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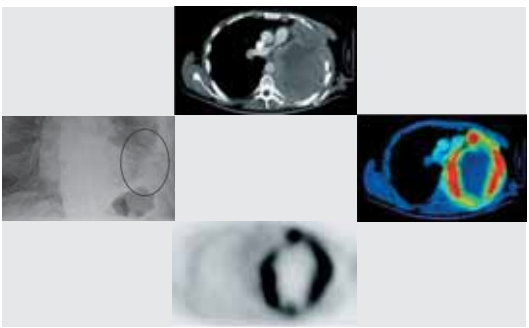
OCCUPATIONAL CANCER:

MALIGNANT MESOTHELIOMA



INSTITUTE FOR OCCUPATIONAL HEALTH
OF THE NATIONAL ACADEMY OF MEDICAL SCIENCES OF UKRAINE

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The monograph expounds main modern scientific information on MM epidemiology, etiology, pathogenesis, classification, clinical manifestations, data, diagnosis, treatment, prevention and evaluation of malignant mesothelioma in relation to workplace conditions.

It is recommended for oncology practitioners, occupational therapists, generalists, pulmonologists, family physicians, labour hygienists, students and trainees of post-graduate advanced programs provided by divisions of higher medical institutions, and scientists.

ISBN 978-966-2144-81-9

CONTENT

LIST OF ABBREVIATIONS

ACI — asbestos-cement industry
ChA — chrysotile asbestos
CI — confidence interval
CT — computed tomography
DNA — deoxyribonucleic acid
^{18}F-FDG — fluorodeoxyglucose
IARC — International Agency for Research on Cancer
ICD-10 — International Statistical Classification of Diseases and Related Health Problems 10th Revision
ICD-O — International Statistical Classification of Diseases for Oncology
ICR — individual cancer risk
ILO — International Labour Organization
MBT — mycobacteria tuberculosis
MM — malignant mesothelioma
MN — malignant neoplasm
MRT — Magnetic Resonance Tomography
NAMS — National Academy of Medical Sciences
NPP — nuclear power plant
OR — odds ratio
PCR — population cancer risk
PET — Positron Emission Tomography
SFM — sheet-forming machine
SV-40 — Simian vacuolating virus 40
TNM — Tumour, Nodus, Metastasis Classification of Malignant Tumours
URi — nhalation cancer unit risk
WHA — World Health Assembly
WHO — World Health Organization

INTRODUCTION

Occupational cancer is a group of malignant neoplasms of multifactorial etiology which is prevailed by carcinogenic factors (chemical, physical, biological etc.) in the workplace environment during operating procedures.

According to the ILO Employment Injury Benefits Convention, 1964 (amended in 1980) (No. 121) and the ILO Recommendation concerning the List of Occupational Diseases and the Recording and Notification of Occupational Accidents and Diseases, 2002 (No. 194), occupational cancer is a special group of occupational diseases. Asbestos has been proved to be one of the agents causing occupational cancer.

According to the WHO International Agency for Research on Cancer (IARC), all forms of asbestos (actinolite, amosite, antofillite, chrysotile, crocidolite, tremolite including asbestos-containing mineral materials) are listed in the Group 1 carcinogens («Carcinogenic to Humans»). Numerous epidemiological and experimental studies evidenced that asbestos causes cancer of the larynx, bronchi and lungs, and ovarian cancer as well as malignant mesothelioma (MM) of pleura, peritoneal mesothelioma and pericardial mesothelioma (IARC Monographs, V. 14, Sup. 7, 100 C.).

Special attention attached to the MM issue during latest decades is associated with WHO's persistent implementation of the Elimination of Asbestos Related Diseases policy started in 2013 as a part of the Goal 4 of the «WHO Global Action Plan for the Prevention and Control of Noncommunicable and Mental Health Diseases 2013–2020» (resolution WHA66.10). MM is recognized to be a pathology which is indicative of exposure to asbestos («signal», «indicative», «sentinel» tumour), that is why it was selected to be the controlled index of the effectiveness in achieving that goal on both national and global levels.

At present, there are two approaches to the elimination of asbestos-related diseases in the world: (1) a total prohibition of use of all types of asbestos which is an approach on which WHO insists; and (2) a total prohibition of use of amphibole asbestos with a «controlled use» of asbestos derived from serpentine minerals (chrysotile asbestos).

According to the ILO Convention «Safety in the Use of Asbestos», 1986 (No. 162), it is recommended to implement both approaches. The Article 10 of the Conventions stipulates: «Where necessary to protect

the health of workers and technically practicable, national laws or regulations shall provide for one or more of the following measures: (a) replacement of asbestos or of certain types of asbestos or products containing asbestos by other materials or products or the use of alternative technology, scientifically evaluated by the competent authority as harmless or less harmful, whenever this is possible; (b) total or partial prohibition of the use of asbestos or of certain types of asbestos or products containing asbestos in certain work processes». Meanwhile, the Convention does not imply a total prohibition of asbestos.

Malignant mesothelioma (MM) (synonyms: cellomic cancer, sarcomatous endothelioma) (ICD-10 code C45.-) is a rare malignant form of neoplasm which develops from multipotent cells of the mesothelium and consists of sarcomatoid spindle-shaped cells and fibrous tissue.

In 1767 J. Lieutaud for the first time described primary pleural tumour; in 1937 D. Klemperer and C. Rabin provided the first description of pleural MM; in 1942 experimental studies conducted by A. Stout and M. Murray allowed to clarify the mesothelial origin of the tumour. For a long time, the isolated cases of pleural MM were reported in the publications, and it was only in 1960 when J. Wagner described 33 cases of pleural MM in workers involved in amphibole asbestos mining. In 1965 I. Selikoff used a representative material to demonstrate that the contact with amphibole asbestos is the major risk factor in the development of pleural MM.

Nowadays, the MM is considered to be an extremely rare malignant neoplasm. For instance, according to the distribution analysis, in 2013 the number of cases of malignant neoplasms in the population of 50 countries worldwide representing the majority of the world population the global MM incidence was ranked 27th (out of total 27 positions) in the malignant neoplasms rating, with higher ranks in Great Britain (21st position), Italy and China (23rd position), and Japan (24th position). Furthermore, in the rating of death causes due to malignant neoplasms, the global MM incidence was ranked 24th position with higher ranks in Great Britain (17th position) and Italy (19th position). Among 28 prevailing groups of malignant neoplasms, MM incidence and mortality rates are 0.5 (0.4—0.8) per 100,000 people; number of MM cases comprise 0.23 % of total malignant neoplasms (34.0 thousand out of 14.9 million cases per year). 70.6 % of all MM cases worldwide are recorded in men.

In 1990—2013, absolute number of years of life lost (YLL) due to MM showed worldwide minor increase (by 29.8 %; and rank changing from 26th to 25th position). However, absolute number of newly identified MM cases increased almost 2-fold (from 17.0 to 33.7 thousand

Dr. Irving J. Selikoff (15.01.1915 – 20.05.1992), an American scientific researcher who in the 1960s found increased incidence of lung and pleural cancer in workers who contacted asbestos at shipyards

Source: http://www.ehatlas.ca/asbestos/public-figures/irving-selikoff

cases per year); and a standardized incidence rate worldwide increased by 15.0 % (from 0.48 to 0.55 per 100,000 world population); in developing countries – by 26.0 % (from 0.31 to 0.39 per 100,000 population), in developed countries – by 14.0 (from 0.7 to 0.8 per 100,000 population); especially strong increase in MM incidence rate is observed in older population groups (Ch. Fitzmaurice et al., 2015). It is assumed that there is one MM case in the total of 100-200 cases of lung cancer (W. D. Travis et al., 2004).

At present, MM occurs in all age groups, but most frequently – in people older than 60 years old. As a rule, this malignant tumour most frequently develops in pleura (with all parts of parietal, and then – visceral pleura affected), more rarely – in peritoneum and pericardium (5 %), and very rare – in testicle, ovaries, joints and other organs (below 1 %).

Modern studies show that in MM etiology, the asbestos role is most thoroughly studied, however there exist data related also to other etiological factors which are not well studied or interpreted, such as ionizing radiation, SV-40 virus, certain carcinogenic chemicals etc.

MM is diagnosed at late stages, it grows rapidly by fast infiltration and tends to metastasize early, and specific MM treatment is low effective. All the above mentioned results in low survival rates in MM patients (after the first rise of clinical symptoms: 10 to 17 months; after the first diagnosis: 7 to 13 months) and in short median survival time for them (with specific treatment: 13 to 15 months; with symptomatic treatment: 7 months) (W. D. Travis et al., 2004; М. Б. Бычков, 2006; П. Н. Музалевский и соавт., 2007).

Taking into account WHO's strong focus on the monitoring the MM incidence as well as the fact that this pathological condition is rare and that there is a strong association between the disease and working conditions, it became necessary to summarize and carry out

the critical analysis of and summarise the currently available information on MM.

Pressing need for such a publication is also necessitated by the fact that in most former Soviet Union countries it is chrysotile asbestos which is widely used in mass production scales and is heatedly debated not only in scientific circles, but also on political arena between proponents of a total prohibition of all kinds of asbestos and advocates for a controlled use of chrysotile asbestos.

Taking into account such a situation, the authors considered it useful and timely to summarize the results of their own studies as well as the literature data. This publication summarises main current knowledge concerning MM epidemiology, etiology, pathogenesis, classification, clinical manifestations, diagnosis, treatment, prevention and occupational expertise. At the same time, authors are far from thinking that their publication fully covers all aspects of this topic. Each of the aspects was subjected to special advanced research and analytical studies; in this publication there are references to monographs which are available to a modern reader due to advanced development of modern information technology tools facilitating the search for scientific information.

This publication is recommended to medical practitioners who provide medical help to workers engaged in operations in hazardous working conditions — oncologists, occupational therapists, plant therapists, occupational health physicians; it may also be useful to family physicians and local health district medical doctors and other interested readers.

Authors will appreciate any constructive comments, wishes and suggestions which would allow to complement and to expand our knowledge concerning this issue.

Part 1

MALIGNANT MESOTHELIOMA INCIDENCE WORLDWIDE AND IN UKRAINE

1.1. Incidence of Malignant Mesothelioma in the General Population

The Laboratory of Carcinogenic Danger and Prevention of Occupational Cancer of the governmental institution «Institute for Occupational Health» of the National Academy of Medical Sciences of Ukraine (NAMS of Ukraine) conducted the study devoted to the evaluation of population incidence of malignant mesothelioma (ICD-10 code: C45.-) in Ukraine in 2001—2011 based on the Ukrainian National Cancer Register (NCR) data (governmental institution «National Cancer Institute» of the Ministry of Health of Ukraine) [1, 2].

Gender- and age-adjusted indices were standardised and statistical processing of data was carried out using the method recommended by the IARC (Cancer Epidemiology: Principles and Methods, 1999). Grouping of the statistical values was performed by cluster analysis. Data for Ukraine were compared with 1993—2002 IARC statistical data (Cancer Incidence in Five Continents, 2002, 2007). Mathematical model was used to predict the MM incidence rates in Ukraine through the year of 2025 using the linear regression analysis which included one single variable.

In accordance with the bioethics principles, depersonalized MM patients' information was used for data analysis.

It was determined that in Ukraine during the epidemiological observational period (2001—2011) there were 2 645 cases of officially documented pleural and peritoneal MM (average number of annual cases: (240.5±29.0) persons per year). During this period MM incidence rates in general population tended to increase reaching up to 58.5 % (from 0.41 to 0.65 cases per 100,000 persons per year) (Tables 1.1 and 1.2). Year-by-year dynamics of MM incidence in the general population followed a wave-shaped pattern and showed a tendency to steady increase (Figure 1.1).

Table 1.1. **Absolute Number of Cases and MM Cumulative Incidence Rates in the Population of Ukraine (2001–2011)**

Administrative region	Absolute number of cases per year (persons)											Total	
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Absolute number	per 100,000 persons per year
Autonomous Republic of Crimea	5	10	9	12	12	18	12	14	15	12	16	135	0.63
Vinnitsa	6	14	22	8	28	11	21	18	15	10	24	177	0.99
Volyn	7	15	14	18	6	8	8	12	16	6	8	118	1.04
Dnepropetrovsk	28	13	21	19	17	13	29	21	22	25	28	236	0.65
Donetsk	5	6	6	6	6	4	5	10	10	11	15	84	0.17
Zhitomir	21	11	11	15	10	8	9	12	15	15	11	138	0.98
Zakarpattya	1	3	5	11	4	1	2	2	6	6	11	52	0.38
Zaporozhie	4	3	4	8	14	7	8	16	6	11	6	87	0.44
Ivano-Frankovsk	9	14	7	15	10	11	7	12	6	5	5	101	0.67
Kiev	13	12	10	15	13	12	8	3	7	8	6	107	0.57
Kirovograd	2	4	5	4	9	12	10	32	26	35	43	182	1.65
Lugansk	18	6	12	12	16	11	14	20	10	14	15	148	0.59
Lvov	7	6	7	6	9	8	6	9	9	6	9	82	0.30
Nikolaev	8	7	16	5	14	6	7	8	5	9	8	93	0.72
Odessa	5	9	3	2	5	3	8	8	13	5	8	69	0.26
Poltava	6	7	4	5	6	5	12	11	11	6	4	77	0.47

Rovno	2	2	5	6	7	4	9	6	6	11	6	64	0.50
Sumy	6	5	4	5	6	5	7	5	3	3	10	59	0.46
Ternopol	3	3	5	4	6	4	4	4	1	9	4	44	0.37
Kharkov	7	9	9	14	14	10	11	17	10	19	13	133	0.44
Kherson	5	6	3	3	5	7	2	6	4	2	7	50	0.42
Khmelnitskiy	4	3	3	4	1	1	0	2	5	1	6	30	0.21
Cherkassy	2	3	10	9	7	7	6	7	7	4	1	63	0.45
Chernigov	3	11	10	10	4	5	6	2	8	3	6	68	0.69
Chernovtsy	10	3	6	4	3	6	2	6	7	4	4	55	0.46
Kiev City	13	10	16	13	17	8	9	25	18	21	13	163	0.54
Sevastopol City	2	1	0	3	4	4	4	4	1	3	4	30	0.72
Ukraine	199	196	227	236	253	199	226	292	262	264	291	2645	0.58
Per 100,000 population	0.41	0.41	0.47	0.50	0.54	0.43	0.49	0.63	0.57	0.58	0.64	—	

Table 1.2. **Average Annual Gender- and Age-standardized MM Incidence Rates in the General Population of Ukraine (per 100,000 population per year)**

Geographic Area (years)	Male	Female	Overall
Ukraine (2001—2011)	0.86	0.30	0.58
World (2003—2007)	0.96	0.25	0.60
Europe (2003—2007)	1.55	0.38	0.96

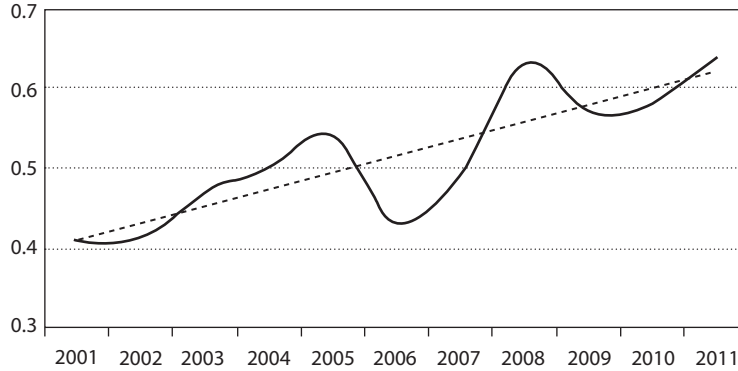

Figure 1.1. Dynamics of MM Incidence Rates in the Population of Ukraine (per 100,000 population per year)

Crude and all gender- and age-standardized MM incidence rates were higher in male population (male/female ratio = 1.5–2.0/1.0).

The comparison of data demonstrated that gender- and age-standardized MM incidence rates in male population in Ukraine (0.86 per 100,000 persons per year) is lower than worldwide (male: 0.96) or in Europe (male: 1.55), and in female population in Ukraine (0.30 per 100,000 persons per year) is lower than in Europe (female: 0.38) (Table 1.2). Taking into account low average male life expectancy in Ukraine (65.2 years in 2011) compared to 27 European Union countries (EU-272008: 76.4 years) certain number of Ukrainian men do not live long enough to develop MM. The increase in MM incidence rates both in male (+ 3.6 % per year) and female population (+ 6.2 % per year) in Ukraine is moderate but somewhat higher than in countries in the WHO European region (+ 3.0 and + 3.1 % per year respectively).

Among countries in the WHO European region, male MM incidence rate in Ukraine is ranked 16th, female – 7th, and the increase in male MM incidence rate is ranked 12th, female – 8th. At the same time, in former USSR countries, MM incidence rates in men (per 100,000 respective population per year) are significantly lower (Latvia: 0.80; Belarus: 0.60; Ukraine: 0.86; Russia: 0.50; Estonia: 0.40; Lithuania: 0.20) than in Western European countries (1.53). The same is true for data in women (Ukraine: 0.30; Lithuania: 0.30; Belarus: 0.20; Russia: 0.20; Estonia: 0.20). Latvia is an exception (0.40) with incidence rates in women greater than average European index (0.38).

However, in former USSR countries the increase in MM incidence rates in men is greater than in countries in the WHO European region

(3.0 % per year): Russia 30.0; Latvia 20.0; Belarus 20.0; Lithuania 10.0; Estonia 6.7; Ukraine 3.6). In women the increase is greater than average European index (3.1 % per year) only in Lithuania (40.0), Russia (20.0), Latvia (20.0) and Ukraine (6.2) (Table 1.3).

All over the world, the highest MM incidence rates in men are observed in those countries where amphibole asbestos or its mixture with chrysotile asbestos have been previously used widely and in an uncontrolled manner: Oceania (1.89; owing to Australia), Europe (1.53; owing to West European countries), North America (1.03; owing to the USA). On the contrary, the lowest levels are observed in those countries that used exclusively chrysotile asbestos: former USSR countries (0.20 – 0.80), Asia (0.34), Central and South America (0.33), Africa (0.20) (Figures 1.2-1.8 and Table 1.4).

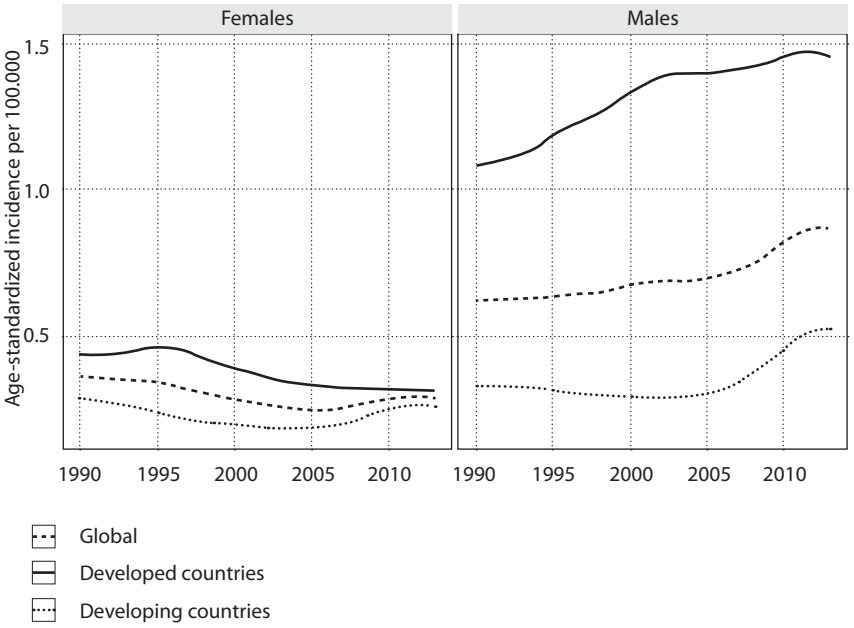

Figure 1.2. Trends in Age-standardized Malignant Mesothelioma Incidence Rates in the World (1990 – 2013)

Source: © The Global Burden of Cancer 2013 / Ch. Fitzmaurice, D. Dicker, A. Pain, H. Hamavid [et al.]; Global Burden of Disease Cancer Collaboration // JAMA Oncol. – 2015. – doi:10.1001/jamaoncol.2015.0735. – Access to: http://oncology.jamanetwork.com/article.aspx?articleid=2294966&utm_source=FBPAGE&utm_medium=social_jn&utm_term=186306261&utm_content=content_engagement|article_engagement&utm_campaign=article_alert&linkId= 14613774#tab4

Table 1.3. **Standardized MM Incidence Rates in Countries in the WHO European Region (per 100,000 populations per year)**

European WHO region countries*	Men			Women		
	1993 – 1997 [1)]	1998 – 2002 [2)]	Δ (%-year)	1993 – 1997 [1)]	1998 – 2002 [2)]	Δ (%-year)
Great Britain	2.64	3.36	5.5	0.38	0.50	6.3
Netherlands	2.67	2.90	1.7	0.33	0.37	2.4
Belgium	1.45	2.15	9.7	0.45	0.35	-4.4
Italy	1.65	1.77	1.5	0.51	0.58	2.7
Switzerland	1.57	1.76	2.4	0.36	0.24	-6.7
Malta	1.00	1.70	14.0	0.10	0.30	40.0
Denmark	1.60	1.70	1.3	0.30	0.30	0.0
Germany	0.60	1.54	31.3	0.10	0.37	54.0
EUROPEAN REGION	**1.33**	**1.53**	**3.0**	**0.32**	**0.38**	**3.1**
Norway	1.30	1.50	3.1	0.20	0.30	10.0
Croatia	1.10	1.40	5.5	0.30	0.30	0.0
Finland	1.10	1.30	3.6	0.20	0.30	10.0
Sweden	1.30	1.30	0.0	0.30	0.30	0.0
France	1.17	1.26	1.5	0.28	0.28	0.0
Slovenia	0.80	1.20	10.0	0.20	0.50	30.0
Iceland	0.90	1.00	2.2	0.20	0.20	0.0
Austria	0.45	0.97	23.1	0.20	0.37	17.0
Ukraine (2001–2011)	–	0.86	3.6	–	0.30	6.2
Latvia	0.40	0.80	20.0	0.20	0.40	20.0
Ireland	0.70	0.60	-2.9	0.10	0.20	20.0
Spain	0.52	0.60	3.1	0.22	0.28	5.5

Belarus	0.30	0.60	20.0	0.30	0.20	-6.7
Russia	0.20	0.50	30.0	0.10	0.20	20.0
Slovak Republic	0.40	0.50	5.0	0.20	0.20	0.0
Czech Republic	0.50	0.50	0.0	0.30	0.30	0.0
Poland	0.35	0.47	6.9	0.23	0.23	0.0
Estonia	0.30	0.40	6.7	0.20	0.20	0.0
Lithuania	0.20	0.30	10.0	0.10	0.30	40.0
Serbia	0.20	0.30	10.0	0.10	0.10	0.0
Portugal	–	0.25	–	–	0.15	–
Bulgaria	–	0.20	–	–	0.20	–

*Note. Data presented in italics are for former USSR countries; [1)]Cancer Incidence in Five Continents / IARC. – 2002. – V. VIII. – P. 594–596; [2)]Cancer Incidence in Five Continents / IARC. – 2007. – V. IX. – P. 522–525.

Table 1.4. **Gender- and Age-standardized MM (C45.-) Incidence Rates in WHO Regions (1993–2002; per 100,000 populations per year)**

WHO regions	Men			Women		
	1993–1997[1)]	1998–2002[2)]	Δ, %-год	1993–1997[1)]	1998–2002[2)]	Δ, %-год
Oceania	2.18	1.89	–2.7	0.34	0.35	0.6
Europe	1.33	1.53	3.0	0.32	0.37	3.1
World	**1.03**	**1.11**	**1.6**	**0.26**	**0.30**	**3.1**
North America	1.08	1.03	–0.9	0.26	0.27	0.8
Ukraine (2001–2011)	–	0.86	3.6	–	0.30	6.2
Asia	0.24	0.34	8.3	0.12	0.15	5.0
Central and South America	0.22	0.33	10.0	0.20	0.23	3.0
Africa	0.37	0.20	-9.2	0.13	0.30	26.2

Note. [1)]Cancer Incidence in Five Continents / IARC. – 2002. – V. VIII. – P. 594–596; [2)]Cancer Incidence in Five Continents / IARC. – 2007. – V. IX. – P. 522–525.

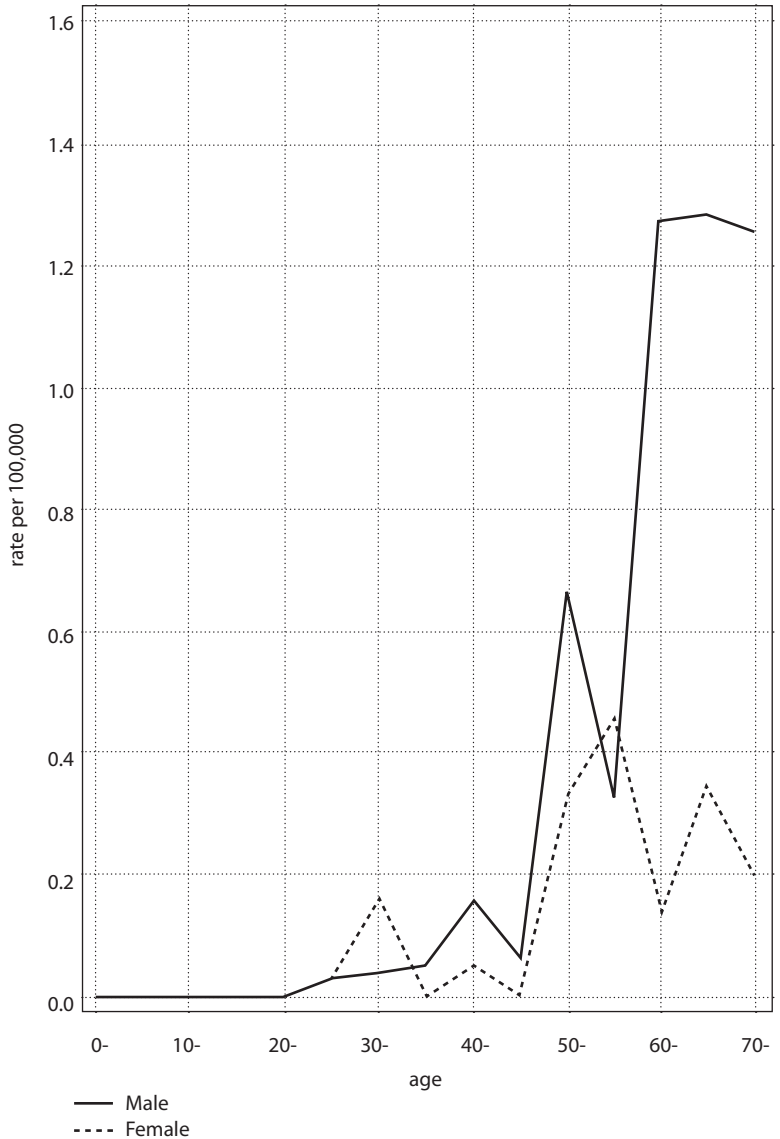

Figure 1.3. Age-standardized Malignant Mesothelioma Incidence Rates in Africa

Source: © CI5 X: Cancer Incidence in Five Continents [electronic version] / Eds.: Forman D., Bray F., Brewster D. H., Gombe Mbalawa C., Kohler B., Piñeros M., Steliarova-Foucher E., Swaminathan R., Ferlay J (2013). — Lyon : IARC, 2013. — V. X. — Access to: http://ci5.iarc.fr/CI5-X/Default.aspx.

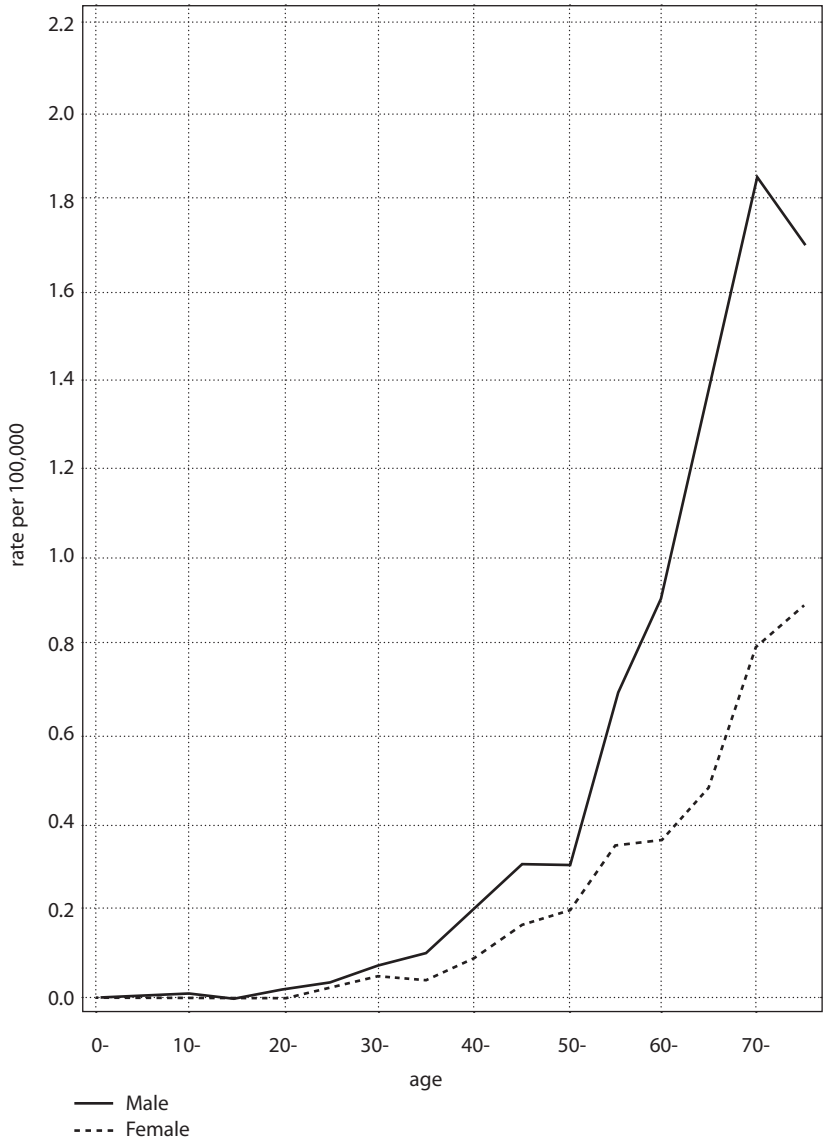

Figure 1.4. Age-standardized Malignant Mesothelioma Incidence Rates in Central and South America

Source: © CI5 X: Cancer Incidence in Five Continents [electronic version] / Eds.: Forman D., Bray F., Brewster D. H., Gombe Mbalawa C., Kohler B., Piñeros M., Steliarova-Foucher E., Swaminathan R., Ferlay J.. — Lyon : IARC, 2013. — V. X. — Access to: http://ci5.iarc.fr/CI5-X/Default.aspx.

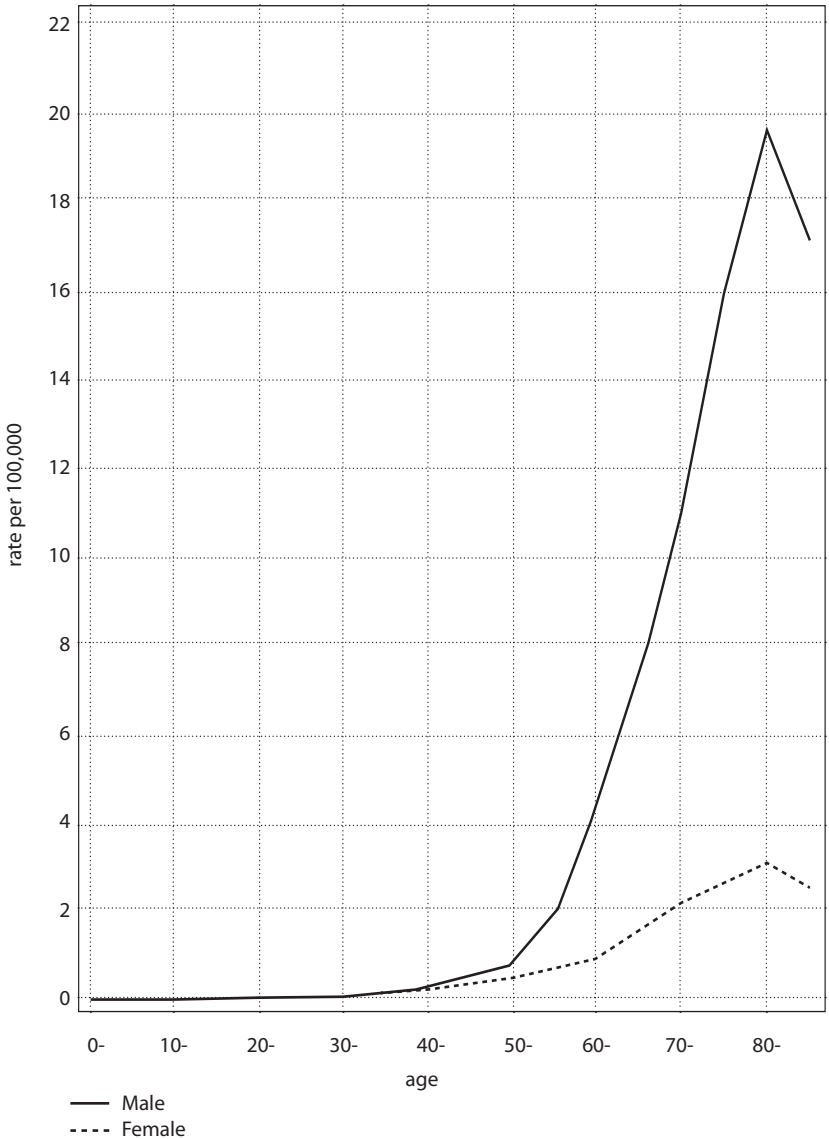

Figure 1.5. Age-standardized Malignant Mesothelioma Incidence Rates in North America

Source: © CI5 X: Cancer Incidence in Five Continents [electronic version] / Eds.: Forman D., Bray F., Brewster D. H., Gombe Mbalawa C., Kohler B., Piñeros M., Steliarova-Foucher E., Swaminathan R., Ferlay J. — Lyon : IARC, 2013. — V. X. — Access to: http://ci5.iarc.fr/CI5-X/Default.aspx.

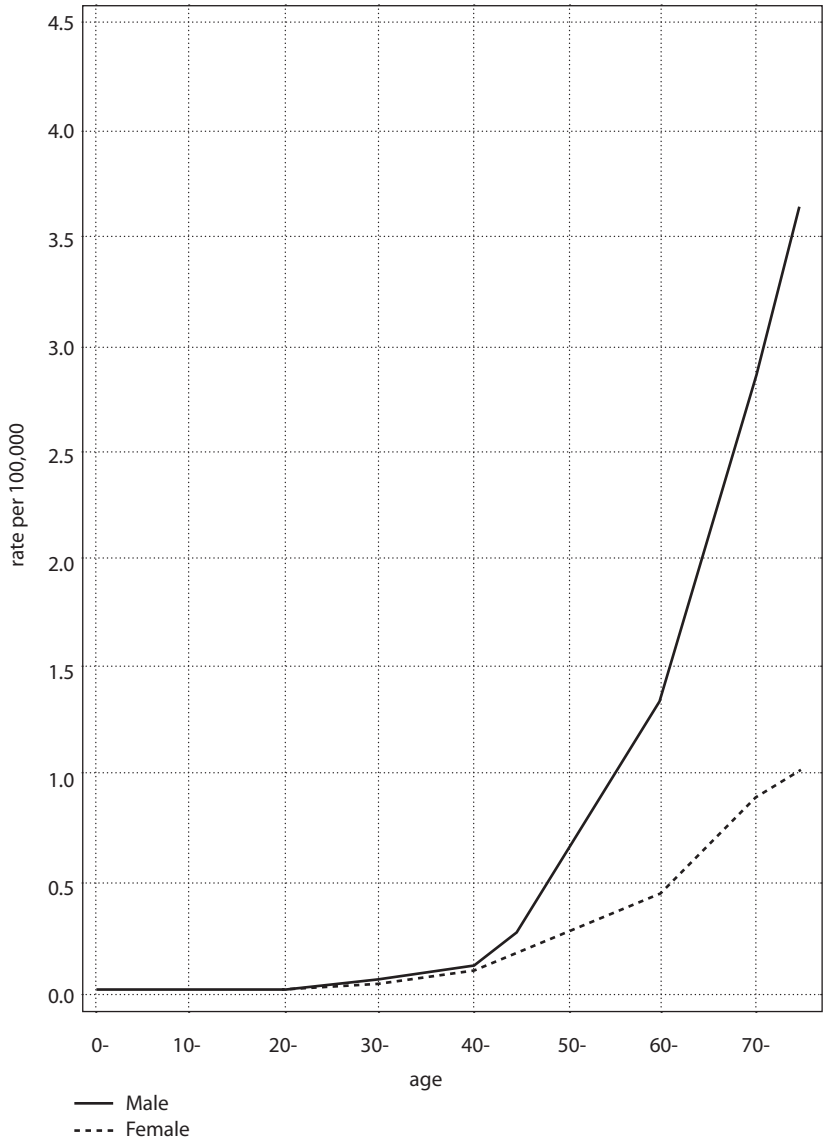

Figure 1.6. Age-standardized Malignant Mesothelioma Incidence Rates in Asia

Source: © CI5 X: Cancer Incidence in Five Continents [electronic version] / Eds.: Forman D., Bray F., Brewster D. H., Gombe Mbalawa C., Kohler B., Piñeros M., Steliarova-Foucher E., Swaminathan R., Ferlay J. Lyon : IARC, 2013. — V. X. — Access to: http://ci5.iarc.fr/CI5-X/Default.aspx.

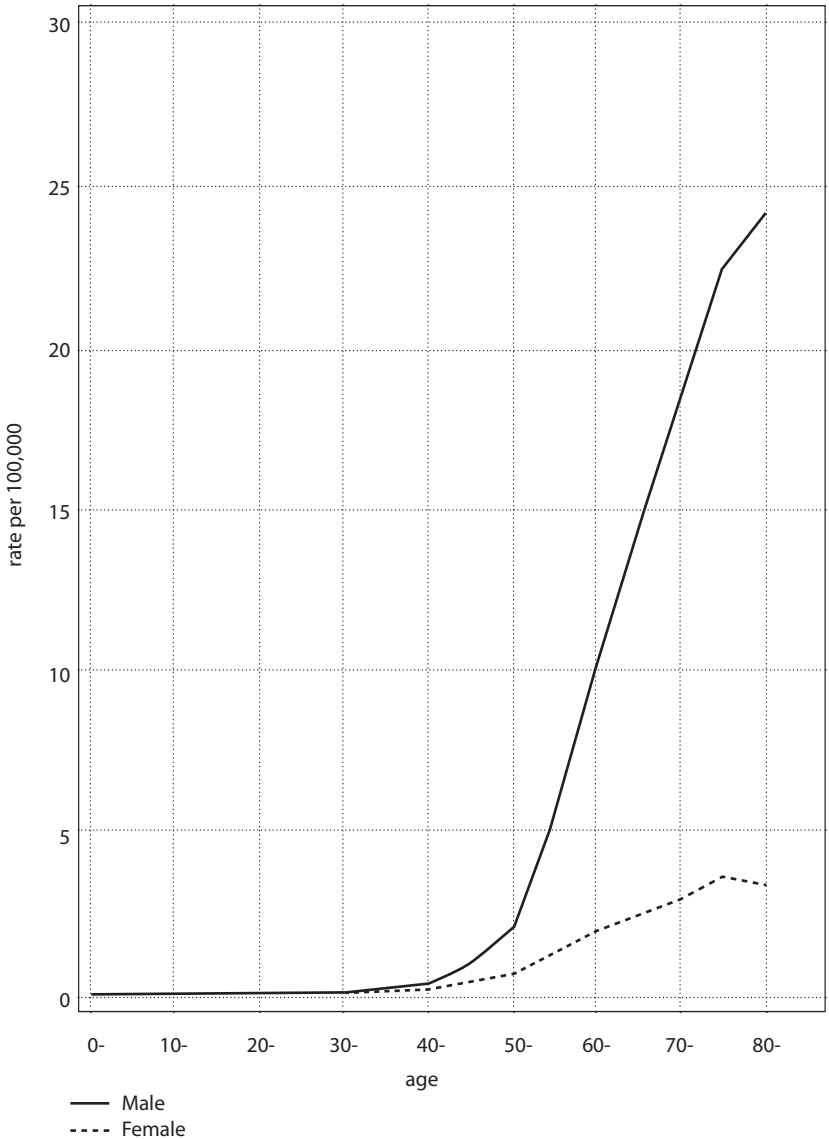

Figure 1.7. Age-standardized Malignant Mesothelioma Incidence in Europe

Source: © CI5 X: Cancer Incidence in Five Continents [electronic version] / Eds.: Forman D., Bray F., Brewster D. H., Gombe Mbalawa C., Kohler B., Piñeros M., Steliarova-Foucher E., Swaminathan R., Ferlay J. — Lyon: IARC, 2013. — V. X. — Access to: http://ci5.iarc.fr/CI5-X/Default.aspx.

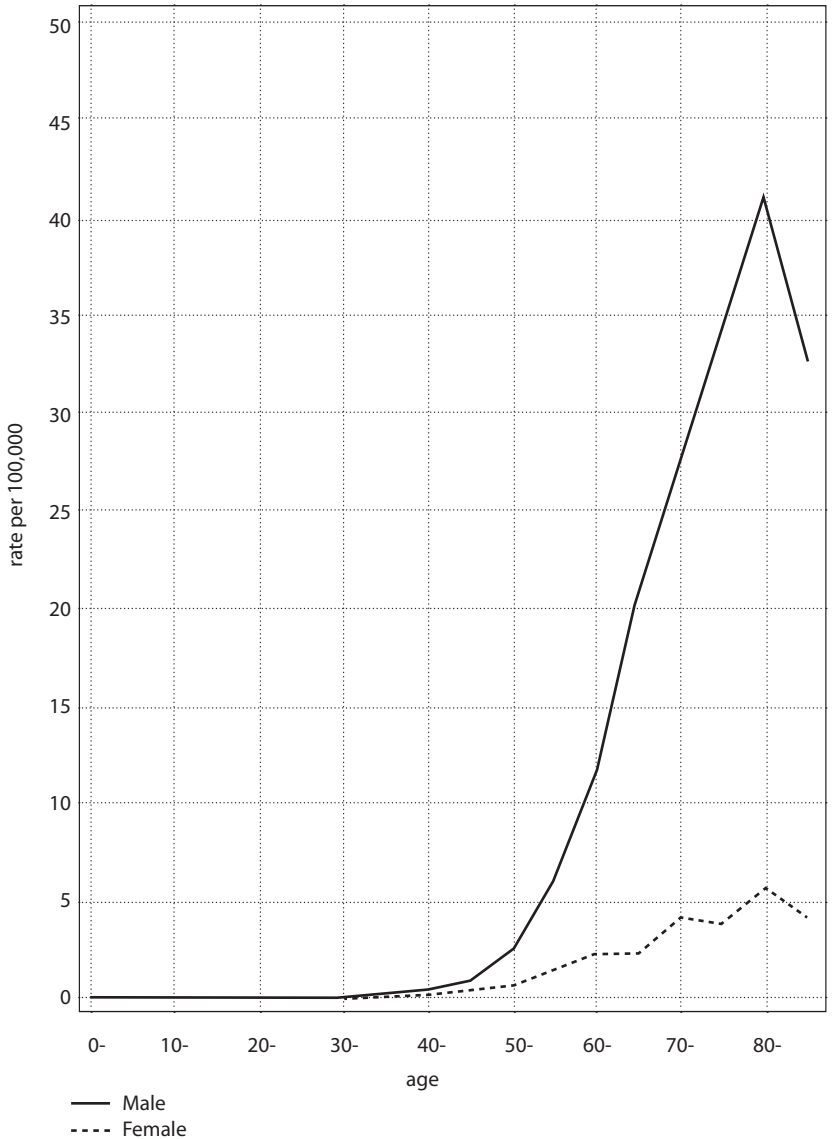

Figure 1.8. Age-standardized Malignant Mesothelioma Incidence Rates in Oceania

Source: © CI5 X: Cancer Incidence in Five Continents [electronic version] / Eds.: Forman D., Bray F., Brewster D. H., Gombe Mbalawa C., Kohler B., Piñeros M., Steliarova-Foucher E., Swaminathan R., Ferlay J. — Lyon : IARC, 2013. — V. X. — Access to: http://ci5.iarc.fr/CI5-X/Default.aspx.

In general, based on cluster analysis, Ukraine nowadays belongs to WHO European region countries with «low» MM incidence rates (≤ 0.8 per 100,000 population) and with «moderate» increase in MM incidence rates (19.0 – 0.1% per year) (Table 1.5).

Till 2025, statistical forecasting predicts future increase in MM incidence rates reaching up to 0.97 (0.70 – 1.18] per 100,000 population in Ukraine. At the same time, in the WHO European region predicted increase in MM incidence rates is 2.68 per 100,000 population. Thus, it means that in Ukraine, annual MM incidence rates in the general population will remain 2.8-fold lower than in Western European countries (at present, in Ukraine, male MM incidence rate is 2.5-fold lower and female rate is 1.2-fold lower than in Western European countries) (Figure 1.9).

Table 1.5. **Ranking of Countries in the WHO European Region Based on MM Incidence Rates and Increase in Incidence Rates (1993–2002; cluster analysis data)**

		Increase in Incidence Rates		
		«High» (≥ 20.0 %-year)	«Moderate» (19.0 – 0.1 %-year)	«Stabilization» and «reduction» (≤ 0 %-year)
Per 100,000 population	«Very high» (≥ 2.50)	–	Great Britain, Netherlands	–
	«High» (1.50 – 2.49)	Germany	Belgium, Denmark, Italy, Malta, Norway, Switzerland	–
	«Medium» (0.90 – 1.49)	Austria	Iceland, Slovenia, Finland, France, Croatia	Sweden
	«Low» (≤ 0.89)	Belarus, Latvia, Russia	Spain, Lithuania, Poland, Serbia, Slovak Republic, **Ukraine,** Estonia	Ireland, Czech Rep.

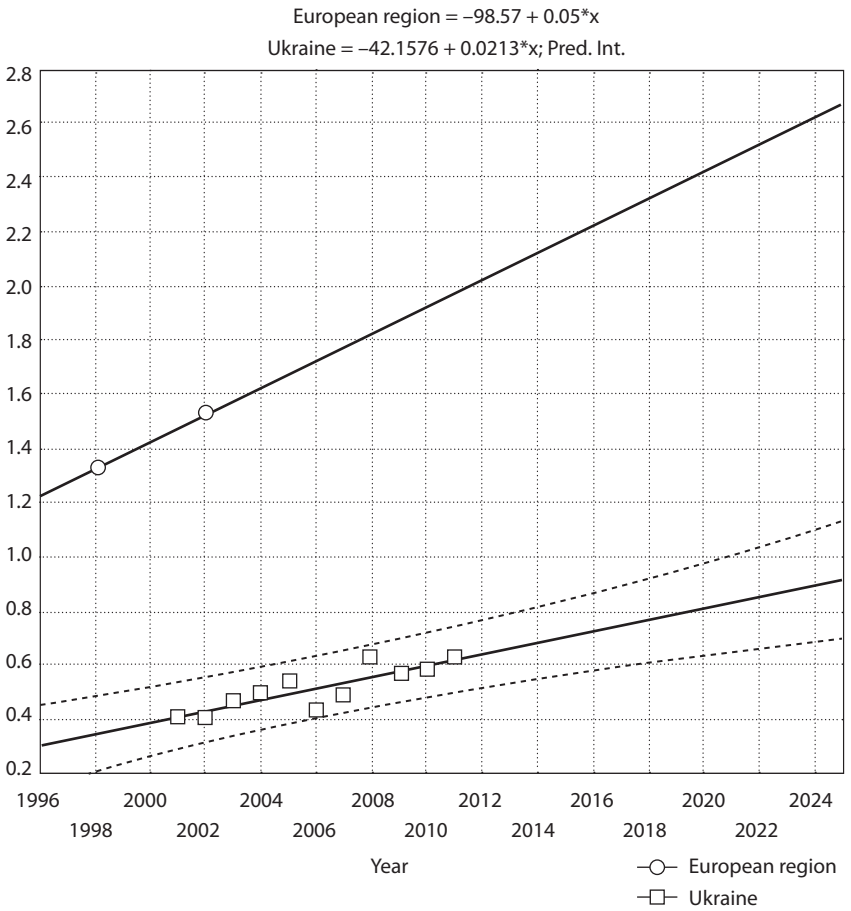

Figure 1.9. Statistical Forecast of MM Incidence Rates in the General Population in Ukraine and in the WHO European Region through the Year 2025 (per 100,000 population per year)

The analysis of geographical profile of MM incidence in the general population in Ukraine (using cluster analysis) demonstrated that MM incidence rate was «very high» (≥ 0.90 per 100,000 population) and «high» (0.51 — 0.89) in eleven (40.7 %) administrative regions: AR of Crimea, Kirovograd oblast, Vinnitsa oblast, Volyn oblast, Zhitomir oblast, Dnepropetrovsk oblast, Lugansk oblast, Ivano-Frankovsk oblast, Kiev oblast, Nikolaev oblast and Sevastopol City (Figure 1.10).

Based on linear regression analysis data, most unfavourable forecast ($r \geq 0.70$) is predicted for AR of Crimea, Kirovograd oblast, Vinnitsa oblast, Dnepropetrovsk oblast, Lugansk oblast and Sevastopol City where a strong increase in the incidence of this disease is observed in the general population (Table 1.6). At present, there is no unbiased data available which would allow to explain the geographical distribution profile of MM incidence in Ukraine.

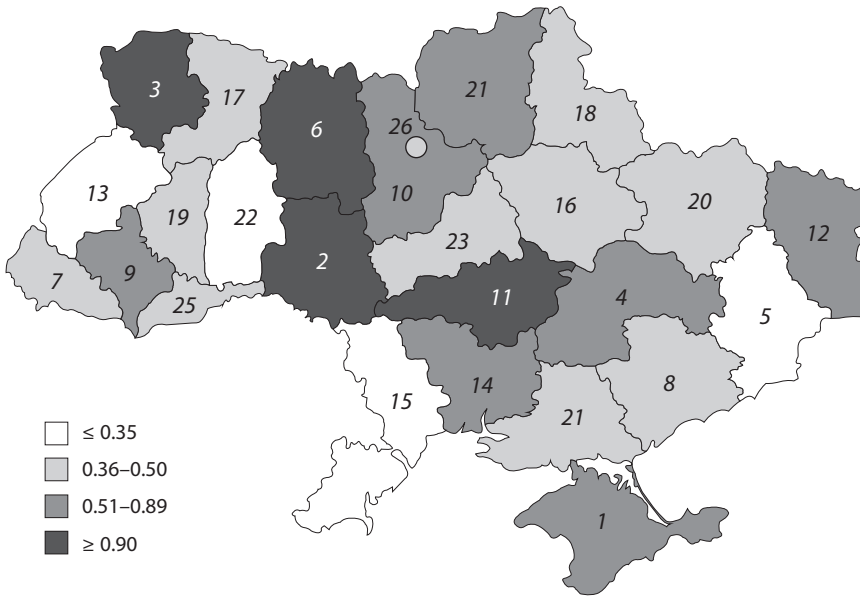

Figure 1.10. Geographic Distribution of Pleural MM Incidence Rates in the General Population in Ukraine (per 100,000 population per year)

1 — AR of Crimea and Sevastopol City, *2* — Vinnitsa oblast, *3* — Volyn oblast, *4* — Dnepropetrovsk oblast, *5* — Donetsk oblast, *6* — Zhitomir oblast, *7* — Zakarpattya oblast, *8* — Zaporozhie oblast, *9* — Ivano-Frankovsk oblast, *10* — Kiev oblast, *11* — Kirovograd oblast, *12* — Lugansk oblast, *13* — Lvov oblast, *14* — Nikolaev oblast, *15* — Odessa oblast, *16* — Poltava oblast, *17* — Rovno oblast, *18* — Sumy oblast, *19* — Ternopol oblast, *20* — Kharkov oblast, *21* — Kherson oblast, *22* — Khmelnitskiy oblast, *23* — Cherkassy oblast, *24* — Chernigov oblast, *25* — Chernovtsy oblast, *26* — Kiev City

Based on analysis data, the median age when the MM occurs in Ukrainian population is similar for men and women (men: 59.5 ± 13.2 years; women: 62.6 ± 13.1 years; $p > 0.05$). However, the frequency analysis by age of MM incidence rates revealed that maximum incidence rates in men are observed at the age of 60–64 years and in women – at the age of 70–74 years showing that in men MM occurs 10–15 years earlier than in women (Figure 1.11). Similar conclusions resulted from the analysis of gender- and age-specific MM incidence rates (Figure 1.12).

Table 1.6. **The Geographical Distribution Profile of MM Incidence in the General Population in the Administrative Regions in Ukraine (2001–2011; cluster and regression analysis data)**

		Dynamics of Incidence Rates through year 2025		
		«High increase» ($r \geq 0.70$)	«Increase» ($r = 0.30–0.69$)	«Stabilization» ($r = 0.0–0.29$). «Decrease» ($r < 0$)
Incidence rates, 2001–2012	«Very high» (≥ 0.90)	Kirovograd oblast	Vinnitsa oblast	Volyn oblast, Zhitomir oblast
	«High» (0.51–0.89)	AR of Crimea	Dnepropestrovsk oblast, Lugansk oblast, Sevastopol City	Ivano-Frankovsk oblast, Kiev oblast, Nikolaev oblast
	«Medium» (0.36–0.50)	Rovno oblast, Kharkov oblast	Zakarpattya oblast, Zaporozhie oblast, Poltava oblast, Sumy oblast, Ternopol oblast, Kiev City	Kherson oblast, Cherkassy oblast, Chernovtsy oblast
	«Low» (≤ 0.35)	Donetsk oblast	Lvov oblast, Odessa oblast, Khmelnitskiy oblast	–

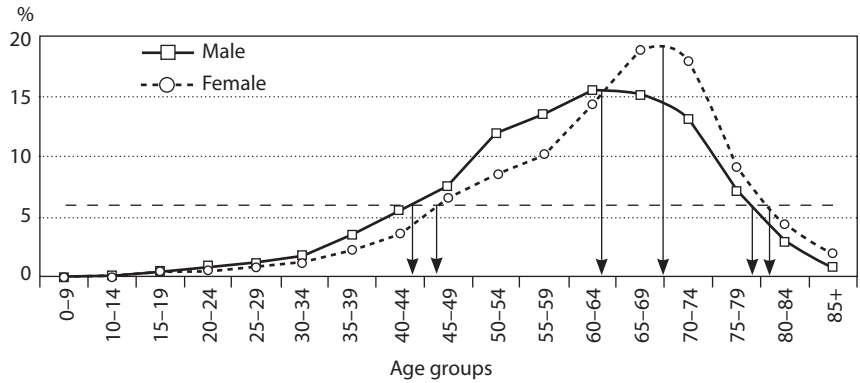

Figure 1.11. Gender- and Age-specific Distribution of MM Incidence Rates in Ukraine in 2001 – 2011, %

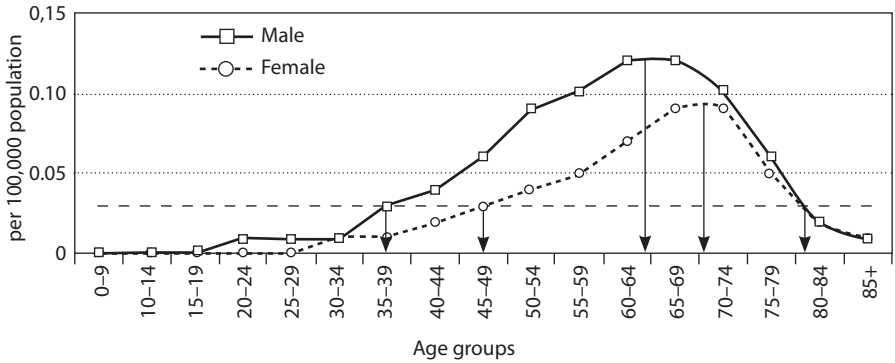

Figure 1.12. Gender- and Age-specific MM Incidence Rates in Ukraine (2001 – 2011; per 100,000 respective population per year)

Most frequently, MM is localized in pleura (men: 95.3 %; women: 89.8 %), less frequently – in peritoneum (men: 3.2 %; women: 9.3 %) and pericardium (men: 0.9 %; women: 0.8 %); other locations (joints, testicle, ovaries etc.) occur very rarely (men: 0.6 %; women: 0.1 %) (Figure 1.13).

In Ukraine, a high rate of the following indices is observed: post mortal MM diagnosis (men: 17.4 %; women: 15.2 %), lifetime late stage (III – IV) MM diagnosis (men: 72.0 %; women: 69.7 %). The rates of the morphologically verified histological MM are high, but not sufficient (men: 77.7 %; women: 79.5 %) (Table 1.7).

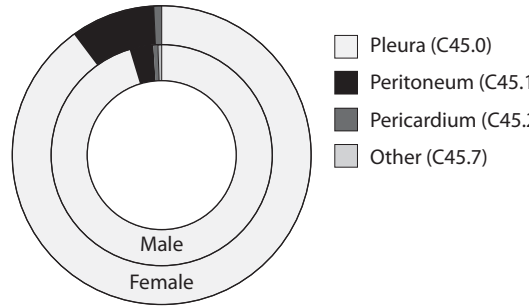

Figure 1.13. Percentage Distribution Profile of MM Locations (Ukraine; 2001–2011)

Table 1.7. **Main Indices of Epidemiological Cancer Profile in MM Patients in Ukraine (2001–2011)**

		Male	Female
Average age at the time of diagnosis, years		59.50 ± 13.16	62.58 ± 13.08
Post mortal diagnosis, %		17.4	15.2
TNM Stage, %	I	5.8	7.2
	II	22.1	23.2
	III	33.3	32.6
	IV	38.7	37.1
Morphological verification, %		77.70	79.53
Disease outcome, %	1-year mortality	78.9	73.8
	5-year survival	2.8	5.4
Median survival, months		9.5	10.7

1.2. Incidence of Occupational Malignant Mesothelioma in Ukraine

Based on information in the occupational cancer patients (in total, 462 persons) register which is maintained at the Laboratory of Carcinogenic Danger and Prevention of Occupational Cancer of the Institute for Occupational Health the NAMS of Ukraine, in 1992–2014 there were 3 pleural MM cases reported in Ukraine (men: 2; women: 1). Two patients had a contact with asbestos in the workplace: one was a docker at the sea port in Odessa oblast, the second was a thermal insulation technician at the heat and power plant in Donetsk oblast, and the third was a drill operator at the uranium mine in Dnepropetrovsk oblast).

During this period, in Ukraine, within the occupational cancer cohort, there were 10 occupational cancer cases reported in workers with occupational exposure to asbestos-containing dust. In addition to the above mentioned two MM cases, there were also malignant neoplasm cases detected in the following location sites: two in the larynx, four in the lungs, one in the thyroid gland, and one in the hemopoietic system (hemoblastosis). In addition to asbestos in the workplace, these workers were also exposed to other carcinogenic agents:

- cases of laryngeal cancer: SiO_2 dust (one person), benzene (one person);
- cases of bronchial cancer and lung cancer: SiO_2 dust (four persons), beryllium (one person), Cr^{+6} compounds (one person.), formaldehyde (one person), ^{222}Rn and gamma-radiation (one person);
- cases of MM: gamma-radiation (one person);
- cases of thyroid cancer: SiO_2 dust and gamma-radiation (one person);
- cases of hemoblastosis (chronic leukemia): SiO_2 dust and basalt fibre (one person).

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Part 2

ETIOLOGY AND PATHOGENESIS OF MALIGNANT MESOTHELIOMA

At present, etiological causes of human MM development which are confirmed by scientific evidence are (1) exposure to asbestos and erionit mineral dust; and (2) exposure to ionizing radiation.

Causative factors that significantly increase the MM risk include (1) genetic predisposition; (2) latent infection caused by monkey Simian vacuolating virus 40 which belongs to Orthopolyomaviruses (SV-40); (3) exposure to other carcinogenic agents; (4) pathological (cicatricial fibrosis) processes occurring in pleural, peritoneal and pericardial tissues.

Despite the fact that since 1960 asbestos exposure was recognized to be a prevailing causative factor in the MM development, there were other MM cases reported in people who never had any exposure to asbestos. Today, the causative effect of other etiological factors is also being evaluated: ionizing radiation, non-asbestos mineral fibres (erionite, carbon nanotubes with structure and size comparable to asbestos fibre), organic substances, certain metals, chronic pleural inflammation of any etiology, and SV-40 virus infection [5, 19, 40, 85].

2.1. Asbestos and Malignant Mesothelioma

Asbestos (in ancient Greek ασβεστος, which means «unquenchable») is a collective name for a group of silicate type minerals with fine fibres. Naturally occurring asbestos has aggregates made up of extremely fine and flexible fibres. It is widely used in a variety of areas (construction, automotive industry, rocket building etc.). At present, several types of asbestos are known which are classified as follows:

- chrysotile asbestos («white asbestos») which is a mineral belonging to a class of serpentine minerals ($3MgO \cdot 2SiO_2 \cdot 2H_2O$);

- amphibole asbestos which is a class of hydrosilicate minerals:
  crocidolite (known as «blue asbestos»)
  $(Na_2Fe_3^{2+}Fe_2^{3+})Si_8O_{22}(OH)_2$);
  amosite $(Fe^{2+},Mg)_7Si_8O_{22}(OH)_2$);
  tremolite $(Ca_2Mg_5Si_8O_{22}(OH)_2$);
  anthophyllite $(Mg, Fe^{2+})_7Si_8O_{22}(OH)_2$);
  actinolite $(Ca_2(Mg,Fe^{2+})_5Si_8O_{22}(OH)_2$);
  fluor-edenite $(NaCa_2Mg_5(Si_7AlO_{22})F_2)$.

The world's largest asbestos deposits are found in Canada (chrysotile), South Africa (crocidolite, amosite and chrysotile) and in Russia (chrysotile in Bazhenovsk and Kiembaev deposits in Ural region; in North Caucasus; and in Tuva). There are also asbestos deposits found in Kazakhstan (Ak-Dovurak and Zhitikarin deposits of chrysotile), China (chrysotile), the USA (chrysotile, amphibole asbestos), Brazil (chrysotile), Zimbabwe (chrysotile), Italy (tremolite, chrysotile), France (tremolite), Finland (anthophyllite), Japan (chrysotile, tremolite, actinolite), Australia (crocidolite, chrysotile), Cyprus (chrysotile). Worldwide chrysotile asbestos extraction profile is as follows (2009): Russia (50 %), China (14 %), Brazil (12.5 %), Kazakhstan (10.5 %), Canada (9 %). Since 2012, Canada stopped the asbestos extraction [13, 24]. Since 2005, production and industrial use of all asbestos varieties is prohibited in EU countries [Directives of the European Union 1999/77/EC and 2003/18/EC]. In Ukraine, chrysotile asbestos of Russian and Kazakhstan origin is used in industry. Ukraine does not have its own asbestos extraction [1].

All asbestos varieties are the first group carcinogens («known human carcinogens») according to the IARC classification. The target organs for malignant neoplasms caused by asbestos exposure are as follows:

- «sufficient evidence»: larynx, bronchi and lungs, ovaries (carcinoma); pleura, pericardium, peritoneum (mesothelioma);
- «limited evidence»: larynx, oesophagus, large intestine and rectum [12].

In the majority of developed countries, more than 90 % of pleural MM cases in men and 20 % in women are associated with prior asbestos exposure. In other countries, where crocidolite asbestos had been previously used widely, especially in Great Britain and Australia, the female MM incidence rates estimates are higher [49].

It is proven that the development of pleural MM shows different profiles depending on the type of asbestos fibre. For instance, amphibole asbestos (amosite, crocidolite) causes pleural MM much more frequently than chrysotile asbestos. Crocidolite is more dangerous

than amosite. Based on multicentre epidemiological studies, it was proven that pleural MM risk ratio in the cohort of exposed workers was as follows: crocidolite : amosite : chrysotile = 500 : 100 : 1. It is estimated that average post-exposure latent period before the development of MM is 30—50 years and rarely below 15 years [38].

According to Kazan-Allen L. (2005), 170 tons of extracted and used crocidolite results in one death caused by pleural MM [47].

The majority of researchers make very unfavourable prognosis concerning further development of MM epidemic. For example, it is estimated, that in Western Europe in the next 35 years about 250 thousand people will die because of asbestos-associated MM (mainly men born in 1945—1950) [79].

In Ukraine, similarly to all former USSR countries, it was only chrysotile asbestos which was used in the industry. Studies conducted in the Russian Federation showed that 12.0—29.4 % MM cases were associated with occupational exposure to asbestos [2].

Pathogenesis of asbestos-induced MM is not enough studied. However, it was found that asbestos fibre has a tropism for serous membranes. After precipitation of asbestos fibres in lung parenchyma, they are migrating to pleura, peritoneum, pericardium and other cavities where they can readily accumulate in great quantities and trigger tumour development. The transfer of asbestos fibres to pleura carried out by macrophages play a crucial pathogenic role in MM development.

It is believed that asbestos fibres are capable to penetrate from lung parenchyma reaching and accumulating in visceral pleura, and from there, via lymph flow directed towards parietal pleura, they are transferred to and spread throughout its entire surface. At pleura sites where asbestos fibres are accumulated, pleural plaques and diffuse pleural thickening are developing, and later, pleural MM is arising.

Mechanisms leading to MM development in abdominal cavity are still not known. It is supposed that asbestos fibres are transported by macrophages from lungs to abdominal cavity via lymph flow. In addition, asbestos fibres may deposit in intestine following the ingestion of asbestos contaminated phlegm [12, 29]. Experimental data show that asbestos is a «complete carcinogen» causing the development of MM due to stepwise progression through initiation and promotion stages [85].

It is assumed that long-term latency period from the moment of asbestos exposure to the moment of MM manifestation is a result of asbestos fibres needing time to saturate the parietal pleura which is hampered by negative pressure in pleural cavity as well as to

accumulate genetic and epigenetic alterations leading to malignant transformation of cells [83].

The molecular mechanisms underlying the malignant transformation of normal mesothelial cells by asbestos fibres remain unclear despite their oncogenic capacity demonstrated in animal studies. It is assumed that asbestos fibres produce combined malignant neotransformation effect on mesothelium cells by executing direct physical (mechanic) impact combined with indirect impact by inflammation mediators secreted by macrophages. Today, there are three hypotheses concerning the pathogenesis of asbestos-induced MM [30, 83]:

1) The «theory of oxidative stress» is based on the fact that asbestos fibres are foreign bodies. According to studies, asbestos containing ions of iron (a catalyst of free-radical oxidative process) are more carcinogenic than other asbestos types [22, 57, 88].

2) The «theory of chromosome tangling» suggests that asbestos fibres are sticking to cells and damage chromosomes when cells are dividing [44].

3) The «theory of adsorption of specific proteins as well as carcinogenic molecules» is based on the fact that asbestos fibres entering the living organism are carrying along also other chemicals including carcinogens (components of cigarette smoke, foreign DNA etc.) [83].

The *«theory of oxidative stress»* is explained by two key pathogenic agents involved, namely, endogenous iron ions in asbestos fibres (group of amphibole asbestos) and macrophages participating in the development of pathology process. It was shown that amosite ($(Fe, Mg)_7Si_8O_{22}(OH)_2$) and crocidolite ($Na_2(Fe^{3+})_2(Fe^{2+})_3Si_8O_{22}(OH)_2$) containing iron ions are the catalysts directly involved in free-radical reactions. Iron is known to exert co-carcinogenic action not only in animals, but also in humans since it is involved in the induction and maintenance of free-radical reactions which is associated with MM pathogenesis. However, this theory does not explain cytotoxic effects of chrysotile asbestos that does not contain iron. Probably, there occurs an accumulation of iron ions released as a result of hemolysis in surrounding tissue [51, 83, 88].

In addition, it was shown that asbestos fibres alter macrophages functions and secretory behaviour thus creating conditions for MM development. Many researches indicate that long and thin (as opposed to short) asbestos fibres in most of the cases cause MM development because they are better phagocytized by macrophage cells [73].

Pathological process induced by asbestos fibres includes the following steps: (1) cellular uptake of asbestos fibres due to phagocytosis;

(2) fibre is coated with hemosiderine; (3) death of phagocytes, release of the fibres and rephagocytosis by other cells [25, 73].

After contact with asbestos, phagocytes and macrophages significantly increase the production of hydroxyl radicals which is a normal by-product outcome in cellular metabolism under anaerobic conditions, and they enhance the activity of cytokines and cell growth factors. Free radicals exhibit strong clastogenic and membrane-damaging properties which at the end result in triggering the carcinogenic mechanisms due to direct or indirect DNA damage, alteration of the cellular membrane-associated activation of oncogenes and blockade of the mechanisms of antioxidant protection in cells [12, 29, 87].

Asbestos is capable to impair functions and secretory activity of macrophages. The macrophages which phagocytized asbestos increasingly generate hydroxyl radicals. In their turn, they are able to activate oncogenesis through interaction with DNA by modifying the cellular membrane-associated processes including the activation of oncogenes and the impairment of antioxidant protection in cell [80].

In addition, there is a hypothesis suggesting that interaction between substances similar to free-radicals and media surrounding macrophages produces toxic effect on mesothelial cells [81].

Asbestos-induced alteration of macrophages results in the release of very strong mitogens that can play a role of the following mesothelial cells neotransformation factors:

- platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β) which respond by inducing and chronically stimulating mesothelial cells proliferation;
- inflammatory cytokines such as tumour necrosis factor-alfa (TNF-α), cyclooxigenase-2 (COX-2), induced nitric oxide synthase (iNOS) and matrix metalloproteinases (MMP9, MMP12) which are maintaining chronic inflammation and promoting MM growth and invasion [34, 51].

The *«theory of chromosome tangling»* suggests that asbestos fibres can be actively phagocytized by epithelial cells (including by mesothelial cells). As a result, asbestos fibres reach not only cytoplasm, but are also able to penetrate into cell nucleus. During cell division, asbestos fibres can bind to chromosomes similarly to other nano-size fibres or particles, but a particular profile of asbestos interaction with specific chromosome regions is still unknown [33, 83].

Experimental analysis of interaction between asbestos fibres and mesothelial cell DNA showed that phagocytized fibres are able to contact chromosomes which results in fibres sticking to chromatin or chromosomes. Such contacts between asbestos fibres and chromo-

somes (structural proteins of mitotic spindle) cause complex cytological alterations. Study using the cytogenetic methods revealed that in MM cells the following abnormalities are frequently found: chromosome 22 monosomy, and structural reconstructions in arms of chromosomes 1p, 3p, 9p and 6q. General abnormalities, genome alterations in MM cell line feature the loss of tumour suppressor genes (NF2 in 22q12, $p16^{INK4a}$, $p14^{ARF}$) [12, 29, 36, 60, 64, 87].

Asbestos-induced chromosomal aberrations can be structural (deletions, translocations, duplications and sister chromatid exchange) or quantitative (aneuploidy, polyploidy, hyperdiploidy). These mutations are associated with asbestos fibres-induced chromosome damage of various types, namely: breaks, fragmentation (in the micronucleus), chromosomes lagging, exchange of segments between two chromosomes, and incorrect segregation of chromosomes [65, 71].

Numerous cytogenetic studies demonstrated that various types of asbestos (chrysotile, crocidolite, amosite, tremolite) cause quantitative chromosomal changes or structural chromosomal aberrations at metaphase and anaphase (lagging chromosomes, formation of bridges, fragments, abnormal exchange) [7, 65]. The results of studies confirmed that most of gene mutations are numerous deletions of base pairs (from thousand to few million) [21, 86]. In addition, asbestos exposure causes increased number of DNA damages (DNA adducts and DNA breaks) [45]. It was shown that the intensity of induced chromosomal aberrations depends on physical and chemical properties and concentration of fibre (crocidolite turned out to be more dangerous than chrysotile) [15, 43, 55, 66].

«The theory of adsorption of specific proteins» is based on the fact that the surface of asbestos fibres has a high affinity for certain proteins and other substances (metals, benzopyrene, foreign DNA etc.). Experimental studies demonstrated that asbestos fibres facilitate the normal cell's uptake of foreign DNA that is able to be integrated into human genome which would cause mutations by various action mechanisms, such as: inactivation of tumour suppressor genes; activation of oncogenes; activation of proto-oncogenes resulted from DNA aberrations in promoter region; activation of DNA repair enzymes prone to mutations; activation of telomerase; disruption of apoptosis [4, 6, 11, 43, 52, 83, 84].

In addition, it was found that asbestos is able to play a role of immunosuppressive agent thus promoting the carcinogenesis process. It was shown that asbestos produces immunosuppressive effect because chrysotile asbestos fibres *in vitro*:

– inhibit the proliferation of phytohemagglutinin-stimulated

peripheral blood lymphocytes;
- inhibit the cell lysis induced by natural killers;
- significantly reduce the viability and recover ability of lymphokine-activated killer cells;
- inhibit the generation of new lymphocytes and suppress the activity of T-killers that are playing a key role in anticarcinogenesis mechanisms;
- develop resistance to chrysotile-induced apoptosis of T-lymphocytes caused by long-term asbestos exposure [12, 14, 29, 41, 46, 87].

2.2. Erionite and Malignant Mesothelioma

Erionite (in Greek «εριον» which means «wool») is a naturally occurring fibrous mineral $(Na_2, K_2, Ca, Mg)_{4,5}Al_9Si_{27}O_{72} \cdot 27H_2O$) that belongs to a group of minerals called zeolites (hydrated aluminosilicate minerals) and is similar to shabasite. It is found in basalt cracks and in tuffs in Georgia, Turkey (Nevsehir), the Check Republic (Bohemia), North Ireland (Antrim), Japan (prefecture Niigata, Honshu Island), Faroe Islands, Australia (New South Wales), New Zealand (Otago Peninsula), Russia (Nizhnyaya Tunguska River basin in Evenkia), the Crimea (in volcanic rocks in Karadag Nature Reserve), the USA (Jersey Valley in Nevada; State of Oregon; Baker County; certain regions in South Dakota and Wyoming). In Ukraine, erionite is not used and is not extracted.

Erionite is a first group carcinogen («known human carcinogens») according to the IARC classification. The target organs for malignant neoplasms caused by erionite exposure with «sufficient evidences» are pleura, pericardium, and peritoneum (mesothelioma).

Epidemiologic studies conducted in Cappadocia (Nevsehir, Kayseri, Aksaray and Nigde Provinces in Turkey) proved the increased pleural MM risk in erionite-exposed population.

Pathogenesis of erionite-caused MM is similar to asbestos-caused MM [28].

2.3. Ionizing Radiation and Malignant Mesothelioma

Ionizing radiation is a first group carcinogen («known human carcinogens») according to the IARC classification. Epidemiologic studies showed increased pleural MM incidence rates in patients exposed to ionizing radiation for diagnostic and treatment purposes. For instance, MM cases were reported 20–30 years after radiation therapy

for Hodgkin's lymphoma, non-Hodgkin's lymphoma, chronic lymphocytic and mielocytic leukemia and other malignant neoplasms [20, 35, 48, 50, 62, 82].

In addition, pleural MM risk is significantly increased by intrapleural diagnostic administration of alpha emitter ($T_{1/2}$: 22 years) thorium dioxide ($^{232}ThO_2$) («Thorotrust») widely used in the 30^{th}—50^{th} of the 20^{th} century in the USA and Western European countries (it is estimated that it was administered to 2-10 million of patients) [35, 56]. On the territory of former USSR countries «Thorotrust» was not used because it was banned.

It is assumed that MM risk is also increased in persons with long-term occupational exposure to low-level ionizing radiation (personnel at nuclear facilities). Increased MM incidence was found in nuclear industry personnel [35, 54]. It was found that risk of untimely death caused by MM is increased in nuclear power plant personnel with average cumulative radiation dose above 20 mSv [82]. Another study showed that MM risk in workers of shipyards serving nuclear-powered ships increases with radiation dose above 10 mSv [18].

The experimental study showed that carcinogenic effects in pleural and lung malignant neoplasm development are enhanced by combined exposure to mineral dust (asbestos, quartz, glass fibre) and radium (^{222}Ra) [42].

Evaluation of chemical and radioactive content of biological material of MM patients detected abnormally high levels of radioactive radium exceeding by million times the levels in sea water. Continuous and long term inner radiation exposure in «hot spots» by radium and its daughter products may cause strong and frequent damage to DNA in lung tissue, trigger the development of various types of tumours including MM. At the same time, the cause of radium accumulation in pleura is not known [9].

There are only isolated studies of ionizing radiation role in MM etiology and pathogenesis.

2.4. Simian Vacuolating Virus 40 (SV-40) and Malignant Mesothelioma

First reports concerning the association of pleural MM with SV-40 appeared in 1994 and were confirmed by the later studies [31, 70]. SV-40 genome expression was found in 60.0 % of pleural MM patients [26, 62].

Molecular genetic studies revealed that genome of certain types of

malignant neoplasms in humans (MM, brain tumours, bone sarcoma, non-Hodgkin's lymphoma) often has the DNA sequence of SV-40 virus [67, 69].

Mass infection of millions of people with SV-40 in several regions throughout the world (Northern America, Europe) was caused by the use of SV-40-contaminated poliovirus vaccines in 1955-1962 (poliovirus was produced in SV-40-infected kidney cells cultures from rhesus monkeys) (A. Sabin, J. Salk).

Causative association between SV-40 latent infection and pleural MM is scantily explored. Some epidemiological studies did not reveal increased pleural MM risk in the population who could have received SV-40-contaminated poliovirus vaccine [17]. However today, the co-carcinogenic effect between SV-40 and amphibole asbestos exposure in the development of MM is already been recognized [23, 63, 69].

Simian vacuolating virus 40 (40 nm in diameter) is an icosahedral unenveloped DNA virus of the polyomavirus family. It was discovered by Maurice Hilleman in 1960 as a contaminant of poliovirus vaccines. Sabin oral and Salk parenteral poliovirus vaccines used for the vaccination were produced in SV-40-infected primary cultures of kidney cells from rhesus and cynomolgus monkeys [74].

Approximate number of US patients inoculated by this vaccine reached 98 million persons [53]. While after the year of 1963, there was no more SV-40 present in the parenteral vaccine, it was still found in the oral vaccine until the 1970th. In 1950—1960th, both vaccines were used in former USSR countries, USA, Japan, Great Britain, Italy, Mexico, selected Central American countries and other countries. In the latest 50 years a great number of studies (some of them are still being continued) investigated various impacts of SV-40 on human health [27].

For instance, *in vitro* experiments in human and animal cell cultures showed that SV-40 exposure leads to malignant transformation of cells as well as *in vivo* administration to animals demonstrated that it exhibits the carcinogenic properties under intraperitoneal and intrapericardial administration. Malignant transformation occurs when SV-40 DNA becomes integrated into the host cell genome or stays in a stable episomal form in the cytosol [32].

In mice, SV-40 induces the no foci malignant transformation by two viral proteins: large T-antigen (Tag) and small t-antigen (tag). Tag is one of the most potent oncogene proteins which produces the transcriptional blocking of tumour suppressor gene. In its turn, tag inhibits phasphatase-2A protein and induces the Tag modulation. Another important role for Tag is to directly bind to and inactivate the p53 and Rb

expression as well as to induce the insulin-like growth factor 1 (I-LGF1) and its receptors. p53-Tag complex is acting as a transcription factor of I-LGF1 promoter induction. Experimental data showed that the combination of factors leading to consistent human cell transformation in vitro includes the co-expression of SV-40 Tag and tag genes, the telomerase activity and the activity of hRAS gene located on the short arm (p) of chromosome 11 (and which encodes the GTPase Hras protein), or the activity of p21 transforming protein which regulates the cell division in response to growth factor stimulation [8, 32, 37].

By using the PCR method, the SV-40 DNA was detected in selected rare tumours such as osteosarcoma, ependymoma, tumours of the brain vascular plexuses and non-Hodgkin's lymphoma [16, 59, 75, 76, 78]. In 1994 Carbone et al. detected SV-40 sequences in mesothelial cell genome in few MM patients which provoked heated debates [72]. In order to resolve the SV-40 issue in human tissues, an International SV-40 Working Group was formed in 1997. Nine laboratories participated in a study funded and organized by the US National Cancer Institute. Each laboratory was given 25 paired-duplicate samples of human mesotheliomas, a single set of 25 normal lung tissue samples, and positive and negative control samples. The results showed that none of the MM specimens was positive for SV-40 DNA [72].

The detection of SV-40 DNA in cells of some MM patients suggested that the virus can be a cofactor in oncogenesis thus be involved in the development of MM in asbestos-exposed persons [77]. At the same time, SV-40 sequences were detected by PCR testing of blood in 16 % of healthy people residing in Casale Monferrato (Italy) with a long-time history of asbestos contamination of local environment [68].

In vitro studies showed that SV-40 becomes integrated into genome only in 20 % of infected fibroblasts or epithelial cells (with a frequency of 1/107). The infection of fibroblasts by SV-40 results in cell lysis thus preventing the malignant transformation of cells. Opposite to fibroblasts and epithelial cells, mesothelial cells are more susceptible to SV-40 infection. At the same time, 80 % of these cells are affected by latent viral infection. Infected mesothelial cells actively express Tag protein, but do not produce viral particles. Mesothelial cells are subject to malignant transformation more readily than other SV-40-infected cells (with a frequency of 1 to 103) [39].

In recent studies, the combined carcinogenic effect of crocidolite asbestos and SV-40 was detected in hamster and human mesothelial cells. Experimental study showed that human mesothelial cells demonstrate similar susceptibility towards genotoxic effect of asbestos and SV-40-induced malignant transformation. The above mentioned

results allowed to assume that the later factor plays a key role in the malignant neotransformation of mesothelium exposed to asbestos fibres [26].

SV-40 produces strong immunogenic effect and activates both specific antibody production and T-lymphocytes response [10].

2.5. Genetic Predisposition and Malignant Mesothelioma

According to NCBI «Gene» data base, at present, there are 118 genes known to define the genetic predisposition to MM development (http://www.ncbi.nlm.nih.gov/gene/?term=Malignant+ mesothelioma%2C+susceptibility+to+Homo+sapiens).

Molecular genetic studies showed that the damage (loss) of suppressor genes (Neurofibromatosis type 2 at 22q12; $P16^{INK4A}$; $P14^{ARF}$ and others) is the main factor in MM pathogenesis [61, 83]. Such an assumption is also supported by MM cases in children [3].

2.6. Other Carcinogenic Agents and Malignant Mesothelioma

In experimental studies, MM is also caused by copper, chromium, nickel, iron, beryllium, silica, artificial mineral fibres, soot, rubber, polyurethane, polysilicone plastic materials, sterigmatocystin (congenial to aflatoxin B1), ethylenoxid, N-methyl-N-nitrosourea, diethylstilbestrol, sinapaldehyde, and also retrovirus of bird myelogenous leukemia (MC-29) [3].

Previous studies conducted in the Russian Federation revealed that in certain geographical regions increased MM incidence rates are caused by nickel and lead pollution of air and soils [2].

2.7. Target Organ Pathology and Malignant Mesothelioma

Fibrotic scarring pathological process in mesothelium. A number of studies showed that pathological processes causing the scarring of the pleura (for instance, after surgical treatment of tuberculosis) increase pleural MM risk in affected patients [2, 85].

2.8. Smoking and Malignant Mesothelioma

At present, there are no conclusive data supporting the increased pleural MM risk due to smocking, though significantly increased risk of other malignant neoplasms (lung and larynx cancer) is detected in smokers exposed to asbestos dust [58, 85].

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Part 3

OCCUPATIONAL ACTIVITIES AND MALIGNANT MESOTHELIOMA INCIDENCE IN UKRAINE

3.1. Analysis of Cancer Incidence and Assessment of Carcinogenic Risk in Asbestos-Cement Industry Workers in Ukraine

In 2012 the Laboratory of Carcinogenic Danger and Prevention of Occupational Cancer of the Institute for Occupational Health conducted the study devoted to the evaluation of risks of oncology diseases associated with occupational exposure to chrysotile asbestos fibres and concomitant factors in working environment [1].

Evaluation and analysis of oncology diseases incidence in asbestos-cement industry personnel was carried out by data linkage method (automatic data comparison) to link records in the following electronic databases: The National Cancer Register of Ukraine (NCRU) and databases of records concerning workers of ten asbestos-cement plants (ACP) in eight oblasts of Ukraine [epidemiological observation period: 17 years (1995—2011); personnel list included 3 066 persons; 45,696 person-years). When the oncological pathology diagnosis record was identified, the Patient with Malignant Neoplasm Case Record form (Form: 027/y) and data concerning his/her occupational contact with chrysotile asbestos (based on results of workplace assessment conducted by the Institute for Occupational Health of the NAMS of Ukraine in 2005) were analysed.

Epidemiological analysis of collected data was carried out in compliance with the recommendations from the WHO International Agency for Research on Cancer (Cancer Epidemiology: Principles and Methods. — IARC, 1999).

Assessment of individual and population cancer risks in ACP workers was carried out using the procedure recommended by the US Environmental Protection Agency (US EPA) (EPA/600/8-87/045).

It was found that during 17 years of epidemiological observation of ACP workers, 72 persons (2.3 % of total workers) developed a malignant neoplasm (MN), average annual MN incidence in ACPs was 138.2 per 100,000 of workers which is less than in the general popula-

tion of Ukraine (in 2010: 341.5 per 100,000 population) ($p < 0,01$) (Figure 3.1 and Table 3.1).

Increased gender- and age-standardized cumulative cancer incidence rates were observed in workers (men: 468.37 per 100,000 (1.8 times more than incidence rate in the general population); women: 217.49 per 100,000 (1.1 times more than incidence rate in general population)) (Tables 3.2 and 3.3).

Gender and age profile of increase in total cancer incidence is as follows:

- male workers 35–39 years old (MN in the mouth, on the lip, of the lung, and Hodgkin's lymphoma);
- female workers 30–34 years old (MN of skin, the mammary gland, the uterine corpus and cervix); 65–69 years old (MN of skin, the mammary gland, the uterine corpus, and large intestine) (Figure 3.2).

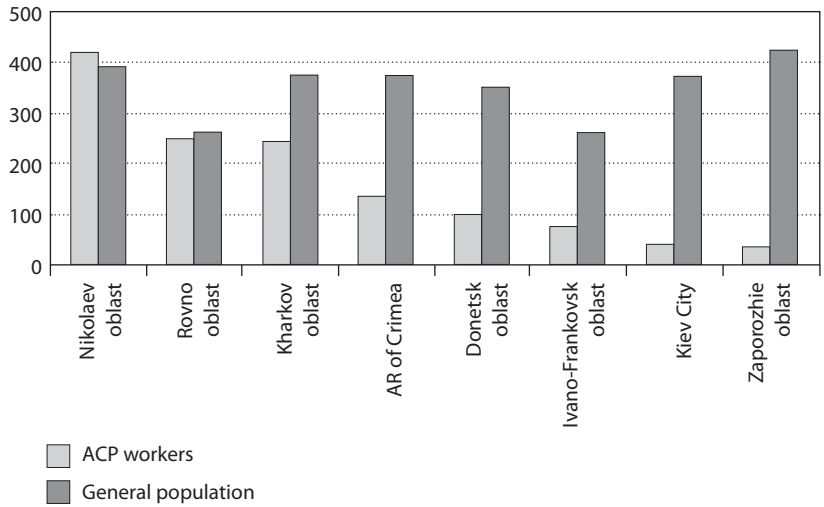

Figure 3.1. Average Annual Total Cancer Incidence Rates in ACP Workers in Ukraine (1995–2011) in Comparison with the General Population Incidence Rates in the Regions/Oblasts (2010) (per 100,000 respective population)

Table 3.1. **Total Cancer Incidence Rates in Asbestos-Cement Plants Workers in Ukraine (1995—2011)**

Administrative Regions	Industrial Plant	Number of workers (person-years)	Number of MM cases (patients)	Average MM incidence per year per 100,000 workers	MM incidence in the region (2010)	*p*
Nikolaev oblast	Delta Bug Company, Ltd	183 (3111)	13	417.9 ± 226.7	385.3 ± 1.0	> 0.05
Rovno oblast	Volyn Slate, Ltd	405 (6885)	17	246.9 ± 117.2	295.3 ± 1.0	> 0.05
Kharkov oblast	Balakleevskiy Slate Industrial Complex «KhZIAM», OAO	217 (3689)	9	244.0 ± 159.2	344.0 ± 1.0	> 0.05
AR of Crimea	Krasnogvardeiskiy Slate Plant «Kriazh», GP PP	345 (5865)	8	136.4 ± 94.5	341.5 ± 1.0	< 0.05
Donetsk oblast	Kramatorskiy Slate, Ltd + Tekhprom, Ltd	835 (14 195)	14	98.6 ± 51.6	338.4 ± 1.0	< 0.01
Ivano-Frankovsk oblast	Ivano-Frankovsk Cement, OAO	624 (10 608)	8	75.4 ± 52.2	266.5 ± 1.0	< 0.01
Kiev City	Kievskiy Slate Plant, Ltd	146 (2482)	1	40.3 ± 79.0	348.2 ± 1.0	< 0.01
Zaporozhie oblast	Zaporozhskiy Asbestos Cement Manufacturing Plant, OAO	309 (5253)	2	38.1 ± 52.8	282.9 ± 1.0	< 0.01
Total		**3064 (52 088)**	**72**	**138.2 ± 31.9**	**341.5 ± 1.0**	< 0.01

Table 3.2. **Age-standardized Average Annual Cancer Incidence Rates in Male ACI Workers in Ukraine (1995–2011; per 100,000 of respective population)**

MN Sites	Values for the standardized rate (gender and age structure of the population of Ukraine in accordance with 2001 All-Ukrainian Population Census)			Strength of the evidence in association with work at ACI (IARC criteria)
	ACI	Population (2009)	p	
Hodgkin's lymphoma	61.86 ± 41.11	2.4 ± 0.1	< 0.05	«sufficient»
Bronchi and lungs*	54.67 ± 18.98	46.3 ± 0.4	> 0.05	«limited»
Larynx*	31.80 ± 32.95	8.0 ± 0.2	> 0.05	«limited»
Skin	34.52 ± 19.31	24.4 ± 0.3	> 0.05	«limited"
Stomach	39.72 ± 19.63	22.4 ± 0.3	> 0.05	«limited»
Bladder	14.09 ± 13.39	13.0 ± 0.3	> 0.05	«limited»
Liver	13.64 ± 38.65	3.0 ± 0.1	> 0.05	«limited»
Oral cavity	13.17 ± 29.48	6.8 ± 0.2	> 0.05	«limited»
Lips	6.56 ± 30.72	2.4 ± 0.1	> 0.05	«limited»
Large intestine and rectum	4.09 ± 8.58	14.8 ± 0.2	> 0.05	«limited»
Kidney	4.09 ± 10.57	10.5 ± 0.2	> 0.05	«limited»
Chronic leukemia	2.69 ± 8.58	7.5 ± 0.2	> 0.05	«limited»
Brain	2.69 ± 10.57	5.2 ± 0.2	> 0.05	«limited»
Pancreas	2.43 ± 8.15	8.4 ± 0.2	> 0.05	«limited»
Prostate	2.27 ± 7.88	20.2 ± 0.3	< 0.05	«sufficient»
Mesothelioma*	0	0.5 ± 0.1	–	absent
Total	468.37 ± 112.90	255.2 ± 1.0	<0.05	«sufficient»

Note. *Target organs with «sufficient» strength of epidemiological evidences for MN development in result of exposure to asbestos dust (according to 2012 IARC data).

Table 3.3. **Age-standardized Average Annual Cancer Incidence Rates in Female ACI Workers in Ukraine (1995-2011; per 100,000 of respective population)**

MN locations	Values for the standardized rate (gender and age structure of the population of Ukraine in accordance with 2001 All-Ukrainian Population Census)			Strength of the evidence in association with work at ACI (IARC criteria)
	ACI	Population (2009)	p	
Mammary gland	46.60 ± 33.97	39.4 ± 0.3	> 0.05	«limited»
Large intestine and rectum	38.63 ± 30.93	10.8 ± 0.2	>0.05	«limited»
Liver	26.79 ± 25.76	1.3 ± 0.1	> 0.05	«limited»
Uterine corpus	26.50 ± 25.62	16.4 ± 0.2	> 0.05	«limited»
Skin	23.00 ± 23.87	19.5 ± 0.2	> 0.05	«limited»
Kidney	20.52 ± 22.55	5.2 ± 0.1	> 0.05	«limited»
Ovary*	20.28 ± 22.41	10.4 ± 0.1	> 0.05	«limited»
Uterus (cervix)	10.52 ± 16.14	14.6 ± 0.2	> 0.05	«limited»
Stomach	7.81 ± 13.91	9.1 ± 0.1	> 0.05	«limited»
Skin melanoma	7.59 ± 13.71	7.0 ± 0.1	> 0.05	«limited»
Brain	3.50 ± 9.31	3.7 ± 0.1	> 0.05	«limited»
Hodgkin's lymphoma	3.21 ± 8.92	2.3 ± 0.1	> 0.05	«limited»
Larynx*	0	0.30 ± 0.01	–	absent
Bronchi and lung*	0	6.20± 0.01	–	absent
Mesothelioma*	0	0.20 ± 0.01	–	absent
Gullet	0	0.70 ± 0.01	–	absent
Total	217.49 ± 73.33	189.8 ± 0.7	< 0.05	«sufficient»

Note. *Target organs with «sufficient» strength of epidemiological evidences for MN development in result of exposure to asbestos dust (according to 2012 IARC data).

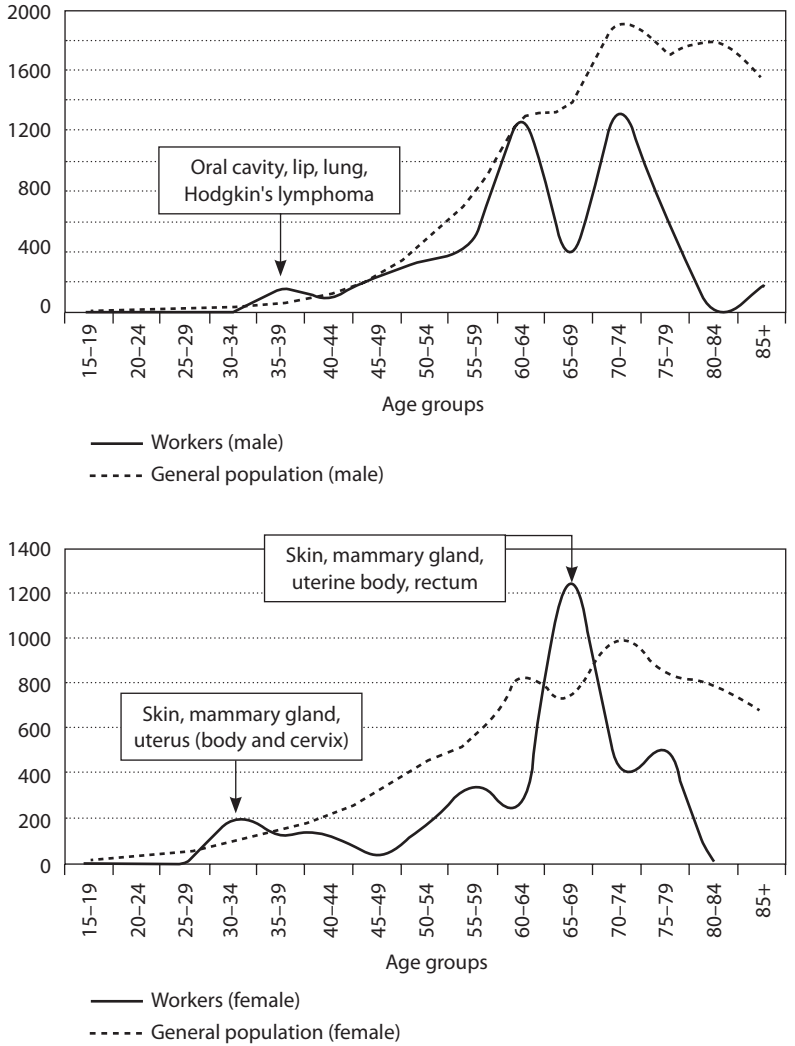

Figure 3.2. Gender-and Age-specific Distribution of Total Cancer Incidence in ACI Workers (1995–2011) in Comparison with the Population Incidence in Ukraine (2010) (per 100,000 respective population)

Gender and age profile of MN locations is as follows:

- in male workers, there are an increase in incidence rate of Hodgkin's lymphoma (25.8-fold in comparison with population rate) and low incidence rate of prostate cancer (8.9-fold) which are of «sufficient» strength of epidemiological evidence according to IARC criteria ($p < 0.05$). At the same time, in male workers, there is an increase of «limited» strength of epidemiological evidence in incidence rate of liver cancer (4.5-fold in comparison with population rate), laryngeal cancer (4.0-fold), lip cancer (2.7-fold), oral cavity cancer (2.0-fold), stomach cancer (1.8-fold), skin cancer (1.4-fold), lung cancer (1.2-fold) and bladder cancer (1.1-fold) ($p > 0.05$). Incidence rate of other MN (large intestine and rectum, kidney, brain, pancreas cancers and chronic leukemia) were lower than in the general population. There were no cases of malignant melanoma detected in male ACI workers (Table 3.2);
- in female workers, there is an increase (comparing to general population) in incidence of liver (20.6-fold), kidney (3.9-fold), large intestine and rectum cancer (3.6-fold), Hodgkin's lymphoma (1.4-fold), mammary gland (1.2-fold), uterine corpus (1.6-fold), skin (1.2-fold), ovary cancer (1.9-fold) and skin melanoma (1.1-fold) which are of «limited» strength of epidemiological evidence ($p < 0.05$). Incidence rate of other MN (cervix of the uterus, stomach and brain cancer) were lower than general population incidence rates. There were no cases of larynx, lung, gullet cancer and malignant melanoma detected in female ACI workers (Table 3.3).

«Case-control» epidemiology data analysis show that odds ratio (OR) of all kinds of MN in ACI workers at different workplaces is the biggest at storehouse ($OR = 5.95$; $p < 0.01$) followed by maintenance service ($OR = 1.39$; $p < 0.01$), slate manufacturing shop ($OR = 1.21$; $p > 0,05$), and transportation service ($OR = 1.52$; $p > 0,05$) (Table 3.4).

Elevated odds ratio of cancer is observed for the following ACI workers: shift man ($OR = 2.94$; $p < 0.01$), maintenance mechanic ($OR = 2.93$; $p < 0.01$), batcher operator ($OR = 2.88$; $p < 0.01$), welder ($OR = 1.68$; $p > 0.05$), storekeeper ($OR = 1.38$; $p > 0.05$), driver ($OR = 1.20$; $p > 0.05$), crane operator ($OR = 1.18$; $p > 0.05$) and crane slinger ($OR = 1.16$; $p > 0.05$) (Table 3.5).

The analysis of MN development at target organs in workers with occupational exposure to chrysotile asbestos dust showed an increase in OR of cancer at the following sites: larynx ($OR = 5.02$; 95 % CI: 0.53-117.92; $p > 0.05$), ovary (female: $OR = 4.84$; 95 % CI: 0.30-77.38;

$p > 0.05$), large intestine and rectum (OR = 1.26; 95 % CI: 0.13-12.40; $p > 0.05$). Odds ratio of cancer at other target organs (including lung and stomach) was not increased (OR < 1.00). There were no cases of mesothelioma, gullet cancer and oesophagus cancer detected in all examined ACI worker groups (Table 3.6).

Respiratory organs (gullet, bronchi, lung and pleura) were proved to be the target organs for the development of MN. According to the IARC data, the causes of MN development in these organs are multifactorial. It is a fact that the gullet, bronchial cancer, lung cancer and

Table 3.4. **Odds Ratio (OR) of Total Cancer Incidence in ACI Workers by Production Area (1995−2011)**

Production areas	Incidence rate (per 100,000 workers)	OR (95 % CI)	p
Storehouse	840.3	5.95 (2.97 − 11.94)	$< 10^{-7}$
Maintenance shop	288.6	1.39 (1.42 − 3.72)	$< 10^{-3}$
Slate manufacturing shop	108.8	1.21 (0.70 − 2.09)	> 0.05
Transportation service	235.3	1.52 (0.56 − 4.17)	> 0.05
Batch and blanking shop	258.6	0.74 (0.43 − 1.28)	> 0.05
Other areas	146.1	0.11 (0.04 − 0.31)	$< 10^{-7}$

Table 3.5. **Odds Ratio (OR) of Total Cancer Incidence in ACI Workers by Professional Occupation (1995−2011)**

Occupation	Incidence rate (per 100,000 workers)	OR (95 % CI)	p
Shift man	452.5	2.94 (1.09 − 8.13)	$< 10^{-2}$
Repair mechanic	386.4	2.93 (1.72 − 4.99)	$< 10^{-4}$
Batch operator	420.2	2.88 (1.38 − 6.00)	$< 10^{-3}$
Welder	261.4	1.68 (0.4 − 6.82)	> 0.05
Storekeeper	215.2	1.38 (0.44 − 4.38)	> 0.05
Driver	187.7	1.20 (0.38 − 3.81)	> 0.05
Crane operator	183.8	1.18 (0.43 − 3.22)	> 0.05
Crane slinger	181.9	1.16 (0.37 − 3.68)	> 0.05
Blanking shop operator	117.0	0.72 (0.33 − 1.56)	> 0.05
SFM operator	67.1	0.67 (0.36 − 1.25)	> 0.05
Loader	97.5	0.60 (0.19 − 1.91)	> 0.05
Electrician	85.9	0.52 (0.19 − 1.42)	> 0.05
Others	64.1	0.33 (0.16 − 0.69)	$< 10^{-3}$

pleural mesothelioma are associated with asbestos exposure. However, there are also other general and more important risk factors, such as age, genetic determination (hereditary predisposition), chronic pathology in these organs, life style specifics (active and passive tobacco smoking, alcohol abuse). In addition, the MN can be also caused by a number of occupational and non-occupational physical, chemical and biological carcinogenic agents (Table 3.7).

For instance, during ACI technological process, workers are exposed to minimum three Group 1 carcinogenic chemical agents (by IARC classification): dust of chrysotile asbestos and silica (quartz) that are the raw materials for asbestos-cement product manufacturing, as well as a number of polycyclic aromatic hydrocarbons (including benzopyrene) that can be generated from natural gas burning used for drying the asbestos-cement products (Table 3.7).

Table 3.6. **Odds Ratio (OR) of Cancer Incidence in ACI Workers Exposed to Chrysotile Asbestos at Workplace (1995–2011)**

Strength of evidence	Locations	Number of MN /Number of workers (person-years)		OR (95 % CI)	p
		Asbestos (+)	Asbestos (–)		
«Sufficient»	Laryngeal cancer	4/20 260	1/25 431	5.02 (0.53 – 117.92)	> 0.05
	Bronchi and lung cancer	4/20 260	10/25 422	0.50 (0.1 – 1.73)	> 0.05
	Pleural, peritoneal, pericardial mesothelioma	0	0	0.00	–
	Ovary cancer (female)	1/2652	[1]*/12 832	4.84 (0.30 – 77.38)	> 0.05
«Limited»	Gullet cancer	0	0	0.00	–
	Oesophagus cancer	0	0	0.00	–
	Stomach cancer	2/20 252	4/25 428	0.63 (0.08 – 3.95)	> 0.05
	Large intestine and rectum cancer	2/20 262	2/25 430	1.26 (0.13 – 12.40)	> 0.05

Note: *potential risk calculated on the basis of incidence in population.

Table 3.7. **Causes of Malignant Neoplasms in Respiratory Organs (based on 2015 IARC data) (http://monographs.iarc.fr/ENG/Classification/index.php)**

Carcinogenic factors	Larynx cancer	Bronchi and lung cancer	MM
Biological factor			
Age	+	+	+
Genetic predisposition (as of September 1, 2015, number of known determinant genes of cancer is 2480) [http://www.ncbi.nlm.nih.gov/gene/ ?term = cancer%2C + susceptibility + to + Homo + sapiens]	**14 (0.6 %)**	**845 (34.1 %)**	**118 (4.8 %)**
Chronic inflammation in target organ	+	+	+
Life style			
Active and passive tobacco smoking	+	+	-
Alcohol abuse	+	-	-
Physical agent			
Ionizing radiation, radon-222	-	+	+
Chemical agent			
Asbestos	+	+	+
Aerosols of inorganic acids containing sulphuric acid	+	-	-
Beryllium and its compounds	-	+	-
Bis(chloromethyl) ether, chloromethyl methyl ether	-	+	-
Dioxin (*2,3,7,8-TCDD*)	-	+	-
Cadmium and its compounds	-	+	-
Silica, crystalline (quartz)	-	+	-
Arsenic and its compounds	-	+	-
Nickel compounds	-	+	-
Polycyclic aromatic hydrocarbons	-	+	-
Carbon nanotubes	-	-	+
Chromium (VI) compounds	-	+	-
Erionite	-	+	+
Biological agent			
Simian vacuolating virus 40 (SV-40)	-	-	+
Human papilloma virus (HPV)	types 6, 11, 16, 18	-	type 16
Retrovirus of bird myelogenous leukemia (MC-29)	-	-	+

Data provided by J. T. Hodgson et al. (2000) show that carcinogenic potential of chrysotile asbestos is lower than of amphibole asbestos in the development of mesothelioma (100-fold lower than amosite; 500-fold lower than crocidolite) and lung cancer (10-fold lower than amosite; 50-fold lower than crocidolite [15].

The results of studies conducted by M. Dodiè fikfak (2003) also demonstrate that chrysotile asbestos has 40-fold lower carcinogenic potential in the development of lung cancer and mesothelioma than amphibole asbestos [11].

Using the US Environmental Protection Agency (US EPA) calculation procedure (EPA document EPA/600/8-87/045), individual cancer risk (ICR) in ACI workers was estimated based on chrysotile asbestos dust pollution levels in working zone. According to US EPA estimates, the carcinogenic potential [in Unit Risk (URi) values] of asbestos (type of asbestos is not specified) in mesothelioma and lung cancer development is 0.23 fibres/sm^3 per year [3].

Taking into account the fact that amphibole asbestos varieties were mostly used in carcinogenic potential experimental studies, in order to evaluate the individual cancer risk in ACI workers exposed to chrysotile asbestos dust in the workplace we applied the scaling down inhalation unit risk factor of 40.0 (based on M. Dodiè fikfak data (2003); for ICR calculation, URi was taken to be $5.8 \cdot 10^{-3}$ fibres/sm^3 per year.

It was found that after 17 years of observation, individual cancer risk in workers of all major manufacturing occupations (batcher operator, blanking area operator, sheet forming machine operator) was «safe» (ICR $\leq 10^{-5}$). At standard length of covered service period for minimum old age pension (for men: 35 years) (Law of Ukraine «On mandatory State Pension Insurance») the individual cancer risk for sheet forming machine operators is «safe», for batcher operators and blanking shop operators it is «acceptable» at occupational exposure conditions (ICR = $10^{-4} - 10^{-3}$) (Table 3.8). Accordingly, safe airborne concentration of chrysotile asbestos fibres averaged over the work shift in ACI working zone should not exceed 6.5 fibres/sm^3 per year (length of service: 35 years; work shift: 8 hours; lung ventilation volume during work shift: 10 m^3; number of working days per year: 249).

The assessment of cancer risk for ACI workers due to workplace exposure to silica (SiO_2) (ICR = $8.9 \cdot 10^{-4}$ mg/m^3 [8]) showed that workers of all major occupations have «acceptable» individual cancer risk (ICR = $10^{-4} - 10^{-3}$) both at observation period (17 years) and at covered service period for old age pension (35 years) (Table 3.9).

Table 3.8. **Individual Cancer Risk for ACI Workers Due to Their Occupational Exposure to Chrysotile Asbestos**

Occupational groups	Length of service, years		Concentrations of asbestos fibres averaged over the work shift, fibres/sm^3	ICR*	Cancer risk associated with occupational exposure
Batcher operator	Observed	17	0.09 – 0.72	$1.9 \cdot 10^{-4}$ ($4.3 \cdot 10^{-5} - 3.5 \cdot 10^{-4}$)	«Safe»
	Max.	35.0		$4.0 \cdot 10^{-4}$ ($8.9 \cdot 10^{-5} - 7.1 \cdot 10^{-4}$)	«Acceptable»
Blanking shop operator	Observed	17.0	0.09 – 0.12	$5.0 \cdot 10^{-5}$ ($4.3 \cdot 10^{-5} - 5.8 \cdot 10^{-5}$)	«Safe»
	Max.	35.0		$1.0 \cdot 10^{-4}$ ($8.9 \cdot 10^{-5} - 1.2 \cdot 10^{-4}$)	«Acceptable»
Sheet forming machine operator	Observed	17	0.09 – 0.11	$4.8 \cdot 10^{-5}$ ($4.3 \cdot 10^{-5} - 5.3 \cdot 10^{-5}$)	«Safe»
	Max.	35.0		$9.9 \cdot 10^{-5}$ ($8.9 \cdot 10^{-5} - 1.1 \cdot 10^{-4}$)	«Safe»

Note. *URi: $5.8 \cdot 10^{-3}$ fibres/sm^3 per year.

Table 3.9. **Individual Cancer Risk for ACI Workers Due to Their Occupational Exposure to Crystalline Silica (quartz) (SiO_2)**

Occupational groups	Length of service, years		Concentration of SiO_2 averaged over the work shift, mg/m^3	ICR*	Cancer risk associated with occupational exposure
Batcher operator	Observed	17.0	2.2 – 7.0	$3.3 \cdot 10^{-4}$ ($1.6 \cdot 10^{-4} - 5.0 \cdot 10^{-4}$)	«Acceptable»
	Max.	35.0		$6.8 \cdot 10^{-4}$ ($3.2 \cdot 10^{-4} - 1.0 \cdot 10^{-3}$)	«Acceptable»
Blanking shop operator	Observed	17.0	0.8 – 2.9	$1.3 \cdot 10^{-4}$ ($5.7 \cdot 10^{-5} - 2.1 \cdot 10^{-4}$)	«Acceptable»
	Max.	35.0		$2.7 \cdot 10^{-4}$ ($1.2 \cdot 10^{-4} - 4.3 \cdot 10^{-4}$)	«Acceptable»
Sheet forming machine operator	Observed	17.0	0.6 – 2.6	$1.1 \cdot 10^{-4}$ ($4.3 \cdot 10^{-5} - 1.9 \cdot 10^{-4}$)	«Acceptable»
	Max.	35.0		$2.3 \cdot 10^{-4}$ ($8.8 \cdot 10^{-5} - 3.8 \cdot 10^{-4}$)	«Acceptable»

Note. *URi: $8.9 \cdot 10^{-4}$ mg/m^3 per year [13].

Calculation of population cancer risk (PCR) for workers of major ACI occupations due to their occupational exposure to chrysotile asbestos and crystalline silica (quartz) dust showed that expected number of additional cancer cases in target organs (larynx, bronchi and lung, pleural mesothelioma) is 0.34 cases in 35 years or 1.34 cases per 100,000 of exposed persons per year. The distribution profile for expected incidence by etiological risk is as follows: 32.3 % (chrysotile asbestos) and 67.7 % (crystalline silica) (Table 3.10). According to these data, expected number of cancer cases in target organs during 17 years of observation is 0.16 cases (including 0.05 cases due to chrysotile asbestos exposure).

During 17 years of ACI worker observation period we have recorded 5 laryngeal cancer cases, 14 bronchial and lung cancer cases and none of MM cases which totals 19 cases. These cases included workers of major occupations (batcher operator, blanking shop operator and SFM operator) who were highly exposed to chrysotile asbestos and crystalline silica dust at their workplace and who had cancer at the following locations: larynx (4 cancer cases which is 80.0 % of all

Table 3.10. **Population Cancer Risk (PCR) for ACI Workers Due to Their Occupational Exposure to Chrysotile Asbestos (ChA) and Crystalline Silica Dust (SiO_2)**

Occupational groups	Number of workers	Individual cancer risk (ICR)			Population cancer risk (PCR)
		ChA	SiO_2	ChA + SiO_2	
Batcher operator	112	$4{,}0 \cdot 10^{-4}$	$6{,}8 \cdot 10^{-4}$	$1{,}1 \cdot 10^{-3}$	0,12
Blanking shop operator	352	$1{,}0 \cdot 10^{-4}$	$2{,}7 \cdot 10^{-4}$	$3{,}7 \cdot 10^{-4}$	0,13
Sheet forming machine operator	263	$9{,}9 \cdot 10^{-5}$	$2{,}3 \cdot 10^{-4}$	$3{,}3 \cdot 10^{-4}$	0,09
Total additional cancer cases in 35 years: — due to ChA exposure — due to SiO_2 exposure					0,34 (100,0 %) 0,11 (32,3 %) 0,23 (67,7 %)
— per 100,000 exposed persons per year					1,34

cancer cases at this location); bronchi and lung (4 cancer cases, i.e. 28.6 %); no MM cases; in total 8 cases (42.1 %). Thus, incidence rate of malignant neoplasm in target organs in ACI workers of major high-risk occupations is 0.47 cases per year. Taking into account the multifactorial nature of malignant neoplasms (see Table 3.7), it is estimated that occupational exposure of ACI workers to studied carcinogenic factors makes no more than 34.0 % (including 10.6 % due to chrysotile asbestos) contribution into the development of this pathology during 17 years).

3.2. Identification of Asbestos and Ionizing Radiation Exposure in Patients with Pleural Malignant Mesothelioma in Ukraine

In 2013-2014 the Laboratory of Carcinogenic Danger and Prevention of Occupational Cancer of the Institute for Occupational Health conducted the study focused on etiologic factors in pleural MM patients (ICD-10 code: C45.0). The cohort included pleural MM patients who at the time of the study were alive or died not earlier than 12 months before the study. The study was conducted by face-to-face or call-in interview of patients and/or their relatives. Overall, 573 respondents (86.9 % of estimated number of the total pleural MM patients) answered the interview questions.

General information concerning the investigated cohort of pleural MM patients. The results of MM patients data processing showed that this malignant neoplasm is found a little bit more frequently in men (58.3 ± 6.5)% than in women (41.7 ± 6.5)% ($p < 0.05$) (Figure 3.3). Average age of examined male MM patients (61.0 ± 0.7) years is statistically lower than the age of female MM patients (64.5 ± 0.8) years ($p < 0.05$) (Figure 3.4). At the same time, 45.4 % of MM patients live in cities.

In the cohort of patients under investigation, the highest MM incidence rates are observed in the following age groups: 50−59 years old (23.0 %), 60−69 years old (26.0 %), and 70−79 years old (28.0 %) (Figure 3.5).

The majority of MM patients lived in Dnepropetrovsk oblast (9.0 %), Vinnitsa oblast (8.0 %), Kirovograd oblast (8.0 %), Kiev City (7,0 %), the AR of Crimea (6.0 %), and Kharkov oblast (6.0 %) (Figure 3.6).

Search for known risk factors in MM etiology did not identify such factors in 66.3 % of investigated MM patients.

In the cohort of MM patients, the workplace exposure to the following risk factors was revealed: ionizing radiation (24.6 ± 1.8) %; dust

of asbestos and asbestos-containing materials (9.1 ± 1.4) % (Table 3.11).

Exposure to ionizing radiation (while serving in the army) in MM patient cohort under investigation. Only two MM patients of cohort under investigation reported exposure to ionizing radiation during military service. These patients lived in the AR of Crimea and Sevastopol City. They developed MM at much younger age (54.0 ± 1.0) years than patients who did not have contact with ionizing radiation (62.5 ± 0.5) years ($p < 0.05$).

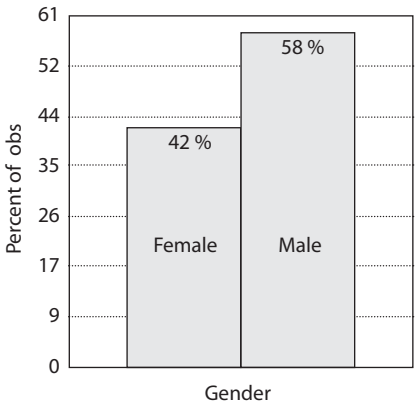

Figure 3.3. Gender Distribution Profile of Patients in the Cohort under Investigation (% MM patients)

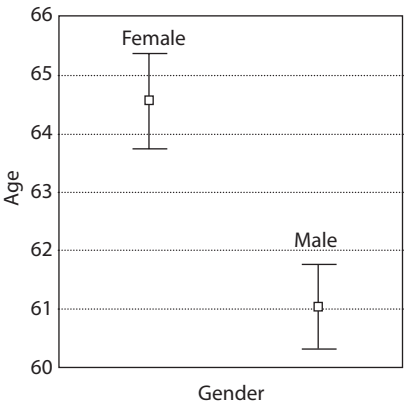

Figure 3.4. Average Age of MM Patients in the Cohort under Investigation (years)

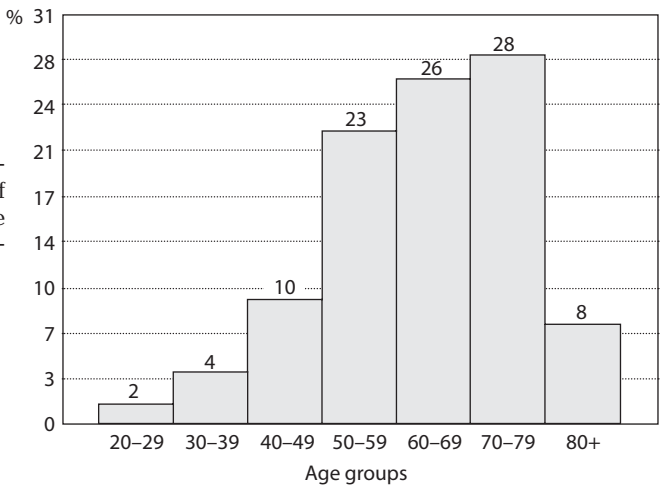

Figure 3.5. Age Distribution Profile of MM Patients in the Cohort under Investigation (years)

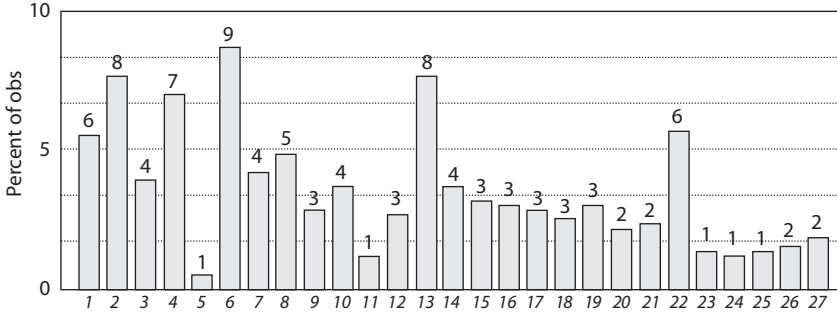

Figure 3.6. Geographical Distribution Profile of Patients in the Cohort under Investigation (% MM patients):
1 — AR Crimea, *2* — Vinnitsa oblast, *3* — Volyn oblast, *4* — Kiev, *5* — Sevastopol, *6* — Dnepropetrovsk oblast, *7* — Donetsk oblast, *8* — Zhitomir oblast, *9* — Zakarpattya oblast, *10* — Zaporozhie oblast, *11* — Ivano-Frankovsk oblast, *12* — Kiev oblast, *13* — Kirovograd oblast, *14* — Lugansk oblast, *15* — Lvov oblast, *16* — Nikolaev oblast, *17* — Odessa oblast, *18* — Poltava oblast, *19* — Rovno oblast, *20* — Sumy oblast, *21* — Ternopol oblast, *22* — Kharkov oblast, *23* — Khmelnitskiy oblast, *24* — Kherson oblast, *25* — Cherkasy oblast, *26* — Chernigov oblast, *27* — Chernovtsy oblast

Table 3.11. **Frequency of Exposure to Etiological Factors in MM Patients under Investigation**

Etiological factors	Kinds of contact	Patients who mentioned previous exposure to this factor (number/%)		p
		Men (n = 334)	Women (n = 239)	
Asbestos	Workplace exposure to asbestos dust	32 / 9.6 ± 1.6	20 / 8.4 ± 1.8	> 0.05
Ionizing radiation	Exposure during military service	2 / 0.6 ± 0.4	—	—
	Victims of accident at the ChNPP	23 / 6.9 ± 1.4	21 / 8.8 ± 1.8	> 0.05
	Work at NPP	2 / 0.6 ± 0.4	—	—
	Work at uranium ore mining and enrichment	19 / 5.7 ± 1.3	—	—
	Risk of exposure to airborne radon-222	61 / 18.3 ± 2.2	42 / 17.6 ± 2.5	> 0.05
Etiological factor was not identified		222 / 66.5 ± 2.6	158 / 66.2 ± 3.0	> 0.05

Exposure to specific factors typical for the Chernobyl NPP accident in the MM patient cohort under investigation. 44 MM patients (7.7 ± 0,4) % lived on the territories affected by the Chernobyl accident or were evacuated from the 30-km zone around Chernobyl NPP (ChNPP).

Significant number of MM patients lived in Cherkassy oblast, Kiev oblast, Khmelnitskiy oblast, Chernigov oblast, and lesser number − in Zhitomir oblast, Volyn oblast, Vinnitsa oblast, Rovno oblast and Ternopol oblast.

The average age of MM onset in patients who suffered from ChNPP accident (60.7 ± 1.9) years and in patients who did not have such experience (62.6 ± 0.6) years was not statistically different ($p > 0.05$).

Exposure to factors typical for the work at NPP in MM patient cohort under investigation. Only two persons (0.3 ± 0.2) % in MM patient cohort had their work at NPPs mentioned in their medical history. These patients lived in Kiev oblast and Rovno oblasts.

They developed MM at much younger age (51.0 ± 1.0) years than patients who did not work at NPP (62.5 ± 0.5) years ($p < 0.05$).

Exposure to factors typical for uranium ore industrial extraction and enrichment in the MM patient cohort under investigation. Nineteen persons (3.3 ± 0.7) % in MM patient cohort had their work at uranium mining and processing facilities recorded in their medical history. These patients lived in Kirovograd and Dnepropetrovsk oblasts.

The average age of MM onset in patients who worked at uranium mining and processing industrial facilities (64.9 ± 3.9) years and those who did not have such experience (62.4 ± 0.5) years was not statistically different ($p > 0.05$).

Risk factors typical for airborne radon-222 exposure in the mesothelioma patient cohort under investigation. 103 MM patients (18.0 ± 1.6) % lived and/or worked for long periods of time (more than 10 years) in basement and/or ground floor premises which were poorly ventilated causing their exposure to airborne radon-222. Such patients were registered practically in all oblasts of Ukraine.

The average age of MM onset in patients who were exposed to airborne radon-222 (61.6 ± 1.3) years and those who did not experience such exposure (62.7 ± 0.6) years was not statistically different ($p > 0.05$).

Risk factors typical for exposure to asbestos dust at workplace in the mesothelioma patient cohort under investigation. 52 MM patients (9.1 ± 1.2) % mentioned that for some time (for more than 10 years) during their life they have been working with asbestos and asbestos-containing materials. These patients lived in Nikolaev oblast, Kharkov oblast, Zaporozhie oblast, Odessa oblast, Rovno oblast and Kiev City.

Patients who had the risk of exposure to asbestos and asbestos-containing materials developed MM at statistically older age (66.9 ± 1.8) yearsthan patients who did not have such a risk (62.1 ± 0.6) years ($p < 0.05$).

Economic sectors distribution profile of the MM patient cohort under investigation. Analysis of data on MM patient cohort showed that patients worked mostly in the following sectors of economy [code]: other sectors [36] (18 %), agriculture [30] (11 %), beverages and food production [19–20] (6 %), public health [8] (5 %), education [11] (5 %), trade and catering service [33] (5 %), and also in other 26 economic sectors (1–4 %) (Figure 3.7).

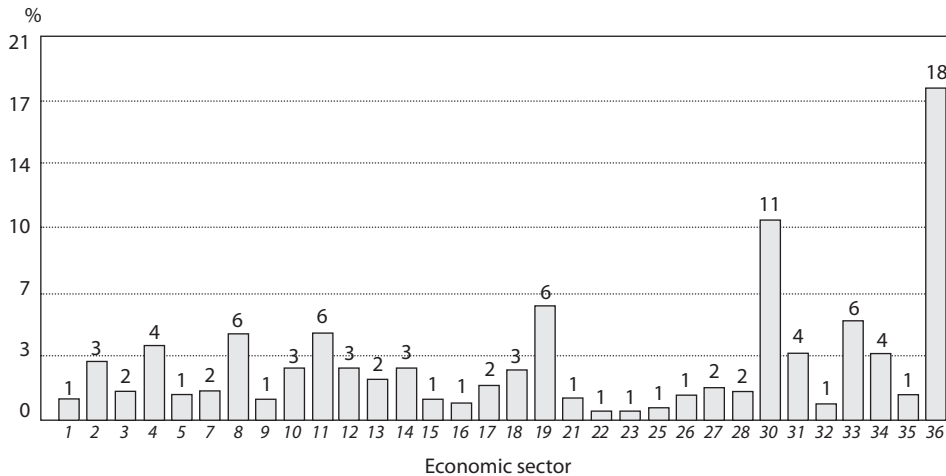

Figure 3.7. Economic Sector Distribution Profile of Patients in Cohort under Investigation (% MM patients)

1 – air transport, *2* – river transport, *3* – coal and brown coal mining, 4 – mineral extraction and earth excavation, *5* – oil and natural gas extraction, *6* – production of electric power, *7* – water intake, purification and supply, *8* – health care, *9* – ground-surface and pipeline transportation, *10* – wood processing and manufacture of wood and cork products, except furniture, *11* – education, *12* – services to individuals, *13* – printing, *14* – postal and courier services, *15* – manufacture of paper and paper products, *16* – production of precious and other non-ferrous metals, *17* – manufacture of computers, electronic and optical products, *18* – manufacture of fabricated metal products, except machinery and equipment, *19–20* – food and beverage industry, *21* – manufacture of plastic products, *22* – manufacture of rubber products, *23* – manufacture of glass and glass products, *25* – production of transportation means, *26* – production of chemicals, oil processing, *27* – cement production, *28* – production of cast iron, steel and ferrous alloys, *29–30* – fishery, agriculture, *31* – building, *32* – textile industry, *33* – trade and catering services, *34* – finances and insurance, *35* – production and repair of machinery and equipment, *36* – other sectors

Association between exposure to etiological factors and MM incidence in patients of the cohort under investigation. Study results show that in Ukraine:

1) male MM incidence is higher than female (1.4:1.0), and men fell ill 3.5 years earlier than women;
2) incidence in countryside population is higher than in city population (1.20:1.0);
3) the following etiological risk factors were identified in MM patients: ionizing radiation (24.6 %), dust of asbestos and asbestos-containing materials at workplace (9.1%), risk factors not identified (66.3 %);
4) the youngest age of MM onset is observed in patients who were exposed to ionizing radiation during work at NPP or military service (51.0 – 54.0 years) (Table 3.12);
5) Spearman correlation analysis of MM patient cohort data showed statistically significant correlation between radon-222 exposure and job at uranium ore extraction industry (rSp = 0.37).

Results of comparative analysis of 26 studies evaluating the frequency of exposure in MM patients showed significant data variability. For instance, the frequency of asbestos exposure in pleural MM patients ranges from 1.5 % to 96.1 % with average cumulative value of (16.4 ± 0.2) % of all patients (Table 3.13).

Table 3.12. **Average Age of MM Onset and Exposure to Risk Factors**

Categories of patients	Age of MM onset (years)
Patients who worked at NPP	51.0 ± 1.0
Patients who were exposed to ionizing radiation (during military service)	54.0 ± 1.0
Victims of ChNPP accident	60.7 ± 1.9
Patients with risk of exposure to airborne Rn-222 in the past	61.6 ± 1.3
Patients who worked in uranium mining and processing industry	64.9 ± 3.9
Patients who were exposed to asbestos dust at the workplace	66.9 ± 1.8
Persons with unknown risk factors	62.1 ± 0.7

Table 3.13. **Frequency of Asbestos Exposure in MM Patients**

Country	Number of MM patients under investigation	MM patients with asbestos exposure in the past, %	Reference
Korea, 1995 – 2012	66	1.5	Ahn S. et al., 2014 [26]
Australia, 1974 – 2013	22048	3.9	Reid A. et al., 2014 [23]
USA, 2013	64	7.8	Lee M. et al., 2013 [19]
Ukraine, 2013 – 2014	573	9.1	Institute for Occupational Health of the NAMS of Ukraine, 2013 – 2014
Mexico, 2014	61	13.1	Hernández-Solís A. et al., 2014 [20]
France, 1998 – 2009	318	19.8	Camiade E. et al., 2013 [6]
Sweden, 1971 – 1993	419	21.0	Järvholm B. et al., 2014 [18]
Italy, 2001 – 2009	600	31.0	Romeo E. et al., 2013 [24]
Canada, 1980 – 2002	1855	35.0	Payne J.I. et al., 2009 [12]
Korea, 2001 – 2012	399	36.8	Jung S.H. et al., 2012 [2]
Great Britain, 2000 – 2004	1420	43.8	Rake C., 2009 [25]
Italy, 2013	834	49.9	De Zotti R. et al., 2013 [10]
Croatia, 1989 – 2008	117	61.5	Kricka O. et al., 2009 [21]
Spain, 1970 – 2006	112	62.0	Tarrés J. et al., 2009 [5]
Turkey, 2014	54	64.8	Sezer A. et al., 2014 [22]
Germany, 1998 – 2011	118	65.0	Ried M. et al., 2013 [28]
Croatia, 1991 – 2006	179	67.0	Sarić M. et al., 2009 [30]
Japan, 2007 – 2008	953	68.5	Kuribayashi K. et al., 2012 [29]
Croatia, 2001 – 2005	64	81.2	Cvitanović S. et al., 2009 [16]
Turkey, 2004 – 2011	252	82.8	Utkan G. et al., 2013 [9]
Turkey, 2005 – 2013	35	82.9	Kaya H. et al., 2014 [27]
Croatia, 2000 – 2007	137	85.4	Mise K. et al., 2009 [17]
Turkey, 1993 – 2010	228	86.0	Berk S. et al., 2012 [7]
Japan, 2005 – 2007	105	88.6	Fujimoto N., 2010 [8]
Denmark, 1984 – 2009	122	91.0	Skammeritz E. et al., 2011 [4]
USA, 2011	238	96.1	Haber S.E. et al., 2011 [14]
Total	**31 371**	**16.4 ± 0.2 (n = 5 158)**	-

At the same time, correlation analysis data show that increased sample size results in decreased frequency in asbestos exposure in MM patients ($r = -0.34$) (Figure 3.8).

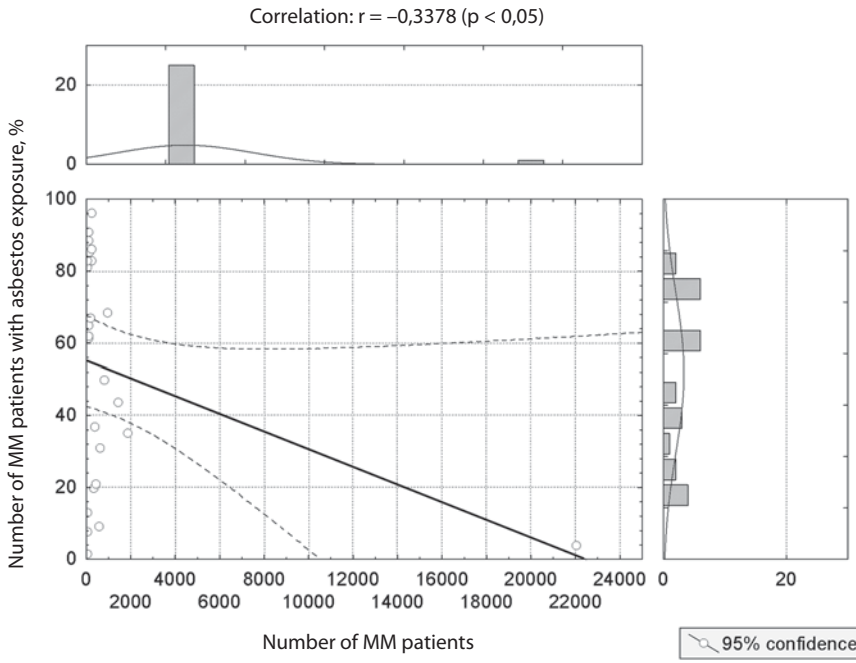

*Figure 3.8. C*orrelation Between the Size of Study Sample and Frequency of Asbestos Exposure in Pleural MM Patients

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Part 4

CLINICAL CHARACTERISTICS, DIAGNOSTICS AND TREATMENT OF MALIGNANT MESOTHELIOMA

4.1. Malignant Mesothelioma Classifications

Today, there are several MM classifications: statistical, pathomorphological and TNM-classification (by disease stages).

Statistical classification. In accordance with International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) (2015 version) [27], mesothelioma is classified as follows:

Chapter II: Neoplasms (C00-D48).

Block C45-C49: Malignant neoplasms of mesothelial and soft tissue.

Category C45: Mesothelioma (included: morphological code M905 with code of neoplasm/3).

Three-digit subcategories:

C45.0 Mesothelioma of pleura. Excluded: other malignant neoplasms of pleura (C38.4).

C45.1 Mesothelioma of peritoneum. Included: mesentery, mesocolon, omentum, peritoneum (parietal) (pelvic). Excluded: other malignant neoplasms of peritoneum (C48.-).

C45.2 Mesothelioma of pericardium. Excluded: other malignant neoplasms of pericardium (C38.0).

C45.7 Mesothelioma of other sites (testicle, ovary, joint, retroperitoneal etc.).

C45.9 Mesothelioma, unspecified.

Pathomorphological classification. In accordance with International Classification of Diseases for Oncology, 3rd Edition/Revision (ICD-O-3.1, 2011) [28].

Pathomorphological classification of mesothelial tumours is as follows:

M905 Tumours of mesothelial tissue.

M9050/0 Mesothelioma, benign (D19.-).

M9050/3 Mesothelioma, malignant (C45.-).

M9051/0 Fibrous mesothelioma, benign (D19.-).

M9051/3 Fibrous mesothelioma, malignant (C45.-). Includes: fibrous mesothelioma, spindled mesothelioma, sarcomatoid mesothelioma, desmoplastic mesothelioma.
M9052/0 Epithelioid mesothelioma, benign (D19.-). Includes: well differentiated papillary mesothelioma, benign, mesothelial papilloma.
M9052/3 Epithelioid mesothelioma, malignant (C45.-).
M9053/0 Mesothelioma, biphasic, benign (D19.-).
M9053/3 Mesothelioma, biphasic, malignant (C45.-).
M9054/0 Adenomatoid mesothelioma, benign (D19.-).
M9055/0 Multicystic mesothelioma, benign. Includes: cystic mesothelioma, benign.
M9055/1 Cystic mesothelioma, not otherwise specified (NOS).

According to this classification, MM (code 9050/3) includes the following: malignant epithelioid mesothelioma (9052/3), fibrous (sarcomatoid) and malignant desmoplastic mesothelioma (9051/3), malignant biphasic mesothelioma (9053/3) (Fig. 4.1-4.4) [28].

Histological classification of pleural tumours is presented in Table 4.1

Table 4.1. **Histological Classification of Pleural Tumours**

Mesothelial tumours	Mesenchymal tumours	Lymphoproliferative disorders
Diffuse MM (9050/3) – Epithelioid mesothelioma (9052/3) – Sarcomatoid mesothelioma (9051/3) – Desmoplastic mesothelioma (9051/3) – Biphasic mesothelioma (9053/3) *Localized malignant mesothelioma (9050/3)* *Other tumours of mesothelial origin:* – Well differentiated papillary mesothelioma (9052/1) – Adenomatoid tumour (9054/0)	*Epithelioid hemangioendothelioma (9133/1)* – Angiosarcoma (9120/3) Synovial sarcoma (9040/3) – Monophasic (9041/3) – Biphasic (9043/3) Solitary fibrous tumour (8815/0) Calcifying tumours of the pleura Desmoplastic small round cell tumour (8806/3)	– Primary effusion lymphoma (9678/3) – Pyothorax-associated lymphoma

Note. Coding of tumours: / 0 – benign tumour, / 3 – malignant tumour, / 1 – borderline or not otherwise specified tumour.

TNM Classification based on tumour stages. The TNM system for describing the anatomic extent of neoplasm is based on three components:

- T (in Latin *«tumor»* – *tumour, swelling*): the extent of the primary tumour;
- N (in Latin *«nodus»* – *node*): the absence, presence and extent of regional lymph node metastasis;
- M (in Greek «μεταστασις» – *spread*): the presence or absence of distant metastasis.

The TNM system is used to describe and record the anatomical extent of disease spread. In order to combine and evaluate the data, the categories can be grouped into stages.

The general rules of the TNM classification system are as follows:

1. All cases should be confirmed microscopically. Any case not so proved must be reported separately.
2. The following methods are used to assess the categories T, N and M:
   - category T: physical examination, imaging, endoscopy and/or surgical exploration;
   - category N: physical examination, imaging, endoscopy and/or surgical exploration;
   - category M: physical examination, imaging and/or surgical exploration;
   - regional lymph nodes are as follows: intrathoracic, hilar, supraclavicular.
3. Pathological anatomy classification (pTNM) corresponds to diagnostic categories of clinical classification (cTNM).
4. After assigning T, N, M and/or pT, pN and pM categories, they are grouped into respective stage of disease. The established TNM categories as well as disease stage grouping must remain unchanged in medical records.
5. Clinical and pathological anatomy classifications may be combined if they complement each other.
6. If there is doubt concerning the correct T, N, or M category to which a particular case should be allotted, then the lower category should be chosen. This will also be reflected in the stage grouping.
7. In the case of multiple simultaneous tumours in one organ the tumour with the highest T category should be classified. At the same time, the multiplicity or the number of tumours should be

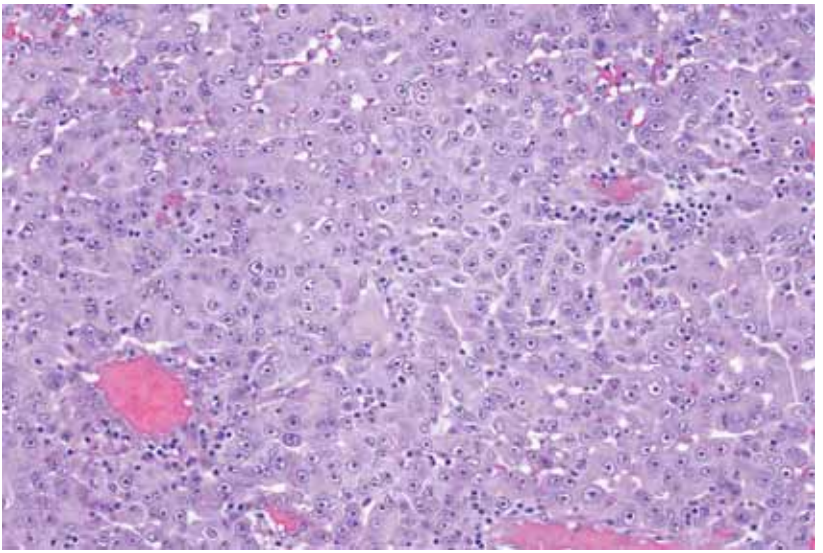

Figure 4.1. Histological Subtypes of Malignant Mesothelioma: Epithelioid Mesothelioma (9052/3)

Source: Figure 4.1 – 4.4: © WebPathology / Dr. Dharam Ramnani. – Access to: http://www.webpathology.com.

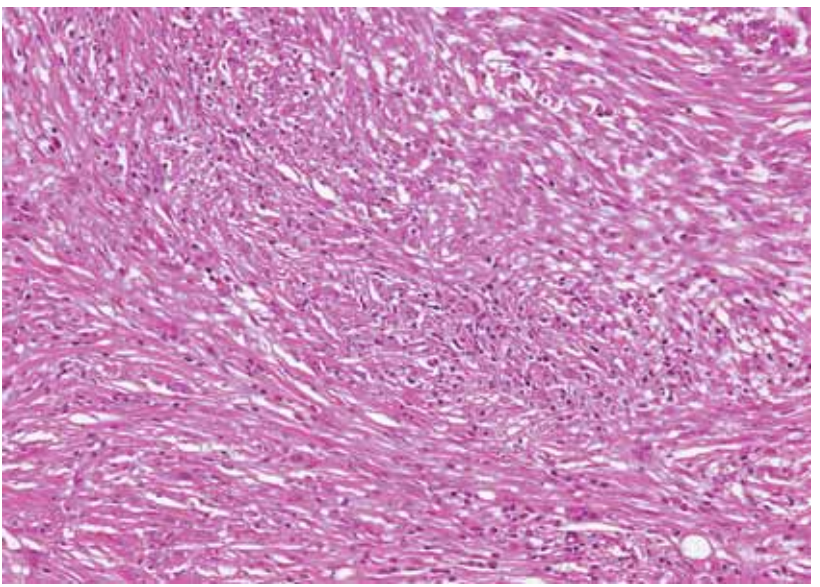

Figure 4.2. Histological Subtypes of Malignant Mesothelioma: Sarcomatoid Mesothelioma (9051/3)

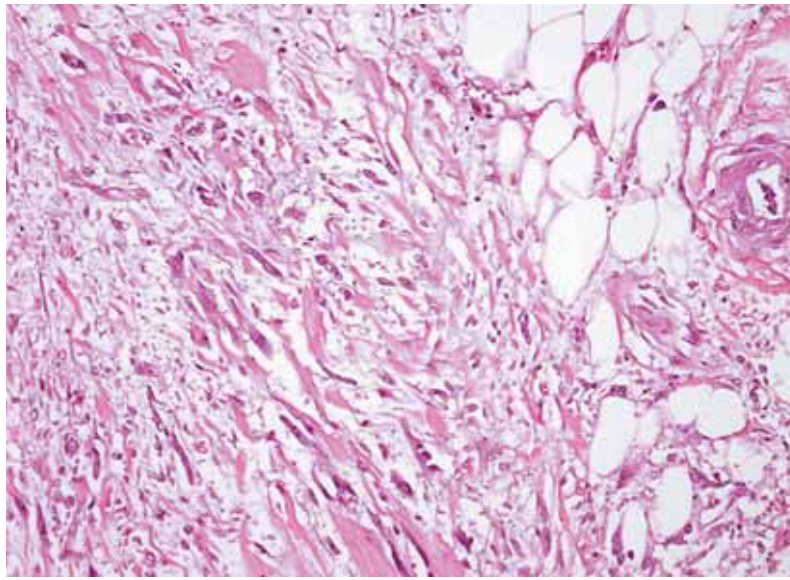

Figure 4.3. Histological Subtypes of Malignant Mesothelioma: Desmoplastic Mesothelioma (9051/3)

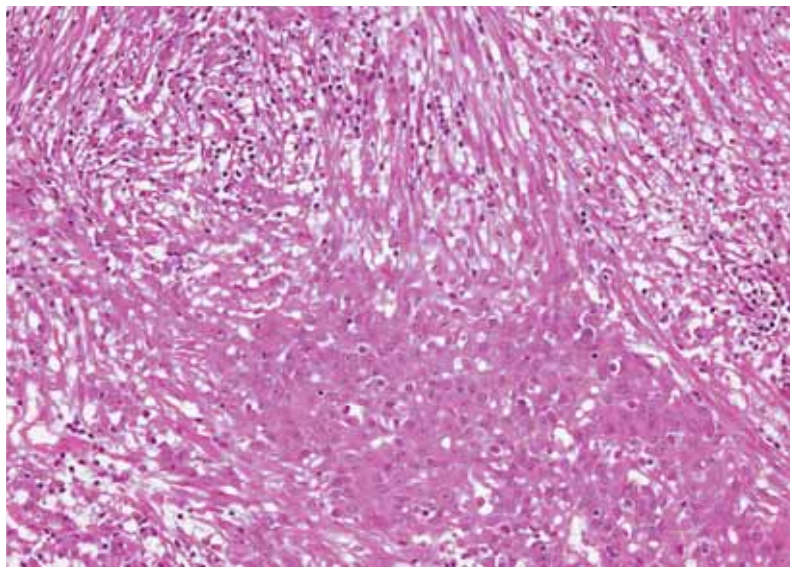

Figure 4.4. Histological Subtypes of Malignant Mesothelioma: Biphasic Mesothelioma (9053/3)

indicated in parentheses, e.g. T2(m) or T2(5). In simultaneous bilateral primary cancers of paired organs each tumour should be classified independently.

8. The TNM classification defines that:
- carcinoma in situ is categorized stage 0;
- tumours that did not extend beyond the organ of origin are categorized stage I and II;
- locally extended tumours and tumours with involvement of regional lymph nodes are categorized stage III;
- tumours with distant metastasis are categorized stage IV.

9. The grouping adopted is to ensure, as far as possible, that each group is more or less homogeneous in respect of survival, and that the survival rates in these groups for each cancer site are distinctive.

At present, the 7th edition of the TNM Classification (2009) can be applied only to pleural MM (C45.0) [57].

The diagnostic criteria for clinical (cTNM) and pathological anatomy (pTNM) classification categories for pleural MM are shown in Table 4.2. The grouping for pleural MM by clinical stages is shown in Table 4.3.

Table 4.2. **Criteria for Clinical (cTNM) and Pathological Anatomy (pTNM) Classification of Pleural Mesothelioma**

Categories	Diagnostic criteria
Primary tumour (cT, pT)	**Tx** – The primary tumour cannot be assessed because of insufficient data **T0** – There is no evidence of a primary tumour **T1** – The tumour is limited to the ipsilateral parietal pleura with or without involvement of the visceral pleura **T1a** – The tumour is limited to the ipsilateral parietal (mediastinal and diaphragmatic) pleura; however, there is no involvement of the visceral pleura **T1b** – The tumour has spread to the ipsilateral parietal (mediastinal and diaphragmatic) pleura, and the visceral pleura is also involved **T2** – The tumour has spread to any ipsilateral pleural surfaces with any of the following features: – tumour has spread to the visceral pleura (which included fistula formation) – diaphragm muscle is involved – tumour has spread to parenchyma of the lung

Table 4.2

Categories	Diagnostic criteria
Primary tumour (cT, pT)	**T3** — The tumour has spread to any ipsilateral pleural surfaces with any of the following features: — tumour has spread to the endothoracic fascia — tumour has spread to mediastinal fat — tumour has locally extended to the soft tissues of the chest wall — nontransmural tumour spread to the pericardium **T4** — The tumour has spread to any ipsilateral pleural surfaces with any of the following features: — diffuse tumour spread or multifocal masses on the soft tissues of the chest wall — any rib destruction; — tumour has spread to the peritoneum through the diaphragm — tumour has spread to any organ of the mediastinum — tumour has spread directly to the contralateral pleura — tumour has spread to the spine — tumour has spread through the internal surface of the pericardium — pericardial effusion containing tumour cells — tumour has spread to the myocardium — tumour has spread to the brachial plexus
Regional lymph nodes (cN, pN)	**Nx** — The regional lymph nodes cannot be assessed because of insufficient data **N0** — Tumour has not spread to the regional lymph nodes **N1** — Metastasis in ipsilateral peribronchial and/or hilar lymph nodes **N2** — Metastasis in ipsilateral bifurcation lymph nodes and/or ipsilateral internal mammary lymph nodes or ipsilateral mediastinal lymph nodes **N3** — Metastasis in contralateral mediastinal, internal mammary, hilar lymph nodes and/or ipsilateral or contralateral scalene supraclavicular lymph nodes
Distant metastasis (cM, pM)	**Mx** — The presence of distant metastasis cannot be assessed because of insufficient data **M0** — No distant metastasis **M1** — Distant metastasis

Note. T3 — locally extended, potentially resectable tumour, T4 — locally extended, technically unresectable tumour.

Table 4.3. **Stage Classification of Malignant Pleural Mesothelioma**

Clinical Stage	T	N	M
Stage IA	Tla	N0	M0
Stage IБ	Tlб	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2	N1	M0
	T1, T2	N2	M0
	T3	N0, N1, N2	M0
Stage IV	T4	N0, N1, N2, N3	M0
	T1, T2, T3, T4	N3	M0
	T1, T2, T3, T4	N0, N1, N2, N3	M1

4.2. Clinical Symptoms of Malignant Mesothelioma

Clinical MM symptoms may manifest themselves 20 — 50 years and even later after the exposure to asbestos.

MM symptoms do not manifest themselves at early stages of the disease. When MM is progressing (the tumour is growing), the clinical symptoms depend on tumour location, and at early stages they are not specific.

At early stages and during the progression of the disease, the intoxication symptoms are observed, such as fatigue, night sweats, fever of unknown origin, weight loss, anemia.

At later stages, the pleural MM is manifested by the following symptoms:

1. Signs of impairment of lower part of respiratory system (mainly, unilateral): shortness of breath at rest, dry cough, blood in the sputum, painful breathing, constant chest pain, signs of exudative pleuritis and pneumothorax.
2. Growing tumour in the chest area (diagnosed by palpation and/or visual examination).

At later stages, the peritoneal MM is characterized by the following symptoms:

1. Signs of impaired peritoneum and intestinal obstruction: abdominal pain, meteorism, nausea, vomiting, diarrhea, ascites which are not associated with food consumption.

2. Growing tumour in the abdominal area (diagnosed by palpation and/or visual examination).

Symptoms of pericardial MM at late stages include the following:

1. Signs of cardiac impairment: pain in the pericardial area, arrhythmia, dyspnoea.

MM metastatic symptoms are as follows:

1. Signs of severe intoxication: anemia, blood clotting disorder, hypoglycemia, cachexia.
2. Signs of obstruction of thoracic organs: hoarseness, difficulty swallowing.
3. Signs of bowel obstruction.
4. Tumour-like neoplasms in the neck or face area (diagnosed by palpation and/or visual examination).
5. Severe complications: thrombophlebitis, DIC syndrome, jaundice, thrombosis of pulmonary artery.

Usually, MM does not spread to the bones, brain or adrenal glands [30, 34, 35, 42, 48, 53].

4.3. Screening and Diagnosis of Malignant Mesothelioma

Malignant mesothelioma is often hard to diagnose because its clinical symptoms are similar to those in other non-tumour and tumour pathologies.

Anamnesis. Occupational contact with etiological factors (primarily with asbestos) increases clinical suspicion for MM.

Clinical examination. General clinical examination is conducted to detect specific MM signs of organ impairment (lung, peritoneum, pericardium).

The X-ray of chest in MM patients can reveal the pleural thickening and exudative pleurisy as well as symptoms of pericarditis. Spirometry test can demonstrate the decreased VC.

Imaging. MM patients undergo CT scan with contrast agent and/or MRT of chest and/or peritoneal cavity. In addition, when MM is suspected the positron emission tomography (PET) scan is conducted with fluorodeoxyglucose (18-fluorine-labeled 2-deoxy-2-fluoro-D-glucose, 18F-FDG).

CT with contrast agent allows to detect the following abnormalities:

— pleural tumour extended to the interlobar pleura;
— circular lobar pleural adhesions;
— pleural effusion;
— pleural plaques (indicating prior asbestos exposure).

MRT is used to evaluate the spreading of tumour into the chest wall and diaphragm.

Since most of mesotheliomas are PET-positive, they are diagnosed by PET with fluorodeoxyglucose which allows to detect MM micrometastasis.

When the tumour is detected by imaging scan, the endoscopy (thorascopy, laparoscopy) should be performed followed by a biopsy and histological examination, and the diagnostic thoracotomy and laparoscopic removal of tumour should be conducted followed by express histological examination [19, 36, 44, 48, 49, 53, 56].

Pathological morphology examination. When exudate is found in the pleural, pericardial or peritoneal cavities, the puncture of respective organ should be performed in order to withdraw the pathology-related fluid to be examined for the presence of malignant neoplasm cells (MM cells). At the same time, absence of malignant cells in the exudate does not exclude completely the MM diagnosis. Recently, in order to increase the diagnostic significance of cytological examination, a fluid cytology with MM-specific molecular markers is widely used.

The histological examination of the tumour (biopsy sample or resection specimen) is still the «gold standard» of MM diagnostic methods.

Clinical and morphological examination should allow to differentiate MM from other types of tumours, namely:

1) benign mesothelioma (reactive mesothelial proliferation — so called «pleural plaque») and pleural fibrosis with calcification;
2) primary pleural tumours (benign and malignant fibroid tumours), primary diffuse pleural sarcoma (angiosarcoma, epithelioid hemangioenothelioma, synovial sarcoma), other mesothelial tumours (well-differentiated papillary mesothelioma, adenomatoid tumour);
3) metastasis to pleura from lung or chest wall which is a lung cancer (adenocarcinoma, squamous cell carcinoma), sarcoma, lymphoma, malignant melanoma;
4) primary and metastatic tymomas;
5) distant metastasis to pleura from renal cell cancer, angiosarcoma, epithelial hemangiosarcoma, synovial sarcoma and other sarcomas, adenocarcinoma of other organs, osteosarcoma;
6) desmoplastic small round cell tumour and Ewing sarcoma family of tumours [22, 34].

In order to improve the accuracy of differential diagnostics of morphological type of the tumour, the immunohistochemical analysis is

performed. However, none of the immunohistochemical markers is MM-specific and does not allow to differentiate MM from cancer or even benign tumour; thus, a set of diagnostic immunohistochemical markers is used for such a differentiation (Tables 4.4 and 4.5).

Final MM pathological morphology diagnosis can be made using the guidelines suggested by the International Mesothelioma Interest Group (2009) [22] below:

1) distinction of benign from malignant mesothelial proliferations;
2) cytologic diagnosis of specific MM cellular atypia;
3) identification of key histologic features of pleural and peritoneal MM;
4) use of electron microscopy, histochemical and immunohistochemical methods for confirming MM diagnosis and for differential MM diagnosis (which allow to differentiate the MM from other various MNs, such as adenocarcinoma and squamous cell carcinoma of lung, mammary gland, ovaries, large intestine, renal cell carcinoma);
5) diagnosis of sarcomatoid mesothelioma excluded.

At present, standard pathological morphology diagnosis does not take into account the asbestos exposure and SV-40-infection of the patient [22].

Screening. Screening tests allow to diagnose MM at the earlier stages than traditional diagnostic methods, thus improving the survival prognosis for patients. However, at present, there are no generally adopted MM screening protocols available yet.

Table 4.4. **Immunohistochemical Markers for Differentiation of Malignant Mesothelioma [22, 31, 35]**

Positive	Negative
– Epithelial Membrane Antigen (EMA) – Wilms Tumour Protein-1 (WT-1) – Calretinin – Mesothelin-1 – Cytokeratin 5/6 – Human Mesothelial cell-l (HBME-1) – Calretinin 1	– Carcinoembryonic Antigen (CEA) – Tumour Associated Glycoprotein B72.3 – MOC-31 – CD15 – Clone Ber-EP4 Epithelial Antigen – Thyroid Transcription Factor-1 (TTF-1) – Vimentin (V9) – Cytokeratin, High Molecular Weight

Table 4.5. **Distinctive Immunohistochemical Features of Malignant Mesothelioma for Differential Diagnosis Purposes [22, 31]**

	Benign mesothelioma	MM	Epithelial MM	Sarcomatoid MM	Adenocarcinoma	Squamous cell carcinoma	Renal cell carcinoma
Epithelial marker							
pCEA			±	-	+ + +	±	-
mCEA			±	-	+ + +	±	-
Ber-Ep4			+	-	+ + +	+ +	+ +
B72.3			±	-	+ + +	+ + +	-
CD15 (Leu-M1)			±	-	+ + +	+	+ + +
TTF-1			-	-	+ + +	-	-
Lewis-BG8			±	-	+ + +	+ + +	+
Mesothelial marker							
Cytokeratin 5/6			+ + +	+	+	+ + +	±
Calretinin			+ + +	+ + +	+	+ +	+
HBME-1			+ + +	-	+ +	-	-
Thrombomodulin			+ +	+	+	-	+
WT-1			+ +	+	±	-	±
Mesothelin			+ + +	-	-	+	-
D2-40			+ + +	-	+	-	-
Podoplanin			+ + +	-	+	-	-
Other marker							
Keratin	±	+ + +					
EMA	±	+ + +					
p53	±	+ + +					
Desmin	+ + +	±					

Currently, the sensitivity and specificity of the following screening serum MM markers are being studied:

- osteopontin [7, 11, 13, 17, 39, 48];
- mesothelin and soluble mesothelin-related proteins (SMRPs) [7, 11, 12, 15–17, 33, 48, 52, 58];
- fibulin-3 [10, 12, 20, 21, 58];
- megakaryocyte potentiating factor (MPF) [11, 33, 48];
- chitinase-3-like-1 (YKL-40) [58].

In addition, the monitoring of biological markers (osteopontin and mesothelin) levels in workers with occupational exposure to asbestos detected sharp increase in serum biomarkers 6-18 months before first clinical MM manifestations [7].

Sensitivity (Se) and specificity (Sp) data for major MM biomarkers are presented in Table 4.6. In view of insufficient sensitivity of MM screening biomarkers, it is recommended to use their combinations as shown below:

- mesothelin + osteopontin [7, 11, 13, 17, 48];
- mesothelin + fibulin-3 [10, 12, 58];
- mesothelin + megakaryocyte potentiating factor [11, 33, 48];
- mesothelin + YKL-40 [58];
- mesothelin + osteopontin + megakaryocyte potentiating factor [11].

Table 4.6. **Most Studied Biomarkers of Malignant Mesothelioma (data of meta-analysis)**

MM Biological marker	Reference value	Sensitivity Se (95 % CI)	Specificity Sp (95 % CI)	Potential false positive results of test in case of other
Osteopontin	<150 ng/mL [7]	0,57 (0,52–0,61) [39] 0,65 (0,60–0,70) [13]	0,81 (0,79–0,84) [39] 0,81 (0,78–0,85) [13]	Lung, mammary gland, prostate and colon cancer
Mesothelin	<2,5 nmol/L [7, 17, 52, 9]	0,47 (0,19–0,68) [52]	0,96 (88,0–100,0) [52]	Lung cancer
Mesothelin-binding protein	<1,35 nmol/L [16, 14]	0,61 (0,58–0,63) [16] 0,64 (0,61–0,68) [15]	0,87 (0,86–0,88) [16] 0,89 (0,88–0,90) [15]	Lung cancer

4.4. Treatment of Malignant Mesothelioma

Prognosis of MM treatment is far from being good. In recent years, slight improvement in survival prognosis for MM patients is achieved due to introduction of new chemotherapy drugs and combination treatment methods into clinical practice [30].

MM clinical picture depends on a number of factors:

- extremely long latent interval between asbestos exposure and onset of the disease (up to 50 years);
- continuity of mesothelial surface of pleural cavity which facilitates the migration of neoplasm cells and, as a result, determines the high speed of primary tumour diffusion within the mesothelial surface;
- intense desquamation of mesothelial cells during breathing which enhances their rapid spreading around the pleural cavity and the metastatic growth;
- histological MM subtype (patients with epithelioid MM better respond to treatment and have better survival prognosis than patients with sarcomatoid MM) [23].

Tumour size is an important prognostic factor for survival of MM patients. Early MM treatment improves survival prognosis, however the number of MM patients diagnosed at this stage of the disease is extremely low [45].

Indices for MM survival. The data of studies showed that the combination of surgical resection with adjuvant chemotherapy and radiation therapy resulted in significant increase in survival (from 3 to 14 years) among patients with favourable prognostic factors [47].

However, in other patient groups the combined treatment resulted in small survival increase (survival median was 14.5 months, and only 29.6 % survived for 2 years) [30].

Surgical intervention. At present, surgical treatment is not considered to be a self-sufficient and effective MM treatment option. Pleurectomy/decortication surgery is the most widely used surgical MM treatment option; extrapleural pneumonectomy is used less frequently. Indications for these interventions depend on tumour size: pleurectomy/decortication lung-sparing surgery is performed in patients at early stages of the disease when it is necessary to remove any tumour masses that are visible («macroscopic complete resection»). Extrapleural pneumonectomy is a more extensive intervention which includes resection of parietal and visceral pleura of lungs, diaphragm and pericardium. This intervention is indicated to patients with advanced tumour [45, 46, 54].

According to studies, median survival after surgical treatment (extrapleural pneumonectomy) was only 11.7 months [30]. Nevertheless, studies showed encouraging results when combined MM treatment methods are used (surgery with radiation therapy and chemotherapy) [5, 43, 53, 55].

Radiation therapy. Radiation therapy is not an effective self-sufficient treatment option because MM is resistant to ionizing radiation. The radiation dose needed for effective MM removal is very high and unacceptable from therapeutic point of view, and often results in damages which are incompatible with life.

Radiation therapy (i.e. irradiation of the chest side where the tumour is located) is used after radical surgical MM resection in combination with chemotherapy resulting in prolonged life expectancy in certain patient groups. However, such treatment can cause serious side effects, including lethal, as a result of radiation-induced pneumonia.

Local radiation therapy is indicated as palliative option to relieve symptoms caused by tumour growth resulting in large blood vessels obstruction [3, 8, 18, 24, 29, 32, 37].

Chemotherapy. At present, chemotherapy is the only efficient MM treatment option which allows to increase patient survival (up to 13.3 months).

There are evidences confirming the efficiency of the following combination of antitumour drugs: cisplatin and pemetrexed («Alimta») or raltitrexed at the background of folic acid (500 mg/day) and vitamin B_{12} (1000 mcg/day). The therapy is well tolerated by patients; their quality of life and lung function indices are improved.

For patients who do not tolerate pemetrexed, a combination of cisplatine and gemcitabine or vinorelbine is used. For patients who cannot use cisplatine, carboplatine is prescribed. Such a replacement resulted in lower response and higher hematopoietic toxicity though patient survival is similar to those with cisplatine administration [2, 4, 5, 23, 38, 41–43, 47, 51, 53, 55].

Immunotherapy. Immunotherapy of MM patients resulted in various outcomes. Intrapleural BCG vaccine administration aimed at immune response stimulation did not bring any benefit to patients.

It was proved that MM cells were sensitive in vitro to interleukine-2 (IL-2), but patients after such therapy experienced serious side effects (fever, cachexia). Alpha-interferon administration studies showed more encouraging results. Thus, 20 % of patients showed more than 50 % decrease in tumour mass with minimal side effects observed [4, 6, 25, 26, 51].

Thermotherapy in combination with local chemotherapy. For MM treatment after tumour resection the methods of intraoperative intracavitary perfusion chemotherapy were used with perfusion of cavities (pleural, abdominal) by drug solutions at 40 – 48 °C for 60 – 120 minutes. The combination of heat and high concentrations of chemotherapy drugs results in increased drug penetration into the tissues and destruction of malignant cells which can remain in the body after tumour resection surgery [40, 43].

4.5. State of MM Diagnostics and Treatment in Ukraine

In 2012 the Laboratory of Carcinogenic Danger and Prevention of Occupational Cancer of the Institute for Occupational Health conducted a study assessing the possibility for patients to get access to MM diagnostics and treatment as well as the efficiency of such diagnostics and treatment. The study was based on the Ukrainian National Cancer Register data (National Cancer Institute of the Ministry of Health of Ukraine) on patients with mesothelioma at all locations (ICD-10 code: C45.-) with 2001-2011 observation period (2645 cases) [1].

The results of study showed that in Ukraine the frequency of the following indicators was high: the number of MM diagnosis post-mortem (men: 17.4 %; women: 15.2 %); the number of lifetime MM diagnosis at late stages of the disease (III – IV) (men: 72.0 %; women: 69.7 %). The effectiveness of morphological verification of MM histological type is high but still insufficient (men: 77.7 %; women: 79.5 %) (Table 4.7).

Chemotherapy is the main MM treatment method used in Ukraine (77.7 – 79.5 % patients); surgical resection (31.0 – 35.5 %) and radiation therapy (15.9 – 18,8 %) are used much more rarely. MM treatment mostly includes monotherapy (72.9 – 73.3 %) or combination of two methods (22.1 – 22.9%) (Table 4.7).

One-year mortality/survival median in MM patients in Ukraine: men: 78.9 %/9.5 months; women: 73.8 %/10.7 months. Minimal five-year survival: men: 2.8 %; women: 5.4 %. Results of MM «survival analysis» are presented in Figure 4.5.

Survival median decreases with advance of disease stage (minimal at stage IV: 6 months), but even with MM detection at early stage (stage I) it is very low (19.3 months) which indicates a very high level of malignancy of this neoplasm (Figure 4.6)

The study showed that the highest median MM survival levels are detected in patients under the following treatments (increase in

Table 4.7. **Profile of Major Treatment Programmes in Malignant Mesothelioma Patients in Ukraine (2001–2011)**

Treatment options		Men	Women
Treatments, %	Chemotherapy	79,2	77,7
	Surgery	31,0	35,5
	Radiation therapy	18,8	15,9
	Immunotherapy	1,9	1,5
	Hormonal therapy	1,2	1,1
Combination of treatments, %	Monotherapy	72,9	73,3
	2 methods	22,9	22,1
	3–4 methods	4,2	4,6
Disease outcome, %	One-year mortality	78,9	73,8
	Five-year survival	2,8	5,4
Survival median, months		9,5	10,7

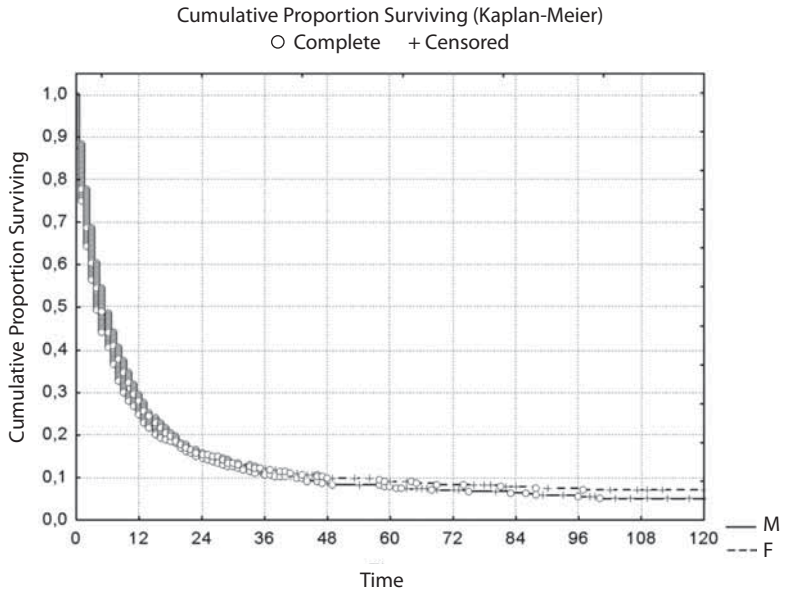

Figure 4.5. Survival Analysis in Patients with Malignant Mesothelioma in Ukraine (2001–2011)

survival time of patients with respective disease stage in comparison with similar patients who underwent only symptomatic therapy):

- at stage I: surgery (1.9-fold), surgery + chemotherapy (2.0-fold);
- at stage II: chemotherapy + immunotherapy (4.1-fold), surgery + radiation- + chemotherapy (4.4-fold), surgery + radiation- + chemo- + immunotherapy (4.8-fold);
- at stage III: surgery + radiation- + chemo- + immunotherapy (2.8-fold);
- at stage IV: surgery + chemotherapy (3.1-fold), radiation- + chemo- + immunotherapy (3.3-fold) (Table 4.8).

The data presented above show that earlier MM detection and adequate treatment can increase survival and lifetime in this patient category.

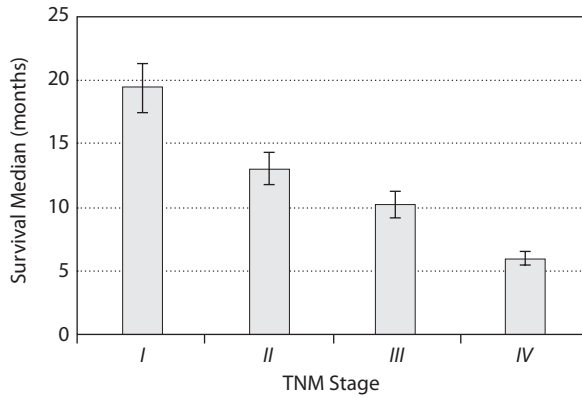

Figure 4.6. Association Between Survival Median and Clinical Stage of Malignant Mesothelioma in Ukraine

Table 4.8. **Association Between Survival Median and Clinical Stage or Specific Treatment Options in Patients with Malignant Mesothelioma in Ukraine (in months)**

Specific combination therapy (methods of treatment)	Stage of disease				Total
	I	II	III	IV	
*Chemotherapy (Chm)**	16,9	12,1	10,3	8,7	11,1
Chm + H	–	15,0	11,0	6,7	11,4
Chm + I	–	37,0	3,3	4,0	8,3
Surgical removal (SR) (pleural pneumonectomy)	36,3	27,1	8,1	5,3	14,6
SR + I	26,0	–	–	5,0	15,5
SR + R	4,0	26,4	10,3	6,6	13,8
SR + Chm	38,6	18,4	18,7	14,3	19,6
SR + R + Chm	21,5	39,9	16,1	11,4	19,2
SR + R + Chm + H	–	16,0	11,0	–	13,5
SR + R + Chm + I	–	43,0	23,0	3,0	23,0
SR + Chm + H + I	–	1,0	–	–	1,0
SR + Chm +I	–	17,0	17,0	–	17,0
Radiation therapy (R) (up to 50 Gy)	14,6	6,0	15,4	5,0	8,9
R + H	–	–	8,0	–	8,0
R + Chm	29,8	17,3	16,7	10,3	15,7
R + Chm + H	13,0	–		–	13,0
R + Chm + I	–	–	16,0	15,0	15,7
R + Chm + H + I	–	–	19,0	–	19,0
Immunotherapy (I) (alpha-interferon and interleukine-2)	26,0	24,5	13,1	6,2	14,2
Hormonal therapy (H) (corticosteroids)	13,0	12,8	12,3	6,7	11,3
Symptomatic (palliative) therapy	*10,8*	*9,0*	*8,1*	*4,6*	*6,9*
Total	**19,3**	**13,0**	**10,2**	**6,0**	**10,0**

Note. *Chemotherapy schemes: doxorubicin + cyclophosphan; doxorubicin + iphosphamide; doxorubicin + cisplatin (carboplatin) ± mitomycin C; campto + cisplatin + mitomycin C; gemcitabine + cisplatin (carboplatin); gemcitabine + alimta; alimta + cisplatin (carboplatin).

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Part 5

PREVENTION OF ASBESTOS-INDUCED DISEASES

5.1. International Guidelines on Prevention of Asbestos-Induced Diseases

Since at present the asbestos theory of MM etiology prevails, all existing international guidelines are aimed at the prevention specifically the asbestos-induced MM.

International Labour Organization (ILO) activities. Main international documents aimed at the prevention of occupational asbestos-induced diseases (including MM) are the following documents: special ILO Convention No. 162 «Convention Concerning Safety in the Use of Asbestos» [7] and ILO Recommendation No. 172 «Recommendation concerning Safety in the Use of Asbestos» [14] adopted by the ILO General Conference at its 72nd session in 1986 (see «Annex»).

Up to date (June 2015), only 35 (out of 175) member countries have ratified the ILO Convention No162: Australia (2011), Belgium (1996), Bolivia (1990), Bosnia and Herzegovina (1993), Brazil (1990), Cameroon (1989), Canada (1988), Chile (1994), Columbia (2001), Croatia (1991), Cyprus (1992), Denmark (2006), Ecuador (1990), Finland (1988), Germany (1993), Guatemala (1989), Japan (2005), Kazakhstan (2011), Republic of Korea (2007), Luxembourg (2008), Montenegro (2006), Morocco (2011), Netherlands (1999), Norway (1992), Portugal (1999), the Russian Federation (2000), Serbia (2000), Slovenia (1992), Spain (1990), Sweden (1987), Switzerland (1992), Macedonia (1991), Uganda (1990), Uruguay (1995), Zimbabwe (2003) [http://www.ilo.org/dyn/normlex/en/f?p=1000:11300:3855678632701485::::P11300_INSTRUMENT_SORT:1]. At the same time, it should be noted that almost all countries where during last nine years asbestos has been extracted in large scale (the Russian Federation, Brazil, Kazakhstan, Canada) have ratified Convention No. 162 (except China).

Ukraine has not yet ratified Convention No. 162, although in 2009 respective attempts were made [http://w1.c1.rada.gov.ua/pls/zweb2/webproc34?id=&pf3511=36721&pf35401=154791.].

It is necessary to stress the importance of special ILO Convention No. 139 «Convention Concerning Prevention and Control of Occupational Hazards Caused by Carcinogenic Substances and Agents» [5] and ILO Recommendation No. 147 «Recommendation Concerning Prevention and Control of Occupational Hazards Caused by Carcinogenic Substances and Agents» [13] adopted by the ILO General Conference at its 59th session in 1974 (see «Annex»).

Up to date (June 2015), only 39 (out of 175) ILO member countries have ratified ILO Convention No 139. Almost all countries where during last nine years asbestos has been extracted in large scale (the Russian Federation, Kazakhstan, Canada and China) did not ratified ILO Convention No. 139 (except Brazil, which ratified the Convention in 1990).

Ukraine ratified ILO Convention No. 139 in 2010 (Law of Ukraine № 1956-VI of March 10, 2010) [http://zakon4.rada.gov.ua/laws/show/1956-17].

Since Ukraine has not yet ratified ILO Convention No. 172 for asbestos-induced cancer risks prevention, more universal ILO Convention No. 139 is being applied.

Thus, the provisions of ILO Convention No. 139 and ILO Recommendation No. 147 fully correspond to the provisions of ILO Convention No. 162 and ILO Recommendation No. 172 which makes them applicable for use in the countries where Convention and Recommendation on asbestos have not been ratified.

In addition, in 1984 the ILO prepared a detailed instruction «Safety in the Use of Asbestos» [2].

World Health Organization (WHO) activities. During the last decade, WHO is actively promoting the elimination of asbestos-related diseases. This issue is a focus of World Health Assembly (WHA) resolutions WHA58.22, WHA60.26 and WHA66.10.

WHO Resolution WHA58.22 «Cancer Prevention and Control» (2005) urges member countries to integrate into national cancer-control programs actions aimed at prevention and reduction of exposure to risk factors including occupational factors (such as chemicals, ionizing radiation in the workplace and the environment), thus limiting cancer incidence (Recommendation No. 5) [11].

In WHO Resolution WHA60.26 «Workers' Health: Global Plan of Action» (2007) [3] in the «Global Plan of Action on Workers' Health 2008–2017», it is suggested to organize «global campaigns for elimination of asbestos-related diseases – bearing in mind a differentiated approach to regulating its various forms – in line with relevant international legal instruments and the latest evidence for effective

interventions...» (Objective 1, item 10).

In *WHO Resolution WHA66.10 «Follow-up to the Political Declaration of the High-level Meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases»* (2013) [9] it is stated that: «Exposure to carcinogens such as asbestos, ... in the living and working environment can increase the risk of cancer».

In adopted «Global Action Plan for the Prevention and Control of Noncommunicable Diseases for 2013—2020» it is stipulated the following: «Cost-effective interventions to prevent occupational lung diseases, e.g. from exposure to silica, asbestos» (Objective 4, Subsection «Chronic respiratory disease»).

In this context, the ILO's tasks and functions are «to promote the implementation of international labour standards for occupational safety and health, particularly those regarding occupational cancer, asbestos, respiratory diseases and occupational health services».

Cost-effective actions aimed at prevention of occupational asbestos-related lung diseases are attributed to economic and political issues.

Elimination of asbestos-related diseases is especially important for countries that are still using chrysotile asbestos. Moreover, WHO provides assistance to those countries where in the past all forms of asbestos were used affecting the health of population.

WHO, in collaboration with the International Labour Organization and other intergovernmental organizations and civil society, works with countries towards elimination of asbestos-related diseases in the following ways:

- by recognizing that the most efficient way to eliminate asbestos-related diseases is to stop the use of all types of asbestos;
- by providing information about solutions for replacing asbestos with safer substitutes and developing economic and technological mechanisms to stimulate its replacement;
- by taking measures to prevent exposure to asbestos in workplace and during asbestos removal (abatement);
- by improving early diagnosis, treatment and rehabilitation services for asbestos-related diseases;
- by establishing registries of people with past and/or current exposure to asbestos and organizing medical surveillance of exposed workers;
- by providing information on the hazards associated with asbestos-containing materials and products, and by raising awareness that waste containing asbestos should be treated as hazardous waste [1, 8].

In order to achieve this goal WHO elaborated the *Preventive Strategy for Elimination of Asbestos-Related Diseases* based on the fact that there is no evidence for a threshold for the carcinogenic effect of chrysotile and amphibole asbestos and that increased cancer risks have been observed in populations exposed to very low levels of these hazards. At the same time, WHO declared that the most efficient way to eliminate asbestos-related diseases is to stop using all types of asbestos.

Continued use of chrysotile asbestos cement in the construction industry is a WHO's particular concern, because the workforce is large, it is difficult to control exposure and in-place materials have the potential to deteriorate and pose a risk to those carrying out alterations, maintenance and demolition.

WHO proposes to replace asbestos by some fibre materials and other products which pose less or no risk to health. Moreover, the asbestos-containing materials should be encapsulated and, in general, it is not recommended to carry out work that is likely to disturb asbestos fibres. At the same time, it is stressed that measures should be taken to avoid replacement of non-asbestos products with those containing asbestos, for instance brake shoes for automobiles. In addition, when working with asbestos-containing materials already in place, it is necessary to apply strict measures to control exposure, such as encapsulation, wet processes, local exhaust ventilation with filtration and regular cleaning.

WHO believes that in order to assess the effectiveness of engineering measures, it is necessary to determine the form of asbestos (e.g. chrysotile or amphiboles) and to carry out the monitoring of exposure levels. Moreover, the use of individual protective equipment — special respirators, safety goggles, protective gloves and clothing — and the provision of special facilities for their decontamination are also needed for persons engaged in working with asbestos.

Medical surveillance should be organized for early detection of any symptoms resulting from asbestos exposure and the assessment of the adequacy of exposure control measures.

It is also necessary to establish national registries of persons exposed to the various forms of asbestos with data storage for at least 40 years. The registries should contain information on the exposure records (intensity, frequency and duration of exposure), medical examination data, as well as information on the employer and the industrial facility.

At the same time, measures for controlling exposure to asbestos and medical surveillance require significant resources, and may be

very difficult to carry out, particularly in countries with constrained resources, limited expertise and infrastructure for occupational health practice and insufficient level of general protection of health and the environment.

WHO believes that the enforcement of such measures may be practically impossible in small- and medium-sized enterprises and in the informal economy. Moreover, even the strictest occupational exposure limits are associated with health risks for asbestos-related diseases as no threshold has been identified for carcinogenic risks of asbestos. That is why the national strategy for elimination of asbestos-related diseases should strive towards stopping the use of all forms of asbestos and replacing it with safer substitutes. The preventive strategy should envisage measures to encourage voluntary efforts by industry and be based on cooperation and consultation with the interested parties at national and enterprise levels. It should set up a framework for elimination of asbestos-related diseases, promote partnerships, commitments and cooperation.

Action *at the national level* should create a political, regulatory and social environment and appropriate institutional framework conducive to elimination of asbestos-related diseases. Such actions should include:

1) political commitment to the elimination of asbestos-related diseases, e.g. to prepare a national report on elimination of asbestos-related diseases to be presented to the Government or the Parliament, including information about past and current use, estimates of the health, economic and social consequences of continuing use of chrysotile asbestos and proposals for a set of measures to be taken to phase out its use and to prevent/contain the epidemic of asbestos-related diseases;
2) ratification of international legal instruments (ILO conventions No. 162 and 139, Basel and Rotterdam conventions) and development of specific laws and regulations to prevent exposure to the different forms of asbestos, to phase out their use and to ensure the prevention of asbestos-related diseases;
3) introduction of fiscal mechanisms to reduce the use of chrysotile asbestos, e.g. import and excise duties, loans for conversion to non-asbestos technologies, establishment of a national fund for elimination of asbestos-related diseases with contribution from duty holders, insurance and compensation boards, governmental subsidy, etc.;
4) update and enforcement of occupational exposure limits for various forms of asbestos, e.g. align national occupational expo-

sure limits to those listed in the IPCS Chemical Safety Card for Chrysotile, establishment of resources for determining the mineralogical form of asbestos and for measuring and monitoring its air concentrations, introduction of practical tools for assessment and management of the risk from potential exposure and creation of a national reference laboratory;

5) provision of an effective system of inspection and enforcement of technical standards and safety measures through strengthening the authority of the enforcement agencies in the areas of labour, building maintenance and construction, environment, public health, accreditation and standardization; provision of guidelines for enterprises and economic undertakings for management of asbestos-related health risks, etc.;
6) organization of early detection, notification, registration, reporting and compensation of asbestos-related diseases through improving diagnostic capacities for early detection of asbestosis and non-malignant asbestos-related disorders, clinical and pathological diagnosis of mesothelioma; establishing the causal relationship between lung and laryngeal cancer with asbestos exposure; inclusion of all asbestos-related diseases in the national list of occupational diseases and development of diagnostic and exposure criteria for their recognition; establishing a fund for compensation of victims of asbestos-related diseases;
7) provision of advisory services to industry, trade and other economic undertakings, workers and their organizations and building owners on the use of safer substitutes for asbestos, application of preventive measures, and raising awareness about the risks related to the use of asbestos;
8) enhancement of international collaboration to stimulate the transfer of know-how on alternatives to asbestos and best practices for prevention of asbestos-related diseases.

At the regional level, local authorities should be involved in the efforts for elimination of asbestos-related diseases. Local authorities are usually responsible for issuing building licenses, monitoring the housing stock, landfills etc. In addition, municipalities may employ workers for building maintenance, reparation and demolition works that may involve exposure to asbestos. Local authorities may be able to take the following actions:

1) introduce requirements for the use of safer substitutes for asbestos products and/or prohibit and enforce the prohibition of the

production and use of chrysotile asbestos and asbestos-containing products;
2) to ensure that work involving potential exposure to the various forms of asbestos, e.g. demolition of structures containing asbestos, reparation and removal of asbestos from structures in which it is liable to become airborne, are carried out only by certified employers or contractors;
3) to take measures to dispose properly of asbestos-containing waste — wetted, transported covered, buried at special landfills and impregnated with agents that form a crust resistant to erosion;
4) to increase awareness among the general public of the hazards of demolition, removal and reparations of friable asbestos insulation in buildings and disseminate information about the risks related to the presence of undisturbed asbestos in buildings;
5) to organize medical surveillance of municipal workers who might be exposed to asbestos in their work.

At the enterprise level the following actions should be taken:
1) to replace chrysotile asbestos with safer substitutes and prevent potential exposure to any other type of asbestos already in place;
2) to stop the use and supply of chrysotile asbestos by their contractors and suppliers;
3) to monitor the work environment for contamination with various forms of asbestos;
4) to ensure compliance with exposure limits and technical standards for working with asbestos;
5) to establish engineering measures for control of the exposure to asbestos at source;
6) to provide special training to workers involved in activities with potential exposure to asbestos;
7) to provide appropriate individual protective equipment;
8) to ensure registration and medical surveillance of workers exposed to asbestos.

In addition, WHO proposed also the «Outline for the Development of National Programmes for Elimination of Asbestos-Related Diseases» [16].

5.2. Health Care Service to Workers Exposed to Asbestos Dust*

The goal of periodic medical examinations is early detection of diseases caused by inhalation of dust that contains asbestos fibre (dust-associated bronchitis; asbestosis; pleural plaques; diffuse pleural thickening; cancer of the gullet, bronchial cancer, lung cancer; pleural, pericardium and peritoneum MM; and other pathologies).

Medical doctor who carries out medical examinations (therapist, occupational pathology therapist) should meet the following criteria:

- education in occupational health (occupational pathology, occupational hygiene);
- special training and experience in the interpretation and classification of radiographs in accordance with the ILO International Classification of Radiographs of Pneumoconioses (2011) [17];
- access to special diagnostic equipment for X-ray checks, pulmonary function tests (using self-recording device which tracks «time-volume» or «volume-flow» ratios during complete forced expiratory effort) as well as the ILO standard radiographs available for reference;
- free access to workplaces and to data on asbestos dust exposure levels and duration.

Medical examination should cover all persons who contact with asbestos regardless of asbestos exposure time and air concentrations in a work environment. Recommended frequency of medical examinations is shown in Table 5.1.

During medical examinations it is necessary to search for early-stage symptoms of the following asbestos-induced pathologies:

1) asbestos-induced lung fibrosis (asbestosis, asbestos-induced pneumoconiosis);
2) pleural plaques;
3) diffuse pleural fibrosis;
4) exudative pleuritis;
5) laryngeal cancer;
6) bronchial and lung cancer;
7) pleural, pericardium and peritoneal MM.

*This section is prepared by integrating recommendations based on evidence-based data [2, 17, 20–22].

Table 5.1. **Recommended Frequency of the Medical Examinations of Workers Exposed to Asbestos Dust [2, 20]**

Type of examination	Category of workers and schedule for their examinations
Pre-employment examination	Before taking up a job with expected asbestos exposure
Initial regular examination	After 12 months after starting a job with asbestos exposure
Further follow-up regular examinations	Not more than once in 12 months and not less than once in 36 months during work with exposure to asbestos dust
Premature follow-up examination	– After an illness lasting for several weeks resulted in the health impairments which limit the worker's ability to continue the work – When the physician considers it necessary to perform the examination of worker's health (because there is a suspected disease) – When requested by an employee with health complains who suspects a casual association between his/her illness and work
Final examination	When leaving a job with asbestos exposure (when quitting a job or being transferred to another job with absolutely no exposure to asbestos dust)

Medical examination should include the following measures:

1. General medical examination:

– review of complains and general anamnesis with special attention paid to the intoxication symptoms of unknown origin (cough, dyspnea, pain);
– detailed review of anamnesis: respiratory distresses, their frequency and effects; unhealthy habits [smoking (non-smokers, smokers, ex-smokers; smoking duration; cigarettes, cigars, pipes: number per day; number of packs per year); alcohol abuse]; exposure to hazardous industrial, environmental and other factors and their health effects;
– detailed review of career history (occupation, length of service, job description, working conditions, exposure to asbestos or

other hazardous factors at the workplace etc.); review of appropriate preventive measures provided to workers during their service (technical, organisational, personal);
- because of the risk of laryngeal cancer, particular attention should be paid to persistent hoarseness and phonation disorders (for more than 3 weeks);
- because of the risk of lung cancer and MM, attention should be paid to the presence and nature of dyspnoea and cough.

2. Special medical examination:
- general medical examination of worker is performed (it is necessary to pay attention to hypoxia, to examine the chest and abdominal, to look for tumours in chest and abdominal area);
- profound clinical (conducted by therapist) examination of respiratory organs, cardio-vascular system (auscultation, palpation, percussion), and measurement of blood pressure, heart rate, breath rate, body temperature is carried out;
- spirometry is conducted to measure lung's forced vital capacity (FVC) and forced expiratory volume in one second (FEV1);
- back-to-front chest X-ray is performed, and its results are interpreted in accordance with the ILO classification [17] and are compared with radiographs of previous years (Fig. 5.1);
- ENT examination is carried out.

3. Supplementary examination:
- if a thoracic organs pathology is suspected, additional lateral radiography is performed;
- if it's impossible to establish the origin of morphological changes based on radiography data, high resolution helical computed tomography is conducted;
- supplementary laboratory tests for screening/early detection of malignant pathology in target organs (bronchial and lung cancer, MM) are performed in workers of a high-risk malignant neoplasm group (Table 5.2);
- if any malignant neoplasm is suspected, patient is observed by oncologist for further examinations: thoracoscopy (Figure 5.2), computed tomography and positron emission tomography with [^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) (Figure 5.3–5.4).

After medical examination, the physician should do the following:
- to evaluate the worker's state of health and fitness to work in asbestos exposure conditions;
- to provide the worker with personal recommendations on preventive measures to avoid asbestos-induced diseases;
- to motivate the worker to stop smoking.

Table 5.2. **Recommended Additional Laboratory Tests for Screening/Early Detection of Malignant Pathology in Target Organs in Workers with Occupational Asbestos Exposure [D. V. Varyvonchyk, 2015]**

Methods of examination	Objective	Category of workers	Frequency of examination
Sputum analysis: gross examination, cytological test for atypical cells and mycobacteria	Early detection of chronic pathology in respiratory organs (bronchitis, pneumoconiosis, bronchial cancer, lung cancer, tuberculosis and other pathologies)	– All workers with cough and sputum production persisting for more than 3 weeks	Once (3 tests, 3 successive days) (for detection of pathological changes in sputum, atypical cells and MBC)
Blood test for levels and dynamics of the following tumour markers: – bronchial cancer and lung cancer (carcinoembryonic antigen; cytokeratin CYFRA-21-1; neuron-specific enolase) – MM (mesothelin; fibulin-3; osteopontin)	Screening/early detection of bronchial cancer, lung cancer and MM	– All workers before starting a job associated with asbestos exposure. – All workers with length of service with asbestos exposure for more than 10 years. – Workers with suspected bronchi and lung cancer and MM (based on X-ray test).	Once (to monitor tumour markers levels comparing to normal reference values) Annually (to monitor the dynamics of changes of the tumour markers levels comparing to normal reference and previous values)
Complete blood test (complete blood count including platelet count)	Detection of signs of hemopoesis disorders, anaemia, inflammation activity and nature, and endogenic intoxication	– All workers	Annually (to monitor the levels comparing to normal reference values)

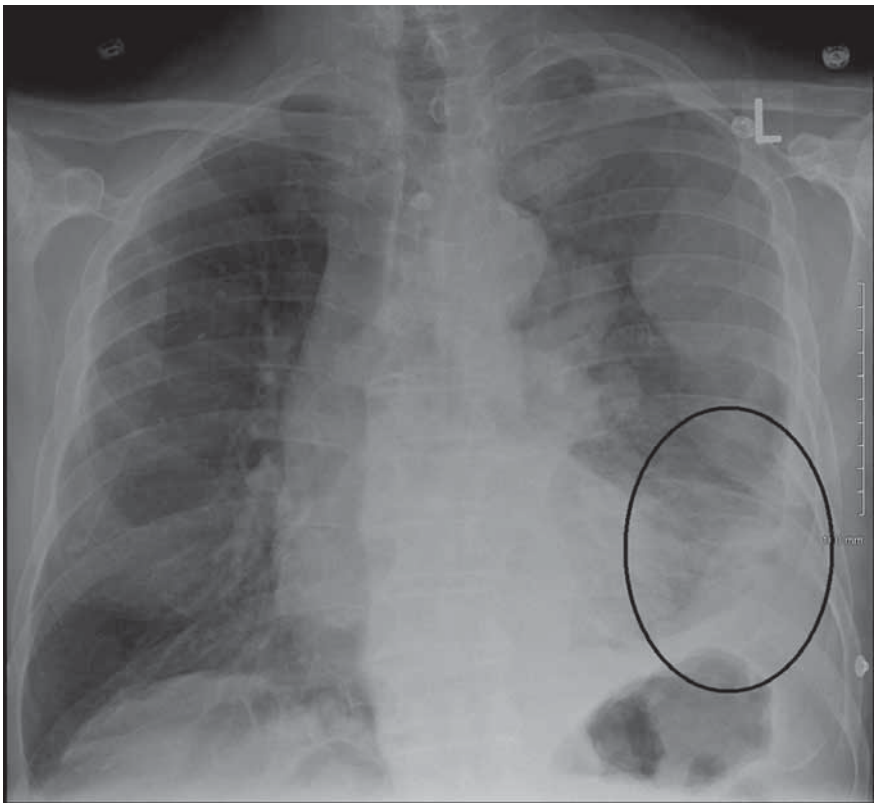

Figure 5.1. X-Ray Imaging of Malignant Mesothelioma: Pleural Mesothelioma on the Left Lower Lung (Back-to-front Image of Thoracic Organs)

Source: © Mesothelioma of the left lower lung / J. Heilman. – Access to: https://en.wikipedia.org/?title=Mesothelioma#/media/File:MesotheliomaCXR.png

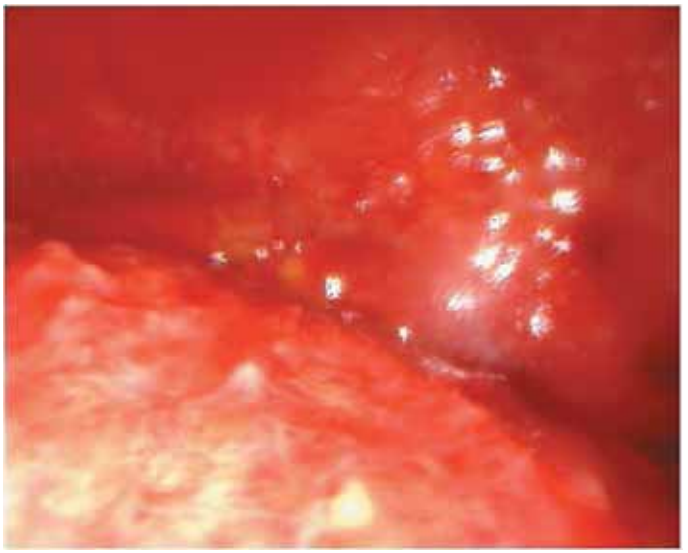

Figure 5.2. Intraoperative Thoracoscopic Image of Malignant Mesothelioma: Left-Side Malignant Pleural Mesothelioma Involving the Visceral and Parietal Pleura*

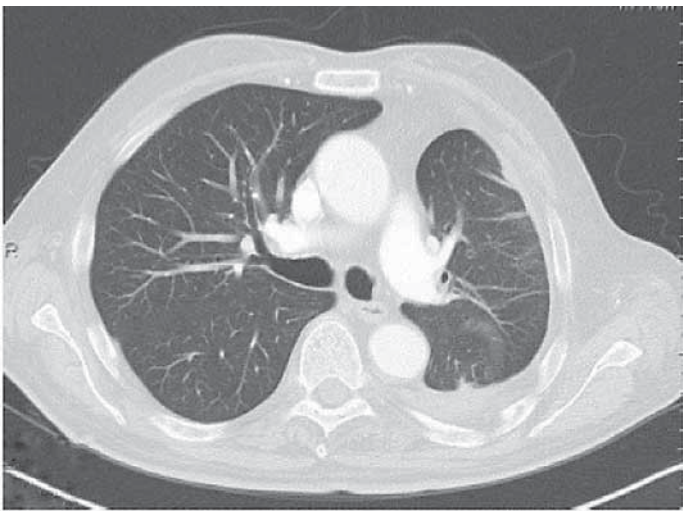

Figure 5.3. Imaging of Malignant Mesothelioma by Helical Computed Tomography: Pleural Thickening on Left Side*

* Source: © Bölükbas S. Video-atlas of radical pleurectomy for malignant pleural mesothelioma / S. Bölükbas, M. Eberlein, J. Schirren // Ann. Cardiothorac. Surg. — 2012. — V. 1, № 4. — P. 534—536.

In each individual case, the medical recommendations should be commensurate with the workplace situation and the results of medical examination.

After preliminary and periodic medical examinations, the decision concerning medical contraindications to work exposing to asbestos dust should be taken. If such contraindications exist, the recommendations concerning further job assignment for the worker should be made. If the disease is suspected as potentially related to asbestos exposure, the worker should be examined by the respective medical

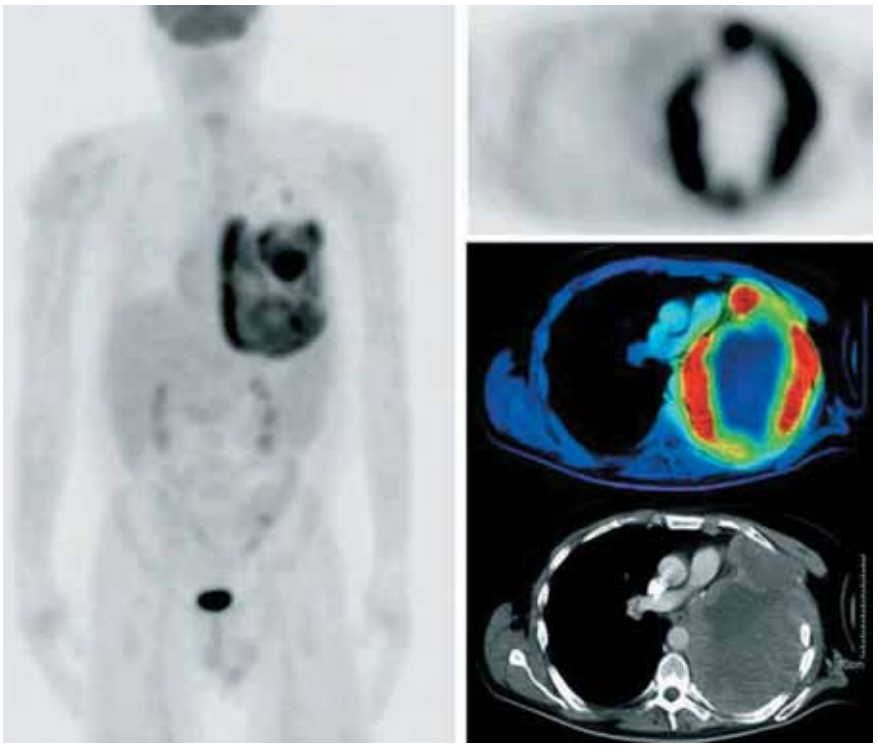

Figure 5.4. Imaging of Malignant Pleural Mesothelioma by Whole-Body and Chest ^{18}F-FDG ([^{18}F]fluoro-2-deoxy-D-glucose) Positron Emission Tomography/Computed Tomography: Increased ^{18}F-FDG Accumulation in Active Areas of Malignant Mesothelioma in Pleura

Source: Usefulness of positron emission tomographycomputed tomography in respiratory medicine / A. Maldonado, F. J. González-Alenda, M. Alonso, J. M. Sierra // Arch. Bronconeumol. — 2007. — V. 43,№ 10. — P. 562—572.

specialists for detailed diagnostic evaluation and assessment of potential causal association between his/her illness and working conditions as well as extent of his/her health deterioration.

After final medical examination (when the worker stops working under asbestos exposure, it means he/she quits the job or is transferred to another workplace with absolutely no contact with asbestos dust) it is necessary to carry out comprehensive medical examination including repeated verification of all previous test data. It is necessary to develop recommendations concerning further health surveillance for the worker, taking into account the duration and levels of asbestos dust exposure as well as the state of his/her health. If further health surveillance is advised, the frequency for medical examinations should be also recommended.

The results of all medical examinations and complementary observations and tests should be recorded in worker's individual medical file and kept confidential.

Person's fitness for a specific kind of work should be confirmed by the appropriate certificate without any medical data. In certain cases, respective measures or preconditions for confirming person's fitness for a job may be stipulated.

The list of contraindications that would restrict a person from getting a job with asbestos exposure includes the following:

- severe disorders and impaired functions of the respiratory system;
- chronic bronchitis, bronchial asthma, pulmonary emphysema;
- pleuritis (chronic or recurrent);
- radiographically detectable pneumoconiosis or other fibrotic or granulomatous lung alterations;
- malformations, tumours, chronic inflammation, pleural fibrosis;
- deformities of the thorax or spine which adversely affect breathing;
- condition following lung resection or injury with functional impairment of the thoracic organs;
- chronic larynx disorders with functional deficits;
- condition after diagnosis and treatment of laryngeal or vocal cord tumour;
- active, extensive inactive tuberculosis;
- insufficient weight (over 30% less than optimum weight determined by Broka's formula), constitutional defects and weaknesses;
- severe disorders and impaired functions of cardiovascular system (cardiac valve defects, cardiac insufficiency, high blood pressure which does not respond to therapy);
- other chronic disorders which reduce general resistance.

5.3. Establishing the Occupational Cancer Diagnosis in Malignant Mesothelioma Patients

In the ILO Convention No. 121 «Convention concerning Benefits in the Case of Employment Injury» (1964) for the first time the list of occupational diseases was established which included «Lung cancer or mesotheliomas caused by asbestos – all work involving exposure to the risk concerned» (item 28, List of Occupational Diseases, amended in 1980) [4].

In the current ILO's List of Occupational Diseases (2010) [19] based on the ILO Recommendation No. 194 «Recommendation Concerning the List of Occupational Diseases and the Recording and Notification of Occupational Accidents and Diseases» (2002) [12] occupational cancer is placed in the separate 3rd group and asbestos exposure is recognized to be one of the causing agents (item 3.1.1 Asbestos).

In the ILO Recommendation No. 121 «Employment Injury Benefits Recommendation» (1964) it is stipulated that «each member should, under prescribed conditions, regard diseases known to arise out of the exposure to substances or dangerous conditions in processes, trades or occupations as occupational diseases» (art. 6, para. 1). At the same time, in the Recommendation, it is stated the following: «Unless proof to the contrary is brought, there should be a presumption of the occupational origin of such diseases where the employee: (a) was exposed for at least a specified period; and (b) has developed symptoms of the disease within a specified period following termination of the last employment involving exposure» (art. 6, para. 2) [15].

The ILO General Conference Protocol of 2002 to the Occupational Safety and Health Convention No. 155 (1981) [6] defines that «the term «occupational disease» covers any disease contracted as a result of an exposure to risk factors arising from work activity» (art. 1, para. b) [10].

In accordance with the decision of the ILO Meeting of Experts on the List of Occupational Diseases (2009), the *main criterial elements* which are to be present in the definition of an occupational diseases are as follows:

- the causal relationship between exposure to a specific factor in the working environment (occupational factor) and a specific disease;
- the fact that the disease occurs among a group of exposed persons with a frequency above the average morbidity of the rest of the population.

At the same time, the general criteria for identification and recognition of occupational diseases include the following:

1) The causal relationship is established on the basis of clinical and pathological data, occupational anamnesis, identification and evaluation of occupational risk factors and other risk factors.
2) Epidemiological and toxicological data are available for determining the causal relationship between a specific occupational disease and its corresponding exposure in a specific working environment or work activity.

Making a decision concerning the cause of a disease is not an «exact science» but should include a consideration of the following aspects:

- Strength of association: the greater the impact of an exposure on person's health, the greater the possibility of the occurrence or development of a disease, the stronger the likelihood of a causal relationship.
- Consistency of data: different research reports on the same hazardous agent effect on worker's health bring in, as a rule, generally similar results and conclusions.
- Specificity: exposure to a specific risk factor results in a clearly defined pattern of disease and morphofunctional changes in the human body.
- Temporality or time sequence: the occupational hazard exposure precedes the disease onset consistent with morphofunctional changes in the body.
- Biological gradient: the greater the level and duration of exposure to hazardous agent, the greater the severity of disease, and vice versa.
- Medical and biological plausibility: the disease development and clinical features can be explained by scientific data based on toxicological, physical and chemical properties and other pattern attributes of the studied hazardous exposure.
- Coherence: a general synthesis of all available scientific evidences (e.g. human epidemiology and animal studies) leads to the conclusion that there is a cause-effect relationship (in a broad sense and in terms of general common sense) between exposure and disease.
- Positive interventional studies: adoption of primary preventive measures for removal or decrease of specific occupational hazard exposure can reduce the risk of specific disease and /or its incidence in workers.

The Meeting of Experts emphasises that the clinical symptoms are, as a general rule, not sufficiently characteristic to diagnose an occupational disease without taking into account existing pathological changes caused by physical, chemical, biological or other factors in

the workplace environment. Therefore, it would be reasonable not to rule out the situation when additional new information regarding the work conditions and new scientific knowledge concerning the origin and pathogenesis of one or another occupational factor, disease clinical progression and diagnosis will allow to make more objective and accurate conclusion concerning the causal relationship between the disease and work conditions [18].

Based on information discussed in Parts 1-5 of this monograph, we would suggest the following **criteria for establishing the diagnosis of «occupational cancer» related to occupational asbestos exposure in MM patients:**

- *Criterion 1.* Clinical diagnosis of pleural, pericardium or peritoneum «malignant mesothelioma (C45)» of any stage according to TNM classification.
- *Criterion 2.* Cytohistochemical confirmation of «diffuse malignant mesothelioma (9050/3)» diagnosis [of any morphological type: epithelioid mesothelioma (9052/3), sarcomatoid mesothelioma (9051/3), desmoplastic mesothelioma (9051/3), biphasic mesothelioma (9053/3)] or pleural, pericardium or peritoneum «localised malignant mesothelioma (9050/3)», regardless of the histology method used (biopsy, surgery or section procedures).
- *Criterion 3.* Cytohistochemical exclusion of other histological types of pleural, pericardium or peritoneum malignant mesothelioma (carcinoma, sarcoma, lymphoma, metastatic tumours etc.) or benign neoplasms (benign mesothelioma and others).
- *Criterion 4.* Confirmed workplace exposure to dust containing any forms of asbestos, with any exposure time and at any exposure levels.
- *Criterion 5.* Post-exposure period of time (from the beginning of occupational exposure to asbestos dust to the moment of MM onset) not less than 10 years and with no further limit.

If the cytohistochemical methods for malignant mesothelioma identification are not available or the differential diagnosis using other histological types of tumours (criteria 2 and 3) is not possible to perform, the diagnosis is established based on histological identification of tumour using the following additional criteria:

- *Criterion 6.* Presence of other asbestos-induced diseases (asbestosis, pleural plaques, diffuse pleural thickening and others) detected by high resolution helical computed tomography.
- *Criterion 7.* Increase in at least two MM tumour markers (mesothelin and/or fibulin-3, osteopontin).

Occupational cancer cannot be diagnosed without histological (cy-

tohistochemical) MM identification and only on the basis of computed tomography, magnetic resonance tomography, positron emission tomography scans because these imaging scan diagnostic techniques do not allow to define the histological type of a neoplasm.

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RECOMMENDATIONS

1. To central executive agencies (Ministry of Health, State Labour Inspection and others):

1.1. On the national level, to intensify the measures to prevent asbestos-related diseases according to ILO Conventions No. 139 and No. 162 and ILO Recommendations No. 147 and No. 172.

1.2. On the national level, to introduce an official ban on use of amphibole asbestos in industry.

1.3. To enhance sanitation and hygiene control over controlled industrial use of chrysotile asbestos.

1.4. To gradually replace the chrysotile asbestos with alternative less harmful substances.

1.5. To develop and establish the National register of persons exposed to carcinogenic agents in the workplace.

1.6. To develop and put into practice a system for lifelong medical surveillance of persons with occupational exposure to carcinogenic agents.

2. To owners of industrial enterprises that are using chrysotile asbestos and asbestos-containing materials:

2.1. To ensure the comprehensive implementation of measures on protecting workers' health and safety by taking the following actions:

- to introduce a system for evaluation and management of industrial risks for workers' health;
- to equip the workplaces with engineering and technical means which would protect workers from dust exposure;
- to provide workers with personal protective means for respiratory organs.

2.2. To ensure the implementation of measures on workers' health protection by taking the following actions:

- to disseminate information about the potential risks for health and ways/methods for risk reduction;
- to carry out comprehensive initial and regular medical examinations of workers;
- to organise individual medical treatment, prevention and rehabilitation services for workers, according to medical recommendations.

3. To scientific research institutions:

3.1. To conduct studies searching for new genetic MM markers.

3.2. To establish a program for individual medical prevention and rehabilitation of persons with occupational exposure to asbestos and asbestos-containing materials.

3.3. To carry out studies on role of SV-40, genetic predisposition and other carcinogenic factors in MM development.

4. To health care institutions which provide medical service to workers exposed to asbestos and asbestos-containing materials:

4.1. To establish and maintain the national register of asbestos exposed workers for lifelong monitoring of their health. To ensure the functional interaction between this register and the National Cancer Register of Ukraine.

4.2. During periodic medical examinations, to strengthen efforts in the detection of pre-cancerous conditions and cancers of respiratory organs (larynx, bronchi, lung, pleura), peritoneum or pericardium by taking the following actions:

- to conduct computed radiography scanning which provides highly informative data and ensures the decreased radiation burden;
- to monitor the dynamic levels of tumour markers (cancer and mesothelioma) at pre-employment time and among workers with service record (more than 10 years);
- to use supplementary imaging methods (computed, magnetic resonance and positron emission tomography), endoscopic and cytohistochemical analysis, if there are clinical indications.

4.3. To ensure that the worker timely leaves a job (i.e. does not have any further contact with asbestos and asbestos-containing materials in the workplace) if he/she has a cancer at any location.

4.4. To timely direct patients with confirmed diagnosis of «malignant mesothelioma» to get medical examination for establishing the occupational disease category («occupational cancer»).

ANNEX

2013 WORLD MM EPIDEMIOLOGY DATA*

2013 Incidence and Deaths for 28 Groups of Malignant Neoplasms

Table 1. 2013 Incidence and Deaths for All Cancers and 28 Cancer Groups[a]

	Incident Cases, Global (thousands)			ASIR, Both Sexes (per 100 000)			Deaths, Global (thousands)			ASDR, Both Sexes (per 100 000)		
Cancer	Total	Male	Female	Developing	Developed	Global	Total	Male	Female	Developing	Developed	Global
All except NMSC and KS	14 943	8048	6894	190.4	327.9	237.4	8196	4723	3473	123.0	147.9	133.1
Esophageal	442	309	133	8.9	3.9	7.1	440	308	132	9.1	3.8	7.2
Stomach	984	630	354	16.9	14.4	16.1	841	530	311	15.3	11.1	13.8
Liver	792	559	233	14.7	7.4	12.5	818	564	254	15.6	7.3	13.0
Larynx	177	155	22	2.8	2.9	2.8	88	75	12	1.5	1.3	1.4
Tracheal, bronchus and lung	1798	1263	535	25.2	37.7	29.4	1640	1155	485	24.1	32.9	27.0
Breast	1804	25	1779	21.0	40.8	27.4	471	7	464	5.9	10.1	7.4
Cervical	485	...	485	8.0	5.0	7.1	236	...	236	4.3	2.2	3.6
Uterine	353	...	353	4.2	7.7	5.4	68	...	68	0.9	1.4	1.1
Prostate	1442	1442	...	14.3	43.2	24.3	293	293	...	3.6	7.4	5.2
Colon and rectum	1573	873	700	16.3	42.3	25.8	771	414	357	9.4	18.2	12.8
Lip and oral cavity	409	275	134	6.7	6.0	6.4	135	87	48	2.3	1.9	2.1
Nasopharynx	84	62	22	1.5	0.4	1.2	60	43	17	1.2	0.3	0.9
Other pharynx	140	117	22	2.0	2.6	2.1	79	63	16	1.3	1.2	1.2
Gallbladder and biliary tract	186	79	107	2.5	3.8	3.1	140	54	86	2.0	2.7	2.3
Pancreatic	350	184	166	3.7	9.5	5.8	352	185	167	3.7	9.6	5.9
Malignant skin melanoma	272	143	130	1.5	10.8	4.2	57	32	25	0.4	1.9	0.9
Ovarian	226	...	226	2.4	5.6	3.5	158	...	158	1.8	3.7	2.5
Testicular	59	59	...	0.6	1.8	0.8	8	8	...	0.1	0.1	0.1
Kidney	295	195	99	2.3	9.7	4.7	134	87	47	1.3	3.7	2.2
Bladder	401	312	89	3.2	12.8	6.7	174	130	44	2.4	3.7	3.0
Brain and nervous system	305	167	137	4.1	5.9	4.5	204	118	86	2.9	3.8	3.1
Thyroid	226	50	176	2.7	4.9	3.3	34	12	21	0.5	0.6	0.6
Mesothelioma	34	24	10	0.4	0.8	0.5	34	24	10	0.4	0.8	0.5
Hodgkin lymphoma	93	56	38	1.2	1.9	1.3	24	14	10	0.4	0.4	0.4
Non-Hodgkin lymphoma	465	264	202	5.2	11.3	7.3	226	133	92	2.9	4.5	3.6
Multiple myeloma	117	64	53	1.0	3.5	1.9	79	42	37	0.7	2.3	1.3
Leukemia	414	243	172	5.1	8.1	6.3	265	149	116	3.5	4.8	4.1
Other neoplasms	1015	496	518	12.0	23.0	15.7	370	195	175	5.4	6.2	5.8

Abbreviations: ASDR, age-standardized death rate; ASIR, age-standardized incidence rate; DALYs, disability-adjusted life-years; GBD, Global Burden of Disease; *ICD-9, International Classification of Diseases, Ninth Revision*; *ICD-10, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*; KS, Kaposi sarcoma; NMSC, nonmelanoma skin cancer; YLDs, years lived with disability; YLLs, years of life lost.

[a] Cancer groups are defined based on *ICD* codes and include all codes pertaining to neoplasms (*ICD-9* 140-239; *ICD-10* C00-D49) except for NMSC and KS. eTable 3 in the Supplement details how the original *ICD* codes were mapped to the standardized GBD cause list.[1] Detailed results for incidence, mortality, YLDs, YLLs, and DALYs by country development status (developed vs developing), region, and country are reported in web tables 1 through 9. Sums might not total precisely due to rounding.

Trends in Global Incidence of Malignant Neoplasm in Selected Locations (both genders; 1990–2013)

Table 2. Decomposition Analysis of Cancer Trends in Global Incidence, Both Sexes, 1990 to 2013

	Incident Cases, No.		Expected Incident Cases, 2013, No.		Change in Incident Cases, 1990 to 2013, %		
Cancer[a]	1990	2013	Given Population Growth Alone	Given Population Growth and Aging	Due to Population Growth[b]	Due to Change in Age Structure[c]	Due to Change in Incidence Rates[d]
All except NMSC and KS	8 510 588	14 942 583	11 486 507	14 515 059	35.0	35.6	5.0
Esophageal	303 510	441 767	409 640	530 592	35.0	39.9	−29.3
Stomach	800 136	984 206	1 079 922	1 401 995	35.0	40.3	−52.2
Liver	465 014	792 203	627 617	800 507	35.0	37.2	−1.8
Larynx	137 785	176 687	185 964	238 499	35.0	38.1	−44.9
Tracheal, bronchus and lung	1 113 162	1 798 179	1 502 405	1 937 791	35.0	39.1	−12.5
Breast	906 618	1 804 209	1 223 637	1 568 145	35.0	38.0	26.0
Cervical	447 344	485 297	603 768	747 821	35.0	32.2	−58.7
Uterine	216 793	353 117	292 599	375 986	35.0	38.5	−10.5
Prostate	454 412	1 442 460	613 308	801 983	35.0	41.5	140.9
Colon and rectum	818 440	1 572 590	1 104 626	1 443 985	35.0	41.5	15.7
Lip and oral cavity	238 789	409 360	322 287	413 567	35.0	38.2	−1.8
Nasopharynx	67 658	83 702	91 316	112 072	35.0	30.7	−41.9
Other pharynx	80 691	139 567	108 907	140 604	35.0	39.3	−1.3
Gallbladder and biliary tract	136 503	186 253	184 234	242 255	35.0	42.5	−41.0
Pancreatic	183 076	350 361	247 093	323 423	35.0	41.7	14.7
Malignant skin melanoma	151 601	272 481	204 612	254 748	35.0	33.1	11.7
Ovarian	137 417	226 204	185 467	234 642	35.0	35.8	−6.1
Testicular	37 982	59 279	51 263	56 101	35.0	12.7	8.4
Kidney	142 463	294 501	192 279	241 697	35.0	34.7	37.1
Bladder	263 307	401 174	355 378	466 220	35.0	42.1	−24.7
Brain and central nervous system	193 980	304 528	261 809	293 291	35.0	16.2	5.8
Thyroid	115 627	225 566	156 058	187 946	35.0	27.6	32.5
Mesothelioma	16 972	33 744	22 906	29 561	35.0	39.2	24.6
Hodgkin lymphoma	103 249	93 345	139 353	142 599	35.0	3.1	−47.7
Non-Hodgkin lymphoma	226 661	465 488	305 918	373 548	35.0	29.8	40.6
Multiple myeloma	62 738	116 947	84 676	110 140	35.0	40.6	10.8
Leukemia	297 404	414 443	401 398	437 862	35.0	12.3	−7.9
Other neoplasms	391 255	1 014 928	528 066	607 480	35.0	20.3	104.1

Abbreviations: GBD, Global Burden of Disease; *ICD-9, International Classification of Diseases, Ninth Revision*; *ICD-10, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*; KS, Kaposi sarcoma; NMSC, nonmelanoma skin cancer; YLDs, years lived with disability; YLLs, years of life lost.

[a] Cancer groups are defined based on *ICD* codes and include all codes pertaining to neoplasms (*ICD-9* 140-239; *ICD-10* C00-D49) except for NMSC and KS. eTable 3 in the Supplement details how the original *ICD* codes were mapped to the standardized GBD cause list.[1]

[b] To estimate the effect of population growth we applied the population size of 2013 onto the rate, sex, and age structure of 1990. Since the global population grew by 35% between 1990 and 2013, and rates and age structure remained the same as in 1990, incidence due to all cancers increased by 35% in this counterfactual scenario.

[c] To estimate the effect of aging on incident cases we applied the age structure of 2013 onto the rate, sex distribution, and population size of 1990. The change in incident cases reported herein shows the proportion of the change in incident cases between 1990 and 2013 that can be attributed to the changing age structure of the population.

[d] To estimate the effect of changing incidence rates on the incident cases we applied the incidence rates for 1990 onto the population size and age structure of 2013. The change in incident cases reported herein shows the proportion of the change in incident cases between 1990 and 2013 that can be attributed to a change in incidence rates.

Ranging of Primary Malignant Neoplasm Cases in 50 Most Populated Countries (both genders; 2013)

Region	Country	Tracheal, bronchus, and lung cancer	Stomach cancer	Liver cancer	Colon and rectum cancer	Breast cancer	Esophageal cancer	Pancreatic cancer	Prostate cancer	Leukemia	Cervical cancer	Non-Hodgkin lymphoma	Brain and nervous system cancer	Bladder cancer	Ovarian cancer	Gallbladder and biliary tract cancer	Lip and oral cavity cancer	Kidney cancer	Larynx cancer	Multiple myeloma	Other pharynx cancer	Uterine cancer	Nasopharynx cancer	Malignant skin melanoma	Mesothelioma	Thyroid cancer	Hodgkin lymphoma	Testicular cancer
Global		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Developed		1	3	7	2	4	11	5	6	8	17	9	14	10	13	15	18	12	21	16	22	20	26	19	23	24	25	27
Developing		1	3	2	4	6	5	9	12	8	7	11	10	14	15	16	13	18	17	22	19	21	20	24	26	23	25	27
High-income Asia Pacific	Japan	1	2	4	3	9	7	5	8	11	16	10	18	12	14	6	17	13	23	15	19	20	24	25	22	21	26	27
	South Korea	1	3	2	4	8	7	5	9	11	13	10	14	12	16	6	20	15	18	17	21	22	24	23	25	19	26	27
High-income North America	Canada	1	7	13	2	3	12	5	4	8	20	6	9	10	11	17	18	14	22	15	23	19	25	16	21	24	26	27
	United States	1	9	8	2	3	13	4	5	7	18	6	12	14	10	20	19	11	21	15	22	17	26	16	23	24	25	27
Southern Latin America	Argentina[a]	1	4	8	2	3	7	6	5	11	10	13	16	14	15	12	19	9	17	20	23	18	26	21	24	22	25	27
Western Europe	France	1	7	6	2	4	11	5	3	8	20	10	14	9	13	17	16	12	21	15	18	22	25	19	23	24	26	27
	Germany	1	6	10	2	3	14	4	5	7	19	11	13	9	12	15	18	8	23	16	20	21	26	17	22	24	25	27
	Italy	1	3	6	2	4	16	5	7	9	22	10	12	8	13	14	18	11	20	15	23	21	26	17	19	24	25	27
	Spain	1	3	7	2	5	14	6	4	9	21	10	11	8	12	16	18	13	17	15	22	19	26	20	23	24	25	27
	United Kingdom	1	7	14	2	3	6	5	4	10	21	8	13	11	9	20	19	12	22	15	23	18	26	16	17	24	25	27
Central Asia	Uzbekistan[a]	2	1	5	7	4	3	10	18	6	9	11	8	16	15	17	12	14	13	24	20	19	23	21	27	26	22	25
Central Europe	Poland	1	3	12	2	4	16	5	6	11	14	15	8	7	9	13	18	10	17	21	22	19	25	20	26	23	24	27
Eastern Europe	Russia	1	3	7	2	4	13	5	6	10	12	16	11	14	9	18	15	8	17	22	21	19	25	20	26	23	24	27
	Ukraine	1	3	14	2	4	16	5	8	11	10	15	12	9	7	18	13	6	17	23	20	21	25	19	24	22	26	27
Andean Latin America	Peru[a]	2	1	6	3	7	17	8	4	9	5	10	12	16	14	11	20	13	22	18	23	15	27	19	24	21	25	26
Central Latin America	Colombia[a]	2	1	7	3	5	12	9	4	8	6	10	11	15	14	13	18	17	16	19	24	22	25	21	27	20	23	26
	Mexico[a]	1	2	3	5	6	15	8	4	9	7	10	13	17	12	14	19	11	16	18	26	22	27	23	25	20	21	24

	Venezuela[a]	1	2	7	4	5	13	8	3	9	6	10	14	17	11	16	19	12	15	18	23	20	25	21	27	22	24	26
Tropical Latin America	Brazil[a]	1	3	8	2	5	7	6	4	11	9	12	10	13	14	18	15	17	16	20	19	21	25	22	26	23	24	27
East Asia	China[a]	1	3	2	5	8	4	6	15	7	12	11	9	13	18	14	20	17	19	22	23	16	10	26	21	24	25	27
	North Korea[a]	1	3	2	4	7	5	10	20	6	9	12	8	11	16	14	19	18	17	22	24	15	13	26	25	23	21	27
Southeast Asia	Indonesia[a]	1	3	6	2	5	14	8	19	7	4	10	9	16	12	13	11	17	20	24	18	21	15	23	25	22	26	27
	Malaysia[a]	1	5	3	2	4	13	7	12	6	10	8	17	15	11	18	16	14	21	20	19	23	9	24	27	22	25	26
	Myanmar[a]	1	7	2	4	5	13	11	20	6	3	9	14	15	8	12	10	17	21	25	19	18	16	24	26	22	23	27
	Philippines[a]	1	6	2	4	3	16	8	11	5	7	10	12	19	9	15	13	17	22	23	21	20	14	24	27	18	25	26
	Thailand[a]	2	4	1	3	6	12	9	16	8	5	13	11	15	14	7	10	17	20	24	19	22	18	23	26	21	25	27
	Vietnam[a]	2	3	1	4	11	5	12	14	9	8	6	7	16	22	19	10	21	15	24	13	18	20	26	27	17	25	23
South Asia	Afghanistan[a]	2	1	5	7	3	12	13	14	4	6	10	9	8	18	17	20	16	11	24	23	21	19	26	25	22	15	27
	Bangladesh[a]	2	3	1	8	9	7	19	18	5	10	4	13	14	11	16	6	20	15	24	12	21	17	25	26	27	22	23
	India[a]	4	1	2	7	5	3	15	20	10	6	11	13	16	12	17	8	19	14	21	9	25	18	22	27	23	24	26
	Nepal[a]	2	3	6	5	4	1	16	20	8	7	11	15	17	10	14	9	19	13	21	12	23	18	25	27	22	24	26
	Pakistan[a]	1	10	5	9	2	3	18	19	8	16	4	13	7	11	15	6	20	12	21	14	22	17	26	27	23	24	25
North Africa and Middle East	Algeria[a]	1	3	9	4	2	18	13	15	5	12	6	8	10	14	7	22	19	16	17	23	24	11	25	26	20	21	27
	Egypt[a]	2	7	1	8	3	11	9	10	5	14	12	4	6	17	16	18	13	15	23	21	20	27	24	25	19	22	26
	Iran[a]	3	1	9	5	8	2	12	7	4	17	14	6	10	16	13	18	15	11	20	24	26	19	22	27	21	23	25
	Iraq[a]	2	5	4	7	1	15	8	11	3	12	10	6	9	13	17	19	14	16	21	23	18	22	25	27	20	24	26
	Morocco[a]	1	3	5	4	2	15	9	6	10	7	11	8	12	14	13	19	17	16	24	23	18	20	25	26	21	22	27
	Saudi Arabia[a]	2	6	1	3	4	12	8	10	7	17	9	5	13	15	11	16	14	18	22	21	25	20	24	27	19	23	26
	Sudan[a]	1	2	6	4	3	12	11	10	5	13	9	7	8	16	15	18	17	14	22	24	23	19	25	27	20	21	26
	Turkey[a]	1	2	10	3	4	16	5	6	7	18	11	8	9	12	15	22	13	14	17	27	19	23	24	21	20	25	26
	Yemen[a]	1	2	6	5	3	13	12	11	4	10	9	7	8	16	14	18	17	15	23	24	20	19	25	26	21	22	27
Central sub-Saharan Africa	DRC[a,b]	6	2	5	4	3	7	11	9	10	1	8	14	12	17	13	15	16	18	21	22	20	24	23	27	25	19	26
Eastern sub-Saharan Africa	Ethiopia[a]	7	6	4	3	5	2	10	9	14	1	8	12	16	17	13	15	11	22	18	21	20	26	23	27	25	19	24
	Kenya[a]	8	4	5	6	3	1	9	11	14	2	7	15	13	10	19	12	18	16	17	22	25	20	24	27	23	21	26
	Mozambique[a]	7	3	4	1	5	9	12	6	13	2	8	11	15	18	14	16	10	21	19	20	22	26	23	25	27	17	24
	Tanzania[a]	8	6	2	3	4	5	13	9	12	1	7	10	16	17	14	15	11	22	19	20	21	25	23	26	27	18	24
	Uganda[a]	9	8	4	6	7	2	13	5	11	1	3	20	12	10	24	16	15	21	18	17	23	14	25	27	19	22	26
Southern sub-Saharan Africa	South Africa[a]	1	9	8	3	5	2	7	4	11	6	10	17	14	12	21	13	16	20	15	22	19	25	18	23	24	26	27
Western sub-Saharan Africa	Ghana[a]	9	3	1	6	5	10	7	4	14	2	8	15	12	11	16	19	17	25	18	24	13	23	21	26	22	20	27
	Nigeria[a]	7	3	1	5	4	10	9	8	13	2	6	15	11	12	14	18	17	21	20	23	16	25	22	26	24	19	27

EPIDEMIOLOGICAL INCIDENCE OF MALIGNANT MESOTHELIOMA (C45) ALL OVER THE WORLD (2008–2012)*

Malignant Mesothelioma Incidence in Africa

Male (all age groups)

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
Algeria, Setif	2	0.1	0.1
Egypt, Gharbiah	25	0.2	0.4
Libya, Benghazi	3	0.1	0.3
Tunisia, North	14	0.2	0.2
Uganda, Kyadondo county	1	0	0
Zimbabwe, Harare: African	1	0	0

Female (all age groups)

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
Egypt, Gharbiah	15	0.2	0.2
Tunisia, North	4	0.1	0.1

* © CI5 X: Cancer Incidence in Five Continents [electronic version] / Eds.: Forman D., Bray F., Brewster D.H., Gombe Mbalawa C., Kohler B., Piñeros M., Steliarova-Foucher E., Swaminathan R., Ferlay J (2013). — Lyon : IARC, 2013. — V. X. — Access to: http://ci5.iarc.fr/CI5-X/Default.aspx.

Malignant Mesothelioma Incidence in Central and South America

Male (all age groups)

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
Argentina, Bahia Blanca	7	1.0	0.9
Argentina, Cordoba	21	0.8	0.9
Argentina, Mendoza	27	0.7	0.6
Argentina, Tierra del Fuego	1	0.3	0.8
Brazil, Aracaju	1	0.1	0.1
Brazil, Belo Horizonte	3	0.1	0.1
Brazil, Cuiaba	1	0.1	0.1
Brazil, Fortaleza	6	0.1	0.2
Brazil, Goiania	1	0	0
Brazil, Sao Paulo	39	0.2	0.2
Chile, Biobio Province	2	0.2	0.2
Chile, Region of Antofagasta	5	0.4	0.3
Chile, Valdivia	1	0.1	0.1
Colombia, Bucaramanga	4	0.2	0.2
Colombia, Cali	17	0.4	0.4
Colombia, Pasto	2	0.2	0.2
Costa Rica	13	0.1	0.2
Cuba, Villa Clara	4	0.2	0.1
Ecuador, Cuenca	1	0.1	0.1
Ecuador, Quito	9	0.2	0.3
France, Martinique	2	0.2	0.2
Puerto Rico	27	0.3	0.2
Uruguay	19	0.4	0.3

Female (all age groups)

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
Argentina, Bahia Blanca	3	0.4	0.1
Argentina, Cordoba	19	0.7	0.5
Argentina, Mendoza	10	0.2	0.2
Brazil, Belo Horizonte	2	0.1	0
Brazil, Cuiaba	1	0.1	0
Brazil, Goiania	6	0.2	0.2
Brazil, Sao Paulo	22	0.1	0.1
Chile, Biobio Province	3	0.3	0.3
Chile, Region of Antofagasta	3	0.2	0.3
Chile, Valdivia	5	0.5	0.4
Colombia, Bucaramanga	2	0.1	0.1
Colombia, Cali	8	0.1	0.2
Costa Rica	5	0	0
Cuba, Villa Clara	5	0.3	0.2
Ecuador, Cuenca	4	0.3	0.3
Ecuador, Quito	4	0.1	0.1
France, Martinique	1	0.1	0.1
Puerto Rico	12	0.1	0.1
Uruguay	10	0.2	0.1

Malignant Mesothelioma Incidence in North America

Male (all age groups)

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
Canada	1860	2.3	1.4
Canada, Alberta	181	2..1	1.6
Canada, British Columbia	312	3.0	1.6
Canada, Manitoba	68	2.3	1.4
Canada, New Brunswick	35	1.9	1.1
Canada, Newfoundland and Labrador	14	1.1	0.7
Canada, Northwest Territories	1	0.9	1.1
Canada, Nova Scotia	43	1.9	1.0
Canada, Ontario	567	1.8	1.2
Canada, Prince Edward Island	5	1.5	0.8
Canada, Quebec	589	3.1	1.9
Canada, Saskatchewan	44	1.8	1.0
Canada, Yukon	1	1.2	1.3
USA, Alabama	148	1.3	0.8
USA, Alabama: Black	27	1.0	0.9
USA, Alabama: White	119	1.5	0.8
USA, Alaska	25	1.4	1.5
USA, Alaska: American Indian	1	0.4	0.3
USA, Arizona	238	1.6	1.0
USA, Arizona: American Indian	3	0.4	0.6
USA, Arizona: Asian and Pacific Islander	2	0.5	0.6
USA, Arizona: Black	4	0.6	0.9
USA, Arizona: White	227	1.7	1.0
USA, Arkansas	93	1.4	0.8
USA, Arkansas: Black	7	0.7	0.7
USA, Arkansas: White	84	1.5	0.8
USA, California	1222	1.4	1.0
USA, California, Los Angeles County	272	1.1	0.9
USA, California, Los Angeles County: Asian and Pacific Islander	12	0.4	0.3
USA, California, Los Angeles County: Black	18	0.8	0.7
USA, California, Los Angeles County: Chinese	2	0.2	0.2
USA, California, Los Angeles County: Filipino	3	0.4	0.3
USA, California, Los Angeles County: Hispanic White	64	0.6	0.8

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
USA, California, Los Angeles County: Japanese	3	1.1	0.9
USA, California, Los Angeles County: Korean	1	0.2	0.1
USA, California, Los Angeles County: Non-Hispanic White	174	2.4	1.1
USA, California, Los Angeles County: White	238	1.3	1.0
USA, California, San Francisco Bay Area	167	1.6	1.0
USA, California, San Francisco Bay Area: Asian and Pacific Islander	14	0.6	0.4
USA, California, San Francisco Bay Area: Black	8	0.8	0.7
USA, California, San Francisco Bay Area: Hispanic White	17	0.9	1.2
USA, California, San Francisco Bay Area: Non-Hispanic White	126	2.5	1.3
USA, California, San Francisco Bay Area: White	143	2.1	1.3
USA, California: American Indian	1	0.1	0.1
USA, California: Asian and Pacific Islander	44	0.4	0.3
USA, California: Black	44	0.7	0.7
USA, California: White	1121	1.6	1.1
USA, Colorado	128	1.1	0.8
USA, Colorado: Asian and Pacific Islander	1	0.3	0.5
USA, Colorado: Black	2	0.4	0.6
USA, Colorado: White	123	1.1	0.8
USA, Connecticut	160	1.9	1.1
USA, Connecticut: Black	3	0.3	0.4
USA, Connecticut: White	156	2.2	1.2
USA, Delaware	54	2.6	1.4
USA, Delaware: White	53	3.4	1.6
USA, Florida	924	2.1	1.0
USA, Florida: Asian and Pacific Islander	3	0.3	0.3
USA, Florida: Black	33	0.5	0.5
USA, Florida: White	882	2.5	1.0
USA, Georgia	195	0.9	0.7
USA, Georgia, Atlanta	44	0.5	0.5

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
USA, Georgia, Atlanta: Black	6	0.2	0.3
USA, Georgia, Atlanta: White	37	0.8	0.6
USA, Georgia: Black	20	0.3	0.4
USA, Georgia: White	174	1.1	0.8
USA, Idaho	55	1.5	1.0
USA, Illinois	582	1.9	1.2
USA, Illinois: Asian and Pacific Islander	5	0.4	0.4
USA, Illinois: Black	21	0.5	0.5
USA, Illinois: White	553	2.2	1.3
USA, Indiana	278	1.8	1.2
USA, Indiana: Black	10	0.7	0.7
USA, Indiana: White	265	1.9	1.2
USA, Iowa	101	1.4	0.8
USA, Kentucky	126	1.2	0.8
USA, Louisiana	184	2.2	1.5
USA, Louisiana, New Orleans	50	3.1	1.9
USA, Louisiana, New Orleans: Black	13	2.0	1.7
USA, Louisiana, New Orleans: White	37	4.2	2.2
USA, Louisiana: Black	36	1.3	1.2
USA, Louisiana: White	148	2.6	1.6
USA, Maine	88	2.8	1.4
USA, Massachusetts	381	2.4	1.5
USA, Massachusetts: Asian and Pacific Islander	1	0.1	0.2
USA, Massachusetts: Black	6	0.5	0.7
USA, Massachusetts: White	371	2.7	1.5
USA, Michigan	432	1.7	1.1
USA, Michigan, Detroit	144	1.5	0.9
USA, Michigan, Detroit: Black	11	0.5	0.4
USA, Michigan, Detroit: White	133	1.9	1.1
USA, Michigan: Black	22	0.6	0.6
USA, Michigan: White	404	2.0	1.1
USA, Mississippi	95	1.4	0.9
USA, Missouri	185	1.3	0.8
USA, Missouri: Black	5	0.3	0.3
USA, Missouri: White	179	1.5	0.8

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
USA, Montana	51	2.2	1.3
USA, Nebraska	68	1.6	1.0
USA, Nebraska: White	67	1.7	1.0
USA, New Hampshire	69	2.2	1.3
USA, New Jersey	541	2.6	1.5
USA, New Jersey: Black	23	0.8	0.7
USA, New Jersey: White	508	3.1	1.6
USA, New Mexico	65	1.4	0.9
USA, New Mexico: Hispanic White	24	1.2	1.1
USA, New Mexico: Non-Hispanic White	34	1.7	0.7
USA, New Mexico: White	58	1.4	0.9
USA, New York State	757	1.6	1.0
USA, New York State: Asian and Pacific Islander	7	0.2	0.2
USA, New York State: Black	36	0.4	0.4
USA, New York State: White	710	2.0	1.1
USA, North Carolina	288	1.4	0.9
USA, North Carolina: American Indian	1	0.4	0.3
USA, North Carolina: Black	27	0.6	0.6
USA, North Carolina: White	259	1.6	1.0
USA, North Dakota	32	2.0	1.0
USA, NPCR (42 States)	10936	1.7	1.1
USA, NPCR (42 States): American Indian	28	0.4	0.4
USA, NPCR (42 States): Asian and Pacific Islander	81	0.3	0.3
USA, NPCR (42 States): Black	494	0.6	0.6
USA, NPCR (42 States): White	10262	1.9	1.1
USA, Ohio	524	1.9	1.1
USA, Ohio: Black	23	0.7	0.7
USA, Ohio: White	496	2.1	1.2
USA, Oklahoma	133	1.5	1.0
USA, Oklahoma: American Indian	8	1.0	1.1
USA, Oklahoma: Black	7	1.0	1.0
USA, Oklahoma: White	118	1.7	1.0
USA, Oregon	165	1.8	1.0
USA, Oregon: Asian and Pacific Islander	2	0.6	0.5

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
USA, Oregon: White	162	2.0	1.0
USA, Pennsylvania	886	2.9	1.5
USA, Pennsylvania: Asian and Pacific Islander	5	0.7	0.7
USA, Pennsylvania: Black	24	0.7	0.7
USA, Pennsylvania: White	854	3.3	1.6
USA, Rhode Island	60	2.3	1.2
USA, Rhode Island: Black	1	0.6	0.5
USA, Rhode Island: White	58	2.5	1.3
USA, SEER (18 Registries)	3090	1.5	1.0
USA, SEER (18 Registries): Asian and Pacific Islander	87	0.5	0.4
USA, SEER (18 Registries): Black	147	0.6	0.6
USA, SEER (18 Registries): Hispanic White	251	0.6	0.9
USA, SEER (18 Registries): Non-Hispanic White	2585	2.2	1.2
USA, SEER (18 Registries): White	2836	1.8	1.1
USA, SEER (9 Registries)	1032	1.5	1.0
USA, SEER (9 Registries): Black	33	0.4	0.4
USA, SEER (9 Registries): White	944	1.8	1.1
USA, South Carolina	149	1.4	0.9
USA, South Carolina: Black	10	0.3	0.3
USA, South Carolina: White	137	1.9	1.0
USA, South Dakota	26	1.3	0.6
USA, Tennessee	205	1.4	0.9
USA, Tennessee: Black	10	0.4	0.5
USA, Tennessee: White	195	1.6	1.0
USA, Texas	670	1.2	0.9
USA, Texas: Asian and Pacific Islander	2	0.1	0.1
USA, Texas: Black	45	0.7	0.8
USA, Texas: White	613	1.3	1.0
USA, Utah	66	1.0	1.0
USA, Vermont	20	1.3	0.8
USA, Virginia	355	1.9	1.3
USA, Virginia: Asian and Pacific Islander	3	0.3	0.3
USA, Virginia: Black	57	1.6	1.5

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
USA, Virginia: White	294	2.1	1.3
USA, Washington State	341	2.2	1.4
USA, Washington, Seattle	245	2.3	1.5
USA, West Virginia	143	3.2	1.8
USA, Wisconsin	306	2.2	1.4
USA, Wisconsin: Black	3	0.4	0.6
USA, Wisconsin: White	301	2.4	1.4
USA, Wyoming	36	2.8	1.7

Female (all age groups)

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
Canada	388	0.5	0.3
Canada, Alberta	31	0.4	0.3
Canada, British Columbia	46	0.4	0.2
Canada, Manitoba	11	0.4	0.3
Canada, New Brunswick	7	0.4	0.2
Canada, Nova Scotia	16	0.7	0.3
Canada, Ontario	116	0.4	0.2
Canada, Prince Edward Island	1	0.3	0.2
Canada, Quebec	152	0.8	0.4
Canada, Saskatchewan	8	0.3	0.2
USA, Alabama	43	0.4	0.2
USA, Alabama: Black	3	0.1	0.1
USA, Alabama: White	40	0.5	0.2
USA, Alaska	6	0.4	0.4
USA, Arizona	68	0.5	0.3
USA, Arizona: American Indian	4	0.5	0.5
USA, Arizona: White	63	0.5	0.3
USA, Arkansas	16	0.2	0.1
USA, Arkansas: Black	1	0.1	0
USA, Arkansas: White	15	0.3	0.1
USA, California	354	0.4	0.2
USA, California, Los Angeles County	96	0.4	0.2

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
USA, California, Los Angeles County: Asian and Pacific Islander	4	0.1	0.1
USA, California, Los Angeles County: Black	6	0.2	0.1
USA, California, Los Angeles County: Chinese	2	0.2	0.1
USA, California, Los Angeles County: Filipino	1	0.1	0.1
USA, California, Los Angeles County: Hispanic White	37	0.3	0.4
USA, California, Los Angeles County: Non-Hispanic White	49	0.7	0.2
USA, California, Los Angeles County: White	86	0.5	0.3
USA, California, San Francisco Bay Area	41	0.4	0.2
USA, California, San Francisco Bay Area: Asian and Pacific Islander	4	0.2	0.1
USA, California, San Francisco Bay Area: Black	3	0.3	0.2
USA, California, San Francisco Bay Area: Hispanic White	8	0.5	0.4
USA, California, San Francisco Bay Area: Non-Hispanic White	26	0.5	0.2
USA, California, San Francisco Bay Area: White	34	0.5	0.2
USA, California: American Indian	1	0.1	0.1
USA, California: Asian and Pacific Islander	18	0.1	0.1
USA, California: Black	13	0.2	0.1
USA, California: White	321	0.5	0.3
USA, Colorado	38	0.3	0.2
USA, Colorado: Asian and Pacific Islander	2	0.5	0.7
USA, Colorado: White	36	0.3	0.2
USA, Connecticut	60	0.7	0.3
USA, Connecticut: Black	2	0.2	0.2
USA, Connecticut: White	56	0.7	0.3
USA, Delaware	12	0.6	0.3
USA, Delaware: Black	1	0.2	0.2
USA, Delaware: White	11	0.7	0.3

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
USA, Florida	245	0.5	0.3
USA, Florida: Asian and Pacific Islander	2	0.2	0.1
USA, Florida: Black	15	0.2	0.2
USA, Florida: White	226	0.6	0.3
USA, Georgia	54	0.2	0.1
USA, Georgia, Atlanta	17	0.2	0.1
USA, Georgia, Atlanta: Black	2	0.1	0
USA, Georgia, Atlanta: White	15	0.3	0.2
USA, Georgia: Asian and Pacific Islander	1	0.2	0.1
USA, Georgia: Black	3	0	0
USA, Georgia: White	50	0.3	0.2
USA, Idaho	14	0.4	0.3
USA, Illinois	187	0.6	0.3
USA, Illinois: Asian and Pacific Islander	1	0.1	0.1
USA, Illinois: Black	13	0.3	0.2
USA, Illinois: White	169	0.7	0.4
USA, Indiana	81	0.5	0.3
USA, Indiana: Black	2	0.1	0.1
USA, Indiana: White	78	0.6	0.3
USA, Iowa	31	0.4	0.2
USA, Kentucky	39	0.4	0.2
USA, Louisiana	56	0.6	0.4
USA, Louisiana, New Orleans	31	1.8	1.0
USA, Louisiana, New Orleans: Black	13	1.7	1.3
USA, Louisiana, New Orleans: White	18	1.9	0.9
USA, Louisiana: Black	13	0.4	0.4
USA, Louisiana: White	43	0.7	0.4
USA, Maine	28	0.8	0.4
USA, Massachusetts	100	0.6	0.3
USA, Massachusetts: Asian and Pacific Islander	1	0.1	0.2
USA, Massachusetts: Black	1	0.1	0.1
USA, Massachusetts: White	97	0.7	0.3
USA, Michigan	145	0.6	0.3
USA, Michigan, Detroit	54	0.5	0.3
USA, Michigan, Detroit: Black	7	0.3	0.2

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
USA, Michigan, Detroit: White	44	0.6	0.3
USA, Michigan: Asian and Pacific Islander	2	0.3	0.4
USA, Michigan: Black	9	0.2	0.2
USA, Michigan: White	130	0.6	0.3
USA, Mississippi	25	0.3	0.2
USA, Missouri	66	0.4	0.2
USA, Missouri: Black	5	0.3	0.2
USA, Missouri: White	61	0.5	0.2
USA, Montana	15	0.6	0.3
USA, Montana: American Indian	1	0.6	0.6
USA, Nebraska	30	0.7	0.4
USA, Nebraska: White	29	0.7	0.4
USA, New Hampshire	11	0.3	0.2
USA, New Jersey	165	0.7	0.4
USA, New Jersey: Black	11	0.3	0.2
USA, New Jersey: White	151	0.9	0.4
USA, New Mexico	29	0.6	0.3
USA, New Mexico: Hispanic White	12	0.6	0.4
USA, New Mexico: Non-Hispanic White	15	0.7	0.3
USA, New Mexico: White	27	0.7	0.4
USA, New York State	246	0.5	0.3
USA, New York State: Asian and Pacific Islander	3	0.1	0.1
USA, New York State: Black	20	0.2	0.1
USA, New York State: White	222	0.6	0.3
USA, North Carolina	74	0.3	0.2
USA, North Carolina: Black	13	0.3	0.2
USA, North Carolina: White	61	0.4	0.2
USA, North Dakota	11	0.7	0.3
USA, NPCR (42 States)	3101	0.5	0.3
USA, NPCR (42 States): American Indian	18	0.3	0.2
USA, NPCR (42 States): Asian and Pacific Islander	45	0.1	0.1
USA, NPCR (42 States): Black	162	0.2	0.1
USA, NPCR (42 States): White	2851	0.5	0.3
USA, Ohio	149	0.5	0.3

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
USA, Ohio: Asian and Pacific Islander	1	0.2	0.2
USA, Ohio: Black	7	0.2	0.1
USA, Ohio: White	141	0.6	0.3
USA, Oklahoma	34	0.4	0.2
USA, Oklahoma: American Indian	3	0.4	0.2
USA, Oklahoma: White	30	0.4	0.2
USA, Oregon	64	0.7	0.3
USA, Oregon: Asian and Pacific Islander	1	0.3	0.2
USA, Oregon: White	61	0.7	0.3
USA, Pennsylvania	201	0.6	0.3
USA, Pennsylvania: Black	11	0.3	0.2
USA, Pennsylvania: White	190	0.7	0.3
USA, Rhode Island	15	0.5	0.2
USA, Rhode Island: White	15	0.6	0.3
USA, SEER (18 Registries)	937	0.5	0.3
USA, SEER (18 Registries): Asian and Pacific Islander	31	0.2	0.1
USA, SEER (18 Registries): Black	53	0.2	0.2
USA, SEER (18 Registries): Hispanic White	117	0.3	0.3
USA, SEER (18 Registries): Non-Hispanic White	728	0.6	0.3
USA, SEER (18 Registries): White	845	0.5	0.3
USA, SEER (9 Registries)	327	0.5	0.3
USA, SEER (9 Registries): Black	17	0.2	0.2
USA, SEER (9 Registries): White	290	0.5	0.3
USA, South Carolina	38	0.3	0.2
USA, South Carolina: Black	5	0.2	0.1
USA, South Carolina: White	32	0.4	0.2
USA, South Dakota	4	0.2	0.1
USA, Tennessee	46	0.3	0.2
USA, Tennessee: Black	4	0.1	0.1
USA, Tennessee: White	41	0.3	0.2
USA, Texas	192	0.3	0.2
USA, Texas: Asian and Pacific Islander	7	0.3	0.3
USA, Texas: Black	14	0.2	0.2

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
USA, Texas: White	166	0.3	0.2
USA, Utah	19	0.3	0.2
USA, Vermont	12	0.8	0.4
USA, Virginia	76	0.4	0.2
USA, Virginia: Black	4	0.1	0.1
USA, Virginia: White	71	0.5	0.3
USA, Washington State	102	0.6	0.4
USA, Washington, Seattle	69	0.6	0.4
USA, West Virginia	31	0.7	0.3
USA, Wisconsin	101	0.7	0.4
USA, Wisconsin: White	101	0.8	0.4
USA, Wyoming	2	0.2	0.1

Malignant Mesothelioma Incidence in Asia

Male (all age groups)

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
Bahrain: Bahraini	12	1.0	1.9
China, Beijing City	95	0.5	0.3
China, Cixian County	2	0.1	0.2
China, Hong Kong	62	0.4	0.2
China, Jiashan County	2	0.2	0.1
China, Macao	1	0.1	0.1
China, Nangang District, Harbin City	13	0.5	0.5
China, Qidong County	3	0.1	0.1
China, Shanghai City	39	0.3	0.1
China, Wuhan City	48	0.4	0.3
China, Zhongshan City	7	0.2	0.2
India, Bangalore	8	0.1	0.1
India, Bhopal	2	0.1	0.1
India, Chennai	12	0.1	0.1
India, Dindigul, Ambillikai	2	0	0
India, Mumbai	15	0	0.1
India, New Delhi	2	0	0
India, Poona	5	0	0.1
India, Sikkim State	1	0.1	0.1
India, Trivandrum	1	0.1	0.1
Iran, Golestan Province	1	0	0.1
Israel	158	1.0	0.8
Israel: Jews	145	1.1	0.9
Israel: Non-Jews	13	0.4	0.7
Japan, Aichi Prefecture	21	0.6	0.3
Japan, Fukui Prefecture	18	0.9	0.4
Japan, Hiroshima	57	2.1	1.0
Japan, Miyagi Prefecture	69	1.2	0.6
Japan, Nagasaki Prefecture	107	3.1	1.4
Japan, Niigata Prefecture	85	1.4	0.6
Japan, Osaka Prefecture	415	1.9	0.9
Japan, Saga Prefecture	40	2.0	0.8
Kuwait	22	0.2	0.5
Kuwait: Kuwaitis	4	0.2	0.3
Kuwait: Non-Kuwaitis	18	0.3	0.9

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
Malaysia, Penang	1	0	0
Malaysia, Penang: Chinese	1	0.1	0.1
Philippines, Manila	3	0	0.1
Philippines, Rizal	4	0	0
Republic of Korea	252	0.2	0.2
Republic of Korea, Busan	18	0.2	0.2
Republic of Korea, Daegu	9	0.1	0.1
Republic of Korea, Daejeon	9	0.2	0.3
Republic of Korea, Gwangju	3	0.1	0.1
Republic of Korea, Incheon	20	0.3	0.3
Republic of Korea, Jejudo	4	0.4	0.3
Republic of Korea, Seoul	50	0.2	0.2
Republic of Korea, Ulsan	7	0.3	0.3
Saudi Arabia, Riyadh: Saudi	4	0	0.1
Singapore	43	0.5	0.5
Singapore: Chinese	37	0.6	0.5
Singapore: Indian	1	0.1	0.1
Singapore: Malay	4	0.3	0.4
Thailand, Bangkok	4	0	0
Thailand, Chonburi	2	0.1	0.1
Thailand, Khon Kaen	1	0	0
Thailand, Lampang	2	0.1	0.1
Turkey, Antalya	59	1.5	1.6
Turkey, Edirne	7	0.9	0.7
Turkey, Izmir	77	0.8	0.8
Turkey, Trabzon	9	0.8	0.7

Female (all age groups)

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
Bahrain: Bahraini	2	0.2	0.2
China, Beijing City	74	0.4	0.2
China, Haining County	1	0.1	0.1
China, Hong Kong	18	0.1	0.1
China, Jiashan County	2	0.2	0.1
China, Macao	1	0.1	0.1
China, Nangang District, Harbin City	18	0.7	0.6
China, Qidong County	1	0	0
China, Shanghai City	30	0.2	0.1
China, Wuhan City	36	0.3	0.2
China, Yanting County	1	0.1	0.1
China, Zhongshan City	5	0.2	0.2
India, Bangalore	4	0	0
India, Bhopal	1	0	0.1
India, Chennai	2	0	0
India, Dindigul, Ambillikai	1	0	0
India, Mumbai	8	0	0
India, New Delhi	7	0	0
India, Poona	1	0	0
India, Trivandrum	2	0.1	0.1
Israel	53	0.3	0.2
Israel: Jews	47	0.4	0.2
Israel: Non-Jews	6	0.2	0.3
Japan, Aichi Prefecture	7	0.2	0.1
Japan, Fukui Prefecture	7	0.3	0.1
Japan, Hiroshima	13	0.4	0.2
Japan, Miyagi Prefecture	19	0.3	0.1
Japan, Nagasaki Prefecture	30	0.8	0.3
Japan, Niigata Prefecture	18	0.3	0.1
Japan, Osaka Prefecture	129	0.6	0.2
Japan, Saga Prefecture	17	0.7	0.3
Kuwait	6	0.1	0.2
Kuwait: Kuwaitis	1	0	0.1
Kuwait: Non-Kuwaitis	5	0.2	0.6
Philippines, Manila	3	0	0
Philippines, Rizal	6	0	0.1

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
Republic of Korea	144	0.1	0.1
Republic of Korea, Busan	11	0.1	0.1
Republic of Korea, Daegu	8	0.1	0.1
Republic of Korea, Daejeon	6	0.2	0.2
Republic of Korea, Gwangju	3	0.1	0.1
Republic of Korea, Incheon	6	0.1	0.1
Republic of Korea, Jejudo	2	0.2	0.1
Republic of Korea, Seoul	22	0.1	0.1
Republic of Korea, Ulsan	3	0.1	0.1
Saudi Arabia, Riyadh: Saudi	6	0.1	0.1
Singapore	9	0.1	0.1
Singapore: Chinese	6	0.1	0.1
Singapore: Indian	1	0.1	0.3
Singapore: Malay	2	0.2	0.1
Thailand, Bangkok	4	0	0
Turkey, Antalya	28	0.7	0.8
Turkey, Edirne	4	0.5	0.3
Turkey, Izmir	41	0.5	0.4
Turkey, Trabzon	6	0.5	0.4

Malignant Mesothelioma Incidence in Europe

Male (all age groups)

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
Austria	314	1.6	0.9
Austria, Tyrol	16	0.9	0.6
Austria, Vorarlberg	14	1.6	1.1
Belarus	196	0.9	0.7
Belgium	824	4.0	2.2
Bulgaria	125	0.7	0.4
Croatia	258	2.4	1.5
Cyprus	30	1.6	1.1
Czech Republic	189	0.8	0.5
Denmark	416	3.1	1.8
Estonia	12	0.4	0.3
Finland	341	2.7	1.5
France, Bas-Rhin	32	1.2	0.7
France, Calvados	44	2.7	1.7
France, Doubs	14	1.1	0.6
France, Haut-Rhin	21	1.2	0.8
France, Herault	47	2.0	1.0
France, Isere	83	2.9	1.7
France, Loire Atlantique	130	4.4	2.5
France, Manche	36	3.0	1.5
France, Somme	40	2.9	1.6
France, Tarn	22	2.5	1.1
France, Vendee	30	2.1	1.0
Germany, Brandenburg	108	1.7	0.9
Germany, Bremen	199	12.4	6.0
Germany, Free State of Saxony	168	1.6	0.7
Germany, Hamburg	302	7.2	3.7
Germany, Mecklenburg-Western Pomerania	54	1.3	0.6
Germany, Munich	286	3.0	1.6
Germany, North Rhine-Westphalia	260	4.1	2.1
Germany, Saarland	75	2.9	1.4
Germany, Schleswig-Holstein	346	5.0	2.4
Iceland	9	1.2	0.6
Ireland	128	1.2	1.0
Italy, Alto Adige	15	1.6	0.9

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
Italy, Biella Province	11	2.5	1.0
Italy, Brescia Province	62	2.9	1.7
Italy, Catania and Messina	36	1.4	0.9
Italy, Catanzaro	5	0.9	0.5
Italy, Ferrara Province	42	5.0	1.9
Italy, Florence and Prato Provinces	29	1.7	0.8
Italy, Friuli-Venezia Giulia	234	8.0	3.6
Italy, Genova Province	249	15.1	5.6
Italy, Latina	18	1.4	0.7
Italy, Lombardy, Como Province	50	3.7	1.7
Italy, Lombardy, Lecco Province	39	4.9	2.6
Italy, Lombardy, Mantova Province	18	3.2	1.7
Italy, Lombardy, Milan	102	4.2	1.8
Italy, Lombardy, Varese Province	96	4.7	2.4
Italy, Modena Province	34	2.1	1.0
Italy, Naples	32	2.4	1.8
Italy, Nuoro	7	1.2	0.7
Italy, Palerme	68	2.8	1.7
Italy, Parma Province	42	4.2	1.7
Italy, Ragusa Province	10	1.3	0.9
Italy, Reggio Emilia Province	57	4.7	2.4
Italy, Romagna Region	88	3.1	1.4
Italy, Salerno Province	40	1.5	0.9
Italy, Sassari Province	21	1.8	1.1
Italy, Sondrio	10	2.3	1.2
Italy, South Lombardy	63	6.0	3.1
Italy, Syracuse Province	42	4.3	2.4
Italy, Torino	98	4.5	1.8
Italy, Trapani	14	1.7	0.6
Italy, Trento	19	1.9	1.1
Italy, Umbria Region	51	2.4	1.1
Italy, Veneto Region	121	2.7	1.3
Latvia	29	0.7	0.5
Lithuania	28	0.4	0.3
Malta	29	2.9	1.9
Norway	337	2.9	1.7

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
Poland, Cracow	14	1.0	0.6
Poland, Kielce	26	0.8	0.6
Poland, Lower Silesia	30	0.4	0.3
Poland, Rzeszow	32	0.6	0.5
Portugal, Azores	1	0.2	0.1
Russia, St Petersburg	66	0.6	0.4
Serbia, Central	36	0.3	0.2
Slovakia	74	0.6	0.4
Slovenia	109	2.2	1.4
Spain, Albacete	3	0.3	0.2
Spain, Asturias	44	1.7	0.8
Spain, Basque Country	121	2.3	1.2
Spain, Canary Islands	14	0.4	0.3
Spain, Ciudad Real	5	0.5	0.4
Spain, Cuenca	6	1.2	0.6
Spain, Girona	25	1.5	0.9
Spain, Granada	12	0.6	0.3
Spain, La Rioja	5	0.7	0.5
Spain, Mallorca	11	0.6	0.4
Spain, Murcia	24	0.7	0.5
Spain, Navarra	25	1.7	1.1
Spain, Tarragona	14	0.8	0.5
Sweden	495	2.2	1.2
Switzerland, Basel	37	3.5	1.7
Switzerland, Geneva	13	1.3	0.7
Switzerland, Graubunden and Glarus	40	7.2	4.0
Switzerland, Neuchatel	6	1.5	0.9
Switzerland, St Gall-Appenzell	58	4.4	2.7
Switzerland, Ticino	17	2.2	1.2
Switzerland, Valais	11	1.5	0.9
Switzerland, Vaud	46	2.9	1.6
Switzerland, Zurich	144	4.6	2.6
The Netherlands	2003	5.0	3.0
The Netherlands, Eindhoven	77	3.0	1.8
UK, England	8224	6.6	3.6

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
UK, England, East of England Region	995	7.3	3.8
UK, England, North Western	1093	6.8	3.6
UK, England, Northern and Yorkshire	1224	7.5	3.9
UK, England, Oxford Region	386	5.6	3.3
UK, England, South and Western Regions	1480	8.8	4.2
UK, England, Thames	1677	5.8	3.6
UK, England, Trent	455	6.2	3.2
UK, England, West Midlands	669	5.1	2.7
UK, Northern Ireland	206	4.9	3.0
UK, Scotland	850	6.9	3.7
UK, Wales	404	5.6	2.7
Ukraine	790	0.7	0.5

Female (all age groups)

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
Austria	149	0.7	0.3
Austria, Tyrol	7	0.4	0.2
Austria, Vorarlberg	5	0.5	0.3
Belarus	161	0.6	0.4
Belgium	162	0.8	0.4
Bulgaria	64	0.3	0.2
Croatia	56	0.5	0.3
Cyprus	11	0.6	0.3
Czech Republic	109	0.4	0.2
Denmark	82	0.6	0..3
Estonia	9	0.2	0.1
Finland	99	0.7	0.3
France, Bas-Rhin	13	0.5	0.2
France, Calvados	19	1.1	0.5
France, Doubs	3	0.2	0.2
France, Haut-Rhin	5	0.3	0.1
France, Herault	20	0.8	0.4
France, Isere	27	0.9	0.5
France, Loire Atlantique	38	1.2	0.5
France, Manche	9	0.7	0.4

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
France, Somme	18	1.3	0.5
France, Tarn	8	0.9	0.4
France, Vendee	8	0.5	0.3
Germany, Brandenburg	50	0.8	0.3
Germany, Bremen	35	2.0	0.8
Germany, Free State of Saxony	86	0.8	0.3
Germany, Hamburg	68	1.5	0.6
Germany, Mecklenburg-Western Pomerania	25	0.6	0.2
Germany, Munich	67	0.7	0.3
Germany, North Rhine-Westphalia	37	0.6	0.2
Germany, Saarland	14	0.5	0.2
Germany, Schleswig-Holstein	78	1.1	0.4
Iceland	2	0.3	0.3
Ireland	27	0.3	0.2
Italy, Alto Adige	3	0.3	0.1
Italy, Biella Province	7	1.4	0.5
Italy, Brescia Province	29	1.3	0.6
Italy, Catania and Messina	23	0.9	0.5
Italy, Catanzaro	2	0.3	0.2
Italy, Ferrara Province	9	1.0	0.3
Italy, Florence and Prato Provinces	13	0.7	0.3
Italy, Friuli-Venezia Giulia	49	1.6	0.6
Italy, Genova Province	64	3.4	1.0
Italy, Latina	3	0.2	0.1
Italy, Lombardy, Como Province	27	1.9	0.8
Italy, Lombardy, Lecco Province	18	2.2	1.1
Italy, Lombardy, Mantova Province	8	1.3	0.6
Italy, Lombardy, Milan	61	2.2	0.8
Italy, Lombardy, Varese Province	51	2.4	0.9
Italy, Modena Province	18	1.1	0.4
Italy, Naples	8	0.6	0.4
Italy, Nuoro	1	0.2	0.1
Italy, Palerme	18	0.7	0.4
Italy, Parma Province	33	3.1	1.3
Italy, Ragusa Province	3	0.4	0.2
Italy, Reggio Emilia Province	26	2.1	1.2
Italy, Romagna Region	26	0.9	0.4
Italy, Salerno Province	25	0.9	0.5

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
Italy, Sassari Province	8	0.7	0.4
Italy, Sondrio	10	2.2	0.9
Italy, South Lombardy	44	4.0	1.3
Italy, Syracuse Province	9	0.9	0.5
Italy, Torino	60	2.6	1.0
Italy, Trapani	6	0.7	0.3
Italy, Trento	8	0.8	0.3
Italy, Umbria Region	19	0.8	0.4
Italy, Veneto Region	38	0.8	0.3
Latvia	28	0.6	0.3
Lithuania	15	0.2	0.1
Malta	3	0.3	0.2
Norway	65	0.6	0.3
Poland, Cracow	11	0.7	0.4
Poland, Kielce	25	0.8	0.4
Poland, Lower Silesia	12	0.2	0.1
Poland, Rzeszow	13	0.2	0.2
Portugal, Azores	1	0.2	0.2
Russia, St Petersburg	88	0.7	0.3
Serbia, Central	16	0.1	0.1
Slovakia	41	0.3	0.2
Slovenia	40	0.8	0.4
Spain, Albacete	1	0.1	0
Spain, Asturias	12	0.4	0.2
Spain, Basque Country	44	0.8	0.4
Spain, Canary Islands	4	0.1	0.1
Spain, Cuenca	1	0.2	0.2
Spain, Girona	6	0.4	0.2
Spain, Granada	2	0.1	0.1
Spain, La Rioja	4	0.5	0.2
Spain, Mallorca	9	0.5	0.2
Spain, Murcia	17	0.5	0.4
Spain, Navarra	17	1.1	0.6
Spain, Tarragona	4	0.2	0.1
Sweden	113	0.5	0.2
Switzerland, Basel	13	1.1	0.6
Switzerland, Geneva	9	0.8	0.4
Switzerland, Graubunden and Glarus	2	0.3	0.2
Switzerland, Neuchatel	1	0.2	0

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
Switzerland, St Gall-Appenzell	7	0.5	0.2
Switzerland, Ticino	3	0.4	0.1
Switzerland, Valais	4	0.5	0.2
Switzerland, Vaud	7	0.4	0.2
Switzerland, Zurich	22	0.7	0.3
The Netherlands	307	0.7	0.4
The Netherlands, Eindhoven	16	0.6	0.3
UK, England	1677	1.3	0.6
UK, England, East of England Region	214	1.5	0.7
UK, England, North Western	208	1.2	0.6
UK, England, Northern and Yorkshire	279	1.6	0.7
UK, England, Oxford Region	67	1.0	0.5
UK, England, South and Western Regions	260	1.5	0.6
UK, England, Thames	403	1.4	0.7
UK, England, Trent	84	1.1	0.5
UK, England, West Midlands	126	0.9	0.4
UK, Northern Ireland	27	0.6	0.3
UK, Scotland	117	0.9	0.4
UK, Wales	70	0.9	0.4
Ukraine	671	0.5	0.3

Malignant Mesothelioma Incidence in Oceania

Male (all age groups)

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
Australia, New South Wales	875	5.2	3.0
Australia, Queensland	492	4.9	3.1
Australia, Tasmania	55	4.7	2.6
Australia, Victoria	518	4.1	2.5
Australian Capital Territory	27	3.3	2.6
New Zealand	398	3.9	2.6
New Zealand: Maori	10	0.7	1.1
New Zealand: Other	382	4.8	2.7
New Zealand: Pacific Islander	6	1.0	1.8
South Australia	222	5.8	3.0
USA, Hawaii	40	1.3	0.8
USA, Hawaii: Chinese	1	0.7	0.2
USA, Hawaii: Filipino	6	1.3	1.3
USA, Hawaii: Hawaiian	8	1.1	1.2
USA, Hawaii: Japanese	11	1.9	0.6
USA, Hawaii: White	13	1.6	0.9
Western Australia	350	6.9	4.5

Female (all age groups)

Population	Cases	Crude Rate, per 100 000	ASR (W), per 100 000
Australia, New South Wales	181	1.1	0.6
Australia, Queensland	92	0.9	0.6
Australia, Tasmania	9	0.7	0.3
Australia, Victoria	112	0.9	0.5
Australian Capital Territory	5	0.6	0.4
New Zealand	60	0.6	0.3
New Zealand: Maori	3	0.2	0.2
New Zealand: Other	56	0.7	0.3
New Zealand: Pacific Islander	1	0.2	0.3
South Australia	49	1.2	0.6
USA, Hawaii	7	0.2	0.2
USA, Hawaii: Japanese	3	0.5	0.4
USA, Hawaii: White	4	0.6	0.4
Western Australia	71	1.4	0.9

EXPOSURE TO ASBESTOS IN 15 EC COUNTRIES* («CAREX», 1990–1993)**

ISIC2 code	ISIC31 code	Sectors of the economy	Working, per year	Exposed	
				per year	at 1000 work
11, 13	01, 05	Agriculture and hunting. Fishing	8 957 988	106 000	1.18
21, 22, 29	10, 11, 14	Coal mining. Crude petroleum and natural gas production. Other mining	1 072 003	84964	7.93
311 – 313	15	Food manufacturing. Beverage industries	3 173 000	50 105	1.58
314	16	Tobacco manufacture	110 900	1	0
321	17	Manufacture of textiles	1 294 000	1281	0.10
331	20	Manufacture of wood and wood and cork products, except	1 041 700	2605	0.25
341	21	Manufacture of paper and paper products	821 100	5300	0.65
342	22	Printing, publishing and allied industries	1 844 600	510	0.03
351, 352	24	Manufacture of industrial chemicals	2 041 800	52 327	2.56
353	23	Petroleum refineries	183 800	9332	5.08
355, 356	25	Manufacture of rubber and plastic products	1 182 100	4280	0.36

* Austria, Belgium, Great Britain, Germany, Greece, Denmark, Ireland, Spain, Italy, Luxemburg, Netherlands, Portugal, Finland, France, Sweden

** © CAREX: Industry Specific Estimates – Summary // Carcinogenic exposure information for the European Union (previous EU-15 combined) / Finnish Institute of Occupational Health (FIOH). – Access to: http://www.ttl.fi/en/chemical_safety/carex/Documents/5_exposures_by_agent_and_industry.pdf

ISIC2 code	ISIC31 code	Sectors of the economy	Working, per year	Exposed	
				per year	at 1000 work
362, 369	26	Manufacture of glass and glass products. Manufacture of other non-metallic mineral products	1 166 100	4347	0.37
371, 372	27	Iron and steel basic industries. Non-ferrous metal basic industries	1 251 300	4201	0.34
381	28	Manufacture of fabricated metal products, except machinery	3 161 100	7736	0.24
382	29	Manufacture of machinery except electrical	3 155 200	12 497	0.40
383	30 — 32	Manufacture of electrical machinery, apparatus, appliances	22 949	2716	11.83
384	34 — 35	Manufacture of transport equipment	20 003	17 287	86.42
385	33	Manufacture of instruments, photographic and optical goods	707 900	1087	0.15
39	39	Other manufacturing industries	4 117 500	375	0.01
41, 42	40, 41	Electricity, gas and steam. Water works and supply	5 877 391	23 490	0.40
5	45	Construction	11 886 300	573 902	4.83
6	50 — 52	Wholesale and retail trade and restaurants and hotels	26 236 979	70 041	0.27

ISIC2 code	ISIC31 code	Sectors of the economy	Working, per year	Exposed	
				per year	at 1000 work
711-713, 719, 72	60—64	Land, water, air transports. Services allied to transport. Communication	9 493 585	62 001	0.65
8	65—67, 70	Financing, insurance, real estate and business services	86 38 279	2000	0.02
92, 931, 933, 95	80, 85, 90, 95	Sanitary and similar services. Medical, dental, other health and veterinary services. Education services. Personal and household services. Other	57 886 816,3	117 933	0.20
In all			**155 344 393**	**1 105 971**	**0.71**

ILO CONVENTION NO. 162 * CONVENTION CONCERNING SAFETY IN THE USE OF ASBESTOS

(Entry into force: 16 June 1989)

Preamble

The General Conference of the International Labour Organisation,

Having been convened at Geneva by the Governing Body of the International Labour Office, and having met in its Seventy-second Session on 4 June 1986, and

Noting the relevant international labour Conventions and Recommendations, and in particular the Occupational Cancer Convention and Recommendation, 1974, the Working Environment (Air Pollution, Noise and Vibration) Convention and Recommendation, 1977, the Occupational Safety and Health Convention and Recommendation, 1981, the Occupational Health Services Convention and Recommendation, 1985, the list of occupational diseases as revised in 1980 appended to the Employment Injury Benefits Convention, 1964, as well as the Code of practice on safety in the use of asbestos, published by the International Labour Office in 1984, which establish the principles of national policy and action at the national level,

Having decided upon the adoption of certain proposals with regard to safety in the use of asbestos, which is the fourth item on the agenda of the session, and

Having determined that these proposals shall take the form of an international Convention;

adopts this twenty-fourth day of June of the year one thousand nine hundred and eighty-six the following Convention, which may be cited as the Asbestos Convention, 1986:

PART I. SCOPE AND DEFINITIONS

Article 1

1. This Convention applies to all activities involving exposure of workers to asbestos in the course of work.

2. A Member ratifying this Convention may, after consultation with the most representative organisations of employers and workers concerned, and on the basis of an assessment of the health hazards involved and the safety measures applied, exclude particular branches

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of economic activity or particular undertakings from the application of certain provisions of the Convention when it is satisfied that their application to these branches or undertakings is unnecessary.

3. The competent authority, when deciding on the exclusion of particular branches of economic activity or particular undertakings, shall take into account the frequency, duration and level of exposure, as well as the type of work and the conditions at the workplace.

Article 2

For the purpose of this Convention:

(a) the term asbestos means the fibrous form of mineral silicates belonging to rock-forming minerals of the serpentine group, i.e. chrysotile (white asbestos), and of the amphibole group, i.e. actinolite, amosite (brown asbestos, cummingtonite-grunerite), anthophyllite, crocidolite (blue asbestos), tremolite, or any mixture containing one or more of these;

(b) the term asbestos dust means airborne particles of asbestos or settled particles of asbestos which are liable to become airborne in the working environment;

(c) the term airborne asbestos dust means, for purposes of measurement, dust particles measured by gravimetric assessment or other equivalent method;

(d) the term respirable asbestos fibres means asbestos fibres having a diameter of less than 3 micrometre and a length-to-diameter ratio greater than 3:1. Only fibres of a length greater than 5 micrometre shall be taken into account for purposes of measurement;

(e) the term exposure to asbestos means exposure at work to airborne respirable asbestos fibres or asbestos dust, whether originating from asbestos or from minerals, materials or products containing asbestos;

(f) the term workers includes the members of production co-operatives;

(g) the term *workers' representatives* means the workers' representatives recognised as such by national law or practice, in conformity with the Workers' Representatives Convention, 1971.

PART II. GENERAL PRINCIPLES

Article 3

1. National laws or regulations shall prescribe the measures to be taken for the prevention and control of, and protection of workers against, health hazards due to occupational exposure to asbestos.

2. National laws and regulations drawn up in pursuance of paragraph 1 of this Article shall be periodically reviewed in the light of

technical progress and advances in scientific knowledge.

3. The competent authority may permit temporary derogations from the measures prescribed pursuant to paragraph 1 of this Article, under conditions and within limits of time to be determined after consultation with the most representative organisations of employers and workers concerned.

4. In granting derogations in pursuance of paragraph 3 of this Article, the competent authority shall ensure that the necessary precautions are taken to protect the workers' health.

Article 4

The competent authority shall consult the most representative organisations of employers and workers concerned on the measures to be taken to give effect to the provisions of this Convention.

Article 5

1. The enforcement of the laws and regulations adopted pursuant to Article 3 of this Convention shall be secured by an adequate and appropriate system of inspection.

2. National laws or regulations shall provide for the necessary measures, including appropriate penalties, to ensure effective enforcement of and compliance with the provisions of this Convention.

Article 6

1. Employers shall be made responsible for compliance with the prescribed measures.

2. Whenever two or more employers undertake activities simultaneously at one workplace, they shall co-operate in order to comply with the prescribed measures, without prejudice to the responsibility of each employer for the health and safety of the workers he employs. The competent authority shall prescribe the general procedures of this co-operation when it is necessary.

3. Employers shall, in co-operation with the occupational safety and health services, and after consultation with the workers' representatives concerned, prepare procedures for dealing with emergency situations.

Article 7

Workers shall be required, within the limits of their responsibility, to comply with prescribed safety and hygiene procedures relating to the prevention and control of, and protection against, health hazards due to occupational exposure to asbestos.

Article 8

Employers and workers or their representatives shall co-operate as closely as possible at all levels in the undertaking in the application of the measures prescribed pursuant to this Convention.

PART III. PROTECTIVE AND PREVENTIVE MEASURES

Article 9

The national laws or regulations adopted pursuant to Article 3 of this Convention shall provide that exposure to asbestos shall be prevented or controlled by one or more of the following measures:

(a) making work in which exposure to asbestos may occur subject to regulations prescribing adequate engineering controls and work practices, including workplace hygiene;

(b) prescribing special rules and procedures, including authorisation, for the use of asbestos or of certain types of asbestos or products containing asbestos or for certain work processes.

Article 10

Where necessary to protect the health of workers and technically practicable, national laws or regulations shall provide for one or more of the following measures:

(a) replacement of asbestos or of certain types of asbestos or products containing asbestos by other materials or products or the use of alternative technology, scientifically evaluated by the competent authority as harmless or less harmful, whenever this is possible;

(b) total or partial prohibition of the use of asbestos or of certain types of asbestos or products containing asbestos in certain work processes.

Article 11

1. The use of crocidolite and products containing this fibre shall be prohibited.

2. The competent authority shall be empowered, after consultation with the most representative organisations of employers and workers concerned, to permit derogations from the prohibition contained in paragraph 1 of this Article when replacement is not reasonably practicable, provided that steps are taken to ensure that the health of workers is not placed at risk.

Article 12

1. Spraying of all forms of asbestos shall be prohibited.

2. The competent authority shall be empowered, after consultation with the most representative organisations of employers and workers concerned, to permit derogations from the prohibition contained in paragraph 1 of this Article when alternative methods are not reasonably practicable, provided that steps are taken to ensure that the health of workers is not placed at risk.

Article 13

National laws and regulations shall provide that employers shall notify to the competent authority, in a manner and to the extent pre-

scribed by it, certain types of work involving exposure to asbestos.

Article 14

Producers and suppliers of asbestos and manufacturers and suppliers of products containing asbestos shall be made responsible for adequate labelling of the container and, where appropriate, the products, in a language and manner easily understood by the workers and the users concerned, as prescribed by the competent authority.

Article 15

1. The competent authority shall prescribe limits for the exposure of workers to asbestos or other exposure criteria for the evaluation of the working environment.

2. The exposure limits or other exposure criteria shall be fixed and periodically reviewed and updated in the light of technological progress and advances in technological and scientific knowledge.

3. In all workplaces where workers are exposed to asbestos, the employer shall take all appropriate measures to prevent or control the release of asbestos dust into the air, to ensure that the exposure limits or other exposure criteria are complied with and also to reduce exposure to as low a level as is reasonably practicable.

4. When the measures taken in pursuance of paragraph 3 of this Article do not bring exposure to asbestos within the exposure limits or do not comply with the other exposure criteria specified in pursuance of paragraph 1 of this Article, the employer shall provide, maintain and replace, as necessary, at no cost to the workers, adequate respiratory protective equipment and special protective clothing as appropriate. Respiratory protective equipment shall comply with standards set by the competent authority, and be used only as a supplementary, temporary, emergency or exceptional measure and not as an alternative to technical control.

Article 16

Each employer shall be made responsible for the establishment and implementation of practical measures for the prevention and control of the exposure of the workers he employs to asbestos and for their protection against the hazards due to asbestos.

Article 17

1. Demolition of plants or structures containing friable asbestos insulation materials, and removal of asbestos from buildings or structures in which asbestos is liable to become airborne, shall be undertaken only by employers or contractors who are recognised by the competent authority as qualified to carry out such work in accordance with the provisions of this Convention and who have been empowered to undertake such work.

2. The employer or contractor shall be required before starting demolition work to draw up a work plan specifying the measures to be taken, including measures to:

(a) provide all necessary protection to the workers;

(b) limit the release of asbestos dust into the air; and

(c) provide for the disposal of waste containing asbestos in accordance with Article 19 of this Convention.

3. The workers or their representatives shall be consulted on the work plan referred to in paragraph 2 of this Article.

Article 18

1. Where workers' personal clothing may become contaminated with asbestos dust, the employer, in accordance with national laws or regulations and in consultation with the workers' representatives, shall provide appropriate work clothing, which shall not be worn outside the workplace.

2. The handling and cleaning of used work clothing and special protective clothing shall be carried out under controlled conditions, as required by the competent authority, to prevent the release of asbestos dust.

3. National laws or regulations shall prohibit the taking home of work clothing and special protective clothing and of personal protective equipment.

4. The employer shall be responsible for the cleaning, maintenance and storage of work clothing, special protective clothing and personal protective equipment.

5. The employer shall provide facilities for workers exposed to asbestos to wash, take a bath or shower at the workplace, as appropriate.

Article 19

1. In accordance with national law and practice, employers shall dispose of waste containing asbestos in a manner that does not pose a health risk to the workers concerned, including those handling asbestos waste, or to the population in the vicinity of the enterprise.

2. Appropriate measures shall be taken by the competent authority and by employers to prevent pollution of the general environment by asbestos dust released from the workplace.

PART IV. SURVEILLANCE OF THE WORKING ENVIRONMENT AND WORKERS' HEALTH

Article 20

1. Where it is necessary for the protection of the health of workers, the employer shall measure the concentrations of airborne asbestos dust in workplaces, and shall monitor the exposure of workers to as-

bestos at intervals and using methods specified by the competent authority.

2. The records of the monitoring of the working environment and of the exposure of workers to asbestos shall be kept for a period prescribed by the competent authority.

3. The workers concerned, their representatives and the inspection services shall have access to these records.

4. The workers or their representatives shall have the right to request the monitoring of the working environment and to appeal to the competent authority concerning the results of the monitoring.

Article 21

1. Workers who are or have been exposed to asbestos shall be provided, in accordance with national law and practice, with such medical examinations as are necessary to supervise their health in relation to the occupational hazard, and to diagnose occupational diseases caused by exposure to asbestos.

2. The monitoring of workers' health in connection with the use of asbestos shall not result in any loss of earnings for them. It shall be free of charge and, as far as possible, shall take place during working hours.

3. Workers shall be informed in an adequate and appropriate manner of the results of their medical examinations and receive individual advice concerning their health in relation to their work.

4. When continued assignment to work involving exposure to asbestos is found to be medically inadvisable, every effort shall be made, consistent with national conditions and practice, to provide the workers concerned with other means of maintaining their income.

5. The competent authority shall develop a system of notification of occupational diseases caused by asbestos.

PART V. INFORMATION AND EDUCATION

Article 22

1. The competent authority shall make appropriate arrangements, in consultation and collaboration with the most representative organisations of employers and workers concerned, to promote the dissemination of information and the education of all concerned with regard to health hazards due to exposure to asbestos and to methods of prevention and control.

2. The competent authority shall ensure that employers have established written policies and procedures on measures for the education and periodic training of workers on asbestos hazards and methods of prevention and control.

3. The employer shall ensure that all workers exposed or likely to be exposed to asbestos are informed about the health hazards related to their work, instructed in preventive measures and correct work practices and receive continuing training in these fields.

PART VI. FINAL PROVISIONS

Article 23

The formal ratifications of this Convention shall be communicated to the Director-General of the International Labour Office for registration.

Article 24

1. This Convention shall be binding only upon those Members of the International Labour Organisation whose ratifications have been registered with the Director-General.

2. It shall come into force twelve months after the date on which the ratifications of two Members have been registered with the Director-General.

3. Thereafter, this Convention shall come into force for any Member twelve months after the date on which its ratification has been registered.

Article 25

1. A Member which has ratified this Convention may denounce it after the expiration of ten years from the date on which the Convention first comes into force, by an act communicated to the Director-General of the International Labour Office for registration. Such denunciation shall not take effect until one year after the date on which it is registered.

2. Each Member which has ratified this Convention and which does not, within the year following the expiration of the period of ten years mentioned in the preceding paragraph, exercise the right of denunciation provided for in this Article, will be bound for another period of ten years and, thereafter, may denounce this Convention at the expiration of each period of ten years under the terms provided for in this Article.

Article 26

1. The Director-General of the International Labour Office shall notify all Members of the International Labour Organisation of the registration of all ratifications and denunciations communicated to him by the Members of the Organisation.

2. When notifying the Members of the Organisation of the registration of the second ratification communicated to him, the Director-General shall draw the attention of the Members of the Organisation to the date upon which the Convention will come into force.

Article 27

The Director-General of the International Labour Office shall communicate to the Secretary-General of the United Nations for registration in accordance with Article 102 of the Charter of the United Nations full particulars of all ratifications and acts of denunciation registered by him in accordance with the provisions of the preceding Articles.

Article 28

At such times as it may consider necessary the Governing Body of the International Labour Office shall present to the General Conference a report on the working of this Convention and shall examine the desirability of placing on the agenda of the Conference the question of its revision in whole or in part.

Article 29

1 Should the Conference adopt a new Convention revising this Convention in whole or in part, then, unless the new Convention otherwise provides:

(a) the ratification by a Member of the revising Convention shall ipso jure involve the immediate denunciation of this Convention, notwithstanding the provisions of Article 25 above, if and when the new revising Convention shall have come into force;

(b) as from the date when the new revising Convention comes into force this Convention shall cease to be open to ratification by the Members.

2. This Convention shall in any case remain in force in its actual form and content for those Members which have ratified it but have not ratified the revising Convention.

Article 30

The English and French versions of the text of this Convention are equally authoritative.

ILO RECOMMENDATION No. 172*
Recommendation concerning Safety in the Use of Asbestos

Preamble

The General Conference of the International Labour Organisation,

Having been convened at Geneva by the Governing Body of the International Labour Office, and having met in its Seventy-second Session on 4 June 1986, and

Noting the relevant international labour Conventions and Recommendations, and in particular the Occupational Cancer Convention and Recommendation, 1974, the Working Environment (Air Pollution, Noise and Vibration) Convention and Recommendation, 1977, the Occupational Safety and Health Convention and Recommendation, 1981, the Occupational Health Services Convention and Recommendation, 1985, the list of occupational diseases as revised in 1980 appended to the Employment Injury Benefits Convention, 1964, as well as the Code of practice on safety in the use of asbestos,published by the International Labour Office in 1984, which establish the principles of national policy and action at the national level, and

Having decided upon the adoption of certain proposals with regard to safety in the use of asbestos, which is the fourth item on the agenda of the session, and

Having determined that these proposals shall take the form of a Recommendation supplementing the Asbestos Convention, 1986,

adopts this twenty-fourth day of June of the year one thousand nine hundred and eighty-six, the following Recommendation, which may be cited as the Asbestos Recommendation, 1986;

I. Scope and Definitions

1.

(1) The provisions of the Asbestos Convention, 1986, and of this Recommendation should be applied to all activities involving a risk of exposure of workers to asbestos in the course of work.

(2) Measures should be taken, in accordance with national law and practice, to afford to self-employed persons protection analogous to that provided for in the Asbestos Convention, 1986, and in this Recommendation.

(3) Employment of young persons of less than 18 years of age in activities involving a risk of occupational exposure to asbestos should receive special attention, as required by the competent authority.

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2. Activities involving a risk of occupational exposure to asbestos should include in particular:

(a) mining and milling of minerals containing asbestos;

(b) manufacture of materials or products containing asbestos;

(c) use or application of products containing asbestos;

(d) stripping, repair or maintenance of products containing asbestos;

(e) demolition or repair of plant or structure containing asbestos;

(f) transportation, storage and handling of asbestos or materials containing asbestos;

(g) other activities involving a risk of exposure to airborne asbestos dust.

3. For the purpose of this Recommendation:

(a) the term asbestos means the fibrous form of mineral silicate belonging to rock-forming minerals of the serpentine group, i.e. chrysotile (white asbestos), and of the amphibole group, i.e. actinolite amosite (brown asbestos, cummingtonite-grunerite), anthophyllite, crocidolite (blue asbestos) , tremolite, or any mixture containing one or more of these;

(b) the term asbestos dust means airborne particles of asbestos or settled particles of asbestos which are liable to become airborne in the working environment;

(c) the term airborne asbestos dust means, for purposes of measurement, dust particles measured by gravimetric assessment or other equivalent method;

(d) the term respirable asbestos fibres means asbestos fibres having a diameter of less than 3 Wm, and a length-to-diameter ratio greater than 3:1. Only fibres of a length greater than 5 Wm should be taken into account for the purpose of measurement;

(e) the term exposure to asbestos means exposure at work to airborne respirable asbestos fibres or asbestos dust, whether originating from asbestos or from minerals, materials or products containing asbestos;

(f) the term workers includes the members of production co-operatives;

(g) the term workers' representatives means the workers' representatives recognised as such by national law or practice, in conformity with the Workers' Representatives Convention, 1971.

II. General Principles

4. The measures prescribed pursuant to Article 3 of the Asbestos Convention, 1986, should be so framed as to cover the diversity of

risks of occupational exposure to asbestos in all branches of economic activity, and should be drawn up with due regard to Articles 1 and 2 of the Occupational Cancer Convention, 1974.

5. The competent authority should periodically review the measures prescribed, taking into account the Code of practice on safety in the use of asbestos published by the International Labour Office and other codes of practice or guides which may be established by the International Labour Office and the conclusions of meetings of experts which may be convened by it, as well as information from other competent bodies on asbestos and substitute materials.

6. The competent authority, in the application of the provisions of this Recommendation, should act after consultation with the most representative organisations of employers and workers.

7.

(1) The employer should use all appropriate measures, in consultation and co-operation with the workers concerned or their representatives and in the light of advice from competent sources, including occupational health services, to prevent or control exposure to asbestos.

(2) In accordance with national law and practice, consultation and co-operation between an employer and the workers he employs might be carried out through:

(a) workers' safety delegates;

(b) workers' safety and health committees or joint safety and health committees;

(c) other workers' representatives.

8. Workers engaged in work with asbestos or products containing asbestos should be required within the limits of their responsibility to comply with the prescribed safety and hygiene procedures, including the use of adequate protective equipment.

9.

(1) A worker who has removed himself from a work situation which he has reasonable justification to believe presents serious danger to his life or health should:

(a) alert his immediate supervisor;

(b) be protected from retaliatory or disciplinary measures, in accordance with national conditions and practice.

(2) No measure prejudicial to a worker should be taken by reference to the fact that, in good faith, he complained of what he considered to be a breach of statutory requirements or a serious inadequacy in the measures taken by the employer in respect of occupational safety and health and the working environment.

III. Protective and Preventive Measures

10.

(1) The competent authority should ensure that exposure to asbestos is prevented or controlled by prescribing engineering controls and work practices, including workplace hygiene, which afford maximum protection to workers.

(2) The competent authority should periodically determine, on the basis of the level of exposure and the circumstances and conditions prevailing in the working environment, and in the light of scientific research and technological progress:

(a) the types of asbestos and products containing asbestos whose use should be subject to authorisation and the work processes which should be subject to authorisation;

(b) the types of asbestos and products containing asbestos whose use should be totally or partially prohibited and the work processes in which the use of asbestos or certain types of asbestos or products containing asbestos should be prohibited.

(3) The prohibition or authorisation of the use of certain types of asbestos or products containing asbestos and their replacement by other substances should be based on scientific assessment of their danger to health.

11.

(1) The competent authority should encourage research into technical and health problems relating to exposure to asbestos, substitute materials and alternative technologies.

(2) The competent authority should encourage research into and development of products containing asbestos, other substitute materials or alternative technologies which are harmless or less harmful, with a view to eliminating or decreasing the risk for the workers.

12.

(1) The competent authority, wherever necessary for the protection of the workers, should require the replacement of asbestos by substitute materials, wherever possible.

(2) Before being accepted for use in any process, all potential substitute materials should be thoroughly evaluated for their possible harmful effects on health. The health of workers exposed to such materials should be continuously supervised, if judged necessary.

13.

(1) With a view to the effective enforcement of the national laws and regulations, the competent authority should prescribe the information to be supplied in the notifications of work with asbestos provided for in Article 13 of the Asbestos Convention, 1986.

(2) This information should include in particular the following:

(a) the type and quantity of asbestos used;

(b) the activities and processes carried out;

(c) the products manufactured;

(d) the number of workers exposed and the level and frequency of their exposure;

(e) the preventive and protective measures taken to comply with the national laws and regulations;

(f) any other information necessary to safeguard the workers' health.

14.

(1) Demolition of those parts of plants or structures which contain friable asbestos insulation materials, and removal of asbestos from buildings or structures in which asbestos is liable to become airborne, should be subject to authorisation, which should be granted only to employers or contractors who are recognised by the competent authority as qualified to carry out such work in accordance with the provisions of this Recommendation.

(2) The employer or contractor should be required before starting demolition or removal work to draw up a work plan specifying the measures to be taken before the commencement of work, including measures to:

(a) provide all necessary protection to the workers;

(b) limit the release of asbestos dust into the air;

(c) inform workers who may be affected of the possible release of asbestos dust into the air, of the general procedures and equipment to be used, and of the precautions to be taken; and

(d) provide for the disposal of waste containing asbestos in accordance with Paragraph 28 of this Recommendation.

(3) The workers or their representatives should be consulted concerning the work plan referred to in subparagraph (2) above.

15.

(1) Each employer should establish and implement, with the participation of the workers he employs, a programme for the prevention and control of the workers' exposure to asbestos. This programme should be reviewed at regular intervals and in the light of changes in the work processes and machinery used or in the techniques and methods of prevention and control.

(2) The competent authority should, in accordance with national practice, undertake activities to assist in particular small undertakings, where technical knowledge or means may be lacking, with the establishment of preventive programmes in cases in which exposure to asbestos may occur.

16. Technical protective appliances and appropriate work practices should be adopted to prevent the release of asbestos dust into the air of workplaces. Even where exposure limits or other exposure criteria are complied with, such measures should be taken so as to reduce the exposure to as low a level as is reasonably practicable.

17. The measures to be taken to prevent or control the exposure, and to avoid exposure, of workers to asbestos should include in particular the following:

(a) asbestos should be used only when its risks can be prevented or controlled; otherwise, it should be replaced, when technically feasible, by other materials or the use of alternative technologies, scientifically evaluated as harmless or less harmful;

(b) the number of persons assigned to work involving exposure to asbestos and the duration of their exposure should be kept to the minimum required for the safe performance of the task;

(c) machinery, equipment and work processes should be used which eliminate or minimise the formation of asbestos dust, and particularly its release into the working and general environment;

(d) workplaces where the use of asbestos may result in the release of asbestos dust into the air should be separated from the general working environment in order to avoid possible exposure of other workers to asbestos;

(e) the areas of activity which involve exposure to asbestos should be clearly demarcated and indicated by warning signs restricting unauthorised access;

(f) the location of asbestos used in the construction of premises should be recorded.

18.

(1) The use of crocidolite and products containing this fibre should be prohibited.

(2) The competent authority should be empowered, after consultation with the most representative organisations of employers and workers concerned, to permit derogations from the prohibition contained in subparagraph (1) above when replacement is not reasonably practicable, provided that steps are taken to ensure that the health of workers is not placed at risk.

19.

(1) Spraying of all forms of asbestos should be prohibited.

(2) The installation of friable asbestos insulation materials should be prohibited.

(3) The competent authority should be empowered, after consultation with the most representative organisations of employers and

workers concerned, to permit derogations from the prohibition contained in subparagraphs (1) and (2) above when alternative methods are not reasonably practicable, provided that steps are taken to ensure that the health of workers is not placed at risk.

20.

(1) Producers and suppliers of asbestos and manufacturers and suppliers of products containing asbestos should be made responsible for the appropriate and adequate labelling of the container or product.

(2) National laws or regulations should require that the label be printed in the language or languages in common use in the country concerned and indicate that the container or product contains asbestos, that the inhalation of asbestos dust carries a health risk, and that appropriate protective measures should be taken.

(3) National laws or regulations should require producers and suppliers of asbestos and manufacturers and suppliers of products containing asbestos to develop and provide a data sheet listing the asbestos content, health hazards and appropriate protective measures for the material or product.

21. The system of inspection provided for in Article 5 of the Asbestos Convention, 1986, should be based on the provisions of the Labour Inspection Convention, 1947. Inspection should be carried out by qualified personnel. The inspection services should be able to obtain from the employer the information referred to in Paragraph 13 above.

22.

(1) The exposure limits should be fixed by reference to the time-weighted concentration of airborne asbestos dust, commonly expressed in terms of an eight-hour day and a 40-hour week, and to a recognised method of sampling and measuring.

(2) The exposure limits should be periodically reviewed and updated in the light of technological progress and advances in technical and medical knowledge.

23. The installations, ventilation systems, machinery and protective appliances for asbestos dust control should be regularly checked and maintained in good working order.

24. Workplaces should be cleaned by a safe method as frequently as is necessary to prevent the accumulation of asbestos dust on surfaces. The provisions of the Asbestos Convention, 1986, and this Recommendation should apply to the cleaning staff.

25.

(1) When hazards from airborne asbestos dust cannot be otherwise prevented or controlled, the employer should provide, maintain and replace as necessary, at no cost to the workers, adequate respiratory

protective equipment and special clothing as appropriate. In such situations, the workers should be required to use such equipment.

(2) Respiratory protective equipment should comply with standards set by the competent authority and be used only as a supplementary, temporary, emergency or exceptional measure and not as an alternative to technical control.

(3) When the use of respiratory equipment is required, adequate rest breaks in appropriate rest areas should be provided for, taking into account the physical strain caused by the use of such equipment.

26.

(1) Where workers' personal clothing may become contaminated with asbestos dust, the employer, in accordance with national laws or regulations and in consultation with the workers' representatives, should provide at no cost to the worker appropriate work clothing, which should not be worn outside the workplace.

(2) Employers should provide workers with adequate information in an appropriate form on the health hazards to their families or others which could result from taking home clothing contaminated by asbestos dust.

(3) The handling and cleaning of used work clothing and special protective clothing should be carried out under controlled conditions, as required by the competent authority, to prevent the release of asbestos dust.

27.

(1) For workers who are exposed to asbestos, double changing rooms, washing facilities, showers and rest areas, as appropriate, should be provided.

(2) Adequate time should be allowed, within working hours, for changing, showering or washing after the work shift, in accordance with national practice.

28.

(1) In accordance with national law and practice, employers should dispose of waste containing asbestos in a manner that does not pose a health risk to the workers concerned, including those handling asbestos waste, or to the population in the vicinity of the enterprise.

(2) Appropriate measures should be taken by the competent authority and by employers to prevent pollution of the general environment by asbestos dust released from the workplace.

IV. Surveillance of the Working Environment and Workers' Health

29. In cases determined by the competent authority, the employer should make arrangements for systematic surveillance of the concen-

tration of airborne asbestos dust in the workplace and of the duration and level of exposure of workers to asbestos and for the surveillance of the workers' health.

30.

(1) The level of exposure of workers to asbestos should be measured or calculated in terms of time-weighted average concentrations for a specific reference period.

(2) The sampling and measurement of the concentration of airborne asbestos dust should be carried out by qualified personnel, using methods approved by the competent authority.

(3) The frequency and extent of sampling and measurement should be related to the level of risk, to changes in the work processes or other relevant circumstances.

(4) In evaluating the risk the competent authority should take into consideration the risk posed by all sizes of asbestos fibres.

31.

(1) For the prevention of disease and functional impairment related to exposure to asbestos, all workers assigned to work involving exposure to asbestos should be provided, as appropriate, with:

(a) a pre-assignment medical examination;

(b) periodic medical examinations at appropriate intervals;

(c) other tests and investigations, in particular chest radiographs and lung function tests, which may be necessary to supervise their state of health in relation to the occupational hazard and to identify early indicators of disease caused by asbestos.

(2) The intervals between medical examinations should be determined by the competent authority, taking into account the level of exposure and the workers' state of health in relation to the occupational hazard.

(3) The competent authority should ensure that provision is made, in accordance with national law and practice, for appropriate medical examinations to continue to be available to workers after termination of an assigment involving exposure to asbestos.

(4) The examinations, tests and investigations provided for in subparagraphs (1) and (3) above should be carried out as far as possible in working hours and should entail no cost to the worker.

(5) Where the results of medical tests or investigations reveal clinical or preclinical effects, measures should be taken to prevent or reduce exposure of the workers concerned and to prevent further deterioration of their health.

(6) Results of medical examinations should be used to determine health status with regard to exposure to asbestos and should not be

used to discriminate against the worker.

(7) The results of medical examinations should be used to help place the worker in a job which is compatible with the status of his health.

(8) Workers subject to supervision of their health should have:

(a) the right to confidentiality of personal and medical information;

(b) the right to full and detailed explanations of the purposes and results of the supervision;

(c) the right to refuse invasive medical procedures which infringe on their corporal integrity.

32. Workers should be informed in an adequate and appropriate manner, in accordance with national practice, of the results of the medical examinations and receive individual advice concerning their health in relation to their work.

33. When an occupational disease caused by asbestos has been detected by health surveillance, the competent authority should be notified in conformity with national law and practice.

34. When continued assignment to work involving exposure to asbestos is found to be medically inadvisable every effort should be made, consistent with national conditions and practice, to provide the workers concerned with other means of maintaining their income.

35. National laws or regulations should provide for the compensation of workers who contract a disease or develop a functional impairment related to occupational exposure to asbestos, in accordance with the Employment Injury Benefits Convention, 1964.

36.

(1) The records of the monitoring of the working environment should be kept for a period of not less than 30 years.

(2) Records of the monitoring of exposure of workers as well as the sections of their medical files relevant to health hazards due to exposure to asbestos and chest radiographs should be kept for a period of not less than 30 years following termination of an assignment involving exposure to asbestos.

37. The workers concerned, their representatives and the inspection services should have access to the records of the monitoring of the working environment.

38. In the case of closure of an undertaking, or after termination of engagement of a worker, records and information kept in accordance with Paragraph 36 above should be deposited in accordance with the directions of the competent authority.

39. In accordance with the Tripartite Declaration of Principles concerning Multinational Enterprises and Social Policy, adopted by the

Governing Body of the International Labour Office, a national or multinational enterprise with more than one establishment should be required to provide safety measures relating to the prevention and control of, and protection against, health hazards due to occupational exposure to asbestos, without discrimination, to the workers in all its establishments regardless of the place or country in which they are situated.

V. Information and Education

40. The competent authority should take measures to promote the training and information of all persons concerned with respect to the prevention and control of, and protection against, health hazards due to occupational exposure to asbestos.

41. The competent authority, in consultation with the most representative organisations of employers and workers concerned, should draw up suitable educational guides for employers, workers and others.

42. Employers should ensure that workers liable to be exposed to asbestos receive periodic training and instructions, at no cost to them, in a language and manner which are easily understood by them, on the effects of such exposure on health, on measures to be taken to prevent and control exposure to asbestos, especially on correct work practices which prevent and control the formation and release of asbestos dust into the air and on the use of the general and personal protective equipment placed at the workers' disposal.

43. Educational measures should draw attention to the particular danger to the health of workers created by the combination of smoking and exposure to asbestos.

44. Employers' and workers' organisations should take positive action to cooperate in and contribute to programmes of training, information, prevention, control and protection in relation to occupational hazards due to exposure to asbestos.

ILO CONVENTION No. 139*
Convention concerning Prevention and Control of Occupational Hazards caused by Carcinogenic Substances and Agents

(Entry into force: 10 June 1976)

Preamble

The General Conference of the International Labour Organisation,

Having been convened at Geneva by the Governing Body of the International Labour Office, and having met in its Fifty-ninth Session on 5 June 1974, and

Noting the terms of the Radiation Protection Convention and Recommendation, 1960, and of the Benzene Convention and Recommendation, 1971, and

Considering that it is desirable to establish international standards concerning protection against carcinogenic substances or agents, and

Taking account of the relevant work of other international organisations, and in particular of the World Health Organisation and the International Agency for Research on Cancer, with which the International Labour Organisation collaborates, and

Having decided upon the adoption of certain proposals regarding control and prevention of occupational hazards caused by carcinogenic substances and agents, which is the fifth item on the agenda of the session, and

Having determined that these proposals shall take the form of an international Convention,

adopts this twenty-fourth day of June of the year one thousand nine hundred and seventy-four the following Convention, which may be cited as the Occupational Cancer Convention, 1974:

Article 1

1. Each Member which ratifies this Convention shall periodically determine the carcinogenic substances and agents to which occupational exposure shall be prohibited or made subject to authorisation or control, and those to which other provisions of this Convention shall apply.

2. Exemptions from prohibition may only be granted by issue of a certificate specifying in each case the conditions to be met.

3. In making the determinations required by paragraph 1 of this Article, consideration shall be given to the latest information contained in the codes of practice or guides which may be established by the

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International Labour Office, as well as to information from other competent bodies.

Article 2

1. Each Member which ratifies this Convention shall make every effort to have carcinogenic substances and agents to which workers may be exposed in the course of their work replaced by non-carcinogenic substances or agents or by less harmful substances or agents; in the choice of substitute substances or agents account shall be taken of their carcinogenic, toxic and other properties.

2. The number of workers exposed to carcinogenic substances or agents and the duration and degree of such exposure shall be reduced to the minimum compatible with safety.

Article 3

Each Member which ratifies this Convention shall prescribe the measures to be taken to protect workers against the risks of exposure to carcinogenic substances or agents and shall ensure the establishment of an appropriate system of records.

Article 4

Each Member which ratifies this Convention shall take steps so that workers who have been, are, or are likely to be exposed to carcinogenic substances or agents are provided with all the available information on the dangers involved and on the measures to be taken.

Article 5

Each Member which ratifies this Convention shall take measures to ensure that workers are provided with such medical examinations or biological or other tests or investigations during the period of employment and thereafter as are necessary to evaluate their exposure and supervise their state of health in relation to the occupational hazards.

Article 6

Each Member which ratifies this Convention:

(a) shall, by laws or regulations or any other method consistent with national practice and conditions and in consultation with the most representative organisations of employers and workers concerned, take such steps as may be necessary to give effect to the provisions of this Convention;

(b) shall, in accordance with national practice, specify the persons or bodies on whom the obligation of compliance with the provisions of this Convention rests;

(c) undertakes to provide appropriate inspection services for the purpose of supervising the application of this Convention, or to satisfy itself that appropriate inspection is carried out.

Article 7

The formal ratifications of this Convention shall be communicated to the Director-General of the International Labour Office for registration.

Article 8

1. This Convention shall be binding only upon those Members of the International Labour Organisation whose ratifications have been registered with the Director-General.

2. It shall come into force twelve months after the date on which the ratifications of two Members have been registered with the Director-General.

3. Thereafter, this Convention shall come into force for any Member twelve months after the date on which its ratification has been registered.

Article 9

1. A Member which has ratified this Convention may denounce it after the expiration of ten years from the date on which the Convention first comes into force, by an act communicated to the Director-General of the International Labour Office for registration. Such denunciation shall not take effect until one year after the date on which it is registered.

2. Each Member which has ratified this Convention and which does not, within the year following the expiration of the period of ten years mentioned in the preceding paragraph, exercise the right of denunciation provided for in this Article, will be bound for another period of ten years and, thereafter, may denounce this Convention at the expiration of each period of ten years under the terms provided for in this Article.

Article 10

1. The Director-General of the International Labour Office shall notify all Members of the International Labour Organisation of the registration of all ratifications and denunciations communicated to him by the Members of the Organisation.

2. When notifying the Members of the Organisation of the registration of the second ratification communicated to him, the Director-General shall draw the attention of the Members of the Organisation to the date upon which the Convention will come into force.

Article 11

The Director-General of the International Labour Office shall communicate to the Secretary-General of the United Nations for registration in accordance with Article 102 of the Charter of the United Nations full particulars of all ratifications and acts of denunciation registered by him in accordance with the provisions of the preceding Articles.

Article 12

At such times as it may consider necessary the Governing Body of the International Labour Office shall present to the General Conference a report on the working of this Convention and shall examine the desirability of placing on the agenda of the Conference the question of its revision in whole or in part.

Article 13

1. Should the Conference adopt a new Convention revising this Convention in whole or in part, then, unless the new Convention otherwise provides:

(a) the ratification by a Member of the new revising Convention shall ipso jure involve the immediate denunciation of this Convention, notwithstanding the provisions of Article 9 above, if and when the new revising Convention shall have come into force;

(b) as from the date when the new revising Convention comes into force this Convention shall cease to be open to ratification by the Members.

2. This Convention shall in any case remain in force in its actual form and content for those Members which have ratified it but have not ratified the revising Convention.

Article 14

The English and French versions of the text of this Convention are equally authoritative.

RECOMMENDATION No.147*
Recommendation concerning Prevention and Control of Occupational Hazards caused by Carcinogenic Substances and Agents

Preamble

The General Conference of the International Labour Organisation,

Having been convened at Geneva by the Governing Body of the International Labour Office, and having met in its Fifty-ninth Session on 5 June 1974, and

Noting the terms of the Radiation Protection Convention and Recommendation, 1960, and of the Benzene Convention and Recommendation, 1971, and

Considering that it is desirable to establish international standards concerning protection against carcinogenic substances or agents, and

Taking account of the relevant work of other international organisations, and in particular of the World Health Organisation and the International Agency for Research on Cancer, with which the International Labour Organisation collaborates, and

Having decided upon the adoption of certain proposals regarding control and prevention of occupational hazards caused by carcinogenic substances and agents, which is the fifth item on the agenda of the session, and

Having determined that these proposals shall take the form of a Recommendation,

adopts this twenty-fourth day of June of the year one thousand nine hundred and seventy-four, the following Recommendation, which may be cited as the Occupational Cancer Recommendation, 1974:

I. General Provisions

1. Every effort should be made to replace carcinogenic substances and agents to which workers may be exposed in the course of their work by non-carcinogenic substances or agents or by less harmful substances or agents; in the choice of substitute substances or agents account should be taken of their carcinogenic, toxic and other properties.

2. The number of workers exposed to carcinogenic substances or agents and the duration and degree of such exposure should be reduced to the minimum compatible with safety.

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3.

(1) The competent authority should prescribe the measures to be taken to protect workers against the risks of exposure to carcinogenic substances or agents.

(2) The competent authority should keep the measures prescribed up to date, taking into account the codes of practices or guides which may be established by the International Labour Office and the conclusions of meetings of experts which may be convened by the International Labour Office, as well as information from other competent bodies.

4.

(1) Employers should make every effort to use work processes which do not cause the formation, and particularly the emission in the working environment, of carcinogenic substances or agents, as main products, intermediates, by-products, waste products or otherwise.

(2) Where complete elimination of a carcinogenic substance or agent is not possible, employers should use all appropriate measures, in consultation with the workers and their organisations and in the light of advice from competent sources, including occupational health services, to eliminate exposure or reduce it to a minimum in terms of numbers exposed, duration of exposure and degree of exposure.

(3) In cases to be determined by the competent authority, the employer should make arrangements for the systematic surveillance of the duration and degree of exposure to carcinogenic substances or agents in the working environment.

(4) Where carcinogenic substances or agents are transported or stored, all appropriate measures should be taken to prevent leakage or contamination.

5. Workers and others involved in occupational situations in which the risk of exposure to carcinogenic substances or agents may occur should conform to the safety procedures laid down and make proper use of all equipment furnished for their protection or the protection of others.

II. Preventive Measures

6. The competent authority should periodically determine the carcinogenic substances and agents to which occupational exposure should be prohibited or made subject to authorisation or control, and those to which other provisions of this Recommendation apply.

7. In making such determinations the competent authority should give consideration to the latest information contained in the codes of practice or guides which may be established by the International Labour Office, and in the conclusions of meetings of experts which may

be convened by the International Labour Office, as well as to information from other competent bodies.

8. The competent authority may permit exemptions from prohibition by issue of a certificate specifying in each case:

(a) the technical, hygiene and personal protection measures to be applied;

(b) the medical supervision or other tests or investigations to be carried out;

(c) the records to be maintained; and

(d) the professional qualifications required of those dealing with the supervision of exposure to the substance or agent in question.

9.

(1) For substances and agents subject to authorisation or control, the competent authority should:

(a) secure the necessary advice, particularly as regards the existence of substitute products or methods and the technical, hygiene and personal protection measures to be applied, as well as the medical supervision or other tests or investigations to be carried out before, during and after assignment to work involving exposure to the substances or agents in question;

(b) require the institution of such measures as are appropriate.

(2) The competent authority should further establish the criteria for determining the degree of exposure to the substances or agents in question, and where appropriate should specify levels as indicators for surveillance of the working environment in connection with the technical preventive measures required.

10. The competent authority should keep the determination of carcinogenic substances and agents made in pursuance of this Part of this Recommendation up to date.

III. Supervision of Health of Workers

11. Provision should be made, by laws or regulations or any other method consistent with national practice and conditions, for all workers assigned to work involving exposure to specified carcinogenic substances or agents to undergo as appropriate:

(a) a pre-assignment medical examination;

(b) periodic medical examinations at suitable intervals;

(c) biological or other tests and investigations which may be necessary to evaluate their exposure and supervise their state of health in relation to the occupational hazards.

12. The competent authority should ensure that provision is made for appropriate medical examinations or biological or other tests or in-

vestigations to continue to be available to the worker after cessation of the assignment referred to in Paragraph 11 of this Recommendation.

13. The examinations, tests and investigations provided for in Paragraphs 11 and 12 of this Recommendation should be carried out as far as possible in working hours and should be free of cost to the workers.

14. If as the result of any action taken in pursuance of this Recommendation it is inadvisable to subject a worker to further exposure to carcinogenic substances or agents in that worker's normal employment, every reasonable effort should be made to provide such a worker with suitable alternative employment.

15.

(1) The competent authority should establish and maintain, where practicable and as soon as possible, in association with individual employers and representatives of workers, a system for the prevention and control of occupational cancer including:

(a) the institution, maintenance, preservation and transfer of records; and

(b) exchange of information.

(2) In establishing such a system of records and exchange of information, account should be taken of the assistance which may be provided by international and national organisations, including organisations of employers and workers, and by individual employers.

(3) In the case of closure of an undertaking, records and information held in compliance with this Paragraph should be dealt with in accordance with the directions of the competent authority.

(4) In any country in which the competent authority does not establish such a system of records and information, the employer, in consultation with representatives of workers, should make every effort to attain the objectives of this Paragraph.

IV. Information and Education

16.

(1) The competent authority should promote epidemiological and other studies and collect and disseminate information relevant to occupational cancer risks, with the assistance as appropriate of international and national organisations, including organisations of employers and workers.

(2) It should endeavour to establish the criteria for determining the carcinogenicity of substances and agents.

17. The competent authority should draw up suitable educational guides for both employers and workers on substances and agents liable to give rise to occupational cancer.

18. Employers should seek information, especially from the competent authority, on carcinogenic hazards which may arise with regard to any substance or agent introduced or to be introduced into the undertaking; when a carcinogenic potential is suspected, they should decide in consultation with the competent authority on the additional studies to be carried out.

19. Employers should ensure that in the case of any substance or agent which is carcinogenic there is at the workplace an appropriate indication to any worker who may be liable to exposure of the danger which may arise.

20. Employers should instruct their workers before assignment and regularly thereafter, as well as on introduction of a new carcinogenic substance or agent, on the dangers of exposure to carcinogenic substances and agents and on the measures to be taken.

21. Employers' and workers' organisations should take positive action to carry out programmes of information and education with regard to the hazards of occupational cancer, and should encourage their members to participate fully in programmes of prevention and control.

V. Measures of Application

22. Each Member should:

(a) by laws or regulations or any other method consistent with national practice and conditions, take such steps, including the provision of appropriate penalties, as may be necessary to give effect to the provisions of this Recommendation;

(b) in accordance with national practice, specify the bodies or persons on whom the obligation of compliance with the provisions of this Recommendation rests;

(c) provide appropriate inspection services for the purpose of supervising the application of the provisions of this Recommendation, or satisfy itself that appropriate inspection is carried out.

23. In applying the provisions of this Recommendation, the competent authority should consult with the most representative organisations of employers and workers concerned.

Наукове видання

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