Risk factors for which no estimates were calculated

Section D1: Ionizing radiation

1. The low-dose-effect relationship controversy

Most of the dose from ionizing radiation received by human beings originates from medical X-rays and background radiation. The term "background radiation" encompasses cosmic radiation and terrestrial radiation, including radon decay products. Terrestrial radiation comes mainly from naturally radioactive atoms present in the earth's surface (e.g., uranium, thorium and their decay products) that can irradiate living beings through close contact, ingestion of water and foodstuffs and inhalation of air containing radionuclides or may be incorporated into the body (e.g., potassium 40, carbon 14 and tritium). There are major geographical variations in cosmic and terrestrial radiation: doses due to cosmic radiation are higher in polar regions and at altitude, and terrestrial radiation depends on concentrations of naturally radioactive atoms that vary greatly between different geological structures (Billon et al., 2005). However, the radiation dose due to radionuclides incorporated into the body is constant across the world, because their uptake is regulated by homeostatic mechanisms. The average annual effective dose delivered by background irradiation including radon is 2.4 mSv, with a typical range between 1 and 10 mSv in most countries, although in some regions it can reach 50 to 80 mSv (UNSCEAR 2000). Most of the effective dose, however, is related to lung dose from radon and its decay products; the average effective dose[1] excluding radon is of the order of 1 mSv.

Most of these sources deliver relatively low doses of less than 20 mSv per year at very low dose rates, i.e. below 2.5 µSv per hour. Most people in France have an average annual exposure below 5 mSv per year from all three sources (natural, medical and industrial). A small fraction of the total population is or may be exposed to higher doses of ionizing radiation for professional (e.g., pilots and aircrews, radiation workers in industry, research or medicine), circumstantial (e.g., high terrestrial content in radioactive products) or medical reasons (e.g., radiotherapy for cancerous diseases).

The old unit of radioactivity is the curie, the more recent one is the becquerel, which is much smaller. The amount of energy deposited in tissue by an exposure to ionizing radiation ("a dose") can be expressed in joules per kilogram. The International Commission on Radiological Units gives 1 joule per kilogram a special name, the gray. However, simply measuring the amount of energy absorbed by tissue from ionizing radiation is not enough to predict the amount of potential harm. There are different kinds of ionizing radiation, such as alpha, beta and gamma rays and neutrons. Experience has shown that a 1-gray dose of alpha rays, for example, is about 10 to 20 times more harmful than a 1-gray dose of gamma rays. Beta rays and X-rays are about as harmful as gamma rays. The relative biological efficiency (RBE) of neutrons versus gamma rays varies inversely with neutron energy down to 0.4 MeV, where it can reach values of 20 and more. To express the size of an exposure in terms of potential harm, a measurement of the absorbed dose in joules per kilogram (hence in grays) in a given organ or tissue is multiplied by "quality factors" for that kind of radiation. The quality factors are chosen so that 1 sievert of radiation is the amount of any kind of radiation which would cause the same amount of harm as would result from absorbing 1 gray of X-rays in the same organ or tissue; in this case the sievert is said to measure "dose equivalent'. The quality factor has been in part determined experimentally (RBE) and in part based on expert judgement. This dimensionless quality factor is chosen by the International Commission for Radiation Protection and the International Commission of Radiological Units. Some authors still use old units. One gray is equal to 100 rad and one sievert to 100 rem.

While the carcinogenic effects of high- and medium-dose radiation are well established, there is much controversy about the carcinogenic effects of low doses (10 to 100 mSv) of ionizing radiation in humans and even more so for very low doses (<10 mSv). This controversy has considerable public health implications, since most human beings are exposed to low or very low doses of ionizing radiation. Even if low-dose radiation entailed very low cancer risk, the proportion of cancer attributable to these sources of radiation might be substantial because everybody is exposed to cosmic, terrestrial and medical radiation. Therefore, a small error in low-dose risk assessment leads to large errors in the number of cancers attributed to ionizing radiation exposures, whether occupational or residential.

Estimation of low-dose risk critically depends on our ability to establish the relationship between dose (and the dose-delivery pattern, e.g., acute or fractionated, protracted) and detrimental effects, in particular within the range of low and very low doses.

A detailed discussion of this controversy is beyond the scope of this report and readers should refer to relevant publications (Rossi and Kellerer, 1972; Tubiana et al., 2004, 2005a, b, 2006a, b; Simmons, 2004; Brenner and Hall, 2003b, 2004; Brenner and Sachs, 2006; US NRC, 2007), but the different positions are summarized below.

There is a consensus based on recent results of biological and animal experimentation that:

- defence against ionizing radiation involves not only cells but their microenvironment and the immunological system ;
- changes in cell signalling and gene transcription (either activation or inhibition) are not the same in response to very low (< 10 mSv), low (< 100 mSv) or higher doses;
- when only a small proportion of cells are damaged, elimination by death is the main cell and tissue response (Rothman, 2003; Collis, 2004).

The position of the International Commission on Radiological Protection (ICRP), the Biological Effects of Ionizing Radiation committee (BEIR VII) is that:

- most of these results were obtained in vitro and have not been confirmed in vivo,
- the initial biophysical cell damage by ionizing radiation is proportional to the dose,
- a cancer arises from transformation of a single cell and cell neoplastic transformation can be induced by a bystander effect or result in genetic instability which could involve a supra-linear low-dose–effect relationship;
- hence, even the lowest dose has the potential to cause a small increase in the risk of cancer; the magnitude of the effect, however, is uncertain and the risk may be lower or higher than that predicted by a linear no-threshold (LNT) model;
- an LNT dose–effect relationship is compatible with epidemiological data and remains the best dose–effect model;
- an LNT dose–effect relationship allows the estimation of cancers attributable to ionizing radiation, whatever the dose, with adjustments taking into account the dose rate;
- any additional dose one receives, be it very low, must be added to doses we receive from other, unavoidable sources, including natural background radiation. On the basis of a lifetime commitment to dose from ionizing radiation (i.e., tens of mSv), we are above any threshold that might be credible from a radiobiological or even epidemiological perspective.

Conversely, the French academies of medicine and science consider that:

Because many organs and tissues of a human being are more or less exposed selectively as a result of internal contamination and localized medical exposures, it is convenient to use an additional concept, that of “effective dose”, which characterizes the overall potential health risk caused by any combination of heterogeneously distributed radiation. The effective dose accounts both for absorbed energy and type of radiation and for susceptibility of various organs and tissues to development of a radiation-induced cancer. This is done using a specific weighting factor for each tissue or organ on the basis of an equivalence of this risk compared to the risk resulting from the same dose equivalent homogeneously delivered to the entire body. The sum of these weighting factors is equal to unity. The sievert is also used as the unit for effective dose.

- multiple and convergent data show that not one single but several strategies provide cell and tissue defence against ionizing radiation;

- these are more effective for low doses and at low dose rates, since in that dose range cell death is predominant. DNA repair (which can be error-prone) is mainly activated against higher doses, in order to preserve tissue function; moreover, elimination of damaged or mutated cells is more effective at low doses and low dose rates (low dose hypersensitivity). Mitotic death eliminates cells with DNA damage when the dose or dose rate is too low to trigger activation of DNA repair.

- the incidence of misrepair is higher at high doses and high dose rates. Adaptive response can increase the efficacy of cell defence. Carcinogenic effect (per dose unit) varies with dose and dose rate.

- the LNT dose–effect relationship is incompatible with some biological data and with data pertaining to cancer induction by alpha emitters;

- for reasons of statistical power, most epidemiological studies amalgamate high-and low-dose exposure data and postulate an LNT dose–effect relationship. This is based on the erroneous hypothesis that cancer induction by radiation and defence mechanisms are similar in both cases ;

- the preliminary meta-analysis of cohort studies for which low-dose data (< 100 mSv) were available show no significant risk excess, either for solid cancer or for leukaemias;

- an LNT dose–effect relationship allows estimation of cancer attributable to ionizing radiation doses of 100–200 mSv, but leads to overestimation for lower doses.

Observational epidemiological studies on workers or patients will probably never have the statistical power to demonstrate a modest increased cancer risk associated with low-dose radiation (e.g., less than 10% excess risk), as such studies would need to include millions of subjects followed up over long periods, with accurate measurements of radiation exposure and appropriate control of numerous potential confounding factors (e.g., smoking, socioeconomic status).

Comparisons of mortality rates between groups deemed to be more highly exposed to radiation and the general population or some adequate control group have often led to the finding of equivalent or lower all-cause death and cancer death rates in the exposed groups. The current explanation for this observation is the so-called “healthy worker effect”, which assumes that subjects professionally exposed to radiation have higher socioeconomic status and probably have healthier lifestyle than average and therefore their cancer risk is lower than that of the average population. (Doll et al., 2005; Cameron 2002; Daunt 2002; Muirhead et al., 1999, 2003). This concept has been criticized and evidence for less smoking and/or drinking among workers has yet to be provided.

Assessment of cancer risk associated with exposure to low doses of ionizing radiation often relies upon model approaches, mainly using logistic models that allow other risk factors, such as tobacco or alcohol consumption, to be taken into account. Most models are based on assumptions about the type of relationship between low-dose radiation and organ-specific cancer risk. The US Committee on the Biological Effects of Ionizing Radiation (BEIR) family model (health risks from exposure to low levels of ionizing radiation) is often used for estimating excess risk of cancer due to low-dose radiation. The BEIR VII report issued in 2006 (BEIR VII 2006) includes the most recent version of this model. The model is based on the LNT hypothesis which postulates that the carcinogenic effect per unit dose is constant, irrespective of the dose and the dose rate. The validity of this assumption has been challenged by the report of the French academies (Tubiana, 2005) which provided biological and epidemiological arguments against this constancy (see above).

An alternative approach is to avoid the use of any model and to estimate the radiation odds-ratios for different dose ranges, taking into account potential confounding factors. This approach can also take into account the fact that the mechanisms of defence against ionizing radiation are not the same for different doses.

Because of the debate surrounding the effects of low doses of radiation, we chose not to estimate the numbers of cancer attributable to ionizing radiation in France, but rather to review briefly issues related to cancer risk and low-dose radiation,

including radon exposure and the consequences of the Chernobyl accident and its impact on thyroid cancer incidence.

2. Exposure in France to ionizing radiation

Background radiation

In France, according to the Institut de Radioprotection et de Sûreté Nucléaire (IRSN 2002), cosmic and terrestrial radiation delivers an average annual dose of 2.4 mSv. According to the BEIR VII model (2006), such exposure could cause nearly 6% of all cancers. However, large studies devoted to natural background exposures have not revealed any increased risk, even for doses 30 times higher. Thus, the existence of a background radiation cancer risk in France is speculative and no reliable attributable fraction can be proposed.

Indoor radon exposure

Release of radon and its decay products from the ground or from building materials results in indoor exposure. Exposure levels in houses are typically one order of magnitude lower than in underground mines. The estimation of an attributable risk due to indoor radon exposure requires dosimetric estimates and relative risk (RR) assessments for low radon concentrations.

The level of exposure of the French population to radon is not known precisely. Radon measurement requires caution and radon levels are highly sensitive to geology, season, weather, type of dwelling (private house or apartment building), construction materials and floor. Surveys carried out in France in 1982–2000, including 12 641 measurements (IRSN database) showed a crude arithmetic mean of 89 Bq/m3 and a geometric mean of 54 Bq/m3 for the entire French population. Weighted for population density, the average was 68 Bq/m3 (Billon et al., 2003). Though the geometric mean of these measurements is close to the weighted average of measurements in 29 European countries (58 Bq/m3) (UNSCEAR, 2000), the latter data are not representative of French population exposure, due to overrepresentation of individual dwellings and ground-floor measurements. These values contrast with those estimated by the Observatoire de la Qualité de l'Air Intérieur (OQAI) (Kirchner et al., 2006) including 570 houses representative of 24 million dwellings in continental metropolitan France: median 31 Bq/m3 in bedrooms and 33 Bq/m3 in other rooms.

A pooled analysis of European studies of residential radon exposure and lung cancer resulted in an RR of 1.08 (95% CI 1.03–1.16) for an increase in radon exposure of 100 Bq/m3 (Darby et al., 2005). The relative risk excess is, however, not significant for radon concentrations lower than 100 Bq/m3.

Range (Bq/m3)	RR	95% CI
< 25	1.00	0.87–1.15
25–49	1.06	0.98–1.15
50–99	1.03	0.96–1.10
100–199	1.20	1.08–1.32
200–399	1.18	0.99–1.42
400–799	1.43	1.06–1.92

These estimates take into account tobacco consumption level, but neither its duration nor environmental tobacco smoke. None of the relevant tobacco risk parameters *("daily amount smoked, duration of smoking, age at onset of smoking, cumulative amount smoked […], environmental tobacco smoke"[2])* were taken into account in the quoted studies of radon risk (Lubin, 1997; Darby et al., 2005).

Consequences of radon exposure increase dramatically for smokers: *"In the absence of other causes of death, the absolute risks of lung cancer by age 75 years at usual radon concentrations of 0, 100, and 400 Bq/m3 would be about 0.4%, 0.5%, and 0.7%, respectively, for lifelong non-smokers, and about 25 times greater (10%, 12%, and 16%) for cigarette smokers."* (Darby et al., 2005).

The calculation of attributable fraction for radon exposure is therefore debatable, since it can rely either on significant proven risk (smokers and significant RR dose range) or on hypothetical extrapolated RR (including non-smokers and using global dose–RR estimates).

An estimate of lung cancer deaths in France attributable to indoor radon exposure (Catelinois et al., 2006) ranges from 1234 (90% uncertainty interval,

[2] Giles G, Boyle P. Smoking and lung cancer. In : Tobacco, Boyle P, et al. Ed., Oxford University Press, 2004; pp. 492-493.

593–2156) to 2913 (90% UI, 2763–3221), depending on the model considered. This estimate used an LNT dose–risk model which results in a high proportion of deaths (47%) related to radon concentration in the range 0–99 Bq/m3.

These results are debatable because of several considerations that lead to overestimation of the burden due to radon:

- epidemiological and animal data show a dose–risk relationship threshold for alpha emitters which should be taken into account;
- no significant risk excess was demonstrated for indoor radon exposure in the 0–99 Bq/m3 concentration range (Darby et al., 2005);
- Catelinois et al. made use of IRSN estimates of the French population exposition to radon (adjusted mean 87 Bq/m3) which are not consistent for French dwellings. Kirchner (2006) estimated that levels are significantly lower (31–33 Bq/m3) and that radon concentrations are higher than 100 Bq/m3 in only about 11% of dwellings, compared with 24% according to IRSN.

Medical radiation

Medical radiation includes diagnostic and therapeutic procedures with X-rays, scintigrams and metabolic radiotherapy (making use of radioactive products). Average doses and total annual doses resulting from diagnostic procedures were calculated for the year 2002 according to two hypotheses (Scanff, 2005). The main results (average of low and high hypothesis estimates) are given in the following table[1].

	Number of acts (%)	**Collective effective dose in man - mSv (%)**	**Average effective dose per act mSv**
Conventional radiology	60 635 575 (89.8%)	16 684 755 (36.6%)	0.28
Computerized tomography	5 109 481 (7.5%)	17 682 526 (38.8%)	3.46
Nuclear medicine	849 620 (1.2%)	3 402 402 (7.4%)	4.00
Interventional radiology	892 385 (1.3%)	7 771 511 (17%)	8.71
Total	67 487 062 (100%)	45 541 194 (100%)	0.67

The average dose per French inhabitant was 0.75 mSv/y. Estimates for 1982 from UNSCEAR (1988) lead to an average effective dose of 1.6 mSv/y, if one redistributes among all French subjects a “collective dose” estimated for each anatomic site of radiographic examination. These site-specific “collective doses” are displayed in the following table :

Collective effective dose equivalent from diagnostic x-ray examinations in France, 1982

a/ Examinations in which fluoroscopy is only used for positioning the patient prior to film radiography.

Examination	Collective effective dose equivalent (man Sv)	Accounted for by fluoroscopie (%)
Cervical spine	1680	18a/
Thoracic spine	2100	16.5 a/
Lumbar spine	8500	13 a/
Sacro-lumbar spine	3400	7 a/
Pelvis, hip	5350	3 a/
Abdomen	4120	6.5 a/
IV urography	20580	11.5 a/
Hysterography	810	17
Cholecystography	4860	34.5
Skull	4990	10 a/
Barium enema	8210	21.5
Barium meal	7460	31.5
Thorax	4110	3 a/
Cerebral angiography	1780	15
Thoracic angiogaphy	680	70.5
Abdominal angiography	5590	34
Inferior limbs angiography	280	15
Phlebography	940	37
Obstetrical abdomen	930	8 a/
Pyelography	370	24

An attributable fraction of cancers calculated from these exposures based on the collective dose of 45 541 194 man Sv is not reliable, since procedures generally involve very low doses for which the levels

of risk are unknown and cannot be merely derived from high-dose data. For example, each of the 5 to 6 million chest radiographic examinations delivers a mean effective dose of 0.02 mSv; each of the 1.5 to 2.2 million head CT scans delivers about 1.8 mSv.

An attributable fraction of cancers could be calculated relying on individual dosimetry estimates for repeated examinations resulting in total doses high enough for reliable risk factors to be available (> 50–100 mSv). Such cases are infrequent, however, and the required data are not available. Moreover, a study conducted in 2001–3 showed that for a given procedure, the dose varies greatly according to the radiographic device. For example, a face + profile chest radiography results in doses ranging from 0.09 to 0.70 mGy, and a profile lumbar column radiography from 9.5 to 36 mGy. Dosimetric estimation derived from the number and type of examinations, without actual dosimetric measurements, is therefore very approximate.

Computations using the BEIR VII model taking into account the age-distribution of medical X-ray examinations performed in the United Kingdom (Berrington et al., 2004) are a subject of controversy (Tubiana et al., 2004).

It may be noted that about twice as many medical X-ray examinations are performed in France as in the United Kingdom, and effective doses for medical X-rays in France are among the highest in industrialized countries (UNSCEAR 2000; Donadieu et al., 2006).

3. Impact of fallout from the Chernobyl accident on cancer in France

The Chernobyl accident occurred on 26 April 1986. Most of central and western Europe received fallout from the accident, with geographical variations in levels, depending on winds and other atmospheric conditions that prevailed in the days after the accident.

International collaborative studies coordinated by IARC and WHO have produced two reports on cancer consequences of the Chernobyl accident, for local populations and for the whole of Europe (Cardis et al., 2006a, b).

Estimation of cancers that could be attributable to fallout, based on food contamination measurements carried out in 1986 by the Service Central de Protection contre les Rayonnements Ionisants (SCPRI), indicated 0.5 to 22 attributable cancers for the whole period 1991–2000 (Verger et al., 2000, 2003). These results are probably biased towards overestimation, since measurements showing no food contamination were discarded. The authors used an LNT relationship but recognized that this model may overestimate the risk.

According to the BEIR VII model, between 0.003 and 0.012% of all cancers occurring before the age of 75 years (i.e., between 8 and 33 cancers) would be attributable to Chernobyl fallout in France in 2000. However, the validity of this model is open to discussion (see above).

Modelling performed by Catelinois et al. (2005) for eastern France, where the level of fallout was higher, indicated that during 1991–2007, out of 894 to 1716 thyroid cancers in subjects below 15 years of age, the excess due to fallout could be between 5 and 63 cases.

These estimates of attributable cancer rely on debatable dose reconstructions and dose–risk relationships. So far, direct epidemiological evidence of an excess in thyroid cancer incidence in France due to fallout is not available, but it should be noted that the power to detect an increase of the order of that predicted by the BEIR VII model is very small.

A sustained increase in thyroid cancer incidence was observed over recent decades (mainly for papillary cancer, little for follicular cancer), with no change in slope of the incidence curve after 1986 (Figure D.1). In contrast, mortality rates from thyroid cancer remain low and steadily decrease with the calendar year, without any noticeable influence of the Chernobyl accident (Figure D.2). The increase in thyroid cancer incidence in France over recent decades is mostly due to the introduction of new diagnostic procedures; a study of diagnostic practices in six centres specializing in thyroid diseases in France by Leenhardt et al. (2004 a,b) showed the following data on methods used for thyroid investigation:

	1980	2000
Ultrasonography	3%	85%
Fine needle biopsy	4.5%	23%

Since thyroid glands (particularly in women) often harbour a few islets of “cancerous” tissues, the more imaging and biopsy methods gain in sensitivity,

the more “thyroid cancers” are found. The clinical significance of most screen-detected thyroid cancers remains questionable because most would remain indolent and would never progress to an invasive cancer.

Increases in thyroid cancer incidence in departments with cancer registries (Colonna et al., 2002) showed no correlation between the magnitude of the annual increase in thyroid incidence and estimates of deposition of caesium 137 or iodine 131 in France in April and May 1986.

In April 2006, the InVS released complete reports on surveillance of thyroid cancer in France, including numerous new data showing that the Chernobyl accident is not likely to have contributed to increasing the incidence and mortality from thyroid cancer in France (Chérié-Challine et al., 2006a,b)[3].

4. Concluding remarks

At present, no direct observational epidemiological data support an association between exposure to low doses of ionizing radiation and cancer occurrence. Hence, observational epidemiological data, which are also compatible with absence of association or with a rather small association, are very difficult to assess. Estimates based on LNT models, on the other hand, may markedly overestimate radiation-attributable cancers.

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Figure D.1.1 - Annual age-standardized incidence and mortality of thyroid cancer in France
(Remontet et al., 2003)

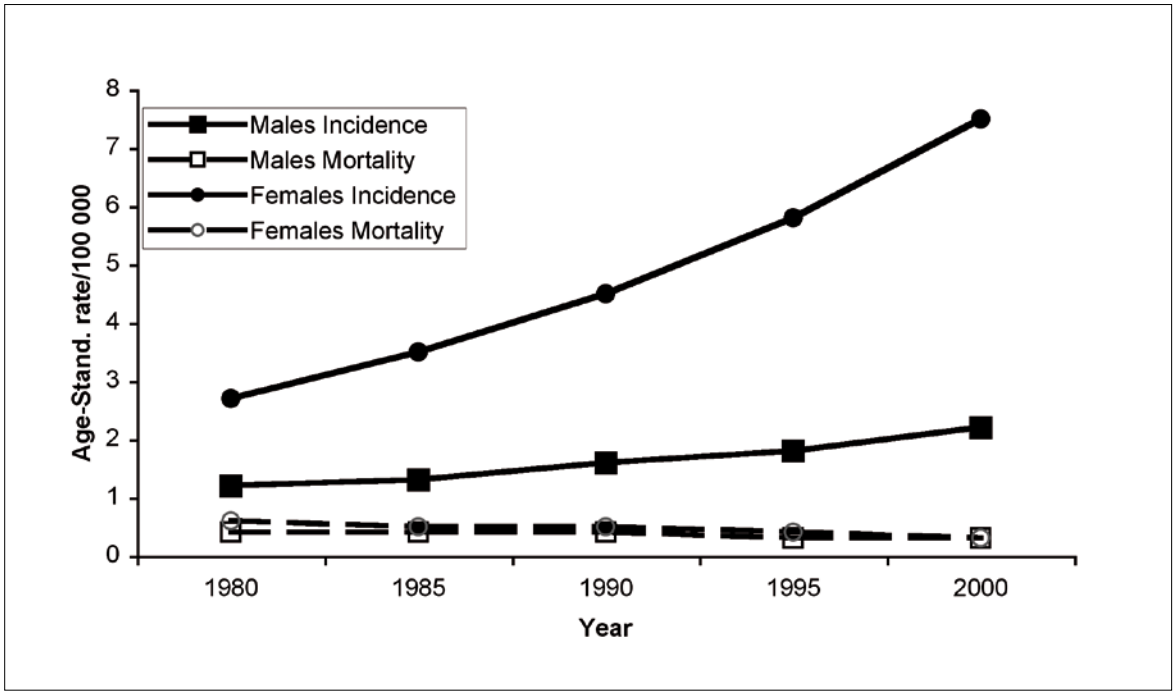
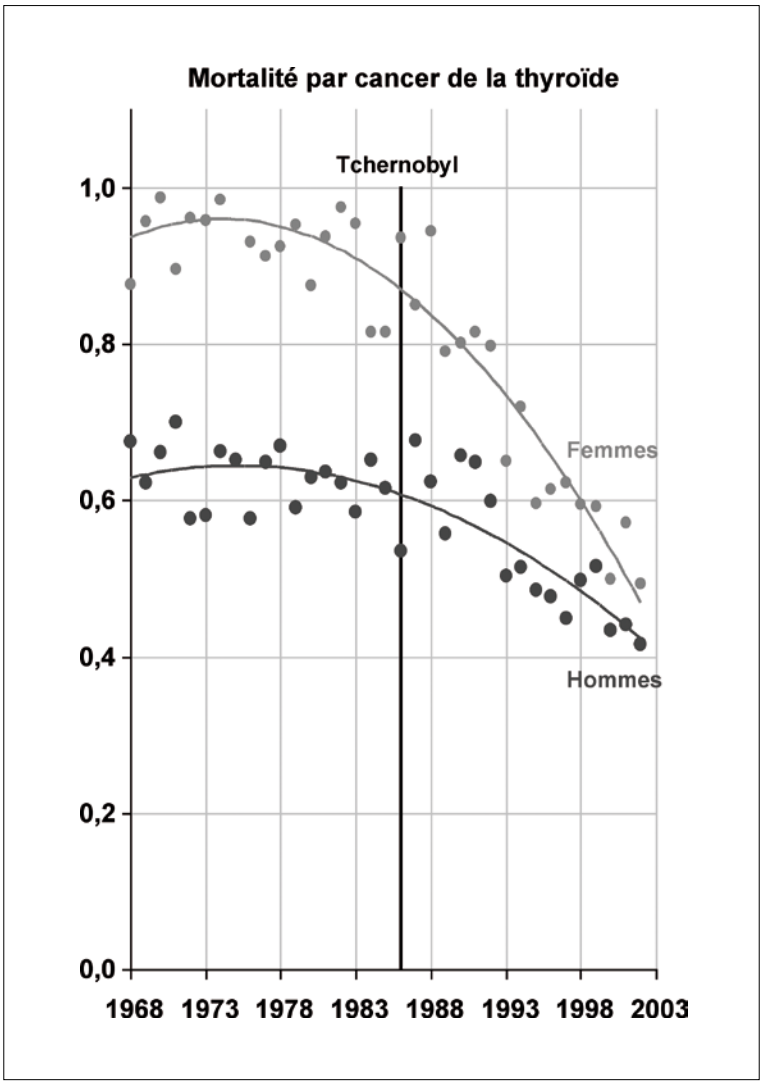


Figure D.1.2 - Mortality from thyroid cancer in France in deaths per 100 000, age-standardization on European Standard Population (Source: C. Hill, Institut Gustave Roussy)



Section D2: Established risk factors for cancer not included in the study

A causal association has been established between human cancer and various agents classified by IARC as Group 1 carcinogens to which a negligible proportion of the French population was or might have been exposed in 1985. Nonetheless, we briefly review these agents, without providing estimates for the number of cancers attributable to these factors.

1. Inorganic arsenic in drinking water

Inorganic arsenic in drinking water causes bladder, skin and lung cancers in humans (IARC, 2004). The most significant exposures, in terms of levels and populations, occur around the Gulf of Bengal, in South America and in Taiwan, China. In Europe, intermediate levels of arsenic in groundwater (below 200 µg/L) are found in areas of Hungary and Romania in the Danube basin, as well as in Germany, Greece and Spain. The studies showing an excess cancer risk have been conducted in areas with elevated arsenic content (typically above 200 µg/L), while the results of studies of bladder cancer conducted in areas with low or intermediate contamination are suggestive of a possible increased risk (IARC, 2004).

No data are available on the proportion of the population in France exposed to arsenic in drinking water, but it is known (Micquel, 2003) that in some regions including Alsace and the Massif central, arsenic levels may be high for up to 200.000 inhabitants which would result in few additional cancer cases each year.

There exist in France pockets of local soil and water contamination due to gold mines, e.g., in Salsigne (Aude). Gold miners from this area were exposed to high arsenic doses (and also to radon and silica) and had twofold higher mortality from lung cancer (Simonato et al., 1994). Excess deaths from lung, pharynx and digestive system cancers were reported in villages surrounding the industrial mining complex (Dondon et al., 2005).

2. Additional cancer risk factors

A number of additional chemical or physical agents, infections, lifestyles or geographical circumstances have been classified as Group 1 carcinogens by the IARC, that are not relevant to France. These factors include:

- Parasitic infections such as *Schistosoma haematobium*, involved in bladder cancer in Africa (IARC 1994c), and *Opisthorchis viverrini*, involved in liver cholangiocarcinoma in south-east Asia (IARC, 1994d). The prevalence of these infections is negligible in France.

- Aflatoxins are toxins produced by natural *Aspergillus* fungi *(A flavus, A nomius, A parasiticus)* that can be found in corn and raw peanuts (IARC, 2002). High intake of aflatoxins is associated with elevated rates of hepatocarcinoma. This association is found mainly in Africa and south-east Asia, where HBV carriers who eat food contaminated with aflatoxins have a more than 100-fold increase in liver cancer risk. Although contamination of foodstuffs may occasionally occur in France, its impact on liver cancer burden is likely to be minimal.

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Section D3: Factors suspected, but not demonstrated, to be causally associated with cancer in humans

A large number of risk factors have been linked to cancer risk in epidemiological studies. For most of them, the current evidence does not allow a conclusion as to the presence or absence of a causal relationship. The present review of avoidable causes of cancer in France is based on established risk factors, selected on the basis of evaluations made by authoritative international panels, chiefly within the IARC Monographs programme. It is not possible to review in detail all suspected causes of cancer. However, because of their importance in the public perception as important causes of cancer, in this chapter we discuss the evidence available for selected factors, including pollutants, non-ionizing radiation (other than UV light) and nutritional factors.

1. Diet

Epidemiological studies have found strong associations between diet and cardiovascular diseases, that have been largely reproduced in laboratory experiments. These findings have led to the development of efficient public health and pharmaceutical interventions. In contrast to cardiovascular diseases, diet and cancer remains at present a most difficult and complicated area of study. Doll and Peto (1981) estimated that 35% of cancer deaths in the USA could be attributable to dietary and nutritional practices, with, however, a wide "range of acceptable estimates" between 10% and 70%. These estimates have been widely quoted and used without comment by subsequent authors addressing the impact of nutrition on cancer burden. Most of the evidence available at the time of Doll and Peto's report was based on case–control studies, and selection and recall biases have been found to be particularly influential in nutrition-related investigations using the case–control design. More recently, Doll and Peto made new estimations according to which 25% of cancer deaths could be due to "diet", with a range of acceptable estimates of 15 to 35% (Doll and Peto, 2005). As for their 1981 estimates, Doll and Peto provided little detail on how these estimates were computed.

Many early studies consistently suggested a link between intake of dietary fat and increased risk of several common forms of cancer. However, several recent, well conducted large-scale cohort studies and randomized trials, conducted mainly in North America, have provided evidence against an major direct role of nutritional factors in cancer occurrence (e.g., for breast cancer: Michels et al., 2007; for colorectal cancer: Marques-Vidal et al., 2006). These studies also found evidence of a lack of association between fibre intake and risk of colorectal cancer (Michels et al., 2005; Park et al., 2005) and no evidence that fat intake influences the risk of colorectal cancer.

The evidence linking high intakes of fruit and vegetables to lower cancer risk has been reviewed by an IARC working group (IARC, 2003): there was no cancer for which the evidence was evaluated as sufficient to conclude that higher fruit or vegetable intake had a preventive effect.

Higher consumption of milk and calcium is associated with lower risk of colorectal cancer, with the inverse association for milk limited to cancers of the distal colon and rectum (Cho et al., 2004). Preserved meat and red meat probably increase the risk of colorectal cancer, but relative risks found so far are of the order of a 30% increase for very high versus very low intakes of red meat (Norat et al., 2005), which is quite lower than anticipated by results of ecological and case-control studies.

In contrast, the recent studies have underlined the role of obesity and overweight in many human cancers (e.g., colorectal cancer, breast cancer and pancreas cancer).

It is worth noting that an evidence-based attempt

to estimate the attributable burden of cancer in the Nordic countries did not try to provide an estimate for nutritional factors, because of lack of evidence of the implication of these factors in cancer occurrence (Olsen et al., 1997).

The importance of dietary factors in cancer must therefore be reconsidered. The following example suggests that one must be cautious with Doll and Peto's 2005 estimate that 25% of cancer mortality could be due to dietary factors. Suppose that a protective nutrient A confers a reduction in the mortality from oro-pharyngeal, oesophageal, gastric, pancreatic and colorectal cancer that reaches 20% among subjects in the highest (fifth) quintile of intake (Table D3.1), as compared to subjects with lowest intake (first quintile), with a linear relationship in the intermediate groups. The 20% reduction is a realistic figure, similar to results found in some of the best conducted studies.

Table D3.1 – Hypothetical population distribution and RR of a protective nutrient A in the French population

Categories	**1 (lowest intake)**	**2**	**3**	**4**	**5 (highest intake)**
% population in each category	20%	20%	20%	20%	20%
RR	1.00 (reference)	0.95	0.90	0.85	0.80

If all the population had an intake of nutrient A similar to that observed in the lowest quintile, i.e., everybody had minimal intake of nutrient A, there would be an 11% increase in cancer deaths associated with this nutrient A (Table D3.2), an increase that would correspond to 2.9% of all cancer deaths in males and 2.7% in females.

Table D3.2 – Theoretical numbers of cancer deaths attributable to protective nutrient A comparing a population whose distribution is presented in Table D3.1, and a population with 100% of subjects in the lowest quintile

	Males	**Females**
Oral cavity and pharynx	435	81
Oesophagus	386	77
Stomach	351	223
Colon-rectum	927	845
Pancreas	403	356
Total	**2502**	**1583**
% of all cancer	**2.9%**	**2.7%**

This example suggests that Doll and Peto's estimate of 25% of cancer mortality attributable to diet in their 2005 report was somewhat excessive. It is thus unlikely that the avoidance of still unknown dietary risk factors or the promotion of still unknown protective nutrients would lead to reductions in cancer mortality of the magnitude proposed by Doll and Peto. In Section E1, new working hypotheses on diet and cancer are presented.

2. Outdoor air pollution

Epidemiological studies and laboratory experiments in animals have shown that air pollution can influence all-cause mortality, mainly through its now well documented impact on acute cardiovascular events and on respiratory diseases. However, the effects of air pollution on cancer mortality, particularly lung cancer mortality, are still a matter of debate.

In most European countries, outdoor air quality has much improved in recent decades (WHO-Europe, 2003). A consistent finding of US and European studies on air pollution has been the steady decrease in air pollutant concentrations over time, and nowadays, on average, air in North American and European cities seems less loaded with particles than 10–20 years ago (e.g., Pope et al., 2002; Filleul et al., 2005).

Epidemiological studies on cancer risk from outdoor air pollution have been conducted for several decades and many definitions of outdoor air pollution exposure have been used. The IARC Monographs programme has not evaluated the carcinogenicity of outdoor air pollution as a complex mixture, although some of its components have been subject to separate evaluations, including benzo[a]pyrene (Group 1), several other polycyclic aromatic hydrocarbons (Groups 2A and 2B) and diesel engine exhaust (Group 2A) (see below). The lung is the main target organ of these agents.

Earlier studies generally compared residents of urban areas, where the air is considered more polluted, with residents of rural areas. For instance, in France, no difference has been found in cancer mortality according to the size of the city (Salem et al., 1999). However, this kind of so-called "ecological" study provides very limited data on typical levels of any pollutants in the areas studied and they are no longer considered as useful for assessing relationships between air pollution and diseases such as cancer.

Various indicators of air pollution used in relevant studies can be considered as three broad groups: (i) components of air pollution which are suspected to exert a carcinogenic effect *per se*, such as different fractions of fine particulate matter (especially particles having a median aerodynamic diameter smaller than 2.5 µm, or $PM_{2.5}$), (ii) components of air pollution which are not expected to cause cancer, but are considered markers of the main sources of pollution, such as sulfur oxides (markers of emissions from major industrial sources and residential heating) and nitrogen oxides (markers of traffic pollution), and (iii) indirect indicators such as residence near sources of pollution such as major industrial emission sources or heavy road traffic.

Boffetta and Nyberg (2003) published a detailed review of these studies, and the remainder of this section concentrates on epidemiological aspects of air pollution most relevant to this report.

Diesel engine exhaust

Diesel engine exhaust (DEE) was classified as a Group 2A carcinogen by the IARC, meaning that diesel engine exhaust was not a proven human carcinogen. However, IARC last evaluated diesel exhaust in 1989 (IARC, 1989). New studies are in progress in both the USA and Europe on health issues related to diesel engine exhaust. Three major cohort studies on diesel engine exhaust and lung cancer are almost complete and publication of their main results is expected soon. These are:

1. Extended follow-up of potash miners cohort in Germany. The first follow-up reported an RR for lung cancer of 2.2 (95% CI 0.8–6.0) (Saverin et al., 1999).
2. Cohort study of US miners.
3. Cohort study of US truckers.

Particulate matter

Particulate matter (PM) suspended in the air has received much attention during the past two decades, mainly since laboratory experiments have shown the ability of these particles to enhance tumorigenesis in animals.

In epidemiological studies, $PM_{2.5}$ particles are those most strongly associated with all-cause

mortality and cardiovascular mortality. Three cohort studies in the USA (Dockery et al., 1993; McDonnell et al., 2000; Pope et al., 2002; Laden et al., 2006) reported on the RR of lung cancer for exposure to $PM_{2.5}$, as measured in the areas of residence of the study subjects (Table D3.3). In all three studies, an increased risk of lung cancer was found for increased air concentrations of $PM_{2.5}$, although the increase was heterogeneous among studies and significant only in the largest of the three studies (Pope et al., 2002). None of the three studies found a significant association between other air pollutants (e.g., NO_2, SO_2, total suspended particles) and lung cancer mortality. The largest of the three studies (Pope et al., 2002) found that the association between exposure to $PM_{2.5}$ and lung cancer was essentially observed among never-smokers, and was restricted to individuals with education equal to or lower than high school, while a statistically significant inverse association was detected in individuals with more than high school education (Krewski et al., 2005). Similarly in the Adventist Health and Smog (AHSMOG) cohort study, the health effects of PM_{10} particles were restricted to non-smokers (Abbey et al., 1999).

The US studies on the long-term effects of air pollution on health and on cancer in particular can be criticized on the following points:

(i) It is unknown whether $PM_{2.5}$ represents a measure of air pollution relevant to its carcinogenic potential.

(ii) Relative risks of lung cancer associated with air pollution, in particular with $PM_{2.5}$ and PM_{10}, typically range between 0.9 and 1.3 (Table D3.3). In this range of values, relative risks are very sensitive to confounding. In studies such as CPS-II, the issue of residual confounding by smoking or other factors remains unresolved. For instance, smoking in a closed area produces about 10 times more $PM_{2.5}$ than a low-emission diesel engine (Invernizi et al., 2004). It follows that the highest air concentrations of $PM_{2.5}$ or PM_{10} particles are encountered in areas where people are smoking, mainly when smoking takes place indoors in non-ventilated rooms. The relative risks of lung cancer with $PM_{2.5}$ have been found to be significantly increased among non-smokers, and not at all among current smokers (Pope et al., 2002), and this effect might be due to residual confounding by indoor exposure to passive smoking. Furthermore, in the ACS study, fine particles were associated with increases lung cancer risk in subject with medium or low educational level but with significantly *decreased* lung cancer risk in subjects with higher education level (Krewski et al., 2005). This sizeable effect modification according to strata of a socio-economic indicator suggests residual confounding by other social class-related factors, such as occupational exposure to lung carcinogens.

(iii) The available data on exposure to air pollution, and to $PM_{2.5}$ in particular, are limited and refer to the present time or the recent past, and not to exposure that took place well before the studies were launched.

Studies on air pollution and lung cancer in Europe

The first European cohort study, in the Netherlands (Hoek et al., 2002) suggested that exposure to traffic-related air pollution including PM was associated with increased mortality from cardio-pulmonary diseases in subjects living close to main roads. Unfortunately, this study included too few subjects for proper assessment of the influence of air pollution on lung cancer (Table D3.3). Since then, other studies in Europe, such as the PAARC study in France and the GENAIR study in seven European countries (Table D3.3), have found no association between air pollutants and lung cancer.

Studies have been reported that suggest a possible increased risk of lung cancer from exposure to nitrogen oxides (NOx) (Hoek et al., 2002; Nafstad et al., 2003; Nyberg et al., 2000; Filleul et al., 2005). NOx is an indicator of exposure to outdoor air pollution, but interpretation of data on NOx exposure is not straightforward, as NOx may be a marker of exposure to a wide variety of components (Boffetta and Nyberg, 2003). Correlations between air concentrations of NOx and diesel engine exhaust (DEE) or particulate matter are stronger in Europe than in the USA. In this respect, the results of European studies on NOx strongly underline that further efforts must be made to determine what outdoor air pollution components or mixtures are relevant to lung carcinogenicity.

Table D3.3 – Relative risk (RR) of lung cancer and outdoor air pollution in studies with quantitative assessment of exposure to air particles; studies are ordered according to last year of follow-up

Location, study period, Reference	No. and sex	RR	95% CI	Exposure contrast	Basis for exposure assessment	Range, mean
ASHMOG study: Seventh-day Adventists USA, California, 1977–92 (McDonnell et al., 2000)	6338 M adults	2.23	0.56–8.94	per 24.3 µg/m3 $PM_{2.5}$	Residential history 1966–92 and local monthly pollutant estimates based on airport visibility data 1966–92	Mean (SD) PM2.5: 59.2 (16.8) µg/m3
The Netherlands, 1986–94 (Hoek et al., 2002)	4492 M+F, age 55–69 y	1.06	0.43–2.63	Exposure to 19.9 vs 10.6 µg/m3 of black smoke §	Traffic air pollutants (black smoke and nitrogen dioxide)	Mean (SD) (range) black smoke: 15.5 (3.2) (9.6–35.8) µg/m3
ASC/CPS-II USA, 1982–98 (Pope et al., 2002)	500 000 M+F adults	1.08	1.01–1.16	per 10 µg/m3 $PM_{2.5}$	City of residence in 1982. Pollutant averages of 1979–1983†	Mean (SD) PM2.5: 21.1 (4.6); study range roughly 5–30 µg/m3
Six US cities, extended follow-up USA, 1975–98 (Laden et al., 2006)	8111 M+F adults	1.27	0.96–1.69	per 10 µg/m3 $PM_{2.5}$	City of residence in 1975. Pollutant average 1979–85	Study range PM2.5: 34.1–89.9 µg/m3
PAARC survey, France, 1974–99 (Filleul et al., 2005)	14 284 M+F adults	0.97	0.93–1.01	per 10 µg/m3 black smoke §	Pollutants measured in 1974–76 and 1978–81 in 24 areas	Range black smoke: 18–152 µg/m3 in 1974–76
GENAIR study 7 European countries, 1990–1999 (7 years FU) (Vineis et al., 2006)	500 000 M+F adults*	0.91	0.70–1.18	per 10 µg/m3 PM_{10}	Place of residence. Traffic-related air pollution 1990–99	Study range PM10:19.9–73.4 µg/m3

* Nested case–control of lung cancer in 91 M + 180 F never-smokers matched with three controls for sex, age, smoking status, country of recruitment and time elapsed between recruitment and diagnosis.

† This study reported results for several other indicators of PM exposure, with results similar to those reported in the table

§ For results of other past studies on black smoke, see Boffetta and Nyberg (2003)

Since the publication of results from the USA, fine particles have received more attention in Europe, but there are still no representative data on average levels of exposure to fine particle pollution in Europe. A study based on 21 monitoring stations in European cities reported wide variations in fine particle concentrations, with mean values in winter in the range 4.8–69.2 µg/m3 $PM_{2.5}$ (median, 19.9 µg/m3) and in summer in the range 3.3–23.1 µg/m3 $PM_{2.5}$ (median, 14.8 µg/m3) (Hazenkamp-von Arx et al., 2003). Two French cities took part in this study: Grenoble (average level 12.9 µg/m3 $PM_{2.5}$ in summer and 28.0 µg/m3 $PM_{2.5}$ in winter) and Paris (15.9 µg/m3 $PM_{2.5}$ in summer and 21.0 µg/m3 $PM_{2.5}$in winter).

No studies in Europe have yet reported data on associations between $PM_{2.5}$ air concentrations and subsequent mortality from lung cancer, or other diseases. Therefore, studies in Europe gathering data on air pollutants have had recourse to relative risks from the American ASC/CPS-II study (Pope et al., 2002; Krewski et al., 2005) for estimating the fraction of lung cancer deaths attributable to $PM_{2.5}$. In France, a recent study in four cities (Paris, Grenoble, Rouen and Strasbourg) used the ASC/CPS-II relative risks and estimated that about 10% of lung cancers were attributable to $PM_{2.5}$ particles (Nerriere et al., 2005). There are three important reasons, however, why the use of these data to calculate an AF for air pollution in France requires caution:

(i) Air pollution in the USA and in Europe has different quantitative and qualitative characteristics; for instance, the higher proportion of diesel cars in Europe accounts for a greater concentration of black smoke. It is therefore not known whether RRs found in US cities are relevant to conditions prevailing in European cities (Katsouyanni, 2005).

(ii) In US cities, increases in RR for lung cancer with $PM_{2.5}$ were observed in never-smokers, while no increased RR was observed in current smokers. Hence, extrapolation of RRs found in US cities to any other place must take into account the proportions of current, former and non-smokers in the different study settings.

(iii) The increase in lung cancer mortality with increasing $PM_{2.5}$ concentration is not linear, being relatively steep below 15 µg/m3 but becoming slower above this concentration (Pope et al., 2002). Moreover, there is no information on RRs at $PM_{2.5}$ concentrations above 25 µg/m3. Thus application of the 8% increase in lung cancer mortality for each 10-µg/m3 elevation in $PM_{2.5}$ is probably not entirely valid, in particular for high $PM_{2.5}$ concentrations such as those prevailing in many European cities.

Air pollution and childhood cancer

A possible impact of air pollution on childhood cancer has been the subject of a recent review of epidemiological results from 15 studies in the USA, the Nordic countries, Italy, France, the United Kingdom and the Netherlands (Raaschou-Nielsen and Reynolds, 2006). The review found no association between various indicators of air pollution and childhood cancer. The review also underlined the poor quality of most studies on this subject.

The review by WHO-Europe on health effects of air pollution

In 2003, a report by the WHO Regional Office for Europe reviewed the health effects of air pollution, and concluded that “long-term exposure to current ambient PM concentrations may lead to a marked reduction in life expectancy. The reduction in life expectancy is primarily due to increased cardio-pulmonary and lung cancer mortality” (WHO-Europe, 2003). The conclusions on lung cancer were based on exactly the same epidemiological studies in the USA summarized in Table D3.3. However, this review did not properly address the issue of residual confounding by risk factors for lung cancer such as passive smoking, radon and occupational exposures, and did not examine why relative risks of lung cancer vary according to educational level. It also did not evaluate the reasons for differences in RR between smokers and non-smokers.

Conclusions on air pollution and cancer

There is thus a clear lack of consensus within the scientific community on the likely impact of air pollution on cancer, in particular lung cancer. Even scientists examining exactly the same data have

come to different conclusions.

It is biologically plausible that heavy levels of exposure to air pollution can cause lung cancer in humans, mainly when air pollution is heavy. However, apart from exceptional circumstances, levels of air pollution observed nowadays in most European and North American cities are usually lower than those observed in the past. The problems and limitations discussed above in assessing the carcinogenic impact of levels of air pollution prevailing 20 years ago in our countries precluded any estimation of the number of cancers attributable to this agent.

The best way to make further progress will be to organize new studies, taking into consideration the experience of prospective studies that were conducted in North America. In view of the uncertainties regarding air pollution and lung cancer, a consortium is being assembled in Europe, under the lead of the University of Utrecht (The Netherlands), to organize air quality assessments in different types of area throughout Europe in parallel with follow-up of disease occurrence and mortality in populations residing in these areas.

In conclusion, because of the uncertainties in the establishment of a causal association between outdoor air pollution and lung cancer risk and the fact that this agent has not been classified by IARC among the established human carcinogens (Group 1), we provided no formal estimate of the proportion of lung cancer attributable to it.

3. Residence near pollution sources

To pinpoint possible industrial emissions responsible for the suggested urban excess of lung cancer and leukaemia, populations living near point sources of air pollution have been studied.

Living near to filling stations or roads carrying heavy traffic could entail exposure to particulate matter (see above), diesel engine exhaust (see above) and benzene. One French study found an elevated risk of leukaemia in children living near filling stations, but no association with proximity of heavy road traffic (Steffen et al., 2004). In contrast, one Italian study found no increase in deaths from leukaemia in a cohort of filling-station attendants (Lagorio et al., 1994) and another found an increased leukaemia risk linked to residence near roads carrying heavy traffic, but none with proximity of filling stations (Crosignani et al., 2004).

Increased risks have been reported for living close to industries such as smelters, foundries, chemical industry and others with various emissions, with up to doubled risk, although confidence intervals were mostly wide (reviewed by Boffetta and Nyberg, 2003). Other studies have shown no relationship, however. In particular, a number of studies concerned residence near sources releasing inorganic arsenic into the air. Ecological studies suggested an increased lung cancer risk, while case–control studies provided mixed results (reviewed in Boffetta and Nyberg, 2003).

Mixed results have been obtained regarding waste dumping sites in relation to serious health conditions including cancer and congenital malformations[4] (Vrijheid 2002; Goldberg et al, 1999; Knox 2000; Jarup et al, 2002; Elliot et al, 2001). Some studies found moderate associations between living near solid-waste incinerators and non-Hodgkin lymphoma or congenital malformations (Floret et al., 2003; Cordier et al., 2004), but others did not (e.g., Morris et al., 2003) and a recent review concluded that so far, no consistent association had been found between living near a waste incinerator and cancer (Franchini et al., 2004).

Excess cancer risks found by ecological studies on residence near waste incinerators are typically in the range of 1 to 10%. In this range of values, residual confounding may play a major role in the apparent associations found (Elliot et al., 1996, 2000). It must be noted that modern waste landfills and incinerators reject less toxic substances into the air and soil than old facilities, and associations with cancer found in some epidemiological studies are related to old types of incineration facilities. In addition, many of the studies done on these topics to date are of sub-optimal quality, and further large-scale studies are needed, including use of biomarkers for exposure assessment.

4. Water chlorination by-products

Chlorination by-products result from the interaction of chlorine with organic chemicals, whose level determines

[4] Similarly to cancers, congenital malformations may also be caused by mutagenic agents. In an area where the presence of mutagenic agents is suspected, absence of increases in congenital malformation rates reinforces the likelihood that an absence of increased cancer incidence rates is not spurious.

the concentration of the by-products (IARC, 1991). Among the many halogenated compounds that may be formed, the most commonly found are trihalomethanes, including chloroform, bromodichloromethane, chlorodibromomethane and bromoform. Drinking, bathing and showering are the main sources of exposure. Concentrations of trihalomethanes depend mainly on water contamination by organic chemicals: average measurements from the USA are of the order of 10 µg/L for chloroform, bromodichloromethane and chlorodibromomethane, while those for bromoform are close to 5 µg/L (IARC, 1991). A pooled analysis of six epidemiological studies resulted in a summary RR of bladder cancer equal to 1.18 (95% CI 1.06–1.32) for exposure above 1 µg/L of trihalomethanes (Villanueva et al., 2004). One of the studies included in the pooled analysis was conducted in France (Cordier et al., 1993); among the controls included in this study, the prevalence of exposure above 1 µg/L was 16%. The interpretation of these data is complicated by several factors. The concentration of by-products in water varies depending on the presence of organic contaminants, which differs by geographical area and by season. In addition, people consume water outside their homes, which is seldom considered in epidemiological studies. Furthermore, although the possible confounding effect of smoking has been taken into account in several studies, confounding by other risk factors such as diet remains a possibility. Bearing in mind these limitations and assuming that a causal association does exist, the figures mentioned above would result in an attributable fraction of bladder cancer of 2.8%, corresponding to 252 incident cases and 91 deaths in men and 50 incident cases and 28 deaths in women. There is no consistent evidence of an effect on other cancers.

5. Pesticides

Several pesticides used in the past have been shown to cause cancer in experimental animals. Very few currently available pesticides are established experimental carcinogens, and none is an established human carcinogen. Studies in humans have failed to provide convincing evidence of an increased risk, even in heavily exposed groups (Siemiatycki et al., 2004).

Difficulties in interpreting the available evidence include the complex nature of exposure to pesticides, including variations in agents used over time and the relative rarity of cancers suspected to be due to pesticide exposure, such as lymphomas and sarcomas.

Childhood and in-utero exposure to pesticides have been the subject of a number of epidemiological studies that examined indoor and outdoor exposures (including use of insecticidal shampoos for treatment of pediculosis) and professional exposure of parents (e.g., Menegaux et al., 2006; Ma et al., 2002; Meinert et al., 2000; Flower et al., 2004; Reynolds et al., 2005; Fear et al., 1998; Kristensen et al., 1995; Daniels et al., 1997; Chen et al., 2005). Results were often contradictory, indicators were too crude for capturing complex exposures, and many studies had methodological limitations (Daniels et al., 1997). Also, a proportion of positive results (i.e., the finding of a statistically significant association) could be due to the large number of statistical tests performed on large data sets collected in these studies (Reynolds et al., 2005). Recall bias probably plays a major role in the apparent association between self-reported parental past exposures to pesticides and cancer occurring in the offpring (Shüz et al., 2003).

Some epidemiological studies that suggested an association between specific pesticides and cancer were often false positive results that were not confirmed by further studies with better study design and large samples. Section B.10 discusses the example of a false positive result for DDE (the active metabolic by-product of DDT) and breast cancer. The eventual effects of pesticides on human health remains however an open field for research.

A recent case-control study in the Department of Gironde (France) on a large sample of patients with brain tumours suggest that moderate to relatively high occupational exposure to pesticides would not be associated with brain tumours, but that heavy occupational exposure to pesticides would be associated with brain tumours (Provost et al., 2007). The few observational studies done on pesticides and brain cancer did not all find an association, and thus results from the Gironde study needs to be replicated.

Given the lack of evidence linking pesticide exposure to human cancer risk, no cases of cancer can be attributed to either occupational or non-occupational exposure to this group of agents.

6. Dioxins

2,4,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is an experimental carcinogen with limited evidence of carcinogenicity in humans. It is classified as a Group 1 human carcinogen by IARC on the basis of strong evidence that the same mechanism (interaction with the Ah receptor) operates in experimental animals and in humans (IARC, 1997). However, no clear excess of cancer has been shown among heavily exposed populations, including chemical workers, US Veterans of the Vietnam war exposed to defoliants, and residents in contaminated areas. For instance, a study in the USA among four cohorts of workers in whom excess cancer rates were observed suggested that high TCDD exposure resulted in an excess of all cancers combined, without any marked site specificity (Steenland et al., 1999). The excess cancer was limited to the most highly exposed workers, with exposures that were likely to have been 100–1000 times higher than those experienced by the general population and similar to the TCDD levels used in animal studies.

The most serious disaster involving dioxins was the explosion at a chemical factory in Seveso, Italy, in July 1976 that resulted in the contamination of residents with high levels of TCDD. Follow-up of the whole population living in the contaminated areas, including linkage with the population-based cancer registry and with mortality registries, has been conducted and studies of this cohort have provided the most informative data on exposure to TCDD and cancer. The study defined three areas around the accident epicentre, one of very high and one of high exposure (zones A and B, around 5750 inhabitants in total) and one of lower exposure (zone R, around 30 000 inhabitants). Table D3.4 shows that in the long-term follow-up (20 years), no excess mortality or breast cancer incidence was detected in any of the three areas, although a small, non-significant excess of breast cancer mortality was reported in one of the intermediate follow-ups for women resident in zones A or B who were aged less than 55 years (Baccarelli et al., 1999; Bertazzi et al., 2001; Pesatori et al., 2003). The only cancers with significantly increased mortality were lymphomas and leukaemias, but only among residents in the area at lower contamination. Altogether, these results do not support a causal role of TCDD in cancer occurrence (Smith and Lopipero, 2001).

A further study was conducted on a subset of 981 women resident in zones A or B from whom serum samples were collected within five years of the accident and analysed for TCCD in 1996-98 (Warner et al., 2002). Fifteen women reported having been diagnosed with breast cancer, and the diagnosis was confirmed by pathology in 13 cases (in the follow-up study until 1991 for cancer incidence in the whole cohort, 23 cases of breast cancer were reported [Pesatori et al., 2001]). The serum TCDD level of cases was slightly higher than that of the whole group of women; after adjustment for risk factors of breast cancer, the RR for a $\log^{10}$ increase in TCDD level was 2.1 (95% CI 1.0-4.6). After exclusion of the two non-confirmed cases, this RR was no longer statistically significant, and the p-value of the test

Table D3.4 - 20-year mortality in dioxin-contaminated areas in Seveso, Italy (Bertazzi et al, 2001). Data are relative risks of dying from cancer among people residing in heavily (heavy) and less heavily (medium) contaminated areas around the disaster epicentre, compared with people residing in areas of low contamination

	No deaths	Heavy exposure	No deaths	Medium exposure
		(15-580 ppt)*		(1.7 - 4.3 ppt)
All causes	96	1.0 (0.9, 1.3)	649	1.0 (0.9, 1.1)
All cancers	27	0.9 (0.6, 1.3)	222	1.1 (0.9, 1.3)
Breast cancer	2	0.8 (0.2, 3.1)	12	0.7 (0.4, 1.3)
Leukemia, lymphoma	2	1.0 (0.8, 1.3)	26	1.9 (1.3, 2.7)

*Average acute exposure dose to dioxins in ppt (parts per trillion)

for trend in the categorical analysis was 0.07. Also, Warner's study was based on a subset of people who gave blood samples in the five years following the accident. Unlike Baccarelli et al., 1999, Bertazzi et al., 2001, and Pesatori et al., 2003, Warner et al. did not perform a proper follow-up of the cohort, but rather interviewed in 1996-98 (i.e., 20 years after the accident) the subset of women with blood samples who were still alive and living in the area (and willing to participate in their new study – about 80% of the original group). So, although in Warner's study, the results of the serum analysis of the subgroup of women living in zones A and B is suggestive of an association between TCDD exposure and breast cancer risk, a causal interpretation is not supported by the lack of increased incidence in the whole cohort, the self-reported nature of the definition of cases, the unclear temporal sequence of serum collection and cancer diagnosis (as some cancers might have been diagnosed around the time or after breast cancer diagnosis), the borderline statistical significance of the association and the lack of an association in other studies of TCDD-exposed women (IARC, 1997).

Given the uncertainties on the relationship between dioxin exposure and cancer risk, and the very small number of European residents likely to be exposed at doses comparable to those included in the available epidemiological studies, no estimate has been made of the number of cases of cancer in France attributable to dioxin exposure.

7. Use of indoor tanning equipment

Sunlight has been classified as a Group 1 carcinogen by the IARC (IARC, 1992). Similarly to UVB and UVA radiation, sunbeds have been classified by the IARC as an agent probably carcinogenic to humans (Group 2A) (IARC, 1992). Biological damage caused by exposure to sunbeds resembles that induced by sun exposure. Systematic review of epidemiological studies shows convincing evidence for increased risk of cutaneous melanoma (RR 1.7) due to sunbed use starting before 30 years of age (IARC, 2006; Gallagher et al., 2005; Veierød et al., 2003, 2004)[5].

In 1985, indoor tanning was very little used by the French population. Therefore, we have not made any estimate of impact of sunbed use on cutaneous melanoma occurrence in 2000. Incidence of cutaneous melanoma associated with indoor tanning will start increasing in 2010, as exposure rates in France increased greatly in the 1990s and 2000s. In 2001–02, about 13% of the French population below 50 years old were using sunbeds (Bataille et al., 2005).

8. Non-ionizing radiation other than UV light

Extremely low-frequency magnetic fields

People are exposed to electric and magnetic fields arising from a wide variety of sources. At extremely low frequencies (ELF), also called power frequencies (in the range 50 to 60 Hz), man-made fields are many thousands of times stronger than natural fields arising from the sun or the earth (IARC, 2002).

High-voltage power lines produce the highest electric field strengths that are encountered by people. The fields diminish with distance, however, and are considerably attenuated by objects; they are one to three orders of magnitude weaker inside homes than outside (NRPB, 2001). The major sources of electric fields inside buildings are therefore electrical appliances and current-carrying plumbing and/or electrical circuits. The electric field strength measured in the centre of a room is generally in the range 1–20 V/m, but close to appliances and cables, may increase to several hundred V/m (NRPB, 2001).

Magnetic fields, on the other hand, pass through most materials. The strength of magnetic fields produced by high-voltage power lines rapidly diminishes with distance and reaches background levels at distances of 50–300 metres from the power line, depending on the line design and current. For the general public, the highest magnetic flux densities are likely to be encountered in the vicinity of appliances or types of equipment that carry large currents. Typical exposure levels are of the order of 0.01–0.2 μT for magnetic fields, with 4–5% of the population having mean exposures above 0.3 μT and 1–2% having median exposures above 0.4 μT (Kheifets et al., 2006).

Health effects on humans related to this non-

[5] A comprehensive report by IARC including a systematic review with meta-analysis on artificial UV and skin cancer is available, and a summary of the report has been published in the International Journal of Cancer in 2006 (IARC, 2005, 2006).

ionizing type of radiation have been investigated in epidemiological studies for over two decades. The first report of an association between childhood cancer and power line exposure (Wertheimer and Leeper, 1979) has been followed by at least 24 studies on the same topic (Ahlbom et al., 2000; IARC, 2002).

Three recent meta-analyses have both shown a significant 1.7–2.0-fold excess of childhood leukaemia for mean and median exposures above 0.3 and 0.4 μT (Ahlbom et al., 2000; Greenland et al., 2000; Kheifets et al., 2006). The evidence linking exposure to ELF electric and magnetic fields with human cancer was evaluated by an IARC Monographs working group. ELF magnetic fields were classified as a possible human carcinogen (Group 2B), based on limited epidemiological evidence of an increased risk of childhood leukaemia for exposures above 0.4 μT (IARC, 2002). In the absence of conclusive evidence of a causal association between exposure to electromagnetic fields and cancer, no cases can be attributed to this agent. If a causal association were considered established, the attributable number of childhood leukaemias due to exposure to ELF fields would range between 100 and 2400 cases per year worldwide, representing between 0.2 and 5% of the 50 500 annual leukaemia cases worldwide in individuals below 15 years old (estimate from Globocan 2002, on www.iarc.fr).

There is inadequate evidence in humans for the carcinogenicity of ELF magnetic fields in relation to all other cancers (IARC, 2002). ELF electric fields were considered not to be classifiable as to their carcinogenicity to humans (Group 3) (IARC, 2002).

Cellular telephones

The frequency of signals emitted from cellular phones ranges between 450 and 2200 MHz, in the microwave/radiofrequency (RF) region of the electromagnetic spectrum. At present, the biological mechanism, if any, by which these signals might increase risk of cancer is unclear. While biological effects of RF fields at levels below current international guidelines have been confirmed (NRPB, 2001; AFSSE, 2005; Health Council of the Netherlands, 2007), there is at present little and inconsistent evidence of any carcinogenic effect in laboratory animals.

The relation between cancer risk and RF exposure from mobile phones has been the subject of a number of epidemiological cohort and case–control studies. Comprehensive reviews of the literature are conducted and updated periodically by a number of national radiation protection bodies (Boice and McLaughlin, 2002, for the Swedish Radiation Protection Authority; NRPB, 2001; AFSSE 2005; Health Council of the Netherlands, 2007). Most of the studies published to date, however, suffer from methodological limitations, including lack of information on the level of RF field exposure of individual study subjects, possible recall and selection bias (in case–control studies) and, importantly, limited numbers of subjects with long-term use of cellular phones.

Results are now appearing of analyses of national data-sets included in the INTERPHONE Study (Christensen et al., 2004, 2005; Hepworth et al., 2006; Lahkola et al., 2007; Lönn et al., 2004, 2005, 2006; Schoemaker et al., 2005; Schüz et al., 2006; Takebayashi et al., 2006), some of which suggest a possible increased risk of acoustic neurinoma and glioma in long-term users of cellular telephones. Upon their completion in 2007, the international analyses of the INTERPHONE study will add considerably to the body of scientific evidence on cellular phone use and cancer risk.

In conclusion, results available at present do not permit a definitive conclusion about a possible association between cellular telephone use and the risk of malignant and non-malignant tumours of the central nervous system or of the parotid gland.

9. Infectious agents

Human herpesvirus 8 (HHV8) was classified by the IARC as a Group 2A carcinogen (IARC Monograph No 70 1997). HHV8 is probably associated with Kaposi sarcoma and possibly other cancers, but formal evidence has been produced only recently.

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