Instituts thématiques Inserm

Institut national de la santé et de la recherche médicale

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Press release

Cancer and the environment

A collective expert report by Inserm

In 2005, the estimated number of new cases of cancer in France was 320,000 in both sexes combined with 180,000 in men and 140,000 in women. The incidence of cancer has increased over the last 20 years and if demographic changes are taken into account (increase and ageing of the French population), the increase in the incidence rate since 1980 may be estimated to be +35 % in men and +43 % in women. It is currently impossible to precisely assess the proportion of this increase that is due to changes in medical practice.

Environmental changes may be partially responsible for this observed increase in the incidence of certain cancers. This hypothesis requires continued investment in research to measure both the exposure of populations to known or suspected carcinogens and to determine the existence and nature of the causal link.

Afsset asked Inserm to conduct an assessment of our knowledge about the links between the environment and nine cancers which were selected during a previous expert report because of their increased incidence over the last 25 years: lung cancer, mesothelioma, hematological malignancies, brain tumors and breast, ovary, testicular, prostate and thyroid cancers.

To prepare this new expert report, Inserm brought together two groups of researchers with skills in the fields of epidemiology, toxicology, clinical and occupational medicine and risk quantification. These experts analyzed data in the international literature for these nine cancers by considering as environmental factors those physical, chemical or biological agents present in the atmosphere, water, soil or food to which individuals are accidentally exposed and which are not generated by specific behaviors. Passive smoking is therefore discussed in this expert report whereas active smoking is not. The investigation takes into account general environmental factors and those present in the work environment.

The impact of an environmental factor on the cancer risk depends both on its link with this cancer and the prevalence of exposure to this factor in the population. An environmental factor conferring an even low or moderate increase in the risk of cancer will therefore have a high impact if it is very widespread in the general population. On the contrary, a potent carcinogenic factor will only have a low impact if very few people are exposed to it.

In many cases this evaluation of the impact of environmental factors is still restricted by the lack of data making it possible to quantify exposure throughout the lifetime of exposed populations and to specify co-exposures. Progress must be made in evaluating the effects of chronic exposure at low doses. This is a major public health issue as it concerns a large proportion of the population.

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(1) belot a, grosclaude p, bossard n, jougla e, benhamou e, et coll. Cancer incidence and mortality in France over the period 1980-2005. *Revue d'Épidémiologie et de Santé Publique* 2008, 56 :159-175

(2) Cancer, approche méthodologique du lien avec l'environnement, Edition Inserm, expertise collective 2005, 92p

Changes in the incidence of the nine cancers

An increase in the incidence of these nine cancers was observed between 1980 and 2000. More recently (2000-2005) the rate of increase has slowed down and, for certain localizations, the incidence has fallen. Cf. Appendix 1.

Prostate cancer

In 2005, prostate cancer was the most frequent of all cancers with 62,245 new cases. This cancer showed the highest increase in incidence rate between 1980 and 2005 (+ 6.3%) and the annual increase was even more marked between 2000 and 2005 (+ 8.5%). Prostate cancer is responsible for approximately 70% of the total increase in cancer in men in France over the last 25 years. The recent increase in the incidence of prostate cancer is mainly explained by changes in screening with the more widespread use of the systematic assay for PSA (*Prostate-Specific Antigen*) in France.

Breast cancer

Breast cancer remains the most frequent cancer in women. The number of new cases for 2005 was estimated to be 49,814, i.e. one of the highest incidence rates in Europe. The incidence rate of breast cancer increased by 2.4% on average per year over the period 1980-2005. It is difficult to quantify the proportion of this rise in the incidence of breast cancer due to changes in environmental or behavioral risk factors and the more widespread use of individual and organized screening.

Lung cancer

The incidence of lung cancer (23,937 new cases in 2005) increased in men until the end of the 1990s and then decreased over the period 2000-2005. On the contrary, in women, the incidence rate has continued to increase (4% per year) over the most recent period 2000-2005.

Thyroid cancer

Women accounted for 76% of the estimated 6,672 new cases of thyroid cancer occurring in 2005. Incidence rates considerably increased between 1980 and 2005 (+ 6%). The increased incidence mainly concerned the forms with a better prognosis due to increasingly early detection.

Hematological malignancies

Non-Hodgkin's malignant lymphomas are the most frequent hematological malignancies in adults with more than an estimated 10,000 new cases during 2005, with a little more than half in men. The incidence of non-Hodgkin's malignant lymphoma regularly increased from 1980 until the end of the 1990s in both sexes. This increase has slowed in women and was no longer observed in men over the period 2000-2005.

Mesothelioma

The incidence rate of mesothelioma (a total of 906 new cases in 2005) increased in men by almost 5% per year between 1980 and 1995 and then fell between 2000 and 2005 corresponding to a reduced incidence in cohorts born after 1930. In women, the incidence rate increased by 3.1% on average over the period 1980-2005. This rise was less pronounced between 2000 and 2005 (+ 1.8%).

Testicular cancer

The incidence rate of testicular cancer (2,002 new cases in 2005) increased by 2.5% over the period 1980-2005. This incidence of testicular cancer is on the rise in most countries of the world and this increase is even more pronounced in Europe.

Brain tumors

The incidence rate of malignant central nervous system tumors (4,090 new cases in 2005) increased regularly by 1% over the period 1980-2005.

Childhood cancers

Childhood cancer surveillance in France is ensured by two specialized national registries, one for hematological malignancies (first case registered in 1990) and the other for solid tumors (first case registered in 2000).
Approximately 1,700 new cases of pediatric cancer are diagnosed each year in France. The most frequent childhood cancer is leukemia with 470 new cases per year. The incidence of leukemia seems to have been stable since 1990 in France. Brain tumors are slightly less frequent with just under 400 new cases per year. Their incidence was stable over the period 1990-1999 according to data in regional pediatric registries. The national registry is still too recent to provide indications about any changes.

Recommendations for the epidemiological surveillance of cancers and exposed populations

- Maintain and improve the quality of cancer surveillance in the general population through the register perpetuation plan and improve the quality of cancer registration in French Overseas Territories (DOM-TOM);
- Encourage the recording of sufficiently precise addresses in the Francim network registries to allow their geocoding and subsequent linking with environmental databases;
- Develop electronic certification of the medical causes of death in order to improve the quality of certification, reduce the time required for this information to become available and facilitate access to these data by cancer registries;
- Complete cancer registration by a better use of the Programme for the Medicalization of Information Systems (PMSI) and national health insurance data (Long-term conditions ALD30) at national level in order to facilitate follow-up of cohorts of exposed subjects by epidemiologists;
- Encourage the formation or maintenance of cohorts (population follow-up) exposed to known environmental factors.

Environmental factors linked with cancers

The demonstration of a causal relationship between an exposure factor and a disease is a complex process. A considerable amount of epidemiological evidence must first be obtained and compared with available toxicological data. The many substances suspected to be involved in cancer development may be classified into three categories by evaluating the abovementioned data, according to the International Agency for Research on Cancer (IARC) classification: definitely, probably or possibly carcinogenic. Cf. appendix 2.

Several environmental factors classified in IARC group 1 of definite carcinogens are involved in the cancers discussed in this assessment. These are mainly occupational risk factors (asbestos, certain metals, aromatic polycyclic hydrocarbons, benzene, ionizing radiation including radon etc). Factors present in the general environment have also been shown to be carcinogenic such as passive smoking, arsenic or radon. The list of putative factors is long and is extremely diverse and includes physical, chemical or biological agents. It should also be noted that the amount of information available about the relationship between environmental factors and cancer is very variable from one factor to another and also according to the cancer considered. Cf. appendix 3.

General recommendations for prevention and precautionary measures

- Ensure effective implementation of the measures for improving the quality of the environment (air, water, food) proposed by the French National Health and Environment Plan;
- Reinforce policies for suspending or reducing occupational exposure to CMR substances (carcinogenic, mutagenic and reprotoxic);
- Set up databases documenting exposure histories in the workplace from representative samples;
- Improve traceability and registration at individual level of past or current exposure to workplace carcinogens; the use of bio-metrology should be reinforced when available;
- Step up actions for informing company staff and employees responsible for prevention about the risks of exposure to workplace carcinogens;
- Improve recommendations concerning the surveillance of populations occupationally exposed to carcinogenic substances, taking recent scientific data into account (using an evidence-based medical approach);
- Set up well-sampled databases of exposure in the general environment, taking into account lifestyles at different ages.

ASBESTOS

Asbestos is a known workplace carcinogen for the lung (even in the absence of asbestosis) and for

mesothelioma. It is the most frequent occupational exposure leading to lung cancer.
Even if recent data show a clear reduction in levels of exposure since 1997 (year in which the use of asbestos was banned in France), different professions may still have to work with materials containing asbestos. There are specific regulatory provisions on interventions involving the replacement of asbestos-containing materials, the inventory and control of the state of conservation of asbestos-containing materials in situ and for the waste management circuit.

Recommendation: reinforce measures for following up exposure to asbestos

- Reinforce prevention and protection measures in industrial sectors in which exposure to asbestos may occur within the scope of the asbestos action plan.
- Provide information to workers about all the sources of residual exposure but also to private individuals carrying out various types of renovation work.

RADON IN THE HOME AND WORK ENVIRONMENTS

Radon is classified as a known lung carcinogen. It may also be involved in adult and childhood leukemia.

It has long been known that radon causes death from lung cancer in miners working in particular in uranium mines. Although these mines have been closed in France since 2001, other workers may be occupationally exposed to high radon concentrations (other mines, thermal spas etc.) or because they sometimes work underground (mushroom beds, wine cellars etc).

It is today recognized that radon represents a risk even at the concentrations found in the home or in public buildings. The excess risk is estimated to be 8-10% for 100 Bq/m^3. A large number of people are exposed. A nationwide measurement campaign was carried out inside the homes of more than 10,000 towns and villages in all French metropolitan *départements* and in Corsica. A radon concentration of more than 200 Bq/m3 was observed in approximately 9% of homes.

Recommendation: reduce exposure to radon in the home and workplace

- Continue to make an inventory of situations leading to radon exposure at work. A reliable estimate of the exposure and the number of workers concerned must be obtained;
- Disseminate information about the risks to all persons potentially exposed at work and to the professionals responsible for their medical follow-up; the radiation protection standards currently in force in mines should be adapted to these populations
- Set up databases on high-risk geographical areas for radon emanation and sites with mining waste that may contaminate rivers;
- Promote tools for informing the public, building workers and environmental health teams about the risks and preventive measures that may reduce exposure;
- Study the feasibility of different intervention strategies in order to achieve the targets fixed by European regulations.

FINE AND ULTRAFINE PARTICLES

Several studies have shown a link between airborne particles and lung cancer. Particles that must meet regulatory requirements (PM_{10}) are a complex mixture varying from place to place and according to the time of year. They are mainly emitted by road transport, heating and industrial activities. Data acquired on diesel particles have played an important role in the understanding of the biological effects. Diesel particles represent in France up to 90% of particulate emissions related to road traffic.

The mean annual concentrations of PM_{10} fell between 1996 (date of the start of their surveillance) and 1999. No clear trend for any further fall was observed from 1999 to 2006 (values of 20 µg/m3 are currently recorded by urban air control stations and these values are higher near roads), despite the reductions in emissions in most sectors.

Fine particles with a diameter of less than 2.5 micrometers ($PM_{2.5}$) are considered to have a higher biological activity than large particles as they can reach the lung alveoli and cross epithelial barriers (ultra-fine particles). Certain studies have estimated that approximately 1,300 and 1,900 lung cancer deaths could be avoided each year in 23 European cities if the mean $PM_{2.5}$ levels were reduced to 20 and 15 µg/m3 respectively. Moreover, some authors have estimated that 10% of lung cancers were caused by exposure to $PM_{2.5}$ by recording the $PM_{2.5}$ concentrations in individuals living in four French urban areas (Paris, Grenoble, Rouen and Strasbourg).

The new European air quality framework directive (published in June 2008) introduced a limit for airborne $PM_{2.5}$ dust which was not regulated until now. The target value of 25 $µg/m^3$ in 2010 will become stricter from 2015.

Recommendation: reduce exposure to fine and ultrafine particles

- Implement the advice of various institutions[3], by introducing in France the daily and annual limit values for $PM_{2.5}$ concentrations of 25 $µg/m^3$ and 10 $µg/m^3$ respectively, proposed by

WHO/Europe, by 2020, with a restrictive annual reduction plan;

- Take the necessary measurements to reduce ambient PM concentrations and therefore the emissions by industrial sites and on air monitoring stations near roads where annual and daily limit values are exceeded;
- Promote the use of devices to reduce the emission of fine and ultrafine particles by motor vehicles and in particular, medium and heavy goods vehicles and buses, which are the main sources.

X AND GAMMA RADIATION

External exposure to ionizing radiation is classified as a definite carcinogen by the IARC. Many studies have shown or suggested an increased risk of several types of cancer (lung cancer, leukemia, thyroid cancer, breast cancer, mesothelioma, brain tumors) after exposure to X and gamma ionizing radiation. The excess risk per unit dose is generally higher for exposure during childhood than at an adult age. In particular, it has been shown that repeated X-ray examinations either in children or adults, increase the risk of breast cancer, and may increase that of other cancers.

The professionals concerned by exposure to X or gamma radiation are workers in the nuclear industry, radiologists and radiologist technicians. More than 250,000 individuals are monitored annually in France for external exposure to ionizing radiation. More than 95% of these radiation workers receive less than 1 mSv (recommended annual dose limit for the public), whereas a few dozen receive more than 20 mSv (mean annual radiation dose limit for radiation workers, established over a 5-year period).

In the general environment, various permanent systems allow continuous monitoring of radiation dose rates in the air or water, complemented by specific campaigns. This data is used as a basis for estimating the exposure of the French population to ionizing radiation.

Approximately 60 to 73 million X-ray diagnostic examinations are conducted each year in France, i.e. approximately one examination per person. An increase of 5 to 8% has been noted in the number of examinations conducted per year. Between 1983 and 1996, the frequency of radiological examinations increased by 10% whereas the average dose per examination increased over the same period by 20% and the annual collective dose by almost 50%. CT scanners are responsible for about 40 % of the collective dose received.

Recommendation: Monitor exposure to X and gamma radiation

- Complete the individual national registration of occupational exposures of radiation workers, currently limited to external exposures. The reconstitution of doses received by internal contamination would improve the estimation of the real exposure levels of workers;
- Carry out a follow-up study of radiological practices in France taking into account the number of people concerned. It is particularly important to better specify the exposure of children, who constitute a particularly susceptible population as well as the doses received, in order to evaluate the long-term risk for health and to target actions to reduce exposure;

[3] Opinion of the *Conseil national de l'air* dated March 22nd, 2006, the *Conseil Supérieur d'Hygiène Publique de France* dated May 12th, 2006 and the *Haut conseil de la santé publique* dated November 7th, 2007

- Set up an individual national register of X-ray diagnostic examinations based on the file that already exists for workers exposed to ionizing radiation;
- Introduce a diary of doses received by each individual. Dosimetric information is given in the report of examinations using ionizing radiation (Official Gazette (JO) of September 29, 2006)

PESTICIDES

Pesticides include different chemical families which have different uses (insecticides, weedkillers, fungicides etc), depending on the agricultural context. IARC has classified the professional application of non-arsenical insecticides among the activities of the probable carcinogenic group (group 2A).

Arsenic is classified as a definite carcinogen, captafol and ethylene dibromide as probable carcinogens (group 2A) and eighteen molecules, including DDT, are classified as possible carcinogens (group 2B). Nearly one thousand molecules have been marketed in France; the risks related to these molecules cannot be evaluated because of the lack of sufficient toxicological and epidemiological data.

Occupational exposure to pesticides has been linked, in particular, with lymphoid hematological malignancies. Studies among farmers suggest that they may also be associated with brain tumors and hormone-dependant cancers (prostate, breast, testicular and ovarian cancer).

Childhood leukemia in children and, to a lesser extent, brain tumors have been linked with the home use of pesticides, in particular household insecticides, by mothers during pregnancy and in their children's early years.

Most studies however are extremely imprecise about the extent and type of exposure to pesticides, and simply report the use or not of pesticides or the major families such as insecticides, fungicides, weedkillers. The real exposure situation in an agricultural setting is much more complex, because of the diversity of sectors, crops, tasks and equipment used.

Pesticides are found in all environmental compartments and may therefore lead to exposure of the general population through food, drinking water, air and dust inside and outside the home. Data concerning the health risk of these contaminations are too fragmentary and cannot therefore be used to define thresholds in different environments.

Recommendation: Reduce exposure to pesticides

- Act both on the type of pesticides and the ways in which these products are used to reduce exposure according to the objectives of the French Interministerial Plan for reducing pesticide-related risks 2006-2009;
- Improve the information given to professional or domestic users of pesticides and training of professionals;
- Develop a better understanding of the contamination of environmental compartments (air, water, soil and food);
- Concerning the follow-up of exposed populations, document exposure for each type of intake; distinguish between the different types of pesticide and the ways in which they are used, evaluate the quantities used, specify the time of year when they are employed and use exposure markers. This data should make it possible to better define the risk related to the use of these products.

Research to improve risk management control

The problem of the effects of chronic exposure to low doses of pollutants and mixtures remain unresolved. Likewise, the possible interaction between different pollutants (synergy, opposition, independence) may be crucial for contaminants that are often found in association (for example pesticides and dioxins) or contaminants present in particles (components of airborne particles). Lastly, many pollutants may have multiple effects and all possible action mechanisms must be examined.

The exposure of the general population to one or more putative chemical or physical carcinogens generally involves exposure to low doses. The question of the risk at low doses may be illustrated by the example of exposure to ionizing radiations.

Epidemiological data on the occurrence of cancer after exposure to radiation was obtained for populations after external exposure of the whole body to high doses over a short period of time. Assumptions must then be made in order to extrapolate the estimated dose-response relations to populations subjected to different types of exposure (chronic exposure, low-level exposure, internal contamination by ingestion or inhalation etc). Many uncertainties persist, in particular about the effects of chronic exposure to low doses and the effects of internal exposure. The effects of ionizing radiation below 100 mSv have not been demonstrated, although the risks potentially associated with this exposure are of major importance for public health insofar as a significant proportion of the general population is exposed to these low doses. This scientifically unresolved situation has meant that many divergent approaches may be adopted as concerns risk management (from the same data). The current system for protection against radiation is based on a linear model of low-dose extrapolation compatible with available knowledge. The importance of taking into account factors such as age at the time of exposure, time since exposure or dose rate in this model has become increasingly clear for the evaluation of the cancer risks at low doses of ionizing radiation.

All individuals do not react in the same way to exposure to carcinogenic agents. There is immense genetic diversity from one individual to another due to the polymorphic nature of the human genome. The efficacy of enzymes involved in DNA repair, and the enzymes which play a role in the metabolism of carcinogens (activation or detoxification for elimination from the body) depends on the different nucleotides present in the genome (genetic polymorphisms). These differences in enzyme efficacy may modulate the genotoxic effects of environmental factors. The situation is still more complex in the case of hormone-dependant cancers since many polymorphic enzymes are involved in hormone metabolism.

Gene-environment interactions have already been investigated in many studies, in particular in tobacco-related cancers such as lung cancer. Very few interactions have been demonstrated in these studies and these are rarely reproduced in the international literature. Recent progress in genotyping techniques (biochips) has made it possible to analyze several hundreds of thousands of polymorphisms simultaneously during epidemiological studies. These technologies may be used during large-scale international studies which should make it possible to define the interactions between environmental factors and genetic polymorphisms in all their complexity, provided that considerable efforts are made to characterize the environment.

Recommendations: Step up epidemiological, toxicological and molecular research

- Promote cutting edge etiological research in the field of environmental cancer risks, with no restrictions on topic, by supporting the recruitment of new researchers and training focused on these problems;
- Support studies on the effects of exposure to low doses of agents recognized to be carcinogens at high doses;
- Support investigations for integrated whole-life risk analysis;
- Continue and step up research to improve the quantification of the links between exposure and risk (determination of dose-effect relationships, modeling);
- Continue and enhance research into the joint effects of exposure to two or more carcinogens (synergy, additivity, antagonism);
- Continue and step up large-scale epidemiological research on the interactions between genetic factors and environmental factors;
- Promote and support fundamental research on the carcinogenic action mechanisms of pollutants;
- Develop new toxicological techniques appropriate to the situation of exposure to mixtures of compounds present in trace amounts. This will require an appropriate ecotoxicogical and pharmacological approach capable of describing cell action mechanisms, transbarrier passage and cell interactions;
- Develop risk-modeling tools and skills, in particular to determine dose-response relations and take into account toxicodynamic and toxicokinetic data.

For further information

What is a collective expert report by Inserm?

Inserm has been conducting collective expert reports since 1994. About sixty collective expert reports have been drafted in numerous fields of medicine.
The aim of Inserm collective expert reports is to provide a scientific viewpoint on a specific medical issue based on a critical analysis and overview of all the international scientific literature. It is conducted at the request of institutions that would like to obtain the most recent research-based data in order to help them in public policy decision-making. The expert report should be considered to be an initial stage before making subsequent decisions.
In order to answer the question raised, Inserm brings together a multi-disciplinary group of recognized experts, consisting of scientists and doctors. These experts collate and analyze scientific publications (approximately 1,800 articles and scientific and medical reports for this collective expert report) and draft a synopsis.
"Key points" are identified, and recommendations are sometimes made.
The conclusions formulated as a result of the collective expert report research foster discussions among the professionals concerned and in society as a whole.

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Appendix 1: Incidence of the cancers studied in men and women in France according to the 1980-2005 data

Women

Localization	2005 Incidence		Change in incidence	
	Number of new cases	Rates[a]	1980 to 2005[b]	2000 To 2005[b]
Breast cancer	49,814	101.5	+2.4	+2.1
Lung cancer	6,714	12.6	+5.1	+5.8
Thyroid cancer	5,073	12.7	+6.0	+6.1
Non-Hodgkin's malignant lymphoma	4,701	8.2	+2.9	+0.4
Ovarian cancer	4,375	8.1	-0.4	-1.0
Multiple myeloma[c]	2,071	2.9	+1.8	+1.1
Tumors of central nervous system	1,865	4.2	+1.1	+0.6
Acute leukemia[d]	1,425	3.5	+0.9	+0.9
Chronic lymphoid leukemia	1,368	2	+1.2	+0.7
Hodgkin’s Lymphoma	757	2.5	+ 1.1	+3.3
Pleural cancer (including mesothelioma)	264	0.4	+3.1	+1.8

Men

Localization	2005 Incidence		Change in incidence	
	Number of new cases	Rates[a]	1980 to 2005[b]	2000 to 2005[b]
Prostate cancer	62,245	121.2	+6.3	+8.5
Lung cancer	23,937	50.5	+0.2	-0.5
Non-Hodgkin's malignant lymphoma	5,523	12.1	+2.7	-0.1
Multiple myeloma[c]	2,445	4.6	+2.2	+1.5
Tumors of central nervous system	2,255	5.7	+0.7	+0.1
Testicular cancer	2,002	6.4	+2.5	+2.7
Chronic lymphoid leukemia	1,856	3.6	+0.6	+0.2
Acute leukemia[d]	1,657	4.5	+0.9	+0.9
Thyroid cancer	1,599	4.2	+5.8	+6.4
Hodgkin’s Lymphoma	787	2.3	-0.9	-0.8
Pleural cancer (including mesothelioma)	642	1.2	+1.7	-3.4

[a] Standardized rate according to the age structure of the world population for 100,000 person-years;
[b] Mean annual rate of change for the standardized rate;
[c] Multiple myeloma and immunoproliferative diseases;
[d] Myeloid and lymphoid;
[e] Mortality data are too low to show any trends

Appendix 2: Classification systems of the plausibility of a causal relationship

Systems used to classify the degree of plausibility of a causal link have been proposed and are routinely used in practice. The IARC regularly brings together experts to assess the carcinogenic nature or not of exposure to substances of all types present in the environment and publishes monographs to describe this evaluation. Data in humans and experimental animals are taken into account in order to obtain a global evaluation for each substance and a five-level classification of the plausibility of the carcinogenicity of a substance in humans:

group 1: Carcinogenic to humans
group 2A: probably carcinogenic to humans
group 2B: possibly carcinogenic to humans
group 3: not classifiable as to carcinogenicity in humans
group 4: probably not carcinogenic to humans

Group 1: The agent (mixture) is carcinogenic to humans[4]

This category is used when there is *sufficient evidence* of carcinogenicity in humans. Exceptionally, an agent (mixture) may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is *sufficient evidence* of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity.

Group 2A: The agent (mixture) is probably carcinogenic to humans

This category is used when there is *limited evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals. In some cases, an agent (mixture) may be classified in this category when there is *inadequate evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent, mixture or exposure circumstance may be classified in this category solely on the basis of *limited evidence* of carcinogenicity in human.

Group 2B: The agent (mixture) is possibly carcinogenic to humans

This category is used for agents, mixtures and exposure circumstances for which there is *limited evidence* of carcinogenicity in humans and less than *sufficient evidence* of carcinogenicity in experimental animals. It may also be used when there is *inadequate evidence* of carcinogenicity in humans but there is *sufficient evidence* of carcinogenicity in experimental animals. In some instances, an agent, mixture or exposure circumstance for which there is *inadequate evidence* of carcinogenicity in humans but *limited evidence* of carcinogenicity in experimental animals together with supporting evidence from other relevant data may be placed in this group.

Group 3: The agent (mixture or exposure circumstance) is not classifiable as to its carcinogenicity to humans

This category is used most commonly for agents, mixtures and exposure circumstances for which the evidence of carcinogenicity is *inadequate* in humans and inadequate *or limited* in experimental animals. Exceptionally, agents (mixtures) for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans. Agents, mixtures and exposure circumstances that do not fall into any other group are also placed in this category.

Group 4: The agent (mixture) is probably not carcinogenic to humans

This category is used for agents or mixtures for which there *is evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents or mixtures for which there is *inadequate evidence of carcinogenicity in humans* but evidence suggesting lack of carcinogenicity in experimental animals, consistently and strongly supported by a broad range of other relevant data, may be classified in this group.

In its 99 monographs (1972-2008), the IARC evaluated 935 substances and classified 105, 66, 248 and 515 in the above groups 1, group 2A, group 2B and group 3 respectively and a single in category 4. Despite the usefulness of these evaluations, it should be noted that the elements taken into account are similar to Hill's criteria and are therefore subject to similar limitations.

[4] Definition of the five groups dated 1999. English language version revised in 2006, accessible on the website http://www-cie.iarc.fr/

Appendix 3: Environmental factors linked with the cancers studied

Cancer	Definite carcinogens (group 1) or probably carcinogens (group 2A)[a]	Putative factors [a]
Lung	Asbestos, X or gamma radiation, radon, silica, cadmium, chromium VI, nickel, tungsten-cobalt carbide, polycyclic aromatic hydrocarbons, passive smoking, arsenic, beryllium, diesel exhaust, chlorotoluene, epichlorohydrin, benzoyl chloride, application of non-arsenical insecticides	Artificial mineral fibers Atmospheric pollution, various fine particles, particles derived from motor vehicles Pesticides Meat industry professions
Mesothelioma	Asbestos, erionite	Artificial mineral fibers Ionizing radiation Infectious agents: SV40 Virus
Hematological malignancies	Ionizing radiation (external exposure to X or gamma radiation), benzene, ethylene oxide, butadiene, HTLV-1, EBV, HHV8, HIV, *Helicobacter pylori, Borrelia burgdorferi*	VLF/EMF radiation (in the child), radon, Solvents, formaldehyde, PCB, HAP Pesticides, dioxins Car exhaust (in the child) Infectious agents: HCV ; other viruses, *Chlamydia psittaci*, *Campylobacter jejuni*
Brain tumors	High-dose ionizing radiation (external exposure during childhood or *in utero)*	Passive smoking (in the child) Pesticides Radio frequencies Lead, N-nitro compounds Infectious agents: SV40 (in the child)
Breast cancer	Ionizing radiation (external exposure to X or gamma radiation). Shift work with disturbance of circadian rhythms	Passive smoking Pesticides, dioxins, PCB, HAP, solvents
Thyroid cancer	Ionizing radiation: external exposure (X or γ radiation), internal exposure (contamination by radioactive iodine)	Pesticides Benzene formaldehyde Infectious agents: HCV, SV40, HTLV1
Ovarian cancer		Pesticides
Testicular cancer		Pesticides
Prostate cancer		Pesticides Cadmium, arsenic, PCB Infectious agents

[a] For the cancer considered