UNSCEAR

BIOLOGICAL MECHANISMS OF RADIATION ACTIONS AT LOW DOSES

A white paper to guide the Scientific Committee's
future programme of work

EVALUATING RADIATION SCIENCE FOR INFORMED DECISION-MAKING

UNITED NATIONS

United Nations Scientific Committee on the Effects of Atomic Radiation

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EXECUTIVE SUMMARY

At its fifty-ninth session (21–25 May 2012), the Scientific Committee considered a short review document on the biological mechanisms of radiation actions at low doses. That document, unlike the Committee's standard full evaluations, was not intended to be comprehensive; it was rather intended to highlight major advances in the field that would provide guidance for developing the Committee's future programme of work. Because the document would be of wider interest, the Committee requested the secretariat to investigate means to issue it as a public document on its website.

The document concludes that understanding of the mechanisms of so-called non-targeted and delayed effects is improving and that there is some evidence for differential responses in gene and protein expression for high- and low-dose radiation exposures, but there is a lack of consistency and coherence among reports. There is as yet no indication of a causal association of those phenomena with radiation-related disease. With regard to immune response and inflammatory reactions, there is a clearer association with disease, but there is no consensus on the impact of radiation exposure, particularly at low doses, on those physiological processes. While the document focuses on mechanisms relevant to carcinogenesis, some of the processes considered may be relevant for tissue reactions, and improved understanding may therefore be helpful for assessing the potential risk of non-cancer diseases at low and protracted exposures.

The Committee agreed to:

(a) Continue to encourage research into the mechanistic understanding of low-dose radiation action that may contribute to disease in humans;

(b) Consider further developing biologically based risk models and a systems biology framework to integrate mechanistic data into risk assessment;

(c) Make the document publicly available; and

(d) Review the subject again in three to four years, as appropriate.

I. INTRODUCTION

1.   At its fifty-sixth session, the Scientific Committee established that one of its thematic priorities for the period 2009–2013 would be improved understanding of the effects from low-dose-rate radiation exposure. The Committee considered several proposals—for its future programme of work—related to mechanisms of radiation actions at low doses, but decided not to initiate work on a full evaluation. Instead it accepted the UK delegation's offer to prepare a 'white paper' reviewing (1) UNSCEAR's position on the mechanisms of radiation actions at low doses, and (2) new knowledge that had become available since 2006. The resulting document was discussed at the fifty-seventh session in August 2010. The Committee agreed that the white paper was helpful and should be updated at appropriate intervals in the future.

2.   At its fifty-eighth session, the Committee agreed that the white paper should be updated. S. Bouffler (UK) made the update, which was reviewed by J. Preston (USA) and W. Müller (Germany) early in 2012 and issued for discussion at the Committee's fifty-ninth session (21–25 May 2012). The document was not intended for submission to the General Assembly like the Committee's standard full evaluations (it was not intended to be comprehensive). It was rather intended to highlight major advances in the field that would provide guidance for developing the Committee's future programme of work. It also was to serve as a vehicle for the Committee to fulfil the commitment stated in its 2006 Report [U3] to '…maintain surveillance of scientific developments in the area of non-targeted and delayed effects…'.

3.   At its fifty-ninth session, the Committee considered the short review document, A/AC.82/R.694/Rev.1, on the biological mechanisms of radiation actions at low doses. Because the document would be of wider interest, the Committee requested the secretariat to investigate means to issue it as a public document on its website. Accordingly the secretariat has arranged for its publication as a white paper, incorporating materials and comments supplied by several delegations during the fifty-ninth session.

II. BACKGROUND

4.   In its evaluations of the health effects of exposure to ionizing radiation at low doses and dose rates, the Committee has recognized the limits to the statistical power of epidemiological analyses. Interpolating the dose–response between data from epidemiological investigations and incremental doses above background exposures requires knowledge of the mechanisms of radiation action and post-irradiation processes that specifically relate to health effects. In establishing nominal radiation risk estimates for low dose exposures, two health endpoints—cancer and heritable effects—are currently considered important by the Committee and by other bodies such as the International Commission on Radiological Protection (ICRP) and the National Council on Radiation Protection and Measurements (NCRP) in the US. Relevant evaluations of the Committee have been published as annex E (Mechanisms of radiation oncogenesis) to the UNSCEAR 1993 Report [U8], annex B (Adaptive responses to radiation in cells and organisms) to the UNSCEAR 1994 Report [U7], annexes F (DNA repair and mutagenesis) and G (Biological effects at low radiation doses) to the UNSCEAR 2000 Report [U5], the annex to the UNSCEAR 2001 Report (Hereditary effects of radiation) [U4] and annex C (Non-targeted and delayed effects of exposure to ionizing radiation) to the UNSCEAR 2006 Report [U3]. More recently concerns have been raised regarding the induction of non-cancer disease, particularly circulatory disease (see annex B of [U3] and [A6]) and cataract

(e.g. [A5] and annex D to the UNSCEAR 2008 Report [U2]) at low doses. The focus of this white paper is on cancer and heritable effects but some of the mechanistic studies reviewed may be of relevance for other diseases. In the past, the Committee defined low doses, as those of 200 mSv or less and low dose rates as 0.1 mGy/min or less for low-LET radiation (e.g. [U1]). The Committee has now agreed low doses be defined as those of 100 mSv or less. This definition is consistent with that used by ICRP [I6] and the BEIR VII report [C6].

5.   Since the publication of the Committee's comprehensive reviews, research has continued that is potentially relevant to understanding the mechanisms resulting in health effects at low doses, including research in the specific areas listed above. Moreover, there continue to be significant technical developments and advances in knowledge in experimental biology. Applying the new techniques and knowledge to radiobiology has started to provide new insight into the mechanisms of radiation action. The aim of this white paper is to provide a brief summary of the major developments in radiobiology as they relate to evaluating risk of health effects at low doses. The intention is not to conduct a comprehensive review for the General Assembly now. It is rather to provide the Committee with a brief review of the state of knowledge and horizon-scanning information to foster informed consideration of the most promising areas for comprehensive review when formulating the future programme of work.

6.   In reviewing the recent developments the focus is on ways in which biological understanding of the actions of radiation can be used to improve evaluations of health risks at low doses. An incomplete understanding of the mechanisms of radiation action at low doses is a major contributor to the current uncertainty on low-dose risk estimates. While improved understanding of the mechanisms per se will not eliminate the uncertainty, it can help reduce the uncertainties and thereby increase confidence in low-dose risk estimates.

7.   Section III of this white paper provides a brief summary of the main UNSCEAR judgements on conventional mechanisms of radiation action presented in the Committee's reports up to 2001, and the UNSCEAR 2006 judgements on non-targeted effects. Section IV provides a brief update on developments related to non-targeted effects of radiation and additionally considers other recent developments of potential relevance to low-dose health effect evaluation. Section V provides some conclusions and recommendations regarding the new developments and their impact on the work of UNSCEAR and the need for future comprehensive reviews.

III. RELEVANT JUDGEMENTS OF THE COMMITTEE UP TO 2006

8.   The health effects of concern following low-dose radiation exposure are deemed cancer and heritable effects. The UNSCEAR 2000 Report [U5] provided an overview of biological effects at low radiation doses. The main relevant conclusions are reproduced in the annex.

9.   The UNSCEAR 1993 Report [U8] provided a more detailed discussion of the mechanisms of radiation oncogenesis. Most of the conclusions and judgements reached were incorporated explicitly or implicitly in the UNSCEAR 2000 Report [U5]. However, [U8] provided a useful additional summary on the monoclonal origin of cancers and the multistep nature of carcinogenesis (see annex).

10.   Judgements made by UNSCEAR up to 2001 on radiation carcinogenesis may be summarized as follows:
  –   Radiation acts primarily by inducing DNA damage in somatic cells. A range of DNA lesions will form through direct energy deposition in DNA or through the indirect

action of free radicals; however, double-strand breaks (DSB) and complex lesions (consisting of multiple lesions in close proximity) in DNA are likely to be most important in causing long-lived mutations.

– Systems exist to repair damage in nuclear DNA. However no repair is completely error-free, although some repair systems tend to be more error-prone than others (e.g. repair of double-strand breaks in DNA are more error-prone than single-strand breaks, which benefit from the presence of a template in the complementary DNA strand to repair base damage. Furthermore, the non-homologous end-joining DSB repair system is generally more error-prone than the homologous recombination repair system). Therefore even the lowest doses of radiation may induce DNA damage that may be converted into DNA sequence mutations.

– Cancer development is best described as a multistep process originating from single cells that have sustained mutations through DNA damage. Either directly or following the accumulation of additional mutations or epigenetic changes, such cells gain growth advantages and progress to a proliferative and ultimately malignant tumour. Radiation is judged to act most commonly by inducing initiating mutations in proto-oncogenes or in tumour suppressor genes; both proto-oncogenes and tumour suppressor genes have normal cellular functions in cell growth, development and regulation. Radiation can also induce apoptosis and influence cell-cycle checkpoints, which together can affect the outcome of a radiation exposure. Most evidence suggests that DNA deletions are the major contributors to the mutations driving radiation carcinogenesis.

– It was recognized that the progression and clonal development of cancers may be subject to modulating activities including immunosurveillance, but there remains uncertainty on the impact of such processes.

– With regard to other potential risk modulating processes, notably adaptive responses to radiation, whereby small radiation exposures may serve to reduce the effect of subsequent higher dose exposures, the Committee remained cautious in drawing conclusions from the available data. The data themselves are inconsistent and the mechanisms by which adaptive responses are mediated are not well established [U5, U7].

11.   While no evidence for the induction of heritable effects by radiation in humans has been obtained, studies with experimental organisms clearly demonstrate that radiation can cause heritable effects. Despite the lack of human data, the Committee [U4] considers there to be a risk to humans because they are unlikely to differ from other organisms. The induction of heritable mutations in the germ line is considered to be the mechanism of induction of heritable effects. This was noted in [U8] (see annex).

12.   In somatic carcinogenesis, radiation-induced initiating events are but one of many steps required for tumour formation. By contrast, direct induction of mutations in the germ line, where compatible with viability, will directly contribute to the burden of heritable mutations and possible heritable disease. Judgements on risks of heritable effects at low doses are therefore subject to fewer mechanistic uncertainties than those for risks of cancer. The BEIR VII report [C6] provides a full discussion of this issue. Thus estimation of risk of heritable disease at low doses is based on a linear no-threshold approach with an estimated doubling dose of around one gray [U5].

13.   The current UNSCEAR judgement on heritable effects can be summarized as follows:
– Radiation acts by inducing DNA damage in germ cells. As with somatic damage a range of lesion types will form and again DNA double-strand breaks and complex lesions are probably the most important for inducing heritable effects.

- DNA repair systems may correctly repair radiation lesions; however no repair system is completely error-free and so some lesions may be converted into mutations.
- Mutations compatible with germ cell viability and embryonic/foetal development may pass to the offspring of an irradiated individual.
- These inherited mutations will contribute to the mutational burden, and some may contribute to the development of heritable disease or disease predisposition in offspring.
- There is no direct evidence of heritable effects of radiation on human populations.

14.   Paragraphs 9–13 above serve to highlight UNSCEAR judgements which place prime importance on the direct induction by radiation of targeted mutations in DNA as the major driver of low-dose health effects. The Committee also judged that absorbed dose is the most appropriate exposure quantity to use in assessing the health effects of ionizing radiation. It should be noted that alternatives, for example based on radiation fluence, have been suggested [I4, K10, W4]. In particular, when considering the effects of exposure to high-LET radiation the distribution of dose within a tissue, cell or cell compartment becomes more important for correct interpretation of experimental results from studies of radiation action. In 2006, UNSCEAR [U3] completed an evaluation of the contribution of non-targeted and delayed effects of ionizing radiation exposure. These phenomena are those whereby effects are observed distant from radiation-induced DNA lesions either spatially (in the case of non-targeted effects) or temporally (in the case of delayed effects). On the basis of data available at that time some key conclusions were reached (see annex).

15.   The judgement of the Committee in 2006 was that non-targeted and delayed effects of radiation may be associated with radiation disease but no evidence for disease causation was found. It was noted that any contribution of non-targeted and delayed effects would be implicitly incorporated in the estimates of risk of radiation-induced health effects derived epidemiologically. However, strictly speaking, this is only valid for the dose range in which epidemiology is able to detect effects (see [U1]); the mechanisms that operate below around 100 mSv for adults and below around 10 mSv for the foetus may be different.

16.   In 2006 the Committee [U3] also provided an assessment of the effects of ionizing radiation on the immune system. The immune system could act to modify cancer risk if radiation exposure served to enhance or diminish the capacity of the body to mount an immune response against developing cancers, be they 'spontaneous' or radiation-induced. While much evidence was examined it remained impossible to judge clearly whether the effects of radiation at low doses served to stimulate or suppress immune responses (see the annex for relevant conclusions of the report).

17.   Section IV below summarizes significant new findings since 2006 regarding non-targeted and delayed effects of radiation, and briefly reviews more recent data on mechanisms of radiation actions relevant for health effects following low doses.

IV. NEW DATA AND TECHNICAL APPROACHES SINCE 2006

18.   Key issues remaining after the UNSCEAR 2006 review of non-targeted and delayed effects of radiation exposure [U3] centred on the relevance of such phenomena to causation of human radiation-induced disease. Only limited evidence for the operation of non-targeted and delayed effects in vivo was available; similarly little information on the mechanisms driving the effects was available. The paragraphs below consider more recent data and approaches relevant to the phenomena of radiation-induced transmissible genomic instability, bystander

effects and adaptive response, particularly in respect of their operation in vivo, their relevance to disease causation and their mechanisms.

19. Since the publication of [U3] increasing evidence for an inter-relation between radiation-induced transmissible genomic instability, bystander effects and adaptive responses (e.g. [H1]) has become available. It is not therefore always possible to make a clear distinction between the phenomena.

A. Genomic instability

20. A long-term study of C3H mice exposed to γ-rays at low dose-rate (20–200 mGy/day) identified that indirect effects of radiation contributed to the induction of complex chromosomal aberrations in spleen cells [T1]. In utero irradiation of BALB/c mice has been observed to lead to a persistent elevation in mutation frequency at expanded simple tandem repeat (ESTR) loci in somatic tissues which can pass transgenerationally to an F1 generation [B1]. In this study ESTR mutations were equally increased in all tissues of the F1 offspring of prenatally irradiated male mice. By contrast, in utero exposure of females did not result in measurable transgenerational changes in their offspring [B1]. Elevated mutation rates at an ESTR locus and at a protein-coding gene (*Hprt*), possibly due to the presence of persistent DNA damage, were also observed in the first generation offspring of irradiated male mice [B11]. Transgenerational induction of chromosomal instability has also been documented in female rats irradiated with 5 Gy of X-rays [C7]. These four studies provide evidence for the induction of transmissible genomic instability by radiation in mice. Such studies need to be viewed in the context of earlier work reviewed (paragraphs 23–27 of annex C, Volume II of [U3]) that failed to detect transmissible instability in some mouse systems. While there are positive findings in earlier mouse studies, not all of the inconsistencies between studies can be attributed to inter-strain variation in the induction of instability. A few reports suggest that genomic instability can be induced by low doses of low-LET radiation [K14, K15, M13]; the data are on the whole sparse and in several cases presented without statistical analysis. By contrast robust reports suggest that instability is not induced by doses of less than 0.1–0.2 Gy, and in some cases higher doses, of low-LET irradiation either in vivo or in vitro, except in transformed or otherwise abnormal cells [J3, K8, K9, Z3]. Recent reviews of the experimental literature [K8, K9] indicate a likely threshold for the induction of transmissible instability of 0.5 Gy low-LET radiation, and recent reports confirm this conclusion [Z3]. Generally, high-LET radiation is considered to be more effective at inducing transmissible instability than low-LET radiation, but there are fewer studies available from which to form a consensus on dose–response relationships.

21. Some more complex systems to detect transmissible genomic instability have been described. Important among these is the CBA mouse in vivo irradiation/CFU-A (colony forming unit type-A) assay [L1]. In vivo irradiation of adult mice was followed by extraction of bone marrow cells and growth of haemopoietic stem cell cultures using the CFU-A method. During growth of CFU-A colonies some 10–13 cell divisions occur. While no evidence for transmissible instability was seen in directly irradiated cells, colonies developing from unirradiated cells grown in medium exposed to irradiated bone marrow for a relatively brief period during extraction (the exact time was not given in the publication) showed evidence of instability (non-clonal chromatid-type aberrations). This work therefore provides evidence for bystander (but not direct) induction of transmissible genomic instability. The authors ascribe this induction to factors released from macrophages including tumour necrosis factor-α (TNF-α), nitric oxide and superoxide.

22.   Further work using the CBA model suggests that this strain, unlike the C57BL/6 (which is resistant to the induction of transmissible instability by radiation), mounts an exaggerated p53-mediated response to radiation in haemopoietic tissue, both immediately after irradiation and months after exposure [C1]. The authors interpret these data as indicating that in CBA mice a persistent induction of DNA damage occurs, probably mediated by reactive radicals as evidenced by elevated 3-nitrotyrosine. Importantly, responses in all individuals of this inbred, genetically homogeneous strain were not the same, thus some non-genetic contribution to the responses can be inferred. The origin of this inter-individual variation is not known. Inter-individual variation in the expression of a genomic instability phenotype has also been observed in primary human cells [K11, K12].

23.   Additional studies directed towards identifying the mechanisms of genomic instability have tended to focus on three main mechanisms: (1) those involving DNA damage and response; (2) those involving damage at telomeric regions; and (3) those involving persistent induction of inflammatory reactions/free radicals. It should also be noted that the induction of delayed cell death has also been described (see annex C of [U3]) and this will act to reduce the impact of induced instability.

24.   Comparison of the induction of instability in a DNA double-strand break repair mutant, a base excision repair mutant, and wild-type hamster cells suggested that the base excision repair pathway was most effective at preventing instability. This indicates that single-stranded breaks and/or oxidized base damage are key drivers of transmissible instability induced by radiation [S1]. Analysis of a range of SV40 immortalized normal human fibroblast lines carrying *HPRT* gene deletions has suggested that cells carrying large deletions are more likely to display delayed chromosome aberrations [T2]. Therefore the nature of directly-induced damage and a reduced ability to repair base and single-stranded DNA damage may promote instability. In addition to direct DNA damage, chromatin-based epigenetic modification has been proposed to play a role in the promotion and maintenance of transmissible instability [B1], see also paragraphs 55-58 below. Finally, there is evidence that radiation-induced dysregulation of centrosomes (cellular organelles with a role in chromosome segregation) can promote genomic instability [M1].

25.   A study of gene expression changes associated with radiation-induced transmissible instability did not identify a single pathway commonly dysregulated in unstable clones [S2] suggesting multiple pathways might be involved. In human B-cell lines displaying instability phenotypes a high level of DNA-PKcs activity was detected along with reduced expression of Ku70, p53 and TRF1 proteins [T3]. This study also therefore argues against DSBs as being critical lesions for the transmission of instability but suggests that telomere function might be relevant. A detailed study has revealed an association between dysfunctional telomeres and inappropriate repair of radiation-induced DNA breaks that lead to transmissible instability [W1]. In this latter model it has been proposed that this instability driven by telomere dysfunction may contribute to radiation-induced carcinogenesis in the breast [W1].

26.   Recent studies such as [L1] discussed above provide further evidence for inflammatory/free–radical-driven processes promoting transmissible instability. These inflammatory/free-radical-driven instabilities are mediated in part by TNF-α [C2, L2, N4]. The importance of base excision repair activity [S1] in protecting against induced instability as discussed in paragraph 24 is also consistent with the operation of a mechanism driven by free radical damage leading to induced instability.

27.   To summarize, some additional data from model systems suggest that radiation can induce transmissible instability in vivo. However, the evidence base in total remains mixed.

Data that provide evidence of radiation-induced transmissible instability in humans in vivo are very sparse. Some positive studies exist with high dose exposures [A7, Z4] but negative findings continue to emerge [H4, T7]. DNA structures (telomeres specifically), the epigenetic state of chromatin, and persistent induction of free radical damage to DNA have been implicated to be of mechanistic importance. It seems likely that there are multiple transmissible instabilities that require improved functional definition and understanding of mechanisms before their importance for radiation-induced health effects can be properly assessed. The emerging consensus that a threshold dose of around 0.5 Gy of low-LET radiation exists for the induction of transmissible instability (see paragraph 20) is potentially important as it strongly suggests that radiation-induced transmissible instability does not contribute to the development of health effects resulting from low doses of low-LET radiation. A role in the development of health effects resulting from high-LET irradiation cannot be excluded, but transmissible instabilities are clearly not required for the development of effects of low dose radiation on health.

B. Bystander effects and abscopal effects

28.   Bystander phenomena had been defined in artificial-skin-tissue models at the time of preparation of [U3]. Evidence for bystander-induced double-strand breaks in DNA is now available for full-thickness human skin and airway-epithelium tissue models [S3]. Bystander-mediated DSBs form over a longer time course than directly-induced DSBs and associate with later waves of apoptosis, senescence and micronucleus formation in bystander cells [S3].

29.   Evidence for long-distance bystander communication in vivo comes from mouse shielded irradiation studies of DNA damage and DNA methylation in skin [K1] and spleen [I1]. Shielded body irradiation has also been reported to lead to changes in spleen micro-RNA expression [I1]. Similar methylation changes may relate to those proposed to be involved in transmissible ESTR instability [B1]. Some of these phenomena are better defined as abscopal effects (effects occurring outside radiation fields in organisms). In these effects systemic responses may also be playing a role.

30.   A potentially important study linking long-distance bystander communication to disease has been described. Mancuso et al. [M2] used the *Ptc1* model of medulloblastoma in combination with shielded irradiation. Medulloblastoma could be induced in brains of mice exposed to shielded head irradiation (3 Gy) at a frequency much higher than that which was induced by the scatter dose to the head. Chromatin changes such as γH2AX foci and apoptosis could be observed in the brains of shielded head irradiated mice, both at frequencies far higher than expected from the direct scatter dose, suggesting the presence of bystander-mediated DNA double-strand damage and apoptosis. The bystander foci and apoptosis were observed largely in highly proliferative areas of the brain. This publication potentially identifies a link between bystander effects and radiation tumorigenesis at least at high doses. It may be relevant that the presence of transplanted tumours in mice can lead to the elevation of DNA damage (as assessed by γH2AX foci and clustered oxidative damage lesions) in distant normal tissues, particularly those which are highly proliferative [R2].

31.   For the mouse haemopoietic system, bystander-cell-mediated induction of transmissible genomic instability has been documented [L2]. However, because the traits of susceptibility to radiation-induced myeloid leukaemia and radiation-induced transmissible genomic instability were not linked, it is not clear how transmissible instability relates to the development of leukaemia in mice [B2]. In another in vivo mouse model of potential bystander effects in

normal cells, no bystander-mediated induction of apoptosis was observed over a broad range of doses [B15, S16].

32.   Perhaps the most extreme form of bystander communication reported involves communication between fish by water-borne signals [M3, M4]. The relevance of this signalling between individuals in a population is very unclear and may be restricted to the aquatic environment although there are reports of the secretion of volatile compounds by mice irradiated at 2–4 Gy that can be detected by unexposed mice (e.g. [A9]). Much more robust and reproducible data would be required before such inter-individual signalling phenomena are considered in the context of low dose risk.

33.   As with transmissible genomic instability, multiple mechanisms might be acting in bystander responses/communication. However, unlike the situation with transmissible instability, there is some evidence for involvement of DNA double-strand break repair, particularly the NHEJ pathway, in mediating bystander-induced mutation [Z1]. The production of responses to bystander signals is p53-independent in this human lymphoblastoid cell system [Z1]. However, the importance of DNA PKcs in bystander DSB signalling is questioned by some studies [B3]. Bystander γH2AX foci, indicative of DSBs, appear to form predominantly in S phase cells in an ATR-dependent and ATM/DNA-PKcs-independent manner [B3]. Interestingly, ATM was found to act downstream of ATR in DNA damage signalling in bystander cells [B12], similar to the response reported for ultraviolet radiation.

34.   Evidence from several systems implicates reactive oxygen and nitrogen species in bystander signalling [B3, S4, Y2]. A range of potential mediators of bystander signals have been identified including nitric oxide [H2], the cytokine TGFβ [B3], other inflammatory response markers [C2] and extra cellular DNA [E1, E2]. Calcium signalling may be implicated in the transduction of bystander signals from the external medium into responding cells [S4]. Ghandhi et al. [G1] investigated gene expression changes in directly irradiated and bystander-irradiated primary human lung fibroblasts. This study reveals differential regulation of p53 response and NFkappaB response in the two cell populations. The authors suggest that this differential regulation is likely to affect the long term consequences for disease attributable to directly irradiated and bystander cells. The study is important in bringing a wider insight into the drivers and possible consequences of responses in bystander cell populations.

35.   The study of bystander-mediated medulloblastoma [M2] clearly implicates bystander signalling as a risk-enhancing phenomenon. However, based on suggestions that bystander signalling can induce a differentiation or senescence programme [B4, S3], a protective function of bystander signalling has also been proposed [B4]. The phenomenon of intercellular induction of apoptosis of transformed cells mediated by non-transformed cells [B5] can also be viewed as a risk-reducing bystander effect. This intercellular mediated killing of transformed cells can be enhanced by low dose alpha- and gamma radiation of the non-transformed 'effector' cells [P2]. Given the lack of consensus further work is needed to establish the impact of bystander signalling on health risk.

36.   In summary there is now better evidence for bystander signalling in vivo and this could conceivably modulate cancer risk. However, it has yet to be established whether bystander signalling increases or diminishes risk (e.g. [L3, T4]); there is no consensus. Reasonably strong evidence for the involvement of radical mediated signalling is available and DNA double-strand break metabolism in cells responding to bystander signals must be involved. However, it should be noted that reports of studies that fail to observe bystander effects continue to appear including in vivo studies and these do not seem to suffer from obvious deficiencies in experimental design (e.g. [B15, F3, S12, S16]). It is also important to note that in addition to

ionizing radiation, a number of other agents have been reported to induce bystander-type responses. These include ultraviolet radiation [A4], heat [J1], medium from cancerous cells, changes in pH, detergents and mechanical stress [D3, S9] and treatment with TGFβ [B3]. These studies suggest that ionizing radiation-induced bystander effects reflect a general stress response. If confirmed, this then may have implications for the significance of bystander effects for low-dose radiation risk assessment in that ionizing radiation would be one of many factors affecting general stress responses. It is particularly important to establish whether bystander-mediated effects are in general risk-enhancing or risk-reducing in respect of radiation-associated diseases.

C. Adaptive response

37.   Establishing the robustness of adaptive responses in vivo remains important and some additional evidence is now available. Mitchel et al. [M5] examined tumour incidence in heterozygous p53-deficient (p53$^{+/-}$) mice exposed to small daily doses (5 days in a week) over 30–90 weeks (total doses 48, 97 or 146 mGy). They identified a lower dose boundary for protection against tumorigenesis in p53$^{+/-}$ mice. The p53-dependence of an adaptive response to the induction of apoptosis in mouse spleen cells in vivo has also been documented [O1]. Adaptive responses have been described in mice irradiated in utero and the analysis of patterns of gene expression suggests that p53-mediated responses are important [V1]. There remain few publications available on adaptive responses in vivo and the impact on health of relatively short-lived modification in radiosensitivity is not clear.

38.   Claims have been made that the growth of human cells in conditions of reduced background radiation increase their sensitivity to acute higher dose exposures [C3]. These have been interpreted as providing evidence for the existence of a persistent adaptive response provided by normal levels of background radiation.

39.   In vitro studies have indicated that several systems might be involved in the induction of adaptive responses including nucleotide excision repair [H3], non-homologous end joining [K13], anti-oxidant defences [F1, O2], and core cell cycle factors such as cyclin D1 [A1]. Recent studies with yeast demonstrate that following the induction of only one double-strand break in one chromosome of an S/G2-phase cell, all chromosomes undergo enhanced sister chromatid cohesion [S8, U19]. This response may improve post-replicational DNA repair processes and consequently provide genome-wide protection of chromosome integrity but has yet to be observed in higher organisms. Some adaptive responses have been reported to be inducible by bystander mechanisms [K13].

D. Summary of genomic instability, bystander and adaptive response

40.   There have been many publications on radiation-induced genomic instability, bystander effects, and adaptive responses since the 2006 review [U3]. As noted above these phenomena appear to be inter-related and there is evidence that they may share some common mechanistic pathways; debate continues on the impact of these phenomena on risk estimation. Significant concerns have been raised on the inherent variability and reproducibility of all these phenomena [H1, S5, S12, S14]. Therefore while some progress has been made in understanding these phenomena, the knowledge has yet to be assembled into a coherent body of understanding that can be readily applied to the assessment of low-dose risk. A consensus is emerging that low-LET irradiation below 0.5 Gy does not cause transmissible instability; this

indicates that transmissible instabilities are not involved in the aetiology of low dose, low LET health effects.

E.   Reactive oxygen metabolism and mitochondrial function

41.   From the discussion above it is apparent that many of the non-targeted effects of radiation may be influenced by the presence of reactive oxygen and other radicals. Understanding the impact of low-dose radiation on mitochondrial function (a major intracellular source of reactive oxygen) and the handling of free radicals is therefore likely to be useful. The relationships between mitochondrial dysfunction, reactive oxygen metabolism and radiation-induced genomic instability have been reviewed [K2]. A range of studies suggest that mitochondrial function and number can be changed following direct and 'non-targeted' exposure to radiation (e.g. [K3, N1]). One study identifies increased intracellular hydrogen peroxide as the source of elevated oxygen stress [D1].

42.   High and low doses of radiation have been reported to affect mitochondrial function differentially [P1]. Hydrogen peroxide and reactive oxygen species play an important part in mediating the phenomenon of intercellular apoptosis [B5]. As noted earlier (paragraph 35), low dose exposure of non-transformed cells to γ or α radiation stimulates apoptosis in transformed cells mediated intercellularly, and the stimulation saturates at 50 mGy and 25 mGy, respectively, for γ and α radiation delivered acutely [P2].

43.   Many of the experiments described in the literature regarding reactive oxygen and mitochondrial effects use in vitro systems where oxygen is present at ambient atmospheric concentrations. In vivo oxygen concentrations in tissues are much reduced (at 3–5% compared to 20% ambient). Cell growth and physiology is known to be affected by oxygen concentration [P3]. A recent report indicates that differentials in radiosensitivity can be affected by the oxygen environment [K7]. Before this knowledge can be fully interpreted, it will be important to establish the impact of low radiation doses on mitochondrial function and reactive oxygen metabolism under more realistic physiological conditions. Inflammatory reactions have recently been identified to play an important role in causing cellular senescence (e.g. [B6]) and inflammatory reactions are considered to play important roles in cancer development, in some cases promoting carcinogenesis and others protecting against it [M6]. Reactive oxygen species may reasonably be expected to be involved in the triggering and maintenance of inflammatory reactions [B6, M6]. Overcoming the 'senescence barrier' is now judged to be an important step in tumorigenesis. On the basis of current knowledge, it is not possible to make a judgement on the impact of radiation-induced alterations in mitochondrial function and reactive oxygen metabolism on cancer risk.

F.   DNA sequence analysis and the impact of genetic polymorphisms

44.   Recently there have been very significant advances in DNA-sequencing technology that allow the detailed analysis of individual genomes from normal or cancer cells. Such 'next-generation sequencing' studies have enabled the putative identification of the specific DNA damage and repair processes that lead to cancer-associated mutations (e.g. [P6, S11]). Furthermore, unexpectedly complex genome rearrangements have been observed in some cancers involving only specific chromosomes or chromosome regions; such complex changes are unlikely to have accumulated over time [C8, L6, R4, S13]. There is a growing appreciation of the role of epigenetic modification of the genome in the development of cancer (e.g. [B7]). Epigenetic modifications include DNA methylation, modification of histones by acetylation

and regulation of gene expression by micro RNAs. These findings serve to demonstrate that current understanding of the nature of the genetic rearrangements and epigenetic modifications that contribute to carcinogenesis is as yet incomplete. While these approaches have yet to be applied to radiation-induced cancers, such work can be anticipated in the future. These approaches hold considerable promise to elucidate further the processes that lead to cancer following radiation exposure at all levels.

45.   Individual genome sequencing efforts have also begun to reveal abundant genetic variation between individuals in terms of single base differences (single nucleotide polymorphisms, SNPs) and blocks of sequence (copy number variations, CNVs) (e.g. [Z2]). Again it appears likely that the application of next-generation sequencing technology could significantly improve the analysis of the effects of low-dose irradiation in causing mutations both in somatic tissue and in germ cells.

46.   The increase in understanding of human genetic variation has led to a much greater appreciation of the impact of naturally occurring genetic variation on disease risk. Studies are beginning to identify gene variants that predispose to disease and some studies are identifying gene variants that affect spontaneous cancer risk. While information on the range of human radiosensitivity is as yet incomplete, twin studies indicate a significant contribution of genetic factors to human variation in processes associated with cancer development [C5, F4, W3]. Cellular studies using γH2AX and MRE11 foci as indicators in fibroblasts indicate that there is a significant range in radiosensitivity at low doses (9 mGy of X-ray and above) and this type of analysis allows the definition of radiosensitive groups, even at low doses [C9]. Modelling studies suggest that genetic variation within populations may profoundly affect the distribution of risk within populations (e.g. [P7]). It is also clear that epigenetic modifications can affect cancer risk and the epigenetic status can be modified by exposure to environmental agents (e.g. [W5]). In the context of radiation-induced cancer, such genetic and epigenetic variation may affect the shape of dose–response curves for individual cancers.

47.   Developments in the understanding of human genetics and epigenetics will continue apace and can be expected to improve understanding of the role in carcinogenesis and heritable effects of the somatic genetic effects and epigenetic modification of low dose irradiation. Furthermore knowledge of the impact of genetic variation on disease risk will improve, and this is likely to improve understanding of the variation between individuals within populations of the risk of radiation-induced disease.

G.   Gene and protein expression

48.   The application of methods developed relatively recently for global analysis of gene and protein expression holds some promise for better understanding of radiation dose–responses. The '-omics' technologies such as genomics (global analysis of genes), transcriptomics (global analysis of gene expression), proteomics (global analysis of protein expression and modification) and functional genomics (screens of responses and phenotypes in genetically altered cells or organisms) continue to develop into powerful analytical tools in biology. The power of these methods comes from the understanding that the behaviour of an individual cell or tissue is determined by the proteins that are expressed. Proteins are coded for by genes, the expression of which is regulated at many levels, by epigenetic modifications such as methylation of DNA, by transcription factor binding and by micro RNAs. Proteins perform structural, enzymatic and signalling functions; and protein function can be regulated by a range of chemical modifications, such as phosphorylation.

49.   Gene expression analysed by microarray methods and quantitative polymerase chain reaction has been shown to be affected by radiation in vitro in a dose and dose-rate dependent fashion (e.g. [A2, D2]). No universal pattern of response has been identified and not all genes change in expression level following radiation exposure. The response of some genes to radiation appears to be dose-rate dependent while for other genes it appears to be dose-rate independent [A2]. There are suggestions that at high doses the responding genes tend to be involved in apoptosis and cell proliferation while low-dose exposures tend to affect genes involved in signal transduction, intercellular signalling, development and DNA damage response [D2]. A recent study comparing gene expression responses to low-LET protons at doses of 2.5 Gy and 0.1 Gy in a 3-D epithelial tissue model system provided additional evidence for differential responses at high compared to low doses [M14]. However there are few studies of gene expression that have carefully examined dose–responses. Those that have suggest that a range of responses can be observed and that genes involved in apoptosis and cell cycle regulation can be affected by doses of 0.1 Gy X-rays [M12].

50.   In vivo exposure of mice at low dose rate (0.032–13 µGy/min; total doses of 21 mGy, 420 mGy or 8,000 mGy) followed by analysis of kidney and testis gene expression using the Illumina bead array system has highlighted the tissue-specificity of response [T5]. As with in vitro irradiation studies, dose and dose-rate dependencies vary between genes. Low-dose radiation (100 mGy) is reported to induce changes in mouse brain gene expression similar to those seen in ageing and some neurological disorders [L4].

51.   Some human data are also available for gene expression changes in lymphocytes of radiation workers [F2], in vivo irradiated skin [B8], and in blood mononuclear cells from healthy persons exposed as a consequence of the Chernobyl accident [A3].

52.   At the present time there are no generally agreed patterns of gene expression changes associated with exposures at different doses or dose rates and no defined transition points can be identified. Several studies have noted inter-individual variation (e.g. [A3, B8, K16]), which is unsurprising given the known genetically-determined variation in basal gene expression (e.g. [C4]). There is also the possibility that different array systems may yield different results and they will certainly have differing sensitivity; thus, caution is required in interpretation of, and particularly comparison between, studies because technical limitations and differences could be playing a role. It is also reported that the statistical method used to analyse large gene expression datasets can affect the conclusions drawn (e.g. [A3]). Despite these caveats, there are reasonably sound indications that gene expression changes are radiation dose and dose-rate dependent. Most changes observed cannot be specifically linked to disease and are generally measured very soon after irradiation. It is therefore currently difficult to judge the use of such data for assessing low dose risk. However, in mice engineered to carry between 0 and 4 *Trp53* gene copies, early (2 hour) post-irradiation responses of p53-dependant genes does correlate with lifetime cancer risk [K17]. This study suggests, therefore, that tests using gene expression changes over short periods that are predictive over longer timescales may be developed in the future. Gene expression profiling has also been successfully used to distinguish between spontaneously arising and radiation-induced rat mammary tumours [I2]. Further refinement of such methods may allow more accurate assessment of the likely aetiology of specific tumours, although in general it remains very difficult to distinguish spontaneous and radiation-induced tumours.

53.   With regard to proteomic analysis two major classes of tool are available, firstly two-dimensional gel electrophoresis and secondly a range of sophisticated mass spectrometry methods. Protein biomarkers of radiation exposure have been identified (e.g. [M7, M8]).

Indeed some low-dose-responsive proteins have been identified (e.g. [M9, N2]) some of which have been suggested to play a role in adaptive response.

54.   As mentioned above, protein function can be affected by phosphorylation. As with gene expression and protein expression studies, some evidence is emerging of radiation dose-dependent patterns of protein phosphorylation [Y1, Y3]. Much of the work described above has emerged from studies searching for novel radiation biomarkers driven by heightened concerns of radiological terror incidents. Such searches continue with new methods being applied, such as metabolomic screening for urinary markers [T6]; it is highly likely that such novel approaches will extend to low-dose studies in the future. Some detailed in vivo dose–response studies provide evidence for non-linear induction of chromosomal protein marker of DNA double-strand breaks, γH2AX [B13]. Recently another publication has also suggested a non-linear response for the induction of another DNA-break-related marker, 53BP1 foci [N6]. In this case, more but smaller foci per unit dose were observed following low dose exposures by comparison with high dose exposures. It will be important that these observations are followed up to ensure that technical artefacts are not playing a role and so the spatial and temporal distribution of breaks is understood. As further novel biomarkers of exposure and disease are validated, dose–response analyses will follow.

55.   Gene expression can be modified through epigenetic alterations to DNA and chromatin. Acute and chronic low-dose radiation exposure in vivo affects overall DNA methylation in a tissue-specific, sex-specific and dose-rate-specific fashion [K4]. Radiation can also affect patterns of histone methylation (histones are chromatin proteins) [P4]. Furthermore there is a rapidly expanding literature on the involvement of chromatin modification in response to and signalling of DNA damage [K5, L5, N3, P5]. Radiation exposure is also known to modulate the expression of micro RNAs that are known to be involved in the regulation of gene expression (e.g. [C10, I5]); some indications of radiation dose and quality dependence as well as time dependence of responses are available [T8]. It can be expected that dose–response relationships for the various modifications of chromatin will be established in forthcoming years.

56.   The role of epigenetics in transmissible instability is demonstrated by Filkowski et al. [F5]. Exposure of male parental mice to 2.5 Gy of X-rays was seen to lead to reduced methylation of DNA repeat elements in offspring. The offspring also had reduced levels of lymphoid specific helicase (LSH), required for maintenance of methylation. These effects were attributed to the upregulation of the micro RNAs miR 29 and miR 29b in the father's germline leading to a decreased expression of the DNA methyltransferase Dnmt3a. Further evidence for a role of DNA methyltransferases and DNA methylation in the generation and propagation of genomic instability phenotypes is provided by Rugo et al. [R3]. These investigations involved an in vitro model of bystander-mediated instability using mouse embryonic stem cells. Conditioned medium from 3 Gy X-irradiated cells induced DNA damage (assessed in the comet assay) and homologous recombination (sister chromatid exchange) in unexposed cells. This effect was not observed in cells in which either of the DNA methyltransferases Dnmt1 or Dnmt3a were inactivated. Furthermore, another study in CHO cells suggests that mutation in a LacZ transgene occurring late after irradiation can frequently be reverted by 5-azacytidine treatment, indicating that the LacZ expression had been 'silenced' by DNA methylation [S15].

57.   Some data indicate that radiation quality can modulate the effects of exposure in DNA methylation [G2]. A good overview of the potential role of epigenetics in genetic instability is available [A8].

58.   Functional genomics screens using, for example, RNA interference to specifically 'knock down' the expression of all or most individual genes one at a time in cells or model organisms potentially provides a powerful method to distinguish high and low dose/dose-rate responses. To date such screens have been carried out using high radiation doses in, for example, the nematode (*C. elegans*) [H5] and human cancer cells [H6], and have identified novel radiation responsive genes and proteins. Application to low-dose exposures will help build a complete picture of responses over a wide dose range.

59.   Clearly there is rapidly expanding knowledge of the detail of radiation response at the molecular level. There is also an expanding range of technologies available that could be applied to further study. Exposure of cells and tissues can alter gene expression, protein expression, and the modification of proteins, genes and chromatin, which will likely affect function. There are indications that low-dose responses and low-dose-rate responses differ from high-dose and high-dose-rate responses qualitatively as well as quantitatively for such endpoints. The unexpected complexity of responses is well demonstrated by a study mapping genes that determine cellular radiation response at high doses [S6]. There is no reason to expect low-dose response networks and determinants to be significantly less complex. There is rapid improvement in understanding of the epigenetic regulation of gene expression and how irradiation affects this regulation. The real challenge is to understand the consequence, particularly in terms of health impact, of this new deeper understanding of mechanisms. Linking these data to health impact is, as noted earlier (paragraph 52), currently very difficult. All of the '-omics' studies need to establish the functional consequences of the molecular changes observed. This is most likely to be achieved through experimental studies combined with systems biology approaches (see below).

H.   Cellular interactions and tissue-level phenomena

60.   As noted already, cellular function and behaviour is determined by patterns of gene and protein expression and modifications within individual cells. Whole organisms are clearly more than the sum of individual cells within the organism. There is organization of cells into tissues and communication between cells within tissues. These interactions and communications are essential for the functioning of individual organs and of the whole organism. The growth of cancer cells may also be regulated to some extent by the tissue context/microenvironment. Observations in the 1970s suggested that malignant tumour cells could be transferred into normal embryos to form hybrids where tumour cells contributed to the development of apparently normal mice [M10]. While such findings were highly controversial and difficult to replicate they suggested that the abnormal growth of tumour cells could indeed be regulated by the cell/tissue environment. Since then, these and subsequent findings have been developed into hypotheses that give greater weight to tissue organization and the cellular interactions in driving the process of carcinogenesis (e.g. [S7]).

61.   It is clear that radiation can affect the tissue microenvironment and that reactive oxygen, inflammation and TGFβ signalling are involved (see [B9] for review). Modification of the tissue microenvironment has been observed to contribute to malignant transformation through reactive-oxygen-mediated alteration of normal epithelial differentiation and induction of genomic alterations [R1]. Transplanted tumours in mice can lead to elevated DNA damage in distant proliferative tissues [R2]. This indicates that tumours can affect distal cells as well, potentially leading to increased mutation.

62.   A recent report provides a clear demonstration that irradiation of host micro-environmental cells can provide a more 'permissive' environment for 'initiated' p53 null

mammary epithelial cells to develop rapidly into tumours [N5]. In these experiments a transplantation assay was employed and transfer of wild type epithelium did not lead to tumour development, indicating that genetic changes to target cells are required for tumorigenesis. The acceleration of tumour development was mediated by TGFβ [N5]. While the tumour-accelerating effect of host irradiation was observed at 0.1 Gy and 1 Gy, no such effect was seen following 0.5 Gy. Also 0.1 Gy and 1 Gy had similar effects with no additional effect of the higher dose. Thus, while the effect on the microenvironment may be observed at the low 0.1 Gy dose, dose–response relationships are clearly complex and apparently highly non-linear. Replication of these studies is required and more work on dose–effect relationships is needed.

63.   It is becoming recognized that humans in their seventies and older carry significant numbers of small dormant tumours and some of these may be 'contained' and restrained from growth by the tissue microenvironment (e.g. [W2]). There is the possibility therefore that disruption of the microenvironment by radiation could allow the growth of such pre-malignant tumours. Some evidence suggests that the immune system plays a major role in tumour dormancy [Q1] and therefore the immunomodulatory effects of radiation [U3] could be important in releasing or containing such dormant growths.

64.   One further way in which cellular interactions may be of importance in controlling tumour cell multiplication has been identified. In vitro studies have demonstrated that transformed cells can be killed by apoptosis, triggered by cytokine and reactive oxygen/nitrogen signalling from non-transformed cells. This process may be considered to represent a natural anti-cancer mechanism. Irradiation of non-transformed rat fibroblasts with doses down to 2 mGy γ-rays or 0.29 mGy ^{238}Pu α particles increased the proportion of apoptotic v-src transformed rat fibroblasts in co-culture [P2]. TGFβ signalling is involved in this response. The extent to which such radiation-stimulated killing of transformed cells operates in vivo has yet to be determined however.

65.   There is increasing interest in the role that inflammation plays in tumorigenesis. Although the precise role(s) have yet to be established [M6], it is clear that the microenvironment is important in modulating inflammatory reactions in tumorigenesis [K6]. Inflammatory reactions and the inter-cellular induction of apoptosis have a common mediator, involving reactive oxygen/nitrogen.

66.   Data are also available that suggest that immune functions can be activated in mice following in vivo exposure to chronic low-dose-rate gamma-radiation [I3] and acute or fractionated low-dose X-rays [N7, N8]. By contrast excessive and damaging immune reactions seen in a mouse model of severe autoimmune dysfunction are reported to be suppressed by exposure to chronic low-dose-rate radiation [S10]. In general it is more difficult to obtain clear and consistent data on the effects of low radiation doses on immune functions [B14], because individual variability in response makes it difficult to observe clear effects. Therefore it appears that radiation-associated immuno-modulation can be positive or negative, and it remains unclear how disease in humans might be affected.

67.   The processes that drive the development of circulatory disease following radiation exposure are not understood and dose–response relationships, particularly at low doses, are not clear (e.g. [A6, U3]). Some recent work in a mouse model indicates that non-linear relationships might apply [M11]. In the *Apo E$^{-/-}$* mouse model, in general low-dose and low-dose-rate exposures reduced the frequency/severity of atherosclerotic plaques in the aorta. It is possible, therefore, that circulatory diseases may follow a complex dose–response relationship, and systemic effects on the vasculature may play a role (e.g. [A6]).

68.   Clearly there is evidence emerging that radiation can affect the tissue microenvironment and that there is interaction between tumours and other tissues in the body. Such modification of the microenvironment could have consequences in terms of cell growth and normal tissue function. Relatively little information on radiation dose–response for such effects is available and so it is currently not possible to judge the impact of these phenomena on low-dose radiation risk. A complete understanding of the effects of low-dose irradiation on tissues will require the study of tissue stem cells, the microenvironment or 'niche' in which they reside and their kinetics. Stem cell biology is now developing rapidly and robust stem cell markers are becoming available (e.g. [R5]). These will be key tools to apply in the future. Similarly there continue to be reports on the impact of radiation exposures on the immune system, although again dose–response data do not yet provide a consistent and clear picture.

I.   Systems biology approaches

69.   The preceding sections demonstrate that irradiation of cells and tissues at the high and low dose levels tested can provoke biological responses. These can be complex at the cell level (e.g. gene and protein expression), at the tissue level (e.g. intracellular signalling and inflammation) and may have complex, non-linear dose–response relationships. One of the current areas of very active interest in biology is the application of 'systems biology'. Systems biology aims to provide a mathematical description of biological processes that allow prediction of the behaviour of the biological system both under normal conditions and in response to perturbation.
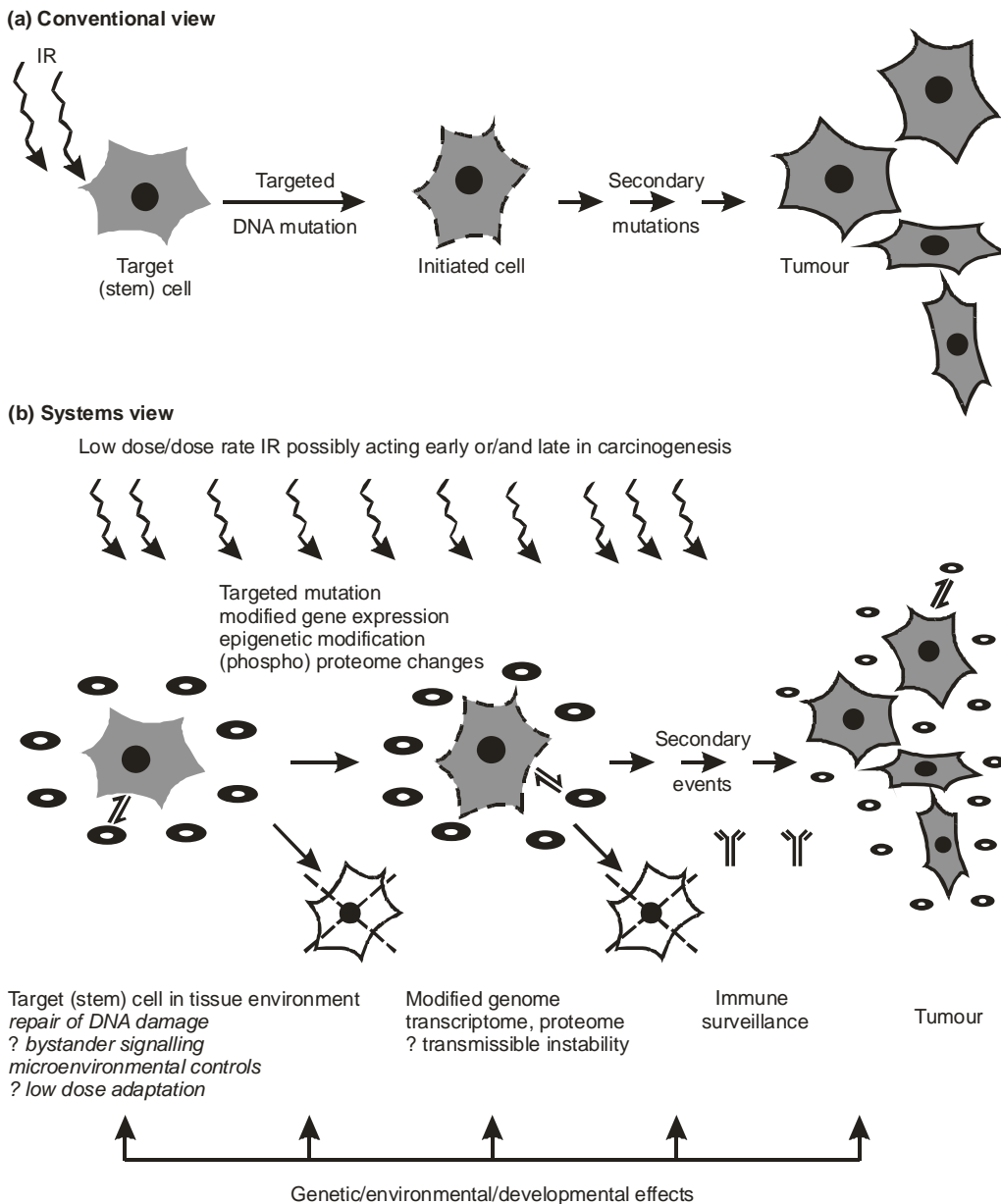
70.   Development of systems biology approaches have been most successful where teams including multiple specialisms work together (e.g. [J2]). Radiobiology is clearly starting to generate data that are moving towards a systems biology approach to understanding and analysis (e.g. [B10]), and it can be hoped that such new approaches will aid low-dose risk assessment. Indeed, several entities (e.g. the NCRP, Electric Power Research Institute (EPRI) and Multidisciplinary European Low Dose Initiative (MELODI)) are paying close attention to the potential value of systems biology. These are of course long-term projects and a full and robust mathematical description of radiation carcinogenesis over all dose levels cannot be anticipated in the near term.

71.   Despite the anticipated long timescale before a broad systems-level description of radiation carcinogenesis is available incorporating intracellular and intercellular aspects, it is valuable to consider the systems approach as a framework that can be used to make use of mechanistic data at the cellular and molecular level for estimation of risk. Large datasets describing radiation-induced alterations of gene expression, protein expression and modification, and epigenetic effects will have to be handled. A key challenge will remain: associating radiation effects with disease development. This is likely to be achieved through experimental animal studies and molecular/biomarker epidemiological studies. An important development will be the identification of biomarkers and bio-indicators of radiation-associated disease that could be used in occupational and public health monitoring.

72.   In considering the results summarized in this review and the integration of these into a framework, figure I provides (a) a comparison of the conventional view on radiation carcinogenesis and (b) a view based on systems-level approaches. While this figure relates to carcinogenesis, broadly similar considerations apply to heritable effects, although the consequences of radiation-induced modification of the genome, epigenome and gene/protein expression would be observed in the offspring of an exposed individual rather than the somatic tissues of the individual.

Figure I. The (a) conventional and (b) systems views of radiation carcinogenesis

(a) In the conventional view ionizing radiation acts primarily by damaging nuclear DNA (much of which is repaired by repair systems) inducing targeted DNA mutations in stem cells thus initiating the cancer development process. Secondary mutations accumulate ultimately leading to development of a malignant neoplasm. (b) The systems view considers the tissue context in which target/stem cells reside and intercellular/bystander signalling. DNA damage may be repaired or converted to mutations; radiation may also affect gene expression, protein modification and epigenetic status. Cells may die through apoptosis, enter terminal differentiation or senescence, or otherwise be selected against, and thus be removed from cancer development pathways (marked as unshaded, crossed cells). Radiation may affect these processes at any stage. The induced alterations to genome, epigenome, transcriptome and proteome together affect cellular differentiation (phenotype); some of these altered states of differentiation may lead to cells having growth or survival advantage and thus are linked to cancer development. Genomic instability may be another outcome. Cells with altered phenotype may be detected and killed by the immune system (note that while an antibody is used below to illustrate an immune response, tumour immune reactions are cellular not humoral). Effects of radiation on all these processes have been observed; but only targeted mutations have an established role in radiation carcinogenesis. Superimposed onto the somatic pathway(s) of cancer development are influences from the individual's inherited genome (e.g. disease susceptibilities and variations in target/stem cell numbers), history of exposure to other environmental agents (e.g. the known interaction between tobacco smoke and radon in lung carcinogenesis) and developmental state (e.g. stem cell development and numbers, and age).

(a) Conventional view

IR

Target
(stem) cell

Targeted
DNA mutation

Initiated cell

Secondary
mutations

Tumour

(b) Systems view

Low dose/dose rate IR possibly acting early or/and late in carcinogenesis

Targeted mutation
modified gene expression
epigenetic modification
(phospho) proteome changes

Secondary
events

Target (stem) cell in tissue environment
repair of DNA damage
? *bystander signalling*
microenvironmental controls
? *low dose adaptation*

Modified genome
transcriptome, proteome
? transmissible instability

Immune
surveillance

Tumour

Genetic/environmental/developmental effects

V. CONCLUSIONS AND RECOMMENDATIONS

60.   It is evident from this selective review that there are now significantly more data available on the biological consequences of low-dose radiation exposure and non-targeted effects such as bystander phenomena and transmissible genomic instability. While mechanistic understanding of non-targeted effects is improving, many studies remain primarily observational. There are also reports of differential gene and protein expression responses at high and low radiation doses and dose rates. As noted, these reports remain mixed in outcome and there is little of the coherence required of robust data that can be used confidently for risk assessment. Similarly there is as yet no indication of a causal association of non-targeted phenomena with radiation-related disease and indeed, some may not operate at low doses in vivo. The systems-level framework noted above should provide a useful guide for future integration of mechanistic data into risk estimation methods.

61.   In the case of radiation-induced perturbation of immune function or induction of inflammatory reactions, there is a clearer association with disease but the impact of radiation is less well understood. Scientific understanding of the processes contributing to radiation-induced disease will be of use in further refinement of judgements on low-dose risk. Research in these areas ought to be encouraged therefore, and the Committee notes that relevant publications continue to appear in the scientific literature. No compelling need for major in-depth reviews has been identified at this time. However the Committee agrees to: (a) continue to encourage research into the mechanistic understanding of low-dose radiation action that may contribute to improved understanding of disease risk in humans and into the factors that can modulate risk; (b) consider developing further biologically based risk models and the systems-level framework to integrate mechanistic data into a risk assessment framework; and (c) commit to reviewing the field again in 3–4 years when further data will be available.

Glossary

Abscopal effect	A radiation effect in a non-irradiated tissue distant from the irradiated tissue.
Adaptive response	The temporary modulation (usually reduction) by small 'priming' doses of the response to subsequent high radiation doses.
Apoptosis	Cell death caused by an intracellular pathway which can be activated by external stimuli.
Bystander effect	Effect observed in non-irradiated cells surrounding cells that were directly irradiated.
Centrosome	The sub-cellular organelle that forms the poles of the mitotic spindle during cell division.
CFU-A	Colony-forming unit–A, a haemopoietic cell colony that grows in soft agar. Generally thought to be from a primitive lineage haemopoietic cell type.
CNV	Copy number variation, a form of DNA sequence variation characterized by varying length of repeat sequences.
Cytokines	Small secreted proteins that mediate intercellular communication and signalling.
DNA methylation	The addition of methyl groups to the 5-position of cytosine by DNA methyltransferases (Dnmts). High level methylation of genes or gene regulatory sequences usually indicates a transcriptionally inactive state. A form of epigenetic modification.
Epigenetic modification	The modification of DNA or associated chromatin proteins that leads to altered expression of genes. DNA methylation, histone acetylation and methylation are among the epigenetic marks currently known.
Expanded simple tandem repeat (ESTRs)	A class of DNA repeat element in the mouse genome characterized by short direct repeat units (4–15 bases) in stretches of between 100 base pairs (bp) and 20 kbp. ESTRs are used as indicators of germ line mutation in mice.
γH2AX foci	Nuclear foci or spots detected by immunofluorescence using antibodies specific for the phosphorylated form of histone γH2AX. An indicator of DNA double-strand breaks. A number of other chromatin proteins from foci after DNA damage.

Genome	The complete DNA sequence of an organism.
Homologous recombination repair	One of the pathways of DNA double-strand break repair that requires an undamaged homologous stretch of DNA to provide a template for repair. Restricted to S and G2 phases of the cell cycle.
Micro RNA	A class of small non-coding RNAs that are involved in the epigenetic regulation of gene expression.
Mitochondria	Sub-cellular organelles that are the main site of energy production. Mitochondria contain a small circular DNA molecule that encodes some of their constituent proteins.
Non-homologous end joining	A DNA double-strand-break repair process that is the predominant pathway of repair in mammalian cells, predominately active in G1.
Proteome	The complete complement of proteins within an individual cell—investigated using the techniques of proteomics.
SNP	Single nucleotide polymorphisms. Variants of the genome at individual base pairs which can be useful in genetic mapping of diseases or susceptibles.
SV40	Similan virus 40. An oncogenic virus that is used to transform cell lines to form permanent lines.
Telomeres	The ends of chromosomes characterized by repeating units of (TTAGGG)n, hairpin structures with unusual base pairing at the ends and a range of associated proteins.
Transcriptome	The complete collection of transcribed RNAs in a cell—investigated using the techniques of transcriptomics.
Transmissible genomic instability	Persistent formation of genetic alterations (commonly mutations or chromosomal aberrations) over many post-irradiation cell generations.

Annex

Quotes from UNSCEAR Reports that summarize the current position on low-dose mechanisms

A1.   Quotes on effects of low radiation doses from the Committee's main report to the General Assembly in 2000 [U5] (original paragraph numbers)

55.   Damage to deoxyribonucleic acid (DNA) in the nucleus is the main initiating event by which radiation causes long-term harm to organs and tissues of the body. Double-strand breaks in DNA are regarded as the most likely candidate for causing critical damage. Single radiation tracks have the potential to cause double-strand breaks and in the absence of fully efficient repair could result in long-term damage, even at the lowest doses. Damage to other cellular components (epigenetic changes) may influence the functioning of the cell and progression to the malignant state.

56.   Numerous genes are involved in cellular response to radiation, including those for DNA damage repair and cell-cycle regulation. Mutation of those genes is reflected in several disorders of humans that confer radiation sensitivity and cancer proneness on the individuals concerned. For example, mutation of one of many so-called checkpoint genes may allow insufficient time to repair damage, because the cell loses its ability to delay progression in the cell cycle following radiation exposure.

57.   Cells have a number of biochemical pathways capable of recognizing and dealing with specific forms of damage. This subject is reviewed in annex F, "DNA repair and mutagenesis". One gene that plays a key role is the tumour suppressor TP53, which is lost or mutated in more than half of all human tumours. The p53 protein produced by the gene controls both arrest of the cell cycle and one pathway of apoptosis (the programmed cell death that is instrumental in preventing some damaged cells from progressing to the transformed, malignant growth stage). Some such biochemical pathways are also implicated in stress response or adaptation processes that act to limit the extent or outcome of damage. Even with such protective processes induced and acting, it is clear that misrepaired radiation damage gives the potential for progression to cancer induction or hereditary disease.

58.   Proto-oncogenes (genes that may be activated inappropriately and then participate in tumorigenesis) and tumour-suppressor genes control a complex array of biochemical pathways involved in cellular signalling and interaction, growth, mitogenesis, apoptosis, genomic stability and differentiation. Mutation of those genes can compromise those controls and contribute to the multi-stage development of cancer.

59.   Proto-oncogene activation by chromosomal translocation is often associated with early stages in the development of leukaemias and lymphomas, although gene loss also occurs. For many solid tumours there is a requirement for a loss-of-function mutation of tumour-suppressor genes that control cellular proliferation in specific tissues. The subsequent onset of genomic instability through further mutations in clones of cells may be a critical event in the transformation from benign to malignant state. Loss of apoptotic control is also believed to be important throughout tumorigenesis.

60.   The multi-stage nature of tumorigenesis is considered in annex G, "Biological effects at low radiation doses". Much knowledge about the process remains to be learned. Although the concept of sequential, interacting gene mutations as the driving force for tumorigenesis is more firmly established, there is a lack of understanding of the complex interplay between those events and the consequences for cellular behaviour and tissue homeostasis; uncertainty

also exists about the contribution made to malignant development of non-mutational (epigenetic) cellular events such as gene silencing and cellular communication changes.

61.   Direct evidence on the nature of radiation-associated initiating events in human tumours is sparse, and rapid progress in the area should not be anticipated. By contrast, good progress is being made in resolving early events in radiation-associated tumours in mouse models. Those molecular observations strengthen the view expressed in the UNSCEAR 1993 Report that radiation-induced tumorigenesis will tend to proceed via gene-specific losses; a contribution from early arising epigenetic events should not, however, be discounted.

62.   Much information points to the crucial importance of DNA repair and other damage-response functions in tumorigenesis. DNA damage-response functions influence the appearance of initial events in the multi-stage process and reduce the probability that a benign tumour will spontaneously acquire the secondary mutations necessary for full malignant development. Thus, mutations of DNA damage-response genes in tumours play an important role in the spontaneous development of genomic instability.

63.   The repair of sometimes complex DNA double-strand lesions is largely error-prone and is an important determinant of dose, dose rate and radiation quality effects in cells. Uncertainties continue to surround the significance to tumorigenesis of adaptive responses to DNA damage; the mechanistic basis of such responses has yet to be well characterized, although associations with the induction of biochemical stress responses seems likely. Recent scientific advances highlight the differences in complexity and reparability between spontaneously arising and radiation-induced DNA lesions. Those data argue against basing judgements concerning low-dose response on comparisons of overall lesion abundance rather than their nature.

64.   The research findings on the adaptive responses to radiation in cells and organisms were reviewed in the UNSCEAR 1994 Report, and the typical expression of an adaptive response is described there. The phenomenon has been interpreted as being the result of an initial small (priming) dose activating a repair mechanism that reduces the response to a subsequent larger (challenge) dose. Apparently, the range of priming doses is limited, the time for presenting the challenge dose is critical and the challenge dose needs to be of a reasonable magnitude. The response varies greatly between individual donors of lymphocytes. Nevertheless, the adaptive response has been seen in many systems, including human lymphocytes, a variety of mouse cells and with some chemical agents such as hydrogen peroxide and bleomycin as well as with radiation. However, so far there appears to be no generally reproducible reduction in tumour induction following low-dose irradiation.

65.   The basic premises of radiation response are that any radiation interaction with DNA results in damage that if not repaired or if incorrectly repaired, may represent an initiating event in the tumorigenesis pathway. The mutation of genes commonly result in modulation of their expression, with loss of gene products (proteins) or alteration in their properties or amounts. The biochemical balance of the cell may then be disrupted, compromising the control of cell signalling or the proliferation and differentiation schedules. In that way, mutated cells, instead of being checked or killed, may be allowed to proceed to clonal growth. Some non-mutational (epigenetic) events or damage may be involved or contribute to those changes. In some cases the genome may be destabilized, allowing further mutations to accumulate, which may promote the progression of tumorigenesis.

66.   The judgement as to whether there might be a threshold level of exposure below which biological response does not occur can be guided by mechanistic considerations. Specifically, there is a need to know whether at very low doses the repair processes are more efficient and perhaps enhanced by the adaptive response, preventing any damage to the cellular components. Such a threshold could occur only if repair processes were totally effective in that dose range or if a single track were unable to produce an effect. The absence of consistent

indications of significant departures from linearity of tumorigenic response at low doses in cellular endpoints (chromosome aberrations, gene mutation, cell transformation), the activity of well characterized error-prone DNA repair pathways and the evidence on the nature of spontaneous DNA damage in mammalian cells argue against adaptive or other processes that might provide for a dose threshold for radiation effects. The cellular processes such as apoptosis and cellular differentiation that can protect against later phases of tumorigenesis are judged to be efficient but can be bypassed; there is no reason to believe that those defences act differently on spontaneous and radiation-induced tumours or have specific dose dependencies.

67.   It may therefore be concluded that, as far as is known, even at low doses radiation may act as a mutational initiator of tumorigenesis and that anti-tumorigenic defences are unlikely to show low-dose dependency. In general, tumorigenic response does not therefore appear to be a complex function of increasing dose. The simplest representation is a linear relationship, which is consistent with most of the available mechanistic data. There may be differences in response for different types of tumour and statistical variations in each data set are inevitable. A departure from linearity is noted for leukaemia data, for which a linear-quadratic function is used. Skin cancer and some cancers induced by alpha emitters may have virtual thresholds. Because of the multi-step nature of the tumorigenesis process, linear or linear-quadratic functions are used for representational purposes only in evaluating possible radiation risks. The actual response may involve multiple and competing processes that cannot yet be separately distinguished.

A2.   Quotes on mechanisms of radiation oncogenesis from Committee's main report to the General Assembly in 1993 [U8] (original paragraph numbers)

37.   There is compelling evidence that most, if not all, cancers originate from damage to single cells. Cancer initiation involves a loss of regulation of growth, reproduction and development in somatic stem cells, i.e. the loss of control over the cell reproduction cycle and differentiation processes. Point mutations and chromosomal damage play roles in the initiation of neoplasia. Initiation can result from the inactivation of tumour suppressor genes, some of which play a central role in the control of the cell cycle. Although cells may have undergone initiating changes, they will not express their properties until they are stimulated ("promoted") to reproduce by chemicals, hormones etc. in their environment. The promoting agents may be independent of the initiation agent.

38.   Single changes in the cell genetic code are usually insufficient to result in a fully transformed cell capable of leading to a cancer; a series of several mutations (perhaps two to seven) is required. In spontaneous cancers, these mutations will have occurred randomly during life. Thus, even after initial cell transformation and promotion, further mutations are needed, and may well be available, to complete the clonal transition from pre-neoplasia to overt cancer. The whole process is called multi-stage carcinogenesis.

39.   It is possible that radiation acts at several stages in multi-stage carcinogenesis, but its principal role seems to be in the initial conversion of normal stem cells to an initiated, pre-neoplastic state. The action of radiation is only one of many processes influencing the development of cancer, so the age at which a radiation-induced cancer is expressed is not likely to be very different from that of cancers arising spontaneously. In some circumstances, however, later stages may be affected by radiation, thus changing the times at which cancers appear.

40.   Cancer initiation provides the target cells with some degree of proliferative or selective advantage, which is expressed after adequate promotion. The advantage may be a shorter reproduction time than that of normal cells or a blocking of normal cell differentiation. On the other hand, the very few transformed cells are immersed in a very much larger number of

normal cells, and their pre-neoplastic properties can be constrained by their neighbours. An escape from these constraints is a crucial feature of the neoplastic process.

41.   Even with their proliferative advantage, transformed cells and their progeny can be eliminated by the random process comprising reproduction, terminal differentiation and death that is at a steady state in mature tissues. The probability of elimination depends on the number of transformed cells and the degree to which they have become autonomous. At least one cell must lead to a clone of modified cells for a cancer to develop. The probability of this occurring is related to dose by the same type of dose relationship (linear or linear-quadratic) as discussed for heritable mutations in the cell. This broadly supports the contention that randomly induced cellular events are responsible for cancer induction.

42.   Many animal experiments confirm the predicted shape of the dose-response relationship. It should be mentioned that, at higher doses, cell killing is substantial, competing with cell transformation and causing the dose-response curve to bend downwards. In particular, the following points should be stressed:

  (a) unless the single cell origin of most cancers is thought to be unlikely, no low-dose threshold is to be expected;

  (b) if radiation acts primarily as an initiating event, providing one among several required mutations, multiplicative models of risk projection in time can be expected to be more realistic than additive models. (See also section II.B.2).

43.   There are problems in assessing the risks of cancer for exposures at low doses and low dose rates, since most human data are available only at high doses and high dose rates. The approach commonly used in risk assessment is to fit a linear dose-response relationship to the data, a procedure that is usually considered to give an upper limit to the risk at low doses. This is because the quadratic term will increase the response at high doses with high dose rates, forcing an increase in the slope of the fitted straight line. From radiobiological considerations, it is then possible to assess the value of the factor by which the slope of the fitted curve should be reduced to give an estimate of the linear component of the linear–quadratic relationship. Direct information on humans exposed at low doses is beginning to emerge and will increasingly provide a check on estimates derived from data at high doses.

44.   Novel systems to study cell transformation in vitro and cellular and molecular studies with these systems and with animal neoplasms appear to be potentially very productive sources of information about the mechanisms of cancer induction. Modern cellular and molecular studies may make it possible to differentiate between radiation-induced cancer and other cancers. If samples of tumours from radiation-exposed human groups were to be systematically stored, they would then be a very important resource for future studies on oncogenic mechanisms and for the establishment of causality between cancer in the population and physical or chemical carcinogens in the environment.

A3.   Quote on heritable effects from Committee's main report to the General Assembly in 1993 [U8] (original paragraph number)

45.   If the change in the genetic code occurs in the germ cells, i.e. the egg or sperm or the cells that produce them, the effect is transmitted and may become manifest as hereditary disorders in the descendants of the exposed individuals. Experimental studies on plants and animals show that such changes may range from trivial to severe, causing gross loss of function, anatomical disorders and premature death.

A4.   Quotes on non-targeted effects of radiation from Committee's main report to the General Assembly in 2006 [U3] (original paragraph numbers)

29.   The risks of cancer after high and moderate doses of radiation are relatively well understood from detailed epidemiological studies of the Japanese atomic bombing survivors and others. However, risks at the lower doses more typical of environmental and occupational exposures are generally extrapolated from the high dose data by incorporating factors to account for low dose and low dose rates. The estimation of the human health risks associated with radiation exposures are based mechanistically on the view that the detrimental effects of irradiation have their origin in irradiated cells or, in the case of heritable effects, in cells directly descended from them. However, a number of so-called non-targeted and delayed effects of radiation exposure have been described that may challenge this view. Annex C to the Committee's 2006 report, entitled "Non-targeted and delayed effects of exposure to ionizing radiation", reviews the evidence for such effects and reflects on how they may influence the mechanistic judgements required for the estimation of risk at low doses and dose rates.

30.   The effects considered include radiation-induced genomic instability, bystander effects, abscopal effects, induced clastogenic factors and hereditary effects, as follows:

   (a)   If a single cell is irradiated and survives, it may produce daughter cells that over generations have increasing numbers of alterations in their genomes, even though the daughter cells themselves were not irradiated. This effect is termed "induced genomic instability". The alterations in the genomes of the daughter cells can include alterations in their chromosomes, changes in the numbers of their chromosomes, mutation of their genes and other deoxyribonucleic acid (DNA) sequences and a reduction in the number of subsequent cells generated through daughter cell replication;

   (b)   The so-called "bystander" effect is the ability of irradiated cells to convey manifestations of damage to neighbouring cells not directly irradiated;

   (c)   An abscopal effect is said to occur if there is a significant response in a tissue that is physically separate from the region of the body exposed to radiation;

   (d)   There is a large body of evidence that blood plasma from irradiated animals and humans can contain so-called "clastogenic factors" capable of inducing chromosomal damage in unexposed cells.

   (e)   Heritable effects are those effects observed in off-spring born after one or both parents has or have been irradiated prior to conception. Transgenerational effects are those that are expressed beyond the first generation.

   (f)   Finally, some of the manifestations of non-targeted and delayed effects noted above can arise spontaneously and after exposure to other agents.

31.   In spite of the large body of new information, there continues to be considerable debate regarding the causal relationship between these non-targeted effects and the observed health effects attributable to radiation. The Committee concludes that at present the available data provide some support for concluding that there are disease associations, but not for causation. In arriving at this conclusion, the Committee stresses that the estimation of the health effects of radiation is based on epidemiological and experimental observations where there is a statistically significant dose-related increase in disease incidence. These direct observations of adverse health outcomes implicitly take account of mechanistic elements relating not only to the targeted (direct) effects of irradiation but also to the non-targeted and delayed effects described in annex C to the 2006 report.

32.   The Committee continues to hold the view that mechanistic information is important for its judgements on radiation-induced health effects at doses below about 0.2 Gy. However, to ascribe a mechanism for the development of a particular health-related biological effect, the data in question need to be independently replicated and to show strong coherence with the particular disease considered. In this respect, the data on microdosimetric energy distribution

in the cell nucleus and the subsequent cellular processing of directly induced DNA damage, reviewed in the Committee's 2000 report, are considered to provide a suitable foundation for judgements on mechanisms that affect risk estimation. However, the Committee recognises that a variety of mechanistic processes will contribute to the development of radiation-induced health effects.

33.   The Committee will maintain surveillance of scientific developments in the area of non-targeted and delayed effects and recommends generally that future research pay particular attention to designing studies that emphasize reproducibility, low dose responses and causal associations with health effects. Ultimately, understanding the range and nature of cellular and tissue responses to radiation will provide insights into the mechanisms by which radiation exposure induces detrimental health effects, thereby improving the scientific basis for the quantitative estimation of the risk of health effects for low doses and low dose-rates.

A5.   Quotes on the effects of ionizing radiation on the immune system from Committee's main report to the General Assembly in 2006 [U3] (original paragraph numbers)

34.   The effects of ionizing radiation on the immune system were first reviewed in detail in the Committee's 1972 report and then briefly described in the 1977, 1982, 1986, 1988, 1994 and 2000 reports. Concepts in immunology have developed and changed considerably in the last three decades and so the Committee had proposed that a completely new review of the effects of ionizing radiation on the immune system was necessary. Thus, annex D to the 2006 report, entitled 'Effects of ionizing radiation on the immune system', reviews data related to radiation-induced alterations of immune responses, considers the possible mechanisms involved and reviews epidemiological studies of the effects of ionizing radiation on the human immune system.

35.   The immune system, one of the most complex systems of the human body, is composed of cells of several types (lymphocytes and accessory cells) strategically spread throughout the body, perfectly positioned to recognize antigens (non-self or foreign substances and cells) and to neutralize or destroy them; this protects against infections and cancer. There are two different but interrelated forms of immunity: innate and acquired immunity. Innate immunity is fully functional before any foreign agent enters the body and thereby provides a rapid defence. Acquired immunity develops after a pathogen has entered the body and maintains memory of previous exposures, yielding a stronger response following subsequent exposure to the same antigen. Acquired immune responses are mainly executed by B-lymphocytes (humoral responses) and T-lymphocytes (cell-mediated responses).

36.   The effects of ionizing radiation on the immune system can be assessed by estimating changes in cell numbers or by using a variety of functional assays. The impact of such alterations in immune response depends on factors such as dose of radiation, its temporal relation to immunization and genetic disposition. Thus:

(a) High doses of radiation produce immunosuppression mainly due to the destruction of cells. Lymphocytes are very radiosensitive and their reduction is currently used as an early indicator of the level of an accidental acute exposure. Radiation-induced changes in immune parameters seem to be more dependent on total dose than on dose rate. Persisting effects on the immune system have been observed after exposure to ionizing radiation.

(b) At low doses and dose rates, the effects of ionizing radiation on the immune system may be suppressive or stimulatory. The long-term impacts of low radiation doses on the immune functions in relation to human health need to be evaluated.

37.   Annex D to the 2006 report discusses some possible mechanisms by which radiation can induce alterations in the immune system and their role in the promotion and control of

cancer. The immune system is able to remove aberrant cells that are potentially capable of forming tumours. It is unclear whether cancer results from a deficiency of the immune system. Immune dysfunction, however, has been associated with several types of human tumour. Understanding the interactions of ionizing radiation with the immune system may open new possibilities for cancer prevention and treatment.

38.   Annex D to the 2006 report describes studies of the effects of ionizing radiation on the human immune system for Japanese atomic bombing survivors, Chernobyl workers and residents. Techa river residents, the population near the Hanford nuclear site and patients undergoing radiotherapy. A cross-comparison of these data indicates some common findings: impairment of cellular immunity, increased humoral immunity and a shift towards an inflammatory profile. Atomic bombing survivors show perturbations to stable immune systems; this was not evident in workers and residents exposed to radiation resulting from the Chernobyl accident.

39.   While the suppressive effects of high doses of ionizing radiation are well documented, annex D to the 2006 report concludes that uncertainty exists regarding the effects of low radiation doses on the immune system; both stimulatory and suppressive effects have been reported.

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In 1955 the United Nations General Assembly established the Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) in response to concerns about the effects of ionizing radiation on human health and the environment. At that time fallout from atmospheric nuclear weapons tests was reaching people through air, water and food. UNSCEAR was to collect and evaluate information on the levels and effects of ionizing radiation. Its first reports laid the scientific grounds on which the Partial Test Ban Treaty prohibiting atmospheric nuclear weapons testing was negotiated in 1963.

Over the decades, UNSCEAR has evolved to become the world authority on the global level and effects of atomic radiation. UNSCEAR's independent and objective evaluation of the science are to provide for—but not address—informed policymaking and decision-making related to radiation risks and protection.