years.

See section on ***Occupational cancers*** in the **Preface**.

□ Asbestos warts

Pronounced thickening and hyperkeratosis on the dorsal and palmar surfaces of the hands and forearms caused by minute asbestos fibres penetrating the skin. A cure can be effected by removing the fibres.

Exposure criteria:

Minimum intensity of exposure: occupational exposure confirmed by history, evidence of which is provided by the subcutaneous presence of asbestos fibres. A single contact is enough for fibres to penetrate the skin.

Pneumoconiosis caused by dusts of silicates

Definition of causal agent

Commercially important silicates include:

3. the phyllosilicate clay minerals kaolin, montmorillonite (fuller's earth and bentonite) and hallyosite.
4. the non-clay phyllosilicates - talc, pyrophyllite, mica and vermiculite
5. the closely-associated minerals attapulgite (palygorskite), sepiolite and meerschaum.
6. orthosilicates ('olivines'), anhydrous aluminium silicates (andalusite, kyanite, sillimanite), woolastonite and the zeolites.

Non-asbestos silicates may be contaminated by silica or by (asbestiform) tremolite fibres.

Main occupational uses and sources of exposure:

The silicates have a very wide range of commercial uses and exposure may occur during their extraction, crushing, drilling, grinding, polishing or other handling.

Toxic effects

☐ Pneumoconiosis

- Some silicates appear, rarely, to be capable of inducing a relatively benign pneumoconiosis. They include kaolin, mica, fuller's earth and possibly talc.
- Most cases of pneumoconiosis arising in workers with exposure to silicates are more probably attributable to contaminating quartz or asbestos fibres.

minimum intensity of exposure: unknown (but variable)

minimum duration of exposure: two years

maximum latent period: none

☐ Other pulmonary

- Inhalation of talc can cause the development of foreign-body granulomas in the lung. These are rare and benign.
- Pleural plaques, mesothelioma and lung cancer in workers with exposure to silicates are attributable to inhalation of contaminating quartz or asbestos fibres.

Broncho-pulmonary ailments caused by dusts from sintered metals

Definition of causal agent

Hard metal is a synthetic material of great hardness based on tungsten carbide. It is manufactured by blending tungsten with carbon in a furnace and mixing it with 3-25% cobalt – sometimes nickel - in a ball mill; other constituents – chromium, titanium, tantalum, vanadium, niobium etc – may be added at this stage. The powdered mixture is pressed and then fused ('sintered') at high temperature.

Main occupational uses and sources of exposure:

Production of hard metals; production of hard metal tools; cutting, drilling, grinding or polishing operations with hard-metal tools.

Toxic or irritant effects

☐ Acute respiratory

- rhinitis
- bronchial irritation
- asthma

Minimum intensity of exposure: >0.05 mg.m⁻³ cobalt dust/fume

Minimum duration of exposure: immediate for acute effects:
1 month for asthma

Maximum latent period: 1 month

☐ Chronic pulmonary

- (partially) reversible pulmonary fibrosis
- hard metal disease: progressive, interstitial pulmonary fibrosis, characterised by giant cells in bronchial biopsy or broncho-alveolar lavage.

Minimum intensity of exposure: >0.05 mg.m⁻³ cobalt dust/fume

Minimum duration of exposure: 1 year

Maximum latent period: 10 years

☐ Lung cancer

Several reports addressing cancer risks among workers in hard-metal production facilities provide evidence of an increased lung cancer risk related to exposure to hard-metal dust. There is thus limited evidence and in humans - and in experimental animals - for the carcinogenicity of metal alloys containing cobalt with tungsten carbide.

Extrinsic allergic alveolitis

Definition of causal agent

Extrinsic allergic alveolitis EAA (also known as hypersensitivity pneumonitis HP) comprises a group of related inflammatory interstitial lung diseases that result from hypersensitivity immune reactions to the repeated inhalation of various antigens derived from fungal, bacterial, animal protein, or reactive chemical sources.

or

Extrinsic allergic alveolitis EAA (also known as hypersensitivity pneumonitis HP) is an inappropriate immune response to inhaled antigens that causes shortness of breath, a restrictive lung defect, interstitial infiltrates seen on lung imaging [chest X ray and high-resolution computed tomography (HRCT)] due to the accumulation of large numbers of activated T lymphocytes in the lungs.

Main occupational uses and sources of exposure:

HP results from inhalation of organic dust or some reactive chemical substances. The examples of causal agents and related diseases are listed in the annex. The list is an open one.

Toxic effects

Annex

Antigen source	Probable antigen	Disease
Microorganisms and plants		
Mouldy hay	<i>Saccharopolyspora rectivirgula</i> <i>Thermoactinomyces vulgaris</i> <i>Aspergillus sp.</i> <i>Penicilium sp.</i> <i>Wallemia sebi</i> <i>Fusarium sp.</i>	Farmer's lung disease
Mouldy pressed sugarcane	<i>Thermoactinomyces sacchari</i> <i>Thermoactinomyces vulgaris</i>	Bagassosis
Mouldy compost and mushrooms	<i>Thermoactinomyces vulgaris</i> <i>Saccharomyces rectivirgula</i> <i>Aspergillus sp.</i> <i>Penicillium sp.</i> Mushroom spores	Mushroom worker's disease

Mouldy cork	<i>Penicillium</i> sp. <i>Aspergillus</i> sp. Cork	Suberosis
Contaminated barley	<i>Aspergillus clavatus</i>	Malt worker's lung
Contaminated wood pulp	<i>Alternaria</i> sp.	Wood pulp worker's disease
Contaminated wood dust	<i>Bacillus subtilis</i> <i>Alternaria</i> sp. Pine sawdust	Wood dust HP
Mould on tobacco	<i>Aspergillus</i> sp.	Tobacco worker's disease
Mould on grapes	<i>Botrytis cinerea</i>	Wine grower's lung
Cheese or cheese casings	<i>Penicillium</i> sp.	Cheese worker's disease
Esparto grass (<i>Stipa tenacissima</i>) used to produce plaster	Esparto grass antigens Thermophilic actinomycetes <i>Saccharopolyspora rectivirgula</i> <i>Aspergillus</i> sp.	Stipatosis
Biomass in air-conditioning system	<i>Cytophaga</i> (gram-negative bacteria)	Nylon plant lung
Contaminated humidifiers, air conditioners, heating systems	<i>Thermoactinomyces candidus</i> <i>Thermoactinomyces vulgaris</i> <i>Penicillium</i> sp. <i>Cephalosporium</i> sp. <i>Candida</i> sp. Amoeba <i>Klebsiella</i> sp.	Ventilator lung Humidifier lung
Contaminated metal working fluid	<i>Pseudomonas</i> sp. <i>Acinobacter</i> sp. <i>Mycobacterium</i> sp.	Metal working fluid HP
Contaminated tractor cab air conditioner	<i>Rhizopus</i> sp.	Tractor lung
Grain weevils in wheat flour	<i>Sitophilus granarius</i> protein	Miller's lung
Animals		
Silk worm larvae	Silk worm larvae proteins	Sericulturists's lung
Rat urine	Rat urine protein	Laboratory worker's HP
Pigeon droppings	Pigeon proteins	Pigeon breeder's disease
Chicken feathers	Chicken feather proteins	Chicken breeder's lung
Chemicals		
Toluene diisocyanate (TDI)	Altered proteins	TDI HP
Diphenylmethane diisocyanate (MDI)	Altered proteins	MDI HP
Hexamethylene diisocyanate (HDI)	Altered proteins	HDI HP
Trimellitic anhydride (TMA)	Altered proteins	TMA HP

Diagnostic criteria:

There is no single diagnostic or clinical laboratory test available to diagnose HP. Diagnosis is made from a combination of characteristic symptoms, physical findings, X-Ray abnormalities, pulmonary function and immunological tests. Confirmation of exposure to the inciting antigen can be obtained

by history, environmental inspection, serum precipitins and/or bronchoalveolar lavage fluid antibodies

□ History

Symptoms consistent with AA that appear or worsen within hours after antigen exposure.

□ Clinical

Acute form: chills, dyspnea, cough, chest tightness, malaise, fever, bilateral inspiratory crackles occurring 3-8 hours after beginning of exposure

Subacute form: progressive increasing shortness of breath, cough which is generally dry, weight loss, inspiratory crackles.

Chronic form: progressive dyspnea, fatigue, anorexia, weight loss, chronic cough often with sputum production, crackles, rhonchi, 'squawks'; in very advanced cases, signs of cor pulmonale.

□ Lung function

Restrictive ventilatory pattern and a decreased diffusing capacity for carbon monoxide; a mild obstructive pattern is sometimes observed. Arterial blood gas analysis usually shows hypoxemia of variable degree.

□ Immunological Findings

Serum: presence of precipitating immunoglobulin (IgG) antibodies against offending antigen.

Bronchoalveolar lavage (BAL): a marked lavage lymphocytosis is found. The lymphocytes are predominantly of the T-suppressor subtype (CD8+) and the ratio CD4+/CD8+ is generally less than 1. Increased BAL neutrophils are observed shortly after antigen exposure.

□ Inhalation Challenge

The use of inhalation challenge in the diagnostics of AA is limited by the lack of standardized antigens and techniques. This test is not essential for diagnosis.

□ Histopathology

Histologic triad – (i) cellular infiltrates of lymphocytes and plasma cells along airways, (ii) interstitial infiltrates of lymphocytes and plasma cells, (iii) single, non-necrotizing granulomata in the parenchyma with some in bronchiolar and alveolar walls, but without mural vascular involvement.

□ Radiology

HRCT is the most useful imaging tool to evaluate AA.

Acute form: Normal or diffuse or patchy air-space consolidation

Subacute form: centrilobular nodules or widespread nodular opacities and ground-glass attenuation

Chronic form: Mid –lung zone fibrosis, honeycombing.

Differential diagnosis :

1. organic dust toxic syndrome
2. infectious pneumonitis
3. lymphocytic leukemia
4. sarcoidosis
5. chronic beryllium disease
6. drug-induced interstitial lung disease
7. bronchiolitis obliterans with organizing pneumonia
8. all types of chronic diffuse pulmonary fibrosis

Exposure criteria:

Minimum intensity of exposure: Although the symptoms usually appear with high concentrations of the antigen in the working environment, there is no good relationship between dose and effect.

Maximum duration of exposure: from few minutes to few months.

Maximum latent period:

- acute form: 8 hours
- subacute form: 8 days
- chronic form: one year

Lung diseases caused by the inhalation of dusts and fibres from cotton, flax, hemp, jute, sisal and bagasse

Definition of causal agent

Respirable fraction of dust from cotton (bracts, leaves, stems), flax (stems), hemp, jute sisal and bagasse.

Main occupational uses and sources of exposure:

Work exposing workers to the inhalation of dusts and vegetable textile fibres: e. g. beating, carding, drawing, combing, spinning, winding and twisting (cotton, flax, hemp, jute, sisal) and sugar cane processing (bagasse).

Inhalation of dusts and fibres of cotton, flax, hemp, jute and sisal produce a clinical picture similar to byssinosis, whereas bagasse produces a different entity, bagassosis, which is a form of extrinsic allergic alveolitis. See Annex I entry nr. 304.01 on *Extrinsic allergic alveolitis*.

Health effects

1. Local effect

☐ Irritant effects

These organic dusts cause irritation to the mucous membranes.

See section on *Occupationally caused irritation of the skin and mucous membranes* in Annex I entry nr. 202.

2. Systemic effects

☐ Byssinosis

Byssinosis is generic name applied to airway disease among workers occupationally exposed to agents mentioned above. The mechanisms of and the etiologic agents causing byssinosis remain obscure. The most probable cause is endotoxin of bacteria living on the textile fibres.

Recently new terminology has been introduced dividing byssinosis into 'acute' and 'chronic' forms.

☐ Occupational asthma

Sometimes exposure to dust from cotton, flax, hemp, jute and sisal may cause occupational allergic asthma.

See Annex I entry nr. 304.06 on *Allergic asthmas caused by the inhalation of substances consistently recognised as causing allergies and inherent to the type of work*.

☐ Bagassosis

Exposure to mouldy sugarcane may cause extrinsic allergic alveolitis.

See Annex I entry nr. 304.01 on *Extrinsic allergic alveolitis*.

□ Acute byssinosis

These set in during the first day of exposure after an induction period of several hours. The effects include shivering, tightness of the chest, dyspnoea, fever and malaise. The symptoms disappear after one or two days. If re-exposure occurs after a period of non exposure, they reappear. There are few objective signs: bronchi may be present on auscultation. Reduced pulmonary function occurs in the acute stage. There are no specific spirometric, radiological or serological signs.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- anamnesis and study of working conditions providing evidence of exposure to these vegetable dusts,
- and, if available:
 - workplace air monitoring: guide value: atmospheric concentration above 0.2 mg/m³ (total dusts).

Minimum duration of exposure: Several hours. Five hours exposure to a dust level of 0.5 mg/m³. (according to GB threshold limit value)

Maximum latent period: 48 hours.

□ Chronic effects

Chronic byssinosis

Obstructive airway disease with late onset of moderate to severe dyspnoea, tightness of the chest, gradually increasing during the working week and over a period of years. Shivering and malaise, as described under acute effects, gradually decreases as the years pass.

Objective signs: reduction of the Forced Expiratory Volume in 1 second (FEV₁). Severe cases display a decrease in Forced Vital Capacity (FVC).

Usually there are no radiological signs.

Exposure criteria:

Bagasse: see document on extrinsic allergic alveolitis

Minimum intensity of exposure:

Occupational exposure confirmed, if possible assessed, by:

- anamnesis and study of working conditions providing evidence of prolonged or repeated exposure to these vegetable dusts,
- and, if available:
 - workplace air monitoring: guide values:
atmospheric concentration above 1.5 mg/m³ (total dusts),
symptoms may occur at lower dust concentration as if actual exposure has occurred for more than 20 years,
- Byssinosis: may be complicated by chronic bronchitis and emphysema. Other factors such as smoking should be taken into account.

Minimum duration of exposure: 10 years exposure to a dust level of 1.5 mg/m³.

Maximum latent period: Five years.

Diagnostic criteria:

Table 1. Grading system for byssinosis according to WHO

Classification	Symptoms
Grade 0	No symptoms
Byssinosis	Chest tightness and/or shortness of breath on most of first days back at work
Grade B1	
Grade B2	Chest tightness and/or shortness of breath on the first and other days of the working week
Respiratory tract irritation	
Grade RTI 1	Cough associated with dust exposure
Grade RTI 2	Persistent phlegm (i.e., on most days during 3 months of the year) initiated or exacerbated by dust exposure
Grade RTI 3	Persistent phlegm initiated or made worse by dust exposure either with exacerbations of chest illness or persisting for 2 years or more
Lung function	
Acute changes	
No effect	A consistent ^a decline in FEV ₁ of less than 5% or an increase in FEV ₁ , during the work shift
Mild effect	A consistent ^a decline of between 5 and 10% in FEV ₁ , during the work shift
Moderate effect	A consistent ^a decline of between 10 and 20% in FEV ₁ during the work shift
Severe effect	A decline of 20% or more in FEV ₁ during the work shift
Chronic changes	
No effect	FEV ₁ ^b 80% of predicted value ^c
Mild to moderate effect	FEV ₁ , 60-79% of predicted value ^c
Severe effect	FEV ₁ ^b less than 60% of predicted value ^c

^aA decline occurring in at Least three consecutive tests made after an absence from dust exposure of 2 days or more.

^bPredicted values should be based on data obtained from local populations or similar ethnic and social class groups.

^cBy a preshift test after an absence from dust exposure of 2 days or more.

Respiratory ailments caused by the inhalation of dust from cobalt, tin, barium and graphite

Definition of causal agent

Respiratory ailments caused by the inhalation of dust from cobalt, tin, barium and graphite are characterized by a chronic lung diseases including in case of exposure to:

Cobalt – occupational asthma (See Annex I entry nr. 304.06 on **Allergic asthmas caused by the inhalation of substances consistently recognised as causing allergies and inherent to the type of work'**.) or/and interstitial lung disease (*hard metal disease*), resulting in interstitial fibrosis

Tin and barium – non-fibrosing benign pneumoconiosis, usually asymptomatic and without alteration of lung function (*stannosis, baritosis*).

Graphite – fibrosing pneumoconiosis (*graphitosis*), clinically similar to coal miners-pneumoconiosis (see above).

Local effects

The massive exposure to cobalt, barium and tin dusts and fumes may cause irritation to the eyes, skin and mucous membranes (including upper and lower respiratory tract).

Main occupational uses and sources of exposure:

Cobalt: production of metal-ceramic articles, tungsten carbide tools, diamond –edged carbide tools, grinding of metal tools, as well as working with cobalt steel, diamond polishing or decoration of ceramics.

Tin: mining, smelting, refining, production and use of tin alloys and solders.

Barium: Barium sulphate is used in the manufacture of radio-opaque materials and as a basis for the production of white pigments. Exposure can occur during extraction of the ore and during the subsequent phases of the industrial processing.

Soluble compounds: these are used in the manufacture of glass, vulcanization of synthetic rubber, pesticides, pigment production, in the foodstuffs industry and in the production of electronic components.

Graphite: graphite mining and milling, ceramics, steel, iron, lubricants, electrodes and car components manufacture. Occupational exposure can occur during the production of artificial graphite articles, ore extraction of the production of artificial graphite from coal or mineral oil.

Diagnostic criteria

History and analysis of working conditions providing evidence of repeated or prolonged exposure to dust or fumes containing these agents. Workplace air monitoring data.

Chest X-ray: diffuse radiological findings: characteristic for non-fibrosing (in *stannosis* and *baritosis*); or fibrosing (in *graphitosis*) pneumoconiosis; in *hard metal disease* – initially the pattern reticular, in more advanced cases – micronodular pattern.

Lung function tests: restrictive (hard metal disease, *graphitosis*) or obturative (cobalt-induced asthma) changes, or mixed changes; in *stannosis* and *baritosis* usually no alteration of lung function are observed. In *hard metal disease* and *graphitosis*, reduction of gas transfer factor may be found.

In some cases, additional evidence may be obtained from bronchoalveolar lavage fluid (*hard metal disease*), sputum test (presence of graphite particles in *graphitosis*) or lung biopsy.

Exposure criteria

Cobalt

Minimum intensity of exposure: Occupational exposure confirmed and, if possible assessed by:

History and study on the working conditions showing evidence of repeated or prolonged exposure to cobalt dust and fumes (>0.05mg/m³)

Minimum duration of exposure: A few months

Maximum latent period: None

Tin

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- History and study of working conditions providing evidence of prolonged/repeated exposure to tin oxide dust or fumes;

and, if available:

- Workplace air monitoring

Guide values; Atmospheric concentration >2µg/m³ inorganic tin

Maximum duration of exposure: Five years

Maximum latent period: Five years

Barium

Minimum intensity of exposure:

Irritant effects:

Atmospheric pollution well above 0.5 mg/m³

See section on ***Occupationally caused irritation of the skin and mucous membranes*** in Annex I entry nr. 202.

Systemic effects:

Workplace air monitoring

Atmospheric concentration > 10mg/m³ [in the event of crystalline silica, the concentration producing effects would be much lower (see document on silicosis)]

Minimum duration of exposure: five years

Maximum latent period: five years

Graphite

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- History and study of working conditions providing evidence of exposure to graphite dust,

Workplace air monitoring;

Guide values: atmospheric concentration well above 10mg/m³ for artificial graphite, 2.5mg/m³ for the respirable fraction of natural graphite.

Minimum duration of exposure: five years

Maximum latent period: five years

Siderosis

Definition of causal agent

Fumes or dust of metallic iron or iron oxide.

Main occupational uses and sources of exposure:

Iron and steel rolling or grinding: fettling: electric arc and oxyacetylene welding: metal, glass or stone polishing with iron oxide powder: boiler scaling: mining or crushing iron ores: mining or milling of emery: manufacture of magnetic tapes: manufacture of pigments.

Toxic effects

1. Local effects

- At high exposures, irritation of mucous membranes

Minimum intensity of exposure: unknown

Minimum duration of exposure: immediate

Maximum latent period: a few minutes for acute irritant effects

2. Pulmonary

- Siderosis: benign pneumoconiosis

Diagnostic criteria:

Prolonged occupational exposure to iron dusts

Asymptomatic

Chest radiograph or CT scan showing numerous, widespread small opacities of high density. Hilar glands not enlarged but may appear radio-dense. No pleural changes.

Lung function normal

Minimum intensity of exposure: unknown

Minimum duration of exposure: 10 years (3 years with very high exposure)

Maximum latent period: none

- Mixed pneumoconiosis may occur from co-exposures to iron and other dusts. eg. sidero-silicosis: arising from co-exposures to iron fume and silica

Allergic asthmas caused by the inhalation of substances consistently recognised as causing allergies and inherent to the type of work

Definition of causal agent

Occupational asthma is a disease characterised by airway inflammation, reversible variable airflow limitation, and airway hyper-responsiveness due to causes and conditions attributable to a particular occupational environment. Specifically, it is induced by workplace exposure to an airborne dust, gas, vapour or fume. Allergic occupational asthma is characterised by a latent period (see exposure criteria); and once established can be provoked by exposure to minimal concentrations of the inducing agent in the workplace.

Main occupational uses and sources of exposure:

Either high-molecular mass agents (usually glycoproteins) of biological origin or chemical substances of low molecular mass. The most common reported causes of occupational allergic asthma are listed below. The list is an open one.

Diagnostic criteria

The diagnosis of asthma is established by the association of episodic dyspnoea with one or more of the following:

- bronchial obstruction significantly reduced by inhaled bronchodilator medication
- non-specific bronchial hyperreactivity
- increased diurnal variability in lung function.

The diagnosis of occupational asthma requires demonstration of a clear relationship between exposure to the causal agent and both clinical and physiological changes. Lung function and bronchial reactivity may become normal after cessation of occupational exposure. Occupational asthma arising from high molecular mass and some chemical agents is associated with the production of specific IgE antibodies.

History:

- occupational exposure to a substance known to induce occupational asthma
- a sequence of symptoms in direct relation to the work schedule. Attacks may begin several minutes or several hours (depending on the allergen) after exposure
- recurrence of symptoms and signs following re-exposure to the same agent

Examination:

There may be no clinical findings on examination but rhonchi can be detected on auscultation of the chest during an asthmatic attack.

Investigations:

For agents that provoke specific IgE antibodies skin prick or serological testing can be used to assess sensitization. Numerous occupational allergens are not standardised and information on the sensitivity and specificity of skin-prick or serological tests is not always available.

Supportive evidence may be provided by:

- serial monitoring of peak expiratory flow or spirometry during periods at and away from work
- specific inhalation challenge (bronchial provocation test). This test is not necessary for disease recognition, however it may be indicated when the diagnosis remains in doubt, in determining the precise causative agent, and in the investigation of new causes of occupational asthma. Testing should be done only in specialised centres with appropriate facilities.

Exposure criteria:

Minimum intensity of exposure: not specified, as there is insufficient evidence for exposure thresholds in occupational asthma and variation in individual susceptibility.

Minimum duration of exposure: occupational allergic asthma requires a sensitisation period usually ranging from a few weeks to years. In exceptional cases it may be as short as a few days.

Maximum latent period: between allergen exposure and the manifestation of clinical symptoms in a sensitized individual - no more than 48 hours. The onset of sensitisation and occupational asthma occur only during employment that involves exposure to the initiating agent.

Induction period: Few weeks to several months. In exceptional cases it may be as short as a few days

Most common reported causes of occupational allergic asthma

Many workplace substances have been identified as capable of inducing occupational asthma. Those that have been well established include:

High molecular mass substances:

- animal-derived allergens (e.g. laboratory animal antigens, cow dander)
- arthropods (e.g. grain mites)
- plant derived allergens (e.g. wheat, rye and soya flour, natural rubber latex)
- enzymes (e.g. protease, amylase)

Low molecular mass substances:

- diisocyanates (e.g. toluene diisocyanate, diphenylmethane diisocyanate)
- acid anhydrides (e.g. phthalic anhydride, trimellitic anhydride)
- amines (e.g. ethylene diamine, paraphenylene diamine)
- fluxes (e.g. colophony)
- components of some wood dusts (e.g. western red cedar)
- metals (e.g. platinum salts)
- drugs (e.g. spiramycin, penicillins, psyllium)
- biocides (e.g. glutaraldehyde, chloramine T)
- plastics (e.g. acrylates)

-
This list is not exhaustive.

Allergic rhinitis caused by the inhalation of substances consistently recognised as causing allergies and inherent to the type of the work

Definition of causal agent

Occupational allergic rhinitis is a disease characterised by allergic inflammation in the nasal mucosa, with nasal congestion, rhinorrhea and sneezing due to causes and conditions attributable to a particular occupational environment. Specifically it is induced by workplace exposure to an airborne dust, gas, vapour or fume. Occupational rhinitis may precede occupational asthma, especially when caused by a high molecular mass allergen.

Main occupational uses and sources of exposure:

The causative agents for occupational allergic rhinitis are similar to those for occupational asthma (See Annex I entry nr. 304.06 on *Allergic asthmas caused by the inhalation of substances consistently recognised as causing allergies and inherent to the type of work*).

Diagnostic criteria

The diagnosis of occupational rhinitis requires demonstration of a clear relationship between exposure to the causal agent and clinical changes.

History:

- workplace exposure to a substance known to trigger occupational rhinitis
- a pattern of symptoms in direct relation to the occupational exposure
- recurrence of symptoms following re-exposure to the same agent

Examination:

Anterior rhinoscopy may show mucosal inflammation and oedema

Investigations:

For agents that provoke specific IgE antibodies, skin-prick or serological testing can be used to assess sensitization. Numerous occupational allergens are not standardised and information on the sensitivity and specificity of skin-prick or serological tests is not always available. Rhinomanometric measurements of nasal airflow and allergen specific nasal provocation testing may be used to support a diagnosis of occupational rhinitis.

Exposure criteria are similar to those of allergic occupational asthma (in Annex I entry nr. 304.06 on *Allergic asthmas caused by the inhalation of substances consistently recognised as causing allergies and inherent to the type of work*).

Cancerous diseases of the upper respiratory tract caused by dust from wood

Definition of causal agent

Dusts (untreated or treated) from hard and softwood species, including plywood.

Hardwoods (especially oak and beech) appear to be more carcinogenic.

Main occupational uses and sources of exposure:

Sawing, milling, planing, sanding and other working of wood.

Malignant effects

8. *Nasal or sinonasal squamous- and adeno-carcinoma.*

Minimum intensity of exposure: unknown

Minimum duration of exposure: 10 years

Maximum latent period: 20 years

For other non-malignant effects from wood dust, see Annex I entry nr. 304.06 on *Allergic asthmas caused by the inhalation of substances consistently recognised as causing allergies and inherent to the type of work* and Annex I entry nr. 304.07 on *Allergic rhinitis caused by the inhalation of substances consistently recognised as causing allergies and inherent to the type of the work.*

Chronic obstructive bronchitis or emphysema in miners working in underground coal mines

Definition of causal agent

Coughing and sputum on most days for a period of at least three months per year for two consecutive years. - Chronic obstructive bronchitis is associated with significant obstructive impairment. Chronic obstructive bronchitis may progress over several years with periods of exacerbation and occurrence of emphysema. Emphysema is defined as the destruction of the alveolar walls.

Main occupational uses and sources of exposure:
Underground working in hard coal mines

Manifestations

Chronic exposure to coal mine dust may cause chronic obstructive bronchitis or emphysema. These diseases are strongly related to cigarette smoking. While the risk in coal workers is independent of that of cigarette smoking it is increased considerably by smoking. Since tobacco smoke is the most common cause of chronic bronchitis and emphysema, it must be considered carefully alongside occupational exposures in attributing an occupational cause.

Diagnostic criteria

- Chronic bronchitis (coughing and sputum) on most days for a period of at least three months per year for two consecutive years, associated with obstructive ventilation impairment in lung function tests.
- Emphysema may be suspected by the presence of dyspnoea on exercise, obstructive ventilatory impairment with increase of the Total Lung Capacity, and/or bullae on Chest X-ray or CT scan.

Exposure criteria:

Minimum intensity of exposure: Confirmation of occupational exposure underground in a hard coal mine, if possible assessed by:

History and working conditions showing significant levels of respirable and inhalable dust, totalling approximately $100 \text{ mg/m}^3 \cdot \text{year}$ or more.

Minimum duration of exposure: 5 years

Maximum latent period: A maximum period cannot be fixed, the occurrence of disease being a function of the cumulative dose.

Broncho-pulmonary ailments caused by dust or fumes from aluminium or compounds thereof

Definition of causal agent

Aluminium is a silvery – white ductile and malleable metal. In nature it is not found as a free metal because of its reactivity. It occurs in the environment as aluminium oxide (alumina), hydroxide, fluoride, chloride, bromide, sulphate, nitrate, and silicate.

Main occupational uses and sources of exposure:

Occupational exposure may occur during: extraction of bauxite, primary aluminium production, metallurgical industry (production and processing of metal alloy), welding, chemical industry (for manufacturing various alumina based chemicals and as a catalyser), preparation and use of synthetic abrasives and production of explosives and fireworks. Aluminium compounds are also used in production of glass, ceramics, rubber, wood preservatives, pharmaceuticals and waterproofing textiles.

Adverse effects

☐ Restrictive pulmonary disease

Exposure to sub-micron size aluminium powder (non-fibrous and fibrous particles) may give rise to fibrosis of the lung that is called Aluminosis. It is a slight fibrosis characterized by slow and benign evolution. The intensity of fibrosis is correlated to duration of exposure and pulmonary levels of aluminium. Non occupational exposed subjects have a pulmonary content to 50 mg/kg wet weight. Aluminium content in the lung of about 1000 mg/kg dry weight is the limit for the initial development of fibrosis.

Shaver's disease is an historic example of rapid and progressive interstitial fibrosis of the lung. It was induced by the inhalation of aluminium fumes together with silicon dioxide and was attributed to the use of bauxite contaminated with percentages of silicon dioxide greater than 30%. Respiratory effects were severe and complications such as pneumothorax, pulmonary emphysema and death were common. Present day control measures may have reduced the risk.

The fibrogenic potency of aluminium dust is undetermined; moreover inhaled powdered alumina was used as a means of preventing silicosis.

Diagnostic criteria:

Symptoms: Shortness of breath and dry cough, but in early stages there may be no symptoms.

Clinical signs: Signs of fibrotic lung disease e.g. crepitations on auscultation but in early stages, there are no clinical signs

Lung function: restrictive or mixed impairment of low degree. Generally lung function decreases as a profusion of small opacities increases.

Chest X-ray: findings range from interstitial infiltrates to slight profusion of small round or irregular opacities.

Exposure criteria:

Minimum intensity of exposure: occupational exposure confirmed and, if possible assessed by:

- History and working conditions showing evidence of exposure to high concentration of aluminium, and if available:
- Workplace air monitoring results. Present information suggests that a level for alumina in air of 10 mg/m³ taking place over a period of 37 years gives rise to a pulmonary aluminium content in the order of 900 mg/kg.

Minimum duration of exposure: 10 years, but this varies with the intensity of exposure.

Maximum latent period: a maximum cannot be determined as the lesions are a function of the cumulative dose.

□ Potroom asthma

The term potroom arises from the use of metal pots for electrolysis processing of alumina. Potroom fumes can cause asthma-like symptoms with continuing lung function impairment even after cessation of occupational exposure. The specific causal agent remains unidentified. The pathogenesis is considered to be bronchial hyper-reactivity induced probably by strong respiratory irritants in the potroom environment (hydrogen fluoride, sulphur dioxide, fluorides in particulates). Potroom fumes also contain vanadium that is known to cause asthma. Attacks similar to potroom asthma have also been reported from other industries with exposure to aluminium fluoride compounds (K₃AlF₆, AlF₃) and cryolite (Na₃AlF₆).

Diagnostic criteria:

Symptoms: episodes of chest tightness, breathlessness, non-productive cough and wheeze.

They may occur during working hours but more typically some hours after leaving work (delayed onset).

The symptoms are work-related; they become more frequent with repeated exposure and improve when away from work. An improvement in symptoms may be expected after cessation of exposure. Increased bronchial reactivity once induced, has a tendency to persist. Atopy does not seem to be significant for the onset and the prognosis.

Clinical signs: those of bronchial obstruction e.g. rhonchi on auscultation.

In the differential diagnosis, other causes of asthma should be considered.

Lung function: bronchial obstruction reversible by bronchodilators; bronchial obstruction triggered by non-specific bronchoconstrictors (metacholine test), normal gas transfer, significant serial peak flow rate variability.

Exposure criteria:

Minimum intensity of exposure: a minimum cannot be established since specific causative agents and thresholds are unknown.

Minimum duration of exposure: the disease may present within a few weeks after the first exposure or less commonly after an interval of several years.

Maximum latent period: several hours.

Broncho-pulmonary ailments caused by dusts from basic slags

Definition of causal agent

Basic (Thomas) slag is a fine powder by-product that separates off in metal smelting and floats as a fused layer on liquid metal. It is obtained in the Thomas process of making steel. Burned dolomite reacts with phosphorus from pig iron to form converter lining. It consists of oxides of phosphor, silicon, calcium, iron, aluminium, magnesium, and manganese contaminated by vanadium.

Main occupational uses and sources of exposure:

Historically, iron production, basic slag mills. Basic slag was used as fertilizer. Rare disease, mainly of historical relevance.

Toxic effects

1. Acute and sub acute effects

Non specific effects are acute bronchitis with cough, sputum, pharyngitis, laryngitis, tracheitis; acute chemical pneumonitis with fever, shivering, cough, dyspnoea and headache. The clinical picture may resemble infectious pneumonia.

Exposure criteria:

Minimum intensity of exposure: Unknown

Minimum duration of exposure: A few days

Maximum latent period before onset of disease: A few days

2. Chronic effects

Chronic bronchitis and emphysema are possible.

Infectious or parasitic diseases transmitted to man by animals or remains of animals

General consideration

Many infectious diseases can be transmitted by occupational exposure to animals or their excreta. This chapter covers **leptospirosis, tularaemia, Lyme disease, psittacosis, avian influenza, Q fever** and **erysipeloid**.

The main occupational groups at risk for these infections are: farmers, mainly animal breeders, abattoir workers, butchers, meat packers, agricultural engineers, laboratory technicians, workers engaged in the preparation of animal skin, forestry workers, and veterinary workers.

Some human diseases which are undoubtedly transmitted by infected animals are too rare to be examined here. They will be recognized as occupational illnesses only by individual assessment in each case, or as a complication of an occupational accident, particularly following bites or stings (rabies, pasteurellosis, malaria, etc.).

Leptospirosis

1. Definition and causal agent

Leptospirosis is caused by the *Leptospira interrogans* complex. Leptospira are thin, highly motile spirochaetes with hooked ends. The organisms are microscopically demonstrable by dark-field illumination and silver staining. There are 19 serological groups.

2. Transmission of infection

2.1 Exposure

Rodents, especially rats, are the most important reservoir. *Rattus norvegicus* and *Mus musculus* carry a broad spectrum of serotypes, though other animals, including cattle, pigs, goats, dogs, foxes and voles, can be infected. The organism may exist in the animal host without causing pathological change. Exposure to urine of these animals is the commonest type of human risk.

2.2 Occupational groups at risk

People working in a rat-infested environment or where there is infected material or water are at greatest risk. These include agricultural workers (especially those working in rice fields), sewer workers, miners, veterinarians, abattoir workers, fish handlers and military personnel.

3. Clinical disease

3.1. Presenting features

The incubation period of 2 to 20 days depends on the host response and the quantity of micro-organisms. In the mild form there may only be a low-grade fever, but the severe form associated (Weil's disease) is characterised by jaundice, renal failure and haemorrhages. Cardiovascular collapse may occur.

The disease has two phases: a septicaemic phase, which lasts 4 to 7 days with fevers, headaches, myalgia and conjunctival infection, whilst renal failure and jaundice (10%-20%) are uncommon but serious features. A second immune phase lasts four to 30 days. The immune phase coincides with the disappearance of the spirochaete from most tissues. Uveitis, rashes, meningitis, encephalitis and myelitis may occur. Liver and kidney abnormalities continue from the first phase.

3.2 Laboratory diagnosis

A history of exposure to rat-infested environments is very helpful in differentiating leptospirosis from other pyrexial illnesses. Leucocytosis with neutrophilia (and in 40% of cases a thrombocytopaenia) with increased plasma fibrinogen levels are supplemented by abnormal urinalysis and the demonstration of leptospira spp. in the urine. Liver function tests may be abnormal. After the second week of the disease, isolation of the organism becomes less likely but serology is then important. Macroscopic slide agglutination is a good screening test supplemented by microscope-type specific agglutination tests, where titres of 1:100 are sufficient to indicate a previous infection.

3.3 Prognosis

Recovery is the rule but older patients and those with severe renal, haematological and hepatic change may succumb. Renal dialysis has greatly reduced previous mortality figures and the long-term follow-up of dialysed patients indicates a good recovery of renal functions.

Exposure criteria:

Acute infections and their complications:

Minimum intensity and duration of exposure: not applicable

Maximum latent period: three weeks

Tularaemia

1. Definition and aetiological agent

Tularaemia is caused by *Franciscella tularensis*. A number of animal species may be infected by this gram-negative bacillus and humans can easily be contaminated, most often through direct contact. The disease is usually characterized by skin lesions with regional ganglion hypertrophy.

2. Transmission of infection

2.1 Exposure

Many animals are natural carriers of *F. tularensis*. They include, particularly, hares, rabbits, squirrels, marmots, musk rats, foxes, mice, rats, quails and pheasants. Humans are very sensitive to tularaemia; the bacteria most often enter directly through the skin, even where there is no existing skin lesion, and only rarely through insect vectors (ticks). The bacillus can also penetrate the body through the mucous membranes, the digestive tract or the respiratory tract.

2.2 Occupational groups exposed

Gamekeepers, foresters; those involved in animal rearing, slaughtering and transport; handling of rabbits, hares and other small furry animals; preparation of animal skins; laboratory work involving contact with rabbits and small rodents.

3. Clinical picture

3.1 Presenting features

The incubation period is usually three to five days. The clinical forms depend mainly on the path of infection, but all involve fever, asthenia, joint and muscle pain and headache. The most common clinical form combines ulceration at the point of infection with regional adenopathy. The eyes, lungs and digestive tract may be affected, depending on the path of infection.

3.2 Diagnosis

Isolation of bacteria from lesions. Serological tests to identify antibodies.

Exposure criteria:

Minimum induction period: a few hours

Maximum latent period: 15 days.

Lyme disease

1. Definition and aetiological agent

Lyme arthritis is caused by the spirochaete *Borellia burgdorferi* and is transmitted to humans through tick bites. It is characterized by chronic migratory erythema sometimes accompanied by joint or neurological disorders.

2. Transmission of infection

2.1 Exposure

Dogs and a number of wild species including deer may carry the bacteria. Some species of tick are responsible for transmitting the disease to humans.

2.2 Occupational groups exposed

All forestry work in areas where the disease is endemic.

3. Clinical picture

3.1 Symptoms

Chronic migratory erythema appears 3 to 20 days following the tick bite. Skin lesions may be accompanied by general signs, arthralgia and myalgia. Encephalitis, myocarditis and arthritis may develop.

3.2 Diagnosis

Isolation of bacteria (difficult).
Serological tests for specific antibodies.

Exposure criteria:

Minimum induction period: 3 days;

Maximum latency period: one month for chronic migratory erythema, Six months for late-appearing sequelae.

Psittacosis

1. Definition and aetiological agent

Ornithosis is caused by *Chlamydia psittaci*. Infection is most often characterized by acute respiratory disease.

2. Transmission of infection

2.1 Exposure

C. psittaci is carried by domestic and wild birds. For humans, the infection is airborne from a bird-contaminated environment.

2.2 Occupational groups exposed

Work involving contact with birds, poultry or their excreta.

3. Clinical picture

3.1 Symptoms

Following an incubation period of usually one to two weeks, infection is usually characterized by an acute, febrile pneumonia. Asymptomatic forms may also be observed.

3.2 Diagnosis

Intracellular isolation of the bacteria is difficult. A number of serological tests can be carried out to identify antibodies. However, cross reactions may be observed between *C. psittaci*, *C. trachomatis* and *C. pneumoniae*. In addition, early treatment with tetracyclines can reduce antibodies.

Exposure criteria:

Minimum induction period: 48 hours

Maximum latent period: 21 days.

Avian influenza

1. Definition and causal agent

Avian influenza is caused by the Orthomyxoviridae virus *Influenza A*. Virus subtypes are identified by their glycoprotein haemagglutinin (H) and neuraminidase (N) antigens. At present 15 H subtypes (H1-H15) and nine neuraminidase subtypes (N1-N9) have been recognised. The virus primarily infects birds but more rarely other species, including pigs and humans. To date, all outbreaks of the highly pathogenic form of avian influenza have been caused by viruses of the H5 and H7 subtypes. Avian H5N1 is a strain with pandemic potential, since it might ultimately adapt into a strain that is contagious among humans.

2. Transmission of infection

2.1 Exposure

Wild waterfowl introduce avian influenza viruses, in their low pathogenic form, to poultry flocks, but do not carry or directly spread highly pathogenic viruses. Other bird species, including domestic poultry, develop disease when infected with avian influenza viruses. All evidence to date indicates that close contact with dead or sick birds is the principal source of human infection with the H5N1 virus.

2.2 Occupational Groups at risk

Workers engaged in slaughtering, plucking, butchering and preparing for consumption infected birds. Swimming in water where the carcasses of dead infected birds have been discarded or which may have been contaminated by faeces from infected ducks or other birds might be another source of exposure.

3. Clinical Disease

3.1 Symptoms

In general, human infection with these viruses has resulted in mild symptoms and very little severe illness. There is one notable exception: the highly pathogenic H5N1 virus. In many patients, the disease caused by the H5N1 subtype follows an aggressive clinical course, with rapid deterioration and high fatality. Initial symptoms include high fever, with a temperature above 38°C, and influenza-like symptoms. Diarrhoea, vomiting, abdominal pain, chest pain, and bleeding from the nose and gums have also been reported as early symptoms in some patients. The spectrum of clinical symptoms may, however, be broader, and not all confirmed patients have presented with respiratory symptoms. In some cases acute encephalitis, in the absence of any respiratory disease, has occurred.

3.2 Diagnosis

Common laboratory abnormalities, include leucopenia (mainly lymphopenia), thrombocytopenia, elevated serum aminotransferases, and evidence of disseminated intravascular coagulation. Isolation and identification of the causative virus. Tests for serum antibodies against H and N antigens are available for some virus subtypes.

3.3 Prognosis

Depending on the type of infection, from very good to fatal. Infection with the H5N1 strain has a poorer prognosis.

Exposure criteria:

Minimum intensity and duration of exposure: unknown.

Maximum latent period: 2 to 17 days (median 7 days).

Q fever

1. Definition and aetiological agent

Q fever is caused by the rickettsia *Coxiella burnetii*. In humans, infection is often benign and unnoticeable, but it can cause intermittent fever and in some cases endocarditis and hepatitis.

2. Transmission of infection

2.1 Exposure

There are two main routes by which humans can acquire infection with *C. burnetii*.

- (i) *via* infected domestic animals, particularly cattle and sheep. Humans can be infected from contaminated placentas, aborted matter, secretions, viscera, etc.
- (ii) *via* infected wild or domestic animals, through tick bites. This route appears to be much rarer.

2.2 Occupational groups exposed

The disease mainly affects sheep and cattle farmers, abattoir workers, veterinary surgeons and laboratory staff working with the bacteria.

3. Clinical picture

3.1 Symptoms

In humans, the disease is most often benign and goes unnoticed. Less often it may cause the sudden onset of an intermittent fever accompanied by general signs. In the acute phase, acute febrile pneumonia and gastro-intestinal disorders may occur. Longer term complications include endocarditis and hepatic complications.

3.2 Biological diagnosis

Isolating the bacteria is difficult. Diagnosis is mainly based on serological tests for specific IgG and IgM antibodies.

Exposure criteria:

Minimum induction period: one week;

Maximum latent period: three weeks.

Erysipeloid

1. Definition and aetiological agent

Erysipeloid is caused by *Erysipelothrix rhusiopathiae*. The bacteria are found in a number of species of domestic and wild animals, particularly mammals, birds, and aquatic animals. Humans can be infected through direct contact. Infection is characterized by skin lesions and is generally benign.

2. Transmission of infection

2.1 Exposure

A number of species of mammals and birds carry *E. rhusiopathiae*. Pigs are the most commonly infected (swine erysipelas). Humans contract the disease through contact with carriers or sick animals, when handling products of animal origin or objects contaminated by the animals. The path of infection is often through wounds or skin abrasions.

2.2 Occupational groups exposed

Gamekeepers, foresters; farmers, veterinary surgeons, abattoir, tripe and meat-processing workers; pig, cattle, poultry, game and other farmers; fishermen and fish-market workers; processing and conserving of food products of animal origin.

3. Clinical picture

3.1 Symptoms

Most often erythematous and oedematous skin lesions on the hands and fingers, following a wound. They may be accompanied by problems in the joints but the development of the disease is usually benign. In exceptional cases, cardiac disorders and septicaemia have been observed.

3.2 Diagnosis

Diagnosis is basically clinical. It may be confirmed by isolating and identifying bacteria from the lesion.

Exposure criteria:

Minimum induction period: a few hours;

Maximum latent period: seven days.

Tetanus

Definition and causal agent

Tetanus is caused by *Clostridium tetani*, an anaerobic, gram-positive, spore-forming bacillus. The resistance of the spores to drying and heating ensures its widespread distribution in soil and animals. Its anaerobic characteristics and the toxin produced within the bacterium during its early stages of growth have meant that tetanus remains a particularly serious sequelum of penetrating wounds, particularly where ignorance and poorly developed health services prevail.

1. Transmission of infection

1.1 Exposure

A world-wide hazard. Soil and faeces are the main source of exposure, with infection occurring through deep and uncleaned wounds.

2.2 Occupational groups at risk

Military forces and agricultural workers are probably at greatest risk due to their increased chances of acquiring penetrating wounds contaminated with soil.

2. Clinical disease

2.1 Presenting features

The (incubation) period from injury to onset of symptoms varies from one day to several months, though rarely exceeds two weeks. The severity of symptoms is related to the initial tissue damage and its contamination; the shorter the incubation period, the more serious the resulting disease. Muscle rigidity precedes muscle spasms and in most cases starts with stiffness of the facial muscles. Involvement of the pharynx or respiratory muscles causes respiratory deficiency. Later the limbs may be involved and full-blown generalized spasms will then follow. In survivors, full recovery takes 4 to 6 weeks.

2.2 Laboratory diagnosis

This is less important than the severe and life-threatening clinical picture, which usually provides the diagnosis.

2.3 Prognosis

The complications of the disease play a dominant role in tetanus. Respiratory paralysis or pneumonia is the most common and most dangerous, though autonomic nervous system damage can cause cardiovascular problems, and fractures of the spine can result from the muscular spasms. In untreated cases, mortality can be as high as 70%, depending on age, severity of the disease and availability of appropriate hospital care facilities.

Exposure criteria:

Minimum intensity and duration of exposure: not applicable

Maximum latent period: one month

Brucellosis

Definition of causal agent

Brucellosis is a zoonosis usually caused, in descending order of virulence, by the coccobacilli *Brucella melitensis*, *Brucella suis* or *Brucella abortus*. The organism grows slowly and is resistant to drying but sensitive to acid and heating. Infection may be acute, subacute, chronic or clinically unapparent. Infective animals may or may not show signs of the disease.

1. Transmission of infection

2.1. Exposure

Infection is most common in males aged 10 to 40 years. The natural reservoirs for the organism are goats, sheep, camels (*B. melitensis*), pigs (*B. suis*) and cattle (*B. abortus*). Dogs, horses and rabbits can also become infected. Infection occurs in humans due to drinking infected milk, tending infected animals or handling infected carcasses, in which case the organism may enter the body through cuts and abrasions.

2.2. Occupational groups at risk

This is a disease mainly of farmers, abattoir workers, butchers, meat packers, agricultural engineers, and laboratory technicians. Among veterinary surgeons, accidental inoculation or conjunctival contamination with brucella vaccine is an additional risk.

3. Clinical disease

3.1 Presenting features

The incubation period varies from several days to several months. The early symptoms of clinical disease are non-specific: fevers (sometimes episodic), chills, night sweats, aches and pain, anorexia and lethargy. Hepatosplenomegaly and lymphadenopathy occur in a minority of cases.

3.2 Laboratory diagnosis

- (i) Isolation of the organism is difficult.
- (ii) Serological tests for specific IgM or IgG antibodies.

3.3 Prognosis

The disease is self-limiting in 90% of cases. Serious or prolonged effects on the joints, heart or nervous system occur in 10% of infections.

Exposure criteria:

Acute infections:

Minimum intensity and duration of exposure: not applicable

Maximum latent period: one week

Chronic infections:

Minimum intensity and duration of exposure: not applicable

Maximum latent period before symptoms appear is difficult to determine and requires specialist medical advice.

Viral Hepatitis

Definition and causal agent

Viral hepatitis refers to infections of the liver caused by a number of viruses including hepatitis A, B, C, E, G, D (due to the delta agent, a defective virus), and epidemic non A. hepatitis. Infections with other viruses such as Epstein-Barr and cytomegalovirus may also cause hepatic disease. Although all these agents can cause occupationally-related infections, by far the most important world-wide occupational risks are from hepatitis B. Infection with hepatitis C and hepatitis A can also be acquired occupationally while other viruses very seldom cause occupational hepatitis.

Causal agent/s:

- Hepatitis A is a non-enveloped RNA virus in the hepatovirus genus of the picornavirus family.
- Hepatitis B virus is a DNA virus from the Hepadnaviridae family (4 serotypes and 7 genotypes of human hepatitis B are known).
- Hepatitis C virus is a RNA virus (6 genotypes and more than 100 subtypes of HCV have been identified).

□ Hepatitis B and C - Transmission of infection

1. Exposure

In general, hepatitis B and C infection occur in any situation in which the blood of an infected person enters the worker's bloodstream. This usually happens in case of occupational injury, but some cases of infection due to mucous and conjunctive contamination are reported. The capacity of the Hepatitis B virus (HBV) to cause infection is higher than that of Hepatitis C (HCV).

Occupational transmission of HBV

The risk of infection is primarily related to the degree of contact with blood at the work place and also to the antigenic profile (HbeAg) of the source person.

Blood contains the highest HBV titres of all body fluids and is the most important vehicle of transmission in the health care setting.

The likelihood of anti-HBV seroconversion after an accidental percutaneous exposure from an HBV-positive source is between 30% (HBsAg+ - HBeAg-) and 50% (HBsAg+ - HBeAg+). There are data to suggest that the threshold for infection is approximately 10^3 viral particles DNA/mL.

Occupational transmission of HCV

HCV is transmitted through occupational exposures to blood. A single exposure is sufficient to cause the infectious disease but the average incidence of anti-HCV seroconversion in health care workers after accidental percutaneous exposure from an HCV-positive source is relatively low (1,8% - range:0%-7%).

1.1 Occupational Groups at risk

For HBV and HCV infections, groups at risk are primarily those whose occupation brings them into contact with infected blood, blood products, or the body fluids or tissues of infected patients. They include health care workers and laboratory personnel (see Annex I entry nr. 407 ***Other infectious diseases caused by work in disease prevention, health care, domiciliary assistance and other comparable activities for which a risk of infection has been proven***). Other groups at risk are the staff of prisons and mental institutions and police, ambulance and other rescue services.

2. Clinical Disease

2.1 Presenting features

After an incubation period of 30–180 days (HBV) or 15–150 days (HCV), anorexia, nausea and vomiting are followed a few days later by jaundice and the passage of dark urine and pale stools. Diarrhoea, skin rashes and low grade fever can occur in a minority of cases. Clinical examination of the jaundiced patient usually reveals a smooth, tender, enlarged liver.

2.2 Laboratory diagnosis

Confirmed by the presence of high serum aminotransferases and the presence of:

- serum antigen markers (HbsAg, HbeAg) for HBV.
- viral RNA for HVC.

2.3 Prognosis

Hepatitis B is a self-limiting disease in up to 90% of patients. Fulminant (and frequently fatal) hepatitis occurs in less than 1% of patients, but some who recover from the acute phase can develop either a carrier stage (5 to 10%), or a chronic active hepatitis which can lead to liver cirrhosis and hepatocellular carcinoma in up to 30%. About 50% of hepatitis C patients develop a carrier stage, evolving, in 20-30% of cases, into chronic active hepatitis, liver cirrhosis or hepatocellular carcinoma.

3. General criteria for recognizing viral B and C hepatitis

3.1 Determination of causal agent

See section “definition of causal agent”

3.2 Diseases caused

Acute hepatitis

Persistent hepatitis

Chronic active hepatitis

Post-hepatitic cirrhosis

Post-cirrhotic liver cancer

Evidence of the effects of the viruses on hepatocytes (e.g. increase of serum transaminase levels), as sign of activity

Presence in the bloodstream of the appropriate combination of viral antigens, antibodies, DNA/RNA.

Qualitative HCV-RNA for HCV diagnosis.

3.3 Definition of specific criteria for identifying the infectious disease from the type of exposure

Type of occupation

Any occupation involving or likely to involve exposure to blood, blood derivatives, body fluids and biological samples.

Definition of exposure criteria:

Evidence of an episode in which the blood of an infected person could have entered the bloodstream of the worker: injury, contact between infected blood and mucous membrane/conjunctiva. An exposure that might place health care workers at risk for HBV and HCV infection is defined as a percutaneous injury (e.g. a needlestick or cut with a sharp object) or contact of mucous membrane or non-intact skin (e.g. chapped, abraded or affected by dermatitis) with blood, tissue or other potentially infectious fluid. In addition to blood and other blood contaminated body fluids, the following fluids are also considered potentially infectious: cerebrospinal, synovial, pleural, peritoneal, pericardial and amniotic fluids. Semen and vaginal secretions are also considered potentially infectious, even if they have not caused reported occupational infections in Health care workers. Faeces, nasal secretions, saliva, sputum, sweat, tears, urine and vomit are not considered potentially infectious unless they contain blood. In any case, the risk of transmission of HBV and HCV infection from these fluids and materials is low

As a general rule, the risk of infection depends on the viral concentration in the medium (in the case of accidents this may be determined directly) and on host factors, particularly previous immunization.

For acute infection

Minimum induction period: 60 days

Maximum latent period before symptoms: 180 days for hepatitis B; 160 days for hepatitis C.

For chronic infection

Maximum latent period: not determinable.

□ Hepatitis A – transmission of infection

1. Exposure

Faeco-oral transmission

1.2 Occupational Groups at risk

For infection with hepatitis A virus (HAV) individuals at risk are primarily those involved in health care or domiciliary assistance and sewage workers (see disease number 407 “Other infectious diseases caused by work in disease prevention, health care, domiciliary assistance and other comparable activities for which a risk of infection has been proven”).

2. Clinical Disease

2.1 Presenting features

After an incubation period of 15-45 days (usually 28 days), anorexia, nausea and vomiting are followed a few days later by jaundice and the passage of dark urine and pale stools. Diarrhoea, skin rashes and low grade fever occur in a minority of cases. Clinical examination of the jaundiced patient usually reveals a smooth, tender, enlarged liver.

2.2 Laboratory diagnosis

Evidence of IgM anti HAV during the acute phase of infection.

Evidence of the effects of the viruses on hepatocytes (increase of serum transaminase levels) as a sign of activity. Infection may be asymptomatic or may be clinically manifest across a range of severities from a mild illness lasting 1-2 weeks to a severe disabling disease lasting several months.

2.3 Prognosis

Usually recovery is complete. People usually do not remain infected for life.

3. General criteria for recognizing viral A hepatitis

3.1 Determination of causal agent

See section “definition of causal agent”

3.2 Diseases caused

Acute hepatitis

Definition of specific criteria for identifying the infectious disease from the type of exposure:

Type of occupation

Exposures that might place *workers* at risk for HAV infection include any situation in which faeco-oral transmission can take place, *e.g.* nursing or handling faecal samples in hospital laboratories. Usually, person to person spread is enhanced by poor hygienic conditions, but intra-institutional spread can also occur.

Minimum intensity and duration of exposure: The risk of infection is primarily related to any oral contact with materials contaminated by faecal material derived from an HAV infected source person. Since no HAV carrier conditions have been identified, the transmission of the infection is presumably related to non-epidemic and unapparent clinical infections. Even a single ingestion can cause the disease.

Minimum induction period: 15 days.

Maximum latent period before symptoms: 45 days.

Tuberculosis

Definition of causal agent

Mycobacterium Tuberculosis: M. Tuberculosis (human tuberculosis is largely confined to infection to this agent), and less frequently Mycobacterium Bovis, Mycobacterium Ulcerans and other mycobacteria.

1. Transmission of infection

1.1 Exposure

M. tuberculosis spreads from humans through contact with pulmonary secretions or sputum of infected persons. The risk of transmission is dependent on: the condition of the patient who is the source of infection (such as the presence of lung cavitation or bacilli in sputum and inappropriate treatment); environmental factors, with an enhanced risk in small or crowded spaces, and where there is inadequate ventilation; and the health status of the contact, including their previous vaccination or immunosuppression. The risk is higher in healthcare facilities located in communities with a high prevalence of TB infection, and especially where there is a high incidence of multidrug-resistant disease. Animal to human spread is unusual, except for M. Bovis in heavily contaminated milk.

1.2 Occupational Groups at risk

Those at risk are mainly health care workers and laboratory personnel, although farmers and veterinary workers can be exposed to M. bovis.

2. Clinical Disease

2.1 Presenting features

The onset of the disease is slow. The primary lesion is a tubercle. Such a lesion may become inactive and is usually asymptomatic.

Skin sensitivity appears within a few weeks. Pulmonary tuberculosis as a symptomatic disease that affects about 5 to 15% of the infected persons. It has a chronic variable course ranging from asymptomatic to widespread dissemination through the lungs and to the organs (kidney, brain, bones, etc.).

Reactivation of a latent tubercle focus is an important differential diagnosis.

2.2 Clinical pictures

Acute, sub-acute or chronic tuberculosis anywhere in the body but usually in the lungs.

Cutaneous forms of M. tuberculosis infection: Erythema nodosum - allergic manifestation which occurs within a few weeks of primary infection and resolves within a further three weeks.

Cervical lymphadenitis: Mainly *M. bovis*, occasionally *M. tuberculosis*. May be chronic and resistant to treatment.

Chronic tuberculosis: a pulmonary involvement is anticipated. In some cases, kidneys can be involved.

2.3 Laboratory and instrumental diagnosis

Presence of acid fast bacilli in sputum

- Evidence of *M. tuberculosis* in cultures of biological specimens

or

- Suggestive clinical picture or chest X-ray examination suggestive for TB and direct Microscopical identification of *M. tuberculosis* in sputum or tissue

or

- Suggestive clinical features or chest X-ray examination suggestive for TB and tuberculin skin test positivity.

Other appropriate investigations depending on organs involved

2.4 Prognosis

Recovery is good if tuberculosis is diagnosed early, as treatment with effective drugs is available.

3. General criteria for recognizing tuberculosis

3.1 Determination of causal agent

See section “definition of causal agent”

3.2 Disease caused

Acute, sub-acute or chronic tuberculosis anywhere in the body but usually in the lungs.

Para-clinical criteria

Possibly isolation of the organism on culture

3.3 Definition of specific criteria for identifying the infectious disease from the type of exposure

Type of occupation

Any occupation involving, or likely to involve exposure to infected patients for *M. Tuberculosis* (see Annex I entry nr. 407 ***Other infectious diseases caused by work in disease prevention, health care, domiciliary assistance and other comparable activities for which a risk of infection has been proven***) or animals (*M. Bovis*).

Definition of exposure criteria:

Exposure criteria for M. Tuberculosis.

Although the most frequent mode of transmission is airborne, cases of percutaneous transmission in case of cutaneous abrasions have also been reported, this last one above all in health care and laboratory workers.

Exposure criteria for M Bovis

Contact with infected animals or their products

Minimum intensity and duration of exposure: A single particle or a single exposure are in theory sufficient to cause the infectious disease (concept of *close contact*: those health care workers that have attended directly patients affected by TBC, even if in only one occasion and for a short time), however an extended exposure to multiple aerosolization is usually necessary, while a short contact implies a much inferior risk.

Maximum latent period:

M. Tuberculosis incubation period

- From contact to infection: 90 days.
- From infection to active TB disease: the risk is greatest during the first two years after infection.
- However, people who become infected with M.Tuberculosis have approximately a 10 to 15% risk of developing active TB during lifetime. The probability is higher and the disease progression more rapid in HIV infected persons.

M. Bovis incubation period

Acute forms: at least four weeks (usually presenting as enlarged lymph nodes).

Chronic: several years – a wide variety of organs may be involved.

Cutaneous forms of M. tuberculosis infection

Erythema nodosum – allergic manifestation which occurs within a few weeks of primary infection and resolves within a further three weeks.

Cervical lymphadenitis

Mainly M. Bovis, occasionally M. Tuberculosis. May be chronic and resistant to treatment.

Amoebiasis

Definition of causal agent

Entamoeba histolytica, a protozoan of 20-60mm diameter

1. Transmission of infection

1.1 Exposure

Infection with cysts of *E. histolytica* is acquired through ingestion of contaminated water or food or by cross-contamination with infected material or body parts such as unwashed hands. Motile trophozoites are released from cysts and, in most cases, remain as harmless commensals in the large bowel.

1.2 Occupational Groups at risk

The disease is endemic in Southern Europe but, mainly due to climate changes, it is now also found in Central and Northern Europe. In Europe, the main occupational groups at risk are those who travel for their work to endemic areas, especially agricultural areas, and sewage workers. Other groups at risk are fish breeders, health care workers, inmates of institutions and those who care for them.

2. Clinical Disease

2.1 Clinical features

The most common outcome of amoebic infection is asymptomatic passage *per rectum* of cysts. Symptomatic amoebic colitis appears 2-6 weeks after infection and is manifest by the gradual development of lower abdominal pain and diarrhoea, followed by malaise, weight loss, and diffuse lower abdominal or back pain. The earliest signs of intestinal infection are micro-ulcerations of the large bowel mucosa.

Caecal involvement may mimic acute appendicitis. Fulminant intestinal infections, with severe abdominal pain, high fever, and diarrhoea can occur. In some cases, megacolon may develop due to severe bowel dilatation with intramural air. Uncommonly, patients can develop a chronic form of amoebic colitis.

Extra-intestinal infection involves the liver, with the development of one or more amoebic liver abscesses. Pleuro-pulmonary involvement is seen in 20 to 30% of patients.

2.2 Diagnosis

Proctoscopy reveals ulcers with heaped up margins and normal intervening mucosa. Rarely, mass lesions ('amoebomas') can be seen. The diagnosis is confirmed by the microscopic finding of characteristic ematophagous trophozoites or cysts in stool specimens or material collected by rectal biopsy or ulcer aspirate. Culture of amoebas is more sensitive, but not routinely available. Kits for the performance of counterimmunodiffusion assays, agar gel diffusion assays and ELISA's are commercially available. Other appropriate investigations depend on which organs are believed to be involved

Exposure criteria:

Minimum intensity and duration of exposure: not applicable

Maximum latent period: six weeks.

Other infectious diseases caused by work in disease prevention, health care, domiciliary assistance and other comparable activities for which a risk of infection has been proven

Definition of causal agent

Almost any communicable infection may occur within the context of the delivery of health care whether this is within a hospital, the home, a laboratory or other related setting. Infections may be acquired as a result of occupational exposure to infectious patients or colleagues or through contact with contaminated equipment or environments.

Causal agents may be classified as:

Biological: micro-organisms, including those which have been genetically modified, cell cultures and human endoparasites, which may be able to provoke any infection, allergy or toxicity

Microbial: any microbiological entity potentially able to reproduce in the human body, or to transfer genetic material into different cells.

From cellular culture: the result of the growth *in vitro* of cells derived from multicellular organisms.

The causal agent, based on its characteristics, can be transferred by:

- ***Direct contact*** through body surface to body surface contact and physical transfer of a micro-organism between a susceptible host and an infected or colonized subject
- ***Indirect contact*** of a susceptible host with a contaminated object.
 - o almost all patient-related healthcare tasks pose a risk of direct or indirect transmission. Agents and diseases that are transmitted in these ways include: *Salmonella* species, *Campylobacter*, hepatitis A virus, hepatitis E virus, *E.coli*, *Clostridium difficile*, scabies, pediculosis and herpes.
- ***Droplet contact*** from conjunctival, nasal or oral mucosal contact with droplets containing microorganisms propelled over short distances and generated by an infected subject through coughing, sneezing, talking or during medical procedures, such as lung function measurement or bronchoscopy. This mode applies to tuberculosis, pertussis, *Meningococcal* meningitis, influenza, rubella, mumps, *Haemophilus influenzae* and *Streptococcus pneumoniae*.
- ***Airborne transmission*** occurs via exposure to

microorganisms contained in droplets that remain suspended in the air over longer distances or to contact with infectious dust particles disseminated by air. Airborne transmission may take place in any indoor space where infectious patients are present, particularly where there is poor ventilation. Measles, tuberculosis, varicella and anthrax may all be transmitted in this way.

- **Bloodborne transmission** requires blood-to-blood transfer of an organism from an infected host to the healthcare worker (HCW). A similar transmission may less commonly arise from blood-mucosal/dermal contact. Bloodborne transmission occurs through accidents involving infected surgical or medical instruments or through contact between infected blood and the skin or mucous membranes of a worker. Tasks that pose a risk of direct contact with patient's blood include surgery, endoscopy, injections and manipulation of venous routes and arteries, paracentesis, dialysis, and oral/dental surgery. Indirect bloodborne transmission is possible while manipulating and transporting biological samples, disposal or cleaning of surgical instruments and the cleaning contaminated surfaces. Hepatitis B and C and HIV are examples of infections transmitted through these routes.

Main occupational uses and sources of exposure:

Virtually all HCW are potentially exposed to various body fluids, medical equipment, environmental surfaces or air which might pose infectious risk. In general, all job tasks entailing direct patient assistance or handling of biological samples may represent a biohazard to the HCW. Health care workers who have frequent contact with patients and their body fluids or environments carry a higher risk of acquiring or transmitting infections through accidental exposures as compared to those HCW who have sporadic and brief contact.

For bloodborne transmission, work that involves "exposure prone procedures" (EPP) is the major determinant of injuries and may influence the transmission of agents such as HBV, HCV and HIV between infected patients and HCW. A current definition of an EPP is:

"Those invasive procedures where there is a risk that injury to the worker may result in exposure of the patient's open tissues to the blood of the worker. These include procedures where the

worker's gloved hands may be in contact with sharp instruments, needle tips or sharp tissues (e.g. spicules of bone or teeth) inside a patient's open body cavity, wound or confined anatomical space where the hands or fingertips may not be completely visible at all times".

Examples of EPPs are sternotomy, arterial cutdown with tissue dissection, many dental procedures, open surgical procedures, assistance to patients with significant risk of biting.

Of the many infectious diseases which can be transmitted to health care workers, some important examples (hepatitis and tuberculosis) are examined separately in other chapters. This chapter describes rubella, SARS, HIV, enteric fevers, scabies and pediculosis.

Airborne pathogens

□ Rubella

1. Definition and causal agent

Rubella is a systemic viral illness caused by the rubella togavirus.

2. Transmission of infection

The main transmission route is through direct droplet contact of the oral or nasal mucous membranes with respiratory secretions from an infected individual; transmission may also occur through direct and indirect contact of oral or nasal mucous membranes with urine from an infant with congenital rubella syndrome.

3. Clinical picture

3.1 Presenting features

Rubella usually presents as a non specific maculopapular rash lasting 3 days or fewer with generalized lymphadenopathy. Asymptomatic infections are common. The rash may be preceded by fever, headache, malaise.

Congenital rubella is a disease contracted during pregnancy. It causes significant disease in the embryo or foetus, characterised by cataract, hearing loss and cardiac malformations. In some cases there are effects on the central nervous, renal, respiratory, hepatic and blood systems. In the most severe cases foetal death is the outcome. Rubella presenting without a rash can pose a risk to pregnant healthcare workers.

3.2 Diagnosis

Typical clinical features with laboratory evidence: rubella IgM antibody positive or four-fold rise in rubella IgG antibody or positive rubella culture of an appropriate specimen.

Exposure criteria:

The incubation period is 14 to 21 days. The period of communicability is from 7 days before to 7 days after the onset of rash. Infants with congenital rubella may be infectious for months after birth.

Minimum intensity of exposure: not applicable.

Minimum induction period: even a single exposure is sufficient to cause the infectious disease.

Maximum latent period: 21 days.

☐ Severe acute respiratory syndrome (SARS)***1. Definition and causal agent***

Pneumonia caused by infection with SARS-associated coronavirus (SARS-coV)

2. Transmission of infection

The main mode of transmission appears to be by close person-to-person contact. The virus is transmitted most readily by respiratory droplets produced when an infected person coughs or sneezes from a short distance and virus is deposited on the mucous membranes of the mouth, nose, or eyes of persons who are nearby. The virus also can spread by direct contact with surfaces or objects contaminated with infectious droplets. In addition, airborne transmission is possible. Transmission may occur from asymptomatic infected persons.

3. Clinical picture***3.1 Presenting features***

Following an incubation period of 2-10 days (median 5), the illness typically begins with fever. After 3-7 days lower respiratory symptoms appear, including a dry, non productive cough or dyspnoea. By day 7 of the illness, most SARS patients demonstrate abnormalities on chest radiographs and the clinical features of an acute pneumonia..

3.2 Diagnostic criteria

Presence of the SARS-coV in patient's sera, secretata or excreta demonstrated by:

- a) Direct immunofluorescence assay addressed at detecting ScoV recombinant antigens
- b) Viral isolation
- c) Detection of virus RNA through RT-PCR assay
- d) Monoclonal antibodies directed against structural components of the virus (nucleocapsid protein)

Chest X-ray signs consistent with pneumonia.

Exposure criteria:

Minimum intensity of exposure: As a general rule, the less serious patients are the less infective, and contagiousity increases with the gravity of the disease. However, in some cases infection has derived from asymptomatic persons.

Minimum induction period: even a single exposure is sufficient to cause the infectious disease.

Maximum latent period: 10 days.

□ Other viral infections/airborne bacterial infections

1. Definitions and causal agents

Other viral infections include: adenovirus, herpesvirus, parvovirus, paramyxovirus morbillae, paramyxovirus, orthomyxovirus influenzae, and any other viruses potentially present in a patient's exhaled air.

Important airborne bacterial infections included:: *Neisseria meningitidis*, *Bordetella pertussis*; *Staphylococcus aureus*, *Streptococcus* group A and *Meningococcus*.

2. Transmission of infection

The main mode of transmission of these agents is through close person-to-person contact, most readily by respiratory droplets. Transmission may also occur by direct contact with surfaces or objects contaminated with infectious droplets; in addition, airborne transmission is possible. Transmission may occur from asymptomatic infected persons.

3. Clinical picture

Evidence of the specific exanthema and/or clinical manifestations

Presence of specific IgM and IgG immunoglobulins if applicable

Presence or culture of the organisms in host's secreta or excreta

Exposure criteria:

Minimum intensity of exposure: not applicable.

Minimum induction period: even a single exposure is sufficient to cause the infectious disease.

Maximum latent period: depending on the agent.

For tuberculosis, see Annex I entry nr. 405 on '**Tuberculosis**'

Blood borne pathogens

The main determinants of occupational transmission of bloodborne pathogens include:

- a. Risk of exposure to blood or body fluids (taking into account working activities, exposure prone procedures, control measures, personal protective equipment and devices etc.)
- b. Prevalence of infection among patients
- c. Efficiency of transmission, determined by type of injury, biological agent and the viral load in the source

-
- d. Effectiveness of post-exposure prophylaxis
 - e. Susceptibility of the injured workers.

For diseases caused by the hepatitis viruses see Annex I entry nr. 404 on '**Viral hepatitis**'.

□ Diseases caused by human immunodeficiency virus

1. Definition and causal agent

Two types of human immunodeficiency virus (HIV) exist: HIV-1 and HIV-2. They result in a similar spectrum of clinical diseases though HIV-2 is thought to be less virulent. HIV-1 is primarily responsible for the HIV/AIDS pandemic while HIV-2 is found mainly in West Africa.

2. Transmission of infection

Occupational acquisition on infection with HIV in a health care setting is almost exclusively through direct contact with infected blood; in most cases through injury. Infection through contact with mucous membranes including conjunctivae is feasible but extremely rare.

3. Clinical picture

3.1 Presenting features:

Infection with HIV is followed by the development of the Acquired Immuno-Deficiency Syndrome (AIDS). AIDS is characterized by HIV infection and clinical evidence of immune deficiency, with an increase of opportunistic such as *Pneumocystis carinii* pneumonia and infection from *Mycobacterial*, *Cryptococcae*, *Cytomegalovirus*, and *Toxoplasma*. In addition there is an increased risk of malignancies such as Kaposi's sarcoma and lymphoma.

3.2 Diagnosis

Presence in the bloodstream of the anti-HIV antibody. Evidence of the effects of the virus on lymphocytes (reduction of T-Helper, reduction of the Helper/suppressor ratio).

Exposure criteria:

Minimum intensity and duration of exposure: not applicable since even a single exposure is sufficient to induce infection. However several factors affect the risk of HIV transmission after an occupational exposure. These include an increased risk after exposure to a substantial quantity of infected blood as indicated by:

- a) Device visibly contaminated with the patient's blood;
- b) Procedure that involved a needle being placed directly in a vein or artery;
- c) A deep injury

NOTE: HIV-infected subjects may transmit virus since early infection

The risk is also increased by exposure to blood from a patient host whose illness is terminal. Although a lower viral load (e.g. <1,500 RNA copies/ml) or one that is below the limits of detection probably indicates a lower intensity of exposure, it does not rule out the possibility of transmission.

Maximum latent period:

- **From contact to seroconversion:** 12 months, taking into account that most subjects who acquire infection after percutaneous exposure develop HIV antibody within 6 months.
- **From seroconversion to AIDS:** dependent on type and timing of therapy after seroconversion.

Other routes of infection

❑ Enteric fever

1. Definition and causal agent

Gastrointestinal disease caused by infection with *Salmonella typhi*; *Salmonella paratyphi A* and *B* or *Salmonella typhimurium*.

2. Transmission of infection

Ingestion of water or food that has been contaminated by a human carrier; occasionally through direct contact with a carrier host.

3. Clinical picture

3.1 Presenting features

Constipation, diarrhoea, abdominal tenderness, fever, headache.

3.2 Diagnosis

Determination of agglutinating antibodies to O or H antigens (Widal test for *S. Typhimurium*).

Leucopenia and neutropenia (25% of patients).

Isolation of the organism in faecal culture.

Exposure criteria:

Minimum intensity and duration of exposure: not applicable

Maximum latent period: 60 days from infection.

❑ Enteric viral infections

1. Definition and causal agents

Gastroenteritis caused by human single-stranded RNA enteroviruses including rotaviruses, Norwalk virus, poliovirus and others.

2. *Transmission of infection*

Ingestion of contaminated food or water. More rarely infection can arise from contact of contaminated fingers with the eyes; airborne transmission can also take place.

3. *Clinical picture*

3.1 *Presenting features*

More than 50% of non-polio and more than 90% of polio virus infections are subclinical, asymptomatic or associated only with mild symptoms. In most cases, the clinical picture is non-specific; diarrhoea, abdominal pain and vomiting in conjunction with fever, headache and sometimes upper respiratory tract symptoms. In a minority of cases of polio infection there is involvement of motor neurones and paralysis.

3.2 *Diagnostic criteria*

Isolation of the viruses in stool or cell cultures.

Exposure criteria

Minimum intensity and duration of exposure: not applicable.

Maximum latent period: 35 days (but usually less than a week.)

□ **Scabies**

1. *Definition and causal agent*

Dermal infestation by the mite *Sarcoptes scabiei*.

2. *Transmission*

Direct contact with infested host, clothing or bedding

3. *Clinical picture*

3.1 *Presenting features*

Localised, itchy rash induced by sensitization to the excreta of the mite.

3.2 *Diagnosis*

Microscopic examination of material obtained from a mite burrow collected with a needle or scalpel blade.

Biopsy showing the mite or its products.

Exposure criteria:

Minimum intensity and duration of exposure: a single contact may result in infestation

Maximum latent period: from contact to initial manifestation of symptoms: 6 weeks. In cases of reinfestation (sensitised): no latency period.

□ Pediculosis

1. Definition and causal agent

Dermal infestation with *Pediculus humanus* var. *capitis/corporis/pubis*.

2. Transmission

Direct contact with infested host, clothing or bedding. The incubation period is 6 to 10 days. The period of communicability continues until 24 hours after effective treatment of lice and ova.

3. Clinical picture

3.1 Presenting features

Localised, intensely itchy maculopapular rash in sensitized persons.

3.2 Diagnosis

Finding of nits or adult lice in hair or clothing.

Exposure criteria:

Minimum intensity and duration of exposure: a single contact may result in infestation

Maximum latent period: from contact to disease: 10 days

Skin effects are also included under these two entries – see below.

Cataracts caused by heat radiation (502.01)

Conjunctival ailments following exposure to ultraviolet radiation (502.02)

Definition of causal agent

Heat and ultraviolet radiation are two forms of non-ionising radiation that can cause cataracts and conjunctival damage. Different ocular and skin effects can also occur from exposure to other forms of non-ionising radiation, and are described below.

The non-ionizing radiations which can cause typical disorders in man are those with wavelengths between 100 nm and 1m e.g.

- ultraviolet radiation (UV) (100 to 400 nm)
- visible light (400 to 760 nm)
- infrared radiation (IR) (760 nm to 3 µm)
- microwaves (1 µm to 1m)

Laser radiation within these wavelengths is also included under this heading.

Non-ionizing radiations with wavelengths > 1 m have no proven effect on health.

Main occupational uses and sources of exposure:

- UV: bactericidal lamps, plasma arc and xenon welding, solar radiation especially at high altitudes, industrial lasers
- IR: solar radiation, sources of radiant heat, industrial lasers

Adverse effects

1. Pathological effects of ultraviolet radiation

The extent to which UV radiation penetrates the body, and its biological effects, vary according to the wavelength:

- UV(C) is absorbed through the skin, conjunctiva and cornea, but does not penetrate any further,
- UV(B) penetrates as far as the lens,
- UV(A) may reach the retina

Acute effects

☐ Keratoconjunctivitis

A painful disorder with conjunctival hyperaemia and photophobia. If the cause is a UV laser, the cornea may be severely affected with subsequent opacification.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- history and study of working conditions providing evidence of intense exposure (intensity greater than the limit values) to UV(C) or UV(B) or UV lasers.

Minimum duration of exposure: About one second.

Maximum latent period: 48 hours.

☐ Photoretinitis

Phototrauma of the retina.

Relatively painless disorder of the retina, with transient blindness, if the damage of the fovea is mild. If the damage is more severe, persistent distortion of visual image and scotoma may occur. Burns outside the foveal area may cause no subjective symptoms.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- History and study of working conditions providing evidence of intense exposure to UV(A), particularly industrial lasers (A).

Minimum duration of exposure: Fraction of a second.

Maximum latent period: Immediate blindness

Chronic effects**☐ Actinic cataract**

This is usually a disorder of the anterior capsule of the lens, extending to the sub-capsular epithelium.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure assessed by:

- History and study of working conditions providing evidence of prolonged or repeated exposure to UV(B) and UV(A)

Minimum duration of exposure: One year.

Maximum latent period: 15 years.

2. Pathological effects of visible light***Acute effects*****☐ Photoretinitis**

Photochemical damage may be caused by blue light emitted at 400 to 550 nm or broad spectrum light emitted at high power (xenon projectors, arc lamps, flashguns). Documented pathological effects are those caused by class III and IV lasers used in visible light, which can cause acute lesions, ocular pain, transient blindness and persistence of visual image, chromatic deficiency.

Photoretinitis can occur also asymptotically during exposure to continuous-wave lasers; a thorough examination may discover the presence of a scotoma.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure assessed by:

- History and study of working conditions providing evidence of intense exposure to the above mentioned forms of radiation.

Minimum duration of exposure: A few seconds.

Maximum latent period: One year.

3. Pathological effects of infrared radiation

Acute effects

☐ Thermal effects on the anterior part of the eye and surrounding areas

Burning sensation on the skin around the eyes, blepharitis and keratitis.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by: history and study of working conditions providing evidence of intense exposure to broad-spectrum (IR)B and IR(C) emitters (sun, incandescent light sources, special lamps) or to industrial lasers.

Minimum duration of exposure: A few minutes.

Maximum latent period: 24 hours.

☐ Heat-related retinal disorders

Burns cause immediate oedematous lesions, which later show pigmentary changes. Often scars related to small burns and those after viral infections are identical in their morphology.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure assessed by:

- History and examination of working conditions providing evidence of intense exposure industrial lasers.

Minimum duration of exposure: About one second

Maximum latent period: 24 hours.

Chronic effects

☐ Glass workers' cataract (Heat-induced cataract)

This starts in the posterior cortex of the lens and forms a web, leading to irregularly shaped discoid posterior opacification.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure assessed by:

- History and study of working conditions providing evidence of prolonged or repeated exposure to IR radiation emitted by incandescent glass or metal (over 1 500°C).

Minimum duration of exposure: One year.

Maximum latent period: 15 years.

4. Pathological effects of microwaves

□ Heat cataract

Cloudy opacities on the posterior cortex of the lens. Spot opacities spread over the lens cortex.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure assessed by:

- History and study of working conditions providing evidence of exposure to microwaves (wavelength of the order of centimetres or even decimetres)

Minimum duration of exposure: Depends on intensity of the radiation. High-energy radiation (several hundred mW/cm²) can rapidly damage the lens.

Maximum latent period: 15 years.

5. Cutaneous effects from exposure to non-ionising radiation

Acute Effects:

Erythema, skin burns. See also Annex I entry nr. 201 on ***Skin diseases and skin cancers***.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure assessed by:

- History and study of working conditions providing evidence of intense exposure to UV(C);
- and if the data is available:

Guide value: exposure of the uncovered parts to UV(C) with intensity of the dose received on skin > 0.03 J/cm².

Minimum duration of exposure: A few minutes.

Maximum latent period: 24 hours.

Chronic effects:

□ Skin cancers

These appear on uncovered parts of the body (head, neck, hands and forearms) and are mainly associated with occupations exposed to solar radiation. They include basal cells and spinocellular epitheliomas and malignant melanomas.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- History and study of working conditions providing evidence of prolonged or repeated exposure to solar radiation.

Minimum duration of exposure: 20 years.

Minimum induction period: Epitheliomas: 20 years; Melanomas: five years.

See section on ***Occupational cancers*** in the **Preface**.

Hypoacusis or deafness caused by noise

Definition of causal agent

Sound is an ondulatory phenomenon by means of which mechanical vibration energy is propagated through an elastic medium, generally air, giving rise to auditory perception. Noise is a class of sounds that are disturbing, harmful or detrimental to hearing.

This document covers only the effects of noise to the auditory system. The risk of noise induced chronic hearing loss depends on the cumulative cochlear noise exposure, which is determined by daily noise exposure level, including impulsive noise, and exposure time in years.

Adverse effects

1. Acute effects

Neurosensory effects

Dizziness, tinnitus, hypoacusis which can lead to total deafness.

The auditory deficit in acute acoustic trauma is neurosensory or mixed (both conductive and neurosensory), symmetric or asymmetric depending on symmetry of exposure, and generally partly reversible, depending on the energy of the sound wave and the duration of exposure.

Physical damage:

Laceration of the tympanic membrane, with bleeding.

The site of the lesion is in the tympanic membrane, middle ear and cochlea.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure assessed by:

- History and study of working conditions providing evidence of sudden exposure to a very loud noise (above 140 dB).

Importance of the notion of suddenness of the causal phenomenon (bang, explosion, etc.)

Minimum duration of exposure: Brief.

Maximum latent period: The symptoms should appear immediately or at most within two days after exposure to the noise.

2. Chronic effects

Occupational hearing loss:

The disease develops slowly and insidiously. It is possible to distinguish various phases which characterize how serious the condition has become. Tinnitus can be heard in each phase. Hypoacusis is characterized by a quantitative reduction in auditory sensitivity, by a loss of the ability to discriminate between sounds and by a qualitative deterioration in the recruitment of the acoustic signal.

The site of the lesion is the cochlea; hypoacusis is of the neurosensory type, more pronounced on the frequencies 3 to 6 kHz. It is bilateral and generally symmetrical, irreversible but usually not progressive once exposure to noise ceased.

Exposure criteria:

Minimum intensity of exposure:

- Occupational exposure assessed by history and study of working conditions providing evidence of prolonged or repeated cochlear exposure to noise of over 85 dB(A) (A-weighted), or to repeated peak noise of over 137 dB(C) (C-weighted).
- Non-occupational exposure should be assessed

It is possible, however, that exposure to the noise levels of over 80 dB(A) and peak noise over 135 (C) dB are already a source of mild occupational hearing loss.

Minimum duration of exposure: Six months with 93 dB(A) daily exposure for the most susceptible individuals. Every 3 dB increase in noise exposure halves the time of onset of adverse effects.

Maximum latent period: Does not apply, but changes in hearing develop gradually in relationship to increasing cumulative exposure.

Diseases caused by atmospheric compression or decompression

Definition of causal agent

Certain disorders are associated with spending time in a compressed atmosphere and are directly due to pressure itself resp. to changes of the pressure or to inhalation of compressed gas mixtures.

Other disorders occur during or after decompression.

These disorders affect professional divers and those working in compressed air.

Acute effects

□ Acute diseases caused by the mechanical effects of pressure

- *Barotrauma of the middle ear*
Haemorrhagic exudate or burst eardrum accompanied by otalgia, otorrhagia, tinnitus aurium or hypoacusis.
- *Barotrauma of the inner ear*
Sometimes dissociated cochleovestibular disorder.
- *Barotrauma of the sinuses*
- *Excess pressure on the lungs*
Breathlessness, haemoptysis

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed by the anamnesis providing evidence of work being carried out in conditions where pressure exceeds atmospheric pressure.

Minimum duration of exposure: Brief.

Maximum latent period: 36 hours.

□ Conditions caused by the toxic effects of inhaled gases

- *Nitrogen narcosis ("rapture of the deep")*

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed by the anamnesis providing evidence of diving work to depths in excess of 50 metres.

Minimum duration of exposure: Brief.

Maximum latent period: A few minutes.

- *Hypo-oxaemic attack*
Convulsions preceded by cramp, dizziness and nausea.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure, confirmed by the anamnesis providing evidence of work involving diving to depths in excess of 100 metres, with inhalation of compressed air.

Minimum duration of exposure: Brief.

Maximum latent period: A few minutes.

- *High pressure neurological syndrome*
Tremors, muscle contractions, dizziness and nausea.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed by the anamnesis providing evidence of work involving diving under helium to depths in excess of 50 metres.

Minimum duration of exposure: Brief.

Maximum latent period: A few minutes.

□ Decompression diseases

- *Bends*
Osteoarticular pain
- *Subcutaneous formication*
- *Neurological disturbances*
Paraplegia, etc.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed by the anamnesis providing evidence of diving work involving rapid resurfacing.

Minimum duration of exposure: Brief.

Maximum latent period: A few hours.

Chronic effects**□ Diseases caused by pressure**

Hypoacusis

Caused by irreversible cochlear damage with or without labyrinthic syndrome.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed by the anamnesis.

Minimum duration of exposure: Three months.

Maximum latent period: One month.

□ Decompression diseases

Dysbaric osteonecrosis

Affecting the shoulder, hip, or knee with characteristic skeletal X-ray picture.

Minimum intensity of exposure: Occupational exposure confirmed by the anamnesis.

Minimum duration of exposure: Three months.

Maximum latent period: 20 years.

Pressure below that of ground level atmospheric pressure

Definition of causal agent

In order to permit passengers of modern aircraft to breathe without using masks the cabins of both pilot and passenger sections are pressurised. However, the pressure level produced is not that of ground level atmospheric pressure but only that equivalent to 2000 m above sea level (moderate low pressure).

Manufacturing or maintenance companies often modify, adapt or repair the equipment of the aircraft during flight without passengers. Similar activity takes place during the testing of new aircraft.

In flight, during repair, changes, and in unplanned incidents, pressure may become considerably lower than that of ground level atmospheric pressure.

Physiologic effects may occur both when low pressure is established and when atmospheric pressure corresponding to ground level is re-established. Organs most susceptible are the middle ear and sinuses.

Another risk is given by modern fire protection systems in store-rooms working by reduction of the oxygen content of the air down to 13 % of oxygen.

Acute effects

□ Barotrauma of the middle ear

Symptoms and signs: Sudden pain, hearing loss, bleeding from the ear. Burst eardrum (confirmed by inspection).

Exposure criteria:

Minimum intensity of exposure: Occupational change of external pressure, confirmed by anamnesis and measurement outprints, if possible.

Minimum duration of exposure: Brief.

Maximum latent period: A few minutes.

□ Effects of modern fire protection systems

Symptoms and signs: Cognitive impairments, Headache, Dizziness, Tiredness, Tachycardia, Lowering of the blood pressure.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed by anamnesis

Minimum duration of exposure: A few minutes

Maximum latent period: 2 hours

Chronic sub-acute effects

□ Barotrauma of the middle ear

Symptoms and signs: Increasing pain, hearing loss, inflammation and bleeding from the ear.

Exposure criteria:

Minimum intensity of exposure: Occupational change of external pressure, confirmed by anamnesis and measurement outprints, if possible.

Minimum duration of exposure: Six months.

Maximum latent period: One month.

□ Effects of modern fire protection systems

Symptoms and signs: Neurological failures.

Exposure criteria:

See above

Osteoarticular diseases of the hands and wrists caused by mechanical vibration (505.01)

Angioneurotic diseases caused by mechanical vibration (505.02)

Definition of causal agent

Mechanical vibration is an oscillating motion about a central fixed position. Vibration frequency, expressed in Hertz (Hz), describes the cyclic nature of vibration. Vibration is separated into two subcategories: hand-arm vibration (HAV) and whole-body vibration (WBV).

This section deals only with HAV. For HAV the relevant nominal frequency range is from 5 to 1500 Hz but frequencies usually occur between 125 till 300 Hz. According to the ISO standard (ISO 5349:1986, revised), the exposure is expressed as an exposure period in combination with an exposure intensity measured in m/s^2 , a frequency weighted and an 8 hour time averaged acceleration total value $a_{\text{hv}}(\text{eq},8\text{h})$ or just $A(8)$. Acceleration is now measured in 3 directions.

Main occupational uses and sources of exposure:

Occupational vibration reaches the worker through different paths or transmission routes. HAV arises when e.g. grinding, spinning, fettling, using a grinding wheel, chainsaw, high pressure water hose, hammer drill, rammer, chisel, chipping hammer or other pneumatic tool, that is, when either pressing the work-piece to a rotating tool, or pressing the tool to the work-piece.

Adverse effects

The majority of *hand-arm vibration syndrome (HAVS)* subjects have a combination of vascular and sensorineural effects. In severe cases there may be osteoarticular diseases. Clinical picture and diagnostic criteria are described for angioneurotic diseases first as the most common disease.

Clinical picture and diagnostic criteria

□ Angioneurotic diseases

Vibration-induced white fingers (Raynaud's phenomenon of occupational origin):

The disease is characterized by attacks of vasoconstriction of the digital arteries. Attacks can last for minutes to hours and are more likely to occur with exposure to the cold.

The Stockholm Workshop (1986) HAVS classification system for cold-induced peripheral vascular symptoms is an internationally recognized grading system:

Stage 1 (mild): Occasional attacks affecting only the tips of one or more fingers precipitated by exposure to a cold environment, touching cold objects or immersion in cold water

Stage 2 (moderate): Occasional attacks affecting distal and middle (rarely also proximal) of one or more fingers

Stage 3 (severe): Frequent attacks affecting all phalanges of most fingers

Stage 4 (very severe): Frequent attacks affecting all phalanges of most fingers with trophic changes in the fingertips.

The diagnostic procedure involves a detailed recollection of symptoms and medical history and may involve additional tests, e.g. a test of cold provocation with measurement of finger blood pressure before and after cooling.

Differential diagnosis: Idiopathic Mb. Raynaud or Mb. Raynaud as part of other medical disease (e.g. scleroderma or other connective tissue diseases, other vascular disease, polycythemia, medication).

Peripheral sensorineural polyneuropathy:

Symptoms include tingling and numbness in finger and hands. In later stages reduced sensation of touch, temperature and vibration and an impairment of manual dexterity.

In the Stockholm Workshop grading system 3 stages are recognized:

Stage 1 (mild): Intermittent numbness with or without tingling.

Stage 2 (moderate): Intermittent or persistent numbness, reduced sensory perception

Stage 3 (severe): Intermittent or persistent numbness, reduced tactile discrimination and/or manipulative dexterity.

The diagnostic procedure involves a detailed analysis of symptoms and medical history and a clinical neurological examination. Quantitative neurosensory tests may contribute to the diagnosis.

Differential diagnosis: Polyneuropathia and carpal tunnel syndrome of other origin.

See Annex I entry nr. 506.45 on *Carpal tunnel syndrome*.

☐ Osteoarticular diseases

- Osteoarthritis of the elbow and wrist;
- Carpal bone diseases
 - Osteonecrosis of the semilunate bone (Kienböck's disease)
 - Pseudoarthrosis of the scaphoid bone

Osteoarticular disease is confirmed by radiography.

☐ Other diseases

There is moderate evidence that contracture of the palmar aponeurosis (Dupuytren's disease) may occur as an effect of HAV.

The prevalence of musculo-skeletal diseases of the upper limb, shoulder or neck is increased in HAV-exposed but it has not been possible to separate the effect of HAV from the effect of other physical factors, i.e. force, repetition and posture.

It is not clear if HAV induces bone injuries such as vacuoles and cysts.

Exposure criteria:

Minimum intensity of exposure: Individual exposure history with confirmation of exposure to occupational HAV. Information about hand-arm vibration levels for specific tools used may be obtained from existing databases.

An inverse relationship between acceleration level and duration exists. If exposed to a frequency weighted and time averaged acceleration $\geq 3 \text{ m/s}^2$ (A(8)) for 10 years 10 % of the exposed will develop vibration induced white fingers. Same exposure level for sensorineural polyneuropathy. The exposure-response relationship for osteoarticular diseases may be different. Thus, HAV with a frequency range below 100 Hz and of high magnitude appears to be associated with joint and bone pathology (pneumatic percussive tools).

According to the EU directive 2002/44/EC the daily exposure limit value (A(8)) shall be 5 m/s^2 and the action value 2.5 m/s^2 .

Minimum duration of exposure: Depending on acceleration level.

$3\text{-}10 \text{ m/s}^2$ (A(8)): 3-10 years

$>10 \text{ m/s}^2$ (A(8)): 1-3 years.

Maximum latent period: Not known, probably months.

Induction period: Same as minimum duration.

Diseases of the periarticular sacs due to pressure

Definition of causal agent

Inflammation of a bursae may occur as a result of several causes.

Occupational bursitis may be caused by trauma, chronic overuse, pressure, friction, awkward posture. The friction type of bursitis may be related to excessive friction associated with specific occupations, for example, prepatellar bursitis is typical for home cleaners (housemaids), carpet layers, roofers, coal miners; olecranon bursitis – for draughtsmen, engravers, polishers, watchmakers; ischial bursitis – for weavers (weaver's bottom). *Sports* that can cause bursitis include jogging, tennis and squash.

Occupational diseases of the periarticular sacs caused by mechanical pressure are called **bursitis**.

Bursitis

Definition

Acute or chronic inflammation of a bursa. Bursitis does not cause joint deformity but can cause significant pain and restrict movement.

Most bursitis occurs in the olecranon, shoulder, knee, but other common forms exist: calcaneal (Achilles), iliopsoas (iliopsoas), ischial and trochanteric.

Other causes

Infective and septic bursitis may be caused by acute or chronic infection by a wide range of organisms, most commonly *Staphylococcus aureus*.

Bursitis may also occur as a result of *systemic diseases*, such as rheumatoid arthritis, ankylosing spondylitis, scleroderma.

Degenerative changes and calcification in a subjacent tendon may irritate the overlying bursa and cause bursitis e.g. Subacromial bursitis secondary to calcific supraspinatus, gout.

Diagnostic criteria

- Occupational history which confirms exposure. A detailed interview of the job tasks, which is essential to understand the work nature and its possible relation to bursitis.
- Clinical symptoms. The main symptoms include pain and tenderness around joints and may include stiffness of the joint with the pain often being most severe at night (see also symptoms at different forms of bursitis).
- Physical symptoms (see different forms of bursitis).
- Laboratory investigations and Xrays are used primarily to exclude other conditions.

Pre-patellar and sub-patellar bursitis

Definition of causal agent

Local trauma, such as resulting from a direct blow or a fall on the knee or occupation requiring excessive kneeling can produce pre-patellar bursitis. Superficial infra-patellar bursitis (*clergyman knee*) is placed more distally than pre-patellar bursitis and is associated with a more upright posture when kneeling. The deep infra-patellar bursa is inflamed less frequently than the superficial infra-patellar bursa.

Main occupations where observed: carpet layers, coal miners, roofers, plumbers, gardeners, homemakers etc.

Definition

Pre-patellar bursitis is the inflammation of the bursa overlying the patella resulting in marked increase of fluid within its space.

Incidence of pre-patellar bursitis is greater in males than females.

Synonyms: “housemaid’s knee”, “carpet layers' knee” and “beat knee”.

Sub-patellar (s. infra-patellar) bursitis is inflammation of the sub-patellar bursa.

The sub-patellar bursa can be divided into superficial and deep components. The deep component lies between the patellar ligament and the upper anterior surface of the tibia, and the superficial component lies between the patellar ligament and the skin.

Synonym: “clergyman knee”.

□ Acute pre-patellar and sub-patellar bursitis

Onset may be sudden if secondary to acute trauma. The inflammation and swelling strike over a few hours or days. If caused by injury, bursitis will resolve after a few days or weeks.

Exposure criteria:

Minimal intensity of exposure: occupational trauma such as a fall on the patella, direct blow to the knee or blunt trauma to the knee confirmed by anamnesis.

Minimal duration of exposure: from a few seconds or minutes to eight hours.

Maximal latent period: three days.

Diagnostic criteria

- History: occupational trauma of the knee.
- Clinical symptoms:
 - Knee pain
 - Swelling of the knee
 - Redness of the knee

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- Difficulty with ambulation
 - Inability to kneel on the affected side.
- **Signs.** During physical examination any of the following signs and symptoms may be noted:
- Tenderness of the patella to palpation
 - Fluctuant oedema over the lower pole of the patella
 - Localised erythema
 - Localised crepitation
 - Decreased knee flexion secondary to pain.

Differential diagnosis

- Anterior Cruciate Ligament Injury
- Medial Collateral and Lateral Collateral Ligament Injury
- Posterior Cruciate Ligament Injury
- Pes Anserinus Bursitis
- Rheumatoid Arthritis
- Presence of infection
- Crystalline inflammatory arthropathy (eg, gout, pseudogout).

Necessary investigations:

Investigations are necessary to exclude other diagnoses

□ Chronic pre-patellar and sub-patellar (infra-patellar) bursitis

Occupational chronic pre-patellar and sub-patellar (infra-patellar) bursitis may develop initially as chronic disease or the development may be gradual without an acute phase (bursopathia). History of recurrent minor injuries associated with overuse (e.g. repeated kneeling) is present. This bursitis may be associated with rheumatoid arthritis and infection.

Exposure criteria:

Minimal intensity of exposure: occupational exposure confirmed, if possible assessed, by the history and analysis of working conditions providing evidence of repeated friction between skin and patella.

Minimal duration of exposure: several months.

Maximal latent period: one month

Diagnostic criteria

- Occupational history
- Clinical symptoms. Pre-patellar bursitis causes pain and swelling felt at the front of the knee, chiefly on kneeling; superficial sub-patellar bursitis causes pain and diffuse swelling over the tibial tubercle and lower portion of the patellar ligament. Most typically the following symptoms could be observed:
 - Increased pain at night
 - Redness of the knee
 - Local heat of the knee
 - Tenderness of the knee.

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- Physical examination:
 - In the case of *pre-patellar bursitis*:
 - fluctuant, well-circumscribed, warm oedema is present over the lower pole of the patella;
 - crepitation may be found upon palpation;
 - pain may be increased on knee flexion due to increased tension over the bursa;
 - knee joint is normal
 - In the case of *sub-patellar bursitis*:
 - the patient has painless passive flexion and extension, however, pain occurs with active flexion and extension at the extremes of the range of motion;
 - Oedema, when visible, is on both sides of the patellar tendon, these sites usually are tender.

Differential diagnosis

- Presence of infection.
- Septic bursitis.
- Rheumatoid arthritis.
- Osteoarthritis.
- Crystalline inflammatory arthropathy (e.g. gout, pseudogout).

Olecranon bursitis

Definition of causal agent

Acute or repetitive (cumulative) microtrauma. Acute injuries could involve any activity causing direct trauma to the posterior elbow (e.g. direct blow, contusion, falling onto hard floor and landing on the olecranon process). Repetitive micro-trauma – prolonged pressure to the elbow, repetitively rubbing olecranon region against a table, chronic overuse.

Main occupations where observed: miners, polishers, draftsmen, engravers, glass-blowers, watchmakers, sportsmen, etc.

Definition

Olecranon bursitis is the inflammation of the bursa overlying the olecranon process at the proximal aspect of the ulna. The bursa is located between the ulna and the skin at the posterior tip of the elbow. Olecranon bursitis is much more common in men.

Synonyms: “draftsman’s elbow”, “student’s elbow” and “beat elbow”.

□ Acute olecranon bursitis

Adverse effects

Acute olecranon bursitis is characterized by pain, localized tenderness and limitation of motion. The bursal wall secretes a serous effusion when inflamed. Swelling on the posterior side of the elbow and redness are frequently present.

Diagnostic criteria

- History: occupational trauma or exposure involving direct trauma to the posterior elbow
- Clinical symptoms:
 - Onset may be sudden if secondary to acute trauma
 - Focal swelling at the posterior elbow
 - Usually pain at the affected site, however, sometimes the swelling is painless
 - Pain often is exacerbated by pressure
 - Increased pain at night
 - Frequent bumping of the swollen elbow occurs because it protrudes further than normal.
- Signs:
 - The most classic finding is localized posterior elbow swelling which is clearly demarcated, appearing as a golf ball over the olecranon process
 - Tenderness to palpation is noted
 - The area may be warm and red
 - Skin inspection may reveal abrasion or contusion if there was recent trauma

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- Elbow range of motion (ROM) usually is normal, but occasionally the end range of elbow flexion may be slightly limited due to pain
 - Elbow pain during active or passive ROM may increase suspicion of fracture of the olecranon process.

Exposure criteria:

Minimal intensity of exposure: occupational trauma or occupational exposure assessed by history providing evidence of work involving pressure being placed on the elbow.

Minimal duration of exposure: from a few seconds or minutes to eight hours.

Maximal latent period: three days.

Differential diagnosis

- Fracture of the olecranon process of the ulna
- Presence of infection
- Crystalline inflammatory arthropathy (eg, gout, pseudogout)
- Ganglion - a cyst on a tendon, the elbow joint capsule or periarticular bursae
- Radial neuropathy
- Tennis elbow – inflammation of tendons surrounding the elbow joint
- Rheumatoid arthritis.

Necessary investigations:

Investigations are necessary primarily for excluding other differential diagnoses.

□ Chronic olecranon bursitis

Occupational chronic bursitis usually developed as initial chronic disease. The development is gradual without acute stadium (bursopathia). History of repetitive pressure at the elbow or chronic irritation is present.

Repetitive microtrauma could cause serous, proliferative and degenerative changes in the bursa. Eventually may develop adhesions, villus formation, tags and calcareous deposits. Pain, swelling and tenderness may result in muscle atrophy and limitation of motion.

Exposure criteria:

Minimal intensity of exposure: occupational exposure confirmed, if possible assessed, by the history and analysis of working conditions providing evidence of work being carried out in conditions with repetitive trauma of elbow.

Minimal duration of exposure: several months.

Maximal latent period: one month.

Diagnostic criteria

- Occupational history
- Clinical symptoms:
 - patients usually notice gradual focal swelling and pain at the posterior elbow, sometimes the Swelling is painless;
 - Sain often is exacerbated by pressure;

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- increased pain at night
 - Chronic recurrent swelling usually is not tender.
- Signs:
- The most typical finding is localized fluctuant posterior elbow swelling
 - The area may be warm and red
 - Tenderness to palpation is noted at the affected site
 - Elbow range of motion usually is normal but may be limited due to big size of localized swelling.

Differential diagnosis

- Presence of infection
- Tennis elbow
- Ganglion – a cyst on a tendon, the elbow joint capsule or periarticular bursae
- Crystalline inflammatory arthropathy (gout, pseudogout)
- Rheumatoid arthritis.

Laboratory studies must be provided if it is necessary.

Shoulder bursitis

Definition

There are several bursae in the shoulder region: the subacromial, the subdeltoid, the subcoracoid, and the subscapular, which, as their names imply, lay beneath the acromion, deltoid, coracoid and scapula, respectively. Although any of the above mentioned bursae can become irritated, inflamed and painful as a result of overuse of or trauma to the shoulder region, the subacromial bursa is by far the most frequently afflicted and often occupational in origin.

□ Subacromial bursitis

Definition

Subacromial bursitis is inflammation of the subacromial bursa.

In the normal shoulder the coracoacromial ligament crosses the supraspinatus and infraspinatus tendon portions of the rotator cuff. In some individuals, contact pressure from this ligament produces an ischemic lesion of the cuff and can produce tendinitis with intervening bursitis in the subacromial bursa.

Definition of causal agent

Acute injuries or repetitive (cumulative) microtrauma.

Irritation is usually a result of friction, which causes the lining of the bursa to thicken, thus increasing the amount of friction. This affects the normal gliding movement of the soft structures over the bony structures of the shoulder.

Shoulder bursitis is typical for occupations where workers must perform repetitive activities with an elevated arm and big amplitude of movements in shoulder.

Main occupations: blacksmiths, sawyers, earth diggers, etc.

Shoulder bursitis is a common disorder often seen in sportsmen who participate in sports that require repetitive throwing and swinging motions and who use the shoulder joint throughout its entire range of motion, such as in swimming, gymnastic and wrestling.

□ Acute subacromial bursitis

Acute subacromial bursitis is characterized by localized pain and tenderness, limitation of motion. If acute mechanical trauma occurs in a pre-existing degenerative area, frank disruption of the cuff may result. Impingement of the inflamed area occurs in the middle range of abduction during normal shoulder elevation, but the impinged area is out of the way during full elevation.

Exposure criteria:

Minimal intensity of exposure: occupational trauma or occupational exposure assessed by anamnesis providing evidence of work involving the overuse of the shoulder.

Minimal duration of exposure: from a few seconds or minutes to eight hours.

Minimal latent period: three days.

Diagnostic criteria

- History: occupational trauma or exposure involving the overuse of the shoulder or intensive use of the shoulder joint throughout its entire range of motion.
- Clinical symptoms:
 - onset may be sudden if secondary to acute trauma;
 - pain;
 - localized tenderness;
 - limitation of motions.
- Signs:
 - pain originates in the subacromial region and often is exacerbated by pressure, during shoulder abduction and internal and external rotation;
 - patients begin to experience anterior shoulder pain when the arm is abducted at 30-40 degrees of elevation; as shoulder elevation beyond 120 degrees is reached, the pain may resolve;
 - in some cases pain is limited to the lateral arm about the deltoid insertion on the humerus (referred pain);
 - tenderness to palpation is noted over the greater trochanter and beneath the deltoid muscle;
 - a limited active range of motion;
 - with significant disruption of the rotator cuff, a patient may have no active elevation past mid range because of lost cuff function.

Differential diagnosis

- Presence of infection (sepsis). Acute shoulder sepsis may mimic acute bursitis because of the comparable severity of pain. Sepsis is usually associated with systemic signs, such as an elevated sedimentation rate and white blood cell count.
- Acute monoarticular arthritis (rheumatoid, tuberculosis, gout).

Investigations may be necessary to exclude other differential diagnoses

□ Chronic subacromial bursitis

Chronic subacromial bursitis may follow previous attacks of acute bursitis or repeated trauma. Occupational chronic subacromial bursitis also may develop as initial chronic disease. The development may be gradual without acute stadium (bursopathia). History of repetitive activities with an elevated arm is present.

The apparent pathology of shoulder bursitis involving the subacromial bursa is attributable to a fibrous build – up and to the presence of fluid that accumulates as a result of the area's constant inflammation. In more chronic situations, there is degenerative rupture of the tendon. If acute mechanical trauma occurs in a pre-existing degenerative area, frank disruption of the cuff may result. Impingement of the inflamed area occurs in the middle range of abduction during normal shoulder elevation, but the impinged area is out of the way during full elevation.

Exposure criteria:

Minimal intensity of exposure: occupational exposure confirmed, if possible assessed, by the anamnesis and analysis of working conditions providing evidence of performing repetitive activities with an elevated arm or repetitive throwing and swinging motions.

Minimal duration of exposure: several months.

Maximal latent period: one month.

Diagnostic criteria

- Occupational history
- Clinical symptoms:
 - limited active range of motion;
 - pain, especially during shoulder abduction and internal and external rotation;
 - night pain;
 - localized tenderness;
 - loss of muscular strength and range of motion.
- Signs:
 - pain is typically caused by abduction and internal and external rotation and originates in subacromial region;
 - tenderness upon palpation of the deltoid and the acromium and over the greater trochanter;
 - muscle atrophy may be noticeable if the condition has been present for several weeks or longer;
 - with significant disruption of the rotator cuff, a patient may have no active elevation past mid range because of lost cuff function.

Differential diagnosis

- Presence of infection;
- Crystalline inflammatory arthropathy;
- Systemic diseases (rheumatoid arthritis, psoriatic arthritis etc.);
- Bone tumours.

Diseases due to overstraining of the tendon sheaths

Definition of causal agent

Prolonged periods of highly repetitive hand movements. The use of force and awkward position of the hand are aggravating factors.

Main occupational uses and sources of exposure:

Repetitive and forceful hand use, e.g. in meat cutting, fish filleting, machine feeding, manual assembly, use of hand-held tools.

Definition

Tenosynovitis: Inflammation of the flexor and extensor tendon synovial sheaths in the hand.

Diagnostic criteria

Pain in the dorsal and/or palmar aspect of the wrist.

Clinical signs: Palpation tenderness of the affected tendon sheaths. Pain elicited when the tendons are activated, e.g. in resisted extension or flexion of the wrist. In the acute phase swelling, redness, warmth, crepitation may be found.

Exposure criteria:

Minimum intensity of exposure: Individual exposure history with confirmation of prolonged occupational exposure to highly repetitive hand motions. Working with the wrists/hands in awkward positions and /or using hand force aggravates the exposure.

Measurements of repetition at the work place (e.g. number of items handled, no. of hand repetitions), assessment of time spent in awkward positions of wrist/hand and assessment of force exerted (e.g. handled weights, applied forces) may add valuable information although threshold limits for exposure are not established.

Highly repetitive procedures (guiding): >10 items handled/minute or >20 repetitions/minute. High force (guiding): >1 kg. handled weights.

Minimum duration of exposure: Days

Maximum latent period: A few days

Induction period: Days

Diseases due to overstraining of the peritendineum

Definition of causal agent

Prolonged periods of highly repetitive wrist/hand movements. The use of force and awkward position of the hand are aggravating factors.

Main occupational uses and sources of exposure:

Repetitive and forceful wrist/hand use, e.g. in meat cutting, fish filleting, machine feeding, manual assembly, use of hand-held tools.

Definition

Peritendinitis: Inflammation of the peritendineum (the fibrous layer around the tendon). The condition is common in the wrist but may involve other tendons.

Diagnostic criteria

Pain in the affected tendon.

Clinical signs: Palpation tenderness of the affected tendons. Pain elicited when the tendons are activated, e.g. in resisted extension or flexion of the wrist. In the acute phase swelling, redness, warmth may be found. Clinically, the condition may be difficult to distinguish from tenosynovitis.

Exposure criteria:

Minimum intensity of exposure

Individual exposure anamnesis with confirmation of prolonged occupational exposure to highly repetitive hand motions. Working with the wrists/hands in awkward positions and /or using hand force aggravates the exposure.

Measurements of repetition at the work place (e.g. number of items handled, no. of hand repetitions), assessment of time spent in awkward positions of wrist/hand and assessment of force exerted (e.g. handled weights) may add valuable information although threshold limits for exposure are not established.

Highly repetitive procedures (guiding): >10 items handled/minute or >20 repetitions/minute. High force (guiding): >1 kg. handled weights.

Minimum duration of exposure: Days

Maximum latent period: A few days

Induction period: Days

Diseases due to overstraining of the muscular and tendonous insertions

Definition of causal agent

Lateral and medial epicondylitis, biceps tendonitis:

Prolonged periods of forceful and repetitive arm movements.

Supraspinatus tendonitis:

Prolonged periods of forceful and repetitive arm and shoulder movements.

Prolonged periods of work with the arms elevated more than 50-60 degrees.

Main occupational uses and sources of exposure:

Repetitive and forceful hand use, e.g. in meat cutting, fish filleting, machine feeding, manual assembly, use of hand-held tools.

Washing and painting of ceilings, mounting fittings, pipes etc. below the ceiling

Definition

Lateral epicondylitis (tennis elbow): Inflammation of the extensor tendons at the lateral epicondyle.

Medial epicondylitis (golf elbow): Inflammation of the flexor tendons at the medial epicondyle.

Biceps tendonitis: Inflammation of the long biceps tendon in the shoulder (the intertubercular sulcus of the humerus).

Supraspinatus tendonitis: Inflammation or degeneration of the supraspinatus tendon in the shoulder (the major tubercle of the humerus).

Diagnostic criteria

Pain in the affected tendon.

Clinical signs: Palpation tenderness of the affected tendon. Local pain elicited when the tendon is activated, e.g. in resisted extension or flexion of the wrist or resisted abduction in the shoulder.

Exposure criteria:

Minimum intensity of exposure: Individual exposure anamnesis with confirmation of prolonged occupational exposure to forceful and repetitive arm motions and/or prolonged periods of work with the arms elevated.

Measurements of repetition at the work place (e.g. number of items handled, no. of hand repetitions), assessment of force exerted (e.g. handled weights) and percent of the work time with the arms elevated may add valuable information although threshold limits for exposure are not established.

Highly repetitive procedures (guiding): More than 10 items handled/minute or more than 20 repetitions/minute. High force (guiding): More than 1 kg. handled weights. Arm elevation (guiding): Arms elevated more than 50-60 degrees more than 50% of the work time.

Minimum duration of exposure: Days

Maximum latent period: A few days

Induction period: Days

Meniscus lesions following extended periods of work in a kneeling or squatting position

Definition of causal agent

Maintaining a working posture involving kneeling or squatting probably in combination with a crouching position and/or heavy lifting. Repeated minor injuries as slipping because of wet or uneven support may play a role.

Main occupational uses and sources of exposure:

Prolonged kneeling or squatting, e.g. miners, floor layers, carpenters, electricians.

Definition

Tear of the lateral or medial meniscus of the knee.

Diagnostic criteria

Pain at the medial or lateral aspect of the knee joint, swelling, locking. Positive provocation test for meniscus injury, e.g. Mc Murray's test. Radiography rules out other causes. MRI scan and ultrasound may show meniscus injury. Arthroscopy confirms the diagnosis.

Other causes, e.g. sports injuries, should be ruled out.

Exposure criteria:

Minimum intensity of exposure

Prolonged kneeling or squatting confirmed by exposure history. The exact dose-response relationship is not known. The evidence is based on studies from the forties and the fifties of miners.

Minimum duration of exposure: Weeks

Maximum latent period: Days

Induction period: Weeks

Paralysis of the nerves due to pressure

Definition of causal agent

Prolonged external pressure on anatomical grooves causing nerve injuries as a result of compression, e.g. the use of handheld tools with repeated or sustained pressure against the carpal bones in median nerve compression or carrying heavy weights on the shoulder in compression of the long thoracic nerve.

Definitions

Carpal tunnel syndrome

Compression of the median nerve in the wrist.

Guyon's cavity syndrome

Compression of the ulnar nerve in the wrist.

Cubital tunnel syndrome

Compression of the ulnar nerve in the elbow.

Tarsal tunnel syndrome

Compression of the tibial nerve in the ankle.

The external popliteal nerve

Compression of the nerve at the neck of the fibula.

The long thoracic nerve

Compression of the nerve at shoulder level

Diagnostic criteria

Neurological symptoms from the innervated structures. Diagnosis is confirmed by neurophysiological testing.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure assessed by history and, if possible, study of the working conditions showing evidence of prolonged and repeated direct pressure on the part of the body concerned. Repetitive movements with extreme flexion and extension and exposure to vibration (carpal tunnel syndrome) can worsen the condition (**see also Annex I entry nr. 506.45 on Carpal tunnel syndrome**).

Minimum duration of exposure: From a few hours to several months.

Maximum latent period: Days

Induction period: Hours

Carpal tunnel syndrome

Definition of causal agent

Prolonged periods of highly repetitive hand movements. The use of force and awkward position of the wrist/hand are aggravating factors.

Hand-arm vibrations (see also Annex I entry nr. 505.02 on *Angioneurotic diseases caused by mechanical vibration*).

Direct pressure causing carpal tunnel compression (see also Annex I entry nr. 506.40 on *Paralysis of the nerves due to pressure*).

Main occupational uses and sources of exposure:

Repetitive and forceful hand use, e.g. in meat cutting, fish filleting, sorting of parcels, manual assembling.

Exposure to hand-arm vibrating tools, e.g. in grinding, polishing, working with a chain saw, drilling.

Working with hand-held tools with pressure against the carpus, e.g. a chisel or repeated impacts against the carpus (e.g. using the hand as a hammer).

Definition

The carpal tunnel syndrome is a condition that consists in compression of the median nerve as it passes through the carpal tunnel.

Diagnostic criteria

Symptoms: Sensory symptoms involve numbness, tingling and/or pain in the median nerve distribution. Symptoms often occur during the night. In more severe cases motor symptoms (weakness and loss of hand function) may occur. Consideration of other known causes for carpal tunnel syndrome such as hormonal factors (e.g. pregnancy), certain medical conditions (e.g. thyroid dysfunction, rheumatoid arthritis) and trauma of the wrist. Diabetes mellitus causing neuropathy should be considered as a differential diagnosis.

Clinical signs: Clinical examination involves Tinel's test (tapping the flexor retinaculum elicits sensory symptoms in the radial 3½ fingers) and Phalen's test (maximal flexion of the wrist for 1 minute elicits symptoms in the radial 3½ fingers). A clinical test for sensibility may show impairment in the median area. Thenar atrophy and reduced hand force may be present in more severe cases.

Electrodiagnostic testing confirms the diagnosis but in obvious cases this may be omitted.

The condition may be uni- or bilateral depending on the exposure.

Exposure criteria:

Minimum intensity of exposure: Repetitive and forceful hand use:

Individual exposure history with confirmation of occupational exposure to highly repetitive hand motions. Working with the hands in awkward or extreme positions and/or using hand force aggravate the exposure.

Measurements of repetition at the work place (e.g. number of items handled, no. of hand repetitions), assessment of time spent in awkward positions and assessment of force exerted (e.g. handled weights, applied forces) may add valuable information though threshold limits for exposure are not established.

Highly repetitive procedures (guiding): >10 items handled/minute or >20 hand repetitions/minute

High force (guiding): > 1 kg. handled weights.

Hand-arm vibrations:

Individual exposure history with confirmation of the use of vibrating handheld tools.

Information on hand-arm vibration levels in different tools may be obtained from existing databases.

Vibration levels: Frequency weighted acceleration >3 m/sec² 4 hours pr. day or more for 8 years or more. Higher acceleration levels diminish the demand for exposure time.

Direct pressure:

Individual exposure history.

Minimum duration of exposure: Repetitive and forceful hand use, direct pressure: Months.

Hand-arm vibrations:

Depending on acceleration level.

3-10 m/s²: 3-10 years.

>10 m/s²: 1-3 year.

Maximum latent period: 1 month.

Induction period: As for minimum duration of exposure

Miners' nystagmus

Definition

Historical occupational disease associated with poor lighting, which involves problems in focusing. Pendular or rotating nystagmus may be accompanied by dizziness and headaches.

Exposure Criteria:

Minimum intensity of exposure: History and evidence of exposure to lighting below the standards prescribed for comfort (in underground work).

Minimum duration of exposure: Years

Maximum latent period: Not known

Diseases caused by ionizing radiation

Definition of causal agent

Charged corpuscular radiation (alpha and beta particles) is the cause of internal irradiation (e.g. inhalation of radon). Neutral corpuscular radiation (neutrons) or electromagnetic radiation (X- or gamma-rays) is dangerous in terms of external irradiation.

Sources of exposure and main occupational uses:
X-ray machines, particle accelerators, gamma radiography sources, cobalt bombs, nuclear reactors, laboratory equipment, work involving isotopes, uranium mines.

Adverse effects

1. *Non-random (non-stochastic) effects*

☐ **Acute effects:**

These are early effects which depend on the dose and the dose rate.

I. Whole body irradiation

Medullar aplasia

With initial lymphopenia and chromosomal aberrations.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure assessed by:

History and study of working conditions providing evidence of external whole-body irradiation in excess of 1 Gray for X-ray or gamma-ray irradiation and 0.3 Gray for neutrons.

Minimum duration of exposure: A few minutes.

Maximum latent period: Two months.

II. Partial-body irradiation

Acute radio-epidermatitis

Exudative lesions developing approximately three weeks after transient erythema, with necrosis as a possible complication.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure assessed by:

History and study of working conditions providing evidence of external X-ray or gamma-ray irradiation in excess of 10 Gray.

Minimum duration of exposure: A few minutes.

Maximum latent period: Two months.

Alopecia

Temporary hair loss after localized irradiation of the scalp.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure assessed by:
History and study of working conditions providing evidence of external X-ray or gamma-ray irradiation in excess of 3 Gray.

Minimum duration of exposure: A few minutes.

Maximum latent period: Two months.

Minimum induction period: 15 days.

Oligospermia and azoospermia

Exposure criteria:

Minimum intensity of exposure: Occupational exposure assessed by:
History and study of working conditions providing evidence of external X-ray or gamma-ray irradiation in excess of 0.3 Gray.

Minimum duration of exposure: A few minutes.

Maximum latent period: Two months.

□ Delayed effects

These appear some time after irradiation, whether this has been brief or prolonged.

Cataract

Crystalline opacities in the lens.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure assessed by:
History and study of working conditions providing evidence of external irradiation involving cumulative doses to the eye exceeding 10 Gray for X-rays and 8 Sv for neutrons (0.8 Gy).

Minimum duration of exposure: Can be brief.

Maximum latent period: Five years.

Minimum induction period: One year.

Chronic radiodermatitis

Atrophy, hyperkeratosis or telangiectasia, possibly complicated by radionecrosis.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure assessed by:

History and study of working conditions providing evidence of repeated external irradiation in excess of 5 mGy/day. Total skin dose > 10Gy.

Minimum duration of exposure: six month.

Maximum latent period: Five years.

☐ Effects on reproduction and teratogenesis

Ionizing radiation is mutagenic to germ cells

In certain accidental circumstances, exposure of a pregnant woman radiation can cause foetal deformities depending on dose received by the foetus and the age of the foetus at the time of irradiation.

Cerebral deformities (e.g. mikrocephalus) and skeletal deformities

Exposure criteria:

Minimum intensity of exposure: Occupational exposure assessed by:

History and study of working conditions providing evidence of brief X-ray irradiation of the foetus in excess of 0.3 Gy during the period of organogenesis.

Mental retardation

Exposure criteria:

Minimum intensity of exposure: Occupational exposure assessed by:

History and study of working conditions providing evidence of brief X-ray irradiation of the foetus in excess of 0.5 Gy beyond the eighth week of intra-uterine life.

2. Random (stochastic) effects

These are delayed effects arising after brief or prolonged irradiation as cutaneous spinocellular epithelioma, leukaemia, primary cancer of the lung, osteosarcoma. There is a causative correlation between the working in uranium mines and the increased incidence of lung cancer.

Minimum intensity: cumulative X-ray dose to the skin in excess of 15 Gy for cutaneous spinocellular epithelioma, cumulative dose in excess of 1 Sv for leukaemia und primary carcinoma of the lung and cumulative dose of the skeleton in excess of 8 Gy for osteosarcoma. For workers in uranium mines with an exposure of 200 WLM (Working Level Month, energy of the alpha radiation multiplied by the number of working month) or more, there is an adequate probability for

occupational induced lung cancer. In individual cases, an exposure of 50 WLM or less can be sufficient. The individual risk can be estimated according to the model of Jacobi.

Minimum induction period: 10 years for the cutaneous spinocellular epithelioma, three years for leukaemia and five years for primary cancer of the lung and osteosarcoma.

See section on **Occupational cancers** in the **Preface**.

Some isotopes present a particular affinity for specific organs (for example: iodine for the thyroid gland). Increased exposure to cosmic radiation during flights has been proposed as a potential occupational risk factor and there is ongoing discussion on the aetiology of the increased risks for breast cancer (females) and malignant melanoma in pilots and flight attendants.

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