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CARCINOGENS IN THE HUMAN ENVIRONMENT

CARCINOGENS IN THE HUMAN ENVIRONMENT

By the second half of the 1960s, it had become evident that several physical, chemical, and biological agents could cause cancer in humans, as reviewed in Richard Doll's book *Prevention of Cancer: Pointers from Epidemiology* in 1967. Alongside epidemiology, long-term experiments with animals (typically mice, rats, or hamsters) exposed to high doses of chemical substances, such as soot and coal tars, clearly showed the capacity of such substances to induce cancer. The two approaches – observations in humans and laboratory experiments with animals – to identify carcinogens, natural or man-made, were at the same time complementary and in "useful tension". Epidemiology is based on direct evidence in humans, and hence it is the litmus test of carcinogenicity, but this very fact implies that several cancers due to a substance have already occurred. From a cancer prevention viewpoint, evidence from animal experiments is far preferable, as it enables the avoidance of exposure of humans to experimentally recognized carcinogens. The drawback is that what happens, or does not happen, in animals does not necessarily match what occurs in humans. Thus, in the mid-1960s, there was one striking discrepancy between epidemiological and experimental evidence: tobacco smoking could be clearly demonstrated to cause cancer in humans, but at the time no proof of carcinogenicity of tobacco smoke could be obtained in animal experiments.

Starting as early as 1969, IARC capitalized on the complementary nature of the two approaches rather than standing aside because of possible discordances. IARC developed two main long-term focus areas aimed at identifying carcinogens in the human environment: the IARC Monographs Programme, with its systematic reviews of all published epidemiological and experimental evidence of carcinogenicity of (initially) chemicals; and epidemiological studies on specific human exposures arising from occupation or the general environment. In addition, during IARC's first two decades, several animal carcinogenicity experiments were conducted at the Agency (see "DDT and transplacental and transgenerational carcinogenesis").

THE IARC MONOGRAPHS, A WORLD REFERENCE FOR ENVIRONMENTAL CARCINOGENS

A systematic approach to the evaluation of scientific evidence

After a preparatory phase, the Monographs Programme was launched in 1971–1972 at the initiative of and under the leadership of Lorenzo Tomatis (see "Lorenzo Tomatis, second IARC Director"). The aim was to develop an instrument capable of evaluating the best evidence available at a given time on carcinogenic agents, in order to provide a sound scientific basis for cancer prevention. Some reviews of the evidence of carcinogenicity had already been published, including Doll's book *Prevention of Cancer: Pointers from Epidemiology*. However, two features made the IARC programme highly innovative:

The effective use of DDT as an insecticide to control malaria was far exceeded by its use for pest control in agriculture and forestry. DDT is one of a host of pesticide chemicals of concern because of their accumulation, persistence, and toxic effects in living organisms.

DDT AND TRANSPLACENTAL AND TRANSGENERATIONAL CARCINOGENESIS

It was not within IARC's remit to develop a large facility for testing suspected carcinogenic substances in long-term experiments in animals. However, IARC laboratories participated in collaborative studies, contributing data to much larger, multilaboratory experiments. In 1981, some 15 years after IARC was established, a dozen such collaborations were active, involving some pesticides, industrial chemicals, and pharmaceutical drugs. More complete studies conducted at IARC focused on issues of prominent public health relevance. Following a 1967 recommendation by a joint meeting of the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations, dichlorodiphenyltrichloroethane (DDT), a chemical widely used as an effective insecticide against the malaria mosquito, was tested in long-term experiments in mice. These involved more than 1000 animals, and more than 3000 when the observation was expanded to cover six generations. An increased incidence of liver-cell tumours was found in DDT-treated mice compared with untreated controls, at the highest doses (250 milligrams per kilogram of body weight) of oral DDT administration. These results were supported by those of smaller studies in mice, rats, and hamsters carried out at other laboratories, leading in 1991 to the evaluation by the IARC Monographs Programme that there is sufficient evidence for the carcinogenicity of DDT in experimental animals.

At that time, the epidemiological data from humans exposed to DDT were inconclusive. Minor increases in the incidence of lung cancer and cancers of the blood and lymphatic organs had been inconsistently reported by studies with limitations in the assessment of exposure to DDT and in the control of other possible carcinogenic factors. Considering the combined evidence in experimental animals and humans, DDT was classified as *possibly carcinogenic to humans*, and epidemiological reports published subsequently, particularly on breast cancer, have not improved the evidence. This immediately posed a dilemma: should use of DDT be continued for malaria control, while paying the price of a possible increase in cancer cases? Balancing benefits and risks of interventions is common in public health. In 2002, Lorenzo Tomatis and his collaborators who had conducted the IARC experiments in the 1960s concluded, "There is a general consensus that limited and strictly controlled use of DDT should be allowed for public health purposes, in particular where other effective, safe, and affordable alternatives are not available, and the benefits are clearly far superior to possible risks. ... A total ban of DDT could only be achieved at a cost that poor countries ... cannot afford without substantial and long-term financial help from the richer countries." Unfortunately, the "strictly controlled use" was not respected, as DDT was later applied far more widely as a pesticide in agriculture and forestry than specifically to combat malaria.

The DDT experiments at IARC were conducted over several generations of mice, and the possible cancer induction in the offspring of parents exposed to carcinogens became a research area in itself, of wider scientific interest well beyond the case of DDT. A collaboration was established with several laboratories to carry out animal experiments investigating the two possible ways in which exposure of parents could in principle induce the appearance of cancers in offspring: because a carcinogen to which the mother was exposed reached the cells of the embryo or fetus via the placenta, or because a carcinogen had affected the germ cells (sperm or ova) of the father and/or the mother. Results from this collaboration suggested that both mechanisms may in fact be operating. These studies were early forerunners of the contemporary expansion of research on transplacental and transgenerational carcinogenesis made possible by advances in molecular genomics and epigenetics.

the systematic approach to examining and evaluating each agent by the same procedures, and the idea that the soundest way to reach the "truth" about the carcinogenicity of an agent is through open discussion and reciprocal cross-checking by leading experts. Given the imperfect nature of all human knowledge, the truth is always approximate, but it can be explicitly stated and qualified by the degree of confidence attached to the statement.

In practice, scientific judgement can be distorted by secondary interests and goals extraneous to, and interfering with, the primary goal of pursuing scientific, reasonable truth, such as financial incentives or advocacy standpoints. Hence, the experts chosen to participate in evaluations had to be as free as possible of such conflicting interests.

LORENZO TOMATIS, SECOND IARC DIRECTOR

Lorenzo Tomatis succeeded John Higginson in 1982 as IARC Director, a post he held until 1993. After graduating from the University of Turin with a degree in medicine, Tomatis pursued a research career in experimental cancer pathology in the laboratory of Philippe Shubik at the University of Chicago, a leading centre in the study of mechanisms of carcinogenesis. His research focused on the induction of cancer by chemical agents, with a special interest in cancers appearing in the offspring of parent animals exposed to carcinogens. Tomatis joined IARC in 1967 as head of the Unit of Chemical Carcinogenesis and was the founder of the IARC Monographs Programme. He consistently supported a close connection between scientific rigour in research and public health interest as enacted through cancer prevention. In 2002, Tomatis wrote, "In the absence of absolute certainty, rarely if ever reached in biology, it is essential to adopt an attitude of responsible caution, in line with the principles of primary prevention, the only one that may prevent unlimited experimentation on the entire human species." He cautioned that "absent or inadequate epidemiological data cannot be considered equivalent to a negative finding and cannot be considered more relevant for public health than positive experimental findings."

Lorenzo Tomatis was IARC Director from 1982 to 1993.

As a keen observer of society, Tomatis was well aware that primary prevention of cancer can be implemented only by overcoming major obstacles. In 2006, he wrote that "primary prevention of cancer has stumbled from the very beginning because of the interference of powerful economic interests which perceived that any data indicating a probable cancer risk after exposure to industrial chemicals jeopardizes their profits, the protection of which being more important than the protection of human health." The high international status of the IARC Monographs Programme stands as a lasting tribute to Tomatis's scientific and humanistic intelligence.

> *Public health measures and decisions were up to countries, but they needed a document that showed clearly that there was evidence, and it was the Monographs.*
> – Ruggero Montesano, former IARC scientist

An evolving programme

To fit its purpose, the Monographs Programme needed to be evolutionary, in the dual sense of incorporating updates of the evidence when relevant new findings become available and of adapting the very criteria used to evaluate such evidence in line with the accruing knowledge about the underlying mechanisms of cancer development. Over more than 40 years, the programme has successfully maintained and strengthened these characteristics, becoming a key reference – often *the* key reference – in both scientific and public health contexts.

The initial selection of agents to be considered centred on chemicals, for several of which data on carcinogenicity had been accumulating. For each compound evaluated, a Monograph was to be prepared and published. From the colour of the cover, the volumes soon became known as the "Orange Books".

Each Monograph was produced by a Working Group composed of the world's leading experts, who met in Lyon for 7–10 days, with staff from IARC serving as the supporting secretariat. During the meeting, initial drafts prepared in advance by different Working Group members were discussed and repeatedly revised to reach the final text of the Monograph sections. Each Monograph reviewed in detail all available reports published in the scientific literature on the occurrence of and human exposure to the compound, studies of cancer in experimental animals and in humans, and other relevant biological data. A summary of the sections and an evaluation of whether the compound should be regarded as carcinogenic to humans concluded each Monograph.

The first volume of the IARC Monographs series was published in 1972. It covered evaluations of some inorganic substances (e.g. beryllium), chloroform, several aromatic amines, nitroso compounds, and natural products (including aflatoxins).

The first two volumes, each containing several Monographs, were published in 1972 and 1973. They already concluded that several chemicals caused cancer in humans, among them aromatic amines, asbestos fibres of all kinds, and nickel. The evaluations were expressed in a narrative style with variable language as suited to each Working Group. Soon, the need emerged to introduce some measure of uniformity and a grading of the evidence of carcinogenicity, which sometimes appeared definite, sometimes was limited, and sometimes was simply absent. Accordingly, the short general Preamble that introduced each Monograph was expanded to provide procedural and writing guidance to the Working Groups. Suggestions from their

THE IARC CLASSIFICATION OF CARCINOGENS

The IARC classification, which was adopted in 1987–1988 on the basis of more than 15 years of experience in evaluating potentially carcinogenic agents, constitutes one of the first evidence-based systems in biomedicine. At about the same time (in the early 1990s), the term "evidence-based medicine" was introduced in clinical research. The classification as it is used today is based on the following five elements.

(a) The evidence of carcinogenicity from studies in humans is evaluated and classified into one of four categories: sufficient evidence of carcinogenicity, limited evidence of carcinogenicity, inadequate evidence of carcinogenicity (which also covers agents for which there are no data), or evidence suggesting lack of carcinogenicity.

(b) The evidence of carcinogenicity in experimental animals is evaluated separately and is classified into one of the same four categories as in (a).

(c) Mechanistic and other relevant data are described.

(d) The body of evidence in (a), (b), and (c) is considered as a whole to reach an overall evaluation in one of the following categories.

Group 1: The agent is *carcinogenic to humans*.

Group 2A: The agent is *probably carcinogenic to humans*.

Group 2B: The agent is *possibly carcinogenic to humans*.

Group 3: The agent is *not classifiable as to its carcinogenicity to humans*.

Group 4: The agent is *probably not carcinogenic to humans*.

(e) A Rationale section explains the main lines of reasoning that the Working Group used to reach its evaluation and classification. Should significant differences of scientific interpretation occur among Working Group members, a summary of the alternative interpretations is provided.

Of 971 agents evaluated so far (many of which have also been re-evaluated when new data have accrued), 114 fall into Group 1, 69 into Group 2A, 283 into Group 2B, 504 into Group 3, and 1 into Group 4. The reason why almost half of the 971 agents have been found to be positive, in different degrees, for carcinogenicity while only one agent has been classified in Group 4 is that agents are selected for evaluation only when information is available that makes them suspected carcinogens. It would not make any sense, and would be wasteful of resources, to pick agents for evaluation at random out of the millions in existence.

The continuously updated evaluations are available on the IARC Monographs website at monographs.iarc.fr. The IARC Group classification is a regular reference when dealing with an agent's carcinogenicity in a scientific or public health context and is also very often quoted in the lay media. Occasionally, however, it appears that the correct meaning has not been grasped, particularly for Group 2 classifications: the expressions *probably* and, even more, *possibly* are interpreted as meaning that the agent is capable of increasing the risk of cancer but that the increase in risk is small. This is incorrect; *probably* and *possibly* do not refer to the size of an increased risk. They indicate higher (*probably*) or lower (*possibly*) probabilities that such an increased risk induced by the agent does in fact exist.

These are not easy scientific judgements, and each evaluation is anything but a mechanical operation of pigeonholing agents into categories. Intensive discussions and repeated revisions of the Monograph text take place during what is nowadays an eight-day-long meeting. The Working Group meets in plenary sessions to examine, modify, and finalize the drafts prepared by specialized subgroups; among these, the subgroup dealing with exposure data for the agent being evaluated is of critical importance. Evenings and weekends are often busy as well, and although Lyon has a well-deserved reputation as a capital of gastronomy, usually only a single escape for a group dinner is possible. Despite the challenges, a shared view within the Working Group most often emerges after the long hours of in-depth scientific debate. Nevertheless, reaching such agreement can be problematic when the evidence seems to straddle the boundary between two adjacent categories. For example, radiofrequency electromagnetic fields as generated by mobile phones were evaluated by the Monographs Programme in 2011 and categorized as *possibly carcinogenic to humans* (Group 2B), a statement widely quoted in the media that reflects different nuances of interpretation of the available evidence. In fact, the section of the Monograph entitled "Rationale of the evaluation of the epidemiological evidence" points out that inconsistencies between the results of different studies were regarded by the majority of the Working Group members as a restriction on the evidence, leading to a judgement of *limited evidence* of carcinogenicity in humans; however, there was a minority opinion that saw the same inconsistencies as more critical, viewing the current evidence in humans as *inadequate*.

experience and discussions in several ad hoc meetings consolidated the guide into formal criteria; the format adopted in 1987–1988 is essentially still used today (see "The IARC classification of carcinogens").

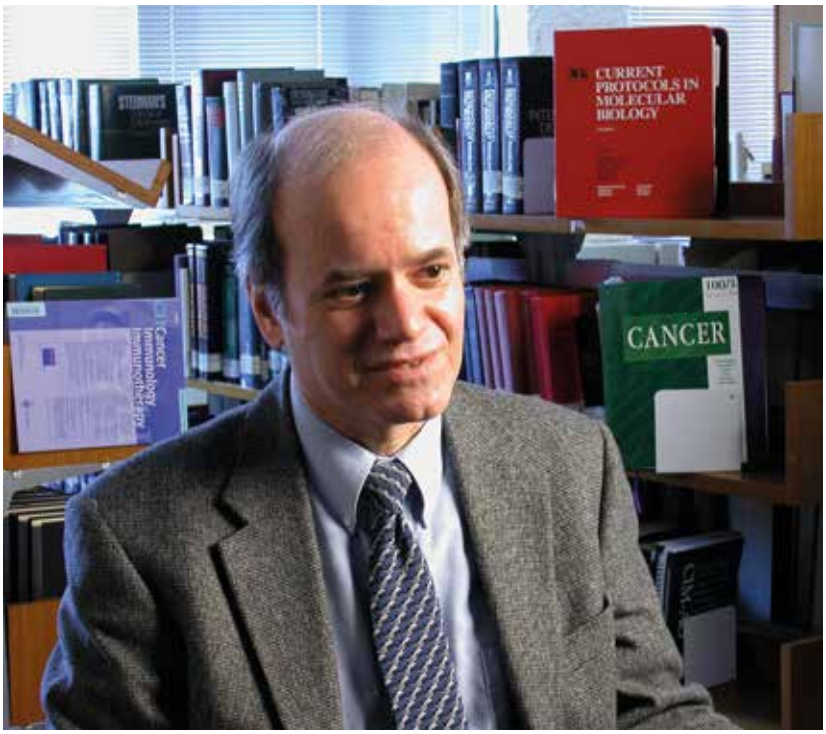
The Monographs Programme had started with the general title of IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man ("man" became "humans" in 1978). Recognizing the high quality of the programme, several leading scientists had argued that it should not be limited to individual

The six-book boxed set of IARC Monographs, Volume 100: A Review of Human Carcinogens.

chemicals but expanded to (in Richard Peto's words) "see chemical carcinogens, lifestyle factors, and chronic infections as being separately important, placing cancer causes in a more balanced perspective." Since its reshaping in 1987–1988, the series has been called the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, to denote the much-enlarged scope of the programme, covering physical, chemical, and biological agents as well as mixtures of compounds (like tobacco smoke) and circumstances not specifiable more precisely (like some occupations). This breadth has led to many important evaluations by the IARC Monographs Programme, for example of infectious agents including viruses (e.g. hepatitis B and C viruses, human papillomaviruses), bacteria (e.g. *Helicobacter pylori*), and parasites (e.g. *Schistosoma mansoni*) and of physical agents including ultraviolet radiation and radon.

> *I was impressed by the thoroughness of the Monographs Programme. It provided an international gold standard for the process, assessment criteria, and presentation of the assessed carcinogenicity of specified exposures.*
> – Tony McMichael, former chair, IARC Scientific Council

Two other major adaptations have taken place over the years. First, taking into account the increasing knowledge about mechanisms through which an agent like a chemical or a virus can induce cancer, mechanistic data have been given increased weight in assessing whether an agent is carcinogenic. Several chemicals have been classified as carcinogenic to humans when the direct epidemiological evidence was insufficient but there was strong evidence in exposed humans that the agent acts through a known relevant mechanism of carcinogenesis. (For example, the molecules of some dyes are metabolized in the human body to benzidine, a molecule for which there is direct epidemiological evidence of carcinogenicity.) For almost all of these agents, there was, in addition, sufficient evidence of carcinogenicity in animals.



Vincent Cogliano, head of the Monographs Programme from 2003 to 2010, coordinated the operation of the Working Groups evaluating the evidence and the production of the Volume 100 books. Cogliano joins Lorenzo Tomatis, Harri Vainio, and Jerry Rice as one of the group of people who have led the Monographs Programme for extended periods over its history.

Second, the roles of the participants at Monographs meetings have been better specified. Working Group members are responsible for the critical reviews and evaluations that are developed during the meeting. Invited specialists and representatives of national and international health agencies contribute their expertise but do not serve as meeting chair or subgroup chair, draft text, or participate in the evaluations. A limited number of observers, for example from industry or nongovernmental organizations, with relevant scientific credentials may be admitted under well-defined guidelines on the restrictions on their participation. IARC staff act as the supporting secretariat, serving as rapporteurs and participating in all discussions.

A recent addition to the programme is Volume 100 of the Monographs series, which consists of six books summarizing the most up-to-date evidence for the 110 agents previously classified in Group 1 (carcinogenic to humans). Volumes 100A to 100F cover pharmaceuticals; biological agents; arsenic, metals, fibres, and dusts; radiation (ionizing and non-ionizing); personal habits and indoor combustions; and chemical agents and related occupations. These summaries include an assessment of the specific organs for which sufficient evidence is available that an agent induces cancer, with the proviso that when an agent is shown to be carcinogenic for some organs it cannot be excluded that other organs might be affected as well.

AFLATOXIN AND PRIMARY LIVER CANCER

Scattered reports from different localities in Africa had pointed out a possible high frequency of primary liver cancer, a rare tumour in developed countries. One of the earliest meetings at IARC, held before the move to the newly constructed IARC tower building, considered the causes of primary hepatoma. Indeed, as early as 1967 a collaborative centre had been established in Nairobi, Kenya, to supervise IARC research projects in East and Central Africa (see the chapter "The birth of IARC").

The Murang'a district of the Central Province of Kenya was selected for an investigation relating cancer occurrence to environmental contamination of the local diet by aflatoxins – metabolites produced by microscopic fungi (*Aspergillus* species) and already known to be potent toxins and liver carcinogens in animals accidentally exposed or treated experimentally in the laboratory. A field survey was conducted to collect random samples of food and beer representative of the actual food consumed by several thousand people, more than half of them children. Laboratory analyses for aflatoxin content were performed at the IARC Regional Centre in Nairobi, and cases of liver cancer were registered in 1967–1970. The data shown in the table on the next page were collected in areas at different altitudes, where conditions of moisture and temperature could be differently favourable to food contamination by Aspergilli. The aflatoxin content of food samples and the proportion of samples positive for the presence of aflatoxin increased with the decreasing average altitude of the sampled area. The frequency of hepatoma (cases per 100 000 adults per year) showed a parallel increase.

Until 1972, IARC was housed in a late-19th-century building in central Lyon, where this October 1968 meeting on the causes of liver cancer took place. Frank Peers (at extreme left), Allen Linsell (fourth from left), and Gregory O'Conor (sixth from left) were the principal investigators for IARC's research projects in Africa on the role of aflatoxin and hepatitis B virus infection. Albert Tuyns (fifth from left) was the IARC epidemiologist who conducted the studies on the causes of oesophageal cancer in north-western France (see the chapter "Innovation in statistical methods").

Aflatoxin contamination of "food from the plate" samples in three areas of the Murang'a district, Kenya

Characteristic	Average altitude of area		
	High	Medium	Low
Aflatoxin content of food samples (micrograms per kilogram)	3.5	5.9	10.0
Proportion of positive samples	39/808	54/808	78/816
Hepatoma incidence:			
Total number of cases (1967–1970)	1	19	12
Number of cases per 100 000 adults per year	1.3	6.3	8.0

As stated in the 1970 IARC Annual Report, "There appears to be a definite correlation between aflatoxin levels and current liver cancer cases in the three sub-areas of different altitude in Murang'a. ... However, it is necessary to extend this study to other areas in the world with different cancer rates and levels of aflatoxin contamination, if the hypothetical association between aflatoxin ingestion in man and hepatocellular cancer is to be adequately tested."

A field team from the IARC Regional Centre in Nairobi visiting a village to collect samples of foodstuffs for the aflatoxin research programme, in 1968.

With characteristic prudence, the first volume of the IARC Monographs (in 1972) reported that in the judgement of the Working Group no causal relationship had been established between cancer occurrence and aflatoxin contamination of diets. As data similar to those from Murang'a became available from other localities, the position had changed by Volume 10 of the Monographs (in 1976): "The studies of liver cancer incidence in relation to aflatoxin intake provide circumstantial evidence of a causal relationship." Ten years later, results from two case–control studies in Shanghai and Taiwan, China and one small cohort study in the Netherlands enabled the definitive conclusion that aflatoxin is carcinogenic to humans. In the meantime, IARC conducted an investigation in 11 areas of Swaziland, in which both aflatoxin consumption and prevalence of hepatitis B virus infection were measured. The results showed that both were related to liver cancer occurrence but that aflatoxin exposure appeared to be more important in explaining the variation in liver cancer incidence. Over the decades, IARC has contributed much further knowledge on the role and mechanisms of action of aflatoxin and its interaction with hepatitis B virus infection, particularly within the Gambia Hepatitis Intervention Study (see the chapter "Viruses and vaccines") and with research on the role of the *TP53* gene and protein (see the chapter "From laboratory to population"). The aflatoxin story continues to unfold, with a focus today on preventive measures against food contamination. IARC's early evidence from Murang'a had paved the way.

EPIDEMIOLOGICAL STUDIES

Since the very beginning, IARC has engaged in a variety of epidemiological studies of possible carcinogens in the general, home, and occupational environments. These studies took different forms in different contexts.

Cancer hotspots

A first type of epidemiological study consisted of building on the suggestions, often coming from clinical observations or crudely recorded data on a geographical basis, that there were hotspots of cancer incidence in areas where some characteristic exposure was reported as common. Most often this occurred in developing countries, and IARC established collaborations in those areas with local health professionals who provided, directly and via official government channels, scientific support to mount rigorous epidemiological and laboratory investigations designed to put the suggestions to the test. Significant results were soon obtained, of value locally for the populations concerned and also of broader significance for the knowledge of new carcinogens.

Early examples of potent environmental contaminants stand out: aflatoxin inducing primary liver cancer by the alimentary route (see "Aflatoxin and primary liver cancer") and erionite mineral fibres inducing mesothelioma by the respiratory route (see "Erionite mineral fibres and mesothelioma"). These two cases offer examples of ways that may lead to the identification of new environmental carcinogens. For aflatoxin, the evidence of carcinogenicity in animals, from accidental ingestion of contaminated food by poultry and rainbow trout, followed by experiments in rodents, inspired the epidemiological studies in human populations. For erionite, the process went in the other direction: the epidemiological findings prompted the subsequent laboratory experiments in rodents.

ERIONITE MINERAL FIBRES AND MESOTHELIOMA

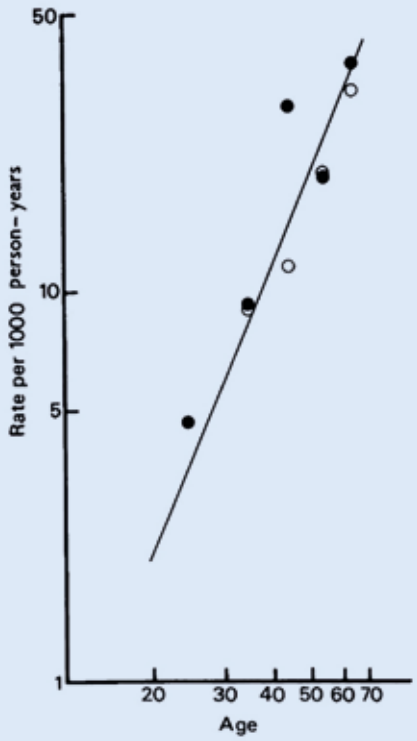
In the early 1970s, interesting cases of chest diseases were reported from rural villages in Central Anatolia, Turkey. The cases had initially been mistakenly diagnosed as tuberculosis, but a senior Turkish chest physician, well acquainted with asbestos-related diseases, astutely observed that they were pleural mesotheliomas. They appeared to be clustered in some small villages, raising the suspicion that they might have originated from exposure to mineral fibres, either of asbestos or of a similarly acting material. A field investigation, conducted by the Department of Chest Diseases of Hacettepe University, Ankara and IARC, confirmed the peculiar epidemiological situation and identified as the cause a specific natural fibre: erionite, a compound of the zeolite family of minerals, some other members of which are in commercial use as adsorbents of molecules from air or liquids.

A landscape typical of villages like Karain in Cappadocia (central Turkey). Caves are used not only for storage but also, particularly in the past, as homes.

Although a few other villages were affected, a most striking feature was the contrast between two villages 3 kilometres apart: Karain, with a population of 554 in 1978, and Karlik, with a population of 479. The cultural, social, and very poor economic conditions were similar in the two villages. Karlik had poorer general hygiene indicators, such as high infant mortality and house overcrowding; some of the homes were cave dwellings in

the rock, as often seen in postcards from the Cappadocia region. However, adult all-cause mortality was 30% higher in Karain. During the period 1970–1978, 50 cases of pleural mesothelioma were ascertained in Karain, all of whom had died within less than 2 years of diagnosis, irrespective of the treatment. During the same period, no cases were ascertained in Karlik. The 50 deaths in Karain, relative to the size of the village's population in the different age groups, correspond to astonishingly high rates of deaths from mesothelioma; for the age group of 20–30 years, the rate reached the highest rates observed in workers exposed to asbestos.

The appearance of the disease at early ages and the regular, steep increase of the rate with age fit the model of a causal agent to which people are exposed from birth. Indeed, geological studies revealed superficial veins of the mineral erionite in the volcanic rock (tuffs) of Karain; erionite was not present in Karlik. The environmental investigation conducted in parallel with the epidemiological study showed that the majority of fibres in the air from the dusty unpaved streets and the rocky house walls in Karain were erionite. Experimental studies began to follow the reported mesothelioma clusters in humans and rapidly showed erionite to be a potent inducer of mesotheliomas, particularly by inhalation in rats. In 1987, erionite was classified by the IARC Monographs Programme as carcinogenic to humans. The findings encouraged local environmental changes to minimize the release of dust, such as paving the streets, using bricks to construct new dwellings away from the caves, and facilitating the relocation of residents to less polluted areas.



Rates of death from mesothelioma in Karain (1970–1978), for ages 20–69 years. Mesothelioma mortality starts at young ages and rises rapidly with age in both sexes (filled circles, men; open circles, women). The line fits a formal mathematical model of cancer development caused by an agent like erionite to which exposure begins at birth.

The multicentre model in populations of workers

Workers in mining, agriculture, industry, and services are exposed to a variety of chemicals, physical agents, or microorganisms, usually at levels higher than exposures experienced by the general population. If an increased cancer risk is induced by some of these exposures, it will show up and will be easier to detect among the workers than in the general population. However, the number of workers in a single factory or workplace is often only a few hundred – not enough to reveal an increased cancer risk (unless it is huge). Therefore, combining populations from several workplaces, often remote from each other, becomes imperative. This fits perfectly with IARC's mandate of conducting multicentre international projects, which took form in a series of occupational epidemiology studies that were typical in their design, size, and organization, and in the collaborative sharing of responsibilities between researchers (see "Three multicentre occupational studies").

THREE MULTICENTRE OCCUPATIONAL STUDIES

Several pesticides resist degradation, thus polluting the general environment for decades. The public health relevance of pesticides, old and new, had prompted IARC's early experimental studies on DDT (see "DDT and transplacental and transgenerational carcinogenesis"). A similar concern was at the origin of a cohort study of workers exposed to herbicides extensively used for weed eradication. An overall cohort of more than 20 000 male and female workers employed in the production or spraying of phenoxy herbicides and chlorophenols often contaminated by dioxins was assembled from 36 cohorts in 12 countries. The workers were observed for an average of 25 years. An increased risk of sarcomas, a rare cancer of the soft tissues, was detected in workers who had been exposed to dioxin-based products. Even in this very large cohort, only six cases of sarcoma were recorded (when three were expected); smaller cohorts, as are available within a single country, would have been inadequate to pick up the warning signal. Dioxins have been classified by the IARC Monographs Programme as carcinogenic to humans.

Man-made vitreous fibres are synthetic products that are widely used, mainly as insulation materials, replacing asbestos in a variety of applications. A Europe-wide study was conducted that included 13 plants and provided a cohort of more than 20 000 workers observed for an average of 20 years. Since the substantial production of these fibres began, in the late 1930s, the industrial processes have evolved considerably, and the level of exposure of workers to fibres dispersed in the plant environment is low. In these settings, no warning signals of increased cancer risks have emerged, and in the IARC Monographs man-made vitreous fibres are categorized as Group 3, not classifiable as to their carcinogenicity to humans.

Different types of ionizing radiation have long been known to be carcinogenic and are categorized as such in the IARC Monographs. A major question that is relevant for the protection of workers and the general population (who are exposed through natural sources and medical diagnostic procedures) is the actual size of the risk associated with low-level, protracted exposures. To investigate this issue, a very large cohort of more than 400 000 radiation workers in the nuclear industry in 15 countries was assembled and observed for an average of 12 years, and close to 5000 cancers were recorded. The results were suggestive of a small excess of solid tissue cancers even at low doses with protracted exposure. This study is currently being extended by prolonged observation of the worker population, which should enable a firmer estimate to be made of what appeared initially as a small excess.

Projects often begin with an enquiry made to epidemiologists belonging to the worldwide network of IARC contacts. Their willingness is explored to conduct a preliminary study to find out whether an investigation is feasible in their country. This involves identifying groups of workers exposed in the past to the substances of interest (e.g. herbicides), following them up until the present, recording cases of cancers and causes of death, and documenting the workers' exposures through job histories and environmental measures, past and current.

If the study is shown to be feasible, a working group is formed, including epidemiologists and industrial hygienists, to define the study plan. Usually, prolonged discussions are necessary to produce a genuine

consensus protocol among all investigators, without which the conduct of the study would soon run into trouble. IARC acts as coordinator and does not dictate the protocol, but once this is agreed upon, it is IARC's task to ensure that it is strictly implemented in all participating countries and centres. An essential element is that IARC epidemiologists participate in the data collection, at the very least through periodic stays at field centres; this is the only way they can become thoroughly familiar with the strengths and weaknesses of the data they will later have to analyse. All such data are kept at each centre, and (after personal identifiers are removed) the files are also copied to IARC, which is in charge, jointly with ad hoc subgroups of national investigators, of the various statistical analyses and of the writing of study reports and papers for publication in peer-reviewed journals. In the 1970s and 1980s, IARC was a key promoter of this type of study, in the occupational field and more generally in epidemiology. Many investigators worldwide contributed to the IARC-coordinated projects, acquiring experience with a study model that has since become much more widely adopted, notably within the multinational epidemiological research projects supported by the European Union.

When nearly everyone is exposed

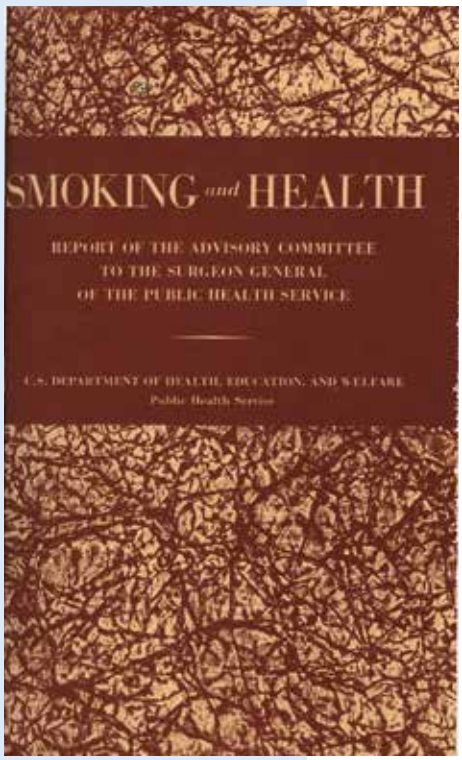
Agents to which all people are exposed more or less uniformly because they are present in the air or water are of great public health relevance, and it is vital to know whether they may induce cancer. However, in many cases the primary evidence that general environmental pollutants – like diesel exhaust – are carcinogenic comes from subgroups exposed at higher levels, typically because of their occupation, as mentioned above. Once such evidence is in, it becomes important to estimate how much of the cancer burden in the total population is in fact attributable to such pollutants. For instance, a study using the IARC European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, recruited in 10 European countries (see the chapter "Nutrition, metabolism, and cancer"), estimated that about one fifth of lung cancers in never-smokers or former smokers could be attributed to involuntary smoking (i.e. exposure to second-hand or environmental tobacco smoke), mostly in the workplace (see "Tobacco and cancer"). One twentieth of the lung cancers in never-smokers or former smokers could be attributed to high levels of air pollution, as judged by nitrogen dioxide levels or proximity to roads with heavy traffic.

Electromagnetic fields, as generated by communication systems or power lines, are today widely present in all environments. In particular, the use of mobile phones has been rapidly expanding, and more than 6 billion are now in use. IARC is a major contributor to generating and evaluating the scientific evidence on the relationship between mobile phones and cancer. IARC coordinated the largest case–control study on brain tumours in adults (the INTERPHONE study) and is involved as a key party in several cohort studies of mobile phone users, still in progress. In addition, at the level of evidence evaluation, a Working Group of the IARC Monographs Programme has assessed radiofrequency electromagnetic fields (see "The IARC classification of carcinogens").

TOBACCO AND CANCER

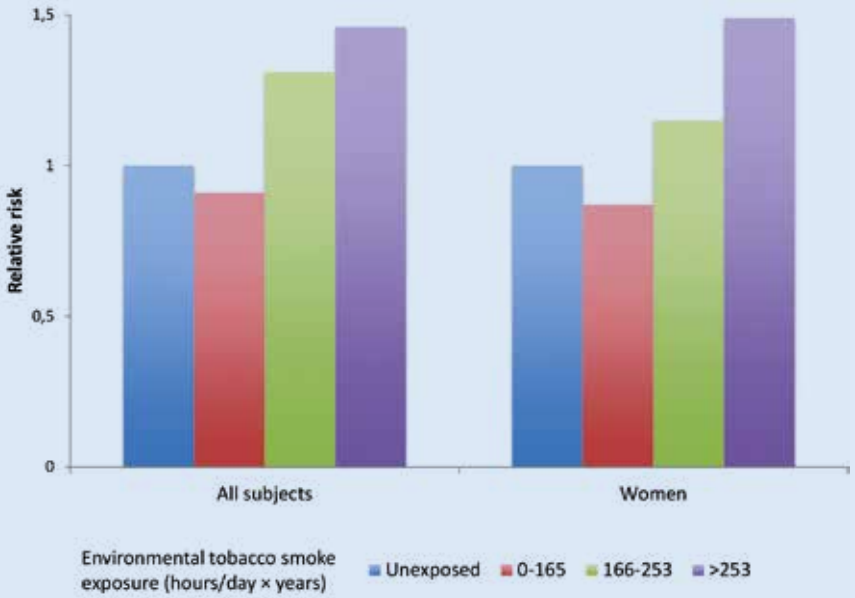
In 1964, two landmark documents in the history of tobacco and health were published: the United States Surgeon General's Report *Smoking and Health* and a two-part paper by Richard Doll and Austin Bradford Hill entitled "Mortality in relation to smoking: ten years' observations of British doctors". Unequivocally, tobacco smoking caused cancers at several sites, notably in the lung and upper respiratory airways. How could the newly formed IARC enter a research field where a lot was already known and more knowledge was added every day by a large number of investigators and institutions operating in the field of tobacco and health?

Based on existing knowledge, information on tobacco smoking had become a must in most epidemiological studies, if for no other reason than to rule out that tobacco smoking, rather than other factors of interest (e.g. workplace exposures to asbestos), was responsible for any observed excess of cancers. Thus, information on tobacco smoking was incorporated into IARC studies whenever feasible. Over more than 40 years, this has generated a host of results, notably on the interactions of tobacco with other agents: from the interaction with alcohol in the causation of oesophageal cancer in the studies in north-western France in the 1960s and 1970s (see the chapter "Innovation in statistical methods") to the recent and current lung cancer studies focused on identifying genetic variants that may enhance or reduce individual susceptibility to developing a tobacco-induced cancer (see the chapter "From laboratory to population").



There were also aspects of tobacco smoking that were less well understood, and IARC selectively concentrated on some of these. A multicentre case–control study of cancer of the larynx and hypopharynx in southern European countries clearly showed a 2-fold higher risk from the use of black, air-cured tobacco than from blond, flue-cured tobacco. In parallel, studies at IARC laboratories examining urine samples for substances capable of inducing DNA mutations clearly showed that the urine of smokers of black tobacco contained twice as much of these substances as the urine of smokers of blond tobacco. This result pointed to the role of black tobacco in the causation of bladder cancer, which was twice as frequent among smokers of black tobacco as among smokers of blond tobacco. Years later, when the issue of the effects of involuntary smoking (exposure to second-hand smoke) was raised and several small to moderately sized studies were published, IARC conducted a large study in seven countries of the risk of lung cancer in never-smokers exposed to second-hand smoke. The study included 650 cases and 1200 controls and showed that people exposed to second-hand tobacco smoke at home and in the workplace experience on average a 20% increase in the risk of lung cancer, with a higher increase for higher accumulated exposures over the years.

IARC's role in providing an international reference for carcinogenic risks prompted a series of timely activities and publications centred on tobacco and cancer. By the mid-1980s, the first clear signs appeared that a major epidemic of tobacco-induced cancers was looming in developing countries. David Zaridze, currently at the Cancer Research Centre in Moscow and then an IARC staff member, took the initiative of organizing a conference of top international scientists in Moscow. The urgency of the message emerging from the conference



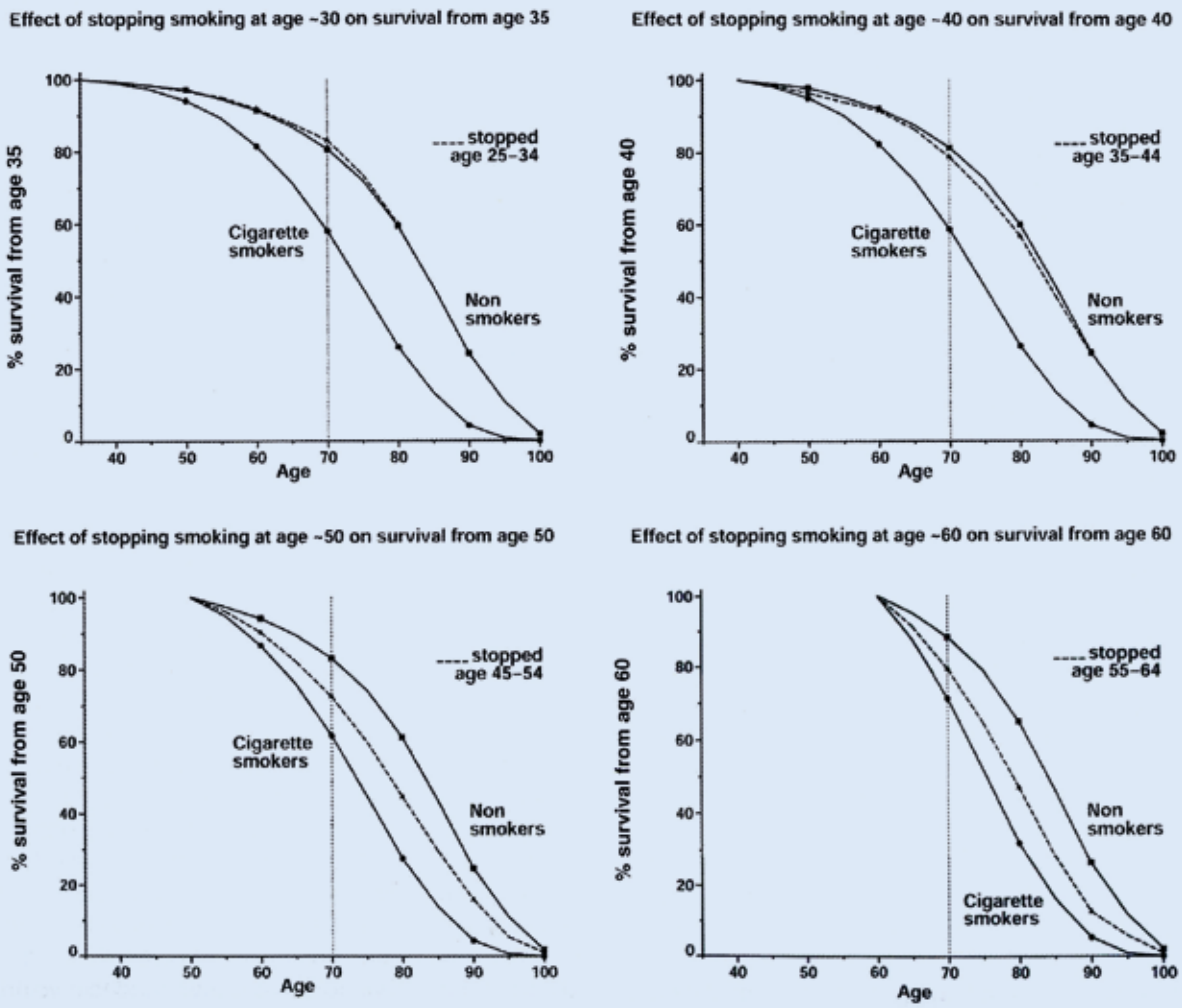
In the multicentre environmental tobacco smoke study, coordinated in Europe by IARC, the risk of lung cancer in non-smokers increases in both men and women with increasing exposure to environmental tobacco smoke; duration of exposure is measured cumulatively as hours per day multiplied by years of exposure.

is expressed in the title of the proceedings: *Tobacco: A Major International Health Hazard*, published by IARC in 1986. It contained a concise set of tobacco control recommendations, including the reduction of the tar content of cigarettes. Although at variance with the general principle of "no smoking" of any type of tobacco, this was a realistic recommendation for countries like those in eastern Europe, where the tar content of cigarettes was still very high. Zaridze believes that the recommendations proved highly influential in the Russian Federation, and more generally in eastern Europe, and "saved hundreds of thousands of lives of people who would otherwise have died of lung cancer."

Volume 83 of the IARC Monographs, *Tobacco Smoke and Involuntary Smoking*, was published in 2004. This massive volume (with more than 1400 pages) updated the evidence on tobacco smoke, to now be regarded as capable of increasing the risk not only of lung cancer but also of cancers at other body sites (14 in all) such as the upper respiratory airways, mouth, pancreas, and bladder. The volume was especially timely to settle the case of involuntary smoking: based on the evidence of more than 50 epidemiological studies, "There is *sufficient evidence* that involuntary smoking (exposure to second-hand or 'environmental' tobacco smoke) causes lung cancer in humans."

Finally, IARC tackled the complex issues bearing on the effectiveness of the great variety of measures hitherto implemented for tobacco control. The review of legislative documents for tobacco control in the European Union countries, coordinated in the 1990s by Annie Sasco, was a first step in this direction. A broader, systematic approach was later developed: from 2006 to 2010, four Working Groups were convened and four volumes published in the IARC Handbooks of Cancer Prevention series, which mirrors (with necessary adaptations) for preventive interventions the procedures, criteria, and format of the IARC Monographs for risk evaluation.

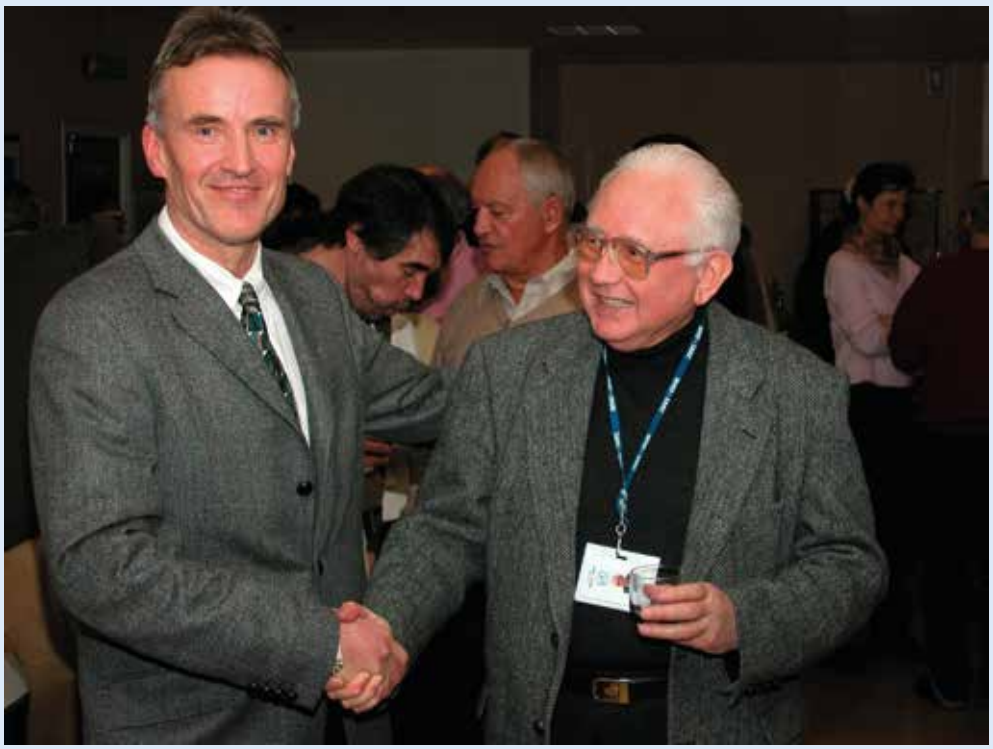
For people who stop smoking cigarettes, the percentage survival increases markedly compared with those who continue smoking. The earlier the age of stopping, the closer the survival curve for those who stop (dashed curve) approaches the curve for lifetime non-smokers. However, even stopping at age 55–64 years is beneficial, as the dashed curve for those who stop at this age still shows better survival than the solid curve for cigarette smokers.



The first tobacco control Handbook, *Reversal of Risk After Quitting Smoking* (published in 2007), was dedicated to Richard Doll, who had died in 2005. In 2003, Doll's 50-year follow-up of "his" cohort of British doctors had shown that about half of all smokers are eventually killed by smoking, that on average smokers lose about 10 years of life expectancy, and that those who have smoked cigarettes since early adult life but stop at age 60, 50, 40, or 30 years gain, respectively, about 3, 6, 9, or almost the full 10 years of life expectancy, compared with those who continue smoking.

The second tobacco control Handbook, *Methods for Evaluating Tobacco Control Policies*, addressed methods and provided a framework for guiding the evaluation of tobacco control policies, including smoke-free environments, limits on marketing, product labelling, and taxation. The third and fourth volumes more specifically covered the evaluation of the effectiveness of smoke-free policies and of the effectiveness of tax and price policies for tobacco control.

Tobacco use remains the leading preventable cause of premature death worldwide, and two thirds of tobacco-related deaths occur in developing countries. Unfortunately for human health, the scourge of tobacco use will not disappear overnight. Tobacco and cancer will continue to be a prominent topic for IARC as a research institution in the service of public health within the framework of WHO. IARC's work and publications provided the sound scientific basis for the WHO Framework Convention on Tobacco Control. The Convention is an international evidence-based treaty that entered into force in 2005 for the worldwide control of the supply and demand of tobacco products via a series of derived regulations and interventions.



The IARC Handbooks of Cancer Prevention programme was launched in 1995 under the coordination of Harri Vainio, who was then responsible for the IARC Monographs Programme. Vainio (left) is seen shaking hands with Nikolai Napalkov, a long-term IARC collaborator who was director of the N.N. Petrov Institute of Oncology in St Petersburg and subsequently Assistant Director-General of the World Health Organization. The first 10 Handbooks covered several potentially preventive measures, including the use of chemopreventive agents like non-steroidal anti-inflammatory drugs, the consumption of fruit and vegetables, and the use of sunscreens. Handbooks 11–14 were devoted to tobacco control. The programme gained fresh impetus in 2014 with a reassessment of breast cancer screening (see the chapter "Cancer screening and early diagnosis").