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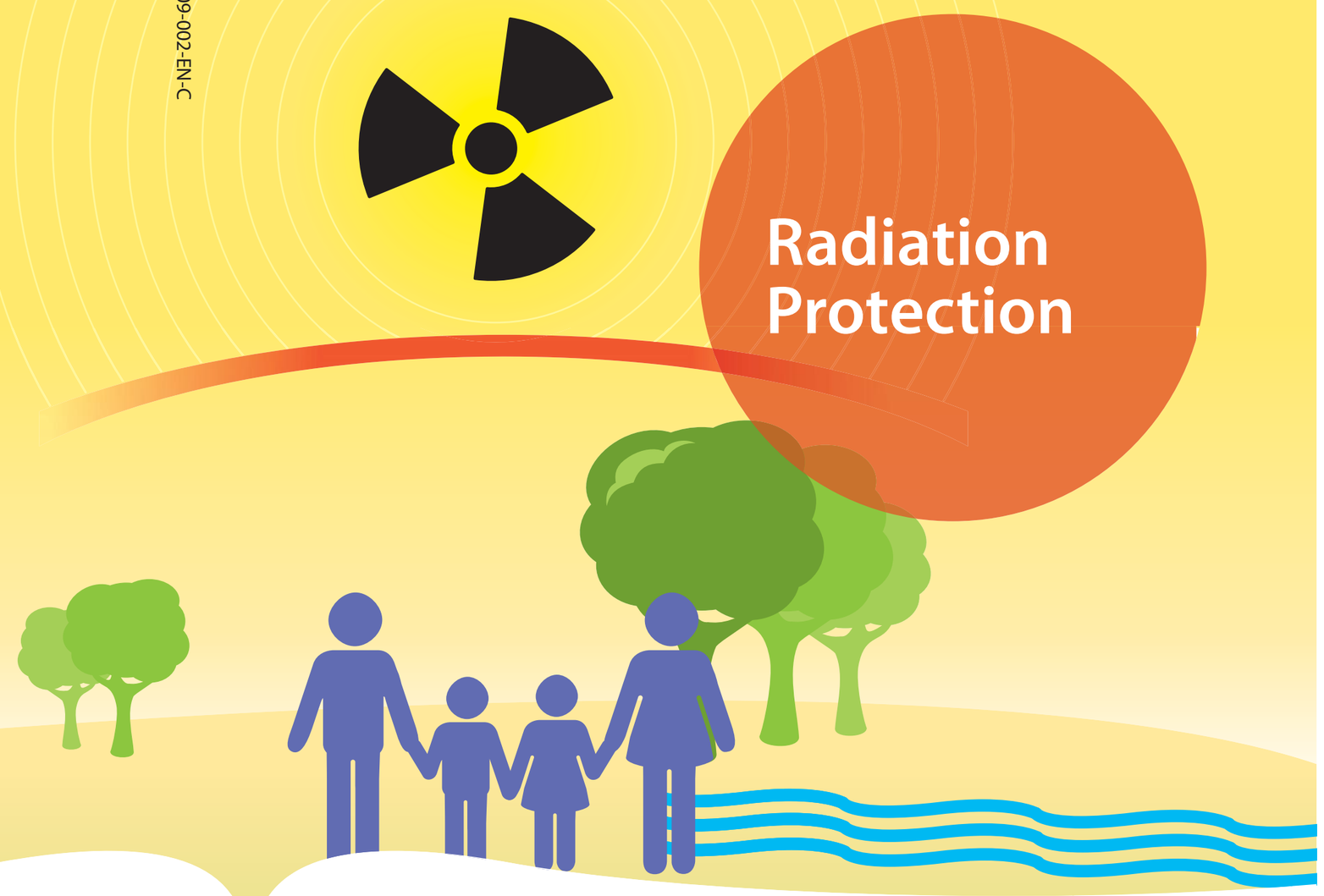

- NO 151 — ALPHA-EMITTERS: RELIABILITY OF ASSESSMENT OF RISK FOR RADIATION PROTECTION (EU SCIENTIFIC SEMINAR 2005)

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"Alpha-Emitters: Reliability of Assessment of Risk for Radiation Protection"

Proceedings of a scientific seminar held in Luxembourg on 21 November 2005

Working Party on Research Implications on Health and Safety Standards of the Article 31 Group of experts

Directorate-General for Energy and Transport
Directorate H — Nuclear Energy
Unit H.4 — Radiation Protection
2009

FOREWORD

Luxembourg, April 2009

Under the terms of the Treaty establishing the European Atomic Energy Community, the Community, amongst other things, establishes uniform safety standards to protect the health of workers and of the general public against the dangers arising from ionizing radiation. The standards are approved by the Council, on a proposal from the Commission, established taking into account the opinion of the Group of Experts referred to in Article 31 of the Treaty. The most recent version of such standards is contained in Council Directive 96/29/Euratom of 13 May 1996 laying down basic safety standards for the protection of the health of workers and the general public against the dangers arising from ionizing radiation.

The European Commission organises every year, in cooperation with the Group of Experts referred to in Article 31 of the Euratom Treaty, a Scientific Seminar on emerging issues in Radiation Protection – generally addressing new research findings with potential policy and/or regulatory implications. Leading scientists are invited to present the status of scientific knowledge in the selected topic. Based on the outcome of the Scientific Seminar, the Group of Experts referred to in Article 31 of the Euratom Treaty may recommend research, regulatory or legislative initiatives. The European Commission takes into account the conclusions of the Experts when setting up its radiation protection programme. The Experts' conclusions are valuable input to the process of reviewing and potentially revising European radiation protection legislation.

In 2005, the Scientific Seminar discussed "Alpha-Emitters: Reliability of Assessment of Risk for Radiation Protection". Renowned scientists reported on non-targeted effects of ionising radiation and their potential implications for radiation protection, on dosimetric uncertainties after exposure to alpha-emitters, and on the reliability of assessment of risk for radiation protection purposes on the basis of epidemiological information.

The Group of Experts discussed this information and drew conclusions that are relevant for consideration by the European Commission and other international bodies.

Augustin Janssens
Head of Radiation Protection Unit

CONTENTS

1 NON-TARGETED EFFECTS OF IONISING RADIATION - IMPLICATIONS FOR RADIATION PROTECTION

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Abstract

The universality of the target theory of radiation-induced effects is challenged by observations on non-targeted effects such as bystander effects, genomic instability and adaptive response. Essential features of non-targeted effects are that they do not require direct nuclear exposure by radiation and they are particularly significant at low doses. This new evidence suggests a need for a new paradigm in radiation biology. The new paradigm should cover both the classical (targeted) and the non-targeted effects. New aspects include the role of cellular communication and tissue-level responses. A better understanding of non-targeted effects may have important consequences for health risk assessment and, consequently, on radiation protection. Non-targeted effects may contribute to the estimation of cancer risk from occupational, medical and environmental exposures. In particular, they may have implications for the applicability of the Linear-No-Threshold (LNT) model in extrapolating radiation risk data into the low-dose region. This also means that the adequacy of the concept of dose to estimate risk is challenged by these findings. Moreover, these effects may provide new mechanistic explanations for the development of non-cancer diseases. Further research is required to determine if these effects, typically measured in cell cultures, are applicable in tissue level, whole animals, and ultimately in humans.

1.1 Introduction

A basic paradigm in radiobiology is that, after exposure to ionising radiation, the deposition of energy in the cell nucleus and the resulting damage to DNA, the primary target, are responsible for the harmful biological effects of radiation (Lea, 1946). The radiation-induced changes are thought to be fixed already in the first cell division following the radiation exposure and health effects are considered to result as a consequence of clonal proliferation of cells carrying mutations in specific genes (Ward, 1999; Prise, et al., 2005). Since the initial damage induced in DNA has been shown to be directly proportional to dose, risk is also be considered to be directly proportional to dose. Risk from multiple exposures is considered to be additive, and risk from high and low LET radiation exposure is assumed to be qualitatively the same. These assumptions are incorporated into the Linear-No-Threshold (LNT) Hypothesis that is used in all radiation protection practices.

These effects have also been termed "non-(DNA)-targeted" (Morgan, 2003b; Morgan, 2003a) and include radiation-induced bystander effects (Nagasawa and Little, 1992; Mothersill and Seymour, 1997; Belyakov, et al., 2001), genomic instability (Kadhim, et al., 1994), adaptive response (Nobler, 1969; Ehlers and Fridman, 1973; Robin, et al., 1981; Sham, 1995), clastogenic factors (Auclair, et al., 1990; Emerit, 1994; Emerit, et al., 1994; Emerit, et al., 1995a; Emerit, et al., 1995b; Emerit, et al., 1995c; Emerit, et al., 1997), delayed reproductive death (Seymour, et al., 1986), premature differentiation of cells (Belyakov, et al., 2002b; Belyakov, et al., 2005a), low dose hypersensitivity (Joiner, et al., 2001) and induction of genes by radiation (Seymour, et al., 1986; Hickman, et al., 1994; Azzam, et al., 1998;

Azzam, et al., 2000; Azzam, et al., 2001). Essential features of non-targeted effects are that they do not require direct nuclear exposure by radiation and they are particularly significant at low doses. This new evidence suggests a need for a new paradigm in radiation biology (Baverstock and Belyakov, 2005; Brooks, 2005). The new paradigm should cover both the classical (targeted) and the non-targeted effects. New aspects include the role of cellular communication and tissue-level responses (Barcellos-Hoff, 2001; Barcellos-Hoff and Brooks, 2001).

A better understanding of non-targeted effects may have important consequences on the health risk assessment and, consequently, on radiation protection. The non-targeted effects may contribute to the estimation of cancer risk from occupational, medical and environmental exposures. In particular, they may have implications for the applicability of the Linear-No-Threshold (LNT) model in extrapolating radiation risk data into the low-dose region. This also means that the adequacy of the concept of dose to estimate risk is challenged by these findings. Moreover, these effects may provide new mechanistic explanations for the development of non-cancer diseases. Further research is required to determine if these effects, typically measured in cell cultures, are applicable in tissue level, whole animals, and ultimately in humans.

The current paper gives an overview on the non-targeted effects, in particular bystander response and genomic instability. Furthermore, the potential implications of non-targeted effects on risk assessment and radiation protection will be discussed.

1.1.1 Bystander effect

Bystander effects are changes in cells that were not directly hit by radiation but were nearby (Nagasawa and Little, 1992; Mothersill and Seymour, 1997; Prise, et al., 1998; Belyakov, et al., 2001; Belyakov, et al., 2003; Belyakov, et al., 2005b). The signal can be transferred via the culture medium, “clastogenic factors” (Auclair, et al., 1990; Emerit, 1994; Emerit, et al., 1994; Emerit, et al., 1995a; Emerit, et al., 1995b; Emerit, et al., 1995c; Emerit, et al., 1997), or cell-to-cell communication as inhibition of cell communication prevents bystander effects (Azzam, et al., 1998; Shao, et al., 2005; Yang, et al., 2005). Bystander effects have been described in a variety of cellular systems and in tissue explants.

Bystander effects are not new. Starting from the 1960’s, there is extensive literature on clastogenic factors and other “compounds” that stimulate or modify responses in cells that were not damaged (Morrison, et al., 1981; Littlefield and Hoffmann, 1993; Hoffmann and Littlefield, 1995; Hoffmann, et al., 2001). Modern microbeam exposure systems capable of exposing single cells or even defined cellular organelles to charged particles or X-rays have facilitated research on bystander effects(Zhou, et al., 2000; Zhou, et al., 2002; Belyakov, et al., 2003; Shao, et al., 2003b; Zhou, et al., 2003; Ponnaiya, et al., 2004; Schettino, et al., 2005); see also reviews (Prise, et al., 2002; Hall and Hei, 2003; Osterreicher, et al., 2003). Such irradiation facilities also make it possible to target subcellular structures, such as nucleus, cytoplasm or mitochondria with either a single or an exact number of charged particles or exact doses of X-rays. The dose-effect relationship for bystander effect invariably shows a plateau below one Gray. Moreover, the effect appears to be determined by dose per hit cell, rather than number of cells hit, and high and low LET radiations appear to be equally effective. Bystander effects are the most likely drivers for the more delayed non-targeted effects such as genomic instability and adaptive response.

A variety of effects has been described in the bystander cells: increases or decreases in damage-inducible and stress-related proteins (Hickman, et al., 1994; Azzam, et al., 1998; Azzam, et al., 2000; Azzam, et al., 2001), increases or decreases in reactive oxygen (Iyer, et al., 2000; Morgan, et al., 2002; Shao, et al., 2005; Yang, et al., 2005) or nitrogen species (Matsumoto, et al., 2000; Matsumoto, et al., 2001; Shao, et al., 2003b; Shao, et al., 2004),

cell death (Mothersill and Seymour, 1997; Schettino, et al., 2005) or cell proliferation (Iyer, et al., 2000; Shao, et al., 2003a), cell differentiation (Belyakov, et al., 2002b; Belyakov, et al., 2005a), radio-adaptation (Kadhim, et al., 2004; Mothersill and Seymour, 2004; Mothersill and Seymour, 2005), induction of mutations (Nagasawa and Little, 1999; Zhou, et al., 2000) and chromosome damage (Prise, et al., 1998; Belyakov, et al., 2001), genomic instability (Watson, et al., 2000; Watson, et al., 2001; Lorimore, et al., 2003; Lorimore and Wright, 2003; Moore, et al., 2005) and neoplastic transformation (Lewis, et al., 2001; Sawant, et al., 2001). Irradiation of cytoplasm has been shown to lead to a mutation in nucleus or in the bystander cell (Wu, et al., 1999) and the mutation spectrum in bystander cells shows point mutations instead of deletions (Zhou, et al., 2000).

Bystander effect has been shown to be induced by very low doses (Michael, et al., 2000), and it is induced by high-LET (Michael, et al., 2000; Belyakov, et al., 2001) and low-LET radiation (Prise, et al., 2003a). The dose response for bystander effect is non-linear, showing first a sharp increase and then a plateau at higher doses (Michael, et al., 2000; Belyakov, et al., 2001; Morgan, 2003b; Morgan, 2003a), see Fig. 1.

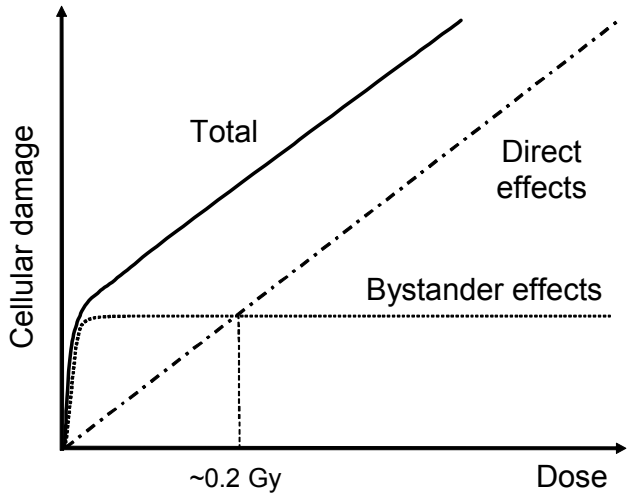

Figure 1. Contribution of bystander and direct component to the radiation induced damage (0.2 Gy is an estimation, based on our results and publications by other groups).

Bystander effect is currently considered to be the most likely driver for genomic instability (Watson, et al., 2000; Watson, et al., 2001; Lorimore, et al., 2003; Lorimore and Wright, 2003; Moore, et al., 2005). Bystander effect has been recently demonstrated also in vivo (Watson, et al., 2001; Xue, et al., 2002; Lorimore, et al., 2005). Genetic factors have been shown to influence bystander signalling in murine bladder epithelium (Mothersill, et al., 2005). However, the health significance of the bystander effect is not known and it is not clear whether it would increase, decrease or have no effect on cancer risk (Goodhead, 2004) and (Belyakov, et al., 2002a).

1.1.2 Genomic instability

Radiation-induced genomic instability means that the progeny of irradiated cells show occurrence of new mutations and/or new chromosomal aberrations or other genomic damage for many generations (Kadhim, et al., 1995). Affected progeny also demonstrate high levels of lethal mutation, which may be measured as delayed reproductive cell death and/or delayed apoptosis. As lethal mutations cannot pass to the next cell generations, it is evident that they are induced de novo in cells that were not exposed to radiation (Kadhim, et al., 1994). Genomic instability occurs in the progeny of irradiated cells at a frequency that is

several orders of magnitude higher than would be expected for a mutation of a specific gene (Suzuki, et al., 2003). Therefore a mutation in, for example, a repair gene is not a likely explanation for the induction of genomic instability. Genomic instability can occur both in the progeny of hit cells and bystander cells (demonstrated both in vitro and in vivo), see (Kadhim, et al., 1995; Watson, et al., 2000; Watson, et al., 2001; Lorimore and Wright, 2003; Lorimore, et al., 2005). Genomic instability is induced both by high-LET and low-LET radiation (Limoli, et al., 2000; Hall and Hei, 2003; Smith, et al., 2003), but not all cell lines show this effect. No individual gene consistently related to induction of genomic instability in gene expression studies (Suzuki, et al., 2003). Genomic instability is induced by very low doses of ionising radiation (Kadhim, et al., 2001). The dose-effect relationship for genomic instability invariably shows a plateau but is a function of time at which effects are scored and there is no obvious dose-rate effect (Smith, et al., 2003; Preston, 2005). High LET is more effective than low LET, but LET also influences the temporal pattern of expression. The perpetuation seems to involve epigenetic mechanisms (Schofield, 1998; Wright, 1998; Huang, et al., 2003). Cytokines and increased oxy-radical generation appear to play a role in the induction of genomic instability.

There is very little evidence on genomic instability induction in human lymphocytes in vivo (Whitehouse and Tawn, 2001). However, this may be partly due to methodological reasons. In human biomonitoring studies, G0 lymphocytes are observed in the first mitosis (48-h culture) and the aberrations scored are exchange-type aberrations derived from misrepaired DSB that have been formed along a track (DNA targeted response). In this case genomic instability is rather caused increased oxy-radical generation, the dispersed oxygen radicals would act like chemical mutagens. Therefore, they would cause base damage and single stand breaks, the effects would be S phase dependent and chromatid aberrations would be expected after a prolonged culture (at least 72 hours). Moreover, one could rather expect an elevation of chromatid breaks in lymphocytes rather than a linear or linear quadratic dose response.

Animal studies indicate that some mouse strains are genetically more susceptible to genomic instability induction than others. These strains also show a higher susceptibility to radiation-induced malignancy. Genotypes that have a less effective apoptotic response seem to be more predisposed to the development of malignancy. The genetic basis for this variability requires further research. Individual sensitivity seems to play a role both in genomic instability and bystander effect. Role of induced instability in radiation cancer risk is not yet clear (Goodhead, 2004).

1.2 Implications for risk assessment and radiation protection

The system of radiation protection has a number of basic assumptions that are challenged by the non-targeted effects. The basic assumptions include the following: knowledge of radiation risk is based on direct epidemiological evidence, as well as scientific study of radiation biology; the system is designed to protect against both deterministic and stochastic effects; a linear, non-threshold (LNT) dose-response relationship is used for all long-term health effects (e.g. cancer, genetic effects); a dose and dose-rate correction factor is used to relate the effects of acute exposures to chronic exposures (DDREF); radiation dose is used as a surrogate for risk; the effects produced by different types of radiation are qualitatively the same doses can be summed to predict overall risk; the objective of the system is to protect the individual; the protection system is generally applicable, in the same fashion, to all age groups and to both sexes; and, the protection includes the principles of justification, optimisation and exposure restrictions. There is broad international agreement among governments that the current system of radiation protection is effective, robust and adequately protects man and the environment.

1.2.1 A shift in radiobiological paradigm

The current paradigm in radiobiology is that, after exposure to ionising radiation, the deposition of energy in the cell nucleus and the resulting damage to DNA, the primary target, are responsible for the harmful biological effects of radiation. Radiation-induced changes are thought to be fixed by the first cell division following the radiation exposure and health effects are considered to result as a consequence of clonal proliferation of cells carrying mutations in specific genes, or deleted and/or transposed sections of chromosomes. Since the initial damage induced in DNA has been shown to be a linear or linear-quadratic function of dose, risk is also be considered to be a similar function of dose, and frequently (for conservatism) risk is assumed to be a linear function of dose. In this case, risk from multiple exposures is considered to be additive, and risk from high and low LET radiation exposure is assumed to be qualitatively the same. These assumptions are incorporated into the Linear-No-Threshold (LNT) Hypothesis that is used in radiation protection practice.

There is now accumulating evidence that challenges the universality of the target theory of radiation induced effects (Morgan, 2003b; Morgan, 2003a). Essential features of non-targeted effects are that they do not require direct nuclear exposure by radiation and they are particularly significant at low doses. A particular feature of non-targeted effects is the highly non-linear dose response, often downward curving at low doses, so that linear extrapolation from the high dose data would no necessarily overestimate low dose risk (Brenner, et al., 2001; Little and Wakeford, 2001). It appears likely that radiation-induced genomic instability may be linked with certain inflammatory responses (Lorimore, et al., 2003). Although the mechanisms of non-cancer health effects are as yet poorly understood, it is very likely that inflammation is involved, particularly in relation to cardiovascular and cerebrovascular disease (Ross, 1999; Lusis, 2000; Basavaraju and Easterly, 2002; Libby, 2002). This would imply a role for a non-targeted radiation effect in these disease endpoints. Since many non-targeted effects display highly non-linear dose response, knowledge of the underlying mechanisms is crucial to estimating low dose risks. New modelling strategies need to be employed to explore possible non-linearity in dose response resulting from complex biological models. This new evidence suggests a need for a new paradigm in radiation biology (Fig. 2). The new paradigm will cover both the classical (targeted) and the new non-targeted effects. New aspects include the role of cellular communication and tissue-level responses.

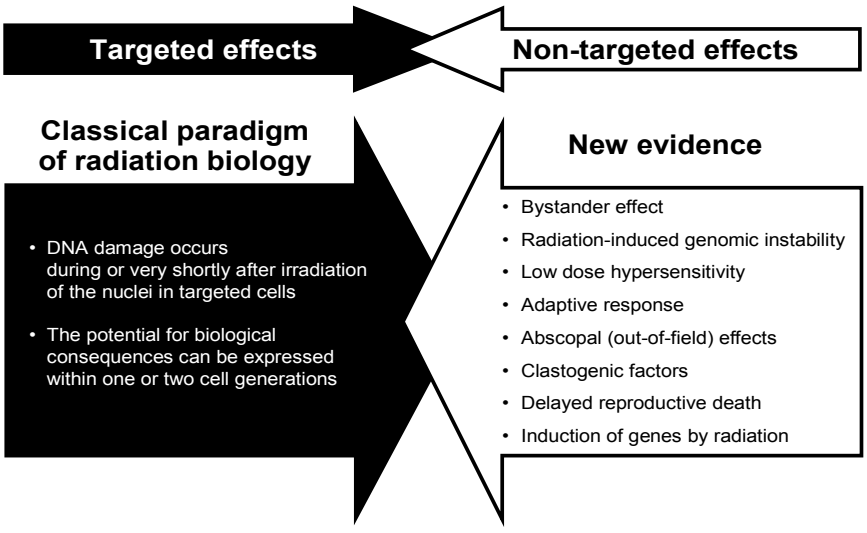

Figure 2. A new paradigm of Radiation Biology

1.2.2 Low-dose effects

The cancer risk at low doses will probably never be fully elucidated by epidemiological studies, as this would require very large populations and accurate dosimetry (Brenner, et al., 2003). The dosimetry of protracted exposures is even more demanding than dosimetry for single exposures (Brenner and Sachs, 2002; Brenner and Sachs, 2003). Uncertainties in dosimetry of epidemiological studies make it more difficult to observe a dose response, which in turn tends to lead to lower risk estimates. Modelling of biological events involved in radiation carcinogenesis may offer a tool to study the risk at the low dose region (Stone, 2005). The input data should contain not only the conventional direct radiation effects but also non-targeted effects which may be important modifiers of risk at the low dose region. It remains to be determined how this would apply to low-level radiation and whether it would increase, decrease, or leave unaltered, current assessments of risk. (Belyakov, et al., 2002a; Salomaa, 2004).The input data for modelling of radiation carcinogenesis should contain not only the classical targeted radiation effects, but also non-targeted effects, which may be important.

Genomic instability and bystander effects are observed already after very low doses. Using a microbeam exposure system, it has been shown that a single alpha particle is able to induce chromosomal instability in the progeny of cultured human cells (Kadhim, et al., 2001). In fact, the dose response data indicate that the relative contribution of these indirect effects as compared to damage caused by direct hits may well be more pronounced in the low dose region, thus giving some support for a potential supralinear response in the low-dose region.

The genomic instability and bystander endpoints are both transmissible (mutational) and non-transmissible (lethal). The balance of these in different cellular systems may lead either to an increased or decreased risk. Some scientists indeed argue that these non-targeted radiation effects are in fact part of the adaptive response to ionising radiation and therefore protective. More research is needed on the delayed damage response systems, such as adaptive response and premature differentiation. An increase in cancer risk can be argued by amplified genomic damage, genomic instability and also by increased proliferation of cells due to cell killing. A decrease in cancer risk can be argued by cell killing removing damaged cells and adaptive response and increased differentiation of cells which may protect. During embryonic and foetal development, however, any changes altering the normal pattern of cell proliferation, cell differentiation and cell migration are likely to be harmful (Streffer, 2004).

1.2.3 Dose-dependency and effect of radiation quality

It was demonstrated that high- and low-LET radiations induce bystander response (Limoli, et al., 2000; Hall and Hei, 2003; Smith, et al., 2003). The dose-effect relationship for the bystander effect invariably shows a plateau below 1 Gy (Michael, et al., 2000; Prise, et al., 2003b), and the effect appears to be determined by the dose per hit cell, rather than number of cells hit (Prise, et al., 2003b; Prise, et al., 2003a). Therefore, the bystander response appears to be an “all-or-nothing” response (Brenner, et al., 2001).

The dose-effect relationship for genomic instability shows a plateau but is a function of time at which the effects are scored, for example (Belyakov, et al., 1999). High LET is more effective than low LET, but LET also influences temporal pattern of expression (Smith, et al., 2003). The apparent difference in the RBEs of high and low LET radiations for bystander effect and genomic instability may also reflect the experimental conditions: in many of the genomic instability studies, the cell cultures contain a mixture of hit and bystander cells, whereas bystander studies, by definition, only concern non-hit cells.

Adaptive response is a biological phenomenon in which resistance to a challenging dose of radiation is established by one or several very small preceding doses. Therefore, adaptive response may be an important modifier of risk in situations where radiation exposure is protracted. Generally, and unlike most data available for genomic instability and bystander

effect, the adaptive response depends on synthesis of proteins, most of which are involved in DNA damage response. Very few studies so far have tried to investigate the relationships between bystander effect, genomic instability and adaptive response. However, it has been shown that the induction of adaptive response by low-LET radiation can protect against bystander damage induced by alpha particles. Moreover, these studies on cell cultures have shown that all three effects (genomic instability, bystander effect and adaptive response) may be observed at time points distant from the initial radiation exposure (Kadhim, et al., 2004). These results extend the adaptive response to include environmentally relevant exposure situations, i.e. where the challenging dose may be far removed from an initial dose, and may affect cells that were not themselves originally irradiated.

The dose dependency for adaptive response and other non-targeted effects appears to follow a similar pattern: the adaptive response to the challenging dose does not depend much on the size of the priming dose, but is rather a “switch on” stress response (Kadhim, et al., 2004; Mitchel, et al., 2004; Mothersill and Seymour, 2004). Unlike bystander response or genomic instability, adaptive response requires protein synthesis (Zhou, et al., 2003).

Since many non-targeted effects display highly non-linear dose response, knowledge of the underlying mechanisms is crucial to estimating low dose risks. New modelling strategies need to be employed to explore possible non-linearity in dose response resulting from complex biological models.

1.2.4 Concept of dose as surrogate of risk

The system of radiation protection is basically built on the linear no threshold model (LNT). A linear dose response means that every increment of dose and the associated risk can be assessed separately, irrespective of prior or future doses, as long as doses are below deterministic effects, that fixed dose increment is always associated with the same additional risk, that doses received by an individual at different time points can be summed up (cumulative dose) and, collective dose can be used to predict risk at the population level.

If linearity does not hold at low doses, this would have major implications for radiation protection. Non-targeted effects challenge the LNT model and thereby the also the concept of dose as surrogate of risk.

1.2.5 Individual susceptibility

Individual sensitivity (genetic predisposition) plays a role both in genomic instability and bystander effect (Mothersill, et al., 2001; Belyakov, et al., 2003). Genotypes that have a more effective apoptotic response seem to be less predisposed to the development of malignancy and genotypes that have a less effective apoptotic response seem to be more predisposed to the development of genomic instability and malignancy (Cheung, et al., 2002). Some mouse strains are more susceptible (McDaniel, et al., 2003) to genomic instability induction than others. Bystander effect and genomic instability are induced by high-LET and low-LET radiation, but not all cell lines show these effects (Mothersill, et al., 2002). Interindividual variation in bystander response has also been shown in human tissue (Mothersill, et al., 2001; Belyakov, et al., 2003). However, there is lack of consensus gene expression changes associated with radiation-induced chromosomal instability (Snyder and Morgan, 2005).

1.3 Potential mechanism for the development of diseases other than cancer

Traditionally, radiation protection regulations have been based on estimates of cancer risk at low doses and low dose rates derived by extrapolation from moderate to high dose and high

dose-rate epidemiological data, in particular the Japanese atomic bomb survivors and various medically exposed groups (ICRP, 1991). Recently there has been emerging evidence of risks of non-cancer health effects, in particular cardiovascular and cerebrovascular disease, in the atomic bomb survivor data and in certain medically-exposed groups (Darby and Hill, 2003; Preston, et al., 2003; Yamada, et al., 2004; Darby, et al., 2005). This is still controversial, because the shape of the non-cancer dose response in all groups, in particular the atomic bomb survivor data is not clear, and the effects have not been observed in a number of other exposed groups.

It appears likely that radiation-induced genomic instability may be linked with certain inflammatory responses (Lorimore and Wright, 2003). Although the mechanisms of non-cancer health effects are as yet poorly understood, it is very likely that inflammation is involved, particularly in relation to cardiovascular and cerebrovascular disease (Ross, 1999; Lusis, 2000; Basavaraju and Easterly, 2002; Libby, 2002). This would imply a role for a non-targeted radiation effect in these disease endpoints. Since many non-targeted effects display highly non-linear dose response, knowledge of the underlying mechanisms is crucial to estimating low dose risks.

Since non-targeted cellular responses to radiation are the products of cell signalling which result in modulation of a variety of genes, including those that produce free radical scavengers and enzymes to repair DNA damage, it is expected that such exposures could impact on the risk of non-cancer effects as well as on the risk of cancer. Research to date indicates that both of these cellular responses show an “all or nothing” type of response to dose, suggesting that the first track of radiation produces the maximum gene response. If this is so, then the radiation protection concept of an effect that is proportional to dose is inaccurate at low doses, and this difficulty may apply equally to non-cancer and cancer endpoints.

1.4 Non-targeted effects induced by other agents

Induction of genomic instability or bystander effects is not unique to ionizing radiation only, but it is known that also UVA (Dahle, et al., 2005a; Dahle, et al., 2005b) and heavy metals (Preston, 2005) can cause such effects. Ionising radiation is, however, a good model for studying delayed damage, because no extra substance is left in the cells after external irradiation (Prise, et al., 2002). In case of chemicals, interpretation of delayed damage is more complicated because of the possibility that traces of chemical may remain in the cells and still cause effects in subsequent cell generations.

The fact that several environmental agents and contaminants are capable of inducing bystander effects and genomic instability, suggests that bystander signalling and related effects may be related to a more universal response system to external stimuli/insults.

1.5 Summary: Potential implications of non-targeted effects from the policy point of view

The observations on non-targeted effects have raised three key questions that are important from the policy point of view. First of all, non-targeted effects may modify the cancer risk in the low dose area and therefore imply a deviation from LNT at low doses. Since many non-targeted effects display highly non-linear dose response, knowledge of the underlying mechanisms is crucial to estimating low dose risks. New modelling strategies need to be employed to explore possible non-linearity in dose response resulting from complex biological models. Secondly, it has been shown that DNA is not the only target for radiation effects, that there are effects in non-hit cells and that the non-targeted effects may amplify

radiation responses over a tissue, a shift in paradigm underlying the radiation induced health effects is warranted. It is now relevant to ask if ionising radiation may also cause non-cancer diseases or modify their risk at low and intermediate doses. The third question relates to differences in the radiation sensitivity between individuals and this issue is very relevant both for targeted and non-targeted effects.

Potential policy implications, in case there would be significant deviation from LNT (and additional detriment by non-cancer diseases) could be i.e. that the conceptual basis of the present system would be undermined, the use of dose as surrogate of risk would be seriously challenged, and the relevance of dose and the target at risk should be re-examined.

However, as interesting as the findings on the new radiobiology are, we should keep in mind that there is a plenty of radiobiological and epidemiological evidence that is in line with the classical paradigm. Therefore, it is advisable to build on the existing knowledge, but to see what new is brought about with the non-targeted effects. The new paradigm needs to cover both the classical (targeted) and the new non-targeted effects. New aspects include the role of cellular communication and tissue-level responses.

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2 DOSIMETRIC UNCERTAINTIES AFTER EXPOSURE TO ALPHA-EMITTERS

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Abstract

The assessment of radiation doses is fundamental to radiological protection although neither the dose in an organ or tissue (equivalent dose) nor the effective dose can be measured directly. Evaluation of these doses requires models to simulate the geometry of the source, the biokinetics of the intake and retention of radionuclides in the human body and the human anatomy. These models and their parameter values have been developed in many cases from experimental investigations and human studies in order to derive the "best estimates" of model parameter values. It is recognized that there may be large uncertainties in the values of the parameters and in the formulation or structures of the models themselves.
Uncertainties may arise from biokinetic models, dosimetric models or from the use of these models. Uncertainties for internal emitters dosimetry may include amounts and chemical forms of the specific intakes, values of the biokinetic parameters, individual variability in biokinetics, inhomogeneities of radionuclides distribution, identification and location of target cells for cancer induction, choice of RBE and weighing factors for dose calculation and assumption of dose response relation-ship. These uncertainties do not really apply for prospective dose assessment for planning purposes but should be defined and taken into account for retrospective dosimetry.

2.1 Introduction

The assessment of radiation doses is fundamental to radiological protection although neither the dose in an organ or tissue (equivalent dose) nor the effective dose can be measured directly. Evaluation of these doses requires models to simulate the geometry of the source, the biokinetics of the intake and retention of radionuclides in the human body and the human anatomy. These models and their parameter values have been developed in many cases from experimental investigations and human studies in order to derive the "best estimates" of model parameter values. It is recognized that there may be large uncertainties in the values of the parameters and in the formulation or structures of the models themselves.
The uncertainty in the central value of a model feature should not be confused with the "variability" of that feature in the population. Variability refers to quantitative differences between different members of a population under similar conditions (inter-individual variability) or within an individual under different conditions (intra-individual variability). For example, the transit time of material through the colon may differ between two persons of the same size, race, age, and gender and having identical diets (inter-individual variability) or may differ in the same person at different times due to changes in diet, state of health, or other conditions (intra-individual variability). Uncertainty refers to the level of confidence that can be placed in a given component (e.g., parameter value) or prediction of a dosimetric model, as an estimate of the central value (usually, an arithmetic or geometric mean) in the population.

In radiological protection, uncertainties may arise from many fields. There are uncertainties in epidemiological, radiobiological and dosimetric data. Risk factors for stochastic effects, from

which w_R and w_T values are derived, have been obtained from epidemiological and experimental radiobiological data in the medium and higher dose ranges. The risk factors for the lower dose ranges, important for radiobiological protection as well as the concept of effective dose, are based on extrapolation from the measured data in the higher dose ranges using the linear no threshold model. This model is an assumption which has not scientifically been proven and it, therefore, also bears a high degree of uncertainty especially in relation to exposures at low doses and low dose rates (UNSCEAR 2000).
Taken as a whole, these extrapolations and assumptions generate many uncertainties in the result of dose calculation and risk assessment. This point is now very well admitted by most of the experts and increasing works are now being published on this subject.

2.2 How to estimate uncertainties

Assessments of uncertainties are of prime importance. Several studies were performed recently on this subject and focused on the reliability and uncertainties of ICRP biokinetic models and doses coefficients (Harrison et al. 1998, Khursheed 1998, Leggett et al. 1998, Harrison et al. 2001, Leggett 2001), assessment of uncertainties in bioassays analyses (Luciani et al. 2003) and uncertainties in thyroid dose reconstruction (Likhtarev et al. 2003). It appears from these studies that there are many mathematical methods to assess uncertainties, none of them being the “reference method”.
The method that will be used in that document is the one previously described by Harrison et al (2001) and adopted in the latest dosimetric model from the ICRP (ICRP 2005).
In this latter document, uncertainty is considered in some major components of the alimentary tract model. The uncertainty in a given quantity is expressed in terms of a subjective confidence interval, that is, an interval of positive values, [A,B], such that the true but unknown value is judged with reasonable confidence to lie between A and B. Here, “reasonable confidence” is defined as a subjective confidence level of 90%. That is, it is judged that there is only a small probability (about 5%) that the true value is less than A and only a small probability (about 5%) that it is greater than B.
For purposes of comparing levels of uncertainty of model components that are expressed in different terms or have different orders of magnitude, it is sometimes convenient to apply the concept of an uncertainty factor (UF). An uncertainty factor for a quantity with subjective confidence interval [A,B] may be defined as $(B/A)^{1/2}$. The quantity is considered to be known within a factor of $(B/A)^{1/2}$ in the sense that all values in the interval are within a factor of $(B/A)^{1/2}$ of the geometric mean of A and B. The description of uncertainties in terms of uncertainty factors is simply a convenient way of summarising conclusions regarding uncertainties in model components and has no implications with regard to the central value or the distribution of possible values of a model component.

2.3 Uncertainties after internal contamination with alpha emitters

Uncertainties in dosimetry are probably the most important in case of internal contamination with short-range emitters. By contrast to external exposure where the location, geometry and activity of the source and the duration of exposure is most often known or easily to assess, estimation of dose after internal contamination lies on many assumptions that increase the level of uncertainties. These assumptions are made on the biokinetic and dosimetric models and the use of these models as well. The main assumptions and associated uncertainties are developed below.

2.3.1 Uncertainties in biokinetic models

A biokinetic model describes mathematically the behaviour of a given radionuclide in the body. Uncertainties in these models may arise because the structure provides an

oversimplified representation of the known process, because unknown processes have been omitted from the model or because part or all the model formulation is based on mathematical convenience rather than consideration of processes (Leggett, 2001).

2.3.1.1 Source of data

The first source of uncertainty is about the type of information used to construct the biokinetic models. These models are based on some combination of many data, coming from different sources of information. Data can come a/ directly from information on humans, i.e. quantitative measurements of the element in human subjects, b/observations of the behaviour of chemically similar elements in human subjects; c/ observations of the behaviour of the element in non-human species and d/ observations of the behaviour of chemically similar elements in non-human species (Leggett, 2001).
Data types b/, c/ and d/ serve as surrogates for a/, which is the preferred type of information on which to base a biokinetic model.
The main problem is that similarities between chemically analogues elements and species do not necessarily imply similar biokinetics. Actinides have all chemical similarities together but uranium, by contrast to the other actinides, has relatively low deposition in liver, is a bone volume seeker and has a high rate of urinary excretion. Similarly, in the alkaline rare earth elements, there is a high faecal excretion of absorbed Ba and Ra but not Ca and Sr. Finally, in the group of alkali metals, K and Na are physiological opposites. K is mainly intracellular and Na is mainly extracellular (Guyton 1986). In the same way, mammals are very close all together but substantial differences in the radionuclide biokinetics may occur. As for example, Pu is rapidly lost from liver in rats, macaque monkeys and baboons, whereas is tenacious retained in hamsters, deer mice, dogs, pigs and man (Taylor 1984).

2.3.1.2 Uncertainties in transfer coefficients

One major source of uncertainty in biokinetic models is about the assessment of the incorporation of the radionuclide. After inhalation, assumptions are made about the diameter and the physico-chemical form of the inhaled particles, that determine the pulmonary deposit, the translocation to blood and therefore the distribution of the element to the organs. After ingestion, similar assessments are made about the fractional absorption from the gastrointestinal tract, that depends again on the physico-chemical properties of the radionuclide.
The uncertainty in intake from the lungs lies to the knowledge available for the particles considered. In absence of any relevant information, the ICRP recommend to use default parameters, which can be considered as central values. It must be pointed out that, for a given radionuclide, difference in absorption according to their chemical form may be of 1 order of magnitude. Any imprecision or mistake in the expert judgment may therefore lead to similar variability in the final dose.

The uncertainty in fractional uptake from the gastrointestinal tract to blood varies considerably from one element to another. In a relative sense, uncertainties in fractional uptake are smallest for elements that are known to be nearly completely absorbed, including hydrogen (as tritium), carbon, sodium, chlorine, potassium, bromine, rubidium, molybdenum, iodine, caesium, thallium, fluorine, sulphur, and germanium. An uncertainty factor in the range 1.1-1.5 might be appropriate for each of these elements, depending on the quality and completeness of the data base for individual elements (Table 1). Average uptake from the gastrointestinal tract is also reasonably well established for several frequently studied elements whose absorption is incomplete but represents at least a few percent of intake, such as copper, zinc, magnesium, technetium, arsenic, calcium, strontium, barium, radium, lead, iron, manganese, cobalt, and uranium. Uncertainty factors for these elements would also vary with the element and generally would be greater than 1.5 but no more than about 3. Relative uncertainties generally are greater for the remaining elements due to sparsity of

direct observations on human subjects (e.g. ruthenium, silver), inconsistencies in reported absorption fractions (e.g. beryllium, antimony, silicon), or absorption too low to be determined with much precision under most conditions (e.g. most actinide and lanthanide elements). Absorption of a few poorly absorbed elements such as plutonium, americium, and curium has been studied under controlled conditions in human subjects, and average uptake in the adult may be known within a factor of 3 – 4 for these elements. Relative uncertainties may be greatest for several elements whose absorption has not been studied in man but for which animal data or other indirect evidence indicates absorption of at most a few hundredths of a percent, such as samarium, gadolinium, dysprosium, erbium, thulium, actinium, yttrium, and scandium. Absorption fractions for these elements are order-of-magnitude estimates.

Table 1. ICRP values for the fractional absorption of elements from the gastrointestinal tract of adults and uncertainty factor UF (modified from Harrison et al., 2001).

Element	ICRP f_1	Range (A-B)	UF [a]
H, C, Na, K, Br, Rb, Mo, Cl, I, Cs, Ta, F, S, Ge	1	0.8-1	1.1
Cu, Zn, Mg, Tc, As, Ca, Sr, Ba, Ra, Pb, Fe, Mg, Co	0.1-0.6	0.02-0.5	2-3
U	0.02	0.006-0.03	
Ru, Ag, Be, Sb,	0.05-0.1	0.002-0.2	4-10
Actinides	$5x10^{-4}$	10^{-4} -10^{-3}	

a : UF: uncertainty factor = $(B/A)^{1/2}$

A second source of uncertainties is linked to paucity of data in certain circumstances of exposure. Chronic exposures for example are treated, from a biokinetic point of view, as a sum of acute intake of radionuclides (ICRP 1995). This may apply in many circumstances but recent data showed that this assumption may be wrong in, at least, some specific cases. Paquet et al. (2005) showed that chronic exposure of rats by daily ingestion of uranium (U) in drinking water cannot be modelled by the current models (Figure 1). Indeed, the current models overestimate by about 1 to 2 order of magnitude the deposition in tissues. According to the authors, this was probably due to physiological mechanisms that first regulated U absorption from the gastrointestinal tract and secondly reduced body content by increasing detoxification processes. These data show that uncertainties, or errors made in dose calculation may be of one order of magnitude.

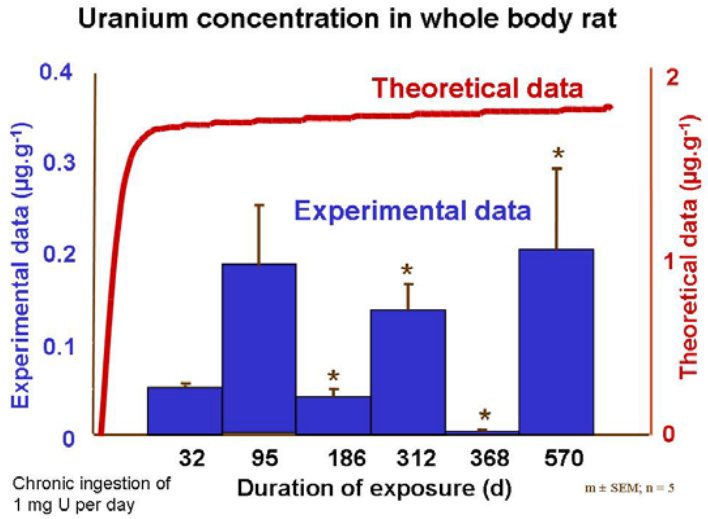

Figure 1: Uranium (U) concentration in whole body rat after chronic exposure to 40 mg.l^{-1} of U in mineral water. Experimental data (blue histogram) are mean ± SEM. Theoretical data (red line) are obtained after iterative use of biokinetic data coming from experimental acute exposure of rats.

2.3.1.3 Uncertainties in transit times

Uncertainties in transit times from one compartment to another may lead to substantial differences in dose assessment. A specific study has been performed under an ICRP task group and is currently in press (ICRP, 2005). This study focussed on uncertainties in transit time of food in the human alimentary tract.

In that study, considering only average residence times in healthy individuals within a population, it was judged that the typical residence time of material in the mouth or oesophagus of the adult male is known within a factor of about 2. The typical residence time of material in the stomach, small intestine, right colon, left colon, or rectosigmoid colon in the adult male is judged to be known within a factor of about 1.5. On this basis, effective dose coefficients and equivalent dose coefficients to the colon have been calculated for the examples of ingestion of ^{90}Sr, ^{106}Ru and ^{239}Pu by adult males, using transit times of 8 hours and 18 hours in each of the three segments of the colon (the default value is 12 hours for each segment). In the cases of ^{90}Sr and ^{106}Ru the uncertainty factors for colon dose are 1.5 and 1.4 respectively, which are nearly the same as that for transit time, reflecting their close association (Table 2). For ^{239}Pu, colon dose arises solely from activity absorbed to blood, and variations in transit time have no effect on colon dose. For ^{106}Ru the colon dose from activity in the contents makes an important contribution to effective dose, and thus the uncertainty in transit times leads to an uncertainty factor in effective dose of about 1.2. In contrast, colon doses from ^{90}Sr and ^{239}Pu contribute very little to effective doses and results are unchanged by variations in transit time.

Table 2. Uncertainty Factors (UF) and ratios of dose coefficients (B/A) resulting from uncertainty in transit times in the colon[a], considering ingestion by adult males (From ICRP, 2005)

Nuclide	Colon dose		CED[b]	
	B/A[c]	UF[d]	B/A	UF
^{90}Sr	2.3	1.5	1.0	1.0
^{106}Ru	2.0	1.4	1.3	1.2
^{239}Pu	1.0	1.0	1.0	1.0

a- for colon transit time, B/A = 2.3 (18/8), and UF = 1.5 ($\sqrt{2.3}$).
b- committed effective dose.
c- A and B values correspond to 5th and 95th percentile confidence intervals.
d- UF = (B/A)$^{1/2}$.

2.3.2 Uncertainties in dosimetric models

Dosimetric models are based on biokinetic models and are designed to produce dose coefficients. Uncertainties in these models may arise because biokinetic models are uncertain or because some assumptions in the location of radionuclides or target cells are wrong. Indeed, the main uncertainties are based on these two points and on the determination of the RBE.

2.3.2.1 Uncertainties in radionuclide location in tissues

Dose to tissues are calculated assuming a uniform distribution of the radionuclides (sources) in the tissues. An exception is made for lungs, bone and gastrointestinal tract (ICRP 1990, ICRP 1994, ICRP 2005).
The assumption of uniform distribution is very convenient for computing purposes but is wrong in many cases. Radionuclide distribution may be heterogeneous in many tissues and even in many cells. Histological data obtained after thorium injection in hamsters showed large concentration of Th in some part of the liver cells (Brooks et al. 1985) (Figure 2). Experimental contamination of rodents with uranium contamination leads cortical deposition and to precipitates in lung macrophages (Figure 3). Contamination with lead, beryllium and neptunium lead to similar types of deposition (Levi-Setti 1988, Berry et al. 1997, Boulhadour et al. 1997, Ceruti et al. 2002).

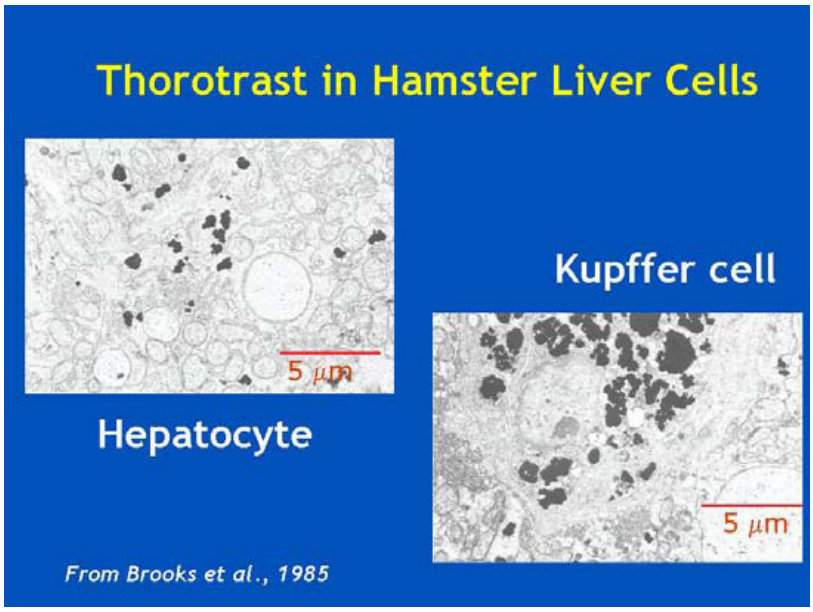

Figure 2: Thorium deposition in hamster liver cells after contamination under thorotrast form (from Brooks et al. 1985).

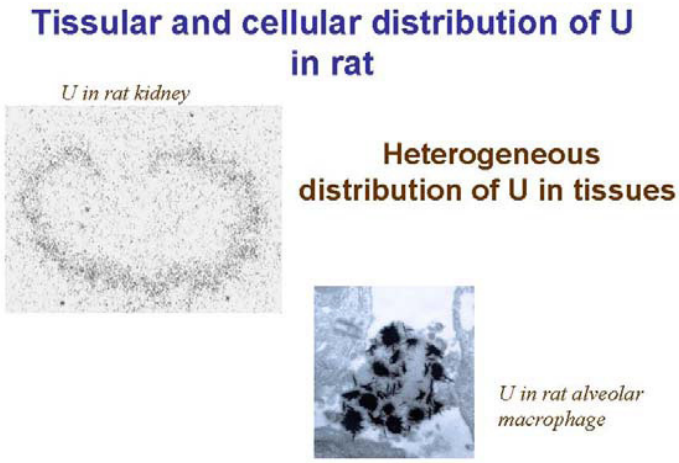

Figure 3: Tissular and cellular distribution of uranium in some tissues (from Paquet et al, personal communication)

2.3.2.2 Uncertainties in the location of target regions for cancer induction

The position of the target cells in a organ or tissue is essential to assess the dose. In the Human Alimentary Tract Model (HATM), it is assumed that the stem cells in the bases of the crypts of the colon are the targets for cancer induction. The consequence is that, due to the depth of these targets (Figure 4), the alpha particles from the GI tract would not reach these cells. However, there are uncertainties both in the depth of the crypts and hence the depth of the stem cells, and whether it is only the stem cells that should be regarded as targets.
Table 3 from ICRP (2005) compares colon doses for different assumptions of target location, normalised to the default assumption that they form a continuous layer at a depth of 280 – 300 μm from the lumenal surface of the colon. Thus, uncertainties in the depth of the crypts and hence the depth of the stem cells, result in differences of about + 10% for ^{115}Cd and smaller differences for the other examples considered. For ^{234}U and ^{239}Pu, there is no dose to the colon wall from activity in the lumen, and thus no change with changing assumptions regarding stem cell depth. Similarly, widening the target to include cells at higher positions up the crypts (200 – 300 μm), and thus increasing the mass of target tissue, results in a maximum change in colon dose of about 10% for ^{115}Cd. The extreme assumption that the target may include all epithelial cells from the base of the crypts to the lumenal surface (0 – 300 μm) results in larger increase in doses. The increase by factors of about 1.5 for ^{234}U and 3 for ^{239}Pu are relative to the dose to the colon resulting from activity absorbed to blood. However, theses increases in colon doses from ^{234}U and ^{239}Pu will make negligible differences to committed effective doses, which are dominated by contributions from doses to tissues and organs from activity absorbed to blood.

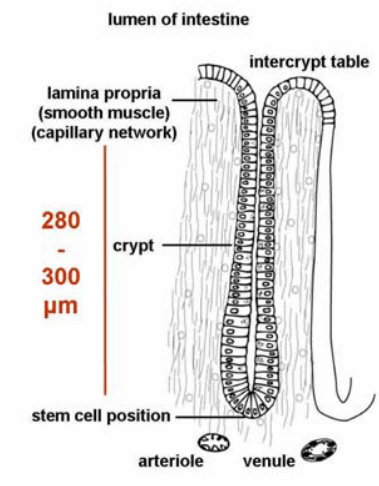

Figure 4: Illustration of the cross-sectional structure of the epithelial lining of the intestine, showing crypts and stem cells position. Published courtesy of Prof. Chris Potten, Epistem, Ltd.

Table 3: Differences (%) in dose coefficients (h) for the colon, compared to the default case, resulting from considerations of target depth in the mucosa, considering ingestion by adult males (from ICRP, 2005).

Nuclide	Assumed location of the target region – depth from lumen, µm			
	220 – 240	340 - 360	200-300	0-300
Fe-55	0%	0%	0%	0%
Fe-59	1%	-1%	1%	6%
Sr-90	7%	-6%	5%	21%
Ru-106	3%	-2%	2%	8%
Cd-115	13%	-9%	9%	38%
U-234	0%	0%	0%	148%
Pu-239	0%	0%	0%	317%

[a]default case assumes a target depth of 280 – 300 µm

2.3.2.3 Uncertainties in the RBE and W_R

Biological effects depend on the absorbed dose and also on the radiation type and energy. This point is especially important in the case of internal exposures, and it was considered by the ICRP, which weights the absorbed dose with a factor reflecting the biological effectiveness of the radiation. This factor is known as the radiation weighting factor (W_R). The ICRP selected the values of these weighting factors to be representative of the relative biological effectiveness (RBE) values for the radiation and has defined W_R values for photons, electrons, neutrons, protons and alpha particles (ICRP 1990).

The ICRP based the weighing factors on the risk appearance of stochastic effects (ICRP, 2003). It considers that the W_R values are the same for all tissues, while acknowledging that no radiobiological data is supporting this concept. It also considers that these factors do not vary with the photon, electron, proton and alpha particle energy. An exception is accepted for neutrons, for which the values differ depending on the energy (ICRP, 1990). RBE and W_R are therefore supposed to be constant parameters depending only on the radionuclide and on the type of emission. There is, however, much cases where these parameters may change. RBE may change first according to the biological effect considered. For early effects caused by cell killing (skin burn, cataract, sterility,..) RBE is generally less than 10 (UNSCEAR 2000). For lung fibrosis from inhaled alpha particles in rats and dogs, RBE is between 7 and 10. For

induction of chromosomes aberrations in human blood with alpha from ^{252}Cf, RBE is 6 compared to X-rays and 18 for gamma rays. For sperm head abnormalities in mice exposed to ^{241}Am, RBE was 245. Finally, for sister chromatid exchange in human lymphocytes after exposure to alpha from ^{241}Am, RBE was found to be infinite (no effects with X-rays irradiation).
RBE may change also according to the species considered (Table 4).

Table 4: Estimated RBEM values for alpha particles

Endpoint	RBE_M	Ref
Bone tumours Dogs Dogs Mice	26 4.0-5.8 25	NCRP 1990 Griffith et al. 1991 NCRP 1990
Lung tumours Various species Dogs Dogs Rats	6-40 10-18 36 25	ICRP 1980 Boecker et al. 1988 Hahn et al. 1991 Hahn et al 1991

These few examples show that both RBE and W_R may change according to the dose the type of contamination, the effects and the species considered. This results in high uncertainties in the determination of these parameters, exacerbated by the fact that few reliable data are available. Indeed human data are available only for certain alpha emitters, such as radon decay products, radium, and more recently, plutonium. No human data is available for assessing the RBE for neutrons and heavy ions, and the knowledge acquired in experimental systems have to be extrapolated to the human being.
In addition to the above, there is now clear evidence which suggests that the shape of the dose-response curve may be different in different tissues, for different effects (types of cancer) and for different types of radiation. Under such conditions W_R becomes scientifically meaningless since it has meaning only if dose-response curves are linear and without threshold.
However, The ICRP position is that, for prospective dose assessment, dosimetric models as well as parameter values should be taken as reference models and values which are not subject to uncertainties. Following accidental exposure or for epidemiological studies, more specific information on the individual and exposure condition are needed. In such situations, sources of uncertainties should be taken into consideration, including individual anatomical and physiological data and so on.

2.3.3 Uncertainties in the use of the models

Uncertainties in dose calculation may arise from the misuse of the adopted models. The third European inter-comparison exercise on Internal dose assessment showed that when a same set of data is given to two different dosimetrists, different methods will be applied and therefore different numerical values will be obtained (Doerfel et al. 2003). Table 5 gives examples of differences obtained by different laboratories when calculating effective dose after hypothetical exposure. This table show great discrepancies between laboratories, and show that the major source of uncertainties for dose assessment after alpha exposure may arise from this latest stage.

Table 5: Dose calculation performed by different laboratories during an intercomparison exercise (Data from Doerfel et al, 2003).

Type of exposure	Nuclide	Committed affective dose (E(50)) Max/min
Intake through skin	^{3}H	77
Accidental intake	$^{90}Sr/^{90}Y$	1900
Continuous ingestion	^{137}Cs	38
Single inhalation	^{239}Pu	9300
Intake long time ago	^{239}Pu	131,000

2.4 Conclusions

Uncertainties after exposure to internal emitters may arise from different points. The assessment of exposure and hence dose need to know the amounts and chemical forms of the specific intake, to define a biokinetic models with biokinetic parameters, to define the location of both radionuclides and target cells, to choose the relevant RBE and the weighing factor and to make assumptions on the dose response relationship. All these processes and data are highly exposed to uncertainties. This does not represent real problem for dose calculation for planning purposes but should be included for retrospective dose assessment. The major challenge for the next decade would be to first identify these sources of uncertainties, to quantify them and to integrate them in the forthcoming dosimetric models.

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3 ALPHA-EMITTERS: RELIABILITY OF ASSESSMENT OF RISK FOR RADIATION PROTECTION - EPIDEMIOLOGY

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3.1 Introduction

Risk estimates for radiation protection are mainly based on the cohort of the atomic bomb survivors from Hiroshima and Nagasaki (ICRP 1991). The atomic bomb survivors were exposed to external gamma radiation. Since there are only very limited data for a quantitative assessment of health risks due to exposures to alpha radiation, radiation protection for alpha exposures are also based on the risk factors derived from the atomic bomb survivors. For this purpose it is recommended to multiply absorbed doses from alpha radiation by a radiation weighting factor of 20. In this context it is assumed that alpha radiation induces a similar carcinogenic effect as gamma radiation with an absorbed dose that is by factor of 20 lower than the absorbed dose from the alpha radiation. This radiation weighting factor has been mainly derived from radiobiological and animal experiments. The present report addresses the question to what degree a radiation weighting factor of 20 for exposure to alpha radiation is supported by the new epidemiological evidence that has been obtained during the past few years.

Exposures to alpha radiation may be subdivided into two groups: i) exposures to radon and its progeny, and ii) exposures to other alpha emitters or other exposure pathways. Considerable improvement of the risk evaluation due to radon indoor exposure has been achieved recently by the European and the American pooling of lung cancer case-control studies (Darby et al. 2006; Krewski et al. 2005). The Article-31 Group has already been informed about these studies. Radon exposures are, therefore, not treated in the present report. The only exception is a short summary of a recommendation of the German Commission on Radiological Protection concerning the relevance and the implications of these studies (Section 3.4.3).

Because of their outstanding relevance, studies of lung cancer mortality among workers of the Mayak Production Association are described first in this report (Section 3.2), followed by a section on other studies of lung cancer associated with alpha radiation exposure (Section 3.3). The Section 3.4 summarises epidemiological evidence for the association of other site-specific solid cancers with alpha particle exposure. Section 3.5 deals with other diseases, including all cancers together.

Many of the publications summarised here denote equivalent doses from alpha radiation in Sievert, assuming a radiation weighting factor 20. Other publications give absorbed doses in Gray. This report uses both quantities and units, in the same way as it is used in the original publications.

3.2 Lung cancer among Mayak workers

The Mayak Production Association (MPA) was founded in 1948. The MPA is located in the Southern Urals. For many years the main purpose of the MPA was the production of plutonium for the atomic weapons of the former Soviet Union. The plutonium was created in nuclear reactors, separated from the fuel rods in the radiochemical plant, and further processed in the plutonium production plant. Work in auxiliary plants was necessary to support these three production units.

Gilbert et al. (2004) analysed a cohort of 21 790 Mayak workers, who were hired in the period 1948 to 1972 (Table 1). 83% of the workers were hired at age younger than 30.

Vital status at the end of the observation period, 31 December 2000, was known for 90% of the cohort members. 8493 workers had died, and the cause of death was known for 97% of the deaths. In total, there were 655 lung cancer deaths. Most of the cases with pathological classification died in Ozyorsk, the closed town in which the Mayak workers live. Among these cases were 37% adenocarcinoma, 29% squamous cell carcinoma, 21% small cell carcinoma, and 13% of other type (Jacob et al. 2005). The frequency of adenocarcinoma is on the borderline of being significantly higher than a frequency of 30% as it was observed in a group of unexposed workers (Torkarskaya et al. 1995).

17 318 (79%) of the workers were monitored for external radiation (Gilbert et al. 2004). Internal exposure of the lung was considered to be mainly due to inhalation of ^{239}Pu. In the radiochemical plant workers were mainly exposed to $^{239}Pu(NO_3)_4$, in the plutonium production plant to $^{239}PuO_2$. 5859 (66%) of the 14 715 workers in the radiochemical and plutonium plants were monitored for internal radiation. Workers of the auxiliary plants and of the reactors were treated as monitored with internal dose 0. In the risk analyses, person-years and cases were stratified among other criteria according to external dose (14 dose categories, the unmonitored were considered to have dose 0) and to internal dose (14 dose categories plus six surrogate categories according to work place for the unmonitored workers of the radiochemical and plutonium plants).

In a linear dose-response model without threshold, lung cancer was found to be significantly associated with internal lung dose for both sexes (Table 2). The estimated excess relative risk (ERR) per internal lung dose for a male at attained age 60 was 4.7 (95% CI: 3.3; 6.7) Gy^{-1}. The ERR per dose for females was estimated to be four times that for males. There was a strong evidence of a decline in the ERR with attained age. There was no evidence that the ERR depended on age at hire. Similar results were obtained
i) when non-monitored workers of the radiochemical and plutonium plants were excluded,
ii) when further only workers with information on smoking were included, and the baseline risk was allowed to be different for smokers and non-smokers.

The best estimate of the ERR per external dose was for females by a factor of 1.9 higher than for males. However, this difference was not significant. In a model in which the modifying effects of gender and attained age were assumed to be the same for internal and external dose, the estimated ratio of the coefficients for internal (alpha-particle) and external (gamma-ray) dose was 33 (95% CI: 14; 98).

Table 1: Number of Mayak workers and lung cancer deaths (in parentheses) by plant, plutonium monitoring status, sex and external dose, $H_p(10)$, and mean values of external and internal dose (after Gilbert et al. 2004).

	All workers	Auxiliary plants	Reactor plants	Radiochemical and plutonium plants			All workers
				Not monitored for plutonium	Monitored for plutonium	Mean internal lung dose among monitored (Gy)	Mean external dose (Gy)
Total	21 790 (655)	2582 (54)	4493 (131)	8856 (252)	5859 (218)	0.26	0.80
Males	16 458 (594)	2084 (54)	3505 (124)	6724 (224)	4145 (192)	0.21	0.80
Females	5332 (61)	498 (0)	988 (7)	2132 (28)	1714 (26)	0.38	0.82
By external dose							
Not monitored	4472 (91)	1273 (26)	520 (8)	2007 (45)	672 (12)	0.058	-
< 0.1 Gy	4744 (76)	811 (16)	841 (9)	1874 (31)	1218 (20)	0.072	0.04
0.1 – 1 Gy	8212 (221)	467 (12)	2315 (70)	3079 (79)	2351 (60)	0.17	0.39
1+ Gy	4362 (267)	31 (0)	817 (44)	1896 (97)	1618 (126)	0.61	2.41

Table 2: Estimates of the ERR and the EAR per unit dose for lung cancer mortality with 95% confidence intervals, as derived from the data for all 21 790 members of the Mayak Worker Cohort (after Gilbert et al. 2004).

Exposure / Sex	ERR per dose[a] $(Gy)^{-1}$	EAR per dose[a] $(10^4$ PY-Gy$)^{-1}$
Internal lung dose /		
Males	4.7 (3.3; 6.7)	115 (81; 156)
Females	19 (9.5; 39)	49 (29; 78)
External dose /		
Males	0.17 (0.052; 0.32)	2.4 (0.56; 4.4)
Females	0.32 (<0; 1.3)	0.43 (<0; 1.6)

[a]: Dose cumulated until 5 years before time of consideration (5-year lagged dose).

The excess absolute risk (EAR) per internal dose was for females by a factor 0f 0.4 smaller than for males. The EAR per internal dose had a maximum at age 65. There was no evidence of dependence on age at hire for internal dose.

In an analysis of categories according to internal dose (reference category: dose 0), risks increased with increasing lung dose, and risks were significantly elevated in all dose categories for males, and in all but the lowest (0 - 0.2 Gy) dose category for females. Evidence of a statistically significant response was found when analyses were restricted to internal doses less than 0.5 Gy. The risk was not significant when restricted to workers with internal doses less than 0.2 Gy. The best estimate of the risk coefficient was, however, still positive. Analyses with time windows of 5-15, 15-25 and 25+ years before the time at risk indicated a negligible risk in the first period, a maximal risk in the period of 15-25 years after exposure, and a smaller risk for the last time period.

Whereas Gilbert et al. (2004) assumed that relative risks due to smoking and due to radiation exposure are multiplicative, these risks were sub-multiplicative in the preferred model of carcinogenesis in a more recent analysis of lung cancer mortality among the Mayak workers (Jacob et al. 2005). The latter is in accordance with results on lung cancer associated with smoking and alpha radiation from inhaled radon and its progeny: sub-multiplicative models were found to describe radon miners data better than multiplicative models (BEIR VI, 1999); in the analysis of pooled European indoor radon case-control studies the best estimate of the ERR was by 50% higher for never smokers than for smokers (Darby et al. 2006). For the Mayak workers smoking was identified as the leading cause of lung cancer mortality (65%), followed by the interaction of smoking and radiation (20%), and cases which were not associated with smoking or radiation (8%). Only 7% of the cases were assessed to be associated with radiation alone.

In the low dose range (D < 0.1 Gy), excess risks depend linearly on dose and are relative independent of dose rate. In contrast to the empirical model of Gilbert et al (2004), there is according to the model of carcinogenesis (Jacob et al. 2005) is a non-linear dependence with a maximum of the risks per unit dose at about 3 Gy and with an inverse dose rate effect.

In both risk models, the empirical model and the model of carcinogenesis, the estimates of the ERR at age 60 per internal lung dose (in Sv) tend to be lower then expected from the atomic bomb survivors and a radiation weighting factor of 20 (Table 3).

Table 3: Estimates of the ERR per unit dose for lung cancer mortality with 95% confidence intervals for male Mayak workers (inhalation of plutonium) and for male atomic bomb survivors of Hiroshima and Nagasaki (acute external radiation).

Mayak workers (w_{Pu} = 20), monitored for plutonium and with information on smoking	Atomic bomb survivors, without information on smoking
0.20 (0.13; 0.29) Sv^{-1} (Gilbert et al. 2004)[a]	0.40 (0.032; 0.86) Sv^{-1} (Gilbert et al. 2004)[c]
0.11 (0.08; 0.17) Sv^{-1} (Jacob et al. 2005)[b]	0.48 (0.23 ; 0.78) Sv^{-1} (Preston et al. 2003)[d]

[a]: empirical model, lag time of 5 years
[b]: Model of carcinogenesis, lag time of 10 years
[c]: age at exposure 15-60
[d]: age at exposure 30

In total, the EAR per internal lung dose (in Sv) of the Mayak workers is similar to the EAR per external dose of the atomic bomb survivors. However, there are differences is the dependence on age attained.

Main weaknesses of the lung cancer studies of Mayak workers are the limited information on the smoking behaviour and uncertainties in evaluations of the lung dose from incorporated alpha emitters. Presently, further information on smoking behaviour is extracted from medical records, and work is performed on improved dose evaluations (Leggett et al. 2005).

3.3 Lung cancer in other studies

Lung cancer from exposure to alpha radiation has been studies for the plutonium workers at plants in Sellafield, Rocky Flats, Hanford and Los Alamos. The first three studies are summarised in the first three sections of this Chapter. The study at Los Alamos comprises only 26 workers and the interested reader is referred to the original publication (Voelz et al. 1997).

In 2005, studies which significantly improved the understanding of lung cancer risk due to indoor radon exposures have been published and discussed in the Article 31 group. Therefore, only a recommendation of the German Commission on Radiological Protection concerning lung cancer risk from indoor radon exposures is summarised here.

3.3.1 Plutonium workers at Sellafield

The Sellafield plant of British Nuclear Fuels (BNFL) is located on the Cumbrian coast in the UK. The plant was developed originally for the production of plutonium for nuclear weapons. Later, plutonium was produced as a consequence of the commercial reprocessing of spent nuclear fuel. Omar et al. (1999) analysed cancer mortality and morbidity among 14 319 workers who were hired between 1947 and 1975 at the Sellafield plant. In the mortality study, follow-up started at the time of hire and extended up to 31 December 1992. In the morbidity

study, follow-up covered the period 1 January 1971 to 31 December 1986 and included 13 206 workers.

The cohort included 10 382 'radiation workers', who were either monitored for external radiation with film badge dosimeters, or for plutonium exposures via urine analyses. The 5203 workers who were ever monitored for plutonium exposure (excluding 47 workers with inconsistent data) were classified as 'plutonium workers'. For 4609 of them, plutonium doses could be assessed. For the remaining, there were either only records 'below the (local) control limit' before 1961 or no usable urine data. Thus, concerning the plutonium workers, the cohort of workers of the Sellafield plant has nearly the same size as the plutonium workers in the Mayak Workers Cohort.

The plutonium exposures at the Sellafield plant were mainly due to ^{239}Pu. In addition there was some exposure to ^{240}Pu and ^{238}Pu. Exposures to other alpha emitting radionuclides were less important. For the 4609 workers, the average cumulative lung dose from plutonium exposure was 0.19 Sv (based on a radiation weighting factor of 20). For the radiation workers, the average cumulative external dose was 0.13 Sv. Three observations may be derived from these values:
i) Lung doses from plutonium and from external radiation are comparable
ii) Lung doses from plutonium are in the Mayak Worker Cohort in average by a factor of 25 higher then in the cohort of workers of the Sellafield plant
iii) External doses are in the Mayak Worker Cohort by a factor of 6 higher then in the cohort of workers of the Sellafield plant.

In total, 246 lung cancer deaths have been registered in the cohort, 105 among the plutonium workers. Mortality rates from lung cancer for plutonium workers were
i) close to those of England and Wales
ii) by 18% higher than for all radiation workers.
There were no significant trends of lung cancer mortality with increasing internal or external dose.

In the period 1971 to 1986, 176 incident lung cancers have been registered. Of them, 81 occurred among the plutonium workers. Lung cancer morbidity rates for plutonium workers were
i) by 15% smaller than in England and Wales
ii) by 18% higher than for the other radiation workers.
There was no significant trend of lung cancer morbidity with increasing internal dose.

3.3.2 Plutonium workers at Rocky Flats

The Rocky Flats Plant, Colorado produced nuclear weapons components from 1952 to 1989. The fabrication at Rocky Flats involved chemical processing of plutonium metal into plutonium dioxide, converting this compound to plutonium metal in reduction furnaces, and rolling and machining the metal into weapons components.

Brown et al. (2004) performed a case-control study on lung cancer among workers at Rocky Flats. In total, 180 workers (cases) were identified who fulfilled the following criteria:
i) employment for at least 6 months at Rocky Flats between 1 January 1952 and 31 December 1989
ii) death before 31 December 1996
iii) death certificate diagnosis of primary lung cancer listed as the underlying or contributing cause of death or cancer registry diagnosis of primary lung cancer.
Four controls were selecting for each case, matching in sex and date of birth (within 2.5 years). Controls were also required to fulfil the condition i) of the cases, to have been alive at

the age at death of the matched case and to have started work at Rocky Flats at an age younger than the age at death of the matched case.

The interquartile range of age at exposure of cases and controls was 42 to 54 years. Thus the exposures occurred at considerably older age than among the Mayak workers.

Lung doses of cases and controls were estimated on the basis of urine bioassay data for plutonium and uranium and lung count data for isotopes of both elements and their decay products. The intake of ^{241}Am was derived from the isotopic ratios in the nuclear materials processed at Rocky Flats. Records from film and thermoluminescent personal dosimeters, together with assumed ratios of neutron to gamma doses were used to estimate external exposures. 18% of the cases and 15% of the controls had internal lung doses exceeding 0.4 Sv. The average internal dose is similar as for the Sellafield plutonium workers.

Histories of smoking frequency were obtained from medical records or by telephone interviews with close relatives or with workers who knew the study subjects well enough to characterize their smoking habits. Data from a job-exposure matrix were used to estimate annual exposures to asbestos, beryllium, hexavalent chromium and nickel.

In a multiple logistic regression model with 5-year lagged doses, odds ratios (reference group: cumulative internal dose 0 Sv) increased in a monotonic fashion from the lowest dose group to the penultimate dose group (0.664 – 0.940 Sv), but diminished in magnitude at the highest dose category. None of the odds ratios was significant.

Among subjects who actually received lung doses, the risk was found to increase with increasing age at first exposure.

The dose-response was maximal for subjects employed for 15 – 25 years. In this subgroup, the odds ratios increased monotonically over all categories of cumulative internal lung dose (lag period of 10 years). The odds ratios for the two highest categories were significant. The test for linear trend was statistically significant.

None of the exposures to external radiation or to the four chemical carcinogens was significantly associated with lung cancer mortality.

3.3.3 Plutonium workers at Hanford

Wing et al. (2004) identified 26 389 workers of the United States Department of Energy Hanford Site in Washington who were hired in the period 1944 to 1978 and who had periods of employment in jobs with routine or non-routine potential for plutonium exposure. The follow-up for cause specific mortality extended up to end of 1994.

The lung cancer mortality rate among the plutonium workers was lower than among the other workers at the Hanford site. At ages 50 and above, however, death rate from lung cancer increased 7.1 ± 3.4% (± standard deviation) per year of employment in routine plutonium jobs. It is difficult to make a general conclusion from these observations.

3.3.4 Indoor radon

Darby et al. (2006) analysed the pooled data of 13 European case-control studies of lung cancer and indoor radon. The data comprised records for 7148 lung cancer patients and 14 208 control persons without lung cancer. Based on measurements in present and past homes, average radon concentrations have been estimated in the living places of the study participants during a period of 5 to 34 years before entering the study. Detailed information was obtained on life-long smoking behaviour and other risk factors for lung cancer.

Lung cancer risk was found to increase with increasing indoor concentration. For never smokers, odds ratios were significantly larger than one for the exposure category 100 – 199 Bq m^{-3}, and for all higher exposure categories. Results for all study members were consistent with these results. The risk coefficient in a linear model with threshold was 0.084 (95% CI: 0.030; 0.155) per 100 Bq m^{-3}. Correcting for dose uncertainties increased the estimated risk by a factor of two. The risk remained significant, if the analysis was confined to study members with radon concentrations in their homes below 200 Bq m^{-3}.

Based on the results of the European pooling study, the German Commission on Radiological Protection (SSK 2005) recommended that decision making regarding the reduction of residential radon should consider also levels below 250 Bq m^{-3}, which were considered previously as save.

3.4 Other solid cancers than lung cancer

3.4.1 Liver cancer

Thorotrast patients. Worldwide several million people have been exposed diagnostically to the radiographic contrast agent Thorotrast, a colloidal solution of thorium oxide (Abatt 1979). About 60% of the Thorotrast load was deposited in the liver, 20% in the spleen, and 12% in the red bone marrow (Kaul 1995). The hepatic dose is non-uniformly distributed with areas of the liver containing bile ducts, from which cholangiocellular carcinomas arise, receiving a 15 times higher dose than that of hepatic cord tissue (Dagle et al. 1992). Given the long biological half-life (400 years) of Thorotrast, patients received life-long exposures to alpha radiation (Hursh et al. 1957).

Travis et al. (2003) conducted a study of patients, who underwent cerebral angiography, 1650 with injection of Thorotrast and 1392 with injection of a non radioactive contrast agent. The examinations were performed in Denmark, Sweden or the United States between 1 January 1935 and 31 December 1963 (last application of Thorotrast in 1955). The actual volume of injected Thorotrast was known for 80% of the patients. Patient age at time of angiography was similar for Thorotrast (mean = 36.4 years, range 0.5-79.1 years) and comparison (mean = 38.1 years, range 0.4-79.2 years) subjects.

Overall 136 primary liver cancers were reported among 440 Thorotrast patients in Denmark and Sweden, and 0 primary liver cancers among 180 comparison group subjects. The standard incidence ratio (SIR) relative to the general population was 109. Relative risks increased significantly with time since Thorotrast injection. The usual latent period of Thorotrast-related liver cancers is several decades, with a minimum of 11 years. The relative risk increased significantly with increasing cumulative radiation dose. As to be expected from the dose distribution, the spectrum of liver cancer in Thorotrast patients (frequent cholangiocellular carcinomas and hemangioendotheliomas) differs from that of non exposed comparison groups (90% hepatocellular carcinomas).

For the US patients, a relative risk for mortality from liver cancer was 22.5. The relative risk increased significantly with time since Thorotrast injection.

Dos Santos Silva et al. (2003) analysed cancer mortality data for 1096 Thorotrast and 1014 unexposed patients who underwent cerebral angiography in Portugal during the period 1928 to 1959. The follow-up extended up to the end of 1996. In total 67 liver cancer deaths were observed among the Thorotrast patients. The mortality from liver cancer was significantly increased for the Thorotrast patients. The best estimate for the relative risk compared to the

control group was 42 (95% CI: 14; 210). The risk increased significantly with time since administration of the contrast medium and with cumulative alpha particle radiation exposure.

Significantly elevated risks for liver cancer incidence and/or mortality have also been reported in the major epidemiological studies of Thorotrast patients in Germany and Japan (van Kaick et al 1999, Mori et al. 1999).

A limitation of the thorotrast studies is that the patients in the comparison groups were not matched or at least no fully matched on indication for the procedure. Discrepancies in underlying disease between the exposed and comparison groups could confound the comparison. Further, in general administrations of the non radioactive contrast agent were performed later than administrations of Thorotrast. As a result, the spectrum of baseline illnesses in the Thorotrast group may not be equivalent to that in the comparison group of patients.

Mayak workers. The Mayak Worker Cohort has been described in Section3.2. Liver cancer mortality has been analysed in a sub-cohort of 11 000 workers who have been hired in the period 1948 to 1958 for the nuclear reactors or for the radiochemical and plutonium production plant (Gilbert et al. 2000). The cohort included 2207 workers with detectable plutonium burdens. Plutonium body burdens were much larger for plutonium plant workers than for radiochemical plant workers.

In total there were 60 deaths from liver cancer, 54 occurred at least 20 years after date of hire. Liver cancer was the underlying cause of death for 56 of the cases. Histological type was known for 44 cancers including 24 hepatocellular carcinomas, 10 hemangiosarcomas and 8 cholangiocellular carcinomas. All ten of the hemangiosarcomas occurred in workers with detectable plutonium burdens, and 8 of these occurred in females, who had in average higher doses than the males. All but one of the workers with hemangiosarcomas had external doses exceeding 1 Sv. Thirty of the 41 male workers with liver cancer consumed alcohol.

There is evidence for an elevated risk among those with estimated body burdens exceeding 7.4 kBq. Evidence was found that liver cancer risk is not a linear function of body burden, and that a pure quadratic function fitted the data reasonably well.

Excess relative risks per body burden were larger for females than for males. This is due at least in part to differences in baseline risk, which are smaller for females than males and which are probably affected by differences in alcohol consumption.

3.4.2 Malignant tumours of the bone

Patients treated with ^{224}Ra (Study I). Nekolla et al. (2000) analysed bone cancer data for 899 patients treated in Germany between 1942 and 1964 with injections of the short lived alpha particle emitter ^{224}Ra (half-life 3.7 d). Among them, 455 patients (including 244 children and juveniles under age 21) had tuberculosis and 393 (mostly male adults) ankylosing spondilitis.

Up to the end of 1998, a total of 56 malignant bone tumours occurred in 55 patients. Most of the cases were observed within the first 25 years after the first ^{224}Ra injections. Among the 42 cases with histopathological classification, 52% were osteosarcoma. The fraction of 29% fibrous-histiocytic sarcomas exceeds considerably their fraction of less than 10% in spontaneous bone sarcomas.

During the first few days after intake, radium concentrates heavily on endosteal bone surfaces and then gradually shifts its deposition to bone volume. About 90% of the ^{224}Ra atoms decay

while on the bone surface. Bone sarcomas are assumed to arise from cells in the bordering tissue of the bone surface within the range of alpha particles.

Dosimetric information was available for 608 adult and 204 children/juvenile patients. The mean bone surface dose in the two groups was 21 Gy and 59 Gy, respectively. In the first group, 11 patients developed a malignant bone tumour. These patients had an average dose of 34 Gy (60% higher than for the whole group). Among those who were treated as children or juveniles, 33 patients developed a malignant bone tumour. Their average dose was 81 Gy (35% higher than for the whole group). All patients with malignant bone tumours had bone surface doses of at least 9 Gy.

For short treatments, the lifetime attributable risk per dose was derived as 0.007 Gy^{-1} after injections at age 5, as 0.004 Gy^{-1} after injections at age 15, and to further decrease to 0.0004 Gy^{-1} after injections at age 60. The risk per dose increased with the duration of exposure. It was similar for males and for females. Assuming a radiation weighting factor of 20, the excess relative risk per unit dose was derived to 0.45 Sv^{-1} after exposure at age 5 and decreasing to 0.04 Sv^{-1} after exposure at age 60. These values are not greatly different from typical values for other solid tumours.

Patients treated with ^{224}Ra (Study II). Wick and Nekolla (2005) analysed data of the group of 1462 patients with ankylosing spondylitis, who have been treated in the period 1948 to 1975 with lower doses of ^{224}Ra than the patients in Study I. A typical cumulative bone surface dose was 6 Gy. By August 2004, 4 malignant tumours of bone and connective tissue have been observed. In addition, most tumours in Study I were osteosarcomas. This tumour type was not found in Study II. The study may suggest that the high excess of osteosarcomas in Study I occurs only at large doses to the bone surface.

Mayak workers. Koshurnikova et al. (2000) analysed bone cancer mortality among a sub-cohort of 11 000 Mayak workers, which has already been described in Section 4.1. Absorbed doses to bone surface cells from incorporated plutonium among those workers with body burdens above the detection limit (0.26 kBq) range from 0.4 to 144 Gy. The analysis included 19 bone cancers (17 were the cause of death) plus four soft tissue cancers that occurred in tissue very close to the bone (three were the cause of death). 16 of the bone cancers were osteosarcomas. Estimates of plutonium doses were available only for seven of the malignant tumours. Nevertheless, there was a significant trend of increasing bone cancer mortality with increasing body burden.

Radium dial painters. Hoel and Carnes (2005) analysed bone cancer data for 755 female dial painters who were first exposed before 1930. The dial painters incorporated ^{226}Ra and ^{228}Ra. In total, 46 bone cancers occurred, all at bone doses larger than 10 Gy. The data were best described with a linear dose-response model with a threshold dose at about 9 Gy.

3.4.3 Other solid cancers

Patients treated with ^{224}Ra. In Section 3.4.2, a description has been given of the German cohorts of patients with ankylosing spondylitis and tuberculosis who have been treated with ^{224}Ra. In the Study I cohort with higher doses cancer incidence rates were increased at many sites, including breast, soft tissues, thyroid, liver, kidney pancreas and bladder (Nekolla et al. 2005). Up to 2004, 31 breast cancer cases were observed. Only 9.1 cases would have been expected without exposure. For those exposed as children or juveniles, the relative risk was 8 (19 observed cases versus 2.3 expected). The point estimate of the excess relative risk per breast dose was 0.2 Sv^{-1} for women treated as adults and 2.2 for women who were treated at younger ages. Thus, as in other epidemiological studies of radiation induced breast cancer, an obvious age at exposure trend was observed. The ERR per dose for breast cancer incidence after exposures of children or juveniles is similar to the value of about 3 Sv^{-1} as it was

observed among the atomic bomb survivors (Thompson et al. 1994). It should be noted, however, that in the Study II cohort with lower exposures no increase of breast cancer incidence has been observed in comparison to the general population (Wick and Nekolla 2005).

3.5 Other diseases

3.5.1 Leukaemia

Thorotrast patients. A combined group of Thorotrast patients in Denmark, Sweden and the USA has been described in Section 3.4.1. About 12% of an injected dose of Thorotrast is deposited in the bone marrow (Kaul 1995). A typical 25-ml injection results in an annual dose to bone marrow of about 0.1 Gy.

Travis et al. (2003) reported 28 incident leukaemia cases excluding chronic lymphocytic leukaemia (CLL) among the exposed in Denmark and Sweden. Compared to the control group, this corresponds to a relative risk of 15 (95% CI: 4; 150). The relative risk increased with increasing cumulative radiation dose. The relative risk increases also with time since Thorotrast injection, which is an indication of the life-long exposure after the injection.

Significantly elevated mortality rates due to all types of leukaemia except CLL have been noted consistently in most major Thorotrast studies (van Kaick et al 1999, dos Santos Silva et al 2003, Mori et al. 1999).

Patients treated with ^{224}Ra. In Section 4.2, a description has been given of the German cohorts of patients with ankylosing spondylitis and tuberculosis who have been treated with ^{224}Ra. In contrast to the Study I cohort with higher doses, an increase of leukaemia incidence has been observed in the Study II cohort with lower exposures (Wick and Nekolla 2005). In total, 16 leukaemia cases have been observed. Among them were 10 cases of myeloid leukaemia. Only 2.8 would have been expected without exposure. The leukaemia cases occurred at latency times up to 34 years and spread over the whole period of observation.

3.5.2 All cancers together

Plutonium workers at Sellafield. The cohort of workers of the Sellafield plant has been described in Section 3.3.1. Cancer mortality and morbidity rates for all radiation workers and for plutonium workers were close to those of England and Wales (Omar et al. 1999).

Plutonium workers at Hanford. The cohort of Hanford workers was described in Section 3.3.3. Wing et al. (2004) found a lower cancer mortality rate among the plutonium workers than among other workers of the Hanford site. This difference persisted even with adjustment for demographic, socioeconomic and employment factor and may due, in part, to medical screening.

Thorotrast patients. Study groups of cerebral angiography patients has been described in Section 4.1. Overall 480 incident cancers were reported among 440 Thorotrast patients in Denmark and Sweden, and 196 cancers among 180 comparison group subjects. The stratified relative risk of 3.4 (95% CI: 2.9; 4.1) was similar for males and for females. The relative risk increased significantly with increasing cumulative radiation dose and remained approximately constant in the whole observation period of 2 to 50 years after angiography.

The relative risk for cancer mortality at all sites was 4.0 (95% CI: 3.5; 6.7) for the US Thorotrast patients. The relative risk increased steadily from 1.4 at 2 to 9 years after

angiography to 15.6 after 40 years. Similar temporal patterns were apparent for males and females.

In the study of patients from Portugal, mortality from all neoplasms was significantly raised among Thorotrast patients relative to the mortality among the unexposed. The best estimate of the relative risk was 6.7 (95%CI: 4.8; 9.5). The risk increased significantly with time since administration of the contrast medium and with cumulative alpha particle radiation exposure.

3.5.3 Non – cancer diseases

Plutonium workers at Sellafield. The cohort of workers of the Sellafield plant has been described in Section 3.3.1. Omar et al. (1999) observed a significant excess of deaths due to cerebrovascular diseases
i) among radiation workers compared with non-radiation workers
ii) among plutonium workers compared with other radiation workers.
For no other cause of death was there a significantly higher mortality rate of plutonium workers compared with other radiation workers.

3.6 Summary and conclusions

Lung cancer. Lung cancer among workers at the Mayak Production Association (MPA) in Southern Urals, Russia, is the prominent source of information on risks due to inhalation of plutonium. The average lung dose of plutonium workers due to alpha radiation exposures was 0.26 Gy. The average external dose of all radiation workers was 0.8 Gy.

In studies of lung cancer mortality among Mayak workers, three observations were made concerning the radiation weighting factor of plutonium:
i) the estimated ratio of the ERR per absorbed dose for internal (alpha-particle) and external (gamma-ray) exposure of Mayak workers was 33 (95% CI: 14; 98)
ii) the ERR per absorbed dose due to plutonium in the lung of Mayak workers tends to be smaller than the twentyfold ERR per dose of the atomic bomb survivors
iii) the EAR per absorbed dose due to plutonium in the lung of male Mayak workers is about twentyfold the EAR per dose of the atomic bomb survivors.
Evaluating these three observations it may be concluded that the current lung cancer risk estimates for Mayak workers support a value of 20 for the radiation weighting factor for plutonium.

Main weaknesses of the lung cancer studies of Mayak workers are the limited information on the smoking behaviour and uncertainties in evaluations of the lung dose from incorporated alpha emitters. Presently, further information on smoking behaviour is extracted from medical records, and work is performed on improved dose evaluations.

The cohort of workers at the Sellafield plant has nearly the same size as the Mayak Worker Cohort. The average exposure to plutonium was by a factor of 25, the average external exposure by a factor of 6 smaller than at MPA. No significant trends of lung cancer mortality or morbidity with increasing internal dose have been observed.

In a case-control study of lung cancer among plutonium workers at the Rocky Flats plant, plutonium exposures were comparable to those at the Sellafield plant. A significant dependence of lung cancer on plutonium dose was only obtained, when the analysis was confined to subjects who were employed for 15-25 years. No quantitative estimates of risk coefficients were reported.

The cohort of plutonium workers at the Hanford plant, Washington is larger than the Mayak Worker Cohort. However, estimates of plutonium doses were not available, and results of an analysis of cause-specific mortality are difficult to evaluate.

Other diseases than lung cancer. A large excess of liver cancers was observed in patients who have been exposed diagnostically to the radiographic contrast agent Thorotrast. An excess of liver cancer was also observed among the Mayak workers. In both cohorts, the relative frequency of cholangiocellular carcinomas and haemangiosarcomas among the liver cancers was much higher than in the general population. In the Mayak study, there was evidence for an increase of the relative risk with increasing plutonium body burden. No quantitative estimates of excess risks per unit dose have been reported.

Increased risks of malignant tumours of the bone have been observed among patients treated with high doses with ^{224}Ra, among the Mayak workers, and among the radium dial painters. There is evidence that excesses of bone cancer occur after bone surface exposures exceeding several Gy. Among those highly exposed with ^{224}Ra, the frequency of fibrous-histiocytic sarcomas exceeds considerably their fraction in spontaneous bone sarcomas.

In several studies excesses and deficits of site-specific solid cancer rates were observed. Most of these observations are based on small numbers. A striking observation was the increase of breast cancer incidence in the German Study I group of ^{224}Ra patients. The derived ERR per dose was comparable to what has been observed for the atomic bomb survivors. It decreased with increasing age at exposure.

Significantly elevated mortality and morbidity rates of leukaemia except CLL have been noted consistently in most major Thorotrast studies. The risks increase with increasing cumulative dose and with time since injection.

Mortality and morbidity risks due to all types of cancer were not increased among plutonium workers at Sellafield or at Hanford. The high exposures of Thorotrast patients, however, resulted in significantly increased cancer risks. No assessments of risks per unit dose have been reported.

Mortality to non-cancer diseases was in general not increased among the Sellafield workers. An exception is a significant excess of mortality due to cerebrovascular diseases.

General conclusions. Several studies prove an increase of solid cancer and leukaemia risks after exposures to alpha radiation. In most studies, the spectrum of cancer types among the exposed is different from that in the general population.

Quantitative risk estimates per unit dose due to exposures to alpha radiation are rare for other radionuclides than radon and its daughter products. First results on lung cancer mortality among Mayak workers are consistent with a radiation weighting factor of 20 for plutonium. Present and future work should be directed to an improvement of dosimetry and of the information on smoking behaviour of the cohort members.

Medical cohorts indicate a decrease of the excess relative risk with increasing age at exposure to alpha radiation. This is consistent with what has been observed among the atomic bomb survivors.

An excess of mortality due to cerebrovascular diseases has been observed among Sellafield workers. In order to further explore this question, a feasibility study of circulatory diseases in

the Mayak Worker Cohort is presently performed within a project of the Sixth Framework Euratom Programme (www.gsf.de/SOUL).

3.7 References

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4 CONCLUSIONS AND POTENTIAL POLICY IMPLICATIONS

Working Party "Research Implications on Health and Safety Standards" of the Article 31 Group of Experts[1]

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4.1 Introduction

This document presents the main conclusions and potential implications of the Scientific Seminar *Alpha-emitters: reliability of assessment of risk for radiation protection*, held in Luxembourg on 21st November 2005. While it is not intended to report in an exhaustive manner all the opinions that were expressed by the speakers or by the audience, it takes account of the discussions that took place during the subsequent meeting of the "Article 31" Group of experts. The content of the document has been prepared with the assistance of a rapporteur then discussed within the RIHSS (Research Implications on Health and Safety Standards) Working Party of the "Article 31" Group of experts. The final text is the responsibility of the RIHSS Working Party.

4.2 RIHSS seminars: rationale

The RIHSS (Research Implications on Health and Safety Standards) Working Party of the Article 31 Group of experts was set up with the task of helping to identify the potential implications of recent research results or new data analysis on the European Basic Safety Standards (BSS) Directive and on the related recommendations and guidance.

The following approach is adopted: each year the Working Party proposes relevant themes to the Article 31 Group of experts based on input from the Group itself and officials of the Directorate General Research of the European Commission. Once a theme is selected, the Group agrees a draft programme. The Working Party handles the practical organisation. The seminars involve invited speakers – mainly leading experts – who are asked to synthesize clearly the state-of-the-art in the field, paying special attention to new information. Additional experts, identified by members of the Article 31 Group from their own country, take part in the seminars and act as peer reviewers. The Commission convenes the seminars on the day before a meeting of the Article 31 Group, in order that members of the Group can discuss the potential implications of the combined scientific results.

4.3 Background and purpose of the seminar

Experimental evidence accumulated in the recent years tends to show that biological effects induced by ionizing radiation do not always require direct interaction with the sensitive target. The effect can be induced by a signal transmitted to a distant cell or tissue via some kind of

[1] This summary was prepared by the Working Party on Research Implications on Health and Safety Standards of the Article 31 Group of Experts. The following members of the Working Party contributed to the preparation of this document: L. Lebaron-Jacobs, W-U Müller, P. Olko, S. Risica, P. Smeesters (Chairman of the WP), R. Wakeford. They were assisted by the following officials of the European Commission: J. Naegele and S. Mundigl (DG TREN) and by invited experts:J. Piechowski, A. Susanna.

biochemical communication. Bystander effects, genomic instability and adaptive response became the most fashionable terms in modern radiobiology. This progress in radiobiology was possible due to the broader availability of facilities, usually based on Van de Graaff accelerators, which allow for enhanced selectivity of irradiation using single ion irradiation techniques. The rationale of using heavy charged particles as microprobes results from their selectivity but in addition low energy protons and α-particles are short-range, densely ionizing particles. The question arises if those radiobiological findings may influence the paradigms of radiation protection such as a linear, non-threshold (LNT) dose-response relationship, the concepts of Quality Factor, Q, or the dose and dose-rate effectiveness factor (DDREF) to relate the effects of acute exposures to chronic exposures. These topics are of interest for radiation protection also due to risk assessment for plutonium and other trans-uranium elements.

The purpose of this seminar was to review the recent radiobiological findings relevant to the radiation action of alpha-particles, epidemiology related to alpha-particle - induced cancers (excluding lung cancer related to radon exposure) and the uncertainty of α-particle dosimetry. The presentations were not related to the exposure of humans to radon and radon progeny. The radon issue will be dealt with at a separate seminar; here, it is only mentioned briefly in the data summary.

The main points arising from the presentations and subsequent discussion have been synthesized into conclusions and potential policy implications.

4.4 Main points arising from the presentations and subsequent discussion

The following scientists kindly agreed to present their invited reviews during the Art. 31 seminar:

- Dr. Sisko Salomaa (Radiation and Nuclear Safety Authority, STUK, Finland): “Non-targeted effects of ionizing radiation – Implications for radiation protection”.
- Dr. François Paquet (IRSN, France):”Dosimetric uncertainties after exposure to alpha emitters”. Since Dr. Paquet was unable to attend the seminar, the presentation was given by Dr. John Harrison (HPA, United Kingdom).
- Dr. Peter Jacob (Institute of Radiation Protection, GSF, Neuherberg, Germany): “Alpha–emitters: reliability of Assessment of Risk for Radiation Protection – Epidemiology”.

4.4.1 Non-targeted effects of ionizing radiation – Implications for radiation protection

Dr. Sisko Salomaa reviewed the historical background and recent findings on non-targeted effects, in particular bystander response and genomic instability, and their potential implications with respect to risk assessment and radiation protection. The presentation was not strictly oriented towards the effects after alpha-particle exposure because non-targeted effects have also been observed for low-LET radiation. The rationale for the application in radiobiology of short-ranged, densely ionizing alpha particles is rather their selectivity, allowing for targeting subcellular structures, such as the nucleus, cytoplasm or mitochondria with an exact number of charged particles. Local irradiation has also been performed with protons, heavy ions and focused X-ray microbeams.

The bystander effect is observed as cell killing or mutation in cells that were not affected directly by radiation but by energy deposition events occurring outside the target region. The effect arises due to cell-to-cell communication at the tissue level and in the cell culture

through signals transduced through the cell culture medium. Irradiation of cytoplasm has been shown to lead to a mutation in the nucleus of the targeted cell or in a bystander cell. The mutation spectrum in the bystander cells differs from that observed in cells irradiated directly, showing point mutations rather than deletions. This might have implications for the risk of hereditary effects.

Non-targeted effects have been observed at low doses and for low- and high LET radiations. The dose response relationship for bystander effect is non-linear, first showing a rapid increase and then a plateau at higher doses. This type of non-linearity could lead to underestimation of the low dose risk when using linear extrapolation from the high dose data. The bystander effect seems to be determined by the dose per cell hit rather than by the number of cells hit. On the other hand, high-and low-LET radiation were found to be equally effective in producing bystander effects. These findings seem to be partly contradictory because exposure to high LET radiation leads to high local dose in the volume of interest.

The radiation health significance of the bystander effect is still under discussion and at this stage it is not clear whether it would modify cancer risk and particularly if it increases this risk. As discussed by the CERRIE committee, "..epidemiologically based estimates of risk from alpha particle irradiation seem to include any theoretical impact from bystander effects". On the other hand, "...epidemiological studies may be insufficiently sensitive to detect the true level of risks especially at very low doses".

Radiation-induced genomic instability is understood as the occurrence of new mutations and/or new chromosomal aberrations in the progeny of hit cells and in the progeny of bystander cells. Similar to the bystander effect, the genomic instability is induced by both high and low-LET radiation, the dose response commencing at very low doses and showing a plateau at higher dose levels. No dose rate effect has been observed. The quantitative contribution of induced genomic instability in radiation cancer risk is not yet known. In particular, it is not possible to assess the relative contribution of induced genomic instability and of direct DNA damage to radiation-induced cancers. Similarly as in the case of the bystander effect, the contribution of radiation-induced genomic instabilities to cancer induction is implicitly included in epidemiological observations (currently in the medium to high dose range). Again it might not apply to the dose range below the epidemiological "detectability" domain.
There are indications that differences in genomic instability and bystander effects determine, at least to some degree, differences in individual radiosensitivity. There are also indications that genomic instability can be transferred to the progeny of radiation exposed animals.

Adaptive response is the phenomenon of stimulating the response of a biological system by an initial dose of radiation, which enhances the resistance of this system to an exposure that follows this first or several low-dose exposures. Thus, the effect of protracted irradiation may be significantly reduced compared to that observed for acute exposures. Non-targeted effects and adaptive response may be interrelated, e.g. adaptive response after low –LET exposure may reduce the bystander effect after alpha-particle irradiation.

After a review of experimental findings, Dr. Salomaa summarized the main implications of non-targeted effects for risk assessment and for the radiation protection system, in particular for understanding low dose effects, dose-effect relationships, effects of radiation quality, individual susceptibility, and potential mechanisms of the development of diseases other than cancer. The central point of the present paradigm of radiation protection is the Linear Non-Threshold (LNT) hypothesis. The main consequence of LNT is that dose and its effect are additive, therefore accumulated dose can be used as a surrogate of radiation risk. The problem is that the dose dependence of non-targeted effects is strongly non-linear at low doses which implies that risk could not be proportional to accumulated dose.

The presented data demonstrate that non-targeted effects are relevant with respect to radiation protection issues but there are not enough quantitative results nor models yet to suggest a new system of radiation protection. Some of the remaining problems are listed below:

- the underlying mechanisms of non-targeted effects are not known, e.g. factors transmitting the biochemical signal have not yet been specifically identified.
- it is unclear whether non-targeted effects can increase or decrease the cancer risk.
- the present epidemiological data already take into account all effects, probably including non-targeted effects, but the epidemiological studies will probably never resolve the problem of risk assessment at low doses
- there are no broadly accepted and verified quantitative radiobiological models of non-targeted effects, able to predict these effects at different radiation qualities, dose levels, dose-rates etc.
- there are indications that genomic instability and bystander effects determine, at least to some degree, individual radiosensitivity. This issue of differences in the radiation sensitivity between individuals is very relevant both for targeted and non-targeted effects.
- the mutation spectrum in the bystander cells differs from that observed in cells irradiated directly, showing point mutations rather than deletions. This might have implications for the risk of hereditary effect.
- the possible role of non-targeted effects in irradiations in utero remains to be explored.

4.4.2 Dosimetric uncertainties after exposure to alpha emitters

Dr. François Paquet (IRSN, France) prepared the paper and the presentation entitled ”Dosimetric uncertainties after exposure to alpha emitters”. Since Dr. Paquet was unable to attend the seminar, the presentation was given by Dr. J. Harrison (HPA, United Kingdom). The presentation well complemented the two other lectures. It dealt not only with dosimetric uncertainties after exposure to alpha emitters, as suggested in the title, but also discussed uncertainties in radiobiology and epidemiology.

Uncertainties in dosimetry are probably the most important in case of internal contamination with short-range emitters due to the numerous assumptions incorporated in dosimetric and biokinetic models.

As far as biokinetic models are concerned, a major source of uncertainties seems to be related to transfer coefficients. For Pu, Am and Cm e.g., the coefficients are known within a factor of 3-4 in the case of adults. It is also problematic to consider the chronic exposures as a sum of acute intakes of radionuclides. Paquet et al. (2005) demonstrated that the application of the acute intake data to predict the results of chronic exposure of rats by daily ingestion of uranium in drinking water, overestimates the deposition in tissues by an order of magnitude. Also the uncertainties of the transit times from one compartment to another can be substantial.

Uncertainties in dosimetric models originate from the build-in biokinetic models but also from assumptions in the location of radionuclides in tissues and in the location of target cells or regions for cancer induction. The assumption of uniform radionuclide distribution is assumed for convenience in computation but the real distributions may be heterogeneous in the tissues and in the cells. Regarding the location of target cells, differences in dose coefficient for the colon calculated for different assumptions of target location reach a factor of 3 for ^{239}Pu. More significant uncertainties are observed for parameters describing the radiation

quality such as RBE, Quality Factor or W_R. The present system assumes the same value of W_R for all X-rays, γ-rays and electrons but some measured RBE_M differ by a factor of 1.5-3. RBE_M for induction of lung cancer in different species after exposure to α-emitters vary by a factor of 7. Since the shape of the dose-response curve may be different in different tissues, for different types of cancer and radiation, the concept of radiation weighting factor W_R becomes scientifically meaningless. Even with the same set of input data, different laboratories may misinterpret the dosimetric models. Intercomparison of internal dosimetric services, organised within a common EULEP/EURADOS exercise, demonstrated that the committed effective dose for intake of ^{239}Pu calculated by different laboratories may differ by up to 4 - 5 orders of magnitude.

The paper of Dr. Paquet draws the attention to the drawbacks and uncertainties of the present radiation protection system for internal α-emitters. The cumulated uncertainties from radiobiology, epidemiology and internal dosimetry are at least one order of magnitude higher than that for the external exposure. This knowledge should be included for retrospective dose assessment, crucial for epidemiological studies.

4.4.3 Alpha–emitters: reliability of Assessment of Risk for Radiation Protection - Epidemiology

Dr. Peter Jacob presented a review of epidemiological data after exposure of human cohorts to isotopes emitting α-particles. The paper included (i) recent results concerning lung cancer among workers in the Mayak plutonium reprocessing plant in Russia, (ii) lung cancer in other studies, (iii) other solid cancers, (iv) lymphatic and haematopoietic neoplasms.

The importance of the Mayak studies of lung cancer mortality results from their high statistical significance, allowing quantitative estimates of cancer risk due to protracted plutonium exposure. Mayak workers were exposed to external (gamma and neutron) radiation, and to internal radiation (α-particles from the intake of plutonium). Among the total number of about 21000 workers, about 6000 were monitored for ^{239}Pu. The mean internal lung dose, based on urine measurements, was equal to 0.26 Gy. In a linear dose-response model without threshold (Gilbert et al), lung cancer was found to be significantly associated with internal lung dose for both sexes (ERR per Gy for females was 4 times that for males).
In a recent study, Jacob et al studied the role of the smoking factor, taking into account the results of the radon studies on the interaction between smoking and internal radiation exposure. By using the so-called sub-multiplicative model, he found slightly lower ERR.
Although ERR (at age 60) was lower in both studies than expected from the Atomic Bomb survivors, EAR (excess deaths per 10^4 PY-Sv) were similar.
Evaluating these three observations he concluded that the current lung cancer risk estimates for Mayak workers *support a value of 20 for the radiation weighting factor* for plutonium.
Main weaknesses of the lung cancer studies of Mayak workers are the limited information on the smoking behaviour and uncertainties in evaluations of the lung dose from incorporated alpha emitters.
In other studies on lung cancer incidence after α-particle exposure, the average lung doses were significantly lower than those in the Mayak radiation workers.
The cohort of workers at the Sellafield plant has nearly the same size as the Mayak Worker Cohort. The average exposure to plutonium was lower by a factor of 25, the average external exposure by a factor of 6. No significant trends of lung cancer mortality or morbidity with increasing internal dose have been observed.
In a case-control study of lung cancer among plutonium workers at the Rocky Flats plant, plutonium exposures were comparable to those at the Sellafield plant. A significant dependence of lung cancer on plutonium dose was only obtained, when the analysis was

confined to subjects who were employed for 15-25 years. No quantitative estimates of risk coefficients were reported.
The cohort of plutonium workers at the Hanford plant, Washington is larger than the Mayak Worker Cohort. However, estimates of plutonium doses were not available, and results of an analysis of cause-specific mortality are difficult to evaluate.

Also for other solid cancers excess risk was identified after α-particle exposure.
A large excess of liver cancers was observed in patients who have been exposed diagnostically to the radiographic contrast agent Thorotrast. An excess of liver cancer was also observed among the Mayak workers. In the Mayak study, there was evidence for an increase of the relative risk with increasing plutonium body burden. No quantitative estimates of excess risks per unit dose have been reported.

Increased risks of malignant tumours of the bone have been observed among patients treated with high doses with ^{224}Ra (ankylosing spondylitis), among the Mayak workers, and among the radium dial painters. There is evidence that excesses of bone cancer occur after bone surface exposures exceeding several Gy.

In several studies excesses and deficits of site-specific solid cancer rates were observed. Most of these observations are based on small numbers. A striking observation was the increase of breast cancer incidence in the German Study I group of ^{224}Ra patients. The derived ERR per dose was comparable to what has been observed for the atomic bomb survivors. It decreased with increasing age at exposure.

Significantly elevated mortality and morbidity rates of leukaemia except CLL have been noted consistently in most major Thorotrast studies. The risks increase with increasing cumulative dose and with time since injection.

The new epidemiological data and some recent analysis of the old results lead to the following conclusions:

- the excess mortality due to lung cancer in Mayak studies was comparable with that observed for atomic bomb survivors.
- There are no indications leading to change the value of the radiation weighting factor for α-particles (w_R=20).
- the influence of smoking and interaction between smoking and radiation known from the uranium miners data has been confirmed for Mayak studies
- Some medical treatments performed in first half of 20th century with radium or thorium isotopes lead to increase of incidence of liver cancer, bone cancer, breast cancer, sarcomas and others. The results are not in contradiction with the current risk estimates.
- There are practically no data concerning risk in infants and children.

4.5 Conclusions and potential implications

- The present data regarding non-targeted effects include a lot of different mechanisms that could be relevant with respect to radiation protection but it is currently too early to assess and quantify their consequences. In particular it is unclear whether non-targeted effects can increase or decrease the cancer risk. The present epidemiological data (currently in the medium to high dose range) are supposed to take into account all effects, including non-targeted effects, but the epidemiological studies will probably never resolve the problem of quantitative risk assessment at low doses (below the epidemiological detection domain).
  Looking to diseases other than cancer, the mutation spectrum in the bystander cells differs from that observed in cells irradiated directly, showing point mutations rather than deletions. This might have implications for the risk of hereditary effect. The possible role of non-targeted effects in irradiations in utero remains also to be explored.

- There are many drawbacks and uncertainties in the present radiation protection system for internal α-emitters. The cumulated uncertainties from radiobiology, epidemiology and internal dosimetry are at least one order of magnitude higher than that for the external exposure. These uncertainties should be taken into account for retrospective dose assessment and for epidemiological studies.

- The new epidemiological data and recent re-evaluation of existing data do not ask for a change in the current estimation of the risk coefficients for alpha-emitters. In particular, the excess mortality due to lung cancer in Mayak studies was comparable with that observed for atomic bomb survivors and there are no indications leading to change the value of the radiation weighting factor for α-particles (w_R=20). The influence of smoking and the interaction between smoking and radiation known from the uranium miners data has been confirmed in Mayak studies (as well as indoor radon studies). It is noteworthy that there are practically no data concerning risk in infants and children.