Journal of Radiological Protection

Official journal of the Society for Radiological Protection

OPINION ARTICLE • OPEN ACCESS

The scientific basis for the use of the linear no-threshold (LNT) model at low doses and dose rates in radiological protection

To cite this article: Dominique Laurier *et al* 2023 *J. Radiol. Prot.* **43** 024003

IOP Publishing J. Radiol. Prot. 43 (2023) 024003 https://doi.org/10.1088/1361-6498/acdfd7

Journal of Radiological Protection

OPEN ACCESS

RECEIVED
7 April 2023

REVISED
18 June 2023

ACCEPTED FOR PUBLICATION
20 June 2023

PUBLISHED
29 June 2023

OPINION ARTICLE

The scientific basis for the use of the linear no-threshold (LNT) model at low doses and dose rates in radiological protection

Dominique Laurier*, Yann Billarand, Dmitry Klokov and Klervi Leuraud

Institute for Radiological Protection and Nuclear Safety (IRSN), Fontenay-aux-Roses, France
* Author to whom any correspondence should be addressed.

E-mail: dominique.laurier@irsn.fr

Keywords: linear no-threshold model, radiobiology, epidemiology, radiological protection

Abstract

The linear no-threshold (LNT) model was introduced into the radiological protection system about 60 years ago, but this model and its use in radiation protection are still debated today. This article presents an overview of results on effects of exposure to low linear-energy-transfer radiation in radiobiology and epidemiology accumulated over the last decade and discusses their impact on the use of the LNT model in the assessment of radiation-related cancer risks at low doses. The knowledge acquired over the past 10 years, both in radiobiology and epidemiology, has reinforced scientific knowledge about cancer risks at low doses. In radiobiology, although certain mechanisms do not support linearity, the early stages of carcinogenesis comprised of mutational events, which are assumed to play a key role in carcinogenesis, show linear responses to doses from as low as 10 mGy. The impact of non-mutational mechanisms on the risk of radiation-related cancer at low doses is currently difficult to assess. In epidemiology, the results show excess cancer risks at dose levels of 100 mGy or less. While some recent results indicate non-linear dose relationships for some cancers, overall, the LNT model does not substantially overestimate the risks at low doses. Recent results, in radiobiology or in epidemiology, suggest that a dose threshold, if any, could not be greater than a few tens of mGy. The scientific knowledge currently available does not contradict the use of the LNT model for the assessment of radiation-related cancer risks within the radiological protection system, and no other dose-risk relationship seems more appropriate for radiological protection purposes.

1. Introduction

In the low dose range of ionising radiation, i.e. at doses of low linear-energy-transfer (LET) radiation below 100 mGy according to the classification proposed by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (UNSCEAR 2015), the radiological protection system is based on the assumption that the radiation-related risk of stochastic effects (cancers and hereditary effects) is directly proportional to the dose received, with no dose threshold below which there is no risk. This model is conventionally referred to as the linear no-threshold (LNT) model.

This LNT model concept was introduced into the radiological protection system in the late 1950s (ICRP 1959). Nevertheless, several forms of dose-effect relationship appear possible at low doses, based on biological considerations (UNSCEAR 2012, 2021, NASEM 2022), and the use of the LNT model has since been the subject of numerous scientific discussions and controversies (Brenner *et al* 2003, Wakeford 2005, Tubiana *et al* 2007, Little *et al* 2009, Calabrese 2016). Some experts or groups argue that the LNT model could overestimate the actual risk, supporting a possible existence of a dose threshold below which there is no risk, or perhaps even health benefits (hormesis effects). In contrast, others criticise it for significantly underestimating the actual risk at low doses of ionising radiation, suggesting that the true relationship between the dose received and the undesirable effect is supra-linear.

Today, the LNT model and its use in the radiological protection system are still the topic of lively debate (Doss 2018, Vuillez 2019, Health Physics Society 2020, Cuttler and Calabrese 2021, Calabrese and Selby

2022). In the United States, the Nuclear Regulation Commission (NRC) received three petitions requesting amendment of regulations at the federal level on the grounds of '*new science and evidence that contradicts the linear no-threshold (LNT) dose-effect model that serves as the basis for the NRC's radiation protection regulations*'. The NRC rejected these complaints in 2021, concluding that '*they fail to present an adequate basis supporting the request to discontinue use of the LNT model*' (NRC 2021).

The objective of this article is to review the history of the LNT model, summarise recent data in radiobiology and epidemiology, essentially since the latest recommendations of the International Commission on Radiological Protection (ICRP) in 2007 (ICRP 2007), and discuss whether these results support the existence of a threshold below which an excess risk does not exist, or whether they support the use of a linear relationship for the assessment of radiation-related risks at low doses, i.e. at doses below 100 mGy of low LET radiation according to the UNSCEAR classification (UNSCEAR 2015).

The present article is essentially directed at low LET radiation, as most of the available results relates to effects of exposure to low LET radiation. In the article, if not otherwise stated, doses are from low LET radiation. Nevertheless, epidemiological results on radon and lung cancer are briefly summarised and aspects related to high LET radiation are considered in the section 5. In addition, although the article focuses on low doses, it also takes into account the results obtained on moderate doses accumulated at a low dose rate.

Because the use of the LNT model in radiological protection is limited to stochastic effects, the synthesis of recent data in this paper focuses on cancer risks and biological mechanisms of carcinogenesis. Non-cancer pathologies are not considered in this document.

To avoid ambiguity, the term 'dose-effect' relationship will generally be used when discussing the results of radiobiological studies pertaining to carcinogenesis and associated mechanisms, and the term 'dose-risk' relationship will generally be used in relation to the frequency of cancer obtained in epidemiological studies.

The initial version of this article served as a basis for an internal consultation procedure within the Institute for Radiological Protection and Nuclear Safety (IRSN), which aimed at underlining, documenting and eventually resolving controversies on the LNT model between a variety of researchers and experts in the field of radiation associated risks and applied radiological protection. Some comments and proposals for modification made in the context of this consultation have been taken into account and are integrated into the present version. The present article and the results of this internal consultation will serve as a basis to consolidate the position of the IRSN on the validity of the use of the LNT model in radiological protection.

2. History of the LNT model

2.1. Scientific basis and introduction of the LNT model in the radiological protection system

In 1927, H J Muller reported having induced transgenerational phenotypical changes (i.e. hereditary mutations of deoxyribonucleic acid (DNA)) in drosophilae (fruit flies) through the use of x-rays (Muller 1928). Subsequently, other authors have confirmed the mutagenicity of x-rays on plants and various animal species. The discovery that mutations can be caused by x-rays led to the Nobel Prize for medicine and physiology being awarded to H J Muller in 1946. Subsequently, the US National Academy of Sciences (NAS) conducted a review of the effects of radiation, which culminated in the recommendation of an LNT model for assessing the risk of radiation-related genetic mutations (NAS 1956). In 1958, the US National Council on Radiation Protection and Measurements (NCRP) extended the application of an LNT model to the induction of radiation-related mutations in somatic cells, and thus potentially to the cancer initiation process (Calabrese 2019).

Until the 1950s, the radiological protection system only considered occupational exposures and aimed at protecting individuals from the occurrence of short-term non-cancer effects (tissue reactions) and leukaemias, after high acute doses of radiation (ICRP 2009).

The LNT model was introduced in 1959 in ICRP Publication 1 (ICRP 1959). The observation of an increased rate of leukaemias among survivors of the atomic bombings in Japan had a profound impact on the radiological protection community, highlighting the possibility that even moderate levels of exposure could produce an excess of cancers in an exposed population. Over time, excess solid cancers (cancers of different tissues and organs) were also observed. These studies have shown that the different cancers could have long latency periods between the time of irradiation and the observation of an increase in the detectable risk of cancer in the exposed population (several years for leukaemia and several decades for solid cancers) (Meinhold and Taschner 1995).

The concept of stochastic effects, where the probability of occurrence rather than the severity varies with dose, was introduced in ICRP Publication 9 in 1966. The question then arose of defining a dose threshold for these stochastic effects, in particular for leukaemia and solid cancers. The choice was made in favour of an LNT model, with the following justification: '*The mechanism of the induction by radiation of leukaemia and other types of malignancy is not known. Such induction has so far been clearly established after doses of more*

than 100 rads [1 Gy, low LET radiation], but it is unknown whether a threshold dose exists below which no malignancy is produced. If such a threshold dose did exist, there would be no risk of the induction of malignancy, as long as the threshold was not exceeded. As the existence of a threshold dose is unknown, it has been assumed that even the smallest doses involve a proportionately small risk of induction of malignancies' (ICRP 1966).

Twenty-five years later, in 1991, the ICRP analysed the dose level for which cancer risks are discernible, as follows: '*The principal source of risk estimation […] will be the Japanese survivors of the atomic bombs who were exposed to a range of doses at high dose rate and in whom statistically significant excess of cancer have been observed at doses down to 0.2 Gy*'. On this basis, the ICRP maintained the use of an LNT model, considering that: '*The simplest relationship between an increment in equivalent dose and the resulting increment in the probability of a defined stochastic effect is that of a straight line through the origin. The human epidemiological data are not sufficiently precise to confirm or exclude that relationship*'. In addition, '*the Commission has decided to reduce by a factor of 2 the probability coefficients obtained directly from observations at high doses and high dose rates […]. The reduction factor is called by the Dose and Dose Rate Effectiveness Factor, DDREF. It has been included in the probability coefficients for all equivalent doses resulting from absorbed doses below 0.2 Gy and from higher absorbed doses when the dose rate is less than 0.1 Gy per hour*' (ICRP 1991). The use of the LNT, with a DDREF, is thus integrated in the construction of the nominal risk and so of the radiological detriment (ICRP 1991). It may be noted that the range of doses and dose rates considered at that time was much wider than that considered today for low doses and dose rates (Lowe *et al* 2022). It can also be noted that, according to this definition, the LNT model is supposed to apply to all types of radiation and not only to low LET radiation.

2.2. Controversy between the French Academies of Science and of Medicine and the US NAS

In the mid-2000s, based on emerging results showing low dose radiation-related adaptive responses, genomic instability and non-targeted effects, some authors suggested that simple linear extrapolation of dose-risk relationships from high to low doses was not justified in all cases.

In particular, a joint report by the National Academy of Medicine and the Academy of Science in France concluded that the LNT model and its use for assessing the risks associated with low doses were not based on scientific evidence (Tubiana *et al* 2005, 2007). The authors reasoned that: '*For low linear energy transfer radiation, experimental animal data show the absence of carcinogenic effects for acute irradiation at doses less than 100 mSv and for chronic irradiation at doses less than 500 mSv*' (Tubiana *et al* 2009). Furthermore, a second argument concerned the results of epidemiological studies: '*For doses greater than approximately 200 mSv, the epidemiology data enables the dose-effect relationship to be assessed with relative precision. On the other hand, for low doses and especially for very low doses, epidemiology cannot confirm the existence of an excess of cancer, nor can it rule out its possibility. However, it shows that this risk, if any, is low. These studies do not detect any effects for doses of less than approximately 100–200 mSv in adults and 80–10 mSv in children, suggesting either that there are no effects or that the statistical power of the surveys was insufficient to detect them*' (Tubiana *et al* 2007). Based on this, Tubiana *et al* suggested the idea of '*practical thresholds*' for carcinogenesis: '*This concept means that below the dose threshold, the carcinogenic risk, if it exists, is so small that it is without clinical importance*' (Tubiana *et al* 2009).

At the same time, a review of the scientific literature carried out by the Biological Effects of Ionising Radiation (BEIR) committee of the US NAS concluded that '*the current scientific evidence is consistent with the hypothesis that there is a linear dose-response relationship between exposure to ionizing radiation and the development of radiation-induced solid cancers in humans*' (NAS 2006).

These almost simultaneous publications of the reports of the French Academies of Science and of Medicine and the US NAS resulted in an intense scientific controversy (Tubiana *et al* 2006, Brenner and Sachs 2006).

In 2005, the ICRP carried out an in-depth analysis of the hypothesis of a cancer risk threshold at low doses. The report concluded that: '*while existence of a low-dose threshold does not seem to be unlikely for radiation-related cancers of certain tissues, the evidence does not favour the existence of a universal threshold. The LNT hypothesis, combined with an uncertain DDREF for extrapolation from high doses, remains a prudent basis for radiation protection at low doses and low dose rates*' (ICRP 2005).

2.3. The LNT model in the current radiological protection system

In its most recent recommendations published in 2007, the ICRP maintained the use of an LNT model, considering that at low doses '*the increase in the incidence of stochastic effects is assumed by the Commission to occur with a small probability and in proportion to the increase in radiation dose over the background dose*'. Ultimately, the Commission reasoned that: '*the adoption of the LNT model combined with a judged value of a DDREF provides a prudent basis for the practical purposes of radiation protection, i.e. the management of risks from low-dose radiation exposure*' (ICRP 2007).

With respect to hereditary effects (effects occurring in the progeny of individuals exposed to ionising radiation), epidemiology does not provide any evidence of an increased risk of such effects upon exposure to ionising radiation in a human population. The risk assessment is thus derived from experimental observations (especially in rodents) and is based not on a dose-risk relationship model, but on an estimate of the 'doubling dose' (dose resulting in a doubling of the mutation rate possibly leading to genetic diseases, estimated to be 1 Gy), then extrapolated linearly to low doses. It is on this basis that the risk of hereditary effects is incorporated in the calculation of radiological detriment (ICRP 2007).

The fact that the ICRP considers that *'the LNT model remains a prudent basis for low-dose, low dose-rate radiological protection'* (ICRP 2007) should be interpreted in the ethical sense of the concept of prudence, which is *'the ability to make informed and carefully considered choices without full knowledge of the scope and consequences of actions'*. In Publication 138, the ICRP confirmed this point, stating that *'The system of radiological protection is based on solid scientific evidence; however, there are remaining uncertainties at low levels of exposure that necessitate value judgements. Decision making requires prudence as a central value. However, prudence should not be taken to be synonymous with conservatism or never taking risks. It describes the way in which decisions are made, and not solely the outcome of those decisions'* (ICRP 2018).

3. Summary of recent radiobiology knowledge

Unlike epidemiological studies in humans where the endpoint is usually the occurrence of, or death from, cancer in populations exposed to ionising radiation, radiobiological studies on the mechanisms of cancer induction and development are concerned with a very wide variety of different mechanisms or events. This is because the process of carcinogenesis is a very complex and lengthy biological process, involving a wide range of events and alterations, at molecular, cellular and tissue levels, and which is not yet fully understood (Hanahan 2022). Consequently, experimental studies examining the responses of biological parameters relevant to cancer after exposure to ionising radiation are very diverse in nature; they range from *in vitro* or *in vivo* studies of various radiation-related responses and alterations at the molecular or cellular level, to *in vivo* studies measuring cancer rates over time in exposed animal groups. A synthesis of the extensive radiobiology literature with respect to mechanisms relevant to carcinogenesis was recently published by UNSCEAR (UNSCEAR 2021).

3.1. Carcinogenesis process: mutation theory

The dominant theory of carcinogenesis is more than 100 years old and is known as the *somatic mutation theory* (SMT) (Barrett 1993). It directly links mutagenesis, which is the process of the formation of mutations in the DNA molecules of somatic cells, to the development of cancer (Vaux 2011). The SMT postulates that DNA mutations in a single cell can cause neoplastic transformation of that cell, resulting in uncontrolled growth of the cell and subsequent tumour formation. DNA mutations cover a wide range of genetic alterations, ranging from point mutations to major chromosomal rearrangements called chromosomal aberrations. These DNA mutations are preceded by the formation of initial DNA lesions induced by a variety of exogenous and endogenous factors. Endogenous factors include DNA replication errors or the production of reactive oxygen species (ROS) during normal cell metabolism, while exogenous factors include, for example, chemical pollutants or ionising radiation. To cope with the inevitable production of DNA damage, cells have developed sophisticated mechanisms for DNA repair or programmed death of the affected cells. However, repair errors can occur and lead to the formation of various DNA mutations, ultimately contributing to tumour formation (Hanahan and Weinberg 2011).

The SMT is supported by a large body of evidence, most of which has been accumulated since the mid-20th century, and which remains valid to the present day. However, the knowledge accumulated over the last two decades has revealed a much more complex nature of carcinogenesis (Hanahan 2022). In the 1980s and early 1990s, the multi-stage mechanism of carcinogenesis was proposed and widely accepted (Barrett 1993). It consists of three stages usually referred to as 'initiation, promotion and progression'. The initiation stage is driven only by mutagenesis, i.e. the formation of mutations is a necessary step for initiation. In the promotion stage, a mutant cell enters uncontrolled cell division resulting in hyperplasia or a small benign tumour. This step does not require mutational events in a target cell, is reversible, and can be induced by non-mutagenic agents (Hecker 1967). It is believed that non-mutagenic alterations in the cell, e.g. in epigenetic regulation, can reprogram cell functions to achieve strong proliferation. Often, however, this stage is also characterised by the formation of additional DNA mutations, most often via indirect mechanisms of genetic instability (Fujiki *et al* 2013). Lastly, the transition from a benign tumour to a metastatic cancer is accomplished in the third stage, known as progression. It appears that this late stage of carcinogenesis can be mediated and controlled by a variety of mechanisms, both intrinsically within the target cell and extrinsically as a result of tissue remodelling. It is in this stage that the function of the immune system and of the tissue

microenvironment plays a key role (Barcellos-Hoff *et al* 2013). Interestingly, mutations are also involved in this stage; however, these mutations are most likely secondary to the initial external stimuli and are mainly caused by chronic inflammation that can trigger the production of ROS that can in turn induce more DNA damage and mutations (Basu 2018).

3.2. Carcinogenesis process: non-mutational theories

Although the SMT has very strong experimental support, there is plenty of evidence suggesting that mutations may not be the drivers of cancer (Vineis *et al* 2010). Indeed, it is well established that many non-mutagenic agents are still capable of causing cancer (Bignold 2003). Such chemical products are likely to act at the promotion stage, when target cells have already acquired initiating mutations, for example during normal oxidative metabolism and cell division. Similarly, the alteration of the tissue microenvironment, which can itself lead to carcinogenesis (Baker *et al* 2009), can in fact create the conditions favouring uncontrolled proliferation of cells with pre-existing mutations. In principle, this evidence of non-mutational mechanisms does not contradict the mutational theory of cancer but complements it. The most obvious evidence against mutational theory as a single basis for carcinogenesis is the possibility of reversing cancer cells back to normal cells of the same or a different tissue type (Bizzarri *et al* 2011). Moreover, when non-cancerous embryonic stem cells are placed in an adult body, they may form a tumour, suggesting that uncontrolled proliferation is encoded in normal cells and can be triggered by non-mutational mechanisms (Damjanov 1993).

3.3. Dose-effect relationship at low doses

According to the SMT, exposure to ionising radiation would lead to an additional load of DNA mutations, and therefore to an increased risk of cancer. Among the different types of DNA lesions, DNA double-strand breaks (DSBs) are the most detrimental and are often associated with mutations, including chromosomal aberrations that are associated with cancer (van Gent *et al* 2001). The development of a new sensitive method of assessing DNA DSBs in the 2000s (Paull *et al* 2000) triggered numerous dose-effect studies for low dose induced DNA DSBs in different cell types and under different irradiation conditions. As a result, it is now well established that DNA DSBs increase linearly with dose, in various *in vitro* (Osipov *et al* 2015, Tsvetkova *et al* 2017, Zaharieva *et al* 2022) and *in vivo* (Rube *et al* 2008, Markiewicz *et al* 2015) models. The role of DNA DSBs and their repair in carcinogenesis was recently demonstrated in a study of the mutational spectra in thyroid cancer in humans exposed to ionising radiation during the Chernobyl nuclear power plant accident (Morton *et al* 2021). Although the authors did not study a dose-response relationship, they demonstrated a key role of mutations arising from DNA DSB repair. Although it is not fully established that the conversion of an initial DNA DSB to mutations follows a linear relationship (effects of repair, removal of damaged cells) (Averbeck 2009, Dalke *et al* 2018), the UNSCEAR provides good reasons to assume that at the mutation level linearity is maintained (UNSCEAR 2021). Therefore, with regard to initial molecular and genetic events, the radiobiological studies support linearity. This is the position adopted by UNSCEAR in its 2021 report: '*The Committee concluded that there remains good justification for the use of a non-threshold model for risk inference given the robust knowledge on the role of mutation and chromosomal aberrations in carcinogenesis*' (UNSCEAR 2021).

However, as stated in the previous section, it is important that, in addition to mutational, non-mutational mechanisms are accounted for in the consideration of dose effects. To this end, it is useful to briefly consider results of dose-effect studies where the effect is a direct measurement of tumour formation. It turns out that such studies produce results that do not directly show linearity (Shin *et al* 2010, Dalke *et al* 2018). In fact, most radiobiological studies that have measured the incidence of tumours (proportion of animals with cancer) and the rate of tumours (number of tumours per animal) in animals exposed to different doses of ionising radiation have reported results that are not consistent with linearity (for example, 6 out of 7 *in vivo* studies reviewed by UNSCEAR in its recent report (UNSCEAR 2021) show no increase in incidence/rate of tumours at the lowest dose used).

One possible explanation of this observation may be related to the ability of cells to accurately repair low levels of DNA damage via various DNA repair pathways (although a fraction of cells may end up with errors) or to the elimination of mutant or critically damaged cells, which overall reduces the probability of cancer. Another possibility lies with the non-mutational mechanisms of cancer described above. Low doses of ionising radiation may not be able to negatively influence the non-mutational mechanisms of carcinogenesis, for example the immunological regulation and chronic inflammation. In this case, even if few cells did transform into pre-neoplastic cells via mutation, the tissue microenvironment may be able to control and suppress their proliferation, thus blocking the promotion and, in particular, progression stages of tumorigenesis.

There exists evidence showing that low doses of ionising radiation can stimulate or activate various protective mechanisms, such as the induction of DNA repair and antioxidant systems in irradiated cells or reinforce antitumour immunity in irradiated organisms. These results are often presented as evidence against the LNT model (Averbeck *et al* 2018, Gueguen *et al* 2019, Scott and Tharmalingam 2019, Tharmalingam *et al* 2019).

Effects can also be observed in cells that are not directly affected by ionising radiation. These effects, called 'non-targeted effects', can be broadly assigned to two groups: bystander effects (effects on cells adjacent to irradiated cells), and abscopal effects (effects on tissues away from the irradiated site). Non-targeted effects can both inhibit and promote the process of tumorigenesis. The latter case is mainly associated with genomic instability, which is an increased rate of DNA and chromosome mutations observed for long periods after exposure to ionising radiation. It may be considered that these mechanisms might contribute to the non-mutational components of carcinogenesis.

The numerous results accumulated over the past 15 years have confirmed the existence of these non-mutational mechanisms in carcinogenesis and suggest that the radiation-related carcinogenesis is not limited to mutational mechanisms. However, as of today, this evidence remains fragmented and overall lacks consistency. These mechanisms are likely to potentiate or mitigate the risk of cancer, but their impact on the risk of radiation-related cancer at low doses is difficult to assess (UNSCEAR 2021, Wojcik 2022). Further research into these non-mutational mechanisms is warranted and expected to strengthen the knowledge about their involvement in carcinogenesis.

3.4. Synthesis and outlook

Although the fundamental mechanisms of carcinogenesis are not yet fully understood, the theory of the SMT, which has existed for more than a century, has seen a significant evolution in the past 20 years, acknowledging a significant role played by non-mutational mechanisms in carcinogenesis.

Induced mutations today appear to be the main driver of carcinogenesis induced by ionising radiation. A large number of radiobiological studies demonstrating a linear dose effect for DNA damage and mutations do tend to support the LNT model in the assessment of cancer risks. These results do not show the existence of a dose threshold below which no effect would be observed, at least from a level of around 10 mGy (Shimura and Kojima 2018; UNSCEAR 2021).

Today, it remains difficult to take into account non-mutational mechanisms due to the inconsistency of relevant results. However, the direct measurement of tumour levels in animal studies does not rule out the possibility of a threshold in a dose-effect relationship for the incidence of cancer at low doses.

This divergence represents a significant challenge for the field of low dose radiobiology and warrants future animal studies. These studies should be designed in such a way that within a single experiment, initial radiation-related mutational events, long-term changes in the tissue microenvironment and immune system can be measured, along with the tumour rate and incidence. This would allow to experimentally test the transition of linearity from a dose-effect relationship to a dose-risk relationship. The development of multidisciplinary approaches involving radiobiology, epidemiology, and modelling (Laurier *et al* 2021), such as the adverse outcome pathway approach (Chauhan *et al* 2022) or mechanistic models (NCRP 2020), should make it possible to better understand the discrepancies between experimental results in animals and observational results in humans (Zhu *et al* 2022).

4. Summary of recent epidemiology findings

Over the past 10 years, the ability of epidemiological studies to reveal stochastic effects associated with low doses of ionising radiation has improved substantially. Several decades of monitoring exposed populations since the 1940s, such as Japanese survivors of the atomic bombings of Hiroshima and Nagasaki (Ozasa *et al* 2012, Grant *et al* 2017) or nuclear workers (Richardson *et al* 2015), allowed for quantification of risks of diseases that develop several years after exposure and more frequently at an advanced age. International collaborative studies, through the pooling of data from several regional cohorts, have also contributed to improving knowledge of effects at low doses, thanks to increased statistical power, thus providing greater precision in risk assessments (Richardson *et al* 2015, Lubin *et al* 2017, Little *et al* 2018).

This section presents an overview of recent informative epidemiological studies on the LNT model, i.e. studies that have quantified cancer risks according to the dose received, with sufficient statistical power to assess the risks at low dose levels and provide information about the form of the dose-risk relationship.

4.1. Risk of cancer at low doses and questions about the existence of an effect threshold

Recent studies have reported excess cancer risks associated with ever lower dose levels. In 2012, the analysis of the risk of death from solid cancers in the life span study (LSS)—the cohort of Japanese survivors of the 1945

atomic bombings—concluded that there was a significant excess risk of solid cancer over the 0–200 mGy dose interval (Ozasa *et al* 2012). The authors had formally tested the existence of a dose threshold below which the excess risk would be zero and had concluded that the most likely value of this threshold was zero, with an upper limit of the 95% confidence interval equal to 150 mGy. A few years later, the study of the risk of solid cancer based on incidence data and longer follow-up of the LSS reported a statistically significant excess risk over the 0–100 mGy dose interval, and again performed tests that did not suggest the existence of a dose threshold (Grant *et al* 2017). In 2015, the association between the risk of death by cancer (other than leukaemia) and cumulative exposure to a series of low doses of ionising radiation was assessed in a cohort of more than 308 000 workers (mostly men) from the nuclear industry in the United States, France, and Great Britain (INWORKS study). In this study, although exposure was received cumulatively over the entire occupational lifetime, the authors revealed a proportional increase in the risk of death from cancer with the cumulative dose. The observed dose-risk relationship was still statistically significant over the limited dose interval of 0–100 mGy, with a slope compatible with that estimated for the entire cohort (Richardson *et al* 2015).

Analysis of the risk associated with low doses for specific cancer sites is more difficult than for all cancers considered together, since the lower number of observed specific cancer site cases leads to lower statistical power. Lubin *et al* (2017) conducted a large-scale study of thyroid cancer, assembling data from nine cohorts, i.e. nearly 108 000 people exposed to doses of external sources of radiation (predominantly low LET) less than 200 mGy during childhood for medical reasons or from the bombings of Hiroshima and Nagasaki. The authors reported highly significant dose-risk relationships, including in the 0–100 mGy dose interval (Lubin *et al* 2017). The authors tested the existence of a dose threshold and estimated that this threshold varied between 0 and 30 mGy, with an upper limit of the 95% confidence interval equal to 40 mGy. In the INWORKS study, the risk analysis for leukaemia mortality revealed a significant dose-risk relationship for cumulative photon doses between 0 and 300 mGy. Over smaller dose intervals, estimates of relative excess risk of leukaemia were of the same magnitude, but associated with broader uncertainties (Leuraud *et al* 2015). The risk of leukaemia has also recently been studied in a cohort of more than 260 000 people from the LSS or exposed to external sources of photons for medical reasons before the age of 21 at cumulative doses of less than 100 mGy (Little *et al* 2018). The authors showed significant dose-risk relationships for acute myeloid leukaemia and acute lymphoblastic leukaemia. For acute lymphoblastic leukaemia, the significant association persisted even for doses of less than 50 mGy (Little *et al* 2018). A recent meta-analysis of 60 studies of *in utero* or early childhood exposures concluded that there is now little doubt that an excess risk of childhood leukaemia extends to the low dose range, down to 50 mGy (Little *et al* 2022).

4.2. Shape of the dose-risk relationship for cancers

Recent studies have also strengthened our knowledge with regards to the shape of the dose-risk relationship for cancers. Analysing the risk of death from solid cancers in the LSS, the authors considered that the dose-risk relationship was generally linear, but an upward curvature of the dose-risk relationship was observed when the analysis was limited to survivors who received a dose to the colon of less than 2 Gy (Ozasa *et al* 2012). In 2017, for the first time, the relationship between the risk of occurrence of solid cancer and the dose received by survivors appeared different between males and females: linear for females, and a marked upward curvature for males (Grant *et al* 2017). The authors suggested that this difference between sexes may be attributed to a different distribution of anatomical sites of cancers between males and females (for example, the proportion of lung cancers was greater in males, while thyroid cancers accounted for a greater proportion of female cancers compared to male), since the dose-risk relationship is likely to take different forms for different types of cancer. However, studies conducted in the LSS on specific anatomical cancer sites (Furukawa *et al* 2013, Cahoon *et al* 2017, Brenner *et al* 2018b, 2020, Sakata *et al* 2019, Utada *et al* 2019, 2021, French *et al* 2020, Sugiyama *et al* 2020, Grant *et al* 2021, Mabuchi *et al* 2021) generally support a linear dose-risk relationship, possibly due to a lack of statistical power. The choice of cancer baseline modelling in the analyses of Grant *et al* (2017), which did not take into account the specific (e.g. temporal) characteristics of each anatomical site but considered all solid cancers together, was also suspected of introducing bias in determining the shape of the dose-risk relationship (Cologne *et al* 2019). The authors concluded that analysis based on all solid cancers grouped together as a single entity is not the optimal method for assessing the risk of solid cancers in the LSS (Cologne *et al* 2019).

In an attempt to explain the differences observed in the shape of the dose-risk relationship for solid cancers in the LSS, between analyses based on mortality data (Ozasa *et al* 2012) and incidence data (Grant *et al* 2017), and between males and females (Grant *et al* 2017), Brenner *et al* (2022) studied in detail the parameters likely to influence the assessment of the dose-risk relationship. Using the most up-to-date dosimetry system and applying identical modelling methods to the mortality data and incidence data, the authors confirm that the dose-risk relationship observed for solid cancers is linear-quadratic in men, with an upward curvature, and that the parameters describing the dose-risk relationship are of the same order of

magnitude between analysis based on mortality data and analysis based on incidence data. For females, the results are more complex: a linear-quadratic relationship is observed for mortality data, but the relationship appears linear for incidence data. According to the authors, the contribution of breast and thyroid cancers (with a good medical prognosis) which is higher for cancer incidence than for deaths could partially explain the linearity of the dose-risk relationship for all solid cancers in females, as the risks of occurrence of breast and thyroid cancer increase linearly with the dose in the LSS (Furukawa *et al* 2013, Brenner *et al* 2018b). Analyses based on age at the time of exposure show that the curvature of the dose-risk relationship in males (mortality and incidence) and females (mortality only) is particularly observed in survivors exposed before the age of 20 (Brenner *et al* 2022).

In the INWORKS study of the risk of solid cancer mortality in workers, the authors revealed a linear increase in the risk of cancer with the cumulative dose, with no evidence supporting a deviation from linearity (Leuraud *et al* 2021). The distribution of anatomical cancer sites in INWORKS (32% of lung cancers, 5% of stomach cancers) (Richardson *et al* 2018) is very different from that observed in the LSS (20% deaths from lung cancers and approximately 28% from stomach cancers in men) (Brenner *et al* 2022). In addition, in INWORKS, individuals were exposed protractedly in adulthood, whereas in the LSS the curvature of the dose-risk relationship seems to be due to acute exposures received before the age of 20. For the risk of leukaemia, the shape of the relationship also appeared linear without deviation from linearity in INWORKS (Leuraud *et al* 2015). Little *et al* (2018) and Lubin *et al* (2017) also reported linear dose-risk relationships for leukaemia and thyroid cancer respectively, with little evidence in favour of a deviation from linearity.

4.3. Critical reviews of recent results

The epidemiological literature was reviewed by the NCRP to examine the validity of the LNT model for radiological protection against exposure to low LET radiation (NCRP 2018, Shore *et al* 2018). The report presents a critical review of 29 studies published after 2000, covering occupational, medical, and environmental exposures. The quality of each study and its degree of support for the LNT model were assessed. In total, only five studies did not support the LNT model, while four studies were considered inconclusive. The report concluded that the majority of the studies assessed, including those with the highest quality levels, showed good consistency with the LNT model for solid cancers and for leukaemia (NCRP 2018, Shore *et al* 2018).

In 2020, the National Cancer Institute (NCI) in the United States published a monograph of epidemiological studies on the risk of cancer after exposure to low doses of ionising radiation with low LET (Berrington de Gonzales *et al* 2020). The analyses included a total of 22 studies published since 2006, with mean doses of below 100 mSv, independent of the dose rate. The objective was to evaluate potential biases in these studies, and to perform a meta-analysis. The authors concluded that '*new epidemiological studies directly support excess cancer risks from low-dose ionizing radiation. Furthermore, the magnitude of the cancer risks from these low-dose radiation exposures was statistically compatible with the radiation dose-related cancer risks of the atomic bomb survivors*' (Hauptmann *et al* 2020).

4.4. Synthesis and outlook

In recent years, most studies that have attempted to estimate a dose threshold have found values compatible with 0 mGy, i.e. an absence of threshold (Ozasa *et al* 2012, Grant *et al* 2017, Lubin *et al* 2017). In conclusion, no dose threshold can be proposed today based on the epidemiological literature available for low LET radiation-related cancer.

With respect to the shape of the dose-risk relationship, the majority of published results remain consistent with the use of a linear model. Observation of a divergence from a linear model in the latest cancer risk monitoring data in survivors of the atomic bombings requires further analysis, in particular to better understand the implications of age at exposure, the temporal course of baseline rates, and the contribution of different types of cancer to this observation. For specific cancer sites, a linear-quadratic relationship is observed in survivors of the atomic bombings only for leukaemia and oesophageal cancer (Hsu *et al* 2013, Sakata *et al* 2019), but this could be due to limited power.

Of course, not all studies provide consistent results on the cancer risks of low dose and low dose rate radiation. For example, the study of the population living in a high background radiation area in Kerala, India, chronically exposed to low dose rate radiation, did not show a positive association between dose rate and solid cancer risk (and even observed a non-significant negative association). The authors concluded that their results suggest '*a possibility that the risk of solid cancer associated with continuous low dose rate radiation exposure is significantly lower than that associated with acute exposure*' (Jayalekshmi *et al* 2021). This reinforces the pertinence of reviews and syntheses, taking into account all available results, to interpret risks at low doses and dose rates, such as those published in recent years (Lubin *et al* 2017, Shore *et al* 2017, NCRP 2018, UNSCEAR 2018b, Hauptmann *et al* 2020, Little *et al* 2022, Rühm *et al* 2022).

The development of 'mechanistic' models (i.e. incorporating information on biological mechanisms in the modelling of the relationship between exposure to ionising radiation and the risk of cancer) appears to be a promising approach to reconcile the results of biology and epidemiological analysis and consolidate the quantification of risks at low doses (NCRP 2020). A review of the mechanistic models applied to epidemiological data has been carried out (Rühm *et al* 2017). Nevertheless, the results show that, to date, the uncertainties involved are considerable and that the models only provide a simplified description of the underlying complexity of carcinogenesis. In addition, few of these studies have included a systematic investigation of the implications for the form of dose response. Based on this review, the authors have concluded that: '*Current hypotheses in radiation protection, including the LNT model, do not contradict what is currently known about the cancer development process*' (Rühm *et al* 2017). Several syntheses or meta-analyses have been published in recent years (Lubin *et al* 2017, Shore *et al* 2017, NCRP 2018, Hauptmann *et al* 2020, Little *et al* 2022, Rühm *et al* 2022), all of which conclude there is an association between dose and risk of cancers at low doses or low dose rates. Based on its review of 2018, the NCRP concluded that '*the LNT model (with the steepness of the dose-response slope perhaps reduced by a DDREF factor) should continue to be utilized for radiation protection purposes.*' (NCRP 2018).

It is generally considered that uncertainties associated with estimates of radiation-related risks in the low dose range are large. A review of the main sources of uncertainty have been published by UNSCEAR (UNSCEAR 2018a). Also, the UNSCEAR performed an evaluation of selected health effects (leukaemia, all solid cancer and thyroid cancer) and inferences of risk from exposure to ionising radiation in specific scenarios of exposure (repeated CT scans during childhood, occupational exposure in the nuclear industry, post-Chernobyl exposure during childhood) (UNSCEAR 2020a). Results showed that most sources of uncertainties were small or very small (less than a factor 1.5), and rarely higher than a factor of 2 (UNSCEAR 2020a). Also, a formal assessment of the potential impact of confounding and biases associated with epidemiological studies at low doses was recently performed by the US NCI (Berrington *et al* 2020). This systematic analysis concluded that '*only a few positive studies were potentially biased away from the null. After exclusion of these studies, the majority of studies still reported positive risk estimates*' (Hauptmann *et al* 2020).

In epidemiology, it is anticipated that in the coming years, a continued follow-up of cohorts that have been in place for several decades (survivors of the bombings of Hiroshima and Nagasaki, patients exposed during childhood, workers in the nuclear industry, etc) will strengthen our knowledge of dose-risk relationships for specific cancer sites, in males and females, and should lead to a reduction in the uncertainties that persist today. Longer follow-up times and ageing populations should increase the capacity of statistical analyses to determine the shape of dose-risk relationships at low doses.

Epidemiological knowledge of cancer risks associated with internal contamination is much less developed than for external exposures. Nevertheless, evidence of an association exists for certain types of cancers and certain exposure situations. Especially, evidence on the risk of lung cancer associated with exposure to radon and its progeny (high LET emitters) is compatible with an absence of threshold and a linear dose-risk relationship (ICRP 2010, UNSCEAR 2020b). An association is also observed between exposure to plutonium and lung cancer (ICRP 2021b). Extension of epidemiological studies on populations exposed due to internal contaminations or to mixture of radiation types (occupational exposure of miners and workers in the nuclear fuel cycle, environmental and post accidental exposure situations…) should improve our knowledge of the dose-risk relationship also for high LET radiation.

5. Discussion

5.1. Limitations of experimental and epidemiological approaches

Both experimental and epidemiological approaches of effects and risks at low doses and low dose rates present limitations. UNSCEAR proposed criteria to assess the quality of experimental studies (UNSCEAR 2021, appendix A) and epidemiological studies of radiation exposure (UNSCEAR 2018a).

For *in vitro* radiobiological studies, the main concern is that observations of cells that are deprived of their normal tissue microenvironment, i.e. lacking a complex 3D structure, interactions with multiple cell types, low oxygen concentration, etc, may not be representative of the mechanisms occurring *in vivo*, especially for such complex processes as tumorigenesis. Additionally, a presumed predominant role of stem cells in carcinogenesis (Trosko 2021) raises many questions on the relevance and usefulness of the results obtained using irradiated non-stem cells for understanding the mechanisms of radiation-related cancer in humans and thus the corresponding risks.

Although *in vivo* radiobiological studies represent a step forward compared to the *in vitro* studies with respect to the above-mentioned aspects, they are facing another major limitation: the transferability of results from laboratory animal models to humans. Although experimental rodent models have long been used in radiobiological studies, it is still unclear whether the results can be systematically applied to humans.

This is partially illustrated by the inability to demonstrate the absence of a threshold for induced cancers/tumours in mouse studies, while evidence of effects at low doses from human epidemiological studies increases with increasing cohort size. Peculiarities of laboratory environment used in animal studies, such as limited space, sterilised food, group housing, inbreeding, etc, although allowing for a better control of experimental conditions and thus group comparison, may in principle affect the process of tumorigenesis compared to natural environments. It is also reasonable to suggest that lifestyle plays a far greater role on cancer risk in humans than in laboratory animals, therefore limiting consistency between radiation epidemiology and radiobiology. For example, it is difficult to demonstrate an increased risk of lung cancer due to smoking in laboratory animals, whereas it is evident in humans. Addressing these issues through laboratory research is challenging. Another limitation of radiobiological studies is related to difficulties in comparing and consolidating results obtained in different strains of laboratory rodents or different species (Snijders *et al* 2012, Rivina and Schiestl 2013). For example, the C57BL/6J strain is more radioresistant compared to the CBA strain (Rithidech *et al* 1999), which may lead to differences in dose-effects, both for DNA damage and for other parameters involved in the carcinogenesis process (Hamasaki *et al* 2007).

As far as epidemiological studies are concerned, the main objective is to measure the health effects of exposure to a risk factor directly in human populations. Nevertheless, the majority of epidemiological studies are observational (i.e. non-experimental), which poses problems of interpretation. Especially, epidemiological studies do not control the parameters of the environment of the individuals, which can also influence the occurrence of the observed effect. Typical limits of epidemiology include methodological biases. Screening bias may lead to studying a group of people that is not representative of the target population due to poor study inclusion criteria (e.g. volunteer-based participation). Classification bias may occur when assigning to a person a different exposure (or dose) than that received (e.g. measurement errors) or a disease that the person has not developed. Confounding applies when a third factor associated independently with the disease and the exposure is not considered and whose absence in the analysis can alter, reverse, or mask the real relationship between the risk factor studied and the disease (Bouyer *et al* 2009). Other risk factors may alter the radiation response if radiation interacts with these other factors, and there is evidence for this, for example, in smoking and radiation and the combined risk of lung cancer. In a recent NCI monograph, the authors systematically analysed the various sources of bias in epidemiological studies and assessed their potential impact on cancer risk assessment at low doses (Hauptmann *et al* 2020, Schubauer-Berigan *et al* 2020). They concluded that low dose risk assessment was not substantially biased and that existing biases were unlikely to explain the results observed in most of the studies.

In addition to these conventional limitations in radiobiology and epidemiology, the constraint of low statistical power must be taken into account when looking at the effects of exposure to low doses of ionising radiation. A lack of statistical power may prevent detection of a small effect or risk at low doses. Failure to observe an effect or risk at low doses should therefore not be considered as evidence of an absence of effect or risk (absence of evidence is not equivalent to evidence of absence). In radiobiology studies, although strict control of exposure conditions and the use of selected strains reduce inter-individual variance in groups of animals, the small number of animals may limit the ability to detect small effects after low dose radiation. In epidemiology, and in particular when studying low doses, the ability to reveal an excess risk may be limited, due to the small number of exposure-related cases compared to the number of background cases expected in the study population. In particular, it may be difficult to detect non-linearity in the estimated relationships between dose and risk of cancer. Indeed, as the linear model is the simplest model to evaluate (only one parameter to assess), a lack of statistical power may limit the ability to prefer a non-linear model (requiring the assessment of more than one parameters). It is therefore parsimonious to interpret the results as consistent with a linear relationship, rather than as a demonstration of linearity.

5.2. Usefulness of the LNT model in the system of radiological protection

In the initial steps of the radiological detriment calculation process, certain cancer risk models derived from the epidemiological literature may be non-linear. This is the case, for example, for leukaemia, for which a linear-quadratic model has been used since the 1990s (ICRP 1991). For solid cancers, the application of a DDREF of 2 implies a difference in the slope of dose-risk relationship models between doses lower or greater than 0.2 Gy (ICRP 1991). The LNT association with dose is invoked when calculating nominal risk coefficients, which reflect, for each organ, the cumulative probability of cancer occurring in that organ over a lifetime, normalised to a dose of 1 Gy. The radiological detriment is then calculated by assigning a weight to each of these nominal risk coefficients, depending on the severity of each cancer and assuming that each organ receives the same dose (Ban *et al* 2022, ICRP 2022).

It is essential to recall that, in order to construct the nominal risk coefficients and radiological detriment, the ICRP uses and aggregates data relating to persons with diverse characteristics (sex, age, two regions), such that the individual to whom the LNT model is applied is in fact a fictitious subject, averaged between a

male and a female, exposed at all ages of their life, and both Asian and American-European (Harrison *et al* 2023). It is therefore irrelevant to try to demonstrate the accuracy of the LNT model in radiological protection, which remains fundamentally a mathematical construction, which cannot be compared to experimental or epidemiological results, but which integrates them.

In particular, this aggregated approach is one of the reasons why it is not recommended to use the nominal risk coefficients to perform risk assessments for specific individuals or categories of individuals (Harrison *et al* 2023). Even more so this statement is applicable to the use of the radiological detriment. The risk assessment must therefore be based on the use of an ad hoc risk model, specific to the type of cancer considered and the dose to the relevant organ, taking into account as far as possible the characteristics of the individual or group of individuals considered (sex, age at exposure, attained age or time since exposure). In this case, the most relevant risk model may be non-linear (UNSCEAR 2008).

Therefore, in the radiological protection system, the LNT model, by design, ultimately results in a directly proportional relationship between radiological detriment and effective dose (Laurier and Clement 2021). The radiological protection system is made operational by the fact that the effective dose, which can only be calculated, can be approximated by a dose measured by a dosimeter on the chest (for external radiation exposure). The ability to account for a complex protection value by means of a simple measurement (with the assumption that external and internal doses, and different LET radiation, can be added meaningfully) represents one of its major strengths.

Radiological protection is based on three main principles: justification, optimisation and limitation of radiation doses (ICRP 2007). With regard to the principle of limitation, the radiation detriment, which is inseparable from the effective dose and the LNT model, is an indispensable tool for assessing the tolerability of a radiation exposure. With regard to the principle of optimisation, the proportionality between effective dose and radiological detriment is decisive for two aspects. Firstly, given the no-threshold character of the relationship between dose and risk, optimisation is not subordinate to a dose level to be reached (i.e. optimisation does not mean minimising doses), and then it constitutes a management approach rather than a quantitative objective. Secondly, it allows the use of the collective dose as a tool for assessing the management performance of a project or an activity with regard to radiological protection. If the relationship between effective dose and radiological detriment were no longer considered linear, then this indicator would lose its meaning, since the same collective dose could mean different levels of risk.

The use of the LNT model in the risk assessment of medical uses of ionising radiation is sometimes presented as exaggerating the risks and not sufficiently considering the medical benefits of these applications (Cuttler 2020). Clearly, the specificity of individual medical exposures must be considered, and the benefits of diagnostic and therapeutic procedures are recognised, but there is currently no scientific support for the assumption that medical exposures result in a fundamentally different risk from other exposure situations. The application of the LNT model in the medical field therefore seems today as justified in the medical field as in other exposure situations (ICRP 2021a, Harrison *et al* 2023). Further reflection on the balance between the health benefits of medical applications and risks associated with radiation exposure may be useful (Zanzonico 2016).

Outside of specific cases, such as radon and lung cancer risk or iodine and thyroid cancer, little evidence of dose risk-relationship exist for internal exposures. The assumption of a LNT model, together with the application of radiation weighting factors W_R, is used to calculate effective dose associated with internal contamination.

5.3. Other major hypotheses of the radiological detriment calculation

The LNT model is not the only hypothesis underlying the radiological detriment calculation (Zhang *et al* 2020). Three of these hypotheses are laid out below.

The first assumption is that, for low LET radiation, the dose-risk relationship is a lower slope at low doses or low dose rates than at high acute doses. This assumption leads to the application of a DDREF of 2 to the dose-risk relationships derived for solid cancers from the monitoring of survivors of the Hiroshima and Nagasaki atomic bombings. This DDREF was introduced in the calculation of radiological detriment in 1991, essentially on the basis of experimental results (Cléro *et al* 2019). A working group was set up by the ICRP to examine the scientific basis of this DDREF in cell biology in animal experimentation and epidemiology. Several articles have been published (Rühm *et al* 2015, Shore *et al* 2017, Tran and Little 2017) and a dedicated report will be published by ICRP.

The second assumption relates to the transfer of cancer risk between populations. In the current system, the dose-risk relationships used are essentially derived from the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki. Assumptions are necessary regarding the relationship between the radiation-related risk and the cancer risk baselines (i.e. the cancer rates observed in the population without additional exposure to ionising radiation), which have resulted in the development of weighting factors between

different transfer models (relative risk transfer and additive risk transfer) and the determination of reference populations. The repetition of epidemiological results in various populations with different baseline cancer rates should help to determine a more relevant transfer of risk between populations in the coming years.

The third assumption is dose additivity. Until the 1990s, little epidemiological data was available to verify the validity of this hypothesis. However, in recent years, several studies involving populations exposed protractedly (workers in the nuclear industry (Leuraud *et al* 2015, Richardson *et al* 2015)) or repeatedly (patients monitored for tuberculosis treatment, young women undergoing fluoroscopy for scoliosis problems (Luan *et al* 2020)), and patients having received CT scans during childhood (Abalo *et al* 2021) show an increase in the risk of certain cancers with the dose accumulated over time (therefore, the cumulative dose from repeated exposures). These studies should allow consolidation of the results on this point in the coming years. This assumption applies also to radiation types other than gamma. To weight the relative biological effectiveness of other radiation types, a radiation weighting factor (W_R) has been proposed. Using that W_R, sum of different radiation types is thought to be contributing to effective dose.

5.4. Comparison with other carcinogens

The LNT model is not unique to the field of ionising radiation exposure. It is also used in different contexts and for different types of populations to assess the risk associated with exposure to other carcinogens. For the assessment of the health risks due to exposure of the general population to chemical substances, the dose-effect relationship is used as a basis when establishing the toxicological reference value (TRV). Specifically, TRV is a generic designation reflecting the association between a dose and an effect, for both threshold and no-threshold effects. TRVs are established by international (World Health Organisation), European (European Food Safety Authority) or national bodies (French National Agency of Sanitary Safety (ANSES)), US Environmental Protection Agency (EPA), Dutch National Institute for Public Health and the Environment for each substance (ANSES 2017). Regarding methodology, the use of human data is to be favoured for constructing these values. However, unlike for ionising radiation, support studies have mainly been experimental studies on animals and continue to remain so for the regulatory evaluation of new chemical substances (Cléro *et al* 2021). This trend is changing. More and more epidemiological studies relating to exposures to chemical substances are available, thus allowing for an update of the related TRVs.

The estimation of the dose-response curve by an LNT model in the field of chemical exposure is mainly applied to carcinogenic substances, and more specifically to substances inducing genetic mutations. The unit of exposure used in the chemical field is a daily intake unit considered over a lifetime which differs according to the route of exposure (mainly ingestion and inhalation). Thus, TRVs for non-threshold substances are associated with a chronic exposure and a given exposure route. To summarise, when the critical effect selected for the substance is the induction of genetic mutations, the method for constructing the TRV consists of using the available data to determine a benchmark dose, associated with an excess risk. Several approaches exist. The two-step approach, recommended by the ANSES and adopted by the US EPA (ANSES 2017), is based on the separation between interpolation in the observable domain and extrapolation to low doses. A line is drawn between the reference dose determined from observable data and the origin. The TRV, known as the unit excess risk, is the slope of this line. There are some similarities between the TRV used for chemical substances and the detriment used for radiation, but also differences, which justify being prudent when comparing the two approaches. In particular, it is the critical effect (effect corresponding to an adverse effect, specific to the substance and occurring at the lowest doses or concentrations in the most vulnerable population) that is used to establish the corresponding TRV, whereas a cumulative approach (sum of cancer risks for a set of organs) is used in radiological protection to calculate the radiological detriment (Cléro *et al* 2021).

Regarding assessment of the robustness of the LNT model, its use in the chemical field does not in itself constitute a confirmation of its validity for radiological protection. The LNT model was indeed chosen by the US EPA in the 1970s for carcinogenic substances inducing genetic mutations, based on the conclusions drawn by the BEIR committee specifying that the model to be used for exposure to radiation was the LNT model (Calabrese 2009). As stated above, it is clear today that a substance does not have to be mutagenic in order to be carcinogenic. The available results show that many carcinogenic substances do not necessarily affect the coding sequence of DNA. The model currently recommended by ANSES for this type of carcinogenic and non-mutagenic substance is a threshold model. For example, ANSES indicated that it was not possible to conclude on the mutagenicity of formaldehyde while recognising the carcinogenic nature of this substance for the nasopharynx above a threshold (ANSES 2018). The US EPA has retained an LNT-type approach for all carcinogens (EPA 2005).

Finally, beyond ionising radiation and chemical substances, a LNT model is not systematically used for estimating the dose-risk relationship for other cancer risk factors. In particular, in a study of the fraction of cancers attributable to 13 known risk factors in France (Marant-Micallef *et al* 2018a, 2018b), the

International Agency for Research on Cancer used different dose-risk models for the different factors. Although all models assumed no threshold, they did not necessarily assume a linear relationship between exposure and cancer risk. For example, the relative cancer risk for alcohol increased almost linearly with daily consumption for colorectal cancer, whereas supra-linearity was assessed for liver and intrahepatic bile ducts cancers (IARC 2018).

6. Conclusions

Evidence that exposure to ionising radiation causes genetic mutations was obtained in the first half of the twentieth century. Subsequently, simplified concepts were formulated and implemented in building a system of radiological protection capable of managing the risk of cancer at low doses or low dose rates. The model of a LNT relationship between radiation exposure and cancer risk is a major one, which has shaped the current system of radiological protection, in particular through the principles of limitation and optimisation.

6.1. Knowledge gained over the last 10 years on the risk of cancer at low doses

In the past 10 years, results of the studies on the effects of radiation, both in radiobiology and epidemiology, have improved our understanding of the risk of cancer at low doses.

In radiobiology, although it is clear that certain mechanisms do not respond in a linear fashion to ionising radiation, the overall process of radiation-related carcinogenesis seems to be consistent with linearity. This is mainly due to the fact that mutational events that are assigned a driving role in carcinogenesis respond linearly to ionising radiation starting from as low as 10 mGy. Although the role of non-mutational mechanisms in carcinogenesis is now well acknowledged, our understanding of these mechanisms remains fragmented, and thus their impact on radiation-related cancer at low doses is currently difficult to assess.

In epidemiology, the available results today show excess cancer risks at dose levels below 100 mGy, at least for all solid cancers combined, as well as for certain specific types of cancer. While some recent results indicate non-linear dose relationships for some cancers, overall the LNT model does not appear to seriously overestimate the risks at low doses or low dose rates.

Current results of epidemiological studies do not demonstrate a dose threshold for the risk of radiation-related cancer. Similarly, current understanding of mutational mechanisms and their responses to ionising radiation does not support a threshold for these mechanisms involved in carcinogenesis. Although uncertainties about the effects of low doses or low dose rates persist, current results in radiobiology or epidemiology do not convincingly show a dose threshold below which a radiation-related cancer risk would not exist. Such a dose threshold, if any, could not be greater than a few tens of mGy.

6.2. Validity of use of the LNT model in radiological protection

Several major international bodies in the field of the effects of ionising radiation (ICRP, NCRP, UNSCEAR, NCI) have recently published syntheses or joint analyses of relevant data. They have concluded that there is enough evidence of the carcinogenic effects of ionising radiation at low doses, and that the model of the absence of a threshold for radiological protection purposes is relevant and reasonable.

On the basis of the state of knowledge summarised in this article and of the consultation procedure performed within our Institute, the LNT model appears to be suitable for estimating the risk of cancer associated with exposure to ionising radiation, in support of the system of radiological protection. The use of this model appears to be a reasonable and prudent choice (in the ethical sense of the word), and not excessively conservative. From a pragmatic point of view, no other dose-risk relationship seems more suitable or justifiable for radiological protection purposes.

A review of the system of radiological protection was recently initiated by the ICRP, aimed at developing the subsequent general recommendations (Clement *et al* 2021). In this context, the validity of the hypotheses underlying the radiation-related risk assessment will be re-evaluated, on the basis of the advancement of scientific knowledge since ICRP Publication 103 (ICRP 2007).

Data availability statement

No new data were created or analysed in this study.

Acknowledgments

The authors would like to thank Michaël Tichauer and Anne Cordelle (IRSN) for coordinating the internal consultation procedure conducted in 2022 within IRSN on the validity of the LNT model for estimating the risk of cancer associated with exposure to ionising radiation in support of the radiological protection system,

as well as all the IRSN experts who contributed to this internal consultation and for improving the manuscript. The authors would also like to thank Aurélie Mathieu and François Pouzaud (ANSES) for their help in comparing risk assessments carried out in the field of chemical substances.

ORCID iDs

Dominique Laurier https://orcid.org/0000-0003-1432-4738
Yann Billarand https://orcid.org/0000-0001-5306-1497
Dmitry Klokov https://orcid.org/0000-0003-1629-1431
Klervi Leuraud https://orcid.org/0000-0001-5492-168X

References

Abalo K D, Rage E, Leuraud K, Richardson D B, Le Pointe H D, Laurier D and Bernier M-O 2021 Early life ionizing radiation exposure and cancer risks: systematic review and meta-analysis *Ped. Radiol.* **51** 45–56

ANSES 2017 *Valeurs Toxicologiques de Référence: Guide D'élaboration* (Maisons-Alfort: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail) (Valeurs toxicologiques de référence (VTR), ANSES—Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail)

ANSES 2018 *Elaboration de VTR par Inhalation Pour le Formaldéhyde* (Maisons-Alfort: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail) (Valeurs toxicologiques de référence (VTR), ANSES—Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail)

Averbeck D 2009 Does scientific evidence support a change from the LNT model for low-dose radiation risk extrapolation? *Health Phys.* **97** 493–504

Averbeck D, Salomaa S, Bouffler S, Ottolenghi A, Smyth V and Sabatier L 2018 Progress in low dose health risk research: novel effects and new concepts in low dose radiobiology *Mutat. Res. Rev. Mutat. Res.* **776** 46–69

Baker S G, Soto A M, Sonnenschein C, Cappuccio A, Potter J D and Kramer B S 2009 Plausibility of stromal initiation of epithelial cancers without a mutation in the epithelium: a computer simulation of morphostats *BMC Cancer* **9** 89

Ban N, Cléro E, Vaillant L, Hamada N, Zhang W, Preston D and Laurier D 2022 Radiation detriment calculation methodology: summary of ICRP Publication 152 *J. Radiol. Prot.* **42** Corrigendum in *J. Radiol. Prot.* **42**

Barcellos-Hoff M H, Lyden D and Wang T C 2013 The evolution of the cancer niche during multistage carcinogenesis *Nat. Rev. Cancer* **13** 511–8

Barrett C 1993 Mechanisms of multistep carcinogenesis and carcinogen risk assessment *Environ. Health Perspect.* **100** 9–20

Basu A K 2018 DNA damage, mutagenesis and cancer *Int. J. Mol. Sci.* **19** 970

Berrington de Gonzalez A *et al* 2020 Epidemiological studies of low-dose ionizing radiation and cancer: rationale and framework for the monograph and overview of eligible studies *J. Natl Cancer Inst. Monogr.* **56** 97–113

Bignold L P 2003 The mutator phenotype theory of carcinogenesis and the complex histopathology of tumours: support for the theory from the independent occurrence of nuclear abnormality, loss of specialisation and invasiveness among occasional neoplastic lesions *Cell. Mol. Life Sci.* **60** 883–91

Bizzarri M, Cucina A, Biava P M, Proietti S, D'Anselmi F, Dinicola S, Pasqualato A and Lisi E 2011 Embryonic morphogenetic field induces phenotypic reversion in cancer cells *Curr. Pharm. Biotechnol.* **12** 243–53

Bouyer J, Hémon D, Cordier S, Derriennic F, Stücker I, Stengel B and Clavel J 2009 Epidémiologie: principes et méthodes quantitatives (Lavoisier)

Brenner A V *et al* 2018b Incidence of breast cancer in the life span study of atomic bomb survivors: 1958–2009 *Radiat. Res.* **190** 433–44

Brenner A V, Preston D L, Sakata R, Cologne J, Sugiyama H, Utada M, Cahoon E K, Grant E, Mabuchi K and Ozasa K 2022 Comparison of all solid cancer mortality and incidence dose-response in the life span study of atomic bomb survivors, 1958–2009 *Radiat. Res.* **197** 491–508

Brenner A V, Sugiyama H, Preston D L, Sakata R, French B, Sadakane A, Cahoon E K, Utada M, Mabuchi K and Ozasa K 2020 Radiation risk of central nervous system tumors in the life span study of atomic bomb survivors, 1958–2009 *Eur. J. Epidemiol.* **35** 591–600

Brenner D J *et al* 2003 Cancer risks attributable to low doses of ionizing radiation: assessing what we really know *Proc. Natl Acad. Sci. USA* **100** 13761–6

Brenner D J and Sachs R K 2006 Estimating radiation-induced cancer risks at very low doses: rationale for using a linear no-threshold approach *Radiat. Environ. Biophys.* **44** 253–6

Cahoon E K, Preston D L, Pierce D A, Grant E, Brenner A V, Mabuchi K, Utada M and Ozasa K 2017 Lung, laryngeal and other respiratory cancer incidence among Japanese atomic bomb survivors: an updated analysis from 1958 through 2009 *Radiat. Res.* **187** 538–48

Calabrese E J 2009 The road to linearity: why linearity at low doses became the basis for carcinogen risk assessment? *Arch. Toxicol.* **83** 203–25

Calabrese E J 2016 LNTgate: how scientific misconduct by the U.S. NAS led to governments adopting LNT for cancer risk assessment *Environ. Res.* **148** 535–46

Calabrese E J 2019 The linear no-threshold (LNT) dose response model: a comprehensive assessment of its historical and scientific foundations *Chem. Biol. Interact* **301** 6–25

Calabrese E J and Selby P B 2022 Cover up and cancer risk assessment: prominent US scientists suppressed evidence to promote adoption of LNT *Environ. Res.* **210** 112973

Chauhan V *et al* 2022 Adverse outcome pathway: a path toward better data consolidation and global co-ordination of radiation research *Int. J. Radiat. Biol.* **98** 1694–703

Clement C *et al* 2021 Keeping the ICRP recommendations fit for purpose *J. Radiol. Prot.* **41** 1390–409

Cléro E, Bisson M, Nathalie V, Blanchardon E, Thybaud E and Billarand Y 2021 Cancer risk from chronic exposures to chemicals and radiation: a comparison of the toxicological reference value with the radiation detriment *Radiat. Environ. Biophys.* **60** 531–47

Cléro E, Vaillant L, Hamada N, Zhang W, Preston D, Laurier D and Ban N 2019 History of radiation detriment and its calculation methodology used in ICRP Publication 103 *J. Radiol. Prot.* **39** R19–R36

Cologne J, Kim J, Sugiyama H, French B, Cullings H, Preston D, Mabuchi K and Ozasa K 2019 Effect of heterogeneity in background incidence on inference about the solid-cancer radiation dose response in atomic bomb survivors *Radiat. Res.* **192** 388–98
Cuttler J M 2020 The LNT issue is about politics and economics, not safety *Dose Response* **18** 1559325820949066
Cuttler J M and Calabrese E J 2021 What would become of nuclear risk if governments changed their regulations to recognize the evidence of radiation's beneficial health effects for exposures that are below the thresholds for detrimental effects? *Dose Response* **19** 15593258211059317
Dalke C *et al* 2018 Lifetime study in mice after acute low-dose ionizing radiation: a multifactorial study with special focus on cataract risk *Radiat. Environ. Biophys.* **57** 99–113
Damjanov I 1993 Teratocarcinoma: neoplastic lessons about normal embryogenesis *Int. J. Dev. Biol.* **37** 39–46
Doss M 2018 Are we approaching the end of the linear no-threshold era? *J. Nucl. Med.* **59** 1786–93
EPA 2005 *Guidelines for Carcinogen Risk Assessment* (Washington, DC: U.S. Environmental Protection Agency)
French B, Sadakane A, Cologne J, Mabuchi K, Ozasa K and Preston D L 2020 Misclassification of primary liver cancer in the life span study of atomic bomb survivors *Int. J. Cancer* **147** 1294–9
Fujiki H, Sueoka E and Suganuma M 2013 Tumor promoters: from chemicals to inflammatory proteins *J. Cancer Res. Clin. Oncol.* **139** 1603–14
Furukawa K, Preston D, Funamoto S, Yonehara S, Ito M, Tokuoka S, Sugiyama H, Soda M, Ozasa K and Mabuchi K 2013 Long-term trend of thyroid cancer risk among Japanese atomic-bomb survivors: 60 years after exposure *Int. J. Cancer* **132** 1222–6
Grant E J *et al* 2017 Solid cancer incidence among the life span study of atomic bomb survivors: 1958–2009 *Radiat. Res.* **187** 513–37
Grant E J, Yamamura M, Brenner A V, Preston D L, Utada M, Sugiyama H, Sakata R, Mabuchi K and Ozasa K 2021 Radiation risks for the incidence of kidney, bladder and other urinary tract cancers: 1958–2009 *Radiat. Res.* **195** 140–8
Guéguen Y, Bontemps A and Ebrahimian T G 2019 Adaptive responses to low doses of radiation or chemicals: their cellular and molecular mechanisms *Cell. Mol. Life Sci.* **76** 1255–73
Hamasaki K, Imai K, Hayashi T, Nakachi K and Kusunoki Y 2007 Radiation sensitivity and genomic instability in the hematopoietic system: frequencies of micronucleated reticulocytes in whole body x–irradiated BALB/c and C57BL/6 mice *Cancer Sci.* **98** 1840–4
Hanahan D 2022 Hallmarks of cancer: new dimensions *Cancer Discov.* **12** 31–46
Hanahan D and Weinberg R A 2011 Hallmarks of cancer: the next generation *Cell* **144** 646–74
Harrison J, Haylock R, Jansen J T M, Zhang W and Wakeford R 2023 Effective doses and risks from medical diagnostic x-ray examinations for male and female patients from childhood to old age *J. Radiol. Prot.* **43** 011518
Hauptmann M *et al* 2020 Epidemiological studies of low-dose ionizing radiation and cancer: summary bias assessment and meta-analysis *J. Natl Cancer Inst. Monogr.* **56** 188–200
Health Physics Society 2020 Position statement of the Health Physics Society PS010-4: radiation risk in perspective *Health Phys.* **118** 79–90
Hecker E 1967 Phorbol esters from croton oil. Chemical nature and biological activities *Naturwissenschaften* **54** 282–4
Hsu W-L *et al* 2013 The incidence of leukemia, lymphoma and multiple myeloma among atomic bomb survivors: 1950–2001 *Radiat. Res.* **179** 361–82
IARC 2018 *Les Cancers Attribuables au Mode de vie et à L'environnement en France Métropolitaine* (Lyon: International Agency for Research on Cancer) (available at: http://gco.iarc.fr/resources/paf-france_fr.php)
ICRP 1959 *Recommendations of the International Commission on Radiological Protection. ICRP Publication 1* (Oxford: Pergamon)
ICRP 1966 Recommendations of the International Commission on Radiological Protection. ICRP Publication 9 *Ann. ICRP* **9**
ICRP 1991 The 1990 recommendations of the International Commission on Radiological Protection. ICRP Publication 60 *Ann. ICRP* **21**
ICRP 2005 Low-dose extrapolation of radiation-related cancer risk. ICRP Publication 99 *Ann. ICRP* **35** 1–140
ICRP 2007 The 2007 recommendations of the International Commission on Radiological Protection. ICRP Publication 103 *Ann. ICRP* **37** 1–332
ICRP 2009 The history of ICRP and the evolution of its policies. ICRP Publication 109 *Ann. ICRP* **39** 75–110
ICRP 2010 Lung cancer risk from radon and progeny and statement on radon. ICRP Publication 115 *Ann. ICRP* **40** 1–64
ICRP 2018 Ethical foundations of the system of radiological protection. ICRP Publication 138 *Ann. ICRP* **47** 1–65
ICRP 2021a Use of dose quantities in radiological protection. ICRP Publication 147 *Ann. ICRP* **50** 9–82
ICRP 2021b Cancer risks from plutonium and uranium exposure. ICRP Publication 150 *Ann. ICRP* **50** 1–143
ICRP 2022 Radiation detriment calculation methodology. ICRP Publication 152 *Ann. ICRP* **51** 9–103
Jayalekshmi P A, Nair R A, Nair R R K, Hoel D G, Akiba S, Nakamura S and Endo K 2021 Background radiation and cancer excluding leukemia in Kerala, India—Karunagappally cohort study *Radiat. Environ. Med.* **10** 74–81
Laurier D and Clement C 2021 Dose and risk: science and protection *Ann. ICRP* **50** 5–7
Laurier D, Rühm W, Paquet F, Applegate K, Cool D and Clement C 2021 International Commission on Radiological Protection (ICRP). Areas of research to support the system of radiological protection *Radiat. Environ. Biophys.* **60** 519–30
Leuraud K *et al* 2015 Ionising radiation and risk of death from leukaemia and lymphoma in radiation-monitored workers (INWORKS): an international cohort study *Lancet Haematol.* **2** e276–81
Leuraud K *et al* 2021 Risk of cancer associated with low-dose radiation exposure: comparison of results between the INWORKS nuclear workers study and the A-bomb survivors study *Radiat. Environ. Biophys.* **60** 23–39
Little M P *et al* 2018 Leukaemia and myeloid malignancy among people exposed to low doses of ionising radiation during childhood: a pooled analysis of nine historical cohort studies *Lancet Haematol.* **5** e346–58
Little M P, Wakeford R, Bouffler S D, Abalo K, Hauptmann M, Hamada N and Kendall G M 2022 Review of the risk of cancer following low and moderate doses of sparsely ionising radiation received in early life in groups with individually estimated doses *Environ. Int.* **159** 106983
Little M P, Wakeford R, Tawn E J, Bouffler S D and de Gonzalez A B 2009 Risks associated with low doses and low dose rates of ionizing radiation: why linearity may be (almost) the best we can do *Radiology* **251** 6–12
Lowe D, Roy L, Rühm W, Tabocchini M A, Wakeford R, Woloschak G and Laurier D 2022 Dose rate effects: what is new and what is needed? *Radiat. Environ. Biophys.* **61** 507–43
Luan F J, Wan Y, Mak K C, Ma C J and Wang H Q 2020 Cancer and mortality risks of patients with scoliosis from radiation exposure: a systematic review and meta-analysis *Eur. Spine J.* **29** 3123–34
Lubin J H *et al* 2017 Thyroid cancer following childhood low-dose radiation exposure: a pooled analysis of nine cohorts *J. Clin. Endocrinol. Metab.* **102** 2575–83
Mabuchi K *et al* 2021 Risk of prostate cancer incidence among atomic bomb survivors: 1958–2009 *Radiat. Res.* **195** 66–76

Marant-Micallef C *et al* 2018a Approche et méthodologie générale pour l'"estimation des cancers attribuables au mode de vie et à l'environnement en France métropolitaine en 2015 *Bull. Epidemiol. Hebd.* **21** 432–41
Marant-Micallef C *et al* 2018b Nombre et fractions de cancers attribuables au mode de vie et à l'environnement en France métropolitaine en 2015: résultats principaux *Bull. Epidemiol. Hebd.* **21** 442–8
Markiewicz E *et al* 2015 Nonlinear ionizing radiation-induced changes in eye lens cell proliferation, cyclin D1 expression and lens shape *Open Biol.* **5** 150011
Meinhold C B and Taschner J C 1995 A brief history of radiation *Los Alamos. Sci.* **23** 116–23
Morton L M *et al* 2021 Radiation-related genomic profile of papillary thyroid carcinoma after the Chernobyl accident *Science* **372**
Muller H J 1928 Artificial transmutation of the gene *Science* **66** 84–87
NAS 1956 *The Biological Effects of Atomic Radiation (BEAR): A Report to the Public* (Washington, DC: The National Academies Press, National Academy of Sciences/National Research Council)
NAS 2006 *Health Risks from Exposure to Low Levels of Ionizing Radiation (BEIR VII Phase 2)* (Washington, DC: The National Academies Press, National Academy of Sciences/National Research Council)
NASEM 2022 *Leveraging Advances in Modern Science to Revitalize Low-Dose Radiation Research in the United States* (Washington, DC: The National Academies Press, National Academies of Sciences, Engineering, and Medicine) (https://doi.org/10.17226/26434)
NCRP 2018 *Implications of Recent Epidemiologic Studies for the Linear-nonthreshold Model and Radiation Protection. NCRP Commentary* No. 27 (Bethesda, MD: National Council on Radiation Protection and Measurements)
NCRP 2020 *Approaches for Integrating Information from Radiation Biology and Epidemiology to Enhance Low-dose Health Risk assessment. NCRP Report* No, 186 (Bethesda, MD: National Council on Radiation Protection and Measurements)
NRC 2021 Linear no-threshold model and standards for protection against radiation. A proposed rule by the Nuclear Regulatory Commission on 08/17/2021 *Federal Register* vol 86 (available at: www.federalregister.gov/documents/2021/08/17/2021-17475/linear-no-threshold-model-and-standards-for-protection-against-radiation)
Osipov A N, Pustovalova M, Grekhova A, Eremin P, Vorobyova N, Pulin A, Zhavoronkov A, Roumiantsev S, Klokov D Y and Eremin I 2015 Low doses of x-rays induce prolonged and ATM-independent persistence of gammaH2AX foci in human gingival mesenchymal stem cells *Oncotarget* **6** 27275–87
Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant E J, Sakata R, Sugiyama H and Kodama K 2012 Studies of the mortality of atomic bomb survivors, report 14, 1950–2003: an overview of cancer and noncancer diseases *Radiat. Res.* **177** 229–43
Paull T T, Rogakou E P, Yamazaki V, Kirchgessner C U, Gellert M and Bonner W M 2000 A critical role for histone H2AX in recruitment of repair factors to nuclear foci after DNA damage *Curr. Biol.* **10** 886–95
Richardson D B *et al* 2015 Risk of cancer from occupational exposure to ionising radiation: retrospective cohort study of workers in France, the United Kingdom, and the United States (INWORKS) *Br. Med. J.* **351** h5359
Richardson D B *et al* 2018 Site-specific solid cancer mortality after exposure to ionizing radiation: a cohort study of workers (INWORKS) *Epidemiol* **29** 31–40
Rithidech K N, Cronkite E P and Bond V P 1999 Advantages of the CBA mouse in leukemogenesis research *Blood Cells Mol. Dis.* **25** 38–45
Rivina L and Schiestl R 2013 Mouse models of radiation-induced cancers *Adv. Genet.* **84** 83–122
Rube C E, Dong X, Kuhne M, Fricke A, Kaestner L, Lipp P and Rube C 2008 DNA double-strand break rejoining in complex normal tissues *Int. J. Radiat. Oncol. Biol. Phys.* **72** 1180–7
Rühm W *et al* 2015 Dose and dose-rate effects of ionizing radiation: a discussion in the light of radiological protection *Radiat. Environ. Biophys.* **54** 379–401
Rühm W, Eidemuller M and Kaiser J C 2017 Biologically-based mechanistic models of radiation-related carcinogenesis applied to epidemiological data *Int. J. Radiat. Biol.* **93** 1093–117
Rühm W, Laurier D and Wakeford R 2022 Cancer risk following low doses of ionizing radiation—current epidemiological evidence and implications for radiological protection *Mutat. Res. Genet. Toxicol. Environ. Mutagen.* **873** 503436
Sakata R *et al* 2019 Radiation-related risk of cancers of the upper digestive tract among Japanese atomic bomb survivors *Radiat. Res.* **192** 331–44
Schubauer-Berigan M K, Berrington de Gonzalez A, Cardis E, Laurier D, Lubin J H, Hauptmann M and Richardson D B 2020 Evaluation of confounding and selection bias in epidemiological studies of populations exposed to low-dose, high-energy photon radiation *J. Natl Cancer Inst. Monogr.* **56** 133–53
Scott B R and Tharmalingam S 2019 The LNT model for cancer induction is not supported by radiobiological data *Chem. Biol. Interact* **301** 34–53
Shimura N and Kojima S 2018 The lowest radiation dose having molecular changes in the living body *Dose Response* **16** 1559325818777326
Shin S C, Kang Y M and Kim H S 2010 Life span and thymic lymphoma incidence in high- and low-dose-rate irradiated AKR/J mice and commonly expressed genes *Radiat. Res.* **174** 341–6
Shore R *et al* 2018 Implications of recent epidemiological studies for the linear non threshold model and radiation protection *J. Radiol. Prot.* **38** 1217
Shore R, Walsh L, Azizova T and Rühm W 2017 Risk of solid cancer in low dose-rate radiation epidemiological studies and the dose-rate effectiveness factor *Int. J. Radiat. Biol.* **93** 1064–78
Snijders A M, Marchetti F, Bhatnagar S, Duru N, Han J, Hu Z, Mao J H, Gray J W and Wyrobek A J 2012 Genetic differences in transcript responses to low-dose ionizing radiation identify tissue functions associated with breast cancer susceptibility *PLoS One* **7** e45394
Sugiyama H, Misumi M, Brenner A, Grant E J, Sakata R, Sadakane A, Utada M, Preston D L, Mabuchi K and Ozasa K 2020 Radiation risk of incident colorectal cancer by anatomical site among atomic bomb survivors: 1958–2009 *Int. J. Cancer* **146** 635–45
Tharmalingam S, Sreetharan S, Brooks A L and Boreham D R 2019 Re-evaluation of the linear no-threshold (LNT) model using new paradigms and modern molecular studies *Chem. Biol. Interact* **301** 54–67
Tran V and Little M P 2017 Dose and dose rate extrapolation factors for malignant and non-malignant health endpoints after exposure to gamma and neutron radiation *Radiat. Environ. Biophys.* **56** 299–328
Trosko J E 2021 On the potential origin and characteristics of cancer stem cells *Carcinogenesis* **42** 905–12
Tsvetkova A *et al* 2017 gammaH2AX, 53BP1 and Rad51 protein foci changes in mesenchymal stem cells during prolonged x-ray irradiation *Oncotarget* **8** 64317–29
Tubiana M, Aurengo A, Averbeck D, Bonnin A, Le Guen B, Masse R, Monier R, Valleron A J and de Vathaire F 2005 *La Relation Dose-Effet et L'estimation des Effets Cancérogènes des Faibles Doses de Rayonnements Ionisants* (Paris: Rapport conjoint de l'Académie des Sciences (Paris) et de l'Académie Nationale de Médecine)

Tubiana M, Aurengo A, Averbeck D and Masse R 2006 Recent reports on the effect of low doses of ionizing radiation and its dose-effect relationship *Radiat. Environ. Biophys.* **44** 245–51

Tubiana M, Feinendegen L E, Yang C and Kaminski M 2009 The linear no-threshold relationship is inconsistent with radiation biologic and experimental data *Radiology* **251** 13–22

Tubiana M, Masse R, de Vathaire F, Averbeck D and Aurengo A 2007 La controverse sur les effets des faibles doses de rayonnements ionisants et la relation linéaire sans seuil *Radioprotection* **42** 133–61

UNSCEAR 2008 *Effects of Ionizing Radiation. UNSCEAR 2006 Report to the General Assembly, with Scientific Annexes. Volume I. Annex A. Epidemiological Studies of Radiation and Cancer* (New York: United Nations Scientific Committee on the Effects of Atomic Radiation) (available at: www.unscear.org/unscear/en/publications/scientific-reports.html)

UNSCEAR 2012 *Biological Mechanisms of Radiation Actions at Low Doses. A White Paper to Guide the Scientific Committee's Future Programme of Work* (New York: United Nations Scientific Committee on the Effects of Atomic Radiation) (available at: www.unscear.org/unscear/en/publications/scientific-reports.html)

UNSCEAR 2015 *Sources, Effects and Risks of Ionizing Radiation. UNSCEAR 2012 Report to the General Assembly, with Scientific Annexes. Annex A: Attributing Health Effects to Ionizing Radiation Exposure and Inferring Risks* (New York: United Nations Scientific Committee on the Effects of Atomic Radiation) (available at: www.unscear.org/unscear/en/publications/scientific-reports.html)

UNSCEAR 2018a *Sources, effects and risks of ionizing radiation. UNSCEAR 2017 Report to the General Assembly, with Scientific Annexes. Annexe A, Principles and criteria for ensuring the quality of the Committee's reviews of epidemiological studies of radiation exposure* (New York: United Nations Scientific Committee on the Effects of Atomic Radiation) (available at: www.unscear.org/unscear/uploads/documents/publications/UNSCEAR_2017_Annex-A.pdf)

UNSCEAR 2018b *Sources, Effects and Risks of Ionizing radiation. UNSCEAR 2017 Report to the General Assembly, with Scientific Annexes. Annexe B, Epidemiological studies of cancer risk due to low-dose-rate radiation from environmental sources* (New York: United Nations Scientific Committee on the Effects of Atomic Radiation) (available at: www.unscear.org/unscear/uploads/documents/publications/UNSCEAR_2017_Annex-B.pdf)

UNSCEAR 2020a *Sources, Effects and Risks of Ionizing Radiation. UNSCEAR 2019 Report to the General Assembly, with Scientific Annexes. Annex A, Evaluation of Selected Health Effects and Inference of Risk due to Radiation Exposure* (New York: United Nations Scientific Committee on the Effects of Atomic Radiation) (available at: www.unscear.org/unscear/uploads/documents/publications/UNSCEAR_2019_Annex-A-CORR.pdf)

UNSCEAR 2020b *Sources, Effects and Risks of Ionizing Radiation. UNSCEAR 2019 Report to the General Assembly, with Scientific Annexes. Annex B, Lung Cancer from Exposure to Radon* (New York: United Nations Scientific Committee on the Effects of Atomic Radiation) (available at: www.unscear.org/unscear/uploads/documents/publications/UNSCEAR_2019_Annex-B.pdf)

UNSCEAR 2021 *Sources, Effects and Risks of Ionizing Radiation. UNSCEAR 2020/2021 Report to the General Assembly, with Scientific Annexes. Volume III. Scientific Annex C. Biological Mechanisms Relevant for the Inference of Cancer Risks from Low-dose and Low-dose-rate Radiation* (New York: United Nations Scientific Committee on the Effects of Atomic Radiation) (available at: www.unscear.org/unscear/en/publications/scientific-reports.html)

Utada M *et al* 2021 Radiation risk of ovarian cancer in atomic bomb survivors: 1958–2009 *Radiat. Res.* **195** 60–65

Utada M, Chernyavskiy P, Lee W J, Franceschi S, Sauvaget C, de Gonzalez A B and Withrow D R 2019 Increasing risk of uterine cervical cancer among young Japanese women: comparison of incidence trends in Japan, South Korea and Japanese-Americans between 1985 and 2012 *Int. J. Cancer* **144** 2144–52

van Gent D C, Hoeijmakers J H and Kanaar R 2001 Chromosomal stability and the DNA double-stranded break connection *Nat. Rev. Genet.* **2** 196–206

Vaux D L 2011 In defense of the somatic mutation theory of cancer *Bioassays* **33** 341–3

Vineis P, Schatzkin A and Potter J D 2010 Models of carcinogenesis: an overview *Carcinogenesis* **31** 1703–9

Vuillez J P 2019 Faibles doses de rayonnements: quand l'hormésis et l'effet abscopal se rencontrent *Med. Nucl.* **43** 354–9

Wakeford R 2005 The risk to health from exposure to low levels of ionizing radiation *Ann. ICRP* **35** v–vii

Wojcik A 2022 Reflections on effects of low doses and risk inference based on the UNSCEAR 2021 report on 'biological mechanisms relevant for the inference of cancer risks from low-dose and low-dose-rate radiation *J. Radiol. Prot.* **42** 023501

Zaharieva E K, Sasatani M and Kamiya K 2022 Kinetics of DNA repair under chronic irradiation at low and medium dose rates in repair proficient and repair compromised normal fibroblasts *Radiat. Res.* **197** 332–49

Zanzonico P B 2016 The neglected side of the coin: quantitative benefit-risk analyses in medical imaging *Health Phys.* **110** 301–4

Zhang W, Laurier D, Cléro E, Hamada N, Preston D, Vaillant L and Ban N 2020 Sensitivity analysis of parameters and methodological choices used in calculation of radiation detriment for solid cancer *Int. J. Radiat. Biol.* **96** 596–605

Zhu S, Wang J, Zellmer L, Xu N, Liu M, Hu Y, Ma H, Deng F, Yang W and Liao D J 2022 Mutation or not, what directly establishes a neoplastic state, namely cellular immortality and autonomy, still remains unknown and should be prioritized in our research *J. Cancer* **13** 2810–43