Dose–effect relationship and estimation of the carcinogenic effects of low doses of ionising radiation: the Joint Report of the Académie des Sciences (Paris) and of the Académie Nationale de Médecine

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Abstract: The aim of the Joint Report of the two French Academies is to discuss the validity of the linear non threshold dose-effect relationship (LNT) for assessing the detrimental effects of small doses such as those delivered by X-ray examinations (0.1 mGy to 20 mGy). The conclusion of the report is that extrapolation with LNT could greatly overestimate those risks and thus may have a detrimental effect for public health by discouraging physicians and patients from performing potentially useful radiological examinations (for example a mammography or a CT scan) when the risk appears to be too large.

This conclusion against the validity of LNT is based on several types of data:

1 Epidemiology has not evidenced cancer excess in humans for doses below 100 mSv.

2 Experimental animal data have not evidenced a carcinogenic effect for doses below 100 mSv. Moreover, dose-effect relationships are very seldom linear; most of them are linear-quadratic or quadratic. A practical threshold or hormetic effects have been observed in a large number of experimental studies.

3 Radiobiology: LNT assumes that the genotoxic risk (per unit dose) is constant irrespective of dose and dose rate and thus that the efficacy of the two guardians of the genome, DNA repair and elimination by death, of cells with DNA damage do not vary with dose and dose rate. This assumption is not consistent with a large number of recent radiobiological data, for example mutational effect and lethal effect vary (per unit dose).

The second assumption is that a given DNA damage has the same probability of initiating a cancer irrespective of the number of other DNA damage in the same cell and in the neighbouring cells. This assumption is also non consistent with recent data and modern concepts of carcinogenesis in which the microenvironment and tissue disorganisation play an important role. The existence of a threshold dose in individuals or animals contaminated by radium or thorium shows that the irradiation of a cell surrounded by non-irradiated cells does not initiate carcinogenesis.

It is the responsibility of the proponents of LNT to demonstrate the validity of these two assumptions in order to justify the use of LNT. The recent reports do not provide such demonstrations.

Keywords: apoptosis, DNA repair, dose, dose-carcinogenic effect relationship, dose rate, epidemiology, experimental data, intracellular signalisation, intercellular signalisation, lethal effect, linear no threshold relationship, mutational effect, oxidative stress, radiocarcinogenesis.

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1 The Joint Report

The main problem for both medical and non-medical uses of ionising radiation is the possible carcinogenic risks associated with small doses of ionising radiation. These eventual risks are also of great importance with regard to natural irradiation, for example it would be of great value to assess the risk of lung cancers caused by various radon concentrations in the air at home or at work, and whether there is a practical threshold below which the risks become negligible.

These questions have been a matter of debate for over a century, since the discovery of the carcinogenic effect of X-rays and radioactive nuclides. Over the past 20 years the French Ministry of Research has twice asked the Académie des Sciences to carry out a critical review of the available data regarding the effects of low doses of ionising radiation on health. The Académie Nationale de Médecine has also published a few analyses of the data. In 2003 the two Academies decided to join their efforts for an update of two main topics: the dose–carcinogenic effect relationship and the carcinogenic

effect of low doses. A working party was set up, its report[**] was accepted after a few modifications suggested by the reviewers, and it was released in March 2005 and published in June 2005.

Following small doses, no excess of cancers has been detected; however, the lack of an increase does not exclude the possibility of a small excess of cancers. Solid tumours and leukemia have a spontaneous incidence that is high and varies according to lifestyle. Moreover, the possible increase in this incidence following irradiation is relatively low, so the studies must have sufficient statistical power, which requires large cohorts. Moreover, in large populations confounding factors are present and they must be taken into account by appropriate statistical methods, because their specific effect can be much greater than the effect of radiation. Thus the effect of low doses remains doubtful. For example, in a study investigating the risk of lung cancer due to radon in homes, not taking smoking into account would make the results impossible to interpret. However, it is highly unlikely that putative carcinogenic risks could be estimated or even established for low doses through case-control studies or the follow-up of cohorts. Even for several hundred thousands of subjects, the power of such epidemiological studies would not be sufficient to demonstrate the existence of a very small excess in cancer incidence or mortality adding to the natural cancer incidence. Because of these epidemiological limitations, the only method for estimating the possible risks of low doses (<100 mSv) is extrapolation from carcinogenic effects observed between 0.2 and 3 Sv.

A linear no-threshold relationship (LNT) is often used for that purpose. The LNT model, used in 1956 by Russell to evaluate the radio-induced mutations in the germ cell line in the mouse, was introduced between 1960 and 1980 for the purposes of regulation in radioprotection with regard to all mutagenic and carcinogenic effects in humans. At that time, LNT was considered a convenient pragmatic relationship but not a model based on scientific data. In the 1960s, the International Commission of Radioprotection (ICRP) introduced it because it allows the addition of sequential irradiation delivering low or high doses of radiation received by an individual whatever the dose rate and the fractionation. Thus it greatly simplifies accounting in radioprotection. However, gradually LNT was interpreted as meaning that the carcinogenic risk is proportional to the dose and that even the smallest dose induces a cancer risk. Thus the LNT has been used for assessing the effect of low and very low doses. This procedure has become a dogma in many radioprotection circles, but the validity of the LNT has been challenged over the past decade for two main reasons: (a) the meta-analyses of the animal data have shown the absence of any carcinogenic effect of doses below 100 mSv; (b) scientific progress has revealed the complexity of carcinogenesis, and the diversity and effectiveness of the responses of a cell to irradiation. Indeed, a cell is not passively affected by the accumulation of lesions induced by ionising radiation. It reacts through several mechanisms.

[**] Académie des Sciences and Académie Nationale de Médecine (Paris) *Dose–effect relationships and estimation of the carcinogenic effect of low doses of ionizing radiation*, M. Tubiana, A. Aurengo, D. Averbeck, A. Bonnin, B. Le Guen, R. Masse, R. Monier, A.J. Valleron, and F. de Vathaire, Paris, 2005; 94 pages, 306 references (English text – March 2005) www.academie-medecine.fr/actualites/rapports.asp

2 Implicit assumptions

The rapidly growing knowledge in molecular biology and radiobiology during the last decade should lead us to examine the validity of the implicit assumptions on which the use of LNT has been based for assessing the carcinogenic effect of low doses (<100 mSv) and *a fortiori* of very low doses (<10 mSv) on the basis of that observed in the range of doses of 0.2 to 3 Sv. The LNT model postulates that the cell reacts in the same way regardless of dose rate and dose, which implies that the probabilities of death and mutation (per unit dose) and the contribution to carcinogenesis of each physical event remains constant irrespective of the number of lesions in the cell and in the neighbouring cells. This constancy implicitly admits several hypotheses.

1 In the range of the doses and dose rates under consideration, there is no physical, chemical or biological interaction between the effects caused by the various tracks of ionising particles in a cell.

2 Any absorbed dose of energy in a cell nucleus leads to a proportional probability of mutation. The probabilities of successful repair or misrepair (per dose unit) are always the same, whatever the number of lesions in the same cell. There should be no impact of dose or dose rate. Similarly, the probability of apoptosis does not vary with dose.

3 Any DNA lesion has the same probability of giving rise to a cancer, irrespective of the number of other lesions in the same cell and the neighbouring cells.

These hypotheses are not consistent with current radiobiological knowledge, which shows that cells do not remain passive when they are irradiated either by solar UV or by ionising radiation. Moreover, intercellular communication systems inform a cell about the presence of an insult in neighbouring cells.

2.1 Oxidative stress

The oxidative stress induced by irradiation triggers several defence mechanisms against the reactive oxygen species. The reactive oxygen species, formed by water radiolysis induced by irradiation, damage some cell constituents and produce oxidative stress. This oxidative stress stimulates enzyme systems that detoxify active species of oxygen formed and induce the synthesis of enzymes that destroy them. In parallel, oxidative stress also activates numerous signalling pathways.

2.2 DNA damage

The physico-chemical events caused by an irradiation trigger a series of signals and reactions that can profoundly alter the fate of the DNA lesions. It is not the initial physico-chemical events that change, but their outcome. The defence mechanisms induced in a cell depend on the degree and the nature of the cellular damage. Modern transcriptional analysis of cellular genes using microarray technology reveals that, without modification of the genome, numerous genes are activated or inhibited following doses much lower than those for which mutagenesis is observed (Mercier, 2004). Moreover, depending on the dose and the dose rate, not the same genes are transcribed. Different signalling systems are activated, in yeast and mammalian cells, after the

passage of an electron damaging cytosol (MAP kinases), mitochondria, or the nucleus (protein kinases). In the nucleus, different degrees of DNA damage lead to the activation of different families of genes (Amundson et al., 2003, 2005; Bishay et al., 2001).

DNA damage or modifications of the chromatin are detected by signalling proteins. The activity of these proteins is modulated by the number of lesions (and therefore by the dose, the dose rate and LET) and by messages from neighbouring cells. These proteins activate phosphokinase transmitters, in particular the protein encoded by the ATM gene (which is mutated in ataxia-telangiectasia) and the ATR gene. In turn, these transmitters modulate the action of proteins involved either in cell cycle control (the interruption of which promotes repair) and DNA repair, or in triggering apoptosis.

Studies carried out with the DNA micro-array technique in yeast show that continuous irradiation, at a dose rate of 20 mGy/h, i.e. lower than the level of irradiation that causes a detectable biological effect (lethal, mutational), is enough to change intracellular signalling without modifying the genome and to activate or inhibit numerous genes involved in the general metabolism and in defences against ionising radiation. Such mechanisms bring into play defences at doses of the same order as those due to natural irradiation, which makes it possible to reduce or prevent its potentially harmful effects. The dose rate determines the average time interval between physical hits; it has a major effect on the cellular response. In general, the biological effects of irradiation (lethality, mutagenesis, chromosomal aberration, etc.) decrease as the dose rate decreases. This may be due to the fact that when the dose rate is low, the number of DNA lesions simultaneously present in the cell is limited. Conversely, a high dose rate leads to the simultaneous presence of a large number of lesions, which interferes with the coordinated action of repair systems, and also increases the probability of error-prone endjoining due to the presence of several double strand breaks (DSBs) in a restricted volume.

2.3 DNA repair

These conclusions regarding differences in the efficacy of the protection system are supported by various experimental or clinical data, which highlight the impact of repair on the biological consequences of irradiation:

2.3.1 Repair and dose rate

The effectiveness of DNA repair systems is evidenced by the lack of any reduction in the mutagenic and lethal effect as the dose rate decreases in the cell lines in which the signalling or the DNA repair systems are impaired or blocked, for example, in hereditary diseases with defects in repair systems (reparatoses). This lack of repair is also observed when yeasts or mammalian cells are exposed to gamma rays at 0 °C (a temperature that inhibits the repair enzymes): at that temperature the numbers of DNA DSBs are then identical at high and low dose rates, whereas at room temperature, the number is much smaller at lower dose rates.

At equal doses, the mutagenic effect varies markedly with the dose rate. When the dose rate increases, the mutation frequency after having passed through a minimum (hormesis?) increases strongly (Vilenchik and Knudson, 2000, 2003). A limited number of lesions induces a reversible arrest of the cell cycle, which enhances repair. A high

amount of lesions prolongs the cell cycle arrest, which can lead to apoptosis. The time taken by repair depends on the complexity of the damage and on the repair systems operating.

A dose of 80 Gy delivered over 14 days (at a dose rate of *ca.* 4 mGy/min) does not cause rearrangements of the genome similar to those caused by DSB misrepair. However, when mutant cells deficient in non-homologous endjoining (NHEJ) are irradiated under the same conditions, rearrangement of the genome can be observed in *ca.* 10% of the cells (Rothkamm et al., 2001). Note that the technique used in this study (pulsed field gel electrophoresis) does not allow the detection of small deletions or point mutations.

2.3.2 A high local density of lesions reduces the repair efficacy (Dikomey)

The lower lethality following *fractionated* irradiation cannot only be explained by the repair of DNA lesions between sessions. Recent data also show that the effectiveness and rapidity of repair depend on the time, the type of tissue and its proliferative status.

2.3.3 Low-dose hyper-radiosensitivity

For some cell types, mortality is very high (per dose unit) at the onset of irradiation (during the first 200 mGy), then falls to a very low level before increasing again. This low-dose hypersensitivity is observed in many cell types leading to a high mortality rate, per dose unit, for doses of less than a few hundred mGy of low LET irradiation. An induced radioresistance is observed at doses of over 0.5 Gy; and the mortality rate per dose unit then becomes very low before increasing again. These variations in the mortality rate (per dose unit) indicate that the cellular defence mechanisms against lethality, which initially show little efficacy, become more effective during irradiation (Chalmers et al., 2004; Joiner et al., 2001; Marples et al., 2004). These rapid changes in the mortality rate (per dose unit) are not correlated with either the cell's capacity to undergo apoptosis or the defect in cell cycle arrest caused by irradiation. Conversely, stimulation of the activity of certain enzyme systems (PARP) by hydrogen peroxide abolishes it, and inversely, a toxic substance, aminobenzamide, a PARP inhibitor, increases it, which demonstrates the role played by the induction of the enzyme systems in these variations of radiosensitivity. This initial hypersensitivity eliminates damaged cells with mutagenic potential after low doses of radiation.

2.3.4 High dose rate

After high dose rate irradiation of short duration, hyperfast changes in radiosensitivity can be observed (increased mortality rate), which seem to depend on the activity of the PARP-1 enzyme (Ponette et al., 2000; Fernet et al., 2000).

The existence of an *adaptive* response is now well established: a first low dose of radiation leads to a reduction in the mortality of organisms *in vivo*, in the number of mutations and in the rate of neosplastic transformations caused by a second irradiation carried out during subsequent hours or days (Wolff, 1998, Redpath, 2004, Mitchell et al., 2002). This inducible and transient protective effect occurs also in humans, and appears to result from a stimulation of cell defence and DNA repair systems. At the cellular level, an increase in lethality may be observed as a result of apoptosis and delayed mortality due to a bystander effect.

3 Elimination by cell death

Besides DNA repair the main defence of the tissue and the organism against potentially mutant cells is their elimination by death, which can be caused by apoptosis or mitotic death. Apoptosis can be initiated by doses as low as a few mSv, and it eliminates cells whose genome has been damaged or misrepaired. The efficacy of the elimination of potentially mutant cells varies with the dose, the cell line, and the tissue. In the case of intestinal crypt cells after gamma irradiation, apoptosis reaches a plateau at doses of 200 to 400 mGy. A very high effectiveness of apoptosis reduces the probability of neoplastic transformation but depletes the pool of cells able to proliferate, in particular stem cells. A high susceptibility of stem cells to apoptosis may explain why some tissues, such as the small intestine, are so resistant to radiocarcinogenesis.

4 Signalling systems

Intracellular signalling systems are not triggered below a certain threshold (a few mSv), therefore ATM and ATR systems are not activated, and the damaged cells die (Collis, 2004).

The experiments of Rothkamm et al. (2003) have shown that there is a linear relationship between DSB number and dose between 1.2 mGy and 2 Gy. But after a low dose (1.2 mSv) there is no evidence of DNA repair, furthermore when cells are cultivated, 24 hours later, after a low dose, no excess in the number of cells with a DSB can be detected; this disappearance can be due either to cell death caused by the absence of repair, or to a combination of error-free repair and apoptosis. When only a few cells are damaged, this elimination strategy seems to be optimal, because repair systems may be error prone and can potentially lead to the emergence of pre-cancerous and subsequently cancerous cells.

When a large number of cells in the same tissue are killed or damaged, repair and proliferation mechanisms are triggered, which are intended to protect the integrity and functions of the tissue. By means of intercellular communication systems the reaction of a cell to irradiation therefore seems to be influenced by the number of cells affected. Hence, the cell reacts to irradiation by a global and integrated response that involves several enzyme systems that govern the efficacy of DNA repair and the probability of cell death or senescence eliminating damaged cells. Although DNA-induced damage is constant (per dose unit), the probability of mutation is modulated within a framework of what could be called a strategy of least cost.

Schematically, one can distinguish between four dose ranges.

1 At doses below a few mGy or low dose rates, no damage can be detected because the damaged cells die. At these doses, the signalling systems are not triggered. Only constitutive repair systems, which are constantly active, operate (such as BER). The doses or dose rates above which apoptosis is stimulated seem to be lower than those that activate the repair systems.

2 For doses between about 10 and 100 mGy or those delivered at low dose rates, damaged cells are eliminated or, whenever possible, repaired by high fidelity mechanisms. When this elimination/repair mechanism has been induced by

irradiation, it also acts on the cells damaged by oxidative metabolism. In combination with the detoxification mechanisms induced by oxidative stress, these defences can also explain the hormesis effect that is frequently observed in experimental animals. However, the possibility of a misrepair cannot be excluded; infallibility does not exist but errors can be very rare.

3 At higher doses, over *ca*. 200 mGy, the concentration of damaged cells increases and the DNA repair systems aimed at avoiding cell death and tissue injuries are associated with a risk of misrepair, which is greater when the number of lesions inside the cells is high. In the absence of apoptosis, which is less effective at high doses, these errors lead to mutations. When apoptosis or senescence predominates, the risk of cancer is very low, but the tissue loses cells. When repair predominates, the risk of cancer increases. This phenomenon is also observed during ultraviolet irradiation of the skin. Because of these variations in the effectiveness of DNA repair and in the probability of apoptosis (in relation to dose or dose rate), the carcinogenicity of irradiation increases more rapidly than the dose, leading to a curvilinear relationship.

4 Above 500 mGy, a stimulated proliferation, in order to compensate for cell deaths, is observed. Cell divisions interfere with repair and increase the likelihood of errors.

The cell response therefore seems to depend on the dose, the dose rate and the cell type, and on the concentration of damaged cells. It varies over time. This strategy of defence that the organism raises against cellular lesions induced by ionising radiation is distinct from, but somewhat similar to the strategy observed after ultraviolet irradiation. Once again, the accumulation of lesions hinders and delays repair, and therefore increases harmful effects per dose unit of exposure.

One can also draw a parallel between dose–effect relationships for ionising radiation and the numerous experimental data that reveal major differences between the toxicities of chemicals depending on dose, and that have shown very small (if any) carcinogenic effects of low concentrations. However, these variations are also partly linked to changes in metabolism, which may contribute to non-linearity.

The lack of validity of the LNT relationship for chromosome aberrations at low doses with low LET radiation is not surprising. The occurrence of a chromosome aberration is much increased when there are two or more DNA DSBs in the same chromosome or neighbouring chromosomes, making it possible that the rejoining of the fragments either does not restore the molecule to its initial condition (inversion or translocation within the same chromosome), or even rejoins fragments that do not belong to the same chromosome. The probability of such error-prone endjoining therefore depends on the number of breaks simultaneously present in a limited volume, and therefore decreases markedly with dose rate and is not proportional to dose but to the square of the dose. LNT cannot be used to predict chromosome aberrations for very low doses. A threshold is conceivable.

The dose–effect relationship for cell lethality is not linear but linear-quadratic. The phenomenon of initial hyper-radiosensitivity (Joiner) shows that it is necessary to introduce a correction into the linear-quadratic relationship for doses of less than 200 mGy.

All data clearly show that the efficacy of defence mechanisms against the lethal effect and the mutagenic effect of ionising radiation varies with the cell line. This efficacy

appears to be in all cell lines very high at low doses and dose rates such as those delivered by the natural irradiation but it declines at higher doses. These variations in the efficacy with dose is not surprising because many mechanisms have emerged during evolution to protect prokaryotic cells against the lethal effect of the natural ionising (or UV) radiation. After the appearance 600 million years ago of multicellular organisms, the aim of defence mechanisms had also the purpose of protecting multicellular organisms against the appearance of mutant cells.

In multicellular organisms the fate of an irradiated cell depends on signals emitted by neighbouring cells (gap junction, bystander effect, contact inhibition, proliferation control mechanisms by means of cytokines). Besides an inhibitory effect (such as contact inhibition), or a stimulation of cell division, intercellular relationships can also elicit damage in neighbouring cells that have not been irradiated; this is known as the bystander effect. It originates from potentially genotoxic signals sent to neighbouring cells. This 'bystander signal' has many consequences for the unirradiated cells (apoptosis, induction of genetic instability, delayed cell death, mutations that are in 90% of cases point mutations). It has been shown both *in vitro* and *in vivo* that *ca*. 10% of the descendants of irradiated cells, or cells submitted to a bystander effect, display an abnormally high frequency of genome modifications, sometimes persisting after several tens of generations. This effect is known as genetic instability.

This research area is developing rapidly. Its aim is to find out whether the bystander effect and genetic instability could play a part in the onset of radio-induced cancers. Overall, at the experimental level, the existence of a direct link between carcinogenic effects and genetic instability remains hypothetical, in particular after low doses of low LET radiation. Genetic instability could be an indicator, cause, or consequence of cellular defects, such as impaired DNA repair. The most convincing evidence against the bystander effect and genetic instability playing a role in inducing human cancers is provided by studies on subjects contaminated by radium or thorium and followed up until their death over 50 years after contamination, and in whom no cancer was detected when the dose was below a few Gy, whereas there were many cancers at higher doses. If present in these individuals, the bystander effects or genetic instability would have shown up as a long-term effect in the form of an increased cancer incidence.

5 Radiocarcinogenesis

The conventional model acknowledged that, by a series of stages, stochastic alterations of the genome confer a selective advantage to a initiated cell, during carcinogenesis. We now know that these phenomena cannot be described by a linear process, during which successive genome damage of one cell accumulates at random. Carcinogenesis cannot be reduced to a series of mutations occurring in the same cell (Brash, 1997). Indeed, it affects all aspects of genome function.

The association of genetic and epigenetic mechanisms is now well-established.

The cell, the tissue and the body all have defences against carcinogenic processes, and these must be successively overcome for carcinogenesis to occur. There are intracellular systems of proliferation control (suppressor genes), and mechanisms involving the death of initiated cells that tend to eliminate or prevent the proliferation of cells in which a proto-oncogene has mutated into an oncogene, or one with damaged

DNA, or one that does not obey systems regulating proliferation, or that is no longer receiving the growth factors required for growth.

Cell death appears to be a main safeguard mechanism, in particular programmed death or apoptosis. The loss of a cell's ability to kill itself may result from changes in the genes involved in this process. Ionising radiation is likely to induce, at different levels depending on the tissues, apoptotic responses, which are the consequence of intra- and intercellular signalling. However, it can also induce mutations, which interfere with apoptosis and therefore permit the survival of damaged cells, which in turn constitutes one of the steps in carcinogenesis (Brash, 1997).

At the tissue level, the control exerted by neighbouring cells must be emphasised (contact inhibition of proliferation, exchange of signalling and regulation molecules via intercellular junctions, bystander effect, secretion of regulation factors by neighbouring cells and stroma). There are multiple interactions between a cell, in which a potentially oncogenic genetic event has occurred, neighbouring cells of the same type, the extracellular matrix and the stroma. These interactions between cells play a crucial role in embryogenesis, in growth, in cell turnover of certain tissues in adults, and in the regeneration of injured tissues. They are involved in the carcinogenic process, either inhibiting or promoting it. The exchange of information between the cell undergoing malignant changes and its microenvironment, the cytokines (notably TGF-β, which plays a crucial role in regulating cell proliferation) can, depending on the context, either slow or accelerate the carcinogenic process. The microenvironment can either stop or stimulate the proliferation of clones of cells undergoing neoplastic transformation and affects the genetic instability (Bhowmick et al., 2004; Radisky and Bissell, 2004). Pathology studies had in fact shown long ago that tissue disorganization almost always precedes the appearance of invasive cancer.

At low doses and low dose rates of ionising radiation, the pro-apoptotic effect dominates and the damaged cells, of which there are only a few, can be eliminated or controlled. But at doses in excess of 0.5 Gy with a high dose rate, the greater number of mutant cells and the accumulation of mutations, the tissue disruption and, above all, the proliferation of the surviving cells to compensate for the death of a high proportion of the cells, allow some initiated cells to escape from these controls, which are intended to maintain tissue integrity and to regulate proliferation. These escape processes vary considerably depending on the tissues, the type of initiated cells (stem cells or progenitor cells) and the type of tumour as has been shown, for example, in the analysis of the carcinogenesis of multiple myelomas and colo-rectal cancer.

In animals that have received chemical carcinogens, irradiation has little influence on the emergence of cancer, whereas, following X-ray irradiation, UV irradiation promotes the appearance of cancers.

At the whole body level, escape from the immune surveillance responsible for eliminating tumour cells is based on the selection of cells that are capable of escaping from it, for instance by the loss of expression of the components of the major histocompatibility complex. Carcinogenesis may be facilitated by a reduction in immune defences (Tanooka, 2001; Euvrard et al., 2003) especially when a large segment of the body has been irradiated.

6 Animal experimentation

Animal experimentation has made a major contribution to our understanding of the carcinogenic effects of ionising radiation. The proportions of radiocancers vary, depending on the species, age, sex and tissues concerned, and the dose–effect relationships are very variable. Despite the favourable conditions of animal experimentation, it has not been possible either to establish a statistically significant carcinogenic risk for doses less than 100 mSv, or to exclude its existence, which is obviously much more difficult. With only a few exceptions, no excess tumours are observed below 500 mGy for low LET radiations.

Animal experiments, notably in the mouse, allow the study of dose–effect relationships for cancer induction over a large range of external exposure levels. A large number of data are compatible with a linear-quadratic model. However, some data are not satisfactorily fitted with this model. In properly conducted studies in the mouse, some data are better fitted by a quadratic relationship without a linear component or by relationships with a threshold than by a model with a linear, no-threshold component. A considerable reduction in the carcinogenic effects has been observed with low LET, low dose and low dose rate radiation. This attenuation is particularly obvious after contamination of the lungs by beta and gamma emitters and even after exposure to radon. It is observed for all the tumours induced by external low LET irradiation. This observation explains why the RBE (relative biological effectiveness) of neutrons increases constantly as an inverse function of the square root of the neutron dose without ever levelling off. This suggests that photons exhibit dose–effect relationships that either have a threshold, or are purely quadratic. Threshold relationships have also been established for pulmonary tumours induced by alpha radiation in rats, and for bone tumours in dogs.

Heterogeneous irradiation, in particular following internal contamination by radionuclides, shows major reduction of the low dose rate effects, with a quasi-threshold, in most cases. This lower efficacy compared with the same dose of uniform irradiation is also observed following irradiation through a grid; it seems to be associated with the control exerted by neighbouring cells. A meta-analysis (Tanooka, 2001) has shown that the carcinogenic effect of a localised irradiation is much smaller than that of a total body irradiation or when a large segment of the body is irradiated, which suggests the impact of immunosurveillance. These two sets of data show that radiocarcinogenesis cannot be interpreted only by the damage caused to the genome of a cell.

Another meta-analysis (Duport, 2003) has shown that among the experimental studies in which the incidence of cancer was sufficiently high in control animals, a reduction of this incidence was observed following low dose irradiation in 40% of them. This observation is consistent with the concept of hormesis. This finding does not justify generalisation of this concept; however, it does confirm its existence.

In summary, animal experiments show the existence of a dose below which no excess in tumour incidence is detectable, which suggests the existence of a practical threshold. Furthermore, most of the dose–effect relationships are not linear but rather linear-quadratic or quadratic, and a hormesis is observed in about 40% of the experiments. The existence of a threshold is particularly obvious following contamination by α-emitter radionuclides. It is of interest that the same observation is made in humans, because it shows that animal data can provide useful information for humans.

7 Epidemiology

7.1 Carcinogenesis by long half-life α-emitting radionuclides

When an α-particle crosses a nucleus, the dose received by the cell is *ca*. 370 mGy and from 1 to 20 events can occur in the DNA molecules, causing important damage. Most cells are killed, but not all because cancers do occur. However, in this study the relatively small number of cells affected are surrounded by normal cells.

Painters of luminous dials contaminated with radium-226 and 228 have been subjected to several investigations covering over 50 years of monitoring. Other investigations have studied patients who had received thorotrast, a thorium-based contrast product used in the past in vascular radiology. They have also been monitored for more than 50 years. Painters of luminous dials have presented a high frequency of osteosarcomas, but no excess cancers have been observed for absorbed doses of less than 10 Gy, contrasting with a marked increase for doses of more than 20 Gy (Carnes et al., 1997). Patients who have received thorotrast have presented hepatomas. In this case also, a threshold is observed: at about 2 Gy for hepatomas.

Several non mutually-exclusive hypotheses have been put forward to explain the lack of effect with lower doses, which contrasts with the very high incidence with larger doses (Tubiana, 2003).

1 It might be necessary for several α-particles to cross the cell to trigger carcinogenesis (Miller et al., 1999).

2 The process triggered in a cell can lead to cancer only if the adjacent cells are non-functional (which, in the case of α-particles would necessitate high doses) and so no longer exercise normal tissue control on the proliferation of the initiated cell.

3 If there are few cells damaged they are eliminated by apoptosis, and this elimination would not take place when there are large numbers of damaged cells.

4 Cells that cause cancers may not be induced directly but by a bystander effect. This mechanism is effective only at high doses.

On the basis of present knowledge, it is difficult to choose between these hypotheses but these data show that, with this type of irradiation, the bystander effect and radiation-induced genomic instability do not cause cancer when the number of damaged cells is small. Moreover, none of these hypotheses is compatible with the postulates on which the LNT relationship is based.

We shall not discuss here other recent epidemiological data and will make only the following remarks.

1 One of the main arguments of the proponents of LNT was the linear dose effect relationship for solid tumours among the survivors of the A-bomb. In fact, the latest analysis reveals that the dose–effect relationship is not linear but curvilinear. These new data benefited from a longer follow-up and from the revision of the dosimetry in 2002. At low doses, the excess risk of death due to solid cancers per Sv (ERR/Sv) is now estimated to be 0.19 (95%CI: 0.03–0.37), i.e. less than half of the previous estimate. The correction of the RBE for neutrons should reinforce the hypothesis of a threshold for the photon contribution.

2 Another main argument of the LNT proponents was based on the results of medical irradiation *in utero* by doses estimated at about 10 mSv. In fact it appears that the data on the carcinogenic effect of *in utero* irradiation has not sufficient robustness to be the basis for evaluating the risk of low doses. Whatever the value of the Oxford study, some inconsistencies in the available datasets call for great caution before concluding the existence of a causal relationship from data showing simply an association. Furthermore, it is highly questionable to extrapolate from the fetus to the child and adult.

3 In Annex 4 (epidemiology), an analysis is carried out on 20 different surveys comprising a total of 415,000 individuals who received doses from 10 to 100 mSv above the usual dose of natural irradiation. The incidence of solid tumours was slightly decreased and that of leukemia was slightly increased. Neither of these two differences was statistically significant. This preliminary study shows the feasibility of a meta-analysis of human data. Currently we cannot conclude from a survey showing a small and non-statistically significant difference in cancer incidence that doses below 100 mSv either increase or decrease cancer incidence.

4 The current uncertainties regarding the carcinogenic effect of low dose irradiation underline the interest of comparing the incidence of cancer and congenital malformations in geographic regions with high or low dose natural irradiation background and similar lifestyle. Currently the data from studies carried out in India and China have not revealed any differences, although chromosomal aberrations in the circulating lymphocytes confirm the high level of irradiation. These data are consistent with the hypothesis of a threshold, but the data are not yet conclusive and the studies must continue.

Current radiobiological data are not consistent with the implicit assumptions on which the LNT is based. All the data show the lower effectiveness of low doses and dose rates. Moreover, the quantitative discrepancy between the results of the various epidemiological and animal experimental studies supports the view that there are several dose–effect relationships rather than only one, and that their parameters depend on the type of cancer, the type of ionising particle, radiation dose, dose rate, fractionation of irradiation, species, breeding line within the same species, target tissue, volume irradiated, age, and individual sensitivity factors. Animal experiment data suggest the existence of a threshold. Some data clearly demonstrate the existence of hormesis. Epidemiological and biological data are compatible with the existence of a threshold but cannot demonstrate its existence or assess its value (somewhere between 10 and 60 mSv).

While LNT may be useful for the administrative organisation of radioprotection, its use for assessing carcinogenic risks induced by low doses, such as those delivered by diagnostic radiology or the nuclear industry, is not based on valid scientific data. For example, the results of the Berrington and Darby article (2004) estimating the number of lethal cancers induced by X-ray examinations should be considered with great caution. This type of data triggers unjustified anxiety among patients who have had radiological or nuclear medicine examinations. The concept of collective dose cannot be used for evaluating the cancer risk in a population.

8 Comparison of the Joint Report and the BEIR 7 Report

The Joint Report was released in March 2005. Four months later, in July 2005, the BEIR 7 Report was published. Contrary to the French Academies report, it concludes that the linear no-threshold relationship (LNT) should be used for assessing the carcinogenic risks of low or very low doses. Because both reports rely to a large extent on the same data, the causes of this disagreement need to be investigated. We shall consider below the various sources of this controversy.

8.1 Epidemiology

Both reports reach the same conclusion that there are no convincing data demonstrating a carcinogenic effect of doses below 100 mSv delivered to infants, children or adults. This is an important conclusion. Not long ago some proponents of the LNT claimed that the analysis of the data of A-bomb survivors (Brenner et al., 2003) showed an excess of solid tumours after low doses. However, this conclusion was open to question because the statistical methodology used in these papers mixed individuals who had received up to 125 mSv. It was therefore felt their conclusions for doses below 100 mSv were not convincing. The same remarks can be made regarding the data on radiation workers (Cardis, 2005).

However, there are two major differences between the Joint Report and the BEIR Report. The first concerns *in utero* irradiation. BEIR 7 acknowledges the existence of a controversy regarding these data but concludes that doses of 10–20 mSv delivered to the fetus were responsible for an excess in the incidence of leukemia and solid tumours. As discussed above, the conclusions of the Joint Report are different. The association may have been linked with various biases, such as an underlying maternal disease leading to both the X-ray examination and the excess of cancer incidence. Furthermore, the doses delivered at that time to fetuses may have been, in some cases, much larger than those calculated. Risks of leukemia were not increased among the offspring of Japanese A-bomb survivors who were pregnant at the time of the bombing; and no increase was observed in twin studies and in several cohort studies or recent surveys (Naumburg et al., 2001; Shu et al., 2002).

The second difference relates to workers contaminated with radium and patients contaminated with thorium. In both series the follow-up is longer than for the A-bomb survivors, the number of individuals contaminated is large, cancers (osteosarcoma or liver cancers) are observed following high doses but not following low doses, and the existence of a threshold is obvious and not disputed (at about 10 Gy for radium [Carnes] and 2 Gy for hepatomas). As discussed above, several hypotheses, which are not mutually exclusive, can be made to explain the absence of cancer (Tubiana, 2003). Whatever the mechanism involved, these data are not consistent with a linear relationship. These data are of great importance because, at equal doses, α-particles are at least as carcinogenic as electrons. The omission of these data from the BEIR 7 Report is surprising. Is it because these data correspond to heavy particles? The BEIR 7 Report is devoted to low doses (below 100 mSv) and yet over 90% of the report discusses effects resulting from much higher doses, which is understandable because data should be put in perspective. Therefore data concerning α-particles should not be omitted. Unfortunately, the carcinogenic effect of low doses of radon is difficult to appreciate in humans because

of the possible bias associated with tobacco; nevertheless the existence of a dose rate effect with radon suggests a non-linearity (Monchaux, 2004).

8.2 Animal data

The BEIR 7 Report acknowledges, as does the Joint Report, that most animal dose–effect relationships are not linear but are linear-quadratic, quadratic or with a practical threshold or even a hormetic effect. However, the BEIR 7 report does not discuss two important review papers, those of Tanooka (2001) and Duport (2003), which showed the high proportion of animal data with practical threshold or a hormetic effect. These two papers are not quoted in the BEIR Report. If this is because the writers of the report disagree with their conclusions, it is regrettable that they do not explain why.

The BEIR Report is entirely based on a technical NRPB memorandum by A.A. Edwards (1992), which unfortunately is not available in the libraries that we consulted. Therefore we were unable to check whether it is consistent with the more recent data. At any rate, there is a clear disagreement between the interpretation of the animal data in the BEIR 7 Report and the Joint Report.

8.3 Biological data

Both reports conclude that there are two safeguard mechanisms of the cell genome: DNA repair and programmed cell death. Both also conclude that the temporal abundance of radiation-induced damage is a major factor in the efficiency/fidelity of DNA repair and hence the frequency of induced mutation (p. 432 of the BEIR Report). The Joint Report argues that in these conditions the incidence of mutations should not increase linearly with doses because the mutagenic effect should be greater at high doses or high dose rate. However, surprisingly, the BEIR Report does not discuss this point.

The BEIR Report feels that the probability of error-free or error-prone repair does not vary with dose and dose rate. During the discussion of the Vilenchik and Knudson data (2000), it rejects a possible variation in efficacy/fidelity of DNA repair and states: “There is evidence that argues against the inducibility of repair genes” in mammalian cells. The Joint Report has a different point of view. It underlines the data that show variations in the efficacy/fidelity of DNA repair. These variations can be due to several mechanisms such as activation of some biochemical phenomena (Sancar et al., 2004; Shiloh, 2003), cell cycle arrest which allows additional time for repair, variations in the efficacy of repair associated with the temporal abundance of damages within a cell (Dikomey and Brammer, 2000), or the existence of a threshold in doses or dose rate below which the radiation damage sensor ATM is not activated (Collis et al., 2004; Rothkamm and Lobrich, 2003). Moreover, the Joint Report feels that Vilenchik and Knudson have convincingly shown that the mutagenic effect, per unit dose, is greater at high dose rate, whereas the BEIR 7 Report remains sceptical regarding these data. The BEIR Report also expresses scepticism regarding phenomena which appear to be related to modulation of DNA repair efficacy, such as low dose hypersensitivity, adaptive response, hyperfast early cell response (Fernet et al., 2000; Ponette et al., 2000). This skepticism is mainly based on the absence of a mechanistic basis. The Joint Report does not share this scepticism about the significance of these data for two reasons: (i) these phenomena are

now not disputed and mechanisms are being uncovered (see above); (ii) the absence of a mechanistic basis has never in science justified the overlooking of data.

DNA repair is only one of the guardians of the damaged genome. The other one is the elimination of damaged cells by death, due either to apoptosis (which is inducible and which varies with dose and dose rate) or to the lack of activation of cell defence mechanisms. These mechanisms and their variation with dose or dose rate are not discussed in the BEIR 7 Report or by the ICRP preliminary report (2004).

The BEIR Report expresses some doubt about the validity of the technology used in the important paper from Rothkamm and Lobrich (2003). It seems to be sceptical about the direct equation between the induction of DSB and the phosphorylation of the histome H2AX. The Joint Report recognises that some verifications are needed but nevertheless concludes that the data must be taken into account for two reasons. First, the convergence between the data of Vilenchik (2000, 2003), Rothkamm and Lobrich (2003) and Collis (2004) cannot be overlooked. Second, the data published recently by Lobrich et al. (2005) confirm the validity of this technique. With regard to this article, it has been argued that because a DNA repair is observed following CT-scan (doses of 10 to 20 mGy) this article contradicts the 2003 one. However, the lack of DNA repair was reported after a much lower dose (1.2 mGy). Hence there is no contradiction between the two sets of data, but the threshold above which the cells do not disappear and repair is triggered is unknown (between 5 and 15 mGy).

The so-called dosimetric argument (Rossi and Kellerer, 1972) is often invoked in favour of the use of LNT even for the smallest dose. But Rossi himself (Rossi and Zaider 1997, Rossi 1997) has vigorously protested against this misuse of his theory.

The BEIR 7 report overlooks the complexity of the defence mechanisms and their high efficacy at low doses (Feinendegen and Neumann 2005).

The BEIR Report refers to the traditional model in which carcinogenesis results from the accumulation in a single cell of several specific alterations (eight to ten). In fact, statistical computations have shown that this accumulation has a low probability (Brash, 1997). Moreover, a large number of recent data have shown the role in carcinogenesis of interaction between the initiated cell, the surrounding normal cells, the stoma, and the immunocompetent cells that infiltrate tissues and tumours. The experimental data concerning contamination by radionuclides (β or α emitters) suggest that a single isolated mutated cell has a very low probability of originating a detectable tumour. This conclusion is consistent with the epidemiological data, discussed above, made on individuals contaminated with α-emitters, such as radium and thorium. The BEIR Report and the tentative ICRP report do not discuss these data.

Although the BEIR 7 Report advocates the use of LNT, it gives a great importance to the DDREF and advises a dose–effect relationship that embodies a DDREF factor and is therefore not linear but curvilinear. However, surprisingly, the BEIR report does not discuss the mechanisms that are involved in the DDREF. It is likely that the lower mutagenic effect of a low dose rate is related to a better DNA repair and is not observed in cells with an impaired DNA repair.

In summary, the divergences between the Joint Report and the BEIR Report are not as great as they may appear. The BEIR 7 report conclusion (p. 443) is: "The committee judges that the balance of evidence from epidemiologic, animal and mechanistic studies tends to favour a simple proportionate relationship at low doses between radiation dose and cancer risk." But, this sentence is followed by a word of caution: "Uncertainties on this judgement are recognised and noted." Nevertheless, the report recommends the use

of LNT for assessing the risks of small or very small doses. Conversely, the Joint Report states that the use of LNT for assessing the risks of doses below 20 mSv is unjustified and should be discouraged. The Joint Report feels that the most recent data clearly show that the efficacy of the two guardians of the genome, DNA repair and programmed cell death, varies with doses and dose rates, whereas the BEIR 7 Report is sceptical and does not take these data into account. With regard to carcinogenesis, the BEIR 7 Report assumes that lesions accumulated in a single cell suffice to initiate a carcinogenic process. However, the Joint Report points out that the analysis of animal data and the lack of a carcinogenic effect in subjects contaminated with α-emitter nuclides is not consistent with this assumption. Moreover, several recent data show that cancer is not simply a cellular disease but also involves dysfunction of the tissue control and immunosurveillance, such as those that are observed after the death of a large proportion of cells. Therefore the basic radiobiological assumptions of the LNT are not in accordance with recent data.

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